Multivalency and Cooperativity in Supramolecular Chemistry

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ABSTRACT

Multivalent interactions, which rely upon noncovalent bonds, are essential ingredients in the mediation of biological processes, as well as in the construction of complex (super)structures for materials applications. A fundamental understanding of multivalency in supramolecular chemistry is necessary not only to construct motors and devices on the nanoscale but also to synthesize model systems to provide insight into how biological processes work. This Account focuses on the application of multivalency to supramolecular chemistry in particular and the nanosciences in general.

Introduction

The assembly of functional nanosystems[1] with a precision analogous to that found in the natural world requires an understanding and control of noncovalent interactions, such as hydrogen bonding[2] and metal−ligand coordination,[3] as well as $\pi-\pi$ stacking,[4] hydrophobic, ionic, and van der Waals forces.[5] The construction of multicomponent supramolecular assemblies, that is, supramolecular synthesis,[6] has been a topic for extensive investigation since the advent of chemistry beyond the molecule.[7] The motivation lies not only in the fundamental understanding of self-assembly and molecular recognition processes pertinent to the origin of life and evolution[8] but also toward the designing of a new class of materials and devices for future technologies.[9] The prospect of building increasingly complex (super)structures using noncovalent chemistry depends on our fundamental understanding of the concept of multivalency,[10−15] the simultaneous binding of multiple ligands on one entity to multiple receptors on another. Multivalent interactions tend to be much stronger than the corresponding monovalent ones, a phenomenon that is often necessary to regulate physiological processes.[10] Multivalent interactions could be an evolutionary consequence of the relative ease of multiplying the number of existing interactions to increase[12] binding affinities, rather than addressing the more complicated task of evolving stronger interactions. The binding of two molecules, both having multiple recognition sites, may occur with an affinity greater than the sum of the corresponding monovalent interactions, a phenomenon that has been defined[13] as the "cluster effect". The contributions of enthalpy and entropy to the binding enhancement observed in biological systems is not fully understood, and efforts to explain them both theoretically[14] and experimentally[15] are usually hampered by the complexities of the systems. Studying multivalency in simple yet information-rich artificial model systems is beneficial not only for understanding the concept but also for transferring it into materials science[16] where multivalency can be harnessed to build motors[17] and devices,[18] analogous to Nature's examples. As the desire to build more elaborate nanosystems grows, multivalency is likely to play an increasingly significant role in the areas of supramolecular,[6,7] medicinal,[19] and materials[9,16] chemistry. This Account discusses multivalency in the context of self-assembling artificial systems as (i) models for biological processes and (ii) a means to order molecules into complex nanoarchitectures.

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Multivalency and Cooperativity

Multivalency and cooperativity are two distinct phenomena. Cooperativity describes how the binding of one ligand can influence a receptor's affinity toward further binding interactions and is most easily assessed for the stepwise binding of monovalent ligands. Cooperativity can be classified[20] as (1) positive (synergistic), when the subsequent binding of another molecule is higher than that for the previous one, (2) negative (interfering), when the binding is lower, and (3) noncooperative (additive), when the binding is identical. Perhaps the best known example[21] in biology is the allosteric oxygenation of hemoglobin. This tetrameric protein binds four individual oxygen molecules with increasing affinity until all four binding sites are occupied in a positively cooperative manner. The concept of cooperativity in self-assembly has been discussed[11] recently. Understanding multivalency and cooperativity is important when approaching the rational design of supramolecular assemblies.

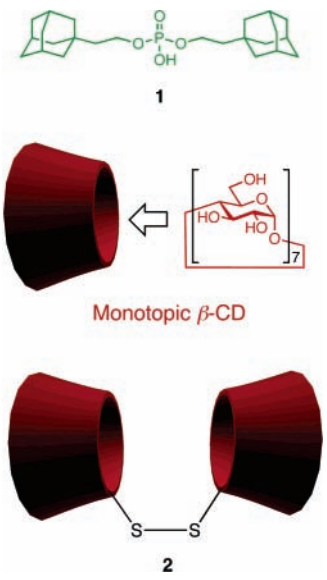


FIGURE 1. Monotopic and ditopic β-CD (e.g., **2**) receptors for binding a divalent guest **1**.

Cyclodextrins (CDs) have a history of forming inclusion complexes with guests that occupy their hydrophobic cavities.[22] Zhang and Breslow[23] have investigated (Figure 1) a bis-adamantyl ligand **1** for its ability to bind monotopic and ditopic β-CD receptors. Two monotopic β-CDs were observed to bind the ligand **1** with negative cooperativity, that is, the binding of a second β-CD to **1** occurs with an affinity ($K_{a2} = 4.39 \times 10^3\ M^{-1}$) 50 times smaller than that of the first β-CD ($K_{a1} = 2.26 \times 10^5\ M^{-1}$). The cooperativity of the system was assessed using eq 1,

$$\frac{K_{i+1}}{K_i} = \frac{i(n-i)}{(i+1)(n-i+1)} \quad (1)$$

which determines[21] the statistical (or noncooperative) ratio of association constants for i monovalent ligands interacting with a multivalent receptor with n binding sites. A system is defined as positively cooperative when the experimental ratio of $K_{(i+1)}/K_i$ is larger than the theoretical ratio calculated in eq 1, and negatively cooperative when the former is smaller than the latter. Since the experimental value for K_2/K_1 is smaller than the calculated statistical value, the binding of β-CD to divalent **1** is negatively cooperative. Covalently bridging two cyclodextrin tori to give receptor **2**, however, increases the affinities by factors of 80 and 4000 with respect to K_{a1} and K_{a2}. However, as Ercolani[11] has demonstrated, a similar analysis for cooperativity in a divalent system would be inappropriate, because the first and second microscopic equilibrium constants have different dimensions. Assessing cooperativity in multivalent systems would require consideration of either (1) effective concentrations[11] of interacting groups within the multivalent ligand or (2) the additivity of free energies.[14,24] Jencks has noted[24] that, in the absence of cooperativity, the free energy change for binding a bivalent ligand can be greater than the sum of ΔG° for the individual fragments by an amount equating to the "Gibbs connection energy" (ΔG^s). ΔG^s is a measure of the energetic penalty associated with the loss of independent translational and rotational degrees of freedom that occurs on bringing two molecules together to form a complex. Although we[25] and others[12,24] have estimated ΔG^s to be ca. +6 kcal/mol at 298 K from studies in aqueous solution, we note that this number may not directly transfer to studies conducted in other solvents. Kitov and Bundle[14] have expanded Jencks's analysis to accommodate the degeneracy (Ω) of microscopically distinguishable complexes that arise in multivalent interactions (eq 2):

