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Spatial Decomposition Analysis of the Thermodynamics of Cyclodextrin Complexation

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Abstract: We propose a method of spatial decomposition analysis (SDA) to study the thermodynamics of association in solution, based on three-dimensional molecular theory of solvation. We decompose the solvation thermodynamics quantities into the excluded volume and solvation shell terms and further break them down into partial contributions of the functional groups of the associating species. For illustration, we applied the SDA method to the complexation of β-cyclodextrin and 1-adamantanecarboxylic acid in water. We calculated the changes in the free energy and in the partial molar volume upon the association and decomposed them into the partial contributions of the functional groups to the excluded volume and solvation shell terms. The SDA shows that the adamantyl group of 1-adamantanecarboxylic acid is responsible for the complexation more than its carboxyl group and that the carboxyl has little contribution to the association process. The SDA results are in good agreement with the observation made in a recent molecular dynamics simulation. The SDA method can reveal a microscopic picture for association processes in solution in a number of areas, including protein stability, and might be a useful tool for rational drug design.

1. Introduction

Association of molecules in solution is one of the most fundamental phenomena observed in a wide variety of fields of chemistry, biology, pharmacy, and material science.[1−4] This includes such processes of practical importance as drug−protein binding, micelle formation, and self-assembly of organic nanotubes. Understanding it from a microscopic viewpoint is of substantial value, both for basic science and for control and rational design of important technological processes. In many cases,[3,5,6] the binding affinity of a macromolecule can be subdivided into contributions from its essential fragments. A viable strategy of controlling association is thus to analyze and rationally design the contribution of each fragment, much as in fragment-based drug design.[7,8] The latter has become an important and powerful tool for discovery and optimization of new drug leads. The design and optimization of the ultimate lead compound is carried out by identifying and optimizing individual fragments, followed by synthetic linking or merging them to produce a high-affinity drug lead.

Association in solution is a challenging theoretical problem because the association free energy is typically determined by a subtle balance between the direct interaction potential and the solvent-mediated effective interaction of the associating macromolecules.[9] Association can be assisted not only by solvent thermodynamic driving forces such as hydrophobic attraction between hydrophobic fragments of the associating solutes but also by solvent bridge formation such as water molecules bridging hydrophilic fragments of the solutes with hydrogen bonding.[10] In order to analyze an association process, one needs to employ such theory that properly accounts for the interplay of all these molecular forces of solvation structure and yields their effect on solvation thermodynamics.

In the present article, we propose an approach resolving contributions of functional groups to association in solution

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by using the method of statistical−mechanical, three-dimensional molecular theory of solvation, also known as the 3D reference interaction site model (3D-RISM).[11−14] Starting with atomistic interaction potentials between solution species (force field), 3D-RISM yields the solvation structure in the form of 3D correlation functions of interaction sites of solvent molecules around a solute (including the 3D density distribution function). It then analytically yields the solvation thermodynamics, including the solvation free energy, solvation entropy and enthalpy, and partial molar volume, which are expressed as integrals in terms of the 3D correlation functions. The integrands thus mean the spatial density of the corresponding thermodynamic quantities, resolved in three dimensions of the direct space. This 3D information on solvation structure and thermodynamics provided by 3D-RISM theory is invaluable for microscopic understanding of association in solution. In particular, in the present article we decompose the thermodynamic properties into two terms coming from the excluded volume and solvation shell of the solute macromolecule. We further subdivide them into partial contributions projected onto spatial fragments corresponding to the functional groups of the solute. This reveals how the excluded volume and solvation shell fragments of each functional group contribute to the association thermodynamics. Below we refer to this method as spatial decomposition analysis (SDA).

To validate our approach, we apply it to the complexation of β-cyclodextrin and 1-adamantanecarboxylic acid in water. Harries et al.[15] and Taulier et al.[16] have recently investigated this system by microcalorimetry and volumetric measurements, respectively. Cyclodextrin is a cyclic oligomer of seven units of α-D-glucose. The glucose units are connected through glycosidic α-1,4 bonds, and, as a result, the seven units constitute a doughnut-shaped molecule with a cavity. The presence of this cavity makes cyclodextrin an attractive nanostructured unit, a subject of many studies.[17−20] We obtain the change in the solvation free energy upon the cyclodextrin−adamantane association and analyze the free energy change upon the association by using SDA to reveal which fragment is the most responsible for the association process. Simultaneously, the partial molar volume change is calculated to see whether the theory and the molecular model reasonably describe the system under study. The results demonstrate that SDA can be a helpful tool in elucidating a microscopic picture of molecular association.

2. Methods

2.1. Molecular Model. The molecular geometry for the complex of 1-adamantanecarboxylic acid and β-cyclodextrin was taken from BOGCAB.pdb.[21] These coordinates include two complexes, and we refer to them as complexes A and B, as shown in Figure 1A. On adding the missing hydrogen atoms, as shown in Figure 1B and C, we used the resulting structures, without any further modification, to calculate the internal energy of the solute system and the solvation thermodynamics of the complexation.

