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Nanostructural Architectures from Molecular Building Blocks

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16.1 Introduction

The concept of a *molecular building block* (MBB) has been used prominently in describing a particular application of small molecules in the design of macromolecules, such as biomolecules, supramolecular structures, molecular crystal lattices, and some forms of polymeric materials. It is also common to refer to MBBs as "molecular subunits, modular building blocks,[1,2] or synthons, which have been defined as structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions."[3] MBBs are, therefore, the structural intermediates between atoms, the most basic of all building units, and macromolecules or extended arrays, of which the MBBs are the common structural element. While many MBB approaches are not directed toward the design of nanostructures or nanoscale materials, all share the same design considerations and are consistent with the criteria used to distinguish the MBB approaches considered here from other nanoscale fabrication techniques.

The fabrication of any structure or material from building blocks requires that the design strategy meet specific criteria. First, relying on a building block as the basis of a fabrication process indicates that this starting material is not the smallest possible component from which the manufacturing process can proceed, but it is itself pre-assembled from more fundamental materials for the purpose of simplifying the building process. It is assumed that the subunit, as a prefabricated structure, has been engineered with an important function in the assembly process of a larger, more complex structure. Second, it is assumed that a means to subunit interconnectivity has been considered in the design process. The method

of connectivity between subunits may be either intrinsic to the subunit, such as a direct bonding connection between them, or available externally, such as a stabilizing electrostatic force between subunits. Third, it is assumed that the subunit is capable of being positioned correctly and precisely in the fabrication process. Fourth, and perhaps most important from a design perspective, is that the subunit provides an intermediate degree of control in the properties of the larger structure. A fabrication process based upon the manipulation of designed subunits may not provide the ultimate in stability, customizability, or structural detail when compared with the design of a system from the most basic materials, but it certainly offers enough control and flexibility for useful applications.

The defining feature of the MBB approach is the use of a molecular subunit that has incorporated within its covalent framework the means for a directed connectivity between subunits. As the MBB is itself a molecule, its synthesis can be considered among the preparative steps in the overall fabrication process and not necessarily an integral part of the actual supramolecular assembly. If "supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond,"[4] then the individual molecule forms the fundamental component in the design of MBB-based nanostructures. The starting point for the final product is the MBB, and the means to assembling the final product is through manipulation of the MBB. The assembly of a nanostructure can be predicted based upon the covalent framework of the MBB and its assembly-forming features. Because this intermolecular connectivity is an integral part of the design process, the means for controlling subunit–subunit interactions needs to be incorporated early in the design of the nanostructure. The self-assembly or self-directing interactions between subunits are based upon the properties of the MBB. The ability to customize the stability and functionality of the resulting materials is, therefore, based upon MBB modification.

The merits and limitations of building block approaches transcend scale. In all cases, the selection of suitable building materials is dictated by their ability to fit together in a precise and controllable manner. Limitations to a particular design or application are imposed partly by the properties of the subunit and partly by the design itself. While all building block designs suffer from one or more limitations, designs can often be successfully employed for a specific application or in a specific environment. For instance, bricks are ideal building materials for the construction of permanent structures, blocks of ice are appropriate for use in below-freezing conditions, and canvas is ideal for structures that require mobility. One would not select ice as a building material in temperate climates, canvas for arctic conditions, or brickwork for temporary residences. Given a set of environmental conditions and the properties of available materials, certain combinations will invariably make more sense than others. In nanostructure design, the important concerns often include solubility, thermal stability, means to assembly, defect tolerance, error correction capabilities, functionality, and chemical reactivity. Chemical environments and ambient conditions limit the feasibility of certain nanostructures just as they limit the choice of molecular subunits. These same issues are key to synthetic chemistry, where factors such as temperature, solvent, reaction duration, and choice of chemical functionalities will always play key roles in the design of chemical pathways and molecular fabrication processes.

All MBB approaches benefit from the ability to accurately predict intermolecular interactions from conceptual and theoretical treatments. Additionally, a vast synthetic background exists from which to make and modify subunits. Experimental precedent for the basic preparative methodology in a number of naturally occurring and man-made systems form a firm foundation for MBB pathways. Not only are the means to nanostructure fabrication facilitated through theoretical investigations, cognizant design strategies, and even Edisonian efforts, but many examples of macromolecular formation exist currently that provide the means for understanding how molecules can be used to construct supermolecular arrays. Concurrent with the design of new nanostructures from MBB approaches is the continued growth of the field of supramolecular chemistry and an enhanced understanding of molecular phenomena "beyond the molecule."[5]

The emphasis on design in molecular nanotechnology from MBBs connotes a certain deliberation in the choice of materials and the means to assembly. It is, therefore, important to stress efforts to engineer macromolecular assemblies from known molecular systems. This chapter begins with a discussion of the chemical and electrostatic interactions important in macromolecular formation. The discussion of these

interactions as applied to nanostructure formation begins with two limiting cases in MBB design, covalent and electrostatic connectivity. With the formal groundwork of connectivity and some useful boundaries established to focus the discussion, a few important areas of MBB-based nanostructure formation are presented to demonstrate the application of the approach and related issues. This chapter is not meant to be rigorously complete, but instead provides a broad overview of current techniques involving the use of molecules as building components in larger systems.

16.2 Bonding and Connectivity

A structure is of limited value for an application without a means of maintaining its strength and functional integrity over the duration of its anticipated lifetime. At the macroscale, stabilization may come in the form of interlocking parts, mechanical or adhesive fixtures, fusing or melting at connection points between materials, or, in much larger structures, gravity. At the nanoscale, the role of gravity becomes unimportant in the formation of supramolecular assemblies,[6] and nearly all stability comes from electronic interactions. These interactions take forms ranging from strong covalent bonds to weak intermolecular (noncovalent) interactions. All molecular-based nanostructures incorporate various combinations of these interactions to maintain shape and impart function. It is therefore important to understand the range and form of the stabilization energies associated with these interactions and their relationship to the structures that incorporate them.

16.2.1 Covalent Bonding

Of singular importance in synthetic chemistry is the manipulation of the covalent bond. The design of any nanoscale architecture from simpler molecules must first address the design of the covalent framework of the MBB itself. The means to any macromolecular stabilization is a result of the inclusion of chemical functionalities onto this stable framework. The role of covalent bonds in the MBB approach is then twofold. First, these bonds are required within the subunit to provide the structural integrity necessary for the prediction and synthesis of nanostructures from MBB components. Second, covalent bonds may be employed as one of the means for fastening MBBs together into larger structures.