$$\Delta G^\circ_{\text{avidity}} = \Delta G^\circ_{\text{inter}} + \Delta G^\circ_{\text{intra}} \sum_{i=1}^{i_{\max}} w_i(i-1) + RT \sum_{i=1}^{i_{\max}} w_i \ln(w_i/\Omega_i) \quad (2)$$

where w_i is the probability of the state with i interacting groups, Ω_i is the degeneracy of the ith state, and $\Delta G^\circ_{\text{inter}}$ is the free energy change for the first receptor−ligand interaction (approximately equal to a monovalent interaction, $\Delta G^\circ_{\text{mono}}$). The $\Delta G^\circ_{\text{intra}}$ term in eq 2 is the free energy change for each additional interaction in the multivalent complex and differs from $\Delta G^\circ_{\text{inter}}$ as a consequence of the connection energy (ΔG^s) and any other contributions ($\Delta G^\circ_{\text{interaction}}$) arising from changes in conformational entropy, bond strain, cooperativity, etc.:

$$\Delta G^\circ_{\text{intra}} = \Delta G^\circ_{\text{inter}} - \Delta G^s + \Delta G^\circ_{\text{interaction}} \quad (3)$$

To describe the free energy of a divalent system using eq 2, one must set $i_{\max} = 2$. Thus,

$$\Delta G^\circ_{\text{avidity-divalent}} = \Delta G^\circ_{\text{inter}} + w_2 \Delta G^\circ_{\text{intra}} + RT[w_1 \ln(w_1/\Omega_1) + w_2 \ln(w_2/\Omega_2)] \quad (4)$$

If we assume that only the divalent species exists in solution, then $w_1 = 0$ and $w_2 = 1$. Therefore,

$$\Delta G^\circ_{\text{avidity-divalent}} = \Delta G^\circ_{\text{inter}} + \Delta G^\circ_{\text{intra}} + RT \ln(1/\Omega_2) \quad (5)$$

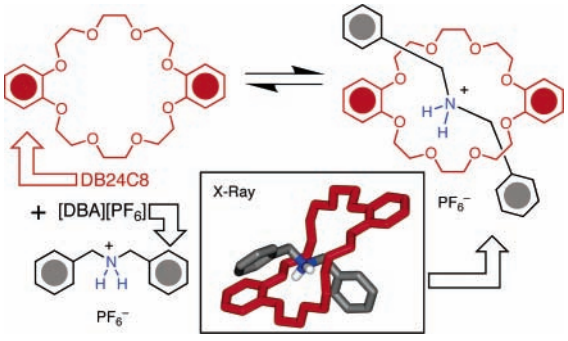


FIGURE 2. Formation of a pseudorotaxane comprised of a DBA^+ guest threaded through a DB24C8 macrocycle, together with the X-ray superstructure of the 1:1 complex.

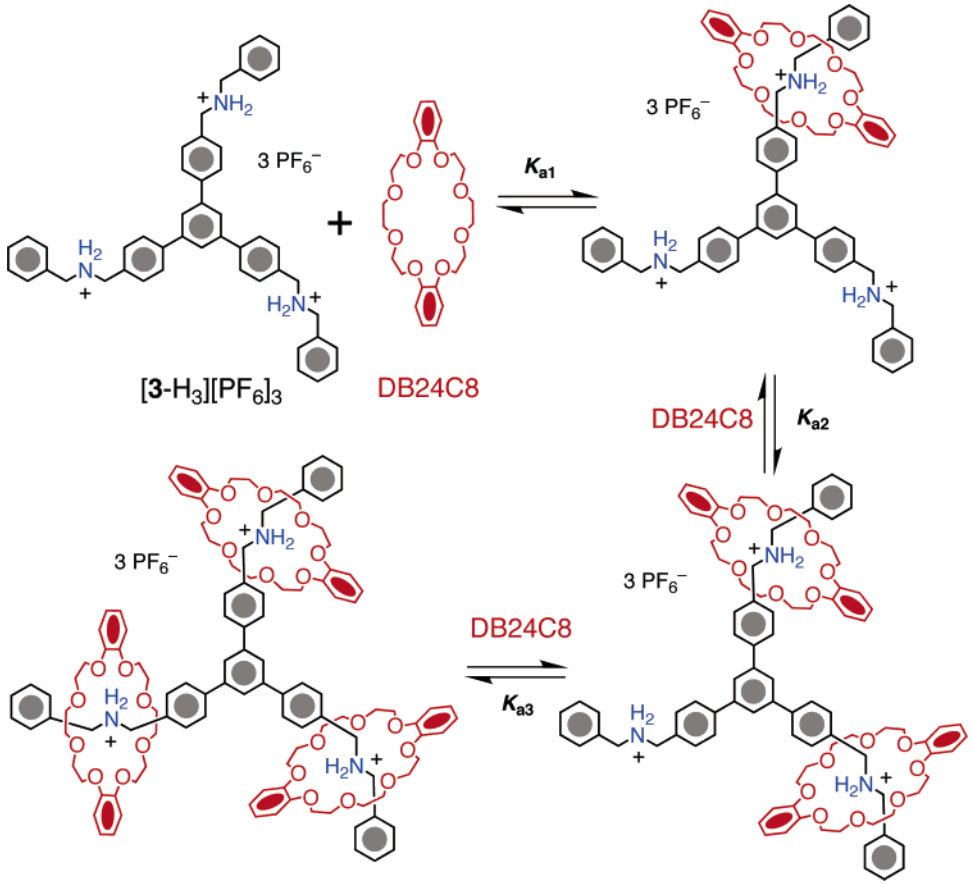
The degeneracy factor Ω_2 will depend on the topology of the system. Substituting eq 3 into eq 5 provides an alternative description of this equation:

$$\Delta G^\circ_{\text{avidity-divalent}} = 2\Delta G^\circ_{\text{inter}} - \Delta G^{\text{s}} + \Delta G^\circ_{\text{interaction}} + RT\ln(1/\Omega_2) \quad (6)$$