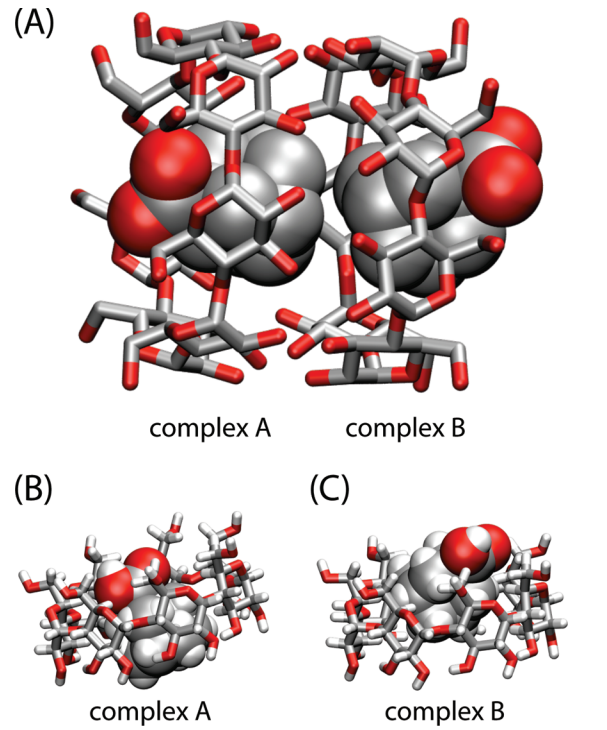

Figure 1. Arrangement of the complex of β-cyclodextrin and 1-adamantanecarboxylic acid. (A) shows the complexes A and B in the arrangement from BOGCAB.pdb.[21] (B) and (C) represent the complexes A and B, respectively, used in the present calculation after adding the hydrogen atoms.

2.2. Three-Dimensional Molecular Theory of Solvation. The 3D-RISM molecular theory of solvation is a powerful tool to study solvation thermodynamics of macromolecules in different environments. In this section, we briefly review the key aspects of the theory which are relevant to the discussion to follow. The 3D-RISM integral equation[11−14]

$$h_\gamma(\mathbf{r}) = \sum_{\gamma'} \int \mathrm{d}\mathbf{r}'\, c_{\gamma'}(\mathbf{r}')\chi_{\gamma'\gamma}(|\mathbf{r} - \mathbf{r}'|) \qquad (1)$$

is coupled with the 3D version of the HNC closure approximation[22]

$$g_\gamma(\mathbf{r}) = \exp\left(-\frac{u_\gamma(\mathbf{r})}{k_\mathrm{B}T} + h_\gamma(\mathbf{r}) - c_\gamma(\mathbf{r})\right) \qquad (2)$$

Here, $h_\gamma(\mathbf{r})$ is the 3D total correlation function related to the 3D distribution function $g_\gamma(\mathbf{r}) = h_\gamma(\mathbf{r}) + 1$, which gives the normalized probability of finding interaction site γ of solvent molecules at position $\mathbf{r}$ around the solute molecule, and $c_\gamma(\mathbf{r})$ is the 3D direct correlation function which has the asymptotics of the solute−solvent site interaction potential: $c_\gamma(\mathbf{r}) \sim -u_\gamma(\mathbf{r})/(k_\mathrm{B}T)$, where $k_\mathrm{B}T$ is the Boltzmann constant times the temperature of the solution. The susceptibility of pure solvent $\chi_{\gamma'\gamma}(r) = \omega_{\gamma'\gamma}(r) + \rho_{\gamma'}h_{\gamma'\gamma}(r)$ splits up into the intramolecular distribution function $\omega_{\gamma'\gamma}(r) = \delta(r - l_{\gamma'\gamma})/(4\pi l_{\gamma'\gamma}^2)$ specifying the geometry of solvent molecules with site separation $l_{\gamma'\gamma}$ and the intermolecular site−site total correlation function $h_{\gamma'\gamma}(r)$ times the solvent site number density $\rho_{\gamma'}$. The radial correlations $h_{\gamma'\gamma}(r)$ of pure solvent are

obtained, in advance of the 3D-RISM calculation, from the dielectrically consistent RISM integral equation theory (DRISM)[23] coupled with the HNC closure. The convolution in the 3D-RISM integral eq 1 is calculated by analytically treating the electrostatic asymptotics of all the correlation functions (both the 3D and radial ones) and applying the fast Fourier transform technique (3D-FFT and 1D-FFT) to the remaining shorter-range part of the correlations.[14,24]

The solvation free energy of the solute is calculated by using the 3D extension[13,14] of the Singer−Chandler formula[25]

$$\mu^{\mathrm{solv}} = k_{\mathrm{B}}T\sum_{\gamma}\rho_{\gamma}\int d\mathbf{r}\,\mathscr{T}(\mathbf{r}) \tag{3a}$$

$$\mathscr{T}(\mathbf{r}) = \frac{1}{2}h_{\gamma}^{2}(\mathbf{r}) - c_{\gamma}(\mathbf{r}) - \frac{1}{2}h_{\gamma}(\mathbf{r})c_{\gamma}(\mathbf{r}) \tag{3b}$$

Under the isochoric condition, the solvation free energy can be decomposed into the solvation energetic and entropic parts

$$\mu^{\mathrm{solv}} = \varepsilon^{\mathrm{solv}} - TS^{\mathrm{solv}} \tag{4}$$

In turn, the solvation energy $\varepsilon^{\mathrm{solv}}$ can be viewed as consisting of two contributions: one arising from creation of a polarized cavity (in pure solvent) and the other corresponding to the energy of embedding the solute molecule into the cavity.[26] By taking the derivative of μ^{solv} with respect to temperature, we can obtain the entropic component $-TS^{\mathrm{solv}}$.[26,27] We calculated the derivative from the equations obtained by analytical variation of the 3D-RISM and DRISM equations, following ref 27.

