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Molecular Recognition at Air−Water and Related Interfaces: Complementary Hydrogen Bonding and Multisite Interaction

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Complementary Hydrogen Bonding in Molecular Recognition and Its Inefficiency in Conventional Aqueous Media

Hydrogen bonding is a highly directional secondary valence force compared with other noncovalent interactions such as electrostatic, van der Waals, and hydrophobic forces. The directionality in intermolecular interaction is crucial to specific molecular recognition between host and guest. In fact, hydrogen bonding plays decisive roles in biological molecular recognition such as replication of nucleic acids, maintenance of the tertiary structure of proteins, and substrate recognition of enzymes.[1] Hydrogen bonding has been used effectively also in artificial recognition systems. Some artificial receptor molecules recognize target molecules by using multiple hydrogen bonds. Well-designed disposition of proton-donating and proton-accepting sites within a receptor molecule leads to highly selective recognition.[2]

Unlike biological molecular recognition, most of these artificial systems are effective only in nonaqueous media due to strong hydrogen bonding with water. For example, monomeric nucleic acids cannot form hydrogen-bonded complementary pairs in water.[3] Addition of water suppressed binding efficiency between receptor and guest in nonaqueous systems.[4,5] Molecular design of the past artificial receptors needs to be improved, since most biologically important molecules are water-soluble and their molecular recognition is effective in aqueous media. It is illuminating to notice this great discrepancy between biological and artificial systems.

Strategies toward Effective Hydrogen Bonding in Aqueous Media

There are several approaches for inducing effective hydrogen bonding in simpler molecular systems in contact with bulk water. It is possible to enhance the effectiveness of hydrogen bonding either by cooperative interaction or by selection of proper microenvironments. In the absence of the cooperative action, hydrogen bonding becomes efficient in hydrophobic environments. We may create hydrophobic environments at three levels of dimensions−microscopic (i.e., molecular), mesoscopic, and macroscopic. At the microscopic level, Rebek *et al.*[6] and Torneiro and Still[7] designed receptor molecules that are capable of hydrogen bond mediated molecular recognition in aqueous media. The hydrophobic contact between receptor and guest enhances binding efficiency, and hydrogen bonding is made more effective in such microscopic hydrophobic environments.

Hydrogen bonding interaction becomes effective when the host−guest combination is placed in a mesoscopic phase where water is not readily accessible. Nowick and co-workers[8] showed binding of adenine and thymine moieties by burying them in the hydrophobic core of aqueous micelles. Bonar-Law[9] used a similar approach for a porphyrin receptor. In the macroscopic regime, specific hydrogen bonding determined the selectivity in extraction of guest molecules from an aqueous layer to an organic layer. For example, Aoyama and co-workers[10] showed that a cyclic resorcinol tetramer extracted monosaccharides selectively from their aqueous solutions. Komiyama and others[11] reported hydrogen bond mediated extraction of aqueous uric acid to a water-insoluble diaminotriazine polymer.

In these approaches, the hydrogen bonding interaction is made effective by placing host−guest functional pairs in hydrophobic environments of various dimensions. The molecular environment of the interacting site is, therefore, close to that of bulk organic media. In contrast, interfacial molecular recognition can offer a different situation. It has been known that the aqueous phase very close to the organic phase displays unique properties that are different from those of bulk water.[12] The interface may be mesoscopic like surfaces of molecular aggregates (micelles and bilayers) and nanoparticles. Or it may be macroscopic like solid substrates or the air−water interface. Unique influences of varied interfaces on the organic chemical process−both natural and artificial−have not been un-

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derstood satisfactorily. The significance of interfacial molecular recognition is at least 2-fold. First, we may be able to create distinct molecular recognition systems by taking advantage of unique physicochemical characteristics of interfaces. Monomolecular layers on water surfaces are especially useful for this purpose, since their structures and properties have been extensively studied in the past 60 years.[13−15] Second, the biological recognition proceeds, in many cases, at the surface of biological macromolecules, and interfacial features that are not necessarily apparent may affect recognition processes significantly.