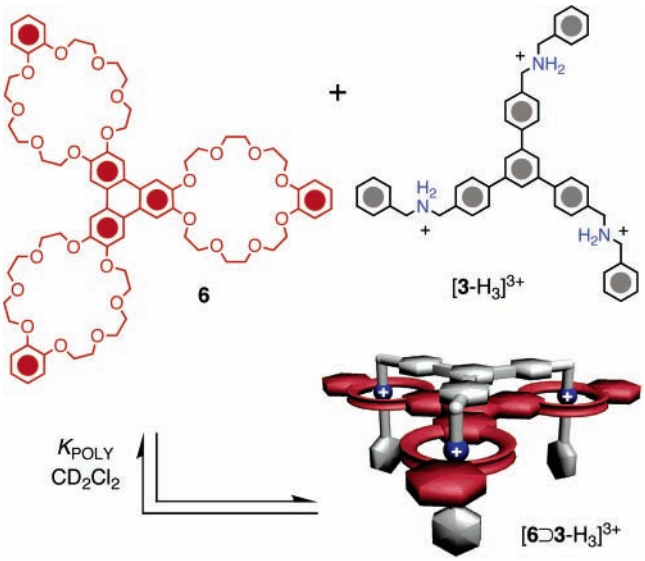
For positive cooperativity, $\Delta G^\circ_{\text{intra}}$ would have to be more negative than $\Delta G^\circ_{\text{inter}} - \Delta G^{\text{s}}$ (eq 3). However, for complexation of **1** and **2**, $\Delta G^\circ_{\text{intra}}$ is smaller in magnitude than $\Delta G^\circ_{\text{inter}}$, and hence, we must conclude that the system exhibits negative cooperativity.

Both cooperativity and multivalency have also been investigated using hydrogen bonding systems, for example, the interaction between $R_2NH_2^+$ ions and monotopic receptors, such as dibenzo[24]crown-8 (DB24C8) derivatives. It has been shown[26] that a range of monovalent $R_2NH_2^+$ ions can interpenetrate the macrocyclic cavity in a monotopic DB24C8 host to form [2]pseudorotaxanes, which have been characterized in the "gas phase", as well as in the solution and solid states. The self-assembly of a [2]pseudorotaxane proceeds (Figure 2) with the formation of [N^+−H···O] hydrogen bonds and [C−H···O] interactions, augmented by other electrostatic and aromatic−aromatic interactions. Whereas the interaction of linear guests containing two NH_2^+ with DB24C8 has been investigated[27] by us, the cooperative self-assembly (Scheme 1) of [2]- and [3]pseudorotaxanes, in addition to a branched [4]pseudorotaxane, containing the trifurcated trisammonium trication **3**-H_3^{3+} and DB24C8 have been reported recently by Gibson and co-workers.[28] The association constants for the binding of the first ($K_{a1} = 4.4 \times 10^2\ M^{-1}$), second ($K_{a2} = 1.4 \times 10^2\ M^{-1}$), and third ($K_{a3} = 0.4 \times 10^2\ M^{-1}$) DB24C8 macrocycles to the **3**-H_3^{3+} in CD_3CN were calculated from ^1H NMR spectra. At 3:1:$^1/_3$, the ratio of $K_{a1}/K_{a2}/K_{a3}$ corresponds to the noncooperative binding of **3**-H_3^{3+} to the DB24C8 macrocycles, indicating that the three consecutive binding steps are independent of each other. Interestingly, tethering first, second, or third generation dendrons to DB24C8 and examining their binding affinities for the trifurcated **3**-H_3^{3+} trication revealed[28] positive cooperativity ($K_{a1}/K_{a2}/K_{a3}$ is 3:3.6:3), a phenomenon that was also confirmed using a Scatchard analysis.[21] It is suggested that the observed positive

Scheme 1. Stepwise Formation of a Multiple Pseudorotaxane



Scheme 2. Formation of the Supramolecular Bundle $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$



cooperativity is a result of dendron-assisted shielding of the NH_2^+ charge from the nonpolar solvent, a phenomenon that facilitates the consecutive binding of the crown ethers to the remaining NH_2^+ centers.

Meanwhile, we have developed[29] a multivalent system incorporating interpenetration. A tritopic receptor **6** in which three benzo[24]crown-8 (B24C8) macrorings are fused onto a triphenylene core and a trifurcated trication **3**-H_3^{3+} wherein three dibenzylammonium ions are linked 1,3,5 to a benzenoid core were employed (Scheme 2). Conformationally nonflexible spacers, if correctly designed, can allow receptors and ligands to interact with only a small entropic loss and minimal enthalpic strain, yielding stable complexes. For this reason, a rigid benzene hub as the central core in **6** and a rigid triphenylene aromatic core in **3**-H_3^{3+} were employed. Indeed, the components **6** and **3**-H_3^{3+} are well suited to each other and give rise to the formation of a 1:1 adduct as a triply threaded, two-component supramolecular bundle $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$ in solution. The X-ray analysis of a single crystal of $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$ confirmed[29] the formation of the bundle stabilized by the stacking interactions between the central aromatic rings, as well as by a combination of [N$^+$−H···O] and [C−H···O] interactions. UV−vis and fluorescence titration experiments also confirmed the 1:1 stoichiometry (Job plot) of binding, wherein the avidity association constant,[14] $K_{avidity}$, in CD_2Cl_2 was found to be 1.5×10^7 M^{-1}. The fact that the K_a value for the corresponding monovalent dibenzylammonium ion−DB24C8 interaction in $CDCl_3$ is 2.7×10^4 M^{-1} ($K_{avidity} \gg K_a$) suggests that a stable interwoven supramolecular bundle is formed as a result of the multivalent interaction. Since ^{1}H NMR spectroscopy did not reveal the presence of any singly or doubly threaded intermediates in the formation of the superbundle $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$, we can assume that only the trivalent species exists in solution. The $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$ superbundle has a topology similar to the radial system described by Kitov and Bundle.[14] However, because the complex can form from either face of trivalent crown **6**, the degeneracy, Ω, for $[\mathbf{6}\supset\mathbf{3}\text{-}H_3]^{3+}$ is doubled to 12. Analysis of the free energy changes, again assuming that the first interaction in the multivalent complex occurs with the same affinity as the monovalent system, leads to the conclusion that $-\Delta G^\circ_{intra} < -\Delta G^\circ_{inter}$ and that the system exhibits negative cooperativity. Nevertheless, the result demonstrates again that cooperativity is not necessary to achieve large increases in functional affinity.

