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Non-directional forces drive guest affinity and discrimination in a calix[5]arene-based receptor

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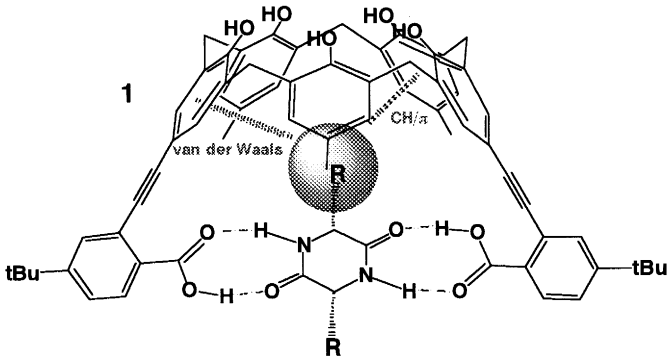
Abstract

In this paper we report the binding behavior of a receptor based on a calix[5]arene possessing two convergent benzoic acids that serve to bind a guest. The receptor recognizes diketopiperazines (DKP) having a variety of alkyl substituents to form a 1:1 host–guest complex. We demonstrate that the receptor shows selectivity for the DKPs based on the size of the alkyl substituent. As a result, the selectivity arises from non-directional forces between the π-basic aromatic ring of the calixarene and the alkyl group of the guest. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: calixarene; hydrogen bonding; molecular recognition; molecular modeling.

Natural systems such as enzymes and antibodies are extraordinarily effective and specific in binding their substrates. Using non-directional forces to control intermolecular associations (van der Waals, CH–π, π–π interactions, etc.) yields moderate substrate selectivity beyond the shape recognition permitted by the binding pocket of enzymes and antibodies.[1,2] An effective approach to artificial receptors utilizes both directional and non-directional forces incorporated into a cleft or a cavity having a well-defined geometry.[3,4]



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We have reported the synthesis of upper-rim-functionalized calixarenes and their binding affinity towards nitrogen-containing guest molecules.[5] The calix[5]arene-based artificial receptor **1** is capable of binding small organic molecules through a four-point, hydrogen-bonding interaction.[6] During the binding process, the alkyl substituent of the DKPs (**2**–**8**) can reside within the π-basic cavity without distortion of the intermolecular hydrogen bonding interactions. Variations of the alkyl substituent should provide information on how the complementary non-directional forces alter the substrate selectivity.

Certain resonance characteristics of the host–guest complex can be observed by ^{1}H NMR spectroscopy. For example, when the receptor was added to the solution of **3**, the N–H resonances become shifted downfield. The Job's plot indicated a 1:1 stoichiometry in the host–guest complex. A non-linear regression analysis[7] on the ^{1}H NMR shifts gave an association constant of 5500 ± 300 M^{-1}. Association constants of the other host–guest complexes were similarly determined and are summarized in Fig. 1. The resonances of the methyl groups of the *i*-propyl substituent also shifted to ca. −0.9 ppm. This characteristic upfield shift leaves little doubt that the *i*-propyl group is fixed within the cavity composed of the five phenolic rings.

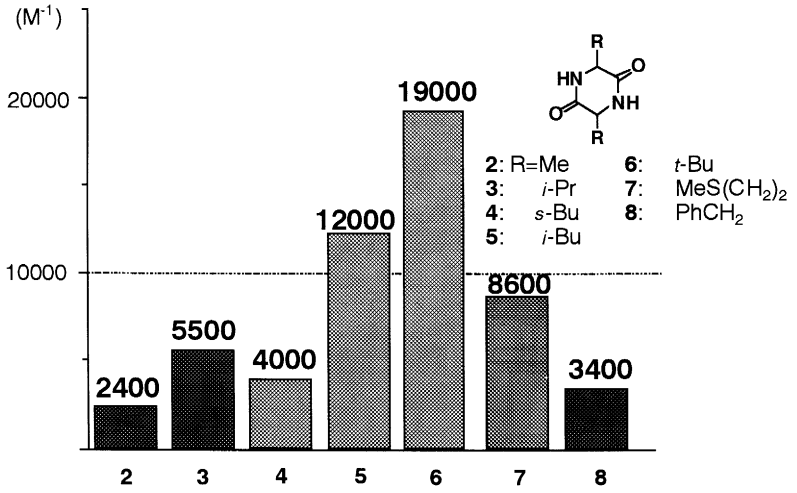

Fig. 1. Association constants of the DKPs. All titrations were carried out in $CDCl_3$ at 25°C. Every standard deviation is less than 10%

It is particularly striking that the selectivity of the binding of DKPs depends on the size of the alkyl substituent. For example, *t*-butyl substituted DKP **6** shows a higher affinity than methyl substituted DKP **2**; the ratio of the association constants is 8:1 indicating a ca. 1.2 kcal/mol difference in affinities.[8] The receptor also displays unique guest selection based on the branching butyl groups of the DKPs. The hydrophobic surface of the *t*-butyl group is a good complement to the concavity of the π-basic inner surface of the calix[5]arene.

