The Shikimate Pathway. Part 7.[1] Chorismate Mutase: Towards an Enzyme Model

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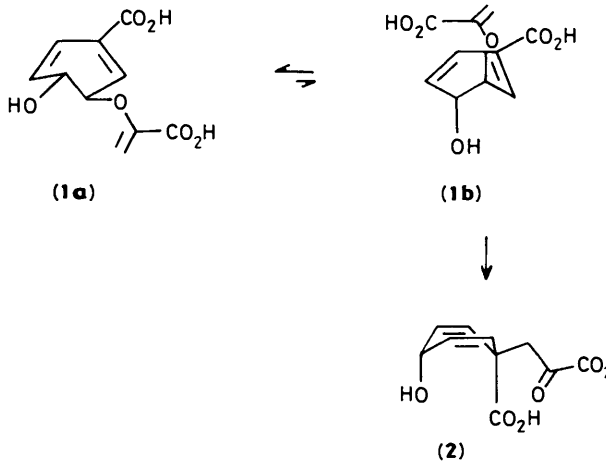
The mode of action of the enzyme chorismate mutase is briefly outlined. Molecular systems whose properties it is intended to develop to mimic those of the native enzyme are discussed. Syntheses of 11 crown-ether based models and studies of the association of alcohols and phenols with several of these—(**18**) and cryptands of the general structure (**16**)—are described.

It is to Eykmann in 1885 that the first description of (−)-shikimic acid as a natural product from *Illicium religiosum* is credited.[2] The full significance of this discovery was, however, not realised until the 1950s when the elegant work of Davis,[3] Sprinson,[4] and later Gibson[5] showed that the acid was a key intermediate in the metabolic pathway which leads from carbohydrate to the aromatic amino acids.[6,7] Chorismate (**1**) which is formed in the final step of the common part of the pathway is a pivotal compound and separate paths lead to the aromatic amino acids, *p*-hydroxybenzoate (ubiquinones) and *p*-aminobenzoate (folate coenzymes). The enzyme chorismate mutase catalyses the rearrangement of chorismate (**1**) to prephenate (**2**). The non-enzymic rearrangement occurs

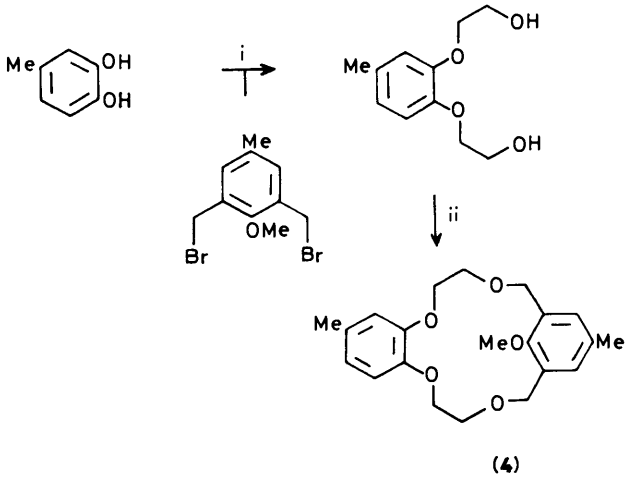


(**1a**) (**1b**) (**2**)

smoothly at 60 °C in neutral aqueous media and the enzyme chorismate mutase effects a rate acceleration of *ca.* 2×10^6 fold at 37 °C.[8] Formally the transformation is a 3,3-sigmatropic shift and if chorismate mutase operates simply by accelerating this change rather than by the provision of an alternative mechanistic pathway then its role would be unique in primary metabolism. It is for this reason that the enzyme has been the subject of considerable attention.[9,10]

The reaction catalysed by chorismate mutase proceeds *via* an activated complex of 'chair-like' geometry[9] and MO calculations[10] suggest that an active-site comprising only two essential binding groups is sufficient to account for catalysis. Based on various observations Gorisch[11] has elaborated a model for the active-site of chorismate mutase in which emphasis is placed on the complementarity of the active-site to the pseudo bis-axial conformer of chorismate (**1b**). In this model it is assumed that both carboxy groups of the substrate are bound by ionic interactions[12,13] and the 4-hydroxy group by hydrogen-bonding to a suitable partner. Studies of the interaction of analogues of the substrate chorismate with chorismate mutase reinforce this picture[14,15] and additionally suggest that hydrophobic or π-electron interactions between the diene system of (**1**) and an aromatic amino acid residue on the protein may also assist in the stabilisation of the transition-state complex. Iodoacetamide[16] at pH 7.2 irreversibly inhibits the chorismate mutase of both *Aerobacter aerogenes* and *Escherichia coli* and this inactivation is readily prevented by prior protection of the enzyme with its natural substrate (**1**) or analogues known to be competitive with (**1**).[15] This inactivation occurs through modification of a single cysteine residue of the protein suggesting a role for this thiol group in the enzyme mechanism. In terms of the various models and mechanisms put forward for chorismate mutase the function of the thiol group however remains, as yet, unexplained unless its action is that of anchor for the 4-hydroxy group of (**1**).

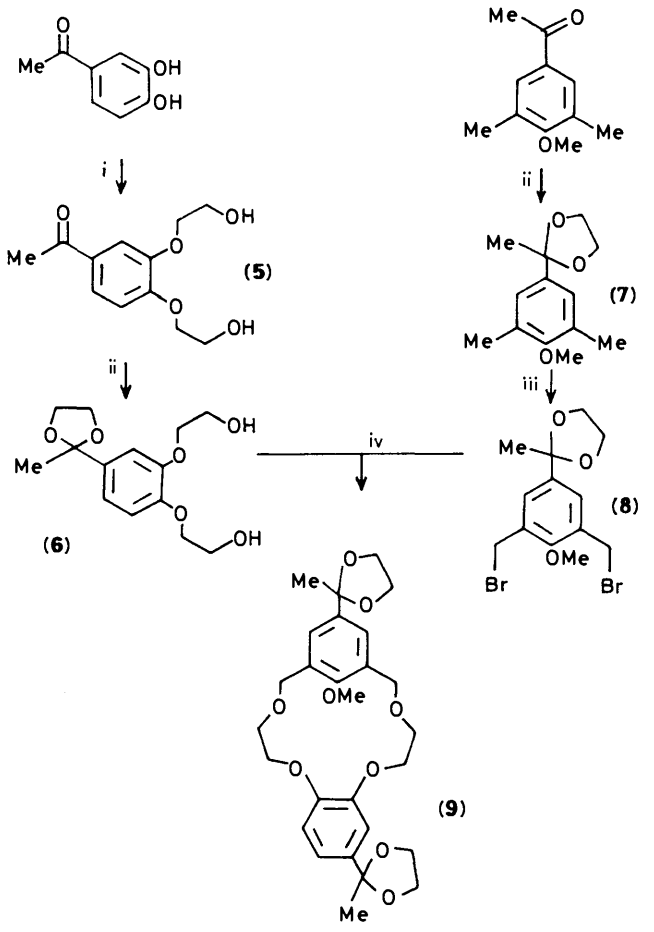
Although the size and complexity of enzymes is thought by many[17,18] to be necessary for the immense catalytic power which they exhibit, the alternative viewpoint that much smaller molecules with the right kind of three-dimensional structure will perform 'the same sort of thing' has also been expressed.[19] With this opinion in mind the principles governing the mode of action of chorismate mutase (the catalysis of a unimolecular rearrangement), have been extrapolated to suggest molecular systems whose properties may mimic those of the enzyme. Attention has been directed initially towards the synthesis of molecules which would furnish a site to lock (*via* hydrogen bonding) the 4-allylic hydroxy group of (**1**) and at the same time interact with the diene fragment of (**1**). Various considerations