Whitesides et al.[30] have carried out (Figure 3) systematic studies on the interaction of mono- and trivalent derivatives of vancomycin with mono- and trivalent D-Ala-D-Ala (DADA) peptide derivatives, respectively, to provide insight into the fundamental parameters underlying multivalency. Monovalent vancomycin binds a monovalent DADA peptide with an association constant (K_a) of 6.3×10^5 M^{-1}, while the trivalent vancomycin derivative **4** binds the DADA trimer **5** to form a 1:1 complex with a K_a value of 2.5×10^{16} M^{-1}. In the context of organic supermolecules, the magnitude of this multivalent interaction—with a binding affinity higher than the monovalent binding interaction between biotin and avidin, one of the strongest noncovalent interactions known[31] in biology—is immense. Moreover, it was demonstrated that, by adding a competing monovalent ligand, the stepwise dissociation of the complex via the doubly and singly interacting complexes is possible.

An important feature of pseudorotaxanes, including those based on hydrogen-bonding interactions between crown ethers and NH_2^+ centers, is the possibility of controlling the dethreading/rethreading processes. ^{1}H NMR spectroscopic experiments of the superbundle $[\mathbf{6}\supset\mathbf{7}\text{-}H_3]^{3+}$ in $CDCl_3/CD_3CN$ (1:1) diluted with CD_3SOCD_3, as a hydrogen-bonding solvent, led to its stepwise decomplexation to the free species via the doubly and singly threaded complexes. Alternatively, the decomplexation can also be induced (Scheme 3) by the addition of 3 equiv of tri-*n*-butylamine (NBu_3). Subsequent addition of 3 equiv of trifluoroacetic acid results in the regeneration of the superbundle. The ability to control the association/dissociation of the multivalent superbundle by acid/base input opens up the possibility of designing molecular machines.[17,18]

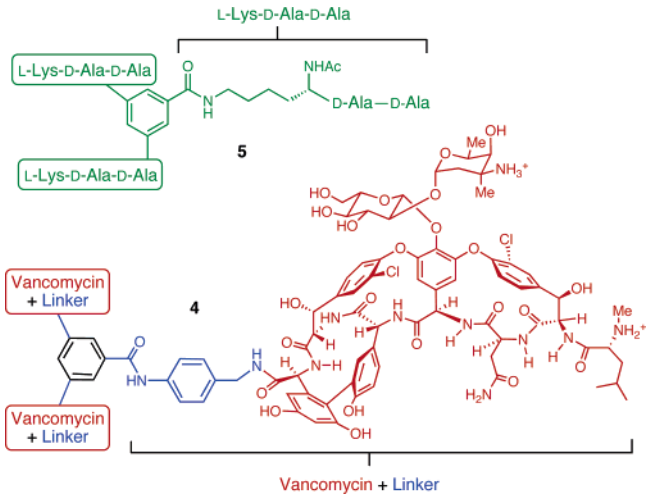
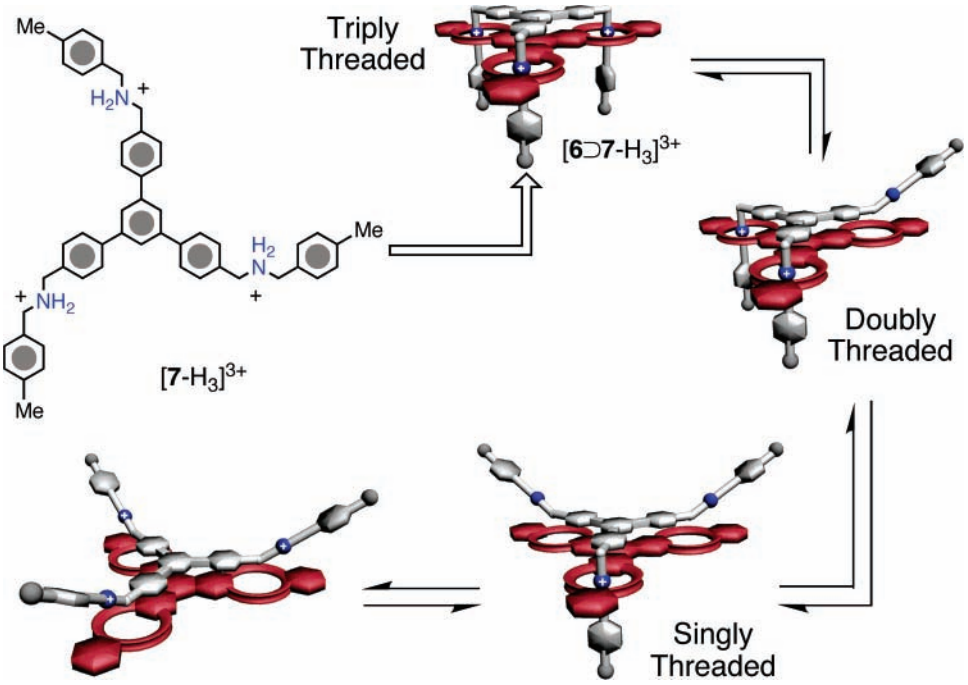


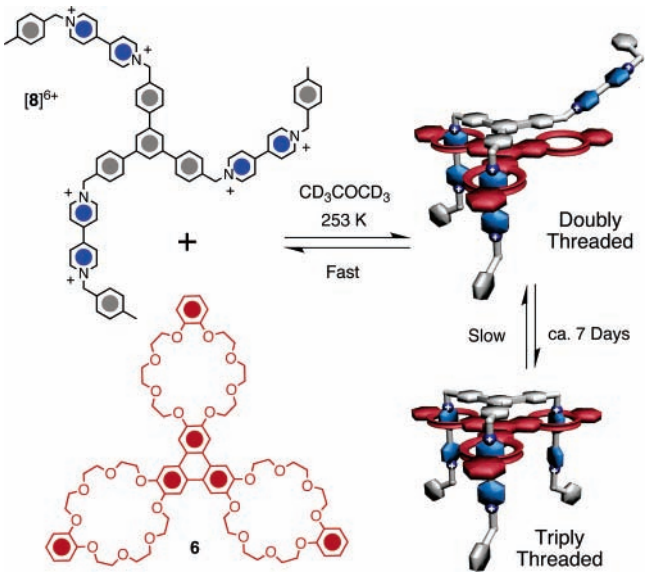
FIGURE 3. Trivalent vancomycin (**4**) and a trivalent D-Ala-D-Ala substrate **5**.