The partial molar volume $\bar{\mathscr{V}}$ is expressed in terms of the 3D correlation function $h(\mathbf{r})$ between solute and solvent as follows

$$\bar{\mathscr{V}} = k_{\mathrm{B}}T\chi_{T} - \int d\mathbf{r}\,h_{\gamma}(\mathbf{r}) = k_{B}T\chi_{T} + \bar{\mathscr{V}} \tag{5}$$

where χ_T is the isothermal compressibility of pure solvent which can be obtained from DRISM theory for the solvent−solvent correlation functions of pure solvent. In eq 5, $k_{\mathrm{B}}T\chi_T$ is the ideal term of partial molar volume and $\bar{\mathscr{V}}$ is the excess term coming from the solute−solvent interaction. The integration in eqs 3a and 5 is performed with analytically treating the long-range, electrostatic part of the integrands and numerically integrating the remaining short-range terms over the volume of the 3D-FFT supercell. The former appears due to ion−ion correlations in electrolyte solution and becomes significant only in the case of finite but relatively small ionic concentrations with the Debye screening length comparable to the supercell size.

2.3. Spatial Decomposition Analysis of Thermodynamic Properties. Several studies have been reported to investigate the thermodynamic properties in subspaces around a solute molecule.[28−33] For instance, Matubayashi et al.[34,35] have introduced the hydration shell model to analyze thermodynamic properties using the Monte Carlo simulation. We extend their concept to three-dimensional molecular theory of solvation (3D-RISM). First, we subdivide the 3D real space of integration in eqs 3a and 5 into two regions: the excluded volume (EcV) of the solute supramolecule and the space outside it we will refer to as the solvation shell region. We estimate the EcV using a water probe of conventional radius 1.4 Å. In order to obtain the association properties, we need to consider three systems: (i) isolated 1-adamantanecarboxylic acid (AD), (ii) isolated β-cyclodextrin (CD), and (iii) supramolecular complex AD−CD. The excluded volumes of the molecules AD and CD are hereafter referred to as EcV(AD) and EcV(CD). For the AD−CD complex in system iii, we decompose the integration domain into the sum of EcV(AD) and EcV(CD) and the solvation shell region of the complex. The same spatial subdivision of the integration domain is used for the systems (i) AD and (ii) CD as well, in order to trace changes in the local solvent environment in the regions EcV(AD) and EcV(CD) upon the association. Thus, the spaces of EcV(CD) in the system i and the EcV(AD) in the system ii are occupied by solvent water molecules which will be excluded by the association process. Figure 2 schematically illustrates the spatial decomposition. In the present study, we counted the region of overlap between the EcV(AD) and EcV(CD) as belonging to EcV(AD). Next, we perform the integration within each space to obtain its local thermodynamic properties. For example, the solvation free energy inside the EcV(AD) in the system i is calculated as (we drop the superscript "solv" from μ^{solv}, $\varepsilon^{\mathrm{solv}}$, and $-TS^{\mathrm{solv}}$ hereafter)

$$\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}} = k_{\mathrm{B}}T\sum_{\gamma}\rho_{\gamma}\int_{\mathrm{V}\in \mathrm{EcV(AD)}} \mathrm{d}\mathbf{r}\,\mathscr{T}(\mathbf{r}) \tag{6}$$

In this way, the thermodynamic properties obtained by eqs 3a and 5 are broken down into several spaces.

It is worth mentioning about the physical meaning of the solvation free energy in the EcV. In the case of $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}}$ and $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$, the local space is occupied by water molecules, and therefore, it is obvious that $\mu_{\in \mathrm{EcV}}$ is the partial contribution of water molecules in that element of space to the total solvation free energy. Then how can we interpret $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$ and $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}$ for the space of EcV holding the solute molecule inside? A general idea can be obtained by representing both solute and solvent molecules simply with hard sphere models and employing the Percus−Yevick closure[22] which is appropriate for hard sphere fluids. We will then get inside the hard sphere cores: $h(\mathbf{r}) = -1$ and $c(\mathbf{r}) = 0$ inside the EcV. Under this condition, the total solvation free energy is equivalent to the total solvation entropy $-TS$. Therefore, $\mu_{\in \mathrm{EcV(AD)}}$ is also equivalent to $-TS_{\in \mathrm{EcV(AD)}}$ which turns out to be equal to the thermal energy times the number of bulk water molecules that can be put inside the empty space of EcV with the factor of 1/2 (because of switching the interaction on). In the present study, we use a more realistic interaction potential (Lennard-Jones plus Coulomb potential between molecular interaction sites) and the HNC closure. Therefore, $\mu_{\in \mathrm{EcV}}$ is strongly perturbed by the direct interaction between solute and solvent molecules. In effect, $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$ calculated as 38 kcal/mol breaks down into $-TS^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$ and $\varepsilon^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$ as 43 and −5 kcal/mol, respectively (based on the computational condition described in the next section).