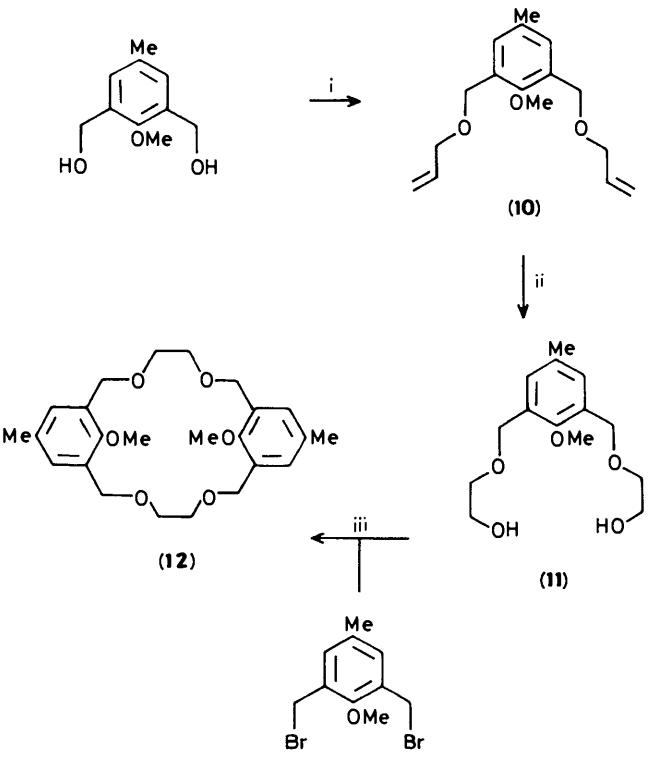
(**4**)

Scheme 1. i, $ClCH_2CH_2OH$–OH^-; ii, NaH–THF

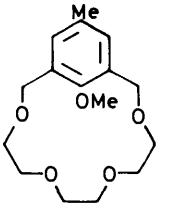
* See F. Vögtle and P. Neumann, *Tetrahedron*, 1970, 5847.



Scheme 2. i, $ClCH_2CH_2OH$–OH^-; ii, $HOCH_2CH_2OH$–*p*-$TolSO_3H$; iii, *N*-bromosuccinimide–CCl_4; iv, NaH–THF

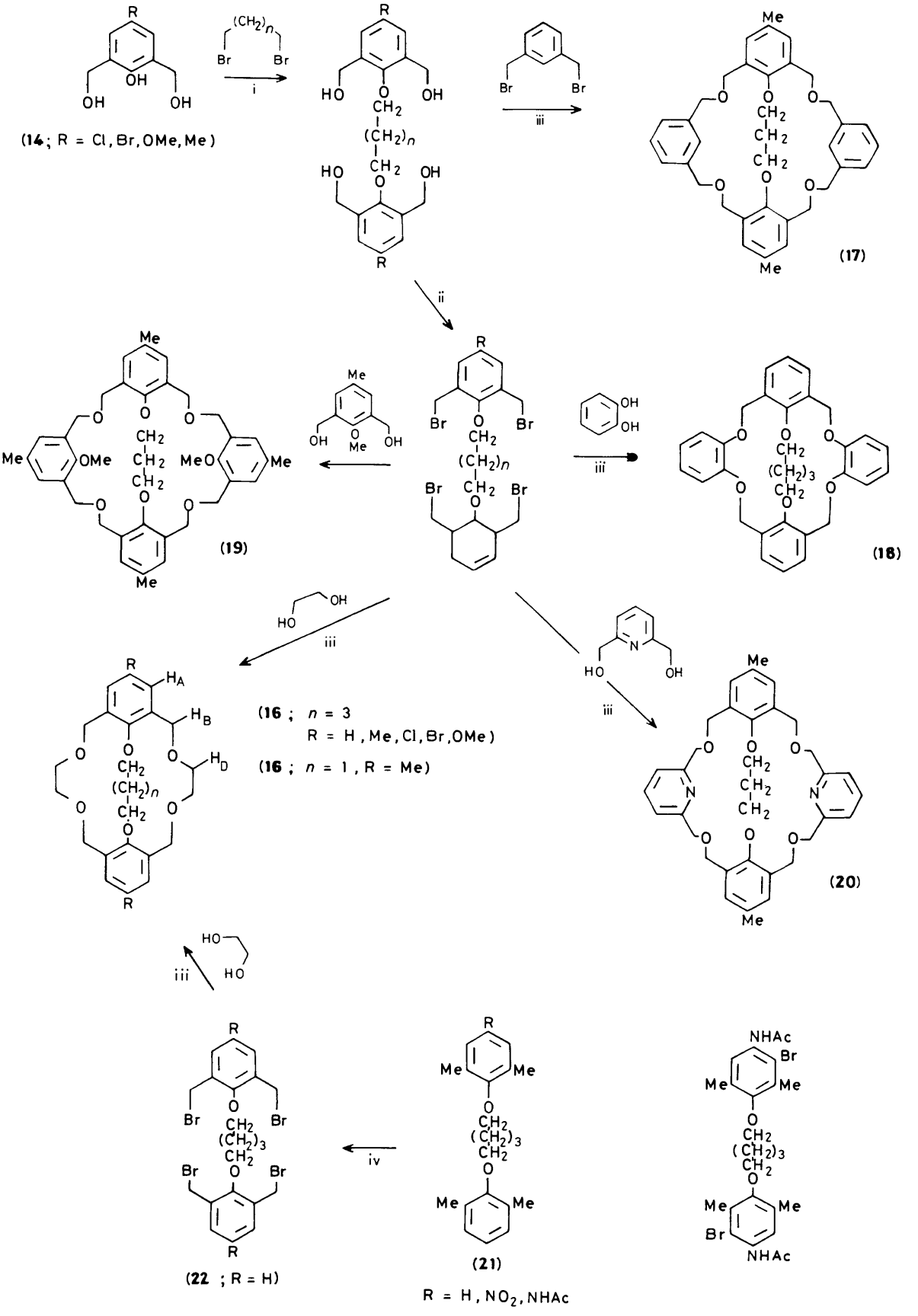


Scheme 3. i, $BrCH_2CH{=}CH_2$–NaH; ii, O_3, $NaBH_4$; iii, NaH–THF

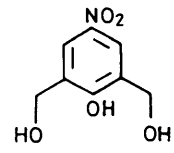


but principally CPK model building and computer graphics modelling (with ICI–Plant Protection p.l.c.) led to the adoption of crown ether systems bearing aryl residues as the initial synthetic targets—in particular the flexible 15-crown-4 systems (**4**), (**9**), (**12**), and (**13**) containing the annular methoxy group and the cryptand systems (**16**), (**17**), (**18**), (**19**), and (**20**). The synthetic schemes utilised to form compounds (**4**) and (**9**) are shown in Schemes 1 and 2. The physical properties of these crown ethers were compared with analogous crown ethers (**12**) and (**13**) prepared previously by Cram and his co-workers.[20] The ether (**12**) was obtained using a modified procedure to obtain the intermediate diol (**11**) (Scheme 3). Interpretation of the ^1H n.m.r. spectra of all the crown ethers (**4**), (**9**), (**12**), and (**13**) was consistent with the view that at 30 °C the intra-annular methoxy group(s) do not readily pass through the macrocyclic crown ether ring system and this gives rise in the ^1H n.m.r. to a distinction between the two faces of the macrocycles. Thus, for example, compound (**4**) shows an AB system (δ 5.13 and 3.98, J_{AB} 14 Hz) for the non-equivalent benzylic protons. Analogously in the ether (**9**) the three protons of one of the methyl groups of a 1,3-dioxalane ring appears in a multiplet at δ 3.7—4.3 whilst the other resonates at δ 1.7. This evidence suggests that in (**9**) one of these methyl groups is held in a position in relation to the aryl ring on the opposite side of the macrocycle such as to give rise to a strong deshielding effect. It also supports the view that although the presence of the methoxy groups in compounds (**4**), (**9**), (**12**), and (**13**) promotes the adoption of a V shaped conformation they do so in such a way as to place the methoxy groups on the outer rim and not in the well of the V. Some of these conclusions were reinforced by qualitative complexation experiments using benzylammonium perchlorate as 'guest'. The ^1H n.m.r. spectra of the complexes formed between compounds (**4**), (**9**), (**12**), and (**13**) and the substrate showed substantial upfield shifts for both the benzylic protons and the methoxy protons of the 'host' and this is consistent with the view that a 'perching' as opposed to a 'nesting' complex is preferred.[21,22] In the case of the bismethoxy derivative (**12**) the eight benzylic protons appear in the ^1H n.m.r. as a singlet (δ 4.38) and cooling to −78 °C only results in a broadening of the signal. This suggests that either there is a low-energy barrier to passage of the two methoxy groups through the macrocycle or alternatively, and more probably, that the energetically preferred conformer has a 'sandwich' structure in which the two methoxy groups lie on opposite faces of the crown ether ring. This latter conclusion is supported by the relatively highfield position of the methoxy group singlet (δ 3.37) in the ^1H n.m.r. spectrum and observations on an analogous bis-allyl ether[1] in related work.

