Design and Syntheses of Macrocyclic Hosts containing Convergent Hydroxy Groups

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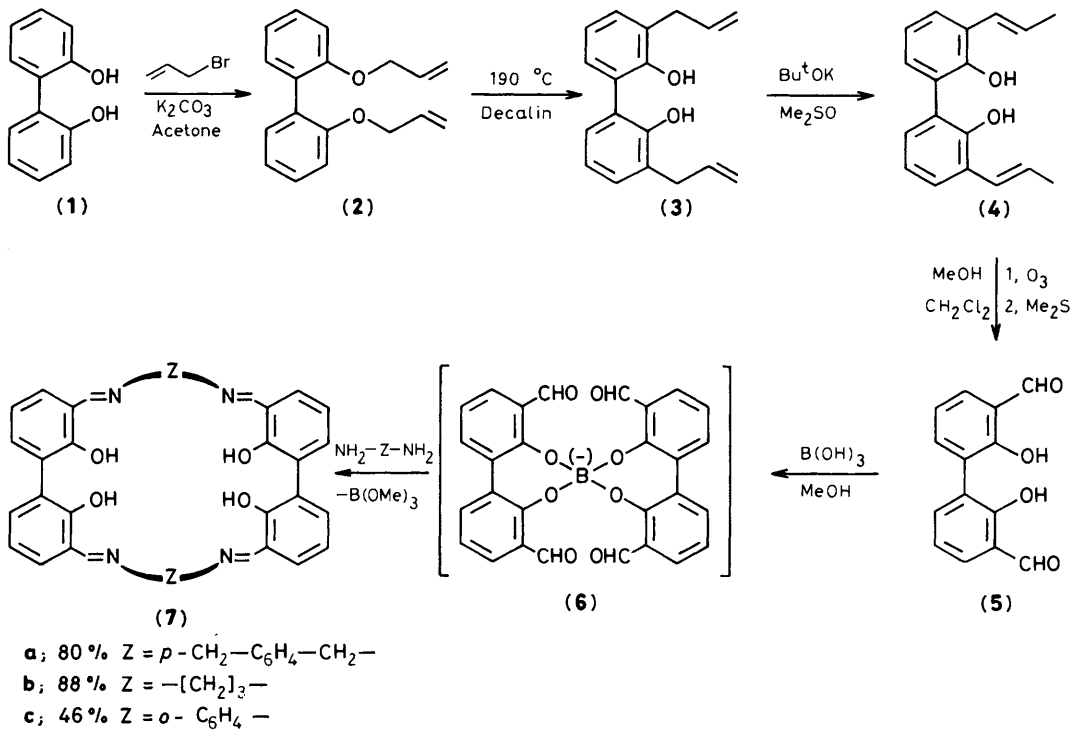
The synthesis of three macrocyclic hosts containing convergent hydroxy groups is described; the cyclisation step is performed by using a 'covalent template' with boron.

Various catalysts based on synthetic binding cavities have been successful as enzyme mimics.[1] A synthetic host molecule should show selectivity in complexation of guest molecules (recognition) and the synthesis of preorganized host molecules presents an interesting challenge.[2] The host molecule should possess multiple and convergent binding sites that are well located in a well-defined structure. To our knowledge, there are few examples of the use of convergent hydroxy groups as primary binding sites.[3—5] Non-ionized hydroxy groups of phenols are found in active sites of enzymes (*e.g.* carboxypeptidase) and play an important role in the way that ionophores wrap around metal ions.[6] Furthermore, artificial



a; 80 % Z = *p*-CH_2—C_6H_4—CH_2—
b; 88 % Z = —$[CH_2]_3$—
c; 46 % Z = *o*-C_6H_4 —

Scheme 1

hosts of the cyclophane type have well-defined molecular dimensions, sizes, and shapes.[7]

The target host molecules (**7**) that we designed present the following features: (i) for each diastereoisomer, the whole size of the cavity is controlled by the building block Z, and the topology of the binding sites is well-defined; (ii) the host molecule provides an exohydrophobic and an endohydrophilic character, that is the reverse of the cyclodextrin balance.

Exohydrophilicity could be exemplified after hydrogenation of the imine groups, by protonation or quaternization of the amine groups. Nitrogen atoms should provide additional binding sites.