Appropriate choice of analytical methodologies is critical for pursuing interfacial molecular recognition. Measurement of surface pressure (π)−molecular area (A) isotherms is indispensable for confirmation of monolayer formation on water. Direct proof of guest binding is obtainable by spectroscopic examination of multilayers transferred onto solid substrates by the Langmuir−Blodgett (LB) technique. We routinely combine X-ray photoelectron spectroscopy (XPS) and FT-IR spectroscopy for quantitative estimation of guest binding. We reported a depth correction of XPS data necessary to obtain precise elemental ratios of oriented LB films by considering the molecular orientation and mean free path of the photoelectron.[16] The quartz crystal microbalance (QCM) is another powerful tool for estimating guest binding onto surface monolayers and determining the bound guest in transferred multilayers.[17,18]

Molecular Recognition by Nucleic Acids and Their Mimics

The most notable example of biological recognition that is based on hydrogen bonding is complementary base pairing in nucleic acids. A pioneering work on the base pair mimic at the air−water interface was reported by Kitano and Ringsdorf.[19] They investigated π−A isotherms of an adenine-functionalized amphiphile on aqueous nucleosides, and proposed that larger expansion of the isotherm on aqueous thymidine relative to other nucleosides was ascribable to formation of the complementary A−T type pair at the interface.

This was a highly inspiring result since it suggested base pair formation even in the presence of water. However, direct evidence for complementary hydrogen bonding was not provided. Thus, we initiated systematic examination of interfacial molecular recognition.[20−33]

Two examples of base pair mimics at the air−water interface are shown in Figure 1. Binding of aqueous thymine and thymidine to a receptor monolayer with the diaminotriazine function (C_{10}AzoAT) was first investigated (Figure 1A).[22] In the FT-IR spectrum (RAS mode) of an LB film of C_{10}AzoAT transferred from 0.01 M aqueous thymidine, the thymidine peak ν(C═O) was detected at 1701 cm^{-1}, and broadening of diaminotriazine δ(NH) and a shift of diaminotriazine ν(C═N) were noticed relative to those of a pure C_{10}AzoAT film. Shifts in the δ(NH) peak that are often observed upon hydrogen bonding could not be recognized clearly, probably because RAS mode IR is sensitive only to vibrations normal to the surface. These spectral changes are consistent with guest binding via complementary hydrogen bonding. XPS elemental analyses revealed equimolar binding stoichiometry. Similar binding behaviors were observed for thymine and uridine but not for adenine and adenosine. The binding constant observed for thymine and thymidine is ca. 3×10^2 M^{-1}, and is comparable to that of a similar combination in aprotic organic solvents (diamidopyridine/butylthymidine).[34] It is known that monomeric base pairs are not readily formed in water due to strong hydration.[3]

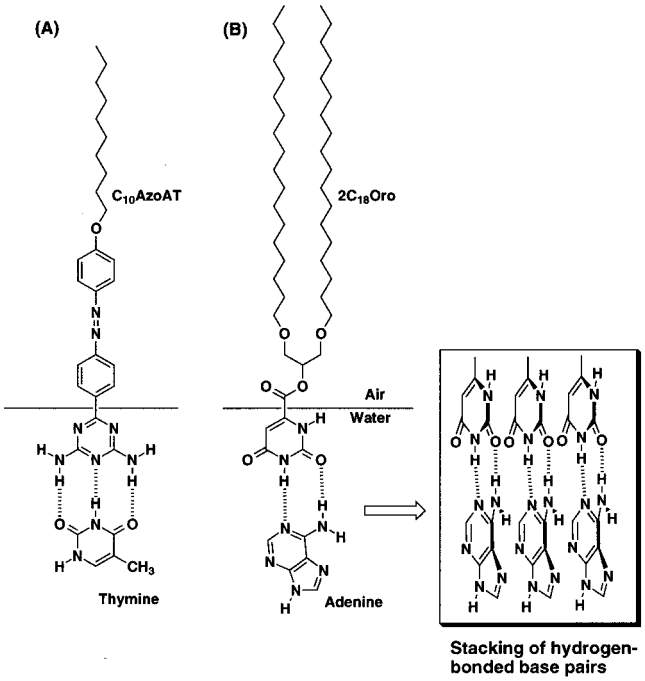

FIGURE 1. Recognition of nucleic acid bases at the air−water interface: A, recognition of thymine by a C_{10}AzoAT monolayer; B, recognition of adenine by a $2C_{18}$Oro monolayer.

The mode of hydrogen bonding is altered in the binding of aqueous adenine to the $2C_{18}$Oro monolayer that possesses the cyclic imide (orotate) function (Figure 1B).[23] In this case, the guest binding curve determined by XPS analysis did not obey a simple Langmuir isotherm. Conceivably, stacking of bound adenine molecules accelerates the binding. The importance of the stacking interaction is well-known in double-helix formation of DNA as well as in artificial receptor systems.[2e]

Shimomura *et al.*[35] investigated the binding of aqueous nucleosides to a cytosine-functionalized monolayer. Fluorescence microscopy observation revealed that the monolayer produced chiral spiral domains[36] on aqueous guanosine. Since the cytosine monolayer does not possess chiral centers, the chiral morphology observed must come from bound guanosine.