In consequence a molecular system in which the two aryl rings were fixed less flexibly in relation to one another was sought and this has led to the exploration of the cryptand systems (**16**)—(**20**) in which the disposition of the two aromatic nuclei is determined primarily by the number of methylene groups [*e.g.* (**16**; n = 1 or 3)]. A general synthesis of cryptands



Scheme 4. i, $BrCH_2(CH_2)_nCH_2Br$–K_2CO_3–Me_2CO; ii, $SOBr_2$; iii, NaH–THF; iv, *N*-bromosuccinimide–CCl_4



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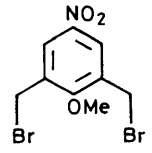

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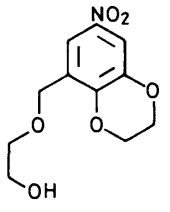

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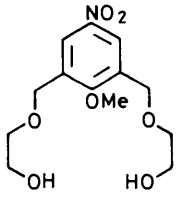

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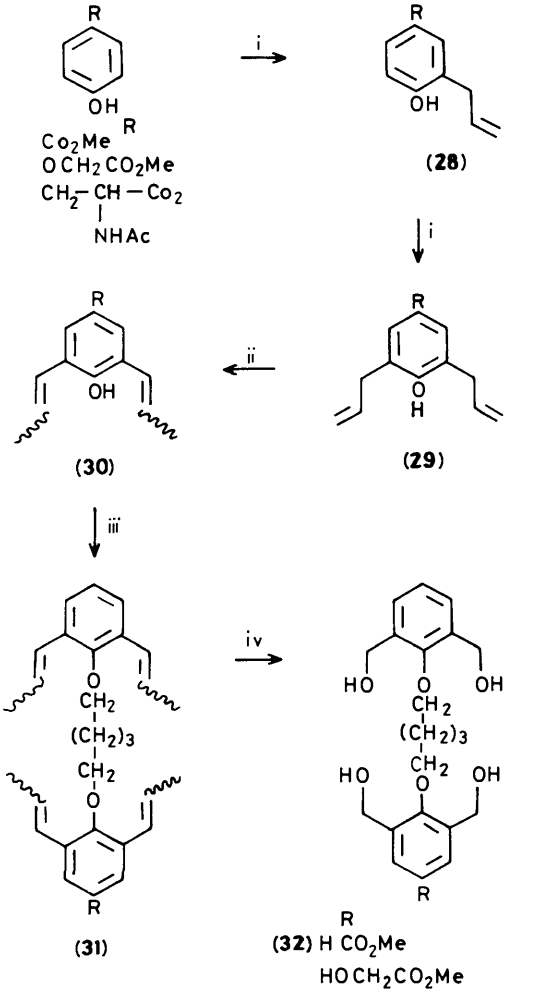

Scheme 5. i, $BrCH_2CH{=}CH_2$–K_2CO_3; $ArNMe_2$–heat; ii, $PdCl_2(PhCN)_2$–C_6H_6; iii, $BrCH_2(CH_2)_3CH_2Br$–K_2CO_3; iv, O_3, $NaBH_4$

of this type is shown in the Schemes 4 and 5. The unsubstituted cryptand (**16**; R = H, n = 3) was obtained *via* 2,6-dimethylphenol and bromination of the derivative (**21**) with *N*-bromosuccinimide. This latter reaction was surprisingly clean but attempts to prepare (**22**; R = NO_2) and (**22**; R = NHAc) by similar sequences failed. In the case of (**22**; R = NHAc) nuclear bromination occurred preferentially to give (**23**). The nitrophenol derivative (**24**) was prepared from 2,6-dimethylphenol but *para*-coupling with trimethylene or 1,5-dibromopentane failed. Alternatively, treatment of the dibromide (**25**) with ethylene glycol–sodium hydride gave poor yields of the diol (**26**) (16%). The major product was the ether (**27**).

The ^{13}C n.m.r. spectra of the various cryptands (**16**)—(**20**) demonstrate the high degree of symmetry in these molecules. For example compound (**16**; R = Me, n = 1) contains 25 C-atoms but shows just 9 signals in its ^{13}C n.m.r. spectrum. Preliminary *X*-ray crystallographic analysis (produced by Dr. C. P. Falshaw) of the cryptand (**16**; R = Me, n = 3) shows that the molecule adopts the desired V shaped conformation in its crystalline state (Figure 1). This view of the crystal structure also confirms that the oxygen atoms of the ring system are alternately 'up' or 'down' and that the hydrocarbon chain is not symmetrical. The common structural features of the cryptands (**16**)—(**20**) give rise to similar ^1H n.m.r. characteristics but (**16**) and (**18**) show important differences. In these compounds the eight benzylic protons (H_B) appear as a characteristic AB quartet indicative of two distinct faces to the cryptand. The cryptands (**17**) and (**20**) show the corresponding benzylic protons as two sharp singlets suggesting that interchange between the various conformers is rapid at ambient temperatures. However, in the cryptand (**19**) the 16 benzylic protons appear as a complex multiplet at 30 °C. A temperature-dependent ^1H n.m.r. study (−20 to +110 °C) indicated that the introduction of the two methoxy groups into the bridging aromatic nuclei leads to conformational restraints which are relieved at higher temperatures. The other feature of significance concerns the ^1H n.m.r. signals from the ring methylene protons (H_D); in (**16**; R = Me, n = 1) these appear as a multiplet but in the homologue (**16**; R = Me, n = 3) they give rise to a singlet resonance (δ 3.50) implying that in the latter cryptand the methylene groups are able to freely rotate but that in (**16**; R = Me, n = 1) there are restraints to conformational freedom.

Complexation studies have been conducted with the cryptands (**16**)—(**20**) and these indicate that these molecules, particularly those (**16**; R = Me, Cl, Br, OMe, Me, n = 1 or 3), provide a suitable binding site for aliphatic hydroxy groups, if they are weakly acidic. Such cryptands however do not bind carboxy groups. ^1H N.m.r. analysis of the complexation of benzylammonium perchlorate[23,24] was initially probed and the results strongly imply that association takes place within the cavity of the cryptands (Figure 1). Thus in the case of (**16**; R = Me, n = 3) the methylene protons (H_C) now appear in the complex as a multiplet (*ca.* δ 3.75) indicative of the loss of conformational freedom. The benzylic protons of the 'guest' benzylammonium ion appear at δ 2.56 [*cf.* δ 4.08 and δ 3.78 for analogous complexes with (**4**) and (**13**)]. This observation is consonant with a strong shielding of these protons between the two aromatic nuclei of the cryptand with the ammonium ion hydrogen bonded with two or three of the potential binding sites (oxygen atoms) of the ether ring system. Measurement of the association constant for complexation of t-butylammonium thiocyanate with the 2,5,2-cryptand (**16**; R = Me, n = 3), according to the method of Cram[25] gave a value of K_{assoc} = 77 200 l mol^{-1} at 24 °C and ΔG (kcal mol^{-1}) = −6.64. Comparison with values obtained for other crown ether systems[23] this result suggests that the relatively strong affinity of (**16**; R = Me, n = 3) for the ammonium ion, compared with other systems may well result from hydrogen-bonding reinforced by hydrophobic interactions in the region of the cleft between the two aryl rings (Figure 1).