Scheme 3. Acid−Base Controlled Threading/Dethreading of the Supramolecular Bundle $[7\supset 3\text{-}H_3]^{3+}$



Whereas the intrinsic complexity of biological molecules imposes limitations on quantitative kinetic and thermodynamic analyses of multivalent molecular recognition processes, small and well-defined artificial model systems, wherein quantification is quite feasible, can in principle contribute enormously to a better understanding of multivalent phenomena. Strict self-assembly of a triply threaded two-component superbundle from a trifurcated trisbipyridinium salt [**8**][PF_6]$_6$ and a tritopic triscrown ether **6** has also been investigated[32] by us (Scheme 4). ^{1}H NMR spectroscopy reveals that the rapid formation of a doubly threaded two-component complex is followed by an extremely slow conversion (1 week at −20 °C in CD_3COCD_3 to reach equilibrium!) of this kinetically controlled product into its thermodynamically controlled analogue, namely a triply threaded two-component superbundle. In biological systems, multivalency is generally assumed to be a thermodynamic phenomenon.[10] It has recently been suggested,[33] however, that multivalent interactions between galactoside-bearing polymers and the carbohydrate-bearing protein XL 35 reach equilibrium very slowly, and a metastable mode of interaction is probably more than enough to guarantee an insurmountable physical block to polyspermy. Furthermore, multivalent polymers displaying different disulfated isomers of the Lewis x trisaccharide exhibit different binding selectivities for L-selectin, depending on whether the assay is conducted under conditions of shear flow.[15] Under the thermodynamic equilibrium conditions of a static binding assay, both polymers bearing 3′,6′- and 3′,6-disulfo Lewis x inhibit the protein from binding to heparin, whereas only the 3′,6-isomer prevents the adhesion of L-selectin-transfected cells on the glycoprotein GlyCAM-1 in a shear flow assay, presumably under kinetic conditions. These observations beg the question, is multivalency in nature expressed as a kinetically controlled process prior to an equilibrium state being reached, and if so, then what are the biological implications, if any? Of course, molecular recognition in organic solvents is subject to different driving forces from the analogous processes in aqueous solution. Nevertheless, our results have demonstrated that an investigation of wholly synthetic systems in unnatural settings can provide insights that have parallels in multivalent biological systems. Almost certainly, an increasing number of biological systems will emerge where multivalency is expressed kinetically and where the consequences of that expression could be important for processes in biology.

Scheme 4. Kinetic (Doubly Threaded) and Thermodynamic (Triply Threaded) Complexes Formed between $[8]^{6+}$ and 6

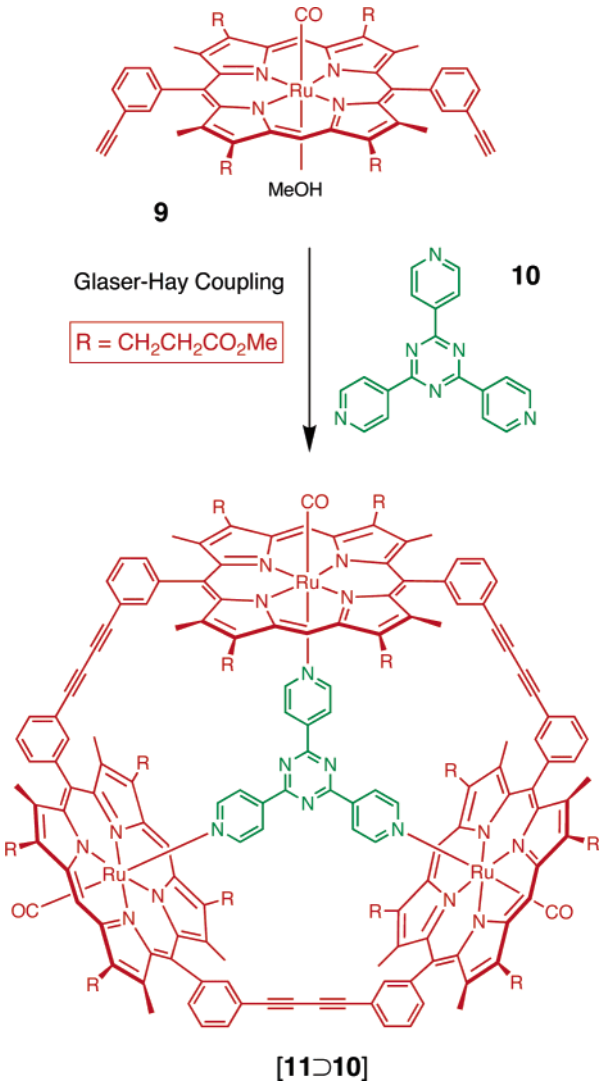


Multivalent Templates in Supramolecular Assistance to Molecular Synthesis

Besides the importance of multivalency in biology and a need to understand the basis for its operation in living systems, another important aspect of multivalency is its ability to be harnessed in the synthesis of discrete molecular entities bound by covalent and mechanical bonds. Template-directed synthesis[34] has become an important tool in synthetic supramolecular chemistry.[6] In pursuit of developing methods for assembling molecular and supramolecular nanoarchitectures, multivalent templates, which capitalize on noncovalent intermolecular bonds, provide a means to engineer simple building blocks into higher-order aggregates. The template controls the size and shape of the resultant (super)structure, that is, whether finite supermolecules or infinite supramolecular arrays are formed.