Complementary hydrogen bonding of melamine with cyanuric acid and barbituric acid is very effective. This combination has been used for designing supramolecular assemblies in organic media and in the solid state.[37−43] Recently Ringsdorf *et al.*[42] have reported binding of triaminopyrimidine (TAP) to barbiturate monolayers and

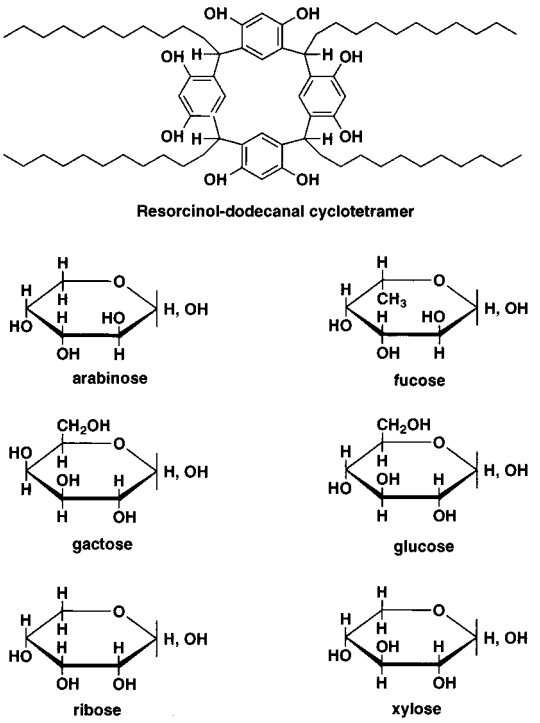

FIGURE 2. Resorcinol−dodecanal cyclotetramer and sugars.

the accelerated hydrolysis of the barbiturate. They interpreted the latter results in terms of activation of water trapped at the interface. We also reported characteristics and limitations of two-dimensional melamine/barbiturate networks.[32,33]

Okahata and co-workers[44] conducted an in situ examination of binding of complementary guest molecules toward a cyanurate monolayer by using a highly sensitive QCM. It was possible to estimate kinetic constants of adsorption and desorption and to calculate binding constants from the ratio of these constants. Their subsequent work included complementary binding of gaseous guests with immobilized nucleic acid base monolayers.[45]

Other Interfacial Receptors

Hydrogen bond based recognition systems other than the nucleic acid mimics have also been found effective at the air−water interface. The Weizmann group reported that monolayers of long-alkyl amino acids were made of specific arrangements of components through hydrogen bonding, inducing growth of α-glycine crystals from the subphase.[15] We have demonstrated recognition of sugars,[24] nucleotides,[20] amino acids,[21] and peptides.[25] Several examples from these results are given below.

Aoyama *et al.*[10] reported that a resorcinol−dodecanal cyclotetramer formed stereoselective complexes with sugars in CCl_4. We examined binding of aqueous sugars to monolayers of the resorcinol−dodecanal cyclotetramer (Figure 2).[24] Sugar binding was confirmed by measuring the surface potential of the LB film transferred on an SnO_2 electrode. The threshold sugar concentration at which the surface potential started to shift gives the following order of affinity: glucose < fucose ≈ galactose ≈ arabinose < xylose < ribose. This order is obviously different from the tendency for complex formation in CCl_4: xylose ≈ galactose ≈ glucose < arabinose < ribose < fucose. Apparently, the affinity is enhanced when the molecular surface of the host−guest complex is compatible with the surrounding medium. As examples, ribose can bind to the monolayer so that it exposes its hydrophilic moiety to the aqueous environment, while the bound fucose in CCl_4 can expose its hydrophobic moiety to the surrounding environment.