These observations were extended by a study of the association (in $CDCl_3$) between various cryptands (**16**; n = 1

Table 1. Changes in chemical shift (δ/p.p.m.) of the *ortho* ($\Delta\delta_o$) and *meta* ($\Delta\delta_m$) protons of *p*-RC_6H_4OH upon complexation to the cryptand (**16**; R = Me, $n = 5$) and changes in chemical shift of the protons of the methyl groups of the cryptand ($\Delta\delta_{Me}$). Concentrations of both RC_6H_4OH and cryptand in $CDCl_3$ = 0.2 mmol l^{-1}

R	pK_a *p*-RC_6H_5OH	$\Delta\delta_o$	$\Delta\delta_m$	$\Delta\delta_{Me}$
NO_2	7.2	−0.36	−0.71	−0.27
Ac	8.1	−0.15	−0.35	−0.14
Cl	9.4	−0.19	−0.39	−0.13
H	10.0	−0.06	−0.20	−0.09
Me	10.3	−0.04	−0.11	−0.03

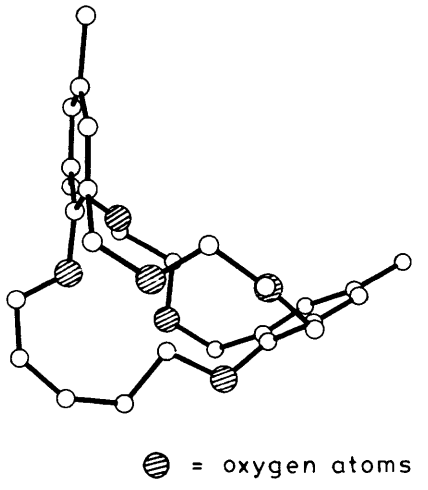

Figure 1. *X*-Ray analysis of the cryptand (**16**; $n = 3$, R = Me)

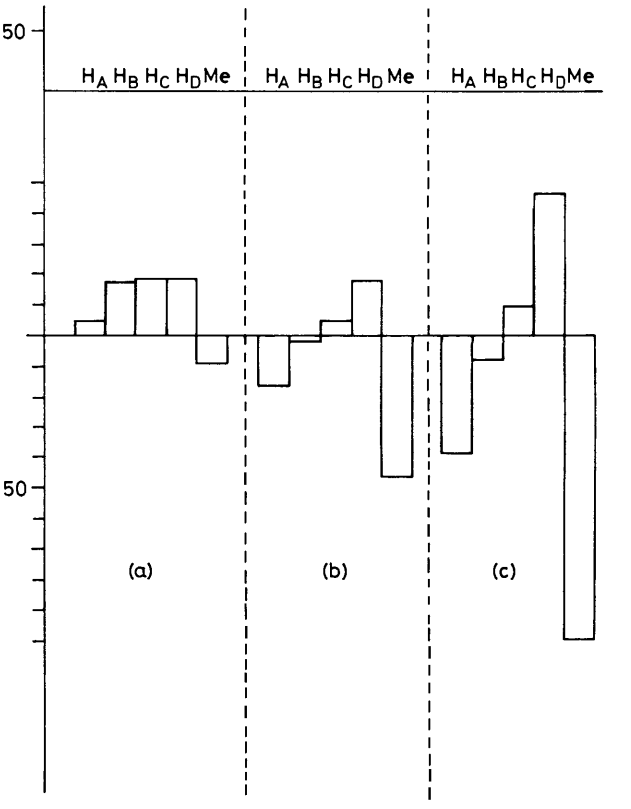

Figure 2. Relative changes in chemical shift for protons of the cryptand (**16**; R = Me, $n = 3$) undergoing complexation with various phenols. Values of the slope Δδ/mol ratio (phenol:cryptand) normalised to 34.7×10^{-2} p.p.m. = 100% (*p*-nitrophenol); (a) *p*-cresol, (b) *p*-chlorophenol, and (c) *p*-nitrophenol. Cryptand protons as in structure (**16**; $n = 3$); $H_c = ArOCH_2$

and 3) and various *p*-substituted phenols. Significant changes occur in the ^1H n.m.r. of the phenol in presence of the cryptand, both *ortho* and *meta* protons (to the substituent) undergo an upfield shift upon complexation; the upfield shift of the *meta* protons is greater than that of the *ortho* pair (Table 1). Entirely analogous observations were made with the 2,5,2-cryptand (**18**) and both sets of data are consistent with the interpretation that complexation occurs by hydrogen bonding of the phenolic group inside the well of the cryptand (Figure 1). With all the cryptands the magnitude of the upfield ^1H n.m.r. shifts of phenolic protons (on an equimolar basis) mirror the relative pK_a values of the individual phenols. If the relative magnitude of these chemical shift changes (on a molar basis) is directly related to the equilibrium constant for 'host:guest' binding then this suggests that the strength of binding is directly related to the acidity of the phenol. In competitive binding experiments (monitored by ^1H n.m.r.) *p*-nitrophenol was bound to the cryptand (**18**) in preference to *p*-chlorophenol which, in turn, was bound preferentially to *p*-cresol. Parallel with these studies, experiments were conducted in which the chemical-shift changes induced by phenolic substrates in the various protons of the cryptands (**16**; $n = 1$ or 3) were plotted as a function of increasing concentration of the phenol. Apart from the methoxy cryptand (**16**; R = OMe, $n = 3$) the pattern of chemical-shift changes were very similar, although on a molar basis the magnitude of chemical shift changes differed from cryptand to cryptand. Figure 2 shows values of Δδ/mol ratio of phenol:cryptand plotted for the complexation of *p*-cresol, *p*-chlorophenol, and *p*-nitrophenol with 2,5,2-cryptand (**16**; R = Me, $n = 3$). In all cases the strongest upfield shift is for the methyl resonances of the cryptand; the strongest downfield for the protons of the bridging methylene groups (H_D).

In the presence of equimolar quantities of the 2,5,2-cryptands (**16**; R = Me, $n = 1$) and (**16**; R = Me, $n = 3$) the fluorine coupled methylene protons of 2,2,2-trifluoroethanol showed upfield shifts in the ^1H n.m.r. of 0.67 and 0.52 p.p.m. respectively. Likewise 2,2,2-trichloroethanol showed analogous shifts of the methylene proton resonance of 0.36 and 0.29 p.p.m. All these observations are consistent with the proposition that 2,5,2-cryptands (**16**; $n = 1$ or $n = 3$) and (**18**) bind phenols and alcohols (weakly acidic) by hydrogen bonding in the cleft of the cryptand (Figure 1). The i.r. spectroscopic procedure reported by Viirret and Virtanen[26] was employed to determine association constants for the complexation of various *p*-substituted phenols and 2,2,2-trifluoroethanol with the 2,3,2-cryptand (**16**; R = Me, $n = 12$) and its homologue (**16**; R = Me, $n = 3$) in carbon tetrachloride. Typical association constants for a 1:1 complex ($K_{1:1}^{298}$) are shown in Table 2. For *p*-substituted phenols and the two cryptands plots of $K_{1:1}^{298}$ *vs.* Hammett σ substituent values were linear and related by the following expressions: (**16**; R = Me, $n = 1$), $\log K_{1:1}^{298} = 1.34\sigma + 1.58$ (regression coefficient 0.996) and (**16**; R = Me, $n = 3$), $\log K_{1:1}^{298} = 1.90\sigma + 1.135$ (regression coefficient 0.997).

