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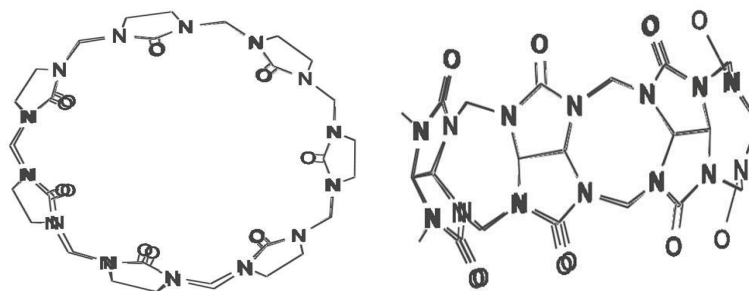
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## Docking Into Artificial Receptors Using Gold: Background

Supramolecular chemistry is a large and important area of research. There is much interest in host-guest systems, where researchers aim to design receptors for molecules to achieve selective binding and/or the catalysis of reactions. Much of this research is inspired by biological systems where the receptors (hosts) are proteins. With this relation it is only natural that computational tools employed to study protein-ligand interactions are extended to the study of supramolecular host-guest systems.

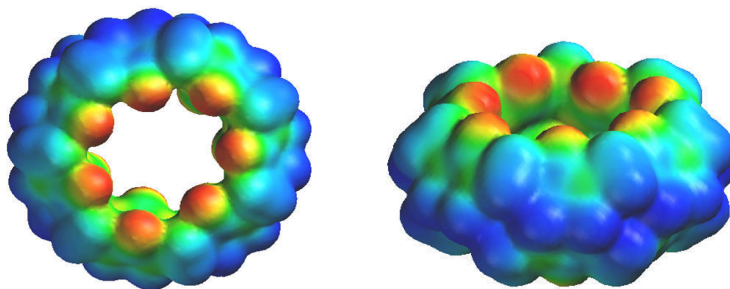
Although GOLD has been designed to dock small drug-like molecules to proteins it can also be used to dock guest molecules to artificial receptors. GOLD relies on atom-type interactions and since many interactions in artificial organic host-guest systems are similar to protein-ligand systems, GOLD is a viable tool to explore these binding conformations. Here we present two case-studies with the macrocyclic receptor cucurbit[7]uril.



**Figure 1** Cucurbit[7]uril

Cucurbit[6]uril was first discovered in 1905, the macrocycle is formed by a condensation reaction of glycoluril and formaldehyde in concentrated HCl. The structure and subsequent applications of cucurbit[n]uril were not fully realised until the beginning of the 1980s, for more information about cucurbit[n]uril, please refer to the comprehensive review in *Angew. Chem. Int. Ed.* **2005**, 44, 4844.

Today the cucurbit[n]uril family has been extended to include cycles with  $n = 5, 7, 8,$  and 10 and several derivatives of these. Cucurbit[n]uril has derived its name from its pumpkin shape, the structure is relative rigid and contains a cavity accessible by two carbonyl-lined portals (see Figure 1). The carbonyl oxygens lining the two portals make for excellent binding of cations while the core is hydrophobic (see Figure 2).



**Figure 2** Electrostatic potential map of Cucurbit[7]uril

## Artificial Receptors: Example 2

For two further recent examples of docking to artificial receptors, please see:

- A. Amadasi, C. Dall'Asta, G. Ingletto, R. Pela, R. Marchelli, P. Cozzini, Explaining cyclodextrin-mycotoxin interactions using a "natural" force field, *Bioorganic & Medicinal Chemistry* (2007), [10.1016/j.bmc.2007.04.006](https://doi.org/10.1016/j.bmc.2007.04.006)
- A. Steffen, C. Thiele, S. Tietze, C. Strassing, A. Kamper, T. Lengauer, G. Wenz, J. Apostolakis, Improved Cyclodextrin-Based Receptors for Camptothecin by Inverse Virtual Screening, *Chemistry, A European Journal* (2007), [10.1002/chem.200700661](https://doi.org/10.1002/chem.200700661)



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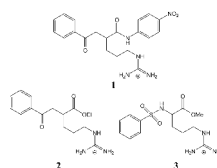
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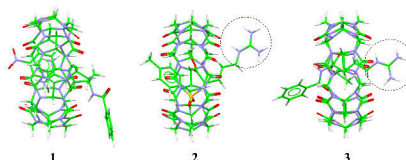
## Artificial Receptors: Example 1

In a recent communication by Nau et al. (*Chem. Commun.*, **2007**, 1614) the effect of complexation between peptides and cucurbit[7]uril and their interaction with proteases has been studied. The authors showed that cucurbit[7]uril afforded protection against hydrolysis by trypsin for some of the peptides, an important feature that could be exploited for drug delivery. Further, the study showed that the complexation of the peptide and cucurbit[7]uril was the cause of the lack of hydrolysis and not interactions with the enzyme.



