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 arms2. 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 cyclopolymerization reaction. If this reaction is a controlled process, reactive groups will remain which can then 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.

Results and discussion*

To diphenylglycoluril (2), four -(CH₂)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 NaBH₄ in dioxane. An alternative route, in which 1,6-dibromohexane is first attached to 2 and subsequently coupled to vanillin, was unsuccessful.

Intramolecular condensation of the vanillyl alcohol sub-units in 9 was achieved by heating in formic acid under high-dilution conditions. Chromatographic work-up afford-
ed two solids, compounds 3 and 4, in approximately 30\% and 10\% yield, respectively. Compound 3 contains a 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\textsuperscript{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 Analyzed 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

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

**Fig. 4. Conformations of cyclotetrameratylene: the "crown" form (a) and the "sofa" form (b).**
suggested that ring closure of 4 to 5 is an unfavourable process. It is known from the literature\(^2\) that cyclotetramericyclo-
three conformations: two related “crown”
forms (C\(_x\), and C\(_z\),). A “sofa” form (C\(_z\),
Fig. 4b). The latter is the most stable, since it has one of its
CPK models suggest that a “sofa” form of the cyclotetramericyclo-
sub-unit in 5 is not possible for steric reasons.

Preliminary experiments show that the CH\(_3\)OH function of the
free arm in 3 can be easily modified. Our efforts are
being directed towards the derivatization of 3 with
imidazoyl functions. These functions can act as a nucleo-
philic catalyst on a substrate bound in the cavity of 3
and 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.

**Compounds**

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

This compound was synthesized according to a literature proce-
dure\(^3\).

**4-(Bromohexoxy)-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\(_2\)OH, 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 and washed three
times with a saturated aqueous sodium chloride solution, dried
(MgSO\(_4\)), filtered over influsorial earth and evaporated under reduced
pressure. The remaining yellow oil was purified by column chroma-
tography (silica, eluent CHCl\(_3/\)CH\(_2\)OH, 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\(_3\)), 2850 (OCH\(_3\)),
1705 (CHO), 1720-1670 (C=O), 1580 (Ar), 1260 (COAr), 1030-950 (COH)
cm\(^{-1}\). \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 9.78 (s, 4H, ArCHO), 7.5-6.5 (m, 22H, ArH),
4.03 (t, 8H, CH\(_2\)ArO), 3.89 (s, 12H, CH\(_2\)Ar), 3.5-7.2 (br m, 8H, NCH\(_2\))
(M + H\(^{+}\))\(^{3}\); other signals were observed at m/z values correspond-
ing to the equation: 1231 \(\rightarrow 82\) (alkyl chain) \(\times\) 152 (vanillyl
m/z, group), \(k\) = 1, 2, 3, 4, \(k\), ..., 3.

**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 (m/z 1185 (M + H\(^{+}\))\(^{3}\), 1121 (M + H\(^{+}\) - 3H\(_3\)O\(^{+}\)), 1167 (M + H + 4H\(_2\)O\(^{+}\)).

1.3.4.6-Tetrasik[6/4-(hydroxymethyl)-2-methoxyphenoxyhexyl/tetra-
hydro-3a,6a-diphenylimidazo[4,5-d/imidazole-2,5(1H,3H)-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, followed by 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 influsorial 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 (\(\leq 100\%\)) of
quantitatively as a white foam. IR (KBr): 3460-3120 (OH), 2920
(CH\(_3\)), 2850 (OCH\(_3\)), 1680 (CO), 1585 (Ar), 1260 (COAr), 1090-950 (COH)
cm\(^{-1}\). \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 7.5-6.2 (m, 22H, ArH), 5.9-4.0 (t, 8H,
CH\(_2\)ArO), 3.89 (s, 12H, OCH\(_3\)), 3.5-2.8 (br m, 32H, CH\(_2\)Ar), between 3.0 and 1.5 (s, 4H, CH\(_2\)OH). FAB MS:
m/z 1293 (M + H\(^{+}\)), 1221 (M + H\(^{+}\) - 3H\(_3\)O\(^{+}\)), 1185 (M + H + 3H\(_3\)O\(^{+}\)), 1167 (M + H + 4H\(_2\)O\(^{+}\)).

1.3.4.6-Tetrahydro3a,6a-diphenylimidazo[4,5-d/imidazole-2,5(1H,3H)-
dione (9)
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