Covalent bonds are formed by the sharing of pairs of electrons between atoms.[7] The most familiar examples of covalent bonding are the connections between carbons in organic molecules. The importance of organic chemistry as a field underscores our desire to understand and modify the covalent framework of carbon-containing molecules for many important applications. Typical covalent bond energies range from 100 to 500 kJ/mol.[8] In the case of multiple bonds between atoms, the total energy may exceed 1000 kJ/mol. While this is a very large range of energies, even the covalent bonds at the low end of the spectrum are rather strong interactions, especially when compared with the noncovalent energies frequently responsible for macromolecular stabilization (*vide infra*). It is because of these large covalent bond strengths that the subunits involved in MBB approaches provide significant internal structural stability and predictability.

Covalent bonding includes a variety of useful motifs in the structural customization of a subunit. The strong σ-bonds, in which a pair of electrons is shared directly along the interatomic axis of two atoms, provide for low-energy rotation in straight-chain molecules and low-energy twisting in closed-ring systems (Figures 16.1A and 16.1B). In organic molecules, σ-bonding plays the initial role of defining the connectivity and general shape of the structure. The formation of π-bonds in molecules involves electrons in atomic orbitals that are not involved in the σ-bonding framework. In such instances, main group atoms involved in the molecular backbone are either sp^2- or sp-hybridized, leaving either one or two p-orbitals through which π-bonding can occur (Figure 16.1C). The π-bonded portion of the molecule is then held planar to maximize p-orbital overlap between atoms. These π-bonds may be delocalized over the entire length of the available π-orbital framework, making them well suited to molecular electronic applications that require both structural stability and electron mobility.[9] Structurally, the π-bonds remove the low-energy rotational freedom from the underlying σ-bond framework. In cases where two π-bonds

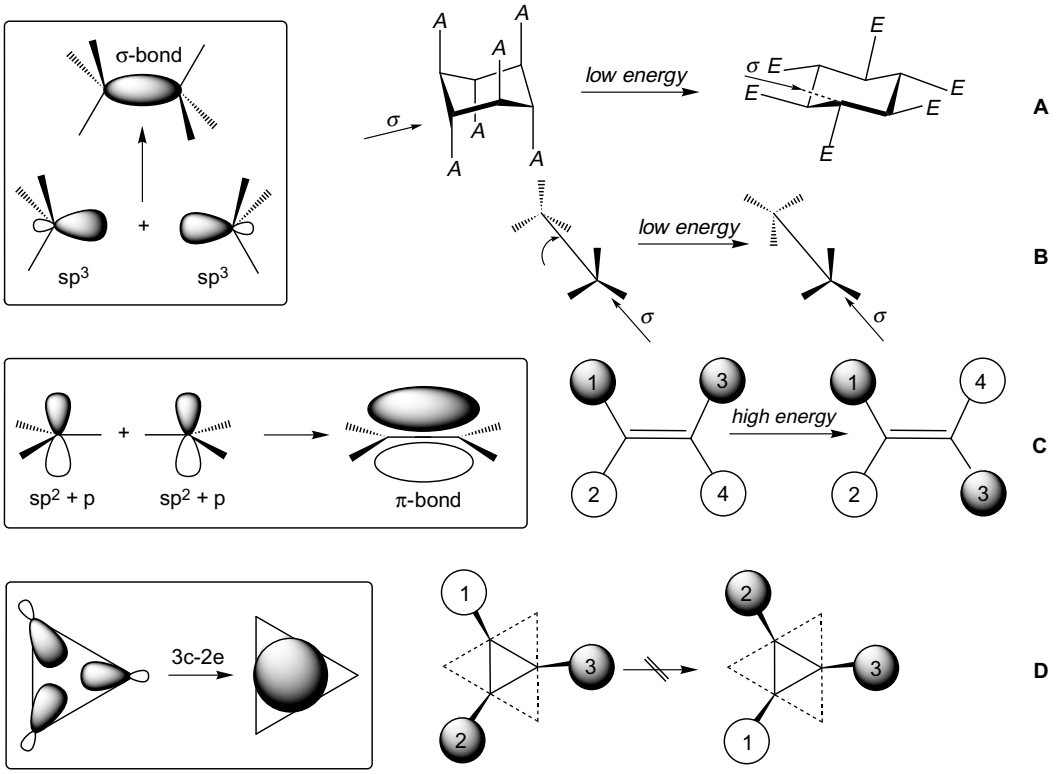

FIGURE 16.1 Rotation in covalent bonds. (A) Ring twisting about a σ-bond (indicated by arrow) with a change in orientation of one set the substituents from axial (A, left) to equatorial (E, right). (B) Free rotation about the σ-bonds in linear chains. (C) High-energy bond breaking is required for rotation about a π-bond. (D) Reorientation of substituents in 3c-2e bonds is highly restricted (extension of cluster framework indicated by dashed lines).

are formed between two adjacent atoms, the resulting π-electron density around the σ-bond is cylindrical, and the molecular fragment behaves as a rigid linear rod.[10] A third motif involves what is often referred to as either *electron deficient* or *three-center-two-electron bonding*. Structural flexibility is fully restricted in three-center-two-electron (3c-2e) bonds. These bonds, observed in main group polyhedra and in many metal clusters, involve three adjacent atoms sharing a single pair of electrons (Figure 16.1D). Molecules employing this mode of bonding are generally three-dimensional, meaning that overall structural flexibility within the molecule is lost due to the cage-like interconnections between atoms. These clusters share some electronic properties with π-bonds, although their delocalized nature is largely limited to their internal skeletal frameworks.[11] As a result, radial bonds from these structures behave very much like typical σ-bonds.

Neglecting the covalent framework of the MBBs and focusing only on the connectivity between subunits, a number of advantages are derived from the application of covalent bonds in nanostructural design. First, intermolecular covalent bonding leads to extremely stable nanostructures. Whereas weaker electrostatic interactions are greatly affected by factors such as temperature and choice of solvent, covalent bonds retain their connectivity until concerted efforts are made to break them. Covalent bonds are, then, structurally dependable, prohibiting the reorganization often observed in the continuous breaking and reforming of the other types of intermolecular interactions. It is this feature that similarly allows the covalent architecture of the subunit to be held constant within the context of the larger nanostructure. Finally, an extensive synthetic precedent also exists for connecting almost any molecular fragment or functional group to another. Where specific types of connections have not been previously addressed, their formation is generally possible by a modification of some other known reaction.