**Figure 1** Peptides forming complexes with cucurbit[7]uril

Three of the peptides that were studied in the communication are depicted in Figure 1. Nau and co-workers found that cucurbit[7]uril successfully inhibited the hydrolysis of **1** but not **2** and **3**. This was surprising since experimental results suggested the formation of similar complexes between cucurbit[7]uril and the three peptides. NMR data indicated interaction between the carbonyl portal and the positively charged arginine side-chain and with the aromatic moieties of the peptides inside the cavity, i.e. the experimental evidence pointed to a similar inhibition for all three substrates.



**Figure 2** Top scoring GOLDScore poses for the three peptides

In an attempt to explain the difference in activity towards trypsin we have performed GOLD docking runs with the three peptides to see if we can see any variance in their binding conformations that can explain the difference. GOLD was run with default settings, each ligand was fully flexible and docked with 10 GA runs. GOLDScore was used to drive the dockings and for the scoring of the final poses. The three top scoring poses are shown in Figure 2. Although more accurate calculations (MM or MD) are probably needed to draw any real conclusions, the GOLD poses give an indication about the difference between the peptides. The results show similar poses for **2** and **3**, the two peptides that are not protected for hydrolysis. The arginine group is important for the enzyme-substrate recognition and although the two poses have one hydrogen bond between the arginine to the carbonyl rim of cucurbit[7]uril most of the arginine is outside the cavity. For **1** the situation is different, the top-scoring pose has the arginine inside the cavity with several hydrogen bonds to one of the carbonyl rims. The results for the GOLD dockings are not conclusive but indicate that **1** binds stronger to cucurbit[7]uril (through more interactions with the arginine group) explaining the difference in activity towards trypsin. The three docked poses serve as excellent starting structures for higher level theory calculations.

[Artificial Receptors: Example 2](#)

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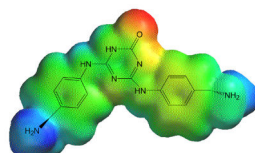
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## Artificial Receptors: Example 2

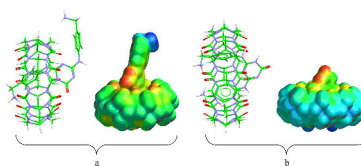
In a detailed study by Lyle Isaacs and co-workers (*J. Am. Chem. Soc.* **2005**, *127*, 15959) the host-guest chemistry of cucurbit[n]uril ( $n = 6, 7, \text{ and } 8$ ) was investigated using H-NMR competition experiments. Among the 24 different guests studied was the large melamine derivative depicted in Figure 1.



**Figure 1** Melamine derivative guest molecule

The competition studies showed that the compound forms a 1:1 complex with both cucurbit[7]uril, (CB7) and cucurbit[8]uril, (CB8). However it was found that the CB8 complex was more than 3000 times more stable than the corresponding CB7 complex, the X-ray crystal structure of the CB8 complex can be found in the CSD (refcode SAXKAE).

The obvious difference between CB7 and CB8 is the size of the cavity and the diameter of the carbonyl oxygen portals, the larger CB8 can accommodate larger guests than CB7. However, this does not readily explain the difference in binding to the melamine derivative, its size should be a good fit for CB7. Since we have access to the X-ray structure of the CB8 complex we have an opportunity to test if GOLD is able to find the correct conformation for the CB8 complex, and to compare this with the pose suggested for the CB7 complex. Default settings were used for the GOLD dockings, and the ligand was fully flexible, 10 GA runs were performed using GOLDScore to drive the dockings and score the final poses. The docking results (top GOLDScore poses) are presented in Figure 2.



**Figure 2** a) Top scoring pose for CB7 together with corresponding electrostatic potential map b) Top scoring pose for CB8 together with corresponding electrostatic potential map

The top scoring pose for the CB7 complex (**a** in Figure 2) has the somewhat predictable structure with one of the amino groups interacting with the carbonyl oxygens of the CB7 portal, while the aromatic benzene ring is inside the cavity. This is a well established binding mode for similar compounds to cucurbituril. From the electrostatic potential map of the docked structure it is clear that there is a problem with this binding conformation. In order to form the energetically favourable interactions between one of the amino groups and the inclusion of the benzene ring, the carbonyl oxygen of the melamine ring comes in close contact with the carbonyl oxygens on the opposite cucurbituril portal rim.

The top scored pose conformation for the CB8 complex (**b** in Figure 2) is surprising but is in full agreement with the X-ray crystal structure found in the CSD. It is surprising due to the u-shaped guest conformation. The two different conformations for the guest in CB7 and CB8 provide an explanation for the difference in binding

strength. The u-shaped conformation of the guest is able to have both of the amine groups interacting with the same portal while at the same time incorporating the two benzyl rings inside the cavity. The two -NH linkers of the melamine interact with the second cucurbituril portal while any clash between the guest's carbonyl oxygen and cucurbituril's carbonyl oxygen rim is avoided. The u-shaped conformation is showed to be ideal for interaction with CB8, forming a maximum number of energetically favourable interactions. The size of CB7, although large enough to be able to incorporate the guest is not sufficiently large to fit the u-shaped conformation.

Comparing the two conformations produced by GOLD the large difference in binding strength is no longer surprising.

[Artificial Receptors: Example 1](#)