2.4. Computational Details. We considered the water solvent with physical density 0.997 g/cm^3 and dielectric constant 78.38 corresponding to the ambient conditions of

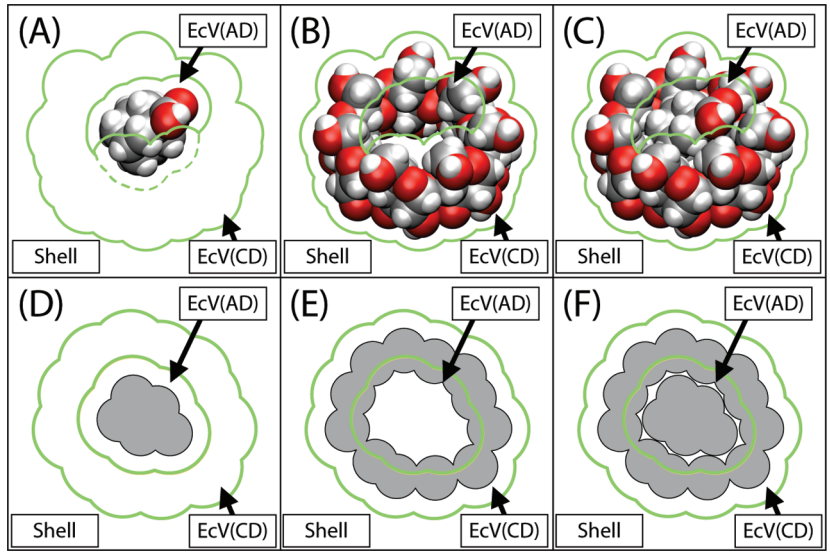

Figure 2. Schematic sketch of the spatial decomposition for systems i−iii (A−C), respectively. The schematic cross section of the space is also shown in (D−F) for systems i−iii, respectively. The entire space is partitioned into three subspaces, EcV(AD), EcV(CD), and Shell, in each system. The green lines indicate the boundary of the subspaces.

Table 1. Solvation Free Energies (in kcal/mol) for the Isolate AD in System i, $\mu^{sys(i)}$, the Isolated CD in System ii, $\mu^{sys(ii)}$, and the Complex in System iii, $\mu^{sys(iii)}$[a]

	$\mu^{sys(i)}$	$\mu^{sys(ii)}$	$\mu^{sys(iii)}$	$\Delta\mu$	E^{int}	ΔA
complex A	22.5	44.6	77.9	10.8	−22.2	−11.4
complex B	24.2	46.0	76.7	6.5	−19.3	−12.8

[a] The association free energy, ΔA, is calculated as the sum of the interaction energy E^{int} between AD and CD and the solvation free energy change upon the association, $\Delta\mu$. The latter is defined as $\mu^{sys(iii)} - \mu^{sys(i)} - \mu^{sys(ii)}$. Data are for complexes A and B (first and second rows, respectively).

Table 2. Partial Molar Volume $\mathcal{V}$ (in cm^3/mol) and Its Change upon the Complexation of AD and CD, versus Experiment[a]

	$\mathcal{V}^{sys(i)}$	$\mathcal{V}^{sys(ii)}$	$\mathcal{V}^{sys(iii)}$	$\Delta\mathcal{V}$
complex A	134.6	693.6	836.0	7.7
complex B	139.7	696.6	825.6	−10.7
exptl	140.5[b]	716 ± 2[c]		∼−5[d]

[a] The data are shown for the isolated AD in system i, $\mathcal{V}^{sys(i)}$, for the isolated CD in system ii, $\mathcal{V}^{sys(ii)}$, for the complex in system iii, $\mathcal{V}^{sys(iii)}$, and for its change, $\Delta\mathcal{V}$, upon the association. $\Delta\mathcal{V}$ is defined as $\mathcal{V}^{sys(iii)} - \mathcal{V}^{sys(i)} - \mathcal{V}^{sys(ii)}$. Theoretical data are for complexes A and B (first and second row, respectively), and experimental results (last row) from references are given in footnotes. [b] Reference 40. [c] Reference 41. [d] Reference 16.

temperature $T = 298.15$ K and pressure = 1 bar. The ideal term in eq 5 was calculated to be 1.5 cm^3/mol by solving the DRISM-HNC equations for pure water. The 3D-RISM-HNC equations were solved on a grid of 128^3 points in a cubic supercell of size 64 Å, large enough to accommodate the complex together with sufficient solvation space around it. We used the OPLS-AA force field[36] for AD and CD and the SPC/E model[37] for water. We have confirmed that the result does not change significantly with the use of of a finer grid of 256^3 points in the same supercell.