The triangular template **10** has been employed (Scheme 5) by the Sanders group[35] to coordinate Ru-containing porphyrin monomers **9** and to promote the formation of a cyclic porphyrin trimer [**11**⊃**10**]. While the template

Scheme 5. Formation of a Trimeric Porphyrin Metal Complex from the Precursor 9 and a Multivalent Template 10



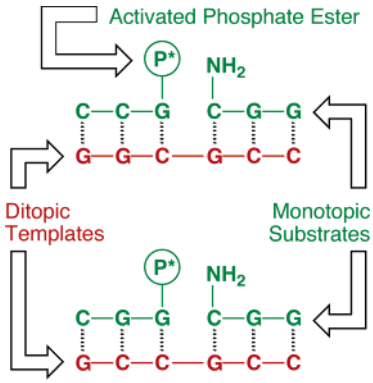
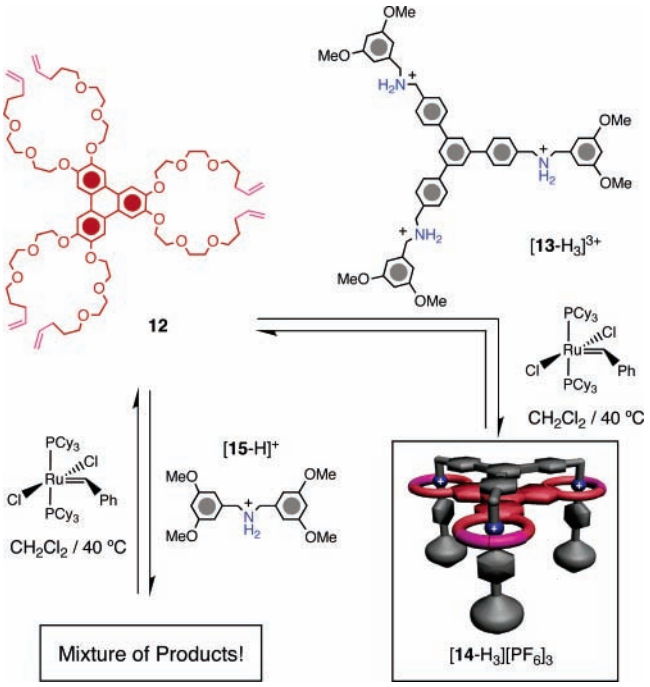


FIGURE 4. Self-replicating and autocatalytic systems based on the recognition between cytosine (C) and guanine (G).

coordinates the Ru ions from inside the macroring, the CO ligands occupy the outside, opposite the template. In the absence of a templating molecule, a mixture of dimers, trimers, and tetramers with Ru atoms coordinated by CO occupying the interior and exterior positions of the cavity were observed. While **10** acted as a template, imparting selectivity during the reaction, the combined strength of the three Ru−N bonds in the trivalent interaction prevented the removal of the template from the cyclic trimer. Nevertheless, it has been possible to reduce the strength of the multivalent interaction between the porphyrin receptor and **10** by templating a mixed-metal porphyrin trimer containing one Ru and two Zn metal centers, taking advantage of the weaker Zn−N bonds to allow the removal of the template from the supermolecule. This phenomenon, where multivalent templates afford selectivity but bind more strongly than desired to the templated product has been dubbed[36] "product inhibition" in synthetic self-replicating and autocatalytic systems. Many groups have investigated receptors that can catalyze bond-making reactions by forming superstructures, which convert an intermolecular reaction into an intramolecular one (as in an artificial enzyme). For example, cross catalytic and self-replicating systems designed (Figure 4) by Sievers and von Kiedrowski[37] use nucleotide base-pair recognition to template the formation of hexanucleotide analogues. The ditopic templates bind two monotopic substrates through a network of hydrogen bonds to orient them correctly into place while phosphoramidate formation occurs. While the templates accelerate the initial rate of production of their corresponding partners selectively, these systems are plagued by product inhibition. The excellent selectivity afforded by using a multivalent template is accompanied by a stronger binding of the product dimer to the template than the initial monomeric components. Thus, to create a truly effective self-replicating or autocatalytic system, product inhibition needs to be minimized.

With the increased interest in dynamic covalent chemistry,[38] it occurred to us that multivalency could be the perfect phenomenon to be probed in this context. Ring-closing metathesis (RCM) and ring-opening, ring-closing metathesis (RORCM), both operating under equilibrium control[39] and mediated by ruthenium alkylidene catalysts, were used[40] in the formation (Scheme 6) of mechanically

Scheme 6. Formation of an Interlocked Molecular Bundle, $[14\text{-}H_3]^{3+}$, Using Reversible Ring-Closing Metathesis



interlocked bundles incorporating a multivalent template. When a mixture of the trivalent trisammonium trication $[\mathbf{13}\text{-}H_3]^{3+}$ and the triphenylene hexaolefin **12** was subjected to RCM using $(PCy_3)_2(Cl)_2Ru{=}CHPh$, the formation of $[\mathbf{14}\text{-}H_3][PF_6]_3$, containing C=C double bonds with both (*E*) and (*Z*) configurations and averaged C_{3v} symmetry, was almost quantitative. This close-on quantitative production of $[\mathbf{14}\text{-}H_3][PF_6]_3$ is presumably a result of the build-up of concerted binding interactions resulting from the three productive RCMs that give rise to the multivalency that characterizes the thermodynamically more stable product. When the triphenylene hexaolefin **12** was subjected to RCM with and without the monovalent template $[\mathbf{15}\text{-}H][PF_6]$ using $(PCy_3)_2(Cl)_2Ru{=}CHPh$ catalyst, none of the desired triply interlocked superbundle was observed. This observation arises from the fact that numerous potential products can be formed by RCM from the triphenylene hexaolefin in the absence of a template. Formation of a tris-crown ether by the monovalent template to give a four-component molecular bundle would meet with a small gain in enthalpy, which is most likely swamped by a considerable loss in entropy. Based on these results and the fact that the multivalency effect is primarily a thermodynamic one, it seems entirely reasonable that multivalent sites between two or more components can be created spontaneously in situ by dynamic covalent chemistry,[38] a concept wherein reactivity is expressed in a thermodynamic fashion.