The strength and chemistry of covalent bonding also has some important limitations. First, the strength of these bonds frequently limits the flexibility of larger molecules.[6,10] Weaker electrostatic interactions must be used if motion and structural rearrangement are required. With this greater flexibility in the weaker electrostatic interactions comes a higher degree of error tolerance. An unplanned covalent bond between two subunits in a molecular architecture is difficult to correct, requiring far more intensive efforts than simple thermodynamic manipulation. Structural designs based on covalent bonding must, therefore, be well conceived initially to avoid subsequent problems in the fabrication process. Finally, the use of the covalent bond in nanoscale assembly requires direct chemical manipulation. Consequently, two subunits may be self-directing in the formation of their bond by the choice of functionalities, but they are typically not self-assembling. A chemical workup is generally required to form a covalent bond and, as necessary, isolate a product from a reaction mixture.

16.2.2 Coordination Complexes

Lying between the strong covalent bonds of the smaller main group elements and the variety of noncovalent interactions are the coordination bonds of metal–ligand complexes. The initial descriptions of metal–ligand compounds as *complexes* stems from the ability of metals to coordinate small, electron-donating molecules (ligands) beyond the typical maximum of four-point substitutions possible with many main group elements.[8] Metal complexes are known to exist with the metal coordinated to anywhere from one to 12 ligands, although the vast majority of coordination compounds exist in the four-coordinate to eight-coordinate regime (Figure 16.2). The interest in the properties and applications of metals in discrete molecules has enriched such diverse fields as molecular orbital theory, crystallography, catalysis, molecular electronics, supramolecular chemistry, and medicinal chemistry.[8] The availability of d-orbitals in the transition metals and f-orbitals in the lanthanides and actinides results in an extension of the geometric and structural variety available with main group elements. A well-developed synthetic precedent also provides the means to exploiting this rich structural variety within a single molecule context.[12]

Metal–ligand bonds form either through the covalent association of ligands to pair single electrons in metal orbitals or, most often, through the coordination of paired electrons from ligands to fill the valence shell of the metal. Examples include single-ligand lone-pair/metal bonds (the metal analogue

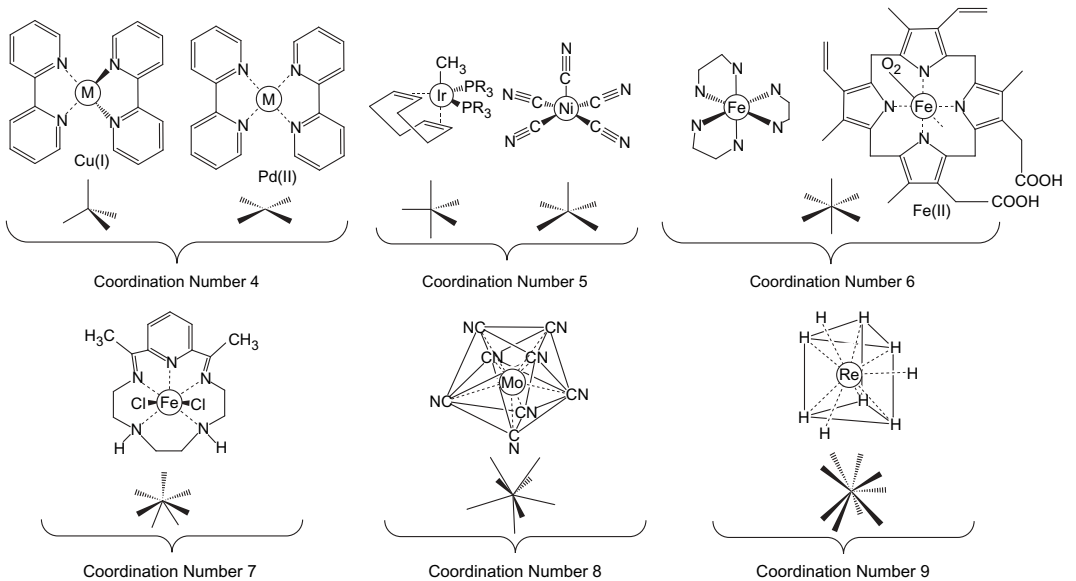

FIGURE 16.2 Examples of coordination geometries among a number of metal complexes.