3. Results and Discussion

3.1. Free Energy and Partial Molar Volume Changes on Complexation. Table 1 shows the free energy change on the complexation of AD and CD in water for complexes A and B. The association free energy, ΔA, is obtained as the sum of the interaction energy E^{int} between AD and CD, and the solvation free energy change upon the association $\Delta\mu$. The association free energies were calculated to be −11 and −13 kcal/mol for the complexes A and B, respectively, which suggests that AD and CD tend to aggregate in water. Our theoretical prediction is in agreement with the calorimetric measurement showing that the association free energy between AD and CD is −7.7 kcal/mol.[38] A conformational difference between the two complexes is how CD holds AD inside the cavity. As can be seen from Figure 1B and C, the adamantyl group of AD in complex A runs off the edge of the cavity, while that in complex B is inside the cavity. Recent molecular dynamics simulation on a copolymer formed by β-cyclodextrin and adamantane dimers[39] has pointed out, based on the MD snapshots, that the adamantyl group penetrating inside the CD cavities stops well before their centroids pass the mean-square plane made by the glycosidic oxygens of CD. Our result that the association of complex B is more favorable than that of complex A agrees with that MD observation.

Table 2 gives the partial molar volume (PMV) change on the complexation along with the experimental data,[16,40,41] and the present theory reproduces the PMVs reasonably well. Interestingly, the theory predicts that two complexes both of which prefer to aggregate show the opposite trend in the volume change: the complex A has a positive PMV change (+8 cm^3/mol), whereas the complex B has a negative change (−11 cm^3/mol). The volumetric measurements by Taulier et al.[16] have revealed that the complexation of AD and CD has the negative PMV change (∼−5 cm^3/mol). Therefore, it is consistent that the 3D-RISM theory predicts that the association free energy of complex B is more favorable than that of complex A. We will use the complex B as a

Table 3. SDA of the Solvation Free Energy μ and Its Change upon the Association[a]

	$\mu_{\in \mathrm{EcV(AD)}}$	$\mu_{\in \mathrm{EcV(CD)}}$	$\mu_{\in \mathrm{Shell}}$	μ (total)
system i	37.928	−9.1112	−4.6353	24.18
system ii	21.984	68.286	−44.288	45.98
system iii	58.148	66.531	−48.022	76.66
Δ	−1.76	7.36	0.901	6.5

[a] The last column shows the total solvation free energy. Δ in the last row represents the association property defined as system iii − system i − system ii.

Table 4. SDA of the Solvation Entropy $-TS$ and Its Change upon the Association[a]

	$-TS_{\in \mathrm{EcV(AD)}}$	$-TS_{\in \mathrm{EcV(CD)}}$	$-TS_{\in \mathrm{Shell}}$	$-TS$ (total)
system i	43.489	−0.3060	−0.8023	42.38
system ii	35.672	188.306	−2.8900	221.09
system iii	68.340	187.640	−2.6974	253.28
Δ	−10.8	−0.360	0.995	−10.2

[a] The last column shows the total solvation entropy. Δ in the last row represents the association property defined as system iii − system i − system ii.

representative model of the association process between AD and CD for further analysis by using SDA in the following sections.

3.2. Spatial Decomposition Analysis of Solvation Energy and Free Energy Changes. In this subsection, we analyze the association solvation free energy $\Delta\mu$ and the association free energy ΔA. The SDA yields the following decompositions of μ:

$$\mu = \mu_{\in \mathrm{EcV(AD)}} + \mu_{\in \mathrm{EcV(CD)}} + \mu_{\in \mathrm{Shell}} \tag{7}$$

Each term in eq 7 for each of the systems i−iii has been compiled in Table 3. In system i, $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}}$ and $\mu^{\mathrm{sys(i)}}_{\in \mathrm{Shell}}$ contribute to the stabilization of AD in water, which is the hydration effect on AD. $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}}$ has a larger negative value of μ than that of $\mu^{\mathrm{sys(i)}}_{\in \mathrm{Shell}}$, because the water molecules in EcV(CD) are closer to AD than those in the Shell. On the other hand, $\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$ contributes to the destabilization of AD in water. This is because EcV(AD) holds AD inside and water molecules are excluded from this volume, resulting in loss of the solvation entropy. In system ii, $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{Shell}}$ contributes to the stabilization of CD in water, which is the hydration effect on CD. $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}$ contributes to the destabilization of CD, because EcV(CD) holds CD inside, resulting in loss of the solvation entropy. It is interesting that $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$ has a positive value of μ, although EcV(AD) includes water molecules inside (the number of water molecules inside this volume is calculated to be about 12). This suggests that water molecules in EcV(AD) unfavorably solvate CD; in other words, EcV(AD) is hydrophobic. Table 4 presenting the decomposition of solvation entropy also confirms that by showing $-TS^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$ has a large positive value. EcV(AD) in system ii covers the cavity space of CD, and there has been a theoretical observation that the cavity is hydrophobic.[42] The SDA conclusion is quite consistent with this observation. In system iii, only $\mu^{\mathrm{sys(iii)}}_{\in \mathrm{Shell}}$ stabilizes the complex in water (hydration effect), and the rest of the terms destabilize the association since they include the cores of the solute molecules.

