A Theoretical Interpretation of Remarkable Enhancement of Intermolecular Binding at the Lipid-Water Interface

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A multidielectric model combined with quantum chemical calculation was applied to interpretate intermolecular binding at the lipid-water interface. The calculation well reproduced the observed binding energy between guanidium cation and AMP.

Hydrogen bonding drives molecular association phenomena in biological systems such as enzyme-substrate, antibody-antigen bindings, and so on. Its specific pairing is indispensable for the realization of precise molecular recognition. However, hydrogen bonding contributes only modestly to the free energy of association of small molecules in aqueous solution, as indicated in synthetic host-guest systems like cyclophane and cyclodextrin.[1] Recently, a major breakthrough in this field has been brought about by an author's (T. K) group,[2] indicating that weak intermolecular interaction such as hydrogen bonding is remarkably strengthened at the lipid (or air)-water interface, formed by a self-assembly of amphiphiles expanded on pure water. In the use of guanidinium-functionalized monolayer, [2a,b] ATP (or AMP), dissolved in the aqueous subphase, binds to the guanidinium group(s) with a binding constant about 10^6 times larger than that between free guanidinium and free phosphate in aqueous solution. The utilization of well-characterized interfaces enables us to realize highly-specific molecular recognition in artificial systems. In spite of such technological and scientific interests, it remains unclear how the intermolecular binding energy is amplified at the lipid-water interface. Here, we provide the first theoretical interpretation of this phenomenon using quantum chemical calculations.

Since guanidinium functionalized amphiphile **1** used in ref. 2 possesses a long hydrophobic chain,[3] the resulting monolayer forms a hydrophobic region which could exert a significant amount of electrostatic screening effects on the aqueous subphase. The monolayer may be thus approximated by a low dielectric medium (dielectric constant $\varepsilon = 2.0$) like liquid *n*-alkane. With the same level of approximation, the aqueous subphase could be regarded as a continuum with a dielectric constant of 80.0. Consequently, the lipid-water interface is represented by a double layer as shown in Figure 1. A pair of interacting molecules was located near/at the interface and explicitly treated with the quantum mechanics. Here, we selected guanidinium cation with an ethyl chain and phosphate anion as model compounds of amphiphile **1** and AMP (or ATP), respectively. The binding energy profile was obtained by calculating the free energy of the whole system as a function of guanidinium-phosphate distance R. Then, the free energy calculation was carried out using a reaction field theory developed by us.[4] The theory has been successfully applied to various multi-dielectric systems approximating the active site of enzyme and its mimetic compounds.[5] Throughout this study, the AM1 hamiltonian[6] was employed, and all the geometrical parameters of the interacting molecules were optimized in vacuo. The resulting geometries were used to calculate the binding energy profile mentioned above. The two NH groups of guanidinium were oriented towards two phosphate oxygens, so as to attain the maximal stabilization of the complex via hydrogen bonding.

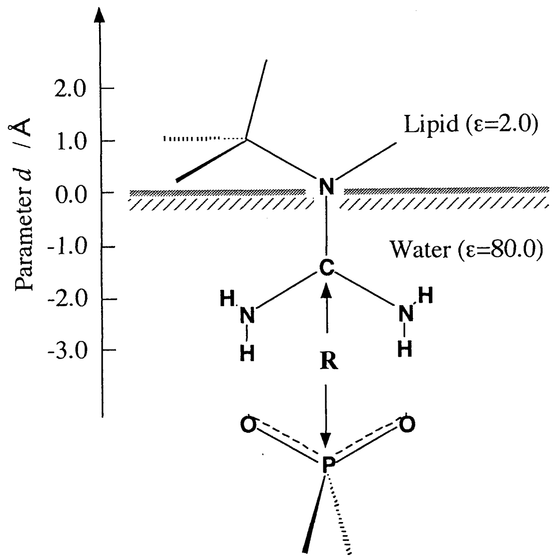

Figure 1. A continuum model of the lipid-water interface. The horizontal line indicates the infinitely-extended dielectric-dielectric boundary, the position of which is given by the parameter *d* (Å). The upper and lower layers represent the hydrophobic region of the lipid and water, respectively. A pair of guanidinium and phosphate is placed at the interface. Here, the parameter *d* is taken to be zero. The parameter R indicates the distance between the guanidium carbon and the phosphorus atom.