Work is in progress to extend these observations and to introduce functional groups into the aryl rings of the 2,5,2-and 2,3,2-cryptands which are capable of development to provide potential binding sites for the carboxy groups of chorismic acid. However in this context, although various standard transformations of the bistetrahydropyranyl ether of (**14**; R = Br) have

Table 2. (i) Association constants for the **1**:1 complex, K_{11}^{298}, between *p*-RC_6H_4OH and various hosts at 25 °C in 1 mol^{-1}. Concentration of both cryptand and phenol = 0.2 mmol l^{-1}

Host	*p*-R Substituent H	Cl	NO_2
18-Crown-6	8.86	19.9	159
(2,3,2)-Cryptand (**16**; R = Me, *n* = 1)	35.2	90.2	451
(2,5,2)-Cryptand (**16**; R = Me, *n* = 3)	12.2	46.1	452

(ii) Association constants for the 1:1 complex, K_{11}^{298}, between 2,2,2-trifluoroethanol and the cryptands (**16**; R = Me, *n* = 1 or 3) at 25 °C in 1 mol^{-1}. Concentrations 0.2 mmol l^{-1} in CCl_4.

(2,3,2)-Cryptand (**16**; R = Me, *n* = 1)	19.8
(2,5,2)-Cryptand (**16**; R = Me, *n* = 3)	34.9

been carried out in which the bromine atom has been replaced by COMe and CO_2Et, similar reactions with the 2,5,2-cryptand (**16**; R = Br, *n* = 3) gave very poor yields of products.

Experimental *

1,2-*Bis*(2,6-*bishydroxymethyl*-4-*methylphenoxy*)*ethane*.—2,6-Bis(hydroxymethyl)-4-methylphenol (16.8 g, 0.1 mol) was dissolved, with heating, in acetone (250 ml). Anhydrous potassium carbonate (20.7 g, 0.15 mol) was then added and the suspension heated under reflux for 1 h. After this time, 1,2-dibromoethane (8.64 ml, 0.1 mol) in acetone (50 ml) was added and the reaction mixture heated under reflux for 63 h. An excess of 1,2-dibromoethane (5 ml) was then added to the reaction mixture, which was heated under reflux for a further 75 h. The hot suspension was filtered and allowed to cool to room temperature. Evaporation of the solvent under reduced pressure gave a yellow oil which was taken up into boiling ethyl acetate. The *title compound* (7.7 g, 43%) then crystallised as colourless plates, m.p. 145—146 °C (Found: C, 66.0; H, 7.3%; *M*, *m/z* 362. $C_{20}H_{26}O_6$ requires C, 66.3; H, 7.2%; *M*, 362); $\nu_{max.}$(Nujol) 3 400—3 040br, 1 355, 1 250, 1 215, 1 200, 1 145, 1 075, 1 040, 1 025, and 865 cm^{-1}; $\delta(C_5D_5N)$ 7.53 (4 H, s, ArH), 6.80—6.40 (4 H, br, OH), 5.14 (8 H, s, $ArCH_2OH$), 4.44 (4 H, s, $ArOCH_2$), and 2.25 (6 H, s, $ArCH_3$).

1,3-*Bis*(2,6-*bishydroxymethyl*-4-*methylphenoxy*)*propane*.—2,6-Bis(hydroxymethyl)-4-methylphenol treated similarly with 1,3-dibromopropane gave the *title compound* (48%) as colourless prisms (ethyl acetate), m.p. 132—133 °C (Found: C, 66.9; H, 7.7%; *M*, *m/z* 376. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%; *M*, 376); $\nu_{max.}$(Nujol) 3 490—3 040br, 1 410, 1 345, 1 245, 1 230, 1 215, 1 200, 1 140, 1 070, 1 040, and 860 cm^{-1}; $\delta(C_5D_5N)$ 7.56 (4 H, s, ArH), 6.48 (4 H, s, OH), 5.07 (8 H, s, $ArCH_2OH$), 4.26 (4 H, t, *J* 7 Hz, $ArOCH_2CH_2$), 2.38—2.17 (2 H, m, $ArOCH_2CH_2$), and 2.25 (6 H, s, $ArCH_3$).

1,4-*Bis*(2,6-*bishydroxymethyl*-4-*methylphenoxy*)*butane*.—2,6-Bis(hydroxymethyl)-4-methylphenol (16.8 g, 0.1 mol) treated similarly with 1,4-dibromobutane gave the *title compound* (42%) as colourless plates (ethyl acetate), m.p. 168 °C (Found: C, 67.6; H, 7.9%; *M*, *m/z* 390. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%; *M*, 390); $\nu_{max.}$(Nujol) 3 440—3 040br, 1 460, 1 235, 1 205, 1 140, 1 065, 1 045, and 860 cm^{-1}; $\delta(C_5D_5N)$ 7.72 (4 H, s, ArH), 6.77—6.63 (4 H, br, OH), 5.12 (8 H, s, $ArCH_2OH$), 4.04 (4 H, m, $ArOCH_2CH_2$), 2.26 (6 H, s, $ArCH_3$), and 2.08—1.96 (4 H, m, $ArOCH_2CH_2$).

1,5-*Bis*(2,6-*bishydroxymethyl*-4-*methylphenoxy*)*pentane*.—2,6-Bis(hydroxymethyl)-4-methylphenol (16.8 g, 0.1 mol) treated similarly with 1,5-dibromopentane gave the *title compound* (61%) as colourless plates (ethyl acetate), m.p. 156—157 °C (Found: C, 68.1; H, 8.0%; *M*, *m/z* 404. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%; *M*, 404); $\nu_{max.}$(Nujol) 3 440—3 040br, 1 480, 1 350, 1 255, 1 220, 1 210, 1 150, 1 140, 1 065, 1 060, 1 040, 1 005, and 860 cm^{-1}; $\delta(C_5D_5N)$ 7.57 (4 H, s, ArH), 6.80—6.48 (4 H, br, OH), 5.09 (8 H, s, $ArCH_2OH$), 3.94 [4 H, m, $ArOCH_2(CH_2)_3$], 2.27 (6 H, s, $ArCH_3$), and 1.86—1.56 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(4-*bromo*-2,6-*bishydroxymethylphenoxy*)*pentane*.—4-Bromo-2,6(bishydroxymethyl)phenol following similar treatment with 1,5-dibromopentane, gave after recrystallisation from ethyl acetate the *title compound* (63%) as colourless prisms, m.p. 136 °C (Found: C, 47.2; H, 4.65; Br, *29.7*. $C_{21}H_{26}Br_2O_6$ requires C, 47.2; H, 4.9; Br, 29.9%); *m/z* 532, 534, and 536 ($C_{21}H_{26}{}^{79}Br^{81}BrO_6$ requires *M*, 534); $\nu_{max.}$(KBr) 3 580—3 100br, 2 930, 2 870, 1 445, 1 360, 1 200, 1 060, 1 050, 1 015, and 870 cm^{-1}; $\delta(C_5D_5N)$ 7.95 (4 H, s, ArH), 6.75—6.40 (4 H, br, OH), 4.99 (8 H, s, $ArCH_2OH$), 3.84 [4 H, t, *J* 7 Hz, $ArOCH_2(CH_2)_3$], and 1.82—1.50 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(4-*methoxy*-2,6-*bishydroxymethylphenoxy*)*pentane*.—4-Methoxy-2,6-bis(hydroxymethyl)phenol, following similar treatment with 1,5-dibromopentane, gave after recrystallisation from ethyl acetate the *title compound* (47%) as colourless needles, m.p. 112—114 °C (Found: C, 63.5; H, 7.7%; *M*, *m/z* 436. $C_{23}H_{32}O_8$ requires C, 63.30; H, 7.40%; *M*, 436); $\delta(C_5D_5N$ 7.53 (4 H, s, ArH), 6.88 (4 H, br s, OH), 5.18 (8 H, s, $ArCH_2OH$), 3.94 (4 H, t, $ArOCH_2CH_2$), 3.70 (6 H, s, ArO*Me*), and 1.9—1.5 [6 H, m, $ArOCH_2(CH_2)_3$].