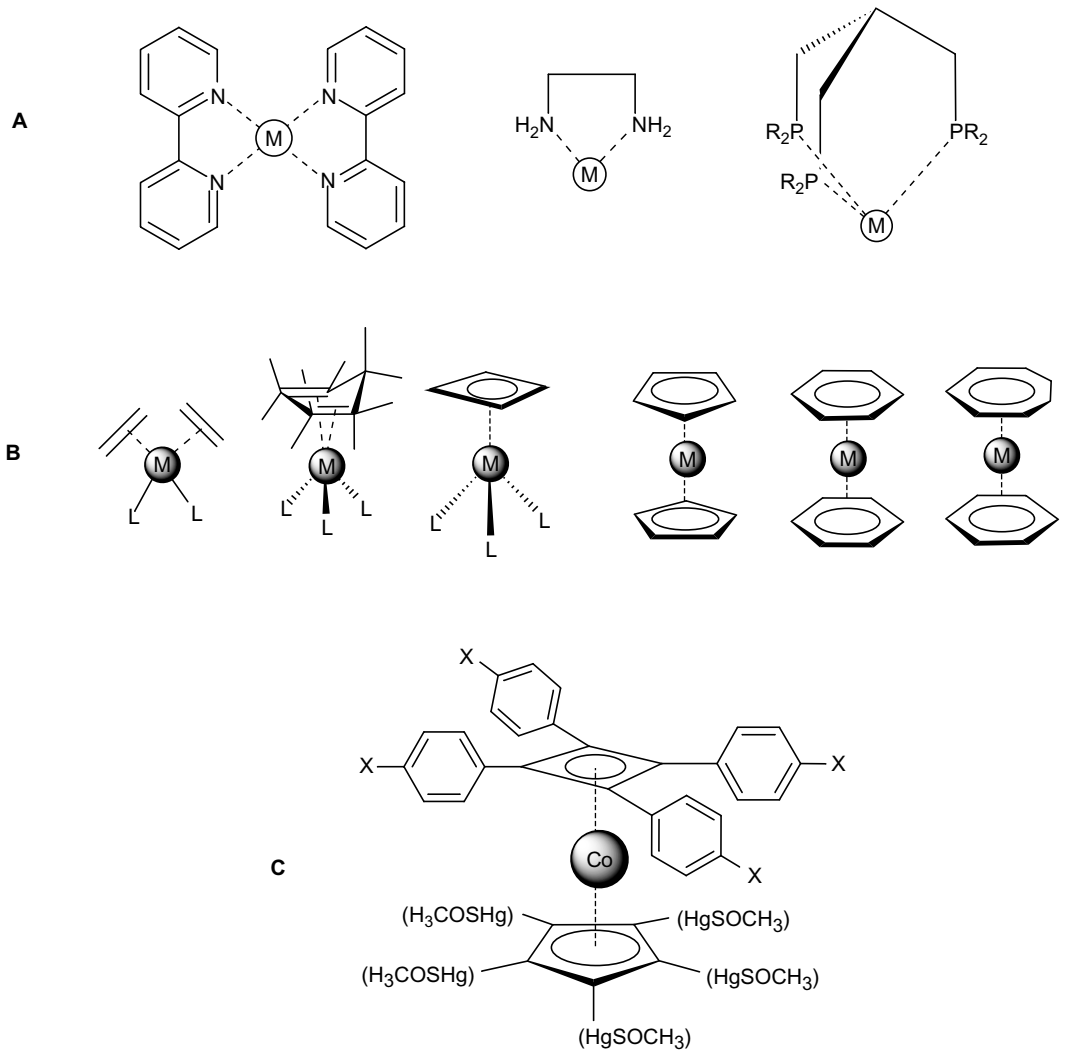

FIGURE 16.3 Metal-ligand bonding. (A) A selection of chelating ligands. (B) Metal–ligand π-interactions including metallocenes. (C) A surface-mounted molecular rotor design.

of a main group σ-bond), chelating ligand bonds (where the ligand is coordinated to the metal by more than one pair of electrons (Figure 16.3A), and metal–ligand π bonds (Figure 16.3B). The low-energy *sharing* of pairs of electrons arises from the coordination sphere of the metal, which can readily accommodate the available electron pairs. Metal–ligand bonds are usually far stronger than other electrostatic interactions because they involve the sharing of pairs of electrons through direct orbital interactions, yet they are generally weaker than the covalent bonds found in organic compounds. To specifically address issues of connectivity, the extensive use of lone-pair coordination to saturate the valence shells of many of the metals adds electron density well in excess of the nuclear charge, pushing the limits of the ability of some metal nuclei to fully accommodate all of the required electrons. Also, the majority of coordinating ligands are stable molecules, and any intermolecular destabilization is typically directed first to the weaker metal–ligand bond. Finally, the molecular volume of the ligand can have a significant effect on the stability of the metal–ligand bond in cases where the metal has a high coordination number, requiring many lone pairs to saturate its valence shell. This last feature of steric saturation is of primary importance in rare earth complexes. In these compounds, orbital

interactions between the metal and ligand are significantly attenuated; and stabilization arises primarily from charge balance and steric saturation of the metal center.

A series of metal–ligand coordination complexes are shown in Figure 16.2 to demonstrate some of the structural variety available from metal coordination. Ligand lone-pair coordination is essentially σ-bonding; and the properties of these bonds are consistent with σ-bonding in organic frameworks, including low barriers to rotation and geometric predictability. One special subset of these lone-pair ligands is the chelating ligands, which coordinate to a single metal center through two or more lone-pair donors on the same ligand (Figure 16.3). This class of ligands, driven to higher metal coordination number through entropic effects[8] has a significant role in the design of nanostructures from coordination-based approaches (*vide infra*).

An important case of metal–ligand π-coordination occurs in the metallocenes, where the entire π-system of an organic ring can be coordinated to the metal center[13] (Figure 16.3B). The most familiar of these systems is the neutral ferrocene, which saturates an iron(II) center by the coordination of two five-member aromatic cyclopentadienyl rings ($[C_5H_5]^-$). In the design of some of the smallest functional nanostructures, such π-coordinated molecules have distinct advantages, including (1) high stability, (2) incorporation of organic frameworks with the potential to substitute onto the framework, and (3) very low barriers to rotation about the axis of the metal and ring center. Small, surface-mounted metal-ring compounds have already been demonstrated as potential systems for molecular rotors[14] (Figure 16.3C).

Metal–ligand bonds, as the intermediary between main group covalent bonding and weaker electrostatic interactions, are well suited to the fabrication of many types of macromolecules and nanoscale arrays. First among their advantages are the higher coordination numbers of these atoms. While a single nonmetallic main group atom generally provides the structural flexibility required to link together from one to four substituents, main group molecules are required to achieve higher connectivity. Instead of designing a six-coordinate center from the smallest molecular octahedron, *closo*-$[B_6H_6]^{-2}$, single-metal atoms readily perform the same task (Figure 16.2). A second advantage of metal-based structures is the number of available metals from which to choose, both for structural complexity and functionality. With this large selection of metal atoms also comes an extensive synthetic precedent,[8,12] allowing the selection of a particular coordination geometry for its known structural features, stability, and chemical accessibility. In instances where lone-pair coordination is used to saturate the valence shell of a metal, the required chemical manipulation is typically too mild to affect the covalent structure of the ligand. Furthermore, because ligands coordinate through weaker bonds, they are also often thermally and photochemically labile under moderate conditions. This ability to form stable structures by thermodynamic or photolytic methods, however, also carries with it the disadvantage of having to control the environment carefully in order to maintain the structural integrity of the final products.

16.2.3 Dative Bonds

A dative bond is an intermolecular interaction between a lone pair of electrons on one atom and a vacant, atom-centered orbital on another. These bonds behave as covalent σ-bonds in many respects, making them close analogs to metal–ligand coordinate bonds (the distinction is made here by limiting dative bonding to main group–main group or metal–metal interactions).[15] While a lone pair of electrons and two atom centers are involved, these interactions are relatively weak when compared with the covalent bonding of the main group elements. The molecules involved in these bonds are themselves independently stable species. The strength of the dative bond is determined by several factors, all of which provide their own means to customization depending on the application.