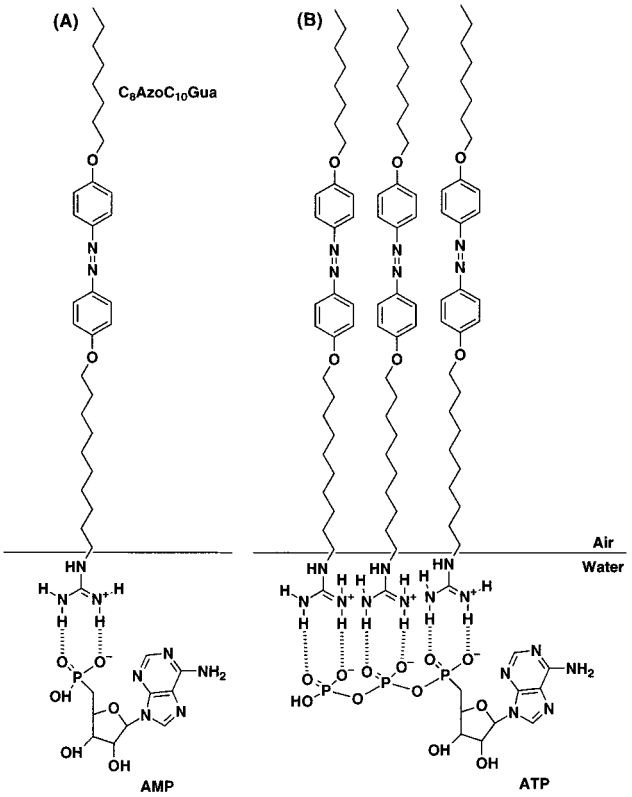

FIGURE 3. Recognition of AMP and ATP by a $C_8AzoC_{10}Gua$ monolayer.

Guanidinium−phosphate pairs are strongly bound in the biological system due to electrostatic interaction and hydrogen bonding.[46−48] We synthesized an azobenzene-derivatized guanidinium amphiphile ($C_8AzoC_{10}Gua$) and investigated the interaction of its monolayer with aqueous nucleotides such as AMP and ATP (Figure 3).[20] The binding behavior of these two closely related guests are different, as reflected in π−A isotherms and reflection−absorption UV spectra. The UV spectral peak of the monolayer shifted from 330 nm on pure water to 350 nm on aqueous AMP. In contrast, the molecular area decreased and the UV spectral shift was opposite (to 310 nm) in the presence of aqueous ATP. These spectral shifts correspond to supression and promotion of stacking of azobenzene chromophores, respectively, upon guest binding.[49]

The amount of the bound guest per receptor amphiphile was estimated from the ratio of P to N obtained by XPS analysis. The binding constants for AMP and ATP are 3.2×10^6 and 1.7×10^7 M^{-1}, respectively (20 °C). These values are surprisingly large compared with those found

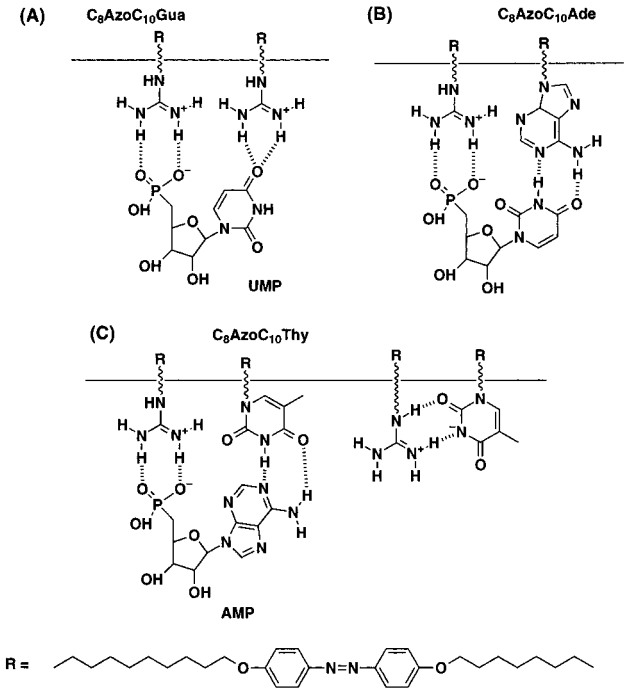

FIGURE 4. (A) Recognition of UMP on a $C_8AzoC_{10}Gua$ monolayer. (B) Recognition of UMP on a $C_8AzoC_{10}Gua/C_8AzoC_{10}Ade$ (1:1) mixed monolayer. (C) Recognition of UMP on a $C_8AzoC_{10}Gua/C_8AzoC_{10}Thy$ (1:1) mixed monolayer.

in bulk water. Molecularly dispersed guanidinium and phosphate in water give a binding constant of 1.4 M^{-1}.[46] Therefore, the binding constants at the air−water interface are 10^6-10^7 times larger than those in bulk water. This enhancement must be related to the unique medium effect of the air−water interface as discussed below.