1,2-*Bis*(2,6-*bis*-*bromomethyl*-4-*methylphenoxy*)*ethane*.—1,2-Bis(2,6-bishydroxymethyl-4-methylphenoxy)ethane (1.09 g, 3 mmol) was partially dissolved, with stirring, in chloroform (25 ml) in a round-bottomed flask connected to an exhaust trap containing water. A solution of thionyl bromide (1 ml, 13 mmol) in chloroform (10 ml) was then added to the reaction vessel and the reaction mixture was stirred for 1 h. Saturated aqueous sodium hydrogen carbonate (15 ml) was then cautiously added to the stirred chloroform solution and the two layers were stirred together until the evolution of carbon dioxide ceased. The chloroform solution was then washed with water, until the water washings were neutral, and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to give a yellow solid which upon recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) provided the *title compound* (0.82 g, 45%) as colourless prisms, m.p. 161—162 °C (Found: C, 39.3; H, 3.8; Br, 52.1. $C_{20}H_{22}Br_4O_2$ requires C, 39.1; H, 3.6; Br, 52.1%); *m/z* 610, 612, 614, 616, and 618 ($C_{20}H_{22}{}^{79}Br_2{}^{81}Br_2O_2$ requires *M*, 614); $\nu_{max.}$(Nujol) 1 365, 1 225, 1 210, 1 205, 1 160, 1 095, 1 060, 890, 870, and 800 cm^{-1}; $\delta(CDCl_3)$ 7.22 (4 H, s, ArH), 4.66 (8 H, s, $ArCH_2Br$), 4.53 (4 H, s, $ArOCH_2CH_2OAr$), and 2.30 (6 H, s, $ArCH_3$).

1,3-*Bis*(2,6-*bisbromomethyl*-4-*methylphenoxy*)*propane*.—1,3-Bis(2,6-bishydroxymethyl-4-methylphenoxy)propane similarly gave the *title compound* as colourless prisms, m.p. 164—165 °C

* Experimental work related to Schemes 1—3 and 5 and to the preparation of compounds (**13**), (**24**)—(**27**) has been treated as a Supplementary publication [SUP. No. 56695 (34) pp.].

* For details of the Supplementary publications scheme, see Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

(Found: C, 40.0; H, 3.65; Br, 50.6. $C_{21}H_{24}Br_4O_2$ requires C, 40.2; H, 3.85; Br, 50.9%); *m/z* 624, 626, 628, 630, and 632 ($C_{21}H_{24}{}^{79}Br_2{}^{81}Br_2O_2$ requires *M*, 628); $\nu_{max.}$(Nujol) 1 485, 1 400, 1 365, 1 240, 1 210, 1 200, 1 160, 1 000, 865, and 785 cm^{-1}; $\delta(CDCl_3)$ 7.16 (4 H, s, ArH), 4.53 (8 H, s, $ArCH_2Br$), 4.37 (4 H, t, *J* 7 Hz, $ArOCH_2CH_2$), 2.53—2.40 (2 H, m, $ArOCH_2CH_2$), and 2.26 (6 H, s, $ArCH_3$).

1,5-*Bis*(2,6-*bisbromomethyl*-4-*methylphenoxy*)*pentane*.—1,5-Bis(2,6-bishydroxymethyl-4-methylphenoxy)pentane treated similarly gave the *title compound* as colourless plates, m.p. 128—129 °C (Found: C, 42.1; H, 4.3; Br, 48.5. $C_{23}H_{28}Br_4O_2$ requires C, 42.1; H, 4.3; Br, 48.7%); *m/z* 652, 654, 656, 658, and 660 ($C_{23}H_{28}{}^{79}Br_2{}^{81}Br_2O_2$ requires *M*, 656); $\nu_{max.}$(Nujol) 1 245, 1 215, 1 165, 995, 870, and 795 cm^{-1}; $\delta(CDCl_3)$ 7.16 (4 H, s, ArH), 4.52 (8 H, s, $ArCH_2Br$), 4.14 [4 H, t, *J* 7 Hz, $ArOCH_2(CH_2)_3$], 4.27 (6 H, s, $ArCH_3$), and 2.08—1.82 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(4-*bromo*-2,6-*bisbromomethylphenoxy*)*pentane*.—1,5-Bis(4-bromo-2,6-bishydroxymethylphenoxy)pentane similarly treated with thionyl bromide gave, after the product was recrystallised from light petroleum (b.p. 60—80 °C), the *title compound* as fine colourless needles, m.p. 151 °C (Found: C, 31.9; H, 2.65. $C_{21}H_{22}Br_6O_2$ requires C, 32.1; H, 2.8%); *m/z* 780, 782, 784, 786, and 788 ($C_{21}H_{22}{}^{79}Br_3{}^{81}Br_3O_2$ requires *M*, 786); $\nu_{max.}$(Nujol) 1 235, 1 210, 880, 870, and 790 cm^{-1}; $\delta(CDCl_3)$ 7.48 (4 H, s, ArH), 4.46 (8 H, s, $ArCH_2Br$), 4.15 [4 H, t, *J* 7 Hz, $ArOCH_2(CH_2)_3$], and 2.08—1.82 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(4-*methoxy*-2,6-*bisbromomethylphenoxy*)*pentane*.—1,5-Bis(4-methoxy-2,6-bishydroxymethylphenoxy)pentane similarly treated with thionyl bromide gave, after crystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C), the *tetrabromide* as fine needles (87%), m.p. 130—113 °C (Found: C, 40.7; H, 9.0; Br, 46.9. $C_{23}H_{28}Br_4O_4$ requires C, 40.4; H, 9.3; Br, 46.2%); *m/z* 684, 686, 688, 690, and 692 ($C_{23}H_{28}{}^{79}Br_4O_4$ requires *M*, 684).

9,2-*Dimethyl*-2,5,14,17,25,29-*hexaoxa*[6.6.5](1,3,2)*cyclophane* (**16**; R = Me, *n* = 1).—A solution of 1,3-bis(2,6-bisbromomethyl-4-methylphenoxy)propane (12.56 g, 0.02 mol) in anhydrous tetrahydrofuran (1 300 ml) was added to a three-necked round-bottomed flask containing sodium hydride (2.88 g, 0.12 mol) under a nitrogen atmosphere. The stirred suspension was then heated to reflux and a solution of ethylene glycol (2.5 ml, 0.045 mol) in anhydrous tetrahydrofuran (200 ml) was added through a Hershberg addition funnel over 16 h. After being heated under reflux, with stirring, for a further 26 h, the reaction mixture was allowed to cool to room temperature when the excess of sodium hydride was carefully destroyed with distilled water. The reaction mixture was then evaporated to dryness under reduced pressure and the organic residues extracted with chloroform. The chloroform solution was filtered to remove inorganic material, dried ($MgSO_4$), and evaporated under reduced pressure to give a brown oil (15 g), which was purified by medium pressure liquid chromatography on silica (150 g). Elution with dichloromethane–ethyl acetate (4:1) afforded the *title compound* (2.0 g, 23%) as a colourless solid which was recrystallised from methanol to yield colourless plates, m.p. 169 °C (Found: C, 69.85; H, 7.7%; *M*, *m/z* 428. $C_{25}H_{32}O_6$ requires C, 70.1; H, 7.5%; *M*, 428); $\nu_{max.}$(Nujol) 1 480, 1 365, 1 250, 1 215, 1 160, 1 105, 1 040, and 860 cm^{-1}; $\delta(CDCl_3)$ 6.89 (4 H, s, ArH), 4.84 (4 H, d, J_{gem} 12 Hz, $ArCH_AO$), 4.43 (4 H, t, *J* 7 Hz, $ArOCH_2CH_2$), 3.93 (4 H, d, J_{gem} 12 Hz, $ArCH_BO$), 3.81—3.54 (8 H, m, OCH_2CH_2O), 2.38—2.22 (2 H, m, $ArOCH_2CH_2$), and 2.17 (6 H, s, $ArCH_3$); $\delta_C(CDCl_3)$ 155.1 (ArC), 132.9 (ArCH), 131.4, 130.3 (ArC), 73.8 ($ArCH_2O$), 69.5, 69.0 (CH_2CH_2O and $ArOCH_2$), 32.0 ($ArOCH_2CH_2$) and 20.6 ($ArCH_3$).