Metallosupramolecular chemistry has also provided many examples of container molecules composed of multivalent ligands binding metal ions leading to a variety of supramolecular architectures including cages,[41] macrocycles,[3] and, recently, the Borromean rings.[42] Multivalent metal−ligand interactions have also been used[16] to assemble well-defined supramolecular arrays, which are reminiscent of the proteins in nature that interact multivalently with carbohydrates to form supramolecular entities.[43] Transition metal atoms provide single points at which a multivalent interaction with one or more ligands, conferring control over the directionality and strength of the interaction, is operative. Increasingly complex architectures, such as the Raymond group's chiral cage compound **16**, have been synthesized (Figure 5) by self-assembly.[44] The nanovessel **16**, comprised of octahedrally coordinated Ga^{3+} ions in a tetrahedral arrangement bound by ditopic 1,5-bis(2,3-dihydroxy-benzamido)naphthalene) ligands encapsulates guest molecules, such as tetra-

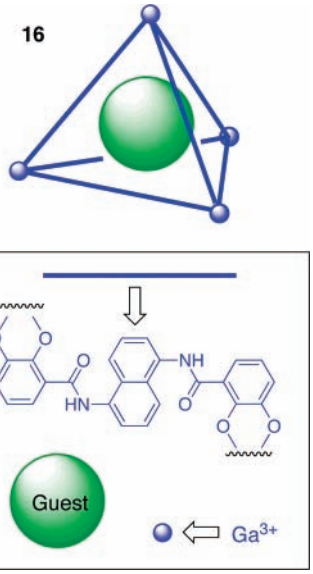


FIGURE 5. A tetrahedral nanovessel **16** containing Ga^{3+} ions, each coordinated octahedrally by a divalent ligand.

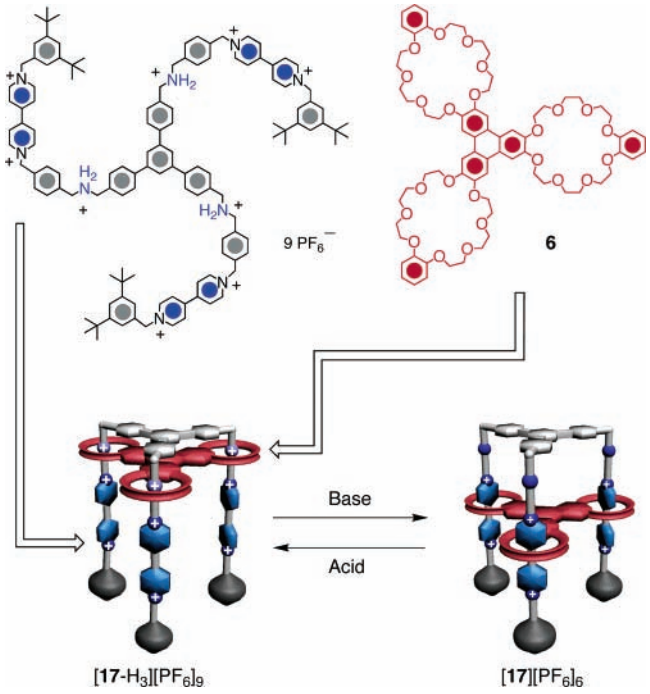


FIGURE 6. Controlling the movements of a molecular elevator between $[\mathbf{17}]^{6+}$ and $[\mathbf{17}\text{-}H_3]^{9+}$ with acid and base.

methylammonium ions. The cage can be isolated as a single stereoisomer that recognizes chiral guests such as Cp*Ru(2-ethylbutadiene)(H_2O).

One of the simplest multivalent ligands, the metal chelate ethylenediaminetetraacetic acid (EDTA) with its four carboxylates and two amino groups participating in binding has been investigated by chemists for over half a century. Recently, Toone et al.[45] have shown that the enhancement of binding with increasing valency is enthalpic in origin.

Multivalency in Nanoscale Architectures and Machines

The structures and working mechanisms of molecular machines encountered in the natural world have only been elucidated in a very few cases.[46] A bottom-up self-assembly approach to building artificial molecular machines by mimicking their natural counterparts is a daunting task, and efforts toward the study of simple molecules that can perform operations controlled by external stimuli has attracted considerable interest.[17,18]

Investigations on the expressions of multivalency in supramolecular systems have inspired[47] us to use this phenomenon as the foundation to proceed on to a mechanically interlocked compound, for example, [**17**-H_3]-[PF_6]$_9$, which can behave (Figure 6) like a nanometer-scale elevator. In addition, two-station [2]rotaxanes, prototypes for the construction of linear motors operated by redox, acid−base, and photochemical stimulations, have also provided the impetus for the preparation of [**17**-H_3][PF_6]$_9$. This nanoactuator consists of a trifurcated rig-like component containing two different "notches", namely, NH_2^+ and bipyridinium ($BIPY^{2+}$) centers, at different "levels" along each of its three "legs" that are interlocked by a tritopic crown ether "platform" made up of "loops" in the form of three B24C8 macrocycles fused trigonally to a central triphenylene "floor". By the use of acid−base chemistry, it can be made to "stop" at the two different levels. The three legs of the rig carry bulky 3,5-di-*tert*-benzyl "feet", which prevent the loss of the platform. ^{1}H NMR, UV−vis, and fluorescence spectroscopies, together with electrochemical measurements, all indicate that [**17**-H_3][PF_6]$_9$ is a triply threaded, mechanically interlocked molecule of C_{3v} symmetry, the preferred binding being that of the three crown ether loops of the platform with the three NH_2^+ centers on the legs of the rig. Addition of 3 equiv of a strong nonnucleophilic phosphazene base to a CD_3CN solution of the elevator caused the crown ether platform to move "down" to the $BIPY^{2+}$ "notch", as evidenced by ^{1}H NMR and fluorescence spectroscopies and electrochemical measurements. Subsequent addition of an excess of trifluoroacetic acid to a previously deprotonated sample completely restored the initial spectroscopic and redox properties, that is, the elevator goes back to the upper level. The incremental addition of a phosphazene base to the elevator (from 0 to 3.5 mol equiv) was followed using UV−vis spectroscopy, and the results revealed three distinct steps that followed the deprotonation processes. They correspond to the stepwise displacement of the three B24C8 "loops" of the platform from their initial positions encircling NH_2^+ "notches" to those where they encircle $BIPY^{2+}$ "notches". The observed one-at-a-time mechanism demonstrates that the switching, within a molecularly constrained environment, is ex-

