Synthesis of a (D_3)-Bis(cyclotriveratrylenyl) Macrocage by Stereospecific Replication of a (C_3)-Subunit

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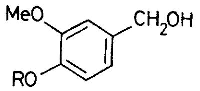
Summary (D_3)-Bis(cyclotriveratrylenyl) (**4**), has been synthesized in racemic and optically active forms by stereospecific replication of a (C_3)-subunit; the absolute configuration of (+)-(**4**) was assigned from that of the (C_3)-precursor.

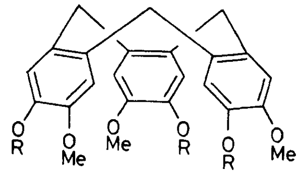
Although D_3 symmetry is readily accessible in octahedral tris(chelate) metal complexes,[1] organic molecules that belong to this point group are very uncommon.[2] We report in this communication the synthesis of (D_3)-bis(cyclotriveratrylenyl) (**4**), a new macrocage in which the chiral D_3 symmetry arises from the spatial arrangement of six equivalent achiral aromatic residues.

Initial attempts to obtain the key compound (C_3)-cyclotriguaiacylene (±)-(**2e**) by acid-catalysed condensation of vanillyl alcohol (**1c**) only afforded intractable material, presumably owing to the presence of the free phenolic group. In contrast, the phenol-protected derivative (**1a**) was found



(1)

a ; R = CH_2CO_2H
b ; R = CH_2CH_2I
c ; R = H

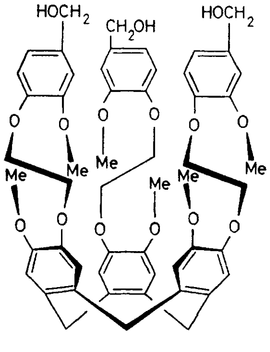


(2)

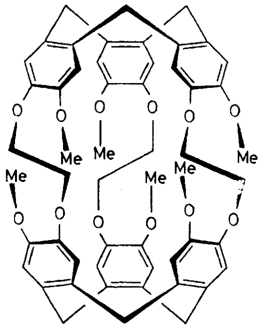
a ; R = CH_2CO_2H
b ; R = CH_2CO_2Me
c ; R = CH_2CH_2OH
d ; R = CH_2CH_2I
e ; R = H

to react satisfactorily in 65% perchloric acid, yielding, as expected,[3] the (C_3)-trimer (±)-(**2a**) as the major product (40%); this triacid was conveniently isolated and characterized (n.m.r.) as its trimethyl ester (**2b**), m.p. 192 °C. Lithium aluminium hydride reduction in tetrahydrofuran (THF) of (**2b**) to give (**2c**), m.p. 218 °C, followed by esterification with methanesulphonyl chloride (pyridine), and conversion of the resulting trimethanesulphonate into the tri-iodide (**2d**), by treatment with sodium iodide in glyme, proceeded in 75% overall yield. Cleavage of the CH_2CH_2I groups in (**2d**) by reaction with zinc powder in acetic acid afforded the desired (C_3)-triphenol, (±)-(**2e**), in 72% yield, as a crystalline solid (m.p. *ca.* 300 °C, decomp.). The structure of (±)-(**2e**) was assigned by comparison of its ^1H and ^{13}C n.m.r. spectra with those of the corresponding enantiomers, previously synthesized by a different route.[3,4]

Reaction of (±)-(**2e**) with the iodide (**1b**), m.p. 90 °C, in hexamethylphosphoric triamide (HMPA), using 25% aqueous NaOH as base (24 h; room temp.), gave the (C_3)-tris(vanillyl alcohol) derivative (±)-(**3**), isolated in 30% yield by t.l.c. (silica gel, ethyl acetate as eluant), as a colourless glass. This product was shown by ^1H n.m.r. spectroscopy to adopt the cyclotriveratrylene-like 'crown' conformation usually found in this series,[4] characterized by the AB n.m.r. quartet of the methylene bridges, at δ 3·50 (H_e) and 4·73 (H_a), J 14 Hz.



