Modelling Studies Of Molecular Receptors

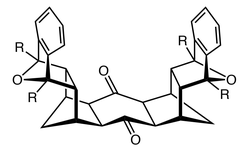
David K. Chalmers,[A] Martin J. Stoermer[a] And David P. Fairlie[b]

[a]Dept. of Medicinal Chemistry, Victorian College of Pharmacy, Monash University (Parkville), 381 Royal Parade, Parkville, 3052, Victoria.
http://synapse.vcp.monash.edu.au
[b]Centre for Drug Design and Development, University of Queensland, 4072, Queensland

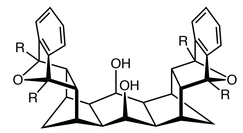
Introduction

Cavitands such as (1) and (2) represent small rigid hydrophobic clefts that incorporate polar functional groups within a framework suitable for the study of host-guest chemistry. We have previously[1,2] established the chemistry to synthesise several such systems and obtained crystal structures of many of these.

Initially we examined the host-guest chemistry of these molecules in solution by NMR but we were unable to definitively observe host guest interactions, presumably due to the weak nature of the hydrogen bonding in these systems.



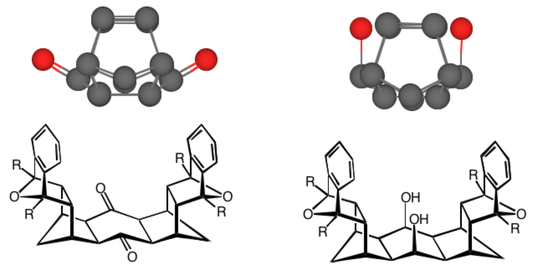
(1)



(2)

Key features of the cavitands

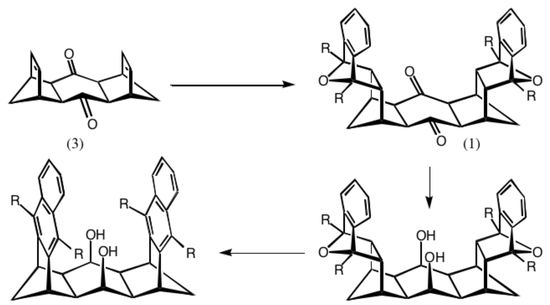
Cavitand diketones and diols display quite different geometries as a result of the differing hybridisation of the central carbon atoms. The diketones are in a boat conformation and sit some 20° out of plane, whereas the sp^3 hybridised diols occupy a diaxial configuration.



(1) (2)

Synthesis of cavitands

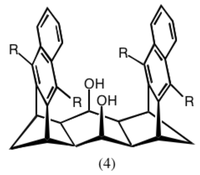
The synthesis of all the cavitands commences with the pentacyclic diketone (3). This is itself prepared in 35% overall yield from benzoquinone in 5 steps.[2] The cavitands are then built up with Diels-Alder additions of isobenzofurans to the isolated double bonds of (3).



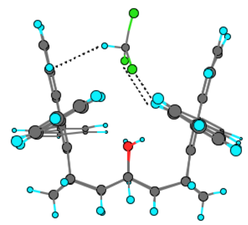
(3) (1) (4) (2)

X-ray crystal structure of cavitand (4)

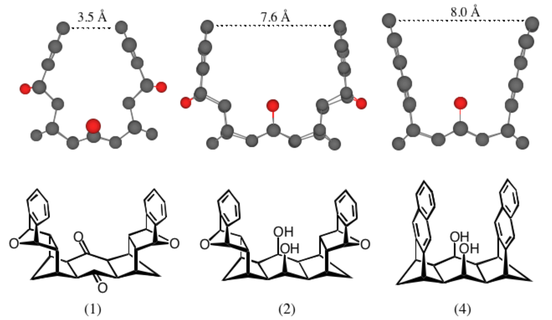
- The cavitand hydroxyl groups do not appear to be involved in binding the ligand.
- There are unusual hydrogen bonds between the *ortho*-hydrogens of three pendant phenyl groups and the chlorine atoms of chloroform.
- There is a hydrogen bond between the chloroform hydrogen atom and the inner face of the aromatic ring.



(4)

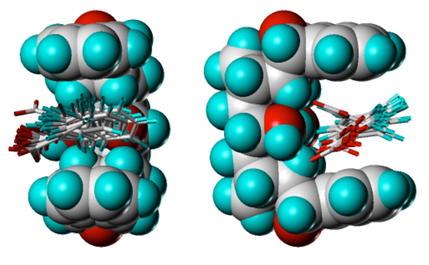


Dimensions of the cavitands



(1) (2) (4)

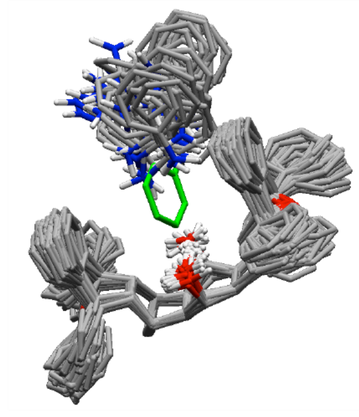
Docking of benzoate into cavitand 2



Orthogonal views of benzoate docked into cavitand (2). The docked structures were calculated using Dock version 4.[3]

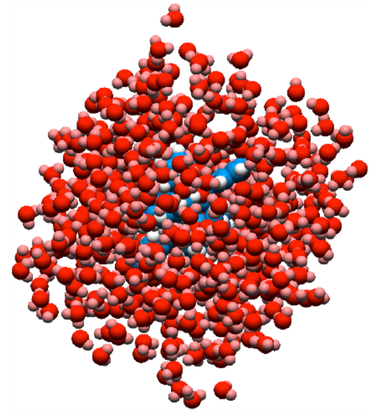
Of greatest interest is the prediction that the carboxylate makes a single hydrogen bond with the cavitand hydroxyl group, and that the hydrophobic aromatic ring makes a π-stacking interaction with the cavitand walls.

Molecular dynamics of aniline and cavitand 2 in a water box



50 superimposed structures with the starting position of the aniline displayed in green. Over the period of the Tinker[4] simulation aniline migrated out of the cavity.

Cavitand 2 in a water box



Simulations used Tinker[4] with the OPLS[5] all-atom forcefield. Each 25 ps run used periodic boundary conditions in a 20Å x 20Å x 20Å water box with a 2 fs timestep at 300 K.