First, we examined the binding energy profile in normal liquid solution, assuming that the guanidinium-phosphate complex is embedded in a homogeneous continuum. As can be seen from Figure 2, the potential minimum, showing the complex formation, becomes shallow with increasing dielectric constant of solvent, and eventually disappears in the aqueous medium. This result is consistent with the available experimental data[7] indicating that the binding constant in water is very small (1.37 M, corresponding to a binding energy of 0.78 kJ mol^{-1}). Thus, the present calculation is sufficiently accurate for describing the normal solution phenomena.

When the complex exists near the lipid-water interface, its binding energy profile depends on the parameter *d* determining the position of the complex with respect to the interface (dielectric-dielectric boundary). The value for the parameter *d* is equal to zero when a guanidinium nitrogen is just on the boundary surface (Figure 1). The decrease of *d* value means

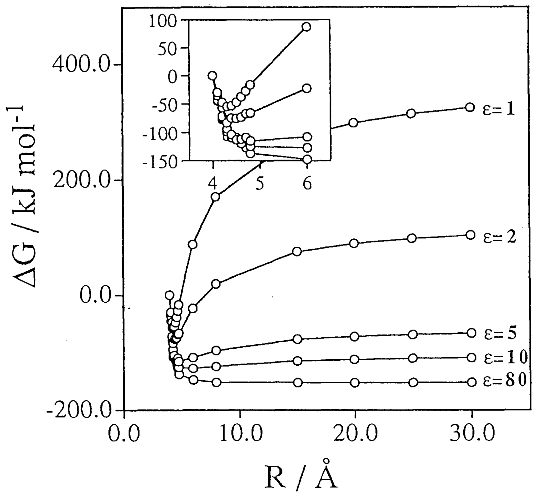

Figure 2. The dielectric constant (ε) dependence of the binding energy profile. The free energy difference ΔG was obtained by subtracting the free energy at R = 4.0 from that at a given R value.

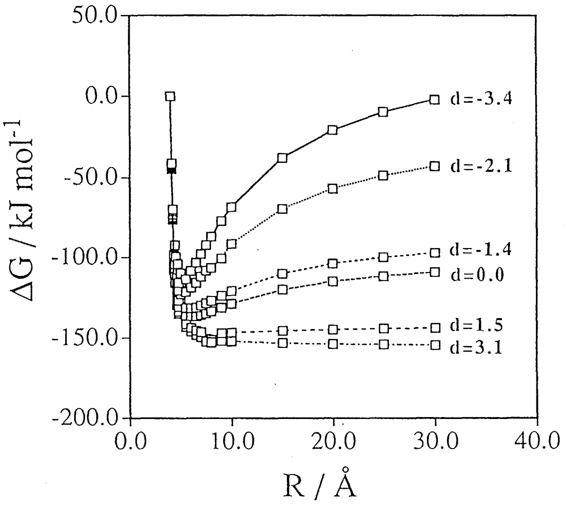

Figure 3. Dependence of the binding energy profile on the parameter *d*. The free enrgy diffence ΔG was obtained in the same way as in Figure 2.

that the complex becomes less exposed to the aqueous subphase. The binding energy profiles were obtained for some values of the parameter *d* (Figure 3). With a decrease in the *d* value, the potential minimum becomes deep, indicating the increase in stability of the complex. The most surprising finding is that the complex is formed even when the binding site (NH---OP) is completely exposed to the aqueous subphase. This is in contrast to the result for the normal aqueous solution mentioned above.

There remains uncertainty for choice of the *d* value. However, considering that the guanidinium moiety of the complex is inherently a member constituting the monolayer, it should be taken to be nearly zero. Then, the interface is formed so as to divide the hydrophobic chain from the guanidinium head group having a strong affinity for the aqueous medium. The binding energies, tentatively estimated from Figure 3, were 27.2 and 34.2 kJ mol^{-1} for *d* values of 0.0 and 1.4 Å, respectively. In the actual guanidinium monolayer-water system,[2] the binding constant of AMP (or ATP) to the guanidinium cation is ca. 10^6-10^7 M, corresponding to a binding energy of ca. 34 kJ mol^{-1}. Therefore, the calculation well reproduces the experimental data.

In conclusion, the interfacial potential of the aqueous medium contacting a sufficiently-extended hydrophobic surface is significantly modified by a synergetic effects of reaction fields generated from both hydrophobic and aqueous regions. As a result of this, molecules present in the vicinity of the interface exhibit unique properties discriminated from those in the bulk water.

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References and Notes

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