The association solvation free energy $\Delta\mu$ is decomposed by SDA as

$$\Delta\mu = \Delta\mu_{\in \mathrm{EcV(AD)}} + \Delta\mu_{\in \mathrm{EcV(CD)}} + \Delta\mu_{\in \mathrm{Shell}} \tag{8}$$

where

$$\Delta\mu_{\in \mathrm{EcV(AD)}} = \mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}} - (\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}} + \mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}) \tag{9}$$

$$= (\mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}} - \mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}) + (-\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}) \tag{10}$$

$$\Delta\mu_{\in \mathrm{EcV(CD)}} = \mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - (\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}} + \mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}) \tag{11}$$

$$= (\mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - \mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}) + (-\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}}) \tag{12}$$

$$\Delta\mu_{\in \mathrm{Shell}} = \mu^{\mathrm{sys(iii)}}_{\in \mathrm{Shell}} - (\mu^{\mathrm{sys(i)}}_{\in \mathrm{Shell}} + \mu^{\mathrm{sys(ii)}}_{\in \mathrm{Shell}}) \tag{13}$$

and has been compiled in the last row in Table 3. By rearranging eq 9 to eq 10, and eq 11 to eq 12, we can decompose $\Delta\mu_{\in \mathrm{EcV}}$ into two parts: the change in the volume space which holds solute molecules inside (first term in rhs of eqs 10 and 12), and the change in the hydration (second term in rhs of eqs 10 and 12).

On the association, AD occupies the cavity space of CD and repels water molecules from the cavity. This can be seen as $-\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$ in eq 10. $-\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}} = -22$ kcal/mol favors the association, because water molecules inside the hydrophobic cavity of CD in system ii favor to be excluded from the cavity. Simultaneously, CD dehydrates AD, which can be seen as $-\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}}$ in eq 12. In contrast to $-\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$, the term $-\mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(CD)}} = +9$ kcal/mol does not favor the association because water molecules in EcV(CD) in system i interact preferably with AD.

It is a little complicated to interpret the change in the volume space which holds solute molecules inside (first term in rhs of eqs 10 and 12). First, let us discuss the value of $\mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - \mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}$ to see what happens with EcV(CD) when AD occupies the CD cavity. Because AD comes very close to EcV(CD), the interaction potential felt by water molecules in EcV(CD) changes, which changes the excluded volume for water molecules (related to the solvation entropy change) and changes the interaction between CD and water molecules (related to solvation energy change). As a result, $\mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - \mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}$ turns out to be −2 kcal/mol, and its thermodynamic decomposition into the energetic and entropic parts of the change gives $\varepsilon^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - \varepsilon^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}} = -1$ kcal/mol and $-TS^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}} - (-TS^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}) = -1$ kcal/mol. On the other hand, what happens with EcV(AD) may be simpler than with EcV(CD). The SDA gives us that $\mu^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}} - \mu^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}} = +20$ kcal/mol, and the thermodynamic decomposition shows that the energetic and entropic parts are $\varepsilon^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}} - \varepsilon^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}} = -5$ kcal/mol and $-TS^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}} - (-TS^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}) = +25$ kcal/mol. This suggests that EcV(AD) in system iii excludes water molecules more than that in system i, and that EcV(AD) in system iii has a stronger repulsive interaction for water molecules. This is related to the fact that EcV(AD) in system iii includes a part of CD and that EcV(AD) in system i does not include it (see Figure 2A, C, D, and F).

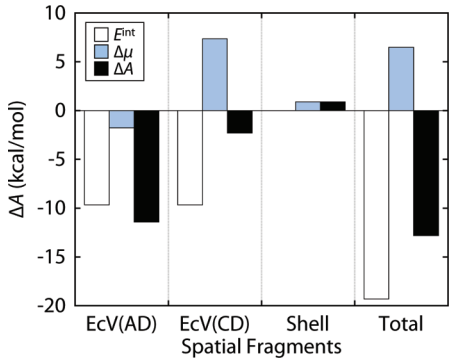

Figure 3. Spatial decomposition of the association free energy ΔA (in kcal/mol). The interaction energy between AD and CD, E^{int}, is divided by 2 and added to $\Delta\mu_{\in EcV(AD)}$ and $\Delta\mu_{\in EcV(CD)}$, respectively. $1/2E^{int}$, $\Delta\mu_{\in EcV(AD)}$, and $\Delta A_{\in EcV(AD)} = 1/2E^{int} + \Delta\mu_{\in EcV(AD)}$ are given in the first column from left, marked as EcV(AD). $1/2E^{int}$, $\Delta\mu_{\in EcV(CD)}$, and $\Delta A_{\in EcV(CD)} = 1/2E^{int} + \Delta\mu_{\in EcV(CD)}$ are given in the second column from left, marked as EcV(CD). $\Delta A_{\in Shell}$ (the third column from left) is defined as being equivalent to $\Delta\mu_{\in Shell}$. The last column marked as total is the sum of these three spatial fragments.

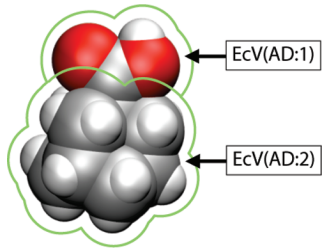

Figure 4. Schematic representation of the spatial decomposition of EcV(AD) into the carboxyl (EcV(AD:1)) and adamantyl (EcV(AD:2)) groups.