Dative bonds are most common among pairs of molecules incorporating Group III(13) and Group V(15) atoms.[16] In such cases, the formation of a dative bond requires the presence of the Group III atom, where an empty orbital remains after the σ-bonds are formed from the three available valence electrons (Figure 16.4). Elements including and beyond Group V usually have at least one lone pair available for donation in bond formation. Dative structures are classic examples of Lewis acids and bases,[17] in which the lone-pair donor is the Lewis base and the lone-pair acceptor is the Lewis acid. Among the strongest and most

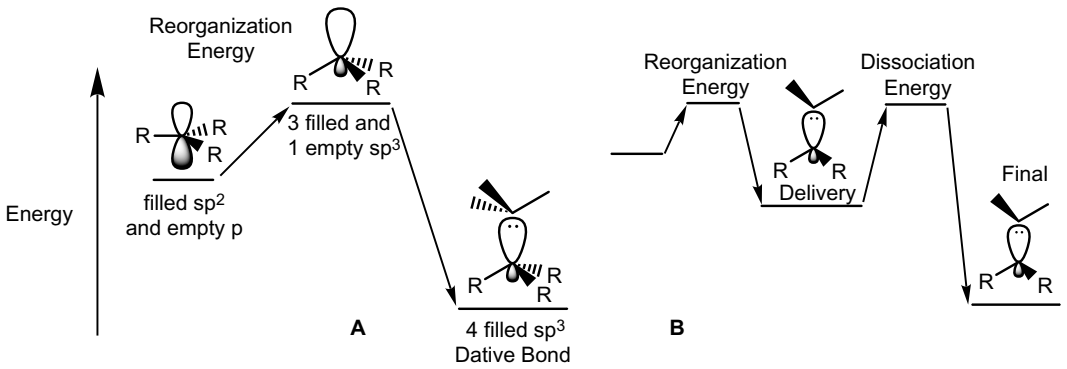

FIGURE 16.4 Dative bonding in main group elements. (A) General pathway for dative bond formation. (B) Energetic considerations of dative bond acceptor "delivery" pathway.

studied dative bonds are those between boron (Group III) and nitrogen (Group V) in cases where the boron is treated as an electron precise (2c-2e) atom.[16] The formation of the three electron precise σ-bonds to boron results in the molecule adopting a trigonal planar conformation, leaving an unoccupied p-orbital to act as an electron pair acceptor (Figure 16.4A). The coupling of an atom with a lone pair of electrons to boron results in a reorganization of the boron center,[18] causing it to change shape and hybridization from trigonal planar (sp^2) to tetrahedral (sp^3). The stability of a dative bond is then dependent upon (1) the choice of lone-pair donor and acceptor, (2) the substituents on the donor and acceptor, and (3) the reorganization energy. These bonds typically range from 50 to 85 kJ/mol, although some have been shown to have bond strengths of 100 kJ/mol.[16] In small systems, such as $H_3B{:}NH_3$ and $F_3B{:}NH_3$, the stabilizing energy is large because there is very little steric congestion from the substituents. Among the systems with significant steric congestion, boraadamantane forms uniquely stable dative structures (Figure 16.5).[18] In boraadamantane, the adamantyl framework forces the boron to be sp^3-hybridized regardless of the presence of a lone-pair donor. The reorganization energy is effectively included in the synthesis of the boraadamantane Lewis acid, leaving the entirety of the lone-pair interaction to form a particularly stable dative bond.[18] Dative bonds provide the directionality of covalent bonds with the lower stabilization energy of electrostatic interactions, giving them useful features for nanoscale design. Dative-based molecular assemblies require the selection of building blocks that limit the lone pairs and vacant orbitals to structurally important sites.[19] The design of connectivity is then a matter of limiting dative bonding everywhere else in the subunits. In organic molecules, incorporating the dative components into the "correct" structural sites on the molecule and including only C-H bonds everywhere else effectively accomplishes this. While the chemistry of organoboron compounds might not be as well developed as that of organonitrogen compounds, a considerable synthetic precedent exists for both. The inclusion of active centers for dative design is possible through the addition of many known organic components. The strength of dative bonds can also be tailored by either changing the donor and acceptor substituents or by changing the initial hybridization of the electron pair acceptor.[16]

The limitations of the dative bond approach stem primarily from the lone-pair acceptor. While the lone-pair donor is often unreactive, lone-pair acceptors, such as the many organoboron compounds, are

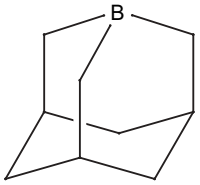

FIGURE 16.5 Boraadamantane.

highly electrophilic and will coordinate with any available electron pairs. Part of the design of these systems must include potential problems with *delivery* to the donor (Figure 16.4B). When a *delivery molecule* is required initially to coordinate to the acceptor prior to assembly, this molecule must be chosen to be more stable than any possible lone-pair donors in solution, yet weakly coordinating enough such that the delivery molecule is easily displaced from the system during assembly. In some instances, the selection of a good delivery molecule can be nontrivial, since an effective choice involves the subtle interplay between the strength of the delivery–acceptor and the final donor–acceptor bond strengths.

16.2.4 π-Interactions

The variety of electrostatic interactions involving the π-systems of aromatic molecules have been shown to play important roles in such diverse areas as the packing of molecules in molecular crystals, the base stacking (as opposed to base pairing) interactions in DNA, polymer chemistry, the structure and reactivity of many organometallic complexes, and the formation, shapes, and function of proteins.[20] The accessible and highly delocalized pool of electrons above and below an aromatic molecular plane is well suited to forming electrostatic interactions with cations, neutral molecular pairs with complementary electron density differences, and other aromatic π-molecular systems.

Because π-systems may be thought of as regions of approachable electron density, noncovalent interactions with aromatic rings occur when a system with a net-positive region is brought within proximity of the aromatic molecule. Three of the most familiar types of π-interactions are (1) aromatic ring/electrophile interactions, where the electrophile is highly positive, (2) phenyl/perfluorophenyl interactions, where the electronegativities of the σ-bond periphery have an overall affect on the charge distribution of the molecule, and (3) lower energy quadrupolar interactions, where weak π-interactions occur based on electron density differences across the molecular plane (Figure 16.6).

Cation-π interactions have long been known to play important roles in molecular recognition, biochemical processes, and catalysis.[21] The most familiar cations used to study these interactions are Group $I^{(1)}$ elements and small protonated Lewis bases (such as NR_4^+). The binding energies of these pairs can be quite large, with the strongest interactions approaching the strengths of weak covalent bonds.[21] Important to the nature of these interactions is the ability of the aromatic rings to compete successfully with polar solvents for the cation. Remarkably, the π-system of the nonpolar benzene molecule has been shown to bind K^+ ions more strongly than the oxygen lone pairs in water.[22] The customization of the cation-π binding energy can be controlled by the choice of Group $I^{(1)}$ cation or the substitutions on the molecular cations, where bulky substituents tend to lower the stabilization by forcing the cation further from the π-system.