Multisite Recognition at the Air−Water Interface

Biological receptors are usually composed of multiple, cooperating functional units. This molecular design is crucial for high precision and strong binding characteristic of the biological receptor. A large number of synthetic efforts have been reported in which multiple recognition sites are covalently created. Noncovalent self-assembly of functional components to form multifunctional receptor sites with precisely defined spatial disposition should be an alternative to this demanding, total-synthetic approach. Monolayers at the air−water interface are uniquely suited for this purpose, as the spatial orientation of the monolayer component is confined to the interface.

We first investigated molecular recognition by binary mixed monolayers.[20b] As shown above, guanidinium amphiphiles recognize the phosphate unit in nucleotides efficiently. Complementary amphiphiles that are capable of hydrogen bonding with the nucleic acid base in nucleotides are appropriate as second components. In our experiments, aqueous UMP is bound to 2 mol of $C_8AzoC_{10}Gua$ due to interaction between uridine carbonyl and guanidinium in addition to phosphate−guanidinium binding (Figure 4A). In contrast, when an equimolar mixed monolayer of $C_8AzoC_{10}Gua$ and $C_8AzoC_{10}Ade$ is

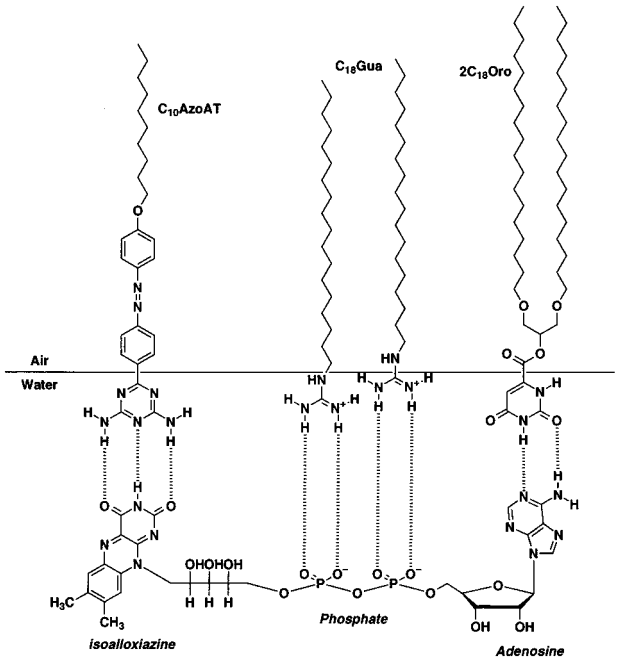

FIGURE 5. Recognition of FAD by a mixed monolayer of $C_{10}AzoAT$, $C_{18}Gua$, and $2C_{18}Oro$.

used, one UMP is bound to two molecules of each component (Figure 4B). The U−A interaction is favored over the carbonyl−guanidinium interaction, and the transferred monolayer contains both monolayer components against one UMP. Aqueous AMP is bound to a complementary monolayer mixture of $C_8AzoC_{10}Gua$ and C_8AzoC_{10}-Thy; however, the binding is partially inhibited by the guanidinium−thymine interaction (Figure 4C).

Ternary monolayers are more interesting. Recognition of aqueous flavin adenine dinucleotide (FAD) was investigated by using mixed monolayers of guanidinium (C_{18}-Gua), orotate ($2C_{18}Oro$), and diaminotriazine ($C_{10}AzoAT$) amphiphiles (Figure 5).[27] In this system, isoalloxazine, phosphate, and adenosine moieties in FAD are recognized through hydrogen bonding by diaminotriazine, guanidiniums, and orotate in the mixed monolayer, respectively. XPS analysis of the $C_{10}AzoAT/C_{18}Gua/2C_{18}Oro$ (1:2:1) film transferred from aqueous FAD (0.01 mM) revealed that one FAD molecule was bound to this three-component (four molecules) unit. It is clear that the binding stoichiomerty proposed in Figure 5 is achieved. Our recent observation of the molecular arrangement in monolayers by AFM is consistent with the scheme of Figure 5.[30]

We also examined recognition of FMN and AMP that have partial functional sites of FAD. Generally speaking, the binding strength of these guests is lessened as the number of hydrogen-bonding sites decreases. At this stage, we found a new problem in using multicomponent monolayer receptors. Recognition of AMP by a $C_{18}Gua/2C_{18}Oro$ mixed monolayer is not as efficient as we expected.[27] This is because the hydrogen-bonding interaction between $C_{18}Gua$ and $2C_{18}Oro$ competes with the binding of aqueous AMP (Figure 6A). This interamphiphile interaction may become influential when the