In this way, $\Delta\mu_{\in EcV}$ is determined by the balance between the change in the volume space holding solute molecules inside and the change in the hydration. We found that the latter is slightly dominant in the present association process. Therefore, we can assign $\Delta\mu_{\in EcV(AD)}$ and $\Delta\mu_{\in EcV(CD)}$ as the changes in the hydration upon the association. By adding the interaction energy between AD and CD, we finally obtain the SDA of association free energy as shown in Figure 3. In order to calculate $\Delta A_{\in EcV(AD)}$ and $\Delta A_{\in EcV(CD)}$, we divided E^{int} by 2 (according to switching the interaction on) and added them to $\Delta\mu_{\in EcV(AD)}$ and $\Delta\mu_{\in EcV(CD)}$, respectively. We can see from the figure that the dehydration from the cavity, $\Delta\mu_{\in EcV(AD)}$, and the dehydration around AD, $\Delta\mu_{\in EcV(CD)}$, cancel each other. As a result of the balance, $\Delta\mu$ turns out to contribute to destabilization of association. On the other hand, the interaction energy strongly favors the aggregation, and in total, the association in water takes place. Our conclusion is consistent with the experimental observations that the complex is predominantly stabilized by strong host−guest van der Waals interactions.[16,43−45]

By further decomposing EcV(AD) into the carboxyl and adamantyl groups (referred to as EcV(AD:1) and EcV(AD:2), respectively) as shown in Figure 4, we can estimate the contributions of these functional groups to ΔA. The result is compiled in Table 5, along with its thermodynamic decomposition. It is interesting that the SDA shows that $\mu^{sys(i)}_{\in EcV(AD:1)}$ has a negative value, although $\mu^{sys(i)}_{\in EcV(AD)}$ given by the sum of $\mu^{sys(i)}_{\in EcV(AD:1)}$ and $\mu^{sys(i)}_{\in EcV(AD:2)}$ has a positive value, as we have seen above. Its energetic component, $\varepsilon^{sys(i)}_{\in EcV(AD:1)}$, has a large negative value because the carbonyl group is a polar group that favorably interacts with water molecules. Its magnitude is larger than that of $-TS^{sys(i)}_{\in EcV(AD:1)}$, and $\mu^{sys(i)}_{\in EcV(AD:1)}$ turns out to have a favorable contribution to the stabilization of AD in water. The rest of the $\mu_{\in EcV(AD)}$ values in Table 5 are all positive, which can be explained by the EcV holding a solute molecule inside and by the hydrophobicity of the cavity, as discussed above. The SDA predicts the solvation terms as $\Delta\mu_{\in EcV(AD:1)} = +1.1$ kcal/mol and $\Delta\mu_{\in EcV(AD:2)} = -2.9$ kcal/mol, whereas the interaction energies between AD:1 and CD and between AD:2 and CD are calculated as −5.4 and −13.9 kcal/mol, respectively. By adding the interaction energies divided by 2 to the $\Delta\mu$s, we obtain that $\Delta A_{\in EcV(AD:1)} = -1.6$ kcal/mol and $\Delta A_{\in EcV(AD:2)} = -12.6$ kcal/mol, showing that the adamantyl group is largely responsible for the complexation and that the carboxyl group little influences it. From the experimental data, it also has been suggested[39] that the polar residue bonded to the adamantyl group scarcely influences the host−guest interaction. Our analysis is in good agreement with this observation. The present results thus show that SDA is a useful tool for fragment-based analysis to elucidate a molecular picture of association processes in solution.

Table 5. SDA of the Solvation Free Energy $\mu_{\in EcV(AD)}$ and Its Thermodynamic Decomposition into the Solvation Energy E and the Solvation Entropy $-TS$, along with Their Changes upon the Association[a]

	$\mu_{\in EcV(AD:1)}$			$\mu_{\in EcV(AD:2)}$		
	ε	$-TS$	total	ε	$-TS$	total
system i	−12.032	9.9536	−2.079	6.4726	33.535	40.01
system ii	−2.9894	5.0261	2.037	−10.699	30.646	19.95
system iii	−12.263	13.338	1.075	2.0715	55.002	57.07
Δ	2.76	−1.64	1.1	6.30	−9.18	−2.9

[a] Δ in the last row represents the association property defined as system iii − system i − system ii.

3.3. Spatial Decomposition Analysis of Partial Molar Volume Change. SDA is applicable not only to the free energy but also to any thermodynamic property which can be obtained from the distribution functions between solute and solvent. For illustration, we apply the SDA to the excess term of PMV and its change upon the association. In the present case, the ideal term of PMV is relatively small, compared to the whole PMV and its change. Therefore we can consider that the excess term is the primary contributor to the association process. The SDA of PMV is in fact very similar to the SDA of μ, and below we just briefly go through the results to give the relevant interpretations.