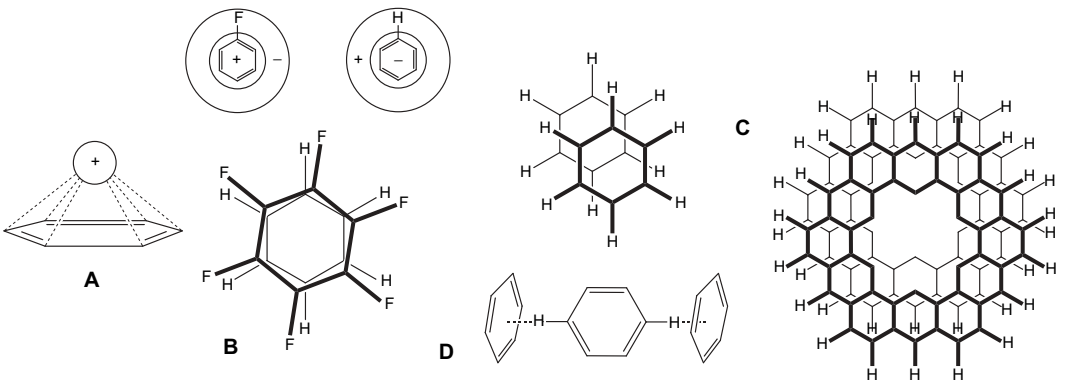

FIGURE 16.6 A selection of π-interactions. (A) π-cation interactions. (B) Ideal π-stacking arrangement of benzene/perfluorobenzene. (C) Staggered π-stacking in benzene (left) and kekulene (right). (D) Preferred herringbone π-stacking configuration of benzene, with hydrogen atoms centered on the π-system of adjacent benzene rings.

Benzene/hexafluorobenzene stacking is a specific example of the general type of π-stabilization that occurs with the pairing of molecules that have large quadrupole moments of opposite sign.[23] In benzene, the regions of highest electron density are the π-system and σ-system of the carbons, leaving the peripheral hydrogen atoms net-positive from inductive effects (Figure 16.6B). In hexafluorobenzene, the charge density is reversed, with the peripheral fluorine atoms containing the highest electron density. Together, the molecular pair is ideally suited for stacking due to the complementary arrangement of their electron densities inside the rings and along the outer periphery of the two molecules. In a classic study of this form of π-stacking, one equivalent of benzene (m.p. 5.5°C) was combined with one equivalent of hexafluorobenzene (m.p. 4°C) to form a mixture with a melting point of 24°C.[24] The actual stacking of these rings was subsequently confirmed by a variety of spectroscopic methods.[25] This same stabilization has been used successfully in the formation of other π-stacking species[26] to align various arenes in molecular crystals, providing a facile means for molecular alignment of thermal and photochemical polymerization reactions.[27]

There are many other important examples and structural motifs in π-stabilizing interactions. These include the stacking of DNA base pairs, the stabilization of tertiary structures in proteins, the aggregation of large porphyrins, and the formation of molecular crystals incorporating aromatic moieties.[20] In benzene and kekulene, for example, stacked structures are most stable when slightly offset, maximizing the overlap of the net-positive periphery and the electron-rich π-system (Figure 16.6C).[20] The offset stacking of the purine and pyrimidine base pairs in DNA plays an important function in stabilizing the double helix. Benzene and many other aromatic systems crystallize as herringbone-shaped structures, with the peripheral hydrogen atom on one ring placed along the central axis of the π-system of a perpendicular ring (Figure 16.6D).[23]

The variety of π-interaction types and structural motifs available among the aromatic rings leads to a number of important features for nanoscale design. First, the π-orbitals exist above and below the molecular plane. An interaction with a π-system is, therefore, often just as likely to occur above the molecular plane as below, allowing these stacking interactions to occur over long distances with many repeating units. For example, crystals of benzene/hexafluorobenzene and the extended π-stacking arrangement in base pairs in a single strand of DNA provide considerable electrostatic stability and alignment. Second, the stability of a π-interaction can be directly controlled by the chemical substituents attached to the ring. The significant change in the properties of benzene/hexafluorobenzene solutions attest to this chemical flexibility.[24] Aromatic heterocycles, such as the purines and pyrimidines in DNA nucleotides, demonstrate the ability to customize these interactions based on directly changing the π-system through hetero-atom substitution. Third, depending upon the surroundings, the π-interactions can be modified by solvent effects. This is demonstrated in the base stacking of DNA, where the stability from heterocycle π-stacking interactions is in addition to the stability gained from minimizing the surface area of the rings exposed to the aqueous environment. Similar arguments have been used to describe the formation of tertiary structure and aggregation of proteins.[20,28] The use of these types of interactions for designing nanostructures is limited, however, by the relatively unpredictable stacking arrangements observed and the sizes of these complex aromatic rings. Stability from aromatic π-stacking requires the use of rings which, when compared to the more direct hydrogen bond or metal–ligand coordination bond, need a larger space and more flexibility to allow for the optimized stacking arrangement to occur.

16.2.5 Hydrogen Bonds

Hydrogen bonding is "the most reliable directional interaction in supramolecular chemistry,"[3] and its role in numerous macromolecular phenomena has been well studied. As a frequently employed electrostatic interaction with vast synthetic and theoretical precedent, a rigorous analysis of this interaction in its many forms is beyond the scope of this discussion on nanoscale design and is left to significantly more detailed treatments in many excellent reviews.[29,30] Important to understanding this type of interaction from a nanoscale design perspective, however, is the nature of the bond, the functional groups responsible for its occurrence, and the relative stabilities that come with different functional groups. Appropriately, these topics are covered here in general with specific examples used to highlight the discussion.

A hydrogen bond is formed when the hydrogen in a polar bond approaches the lone pair of electrons on an ion or atom.[8] A polar bond to hydrogen occurs when the hydrogen is attached to an atom of high electronegativity, such as nitrogen, oxygen, or fluorine. Because hydrogen atoms have no inner core of electrons, the pull of electron density from them exposes a significant positive nuclear charge to interact electrostatically with nearby electron density. This is further strengthened by the very small size of the hydrogen atom. The electronegativity difference between carbon and hydrogen is small enough that a significant dipole is not produced, resulting in very weak hydrogen bonds involving C-H bonds. The strength of the hydrogen bond is determined by the polarity of the bond in which the hydrogen is covalently bound and the electronegativity of the atom to which the hydrogen is electrostatically attracted. Hydrogen bonds can be divided into *strong* (20–40 kJ/mol) and *weak* (2–20 kJ/mol) interactions,[3] each of which is important to certain types of supramolecular assembly.