To assess the conformations of the complexes, molecular mechanics calculations were performed using MacroModel V. 6.5.[9] Initial geometries of the complexes were generated by a LowMode search,[10] and the resulting structures were optimized by using the Modified Merck Force Field. The solvation treatment using GB/SA $CHCl_3$ was applied to all the calculations. The lowest energy structure of the complexes is shown in Fig. 2. In all cases, the receptor binds the DKPs through the four-point hydrogen bonding interactions and the alkyl substituents are held within the cavity.[11] Based on the calculated results, the selective binding of the receptor to the DKPs seems to arise from complementary intermolecular interactions between the aromatic walls of the π-basic cavity and the alkyl substituent.

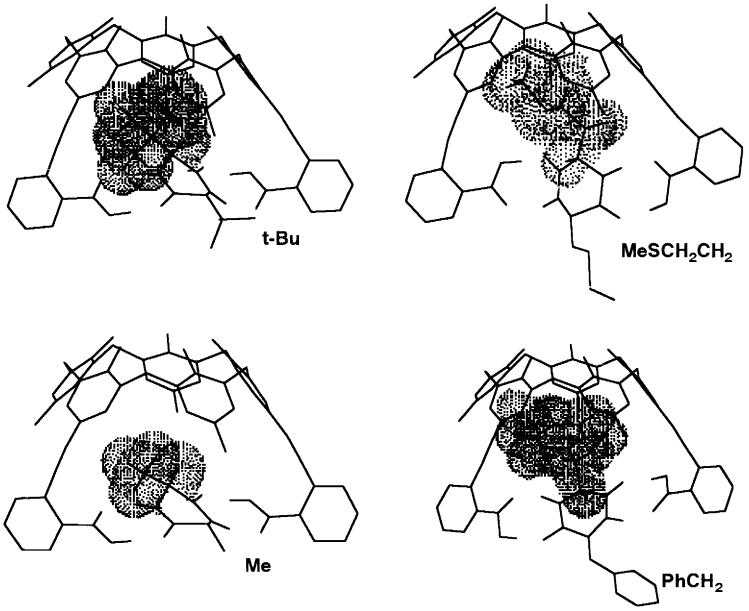

Fig. 2. The calculated structures of the complexes. Van der Waals surface of the inner substituents is represented as dot surface

It is particularly difficult to evaluate how the substituents fit into the interior cavity. Molecular modeling calculations can help to measure the sizes of the alkyl substituents. Although determination of the cavity volume of the receptor is difficult, the volume of a similar calix[5]arene having methyl groups at each *para* position of the phenolic ring was determined to be about 100 Å^3 using the Grasp program.[12,13] The receptor **1** should have a similar cavity volume to this analogous calix[5]arene. The volumes of the alkyl substituents were estimated with the Grasp program (Table 1). For the DKPs **5**, **6**, and **7** that bind strongest, the substituents fill about 50–80% of the cavity. This provides sufficient contacts to facilitate the non-directional interactions. The smallest alkyl substituent, the Me group, does not provide enough complementarity for the cavity. Although the $PhCH_2$ occupies a 98% volume of the cavity, the association constant is not so large. Presumably, the $PhCH_2$ group is too large to fit into the cavity. These measurements suggest that the guests having alkyl substituents that occupy about 70% of the available space in the cavity, show the largest association constants.[14]

Table 1
The calculated volumes of the alkyl substituents (Å^3)

Me	23	$MeS(CH_2)_2$	77
i-Pr	54	$PhCH_2$	93
t-Bu	70		

This study demonstrates that non-directional forces play an important role in the substrate selectivity in the host–guest complexation.

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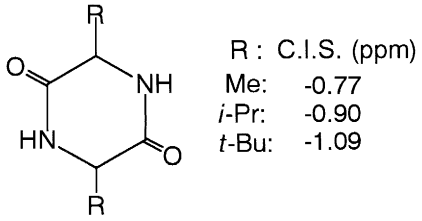

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