The SDA of the excess term in eq 5 yields the following decomposition:

$$\bar{\mathcal{V}} = \bar{\mathcal{V}}_{\in EcV(AD)} + \bar{\mathcal{V}}_{\in EcV(CD)} + \bar{\mathcal{V}}_{\in Shell} \qquad (14)$$

The values of all the components are compiled in Table 6. As we have seen in Table 3, the values $\bar{\mathcal{V}}^{sys(i)}_{\in EcV(CD)}$, $\bar{\mathcal{V}}^{sys(i)}_{\in Shell}$, $\bar{\mathcal{V}}^{sys(ii)}_{\in Shell}$, and $\bar{\mathcal{V}}^{sys(iii)}_{\in Shell}$ represent the hydration effect on the

Table 6. Spatial Decomposition Analysys (SDA) of the Excess Term of the Partial Molar Volume $\bar{\mathcal{V}}$ and Its Change upon the Association[a]

	$\bar{\mathcal{V}}_{\in \mathrm{EcV(AD)}}$	$\bar{\mathcal{V}}_{\in \mathrm{EcV(CD)}}$	$\bar{\mathcal{V}}_{\in \mathrm{Shell}}$	$\bar{\mathcal{V}}$ (total)
system i	209.43	−53.807	−17.367	138.3
system ii	126.87	719.69	−151.44	695.1
system iii	274.79	716.34	−166.97	824.2
Δ	−61.5	50.5	1.84	−9.2

[a] Δ in the last row represents the association property defined as system iii − system i − system ii.

PMV and contribute to the decrease of PMV, which is the so-called electrostriction effect. The term $\bar{\mathcal{V}}^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$ is also the hydration effect on the PMV; however, this term contributes to the increase of PMV. The positive value of PMV is caused by the fact that the distribution of water molecules in EcV(AD) is less than that in the bulk ($g(\mathbf{r}) < 1$), as can be seen from eq 5. This is the manifestation of hydrophobicity inside the CD cavity, which is consistent with the discussion about $\mu^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(AD)}}$ in the previous section. The terms $\bar{\mathcal{V}}^{\mathrm{sys(i)}}_{\in \mathrm{EcV(AD)}}$, $\bar{\mathcal{V}}^{\mathrm{sys(ii)}}_{\in \mathrm{EcV(CD)}}$, $\bar{\mathcal{V}}^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(AD)}}$, and $\bar{\mathcal{V}}^{\mathrm{sys(iii)}}_{\in \mathrm{EcV(CD)}}$ are essentially the geometrical volume of EcV of the molecules, being perturbed by the interaction between AD and CD. From the SDA of the PMV change upon the association, we can see a large negative change of −62 cm^3/mol in EcV(AD) and a large positive change of +51 cm^3/mol in EcV(CD). The former is due to the fact that AD occupies the CD cavity and decreases the cavity volume, accompanied by desolvation of water molecules from the cavity. The latter is due to the desolvation of water molecules around AD. Much as for μ, we found that the PMV change is determined by the balance between the two dehydration events. The magnitude of $\Delta\bar{\mathcal{V}}_{\in \mathrm{EcV(AD)}}$ is larger than that of $\Delta\bar{\mathcal{V}}_{\in \mathrm{EcV(CD)}}$, which suggests that the dehydration from the CD cavity is the predominant factor for the PMV change, and as a result, the PMV change becomes negative, as has been observed in experiment.[16]

4. Concluding Remarks

In the present article, we have presented a method to analyze the association process by decomposing the thermodynamic property into several three-dimensional spaces, based on three-dimensional molecular theory of solvation, also known as 3D-RISM. We refer to this method as spatial decomposition analysis (SDA). In the present SDA, we divided the thermodynamic property into two spaces, the space inside the excluded volume of solute molecules and the outside space. The thermodynamic property projected onto the excluded volume is further divided into a few fragments and is discussed to see how each fragment contributes to the thermodynamic property change upon the association. To demonstrate the SDA, we applied the method to the complexation of β-cyclodextrin (CD) and 1-adamantanecarboxylic acid (AD) in water. By applying the SDA to the association free energy, we found that the complexation is determined by the balance between the interaction between the two molecules and the dehydration contributions from the CD cavity and around AD upon the association. We also found that the adamantyl group of the 1-adamantanecarboxylic acid is largely responsible for the association, whereas the carboxyl group makes a small contribution to the association. In addition, by applying the SDA to the change of the partial molar volume upon the association, we found that the sign of the change is determined by the same balance between the dehydration terms. Our analysis is in good agreement with the observations in the recent study on a copolymer formed by β-cyclodextrin and adamantane dimers by using molecular dynamics simulation.[39] This suggests that the SDA method can be used to elucidate a microscopic picture of a wide range of host−guest association processes in solution.

There are several ways of partitioning the solvation thermodynamics into spatially resolved contributions in the SDA method. For example, the solvation shell region can be further decomposed into the volume parts corresponding to fragments of the solute molecules. This way of partitioning the solvation shell is necessary for associating systems with charged molecules. Although the contribution from the shell region is relatively small in the present case, our preliminary calculations show the possibility of a large contribution to the association process in such systems. SDA would also be particularly useful to study the thermodynamic stability of proteins so as to see which fragment (or residue) of the protein contributes most to its stability. This might render SDA as a useful tool for rational drug design.

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