11,22-*Dimethyl*-1,7,15,18,27,30-*tetraoxa*[7.6.6](1,2,6)-*cyclophane* (**16**; R = Me, *n* = 3).—A solution of 1,5-bis(2,6-bisbromomethyl-4-methylphenoxy)pentane treated similarly with ethylene glycol gave the *title compound* (2.32 g, 25%) as a colourless solid (prolonged evaporation, with heating, under reduced pressure was required to remove the diochloromethane from the product). The product recrystallised from hexane to give colourless prisms, m.p. 102 °C (Found: C, 71.3; H, 8.0; *M*, *m/z* 456. $C_{27}H_{36}O_6$ requires C, 71.0; H, 7.95%; *M*, 456); $\nu_{max.}$(Nujol) 1 480, 1 360, 1 255, 1 225, 1 155, 1 090, 1 045, and 860 cm^{-1}; $\delta(CDCl_3)$ 6.89 (4 H, s, ArH), 4.87 (4 H, d, J_{gem} 12 Hz, $ArCH_AO$), 4.09 (4 H, t, *J* 7 Hz, $ArOCH_2CH_2$), 3.96 (4 H, d, J_{gem} 12 Hz, $ArCH_BO$), 3.50 (8 H, s, OCH_2CH_2O), 2.17 (6 H, s, $ArCH_3$), and 2.12—1.80 [6 H, m, $ArOCH_2(CH_2)_3$]; $\delta_C(CDCl_3)$ 155.0 (ArC), 131.4 (ArCH), 130.6, 129.8 (ArC), 74.5 ($ArCH_2O$), 68.4, 68.0 (CH_2CH_2O and $ArOCH_2$), 29.0 ($ArOCH_2CH_2CH_2$), 22.1 ($ArOCH_2CH_2CH_2$), and 19.6 ($ArCH_3$).

11,22-*Dibromo*-1,7,15,18,27,30-*tetraoxa*[7.6.6](1,2,6)*cyclophane* (**16**; R = Br, *n* = 3).—A solution of 1,5-bis(4-bromo-2,6-bisbromomethylphenoxy)pentane treated similarly with ethylene glycol gave the *title compound* (1.32 g, 10%) as colourless prisms, m.p. 161 °C, after prolonged evaporation, with heating, under reduced pressure to remove dichloromethane (Found: C, 50.9; H, 5.1; Br, 27.1. $C_{25}H_{30}Br_2O_6$ requires C, 51.2; H, 5.2; Br, 27.3%); *m/z* 586 ($C_{25}H_{30}{}^{79}Br^{81}BrO_6$ requires 586); $\nu_{max.}$(Nujol) 1 365, 1 270, 1 220, 1 130, 1 100, 1 050, and 870 cm^{-1}; $\delta(CDCl_3)$ 7.26 (4 H, s, ArH), 4.87 (4 H, d, J_{gem} 12 Hz, $ArCH_AO$), 4.12 (4 H, t, *J* 7 Hz, $ArOCH_2CH_2$), 3.96 (4 H, d, J_{gem} 12 Hz, $ArCH_BO$), 3.53 (8 H, s, OCH_2CH_2O), and 2.02—1.82 [6 H, m, $ArOCH_2(CH_2)_3$]; $\delta_C(CDCl_3)$ 157.2 (ArC), 134.2 (ArCH), 133.2 (ArC), 114.8 (ArCBr), 75.4 ($ArCH_2O$), 69.3, and 68.9 (CH_2CH_2O and $ArOCH_2$), 29.8 ($ArOCH_2CH_2CH_2$), and 22.8 ($ArOCH_2CH_2CH_2$).

11,22-*Dimethoxy*-1,7,15,18,27,30-*tetraoxa*[7.6.6](1,2,6)*cyclophane* (**16**; R = OMe, *n* = 3).—Similar treatment of **1**,5-bis(4-methoxy-2,5-bisbromomethylphenoxy)pentane gave the *title compound* as white prisms, m.p. 161—216 °C (Found: C, 64.9; H, 7.5; *M*, *m/z* 488. $C_{27}H_{30}O_8$ requires C, 64.4; H, 7.4%; *M*, 488); $\delta(CDCl_3)$ 6.65 (4 H, s, ArH), 4.87 (4 H, d, *J* 9.8 Hz, $ArCH_2O$), 4.00 (4 H, d, *J* 9.8 Hz, $ArCH_2O$), 4.06 (4 H, t, $ArOCH_2CH_2$), 3.66 (6 H, s, ArO*Me*), 3.53 (8 H, s, $ArCH_2OCH_2CH_2$), and 1.71—2.10 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(2,6-*dimethylphenoxy*)*pentane* (**21**; R = H).—2,6-Dimethylphenol (12.2 g, 0.1 mol) was dissolved, with heating, in anhydrous acetone (250 ml). Anhydrous potassium carbonate (20.7 g, 0.15 mol) was then carefully added and the suspension heated under reflux, with stirring for 15 min. After this time 1,5-dibromopentane (8.5 ml, 62.5 mmol) in acetone (50 ml) was added and the reaction mixture heated under reflux for 5 days. The hot solution was then filtered and the inorganic residues subjected to Soxhlet extraction with acetone for 3 days. Evaporation of the combined acetone solutions under reduced pressure gave a yellow oil which was purified by fractional distillation to afford the *title compound* (**21**; R = H) (15.6 g, 50%) as colourless prisms, m.p. 37—39 °C (b.p. 180 °C/0.06 mmHg) (Found: C, 80.5; H, 8.95%; *M*, *m/z* 312. $C_{21}H_{28}O_2$ requires C, 80.8; H, 9.0%; *M*, 312); $\nu_{max.}$(Nujol) 1 590, 1 260, 1 205, 1 160, 1 125, 1 090, 910, 830, and 765 cm^{-1}; $\delta(CDCl_3)$ 6.98 (4 H, d, J_o 7 Hz, ArH), 6.87 (2 H, t, J_o 7 Hz, ArH), 3.79 [4 H, t, *J* 9 Hz, $ArOCH_2(CH_2)_3$], 2.27 (12 H, s, $ArCH_3$), and 1.95—1.60 [6 H, m, $ArOCH_2(CH_2)_3$].

1,5-*Bis*(2,6-*bisbromomethylphenoxy*)*pentane* (**22**; R = H).—To a solution of 1,5-bis(2,6-dimethylphenoxy)pentane (0.9 g, 2.9 mmol) in anhydrous carbon tetrachloride (10 ml) was added *N*-bromosuccinimide (2.26 g, 12.7 mmol) in which was mixed dibenzoyl peroxide (0.03 g, 0.13 mmol). The mixture was then heated under reflux, with stirring, until all the *N*-bromosuccinimide had been consumed (*ca.* 1 h). The hot reaction mixture was immediately filtered and the solid residues washed with carbon tetrachloride (10 ml). The combined filtrates were then washed with water (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow solid (1.69 g, 93%) which was recrystallised from ethyl acetate, to afford the *title compound* (**22**; R = H) as white needles, m.p. 118—120 °C (Found: C, 40.0; H, 3.9. $C_{21}H_{24}Br_4O_2$ requires C, 40.1; H, 3.8%); *m/z* 624, 626, 628, 630, and 632 ($C_{21}H_{24}{}^{79}Br_2{}^{81}Br_2O_2$ requires *M*, 628); $\nu_{max.}$(Nujol) 1 590, 1 235, 1 205, 1 070, 990, and 755 cm^{-1}; $\delta(CDCl_3)$ 7.39 (4 H, d, J_o 7 Hz, ArH), 7.10 (2 H, t, J_o 7 Hz, ArH), 4.60 (8 H, s, $ArCH_2Br$), 4.21 [4 H, t, *J* 9 Hz, $ArOCH_2(CH_2)_3$], and 2.15—1.75 [6 H, m, $ArOCH_2(CH_2)_3$].