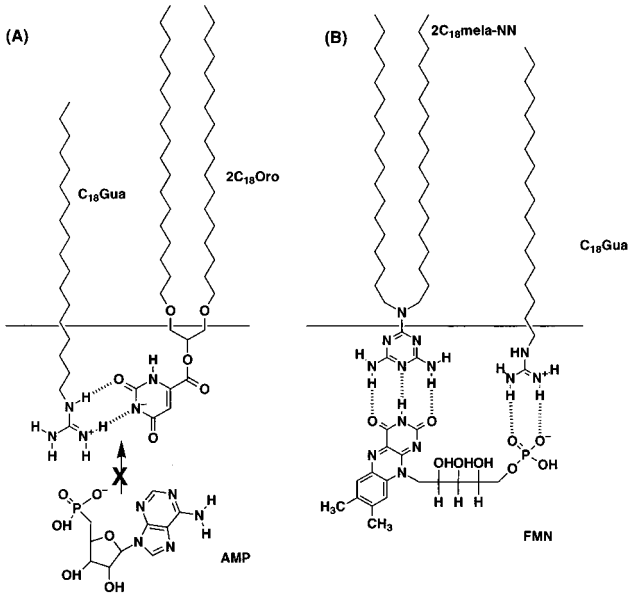

FIGURE 6. (A) Intramonolayer interaction of a C_8Gua/$2C_{18}$Oro (1:1) monolayer and inhibition of AMP binding. (B) Recognition of FMN on a C_{18}Gua/$2C_{18}$mela-NN (1:1) mixed monolayer.

interaction with the aqueous guest is not strong enough. On the other hand, recognition of aqueous FMN by a mixed monolayer of C_{18}Gua/$2C_{18}$mela-NN was quite efficient with a binding constant of more than 10^7 M^{-1} (Figure 6B).[28] In the latter monolayer, the two monolayer components cannot form hydrogen bonds between them.

The preceding examples establish that the mixed monolayer approach is an efficient tool to create multifunctional receptors. Self-assembly of varied recognition units is possible at the air−water interface. Unique molecular ordering at this interface plays an indispensable role for juxtaposing these units. It must be mentioned, however, that simple selection of the individual units does not warrant multisite recognition. Direct interaction of monolayer components would often suppress receptor capability, as typically shown by Figure 6A. The anisotropic molecular orientation at the air−water interface can be used to avoid this detrimental effect.

Molecular Recognition at Mesoscopic Interfaces Dispersed in Water

As amply demonstrated in the preceding sections, hydrogen bonding is effectively employed for molecular recognition at the air−water interface. It is interesting to test the implication of these results at other interfaces. Thus, we prepared aqueous micelles and bilayers with guanidinium units and studied binding of nucleotides (AMP etc.).[50] These molecular aggregates provide mesoscopic interfaces, whereas the air−water interface is macroscopic. The mesoscopic interface is typical of biological interfaces. In actual experiments, guanidinium-functionalized micelles and bilayers were dispersed in water together with guest molecules, and the mixture was filtered through an ultrafilter with a molecular weight cutoff of more than 5000. Since guest molecules bound to the aggregate cannot pass the filter, the extent of guest binding can be estimated from the ratio of guest concentrations between the filtrate and the original solution. The Langmuir analysis with varied guest concentrations gave binding constants of 10^2−10^4 M^{-1} for AMP binding (Figure 7). These values are significantly larger than that between molecularly dispersed guanidinium and phosphate in water (1.4 M^{-1}).[46] Therefore, we can conclude that the guest binding is also enhanced at aqueous mesoscopic interfaces. However, it is much smaller than the corresponding value observed at the air−water interface (10^6−10^7 M^{-1}). It appears that the binding strength between guanidinium and phosphate depends on the size of interfaces.

Nature of Host−Guest Interaction at Interfaces

The enormous enhancement of guanidinium−phosphate binding observed at the air−water interface may be related to unique features of the interface. To answer this question, a quantum chemical calculation was performed on the basis of a multi-dielectric model for the guanidinium−phosphate system placed at an interface as illustrated in Figure 8.[51] Dielectric constants for aliphatic and water phases are set to be 2 and 80, respectively. A free energy calculation was carried out using a reaction field theory which has been successfully applied to various multidielectric systems approximating the active site of the enzyme and its mimetic compounds.[52] The binding profile was obtained by calculating the free energy of the whole system as a function of the guanidinium−phosphate distance R, and the binding energy was estimated as the difference in free energy between that at the potential minimum and that at $R = \infty$. When d, the position of the interface, is a large positive value, i.e., the recognition site is buried deeply in water, a potential minimum is not observed. This agrees with the fact that only a small binding constant was observed in water. In contrast, when a d value close to zero is adopted, the calculation gives a binding energy around 30 kJ·mol^{-1}. In the actual guanidinium monolayer system, the binding constant of AMP is 3×10^6 M^{-1}, corresponding to a binding energy of 34 kJ·mol^{-1} (0 °C). Therefore, the computational estimate reproduces the experimental data satisfactorily.

