

## 論文の内容の要旨

### 論文題目

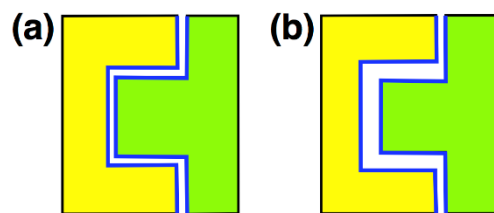
Development of a semiquantitative analysis of the complementarity between molecular surfaces in supramolecular complexes

(超分子会合体における分子表面間の相補性の半定量的解析法の開発)

氏 名     田中 成

## Introduction

Molecular recognition, a phenomenon where a particular molecule is selectively complexed with or captured by other species, plays a very important role in many biological phenomena and construction of artificial supramolecular structures. Molecular recognition employs many intermolecular interactions, not only strong interaction, but also weak interactions such as van der Waals (vdW) force and hydrophobic effect. In artificial systems, these non-selective and isotropic interactions are less often employed because of their difficulty in constructing well-defined structures. Despite that, deep understanding of molecular recognition and its application require the evaluation of the intensity of the weak interactions because they are universal and largely affect the association affinity. Although the energetic contribution of these interactions has been typically considered to be proportional to contact surface area, precise prediction of association constants also requires other factors such as intersurface distance, which strongly alters the intensity of vdW force. Considering two binary complexes (Fig. 1), both of the complexes have similar contact surface areas, and hence similar degree of classic hydrophobic effect. Nevertheless, the tighter complex (a) has smaller intersurface distance and is more stabilized by vdW force than (b). A novel method to evaluate and visualize the distribution of intersurface distance of a given structure can therefore refine and facilitate the prediction of the association constant. This thesis describes the development of such a semiquantitative method, Surface Analysis with Various Probe Radius (SAVPR).



**Fig. 1.** Two schematic examples of binary complexes with similar contact surface areas (indicated by the blue lines) and different intersurface distances.

## Development of Surface Analysis with Various Probe Radius (SAVPR) Method

The SAVPR method deals with the molecular surface of the complex in question. There are several concepts to represent molecular surface such as vdW surface and Connolly surface. The most fundamental and widely adopted one is vdW surface. In this concept, atoms are viewed as a sphere of a certain radius determined by the atom type (vdW radius). Molecules are simply viewed as overlapped spheres that represent atoms. Connolly surface is defined based on vdW surface. To obtain Connolly surface, a probe sphere, which cannot overlap with the atoms of their vdW radii in a given structure, is rolled over the structure. Connolly surface is thus obtained as the boundary surface of the domain which a probe sphere cannot enter.

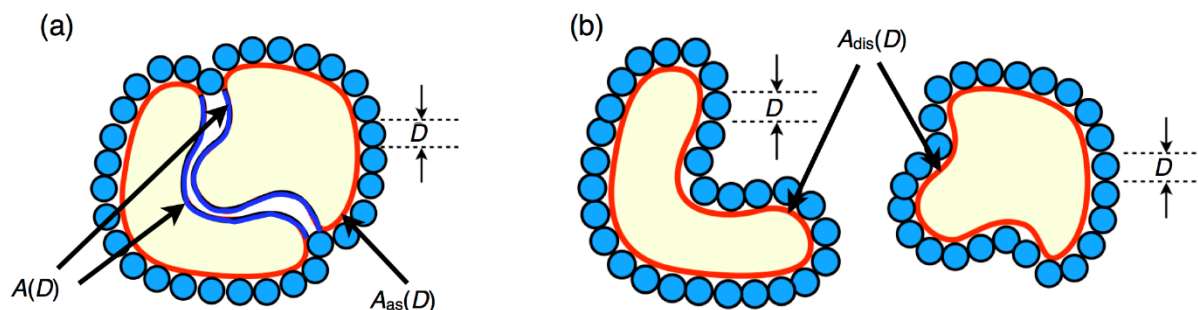
SAVPR utilizes the Connolly surface areas of an associated form  $A_{as}(D)$  and a dissociated form  $A_{dis}(D)$  with various probe diameters  $D$  (Fig. 2). Then,  $A(D)$  is defined as the difference of these two values:

$$A(D) := A_{dis}(D) - A_{as}(D)$$

A probe sphere of diameter  $D$  cannot enter the intersurface space whose intersurface distance is less than  $D$ . From this consideration,  $A(D)$  can be viewed as the contact surface whose intersurface distance is less than  $D$ . Therefore, the area of the contact surface of the intersurface distance between  $D$  and  $D + \Delta D$  can be estimated to  $A(D + \Delta D) - A(D)$ , where  $\Delta D$  is the interval of intersurface distance:

$$\text{ContactSurfaceArea}(D, D + \Delta D) = A(D + \Delta D) - A(D)$$

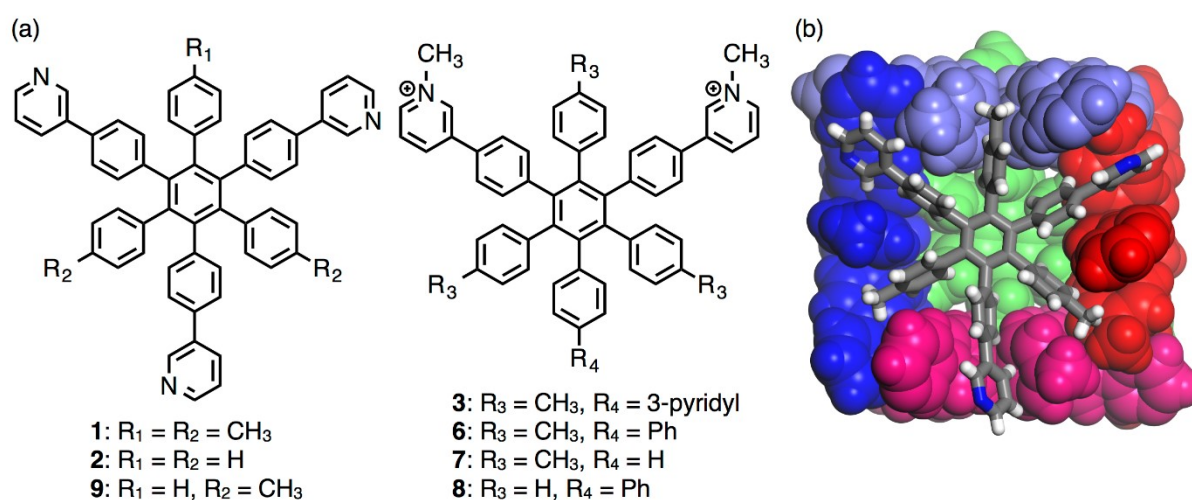
From this relation, the histogram of intersurface distance, intersurface distance distribution, can be drawn.



**Fig. 2.** Schematic representation of the SAVPR method; (a) an associated form and (b) a dissociated form of a given structure. Light blue circles are probe spheres. The red lines are the Connolly surface of the structures, while the blue lines are the contact surface whose intersurface distance is less than  $D$ , which corresponds to  $A(D)$ .

## Effect of Intersurface Distance Density on Association Affinity

As mentioned above, only considering the contact surface area of given structure is insufficient to predict the association affinity. An example of the insufficiency is nanocube, a supramolecular structure comprised of six molecules of amphiphilic hexaphenylbenzene species. The amphiphile **1** spontaneously and hydrophobically assembles into a nanocube **1<sub>6</sub>** in aqueous methanol (Fig. 3), while its analog **2**, only without three methyl groups, does not. If **2<sub>6</sub>** is assumed, the ratio of the contact surface area of **1<sub>6</sub>** to that of **2<sub>6</sub>** is about 1.16:1 whereas the ratio of association Gibbs energy is at least 1.68:1. Similar discrepancies exist in the cationic nanocubes, **3<sub>6</sub>**, **6<sub>6</sub>**, **7<sub>6</sub>**, and **8<sub>6</sub>**.



**Fig. 3.** (a) The structures of hexaphenylbenzene derivatives. (b) Crystal structure of **1<sub>6</sub>**⊃2\* tribromomesitylene (guest molecules are not shown). In (b), one of the monomers is shown in stick model and the others in CPK model.