Hydrogen bonds can be used to stabilize structures ranging from small dimers to extended arrays of massive molecules. The most commonly encountered strong molecular hydrogen bonds tend to favor the use of oxygen or nitrogen, a result of their large electronegativity differences with hydrogen. Also important for MBB assembly is the ability of oxygen and nitrogen to covalently bond to more than one atom, allowing them to be incorporated into larger molecular frameworks. This is in contrast with fluorine, which can only be used to terminate a covalent framework, making its role in typical hydrogen-bonded nanostructures rather limited. There are numerous combinations of hydrogen bonding interactions that can be incorporated into a covalent framework from the available organic precedent for the manipulation of functional groups such as O-H, C = O, N-H, C = N, COOH, NH_2, and NOO^- (Figure 16.7A). Weak hydrogen bonds have also been shown to play important roles in the shapes and stabilities

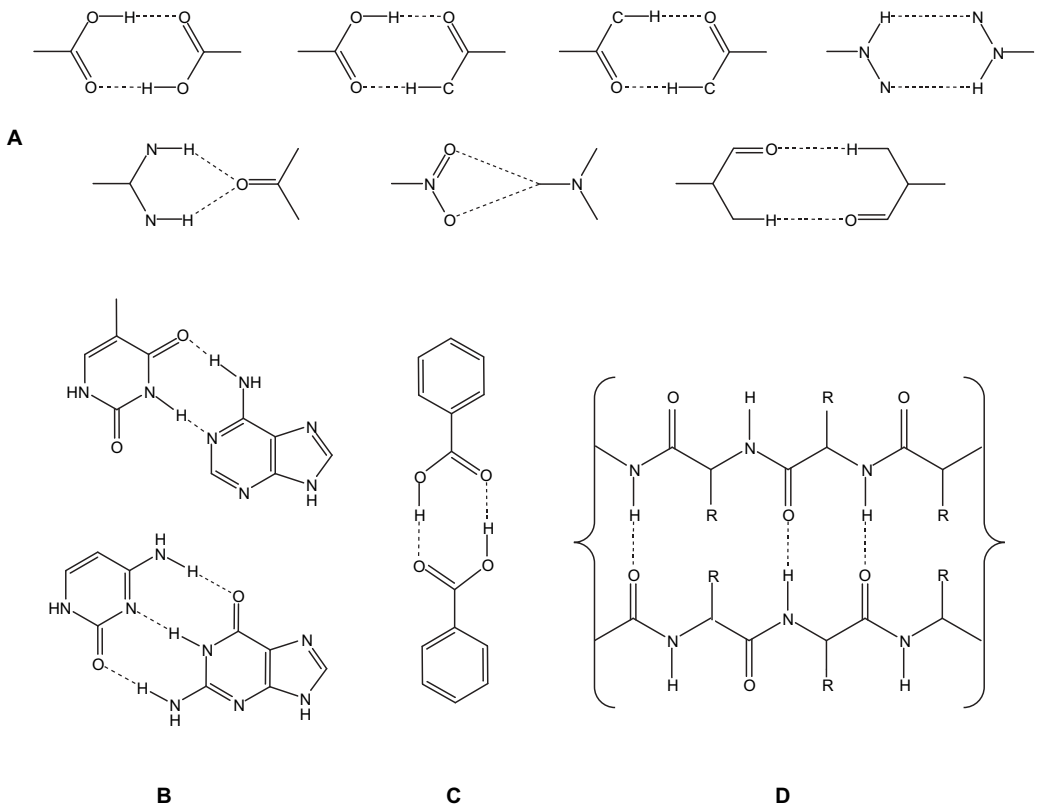

FIGURE 16.7 Hydrogen bonded structures. (A) A selection of hydrogen-bonded structures. (B) Thymine–adenine (top) and cytosine–guanine (bottom) base pairing. (C) Hydrogen-bonded carboxylate dimer. (D) Portion of hydrogen bonding network in peptide β-sheets.

of macromolecular assemblies and crystals that do not include functional groups capable of strong hydrogen bonds.[31,32] These weaker bonds include interactions such as OH···π and NH···π.

A small selection of relevant hydrogen-bonded complexes is provided in Figures 16.7B through 16.7D. The most familiar hydrogen-bonding interaction, outside of ice crystals, occurs in the nucleotide base pairs of DNA, where strongly bonding functional groups are incorporated into small, aromatic heterocycles. The bonds form so as to stabilize particular pairs (thymine/adenine and cytosine/guanine) in the formation of the double-helical structure. Strong hydrogen bonding also occurs between the C=O and N-H groups of amino acids in the formation of the secondary structure of proteins (i.e., α-helices and β-sheets). Artificial superstructures employing hydrogen bonding include simple dimers, linear arrays, two-dimensional networks, and, with the correct covalent framework, three-dimensional structures.

There are many advantages to using hydrogen bonding in the formation of macromolecules and extended arrays. First, these interactions are both self-assembling and self-directing. Stable structures based solely on electrostatic interactions are free to form and dissociate with relatively little energy required. Unlike covalent bonds, which require specific reaction conditions, hydrogen bonds (and other electrostatic interactions) require only the appropriate medium through which to form stable structures. The spontaneity of protein secondary structure formation in aqueous media is, perhaps, the most remarkable example of this phenomenon. Second, there are many functional groups that can act as either hydrogen donors (X-H bond) or acceptors (lone pair). This availability comes from both an extensive synthetic precedent and a large number of different donors and acceptors that can be employed to customize the strengths of hydrogen bonds. Third, hydrogen bonds are typically directed interactions with small steric requirements. Whereas π-stacking requires both a large surface area and very specific electronic distributions in the aromatic rings, hydrogen bonds can form with molecules as small as hydrogen fluoride. Fourth, directional interactions such as hydrogen bonds are relatively easy to incorporate into larger molecules, provided the attached covalent frameworks are shaped correctly to allow the interactions to occur. The pairing of nucleotides in DNA are specific examples of where the selected covalent frameworks determine the optimum orientations of the hydrogen bonding interactions. In crystal engineering, many molecular architectures are based on the inclusion of known pairs of hydrogen-bonding functionalities into organic frameworks.[3] Another advantage that stems from the small size and unidirectional nature of the hydrogen bond is the ability to incorporate multiple interactions within a very small space. Again, base pairing in DNA is an example of where either two (A with T) or three (C with G) hydrogen bonds occur in small heterocytes (Figure 16.7B). The ability to incorporate multiple hydrogen bonds into a single framework also allows orientational specificity to be designed into a structure. Not only do nucleotides pair specifically according to the number of hydrogen bonds (A with T and C with G), but they form stable interactions in only one dimeric conformation.