1,7,15,18,27,30-*Tetraoxa*[7.6.6](1,2,6)*cyclophane* (**16**; R = H, *n* = 3).—A solution of 1,5-Bis(2,6-dibromomethylphenoxy)pentane (6.28 g, 100 mmol) in anhydrous tetrahydrofuran (650 ml) was added to a three-necked round-bottomed flask containing sodium hydride (1.44 g, 60 mmol) under a nitrogen atmosphere. The stirred suspension was then heated to reflux and a solution of ethylene glycol (1.25 mol, 23 mmol) in anhydrous tetrahydrofuran (100 ml) was added through a Hershberg addition funnel over 16 h. After being heated under reflux, with stirring, for a further 6 days, the reaction mixture was allowed to cool to room temperature when the excess of sodium hydride was carefully destroyed with distilled water. The reaction mixture was then evaporated to dryness under reduced pressure and the organic residues extracted with chloroform. The chloroform solution was filtered, to remove inorganic material, dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil (7.5 g), which was purified by medium pressure liquid chromatography on silica (100 g). Elution with dichloromethane–ethyl acetate (8:2) gave the *title compound* (0.77 g, 18%) as a colourless solid which was recrystallised from ethyl acetate to yield colourless plates, m.p. 108 °C (Found: C, 69.9; H, 7.6%; *M*, *m/z* 428. $C_{25}H_{32}O_6$ requires C, 70.1; H, 7.5%; *M*, 428); $\nu_{max.}$(KBr) 2 920, 2 860, 1 595, 1 470, 1 450, 1 365, 1 350, 1 285, 1 270, 1 210, 1 165, 1 130, 1 090, 1 040, 970, 790, and 765 cm^{-1}; $\delta(CDCl_3)$ 7.09 (4 H, d, J_o 7 Hz, ArH), 6.84 (2 H, t, J_o 7 Hz, ArH), and 4.90 (4 H, d, J_{gem} 12 Hz, $ArCH_AO$).

Reaction of 1,5-*Bis*(2,6-*bisbromomethyl*-4-*methylphenoxy*)*pentane with Benzene*-1,2-*diol Synthesis of the Pyrocatechol derived Cyclophane* (**18**).—A solution of 1,5-bis(2,6-bisbromomethyl-4-methylphenoxy)pentane (6.56 g, 10 mmol) in anhydrous tetrahydrofuran (650 ml) was added to a three-necked round-bottomed flask containing sodium hydride (1.44 g, 60 mmol) under a nitrogen atmosphere. The stirred suspension was then heated to reflux and a solution of benzene-1,2-diol (2.42 g, 22 mmol) in anhydrous tetrahydrofuran (100 ml) was added through a Herschberg addition funnel over 8 h. After being heated under reflux, with stirring, for a further 3 days, the reaction mixture was allowed to cool to room temperature when the excess of sodium hydride was carefully destroyed with distilled water. The reaction mixture was then evaporated to dryness under reduced pressure and the organic residues extracted with chloroform. The chloroform solution was filtered to remove inorganic material, dried ($MgSO_4$), and evaporated under reduced pressure to give a brown solid which was purified by medium pressure liquid chromatography on silica (100 g). Elution with chloroform–ethyl acetate (29:1) gave the *title compound* (**18**) (2.66 g, 48%) as a white crystalline solid. Recrystallisation from chloroform–cyclohexane afforded colourless needles, m.p. 186—188 °C (Found: C, 76.4; H, 6.8% *M*, *m/z* 552. $C_{35}H_{36}O_8$ requires C, 76.1; H, 6.5%; *M*, 552); $\nu_{max.}$(Nujol) 1 595, 1 505, 1 330, 1 245, 1 220, 1 120, 1 005, and 735 cm^{-1}; $\delta(CDCl_3)$ 7.10 (4 H, s, MeAr*H*), 6.96 (8 H, m, ArH), 5.06 (4 H, d, J_{gem} 9 Hz, $ArCH_AO$), 4.69 (4 H, d, J_{gem} 9 Hz, ArH_BO), 4.04 [4 H, t, $ArOCH_2(CH_2)_3$], 2.20 (6 H, s, $ArCH_3$), 1.60—1.20 [6 H, m, $ArOCH_2(CH_2)_3$], 4.15 [4 H, t, *J* 7 Hz, $ArOCH_2(CH_2)_3$], 4.00 (4 H, d, J_{gem} 12 Hz, $ArCH_BO$), 3.50 (8 H, s, OCH_2CH_2O), and 2.05—1.80 [6 H, m, $ArOCH_2(CH_2)_3$]; $\delta_C(CDCl_3)$ 158.2 (ArC), 131.8 and 131.0 (ArC and ArCH), 122.3 (ArCH), 75.3 ($ArCH_2O$), 69.4 and 69.0 (OCH_2CH_2O) and $ArOCH_2$), 29.9 ($ArOCH_2CH_2CH_2$), and 22.9 ($ArOCH_2CH_2CH_2$).

Synthesis of Cyclophane (**20**).—2,6-Bishydroxymethylpyridine (2.78 g, 0.02 mol) and sodium hydride (2.40 g, 0.05 mol) were refluxed with continual stirring in tetrahydrofuran (750 ml) for 1 h. Over a period of 16 h 1,3-bis(2,6-bisbromomethyl-4-methylphenoxy)propane (5.02 g, 8 mmol) in tetrahydrofuran (500 ml) was added to the refluxing solution from a Herschberg funnel. After a further 168 h under reflux, the solution was cooled, distilled water (10 ml) was slowly added and the whole reduced to dryness at 30 °C under reduced pressure. The organic products were dissolved in chloroform (500 ml) and the solution dried ($MgSO_4$). Flash chromatography on silica gel using ethyl acetate–dichloromethane (1:20) gave the *title compound* (**20**) after crystallisation from ethanol as white monoclinic crystals (0.59 g), m.p. 169—170 °C (Found: C, 71.9; H, 6.5; N, 4.70. $C_{35}H_{38}N_2O_6$ requires C, 72.1; H, 6.6; N, 4.81%); $\delta(CDCl_3)$ 7.65 (2 H, t, *J* 8 Hz, Ar_NH), 7.34 (4 H, d, *J* 8 Hz, Ar_NH), 7.21 (4 H, s, ArH), 4.65 and 4.48 (8 H, and 8 H, 2 s, $ArCH_2O$ and Ar_NCH_2O), 3.52 (4 H, t, *J* 4.5 Hz, $ArOCH_2CH_2$), 2.30 (6 H, s, Ar*Me*), and 1.67 (2 H, m, $ArOCH_2CH_2$).

Synthesis of the Cyclophane (**19**).—2,6-Bishydroxymethyl-4-methylanisole and 1,3-bis-2,6-bisbromomethyl-4-methylphenoxy)propane treated as above gave the *cyclophane* (**19**) as trigonal prismatic crystals (18.5%) after crystallisation from methanol, m.p. 160—166 °C (Found: C, 72.9; H, 7.7%; *M*, *m/z* 668. $C_{41}H_{48}O_8$ requires C, 73.6; H, 7.2%; *M*, 668); ^1H n.m.r. signals were broadened due to atropisomerism $\delta(CDCl_3)$ 7.15—7.19 (8 H, ArH), 4.0—5.0 (16 H, $ArCH_2O$), 3.60 (6 H, s, ArO*Me*), 3.3 (4 H, m, $ArOCH_2CH_2$), 2.26—2.28 (12 H, s, Ar*Me*), and 1.3 (2 H, m, $ArOCH_2CH_2$).

Synthesis of the Cyclophane (**17**).—2,6-Bisbromomethyl benzene and 1,3-bis(2,6-bishydroxymethyl-4-methylphenoxy)propane treated as above gave the cyclophane (**17**) as monoclinic crystals (24.5%) after crystallisation from ethyl acetate, m.p. 181—182 °C (Found: C, 75.8; H, 7.1%; *M*, *m/z* 580. $C_{37}H_{40}O_6$ requires C, 76.5; H, 6.9%; *M*, 580); $\delta(CDCl_3)$ 7.20 (4 H, s, ArH), 4.42 and 4.58 (8 H, and 8 H, 2 s, $ArCH_2O$), 3.67 (4 H, t, *J* 4.5 Hz, $ArOCH_2CH_2$), 2.31 (6 H, s, ArMe), and 1.83 (2 H, m, $ArOCH_2CH_2$).

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