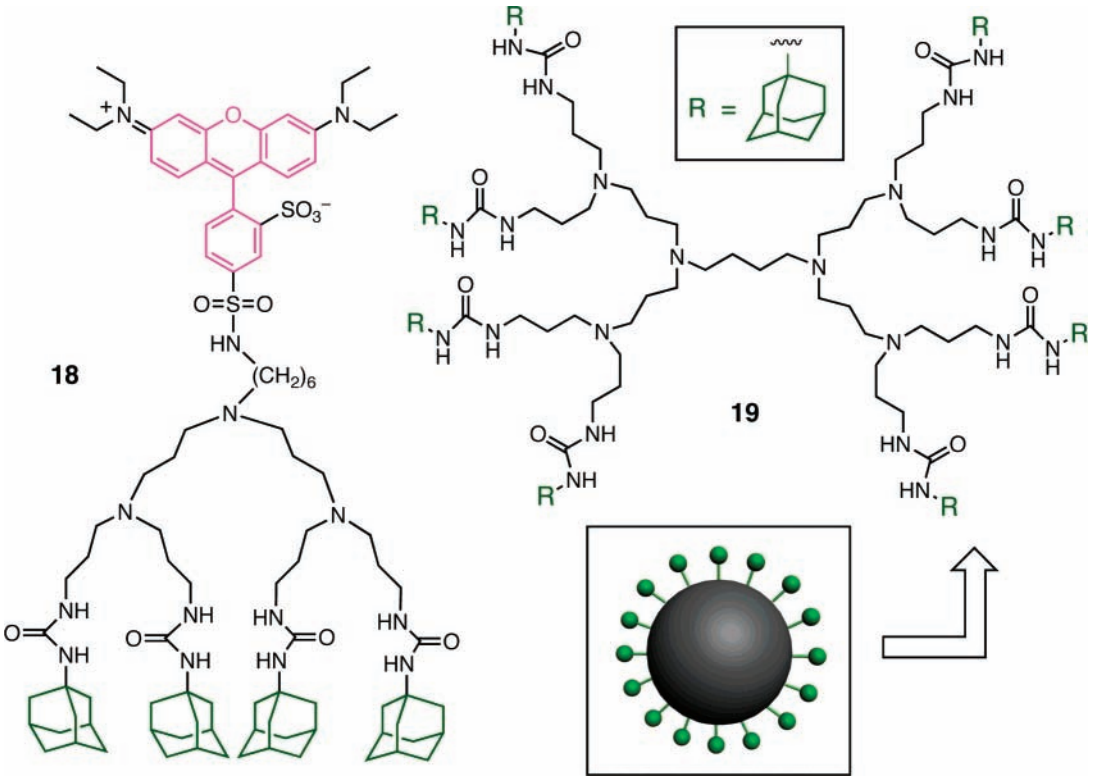


FIGURE 7. The multivalent fluorescent dendron **18** and the dendrimer **19** for binding to surfaces containing a monolayer of β-CDs.

pressed in series rather than in parallel. From a mechanistic standpoint, multivalency is intuitively assumed to be a stepwise process, and importantly, this artificial model system provides support for it. Harnessing multivalency in building artificial molecular machines has proven itself in the making and workings of the molecular elevator. The design of more sophisticated and practical nanosized molecular machines is ongoing.

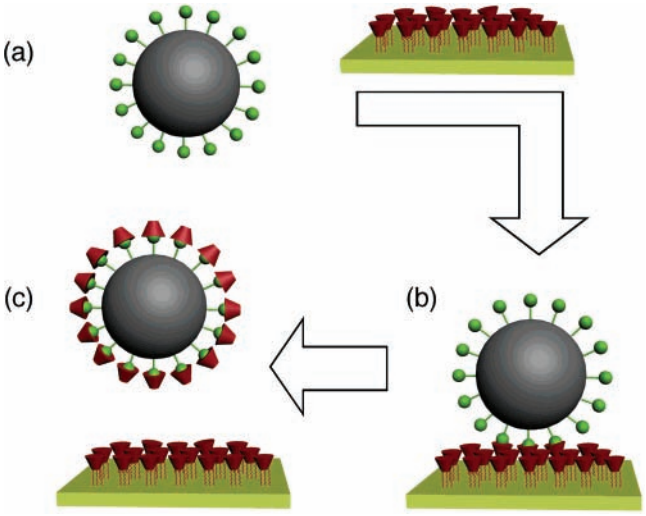


FIGURE 8. Proposed mode of interaction between the dendrimer **19** and a monolayer of β-CDs (a). Although the dendrimer interacts with the surface multivalently (b), in the presence of excess of β-CD, **19** can be removed from the surface (c) with all the adamantyl groups bound by β-CDs.

An important component of nanoengineering is the ability to fabricate and integrate devices on surfaces. While current technologies rely on the fabrication of devices in a top-down fashion, these methods are reaching their limitations in terms of miniaturization.[48] Consequently, there is an impetus to develop bottom-up approaches to construct nanoscale devices. Indeed, it has been demonstrated[49−51] recently that multivalency may be useful in the fabrication of devices. Reinhoudt and co-workers[50] have taken the inherently weak interaction between a single cyclodextrin and its hydrophobic ligand and incorporated it (Figures 7 and 8) into higher affinity multivalent interactions at a surface. Gold and silicon oxide surfaces were coated with a self-assembled monolayer of β-CD derivatives creating a multivalent surface, which can anchor molecules bearing multiple complementary ligands by noncovalent interactions to create a "molecular printboard". The adamantyl-bearing tetravalent dendron **18** and fifth generation dendrimer **19** were patterned onto a β-CD-coated surface using microcontact printing[52] and dip-pen nanolithography.[53] These approaches, capable of creating line patterns with 100 nm resolution, provide a versatile means of nanofabrication with the added feature that the patterns can be erased by rinsing the surface with 10 mM β-CD to compete for the multivalent interactions at the surface. Moreover, the Reinhoudt group[49] has demonstrated that dendrimers bearing multiple ferrocenyl units at the periphery also interact noncovalently with the surface, an observation that opens the possibility of using electrochemical means to control surface interactions. These systems also provide[54] a model for investigating the concept of multivalency at interfaces, a consideration that is pertinent to the life sciences since so many multivalent interactions take place at cell surfaces.

Conclusions

Synthetic multivalent architectures, using noncovalent bonding interactions as the supramolecular "glue", provide (1) well-defined systems for studying the concept of multivalency in nature and (2) building blocks for constructing nanoscale materials. By use of ligands and receptors bound to a conformationally rigid scaffold, whether it is an aromatic ring or a gold surface, multivalency can be harnessed to organize molecules into functioning materials. Self-assembly using multivalent interactions has become an important component[55] of supramolecular synthesis. It will become of paramount importance as we seek to create architectures of even greater complexity.

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