(P)-(−)-(3)



(+)-(4)

When a 0·8 × 10^{-3} M solution of (±)-(**3**) in formic acid was heated at 90 °C for 30 min, a smooth intramolecular reaction occurred which resulted in the formation of a *single* product, besides some polymeric material, as shown by analytical t.l.c. and by the n.m.r. spectrum of the crude mixture; the product, which was assigned structure (**4**), was isolated in 60% yield by t.l.c. (dichloromethane as the eluant), and was crystallized from ethanol–chloroform yielding solvated crystals† which decomposed above 350 °C (differential scanning calorimetry). The ^1H n.m.r. spectrum ($CDCl_3$) consisted of four singlets at δ 3·79 (OCH_3), 4·16 (OCH_2), 6·67, and 6·76 (ArH), together with the AB quartet characteristic of the crown structure at δ 3·40 and 4·60; it is interesting that these values are shifted upfield (by *ca.* 0·15 p.p.m.) with respect to the corresponding resonances in (**2e**), or in cyclotriveratrylene,[4] suggesting a mutual interaction between the molecular units. On the other hand, the ^{13}C n.m.r. spectrum of (**4**) (Table) is very similar to that of (**2e**). The structure was confirmed by mass spectrometry: *m/e* 894 $[(C_9H_9O_2)_6]$, 863, 833, 447 (M^{2+}), 364, 341, and 163.

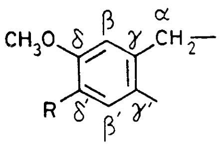


TABLE. ^{13}C N.m.r. data (δ values in p.p.m. with respect to Me_4Si; $CDCl_3$ solutions).

	α	β/β'	γ/γ'	δ/δ'	OCH_3	R
(2e)	35·2	112·7	130·0	144·2	55·5	(OH)
		115·9	131·8	145·3		
(4)	36·1	113·8	131·6	146·6	55·6	69·2 (OCH_2)
		120·8	134·0	149·6		

None of the foregoing data can provide useful information on the stereochemistry of (**4**), which may correspond either to an achiral (*meso*) or to a racemic (±) structure, according to whether the newly formed and the original (C_3) ring have opposite or identical chiralities, respectively. In order to investigate this point, we started from the known[3,5] triphenol (M)-(+)-(**2e**) (enantiomeric excess, e.e. > 90%), which was converted into the optically active (P)-(−)-(**3**), $[\alpha]^{25}$ − 65° (chloroform), by using the same conditions as above. Reaction of (−)-(**3**) in formic acid as described for the racemate similarly afforded a single product, identical (t.l.c., n.m.r.) with the above sample of (**4**); however, it was optically active, $[\alpha]_D^{25}$ + 180° (chloroform). This experiment shows that (**4**) should be assigned the chiral D_3 structure, or, in other words, that *the new ring is formed with the same chirality as the parent* (C_3)*-ring*. Inasmuch as we were unable to detect the *meso* isomer in the reaction mixture, the intramolecular cyclization (**3**) → (**4**) may be described as an example of stereospecific *replication*; a somewhat similar process, also virtually stereospecific, has been reported recently in a binaphthyl system.[6]

The ease with which the cyclization proceeds in formic acid is noteworthy; the formation of cyclotriveratrylene rings from appropriate benzylic alcohols usually requires strong acidic conditions [as, for example, the reaction (**1a**) → (**2a**)]. Although this result certainly illustrates the 'template effect,' the somewhat surprising stereospecificity suggests that the conformational requirement of the (OCH_2CH_2O) and (OCH_3) groups governs, to a large extent, the formation of the D_3 isomer, rather than the *meso*.

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† Elemental analyses are consistent with the formation of a 1 : 1 complex between (**4**) and $CHCl_3$; the presence of chloroform was also detected by n.m.r. and mass spectrometry.

The absolute configuration of (+)-(**4**) shown in the structural formula was inferred from that of the starting triphenol[5] (*M*)-(+)-(**2e**). The optical purity of the sample of (+)-(**4**) obtained is unknown. The activation parameters for the 'crown-to-crown' interconversion of the precursor (−)-(**3**) were calculated from its racemization rates at 37, 46, and 56 °C: $E_a = 26{\cdot}5$ kcal/mol,‡ with $A = 0{\cdot}5 \times 10^{-13}$. A racemization half-life of *ca.* 630 s at 90 °C can be estimated from these data. Since the cage (+)-(**4**), once formed, cannot racemize, the optical purity of the sample (isolated by t.l.c.) should depend on the rate of the conversion (**3**) → (**4**), which has not been measured.

Studies on the complexing properties, and on the chiroptical properties (c.d.) of (**4**) are in progress.

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‡ 1 cal = 4·184 J.

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