The intersurface distance distributions of nanocubes were calculated (Fig. 4). The nanocube **3<sub>6</sub>** and **6<sub>6</sub>** have larger contact surface area of short intersurface distance (<1.5 Å) than **7<sub>6</sub>** and **8<sub>6</sub>**. The structural differences of the monomers will reduce the contact surface, especially of short intersurface distance, in **2<sub>6</sub>**, **7<sub>6</sub>**, and **8<sub>6</sub>**. In other words, these nanocubes possess not only smaller but also looser contact surfaces. Such loose contact surfaces should weaken their vdW forces and lower the association constants.

To further consider the influence of the intersurface distance distribution, the relation between the structures and the reported association constants of host-guest systems with alpha-cyclodextrin (αCD) or cucurbit[7]uril (CB[7]) was investigated. The αCD complexes have relatively small differences in intersurface distance distributions and the association constants. On the other hand, some association constants of the CB[7] complexes clearly surpass the values expected from their contact surface areas, implying strong vdW force by short intersurface distance. SAVPR showed that the order of the area of the contact surface of short intersurface distance in these systems coincides with that of the association constants. This result strongly indicates the correlation between the intersurface distance distribution and the association constant of the systems.

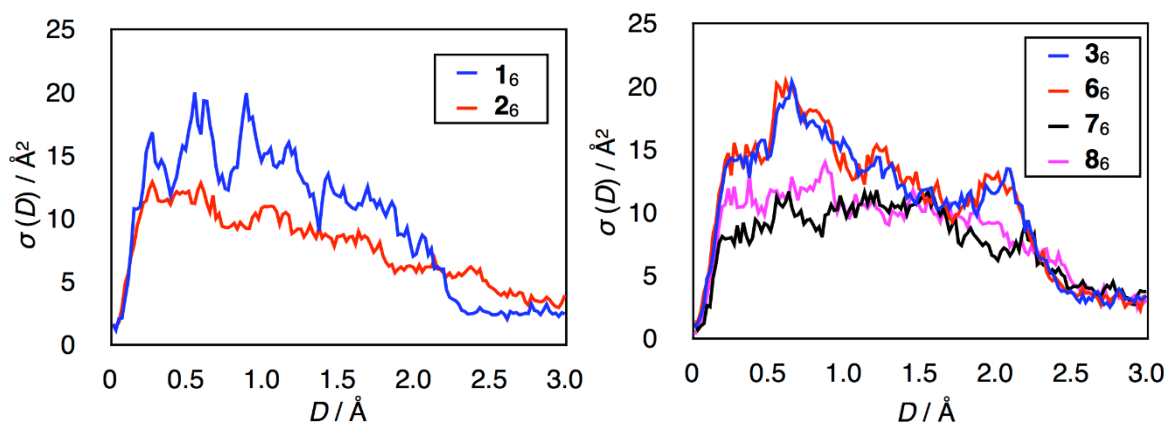


Fig. 4. Intersurface distance distributions for the nanocubes.

## Effect of Small Structural Difference on Self-Assembly

To obtain the information about the effect of one methyl group on the formation of nanocube and their driving force, a new amphiphile **9**, where **1** is deprived of only one methyl group, was synthesized and its association behavior was investigated. The NMR spectra with shifted broad peaks suggested that **9** associated into not an unambiguous and unique nanocube structure but a mixture of some isomers of **9**<sub>6</sub>. To confirm the formation of such a mixture, some characteristic isomers of **9**<sub>6</sub> among all of the possible ones were theoretically investigated. MM calculation revealed that some of the isomers have similar formation energies, which were smaller than the other investigated isomers. The SAVPR method showed that the areas of the contact surface of short intersurface distance in the isomers had a similar trend with the formation energy. These analyses indicate that several species can be simultaneously stable among the isomers and coexist as a mixture. This different association behavior of **9** from those of **1** and **2** should be an important example where only one methyl group largely affects the intermolecular interactions and the self-assembly behavior.

## Conclusion

The SAVPR method efficiently evaluates and visualizes the intersurface distance distribution of a given structure. Because intersurface distance has very large influence on the strength of intermolecular interaction, this distribution enables semiquantitative estimation of the association constant of a given supramolecular structure.

Comprehensive knowledge on intermolecular interactions should be a fundamental key to future sciences. Such knowledge encourages deeper understanding of biologic systems and technological applications such as development of molecular machines and medicines. In these practical contexts, the SAVPR method will offer such knowledge and contribute to the development of culture and civilization.