This calculation demonstrates that guanidinium−phosphate binding is enhanced when the receptor site is located very close to the hydrophobic phase. The interfacial potential of the aqueous medium in contact with a hydrophobic surface appears to be significantly modified through a synergetic effect of reaction fields generated from both hydrophobic and aqueous regions. Molecules present in the vicinity of the interface must exhibit unique properties due to altered microenvironments different from those in bulk water. It is assumed in our computational approach that the interface is infinitely extended. The peculiar effect of the interface will be related to the extent of its expansion, and a macroscopic interface would be more effective than a mesoscopic interface. The air−

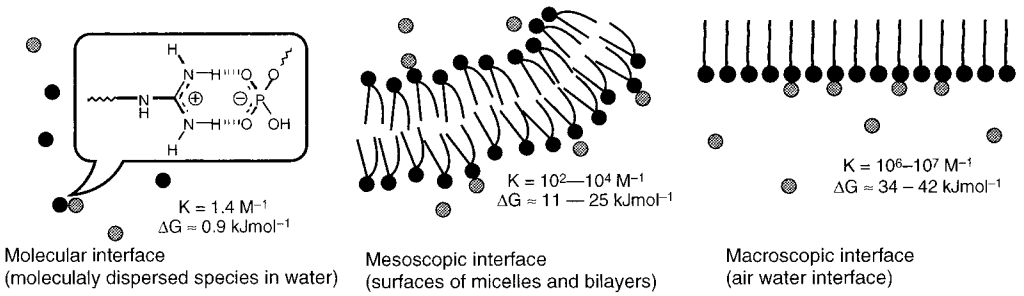

FIGURE 7. Typical binding constant (K) and binding energy (ΔG) of guanidinium−phosphate pairs at varied interfaces.

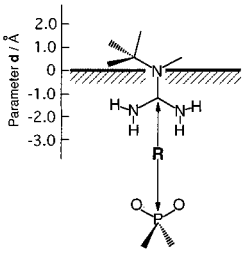

FIGURE 8. A continuum model of the lipid−water interface for the interaction of guanidinium and phosphate. d = the position of the guanidinium nitrogen with respect to the interface (dielectric boundary). Here, the parameter d is taken as zero. R = the distance between the guanidinium carbon and the phosphorus atom.

water interface is much larger and smoother than the surface of micelles and bilayers.

Surface force measurements, which evaluate molecular force between two opposing planes, give useful information on the interfacial molecular recognition. The force measurement was performed between two hydrogen-bonding monolayers.[53] An attractive force appeared from a separation distance of 20 nm between complementary monolayers containing adenine and orotate.[53a] It was invariably present between thymine and adenine monolayers independent of distance and solution pH.[53b] These findings suggest guest binding to the surface might not depend solely on molecular contact at the surface. The latter concept, if verified, would possess a profound implication for interfacial molecular recognition.

Future Prospects of Interfacial Molecular Recognition. Unique Features, Combinatorial Approach, and Molecular Patterning

The preceding experimental results unambiguously demonstrated that hydrogen bond based molecular recognition is highly effective at the air−water interface. This was, at first, surprising, since it has been known that efficiency of hydrogen bonding is quite limited in contact with bulk water. Figure 9 illustrates additional examples of hydrogen bond mediated interfacial recognition. Together with other examples given in the preceding figures, the chemical structures of such monolayer receptors are versatile. These receptor sites invariably include hydrogen-bonding units such as phenolic hydroxyl, carboxylic acid, aromatic nitrogen base, amino and amide groups, and guanidinium, and effective hydrogen bonding is a common feature. The peculiar behavior of water molecules in the vicinity of macroscopic interfaces has been pointed out by many researchers. This phenomenon must be related to the unique characteristics of the air−water interface. As shown by the computational approach of