We now report our preliminary results. The synthesis of (**7a—c**) was carried out as shown in Scheme 1.†

Compound (**3**) has been previously synthesized with slightly different experimental conditions.[8] The key step of the synthesis is cyclisation *via* the imination reaction of (**5**) with diamines H_2N–Z–NH_2. Attempted cyclisations under various high dilution conditions led only to polymeric materials. Attempted template syntheses using barium salts also led to polymeric materials. The desired products were synthesized in fairly good yield by using a 'covalent template' with boron.

The idea of performing a boron-assisted cyclisation arose from examination of Corey's work on the aplasmomycin antibiotic.[9] However our work constitutes, to our knowledge, the first effective boron-templated synthesis of a macrocycle. Boronated intermediates (**6**) have not been isolated and the proposed formula in the Scheme 1 should be considered as hypothetical. The structures of (**7a—c**) were established on the basis of the n.m.r. spectral data, fast atom bombardment mass spectra in a thioglycol matrix which exhibit significant $(M + H)^+$ peaks, and satisfactory elemental analyses.‡

According to Corey–Pauling–Koltun molecular models of (**7a—c**) the aryl groups cannot rotate, at ambient temperature, with respect to their attached aryl groups if the two *ortho* OH groups must pass one another. However, molecular models of (**7a,b**) suggest that the size of the central cavity is sufficient for one aryl to rotate 180° with respect to the other, with only *ortho* H and OH groups having to pass one another for stereoisomer interconversion. Molecular models of (**7c**) indicate that the aryl groups cannot rotate 180° relative to one another in any possible way. A mixture of stereoisomers is probably produced in the synthesis of (**7a,b**) as shown by the broad melting range of the material. In the synthesis of (**7c**) only one isomer is probably obtained (sharp melting point at 207 °C).

The crude solid material obtained in the last step of the reaction sequence for (**7a**) and (**7b**) affords in its ^1H n.m.r. spectrum ($CDCl_3$, 30 °C, Me_4Si) a signal located at δ 3.35 with a relative intensity revealing 9 protons. Even after drying the sample for 48 h under high vacuum this signal remains. However, this ^1H n.m.r. signal is no longer present after dissolution of the crude solid material in Me_2SO, followed by evaporation of the solvent. This signal was never observed in the course of similar synthesis of the open chain analogues. It

† All reactions were carried out under dry argon. Satisfactory i.r., ^1H n.m.r., and mass spectral data were obtained for each stable intermediate (**1**)—(**5**) by using chromatographically purified and homogeneous samples.

‡ We have synthesized for comparison the open chain compounds from salicylaldehyde and the diamines H_2N–Z–NH_2, in methanol with or without boric acid.

was readily shown that the δ 3.35 signal must be attributable to methanol: the complexation of three molecules of methanol arises in the solid state; this phenomenon is not observed with (**7c**).

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1 For a recent review, see I. Tabushi, *Tetrahedron*, 1984, **40**, 269.

2 See for example: D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8.

3 The work of Cram and co-workers (K. E. Koenig, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, 1976, **98**, 4018) describes the binding characteristic toward alkali metal and ammonium ions, performed by macrocyclic polyethers containing two convergent phenolic groups. Furthermore, Gutsche has shown that the hydroxy groups of calixarenes are external to the molecular hydrophobic cavity (see C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161).

4 One ionized hydroxy group is involved in the binding of ammonia and amines by a crown-ether phenate (M. A. McKervey and D. L. Mulholland, *J. Chem. Soc., Chem. Commun.*, 1977, 438). A phenate group is also involved in the complexation of metal cations by crown-ether dyes bearing an intra-annular phenolic group (S. Kitazawa, K. Kimura, and T. Shono, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3253). Some transition metal complexes of synthetic macrocyclic ligands involve linkages between phenolic oxygen atoms and the transition metal (see for example: H. Okawa and S. Kida, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1759 and N. H. Pilkington and R. Robson, *Aust. J. Chem.*, 1970, **23**, 2225).

5 Very recently, a macrobicyclic compound involving three catechol subunits has been described (W. Kiggen and F. Vogtle, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 714). An octahedral donor geometry for metal cations is formed in the hexa-anion which acts as a siderophore.

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