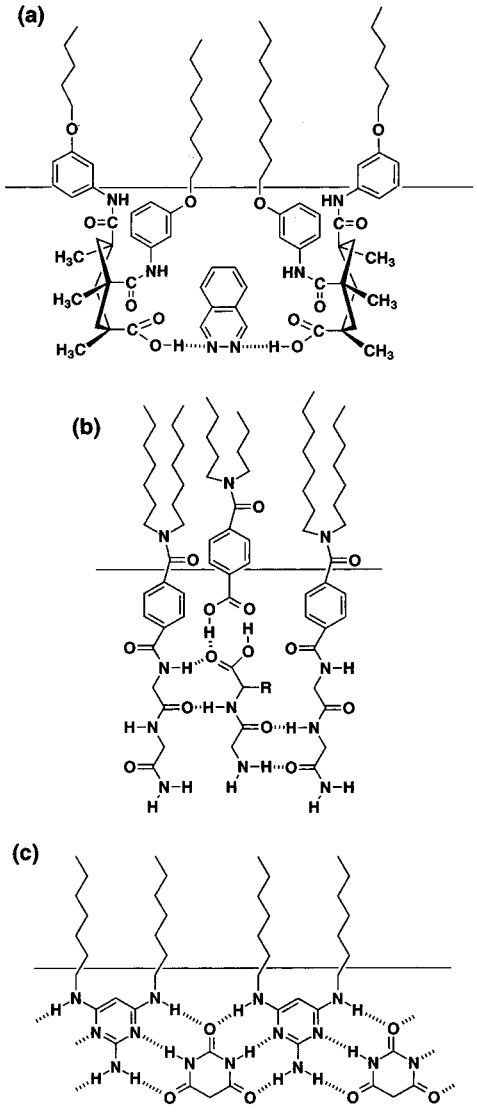

FIGURE 9. Additional examples of the interfacial molecular recognition: a, recognition of aromatic amines by monolayers of a Kemp's acid derivative;[33] b, specific binding of dipeptides by a mixed monolayer with peptide and carboxylate functions;[37] c, formation of an interfacial network of hydrogen bonds by melamine and barbituric acid.[44,45]

Sakurai, the multi-dielectric nature of the interface would be associated with this characteristic.[51]

The enhanced effectiveness of hydrogen bonding leads to exciting possibilities in molecular recognition of other physiologically active molecules. In the examples cited in this Account, we restricted the kind of receptor functional units to rather simple ones in order to clarify the pattern of specific guest binding unambiguously. Once the unique feature of the interfacial recognition is established, a similar approach is readily extended to more complex molecules. A typical example in this respect is the design of peptide receptors. We showed that highly water-soluble dipeptides were bound from the aqueous subphase to monolayers of peptide-derivatized dialkyl amphiphiles selectively.[25a] The binding specificity was apparently determined by the manner of hydrogen bonding and the extent of hydrophobic interaction between peptide segments of the host and guest. In a more recent example, mixed monolayers that contain a peptide polar group and a second proton-accepting function showed altered specificity due to multisite binding of guest peptides toward the individual monolayer components (Figure 9b).[25b,c] It is now clear that we can design elaborate receptor structures for peptides and other physiologically important molecules by self-assembly of monolayer components.

The specific molecular arrangement of the receptor site is generated spontaneously in the mixed peptide monolayer upon guest binding. This situation may be analogous, though remotely, to the formation of innumerable receptor sites in antibodies from combination of DNA fragments. Thus, the combinatorial approach could be a highly effective means to create unique binding sites from a versatile pool of functional monolayer components. A vast number of receptor sites are readily created by combination of relatively few kinds of the monolayer components.

Spontaneous generation of binding sites from multiple monolayer components has been observed for FAD and peptides. In these cases, monolayer components are necessarily organized in given spatial arrangements to provide specific binding patterns. This presumption leads to an exciting prospect of molecular patterning. We already found that the Langmuir−Blodgett film of a mixed monolayer of C_{18}Gua/2C_{18}Oro on FAD gave an AFM image with a periodic oblique pattern composed of two methyl peaks of different heights.[30] This observation is ascribed to formation of ordered molecular arrangements of the two monolayer components due to simultaneous binding with FAD. Similar molecular patterning has been detected in other examples of interfacial molecular recognition.[31,32] This visual information would help in the understanding of molecular details of the multisite interaction.

In this Account, we discussed current progress in hydrogen bond based molecular recognition at the air−water interface. The most interesting future directions in this area may be (a) development of highly specific receptor sites by design of appropriate monolayer components and by application of the combinatorial approach and (b) creation of molecularly precise patterns with the help of interfacial molecular recognition.

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