The greatest limitation in hydrogen bonding comes from the relative stabilities of these bonds and the potential for such bonding throughout an ensemble of molecules. While certain interactions can be predicted to be most stable based on their conformation and functional groups, there are usually many other interactions that form the macromolecular equivalent of metastable structures in solution; and the directing of a single, preferential hydrogen-bonded framework can be difficult to predict or control. In polar solvents, such as water, this predictability becomes even more difficult. The local hydrogen bonds that form with aqueous solvation approach the strengths of many other hydrogen-bonding interactions. Although the formation of the DNA double helix in aqueous media is driven by entropy, the relative stability of nucleotide–water interactions is significant, providing local instabilities in the DNA double helix.[33] This same dynamic equilibrium in DNA between water–nucleotide and nucleotide–nucleotide interactions, however, is also partially responsible for its biological activity, as a DNA helix unable to be destabilized and "unzip" is poorly suited to providing genetic information. As with all of the bonding motifs discussed, the merits and limitations of hydrogen bonding in nanostructural design and formation are sometimes subjective; and the specifics of a system and its surroundings play important roles in determining the best choice of macromolecular stabilization.

16.3 Molecular Building Block Approaches

The overriding goal of the MBB approach is the assembly of nanostructures or nanoscale materials through the manipulation of a subunit by chemical methods or electrostatic interactions. The MBB is selected or designed with this manipulation in mind. The MBB is, ideally, divisible into one or more chemically or electrostatically active regions and a covalent framework, the purpose of which is simply to support the active regions of the subunit. With the division between covalent architectures and lower energy electrostatic systems in mind, the range of MBB designs can be bounded by those systems fabricated through only covalent bonds between subunits and those including only weak interactions between otherwise covalently isolated subunits. Appropriately, these two cases will be considered first. With the definition of the boundaries of what can be done with MBBs in the limit of structural interconnectivity requirements, intermediate systems that balance relative degrees of covalent and electrostatic character, including familiar biological systems, coordination nanostructures, and dendritic systems, are then considered.

16.3.1 Supramolecular Chemistry

Supramolecular chemistry is the science of electrostatic interactions at the molecular level. Direct correlations of structure and function exist between molecular chemistry and supramolecular chemistry, and many parallels can be drawn between the two that highlight the utility and importance of chemical design from noncovalent interactions. The range of covalent bonding and chemical functionalities within a molecular framework gives rise to a range of noncovalent interactions that can be used to form stable structures composed of many molecules. The chemistry of the covalent bond also allows for the engineering of electrostatic interactions. Just as a molecular chemist would employ reaction conditions and various functionalities to direct a particular chemical synthesis, the supramolecular chemist employs the surroundings and the entire molecule to tailor stabilizing interactions into a macromolecular framework. The energies of the interactions between molecules in supramolecular design are far weaker than those interactions within the molecular framework. Consequently, in supramolecular chemistry, the entirety of the covalent framework of the molecular subunit is treated as a whole; and the assembly of the supramolecular array progresses from the MBB just as the synthesis of a molecule is treated as an assembly of discrete atoms.

Supramolecular chemistry is, however, unique in many respects. The formation of new structures in both molecular chemistry and supramolecular chemistry is based upon understanding and predicting chemical interactions. In the case of molecular chemistry, structure formation is based on reaction centers with the covalent framework of the molecule altered to form a new structure. In supramolecular chemistry, superstructure formation is based on interaction centers in which the covalent framework of the molecule as a whole remains unaffected by the stabilizing interactions that occur beyond it. In molecular chemistry, the covalent frameworks of the precursor molecules must be altered through energy-intensive chemical manipulation. Reactions may be self-directing based on the positions of functional groups and reaction conditions; but the actual formation of a molecule requires some form of external manipulation, such as a naturally occurring enzyme or catalyst, or a particular reaction pathway to facilitate the breaking and formation of chemical bonds. A self-assembling molecular reaction is then a fortuitous occurrence of both the correct molecules and the correct chemical environment. In supramolecular chemistry, interactions between molecules are self-directing and spontaneous in solution. Because significant changes to the covalent framework of the subunits are not part of the superstructure formation process, stabilization from noncovalent interactions is based only on localized chemical environments. Provided that the stabilizing interactions between subunits are sufficiently large, molecules will spontaneously form into larger structures. The goal of supramolecular chemistry is the application of this spontaneity in the rational design of larger structures. The total stabilization energy for a supramolecular array from its component molecules is smaller than the total covalent energy between a molecule and its component atoms. Consequently, the formation and

degradation of a supramolecular array is far less energy-intensive than the formation and breakage of covalent bonds. In many instances, stabilization in supramolecular designs benefits from the similarities in energy between MBB interactions and the energy of the surroundings, including the stability gained from the interactions between subunits and solvent molecules. The dynamics of proteins in aqueous media are excellent examples of where a macromolecular structure and the environment can be used in concert to create both stability and function in chemically massive molecules.

Supramolecular chemistry broadly encompasses the use of any electrostatic interaction in the formation of larger molecule-based structures. As such, any system that is based on interactions *beyond the molecule* falls under the supramolecular heading. Supramolecular chemistry, as it is then loosely defined, is an outgrowth of many related disciplines which serve to study phenomena beyond the molecular boundary, including biochemistry, crystal engineering, and significant portions of inorganic chemistry. Much of our initial understanding of molecular interactions comes from the study of naturally occurring structures in these well-established fields. To study the secondary structure of proteins and DNA is to study specific examples of the supramolecular aspects of biochemistry. The functions of these macromolecules in the intracellular matrix are based on noncovalent interactions, including the enzymatic activity of proteins on a substrate, the binding of cations to a protein, the dynamics of DNA duplication, and protein folding. The periodic lattices of many molecular crystals provide examples of how electrostatic interactions direct the alignment of molecules in the solid state. For instance, the unique properties of ice crystals relative to liquid water demonstrate how intermolecular interactions can be just as important as intramolecular interactions in defining structure and properties.

As a unique discipline, supramolecular chemistry emphasizes the design of novel molecular architectures based on the rational incorporation of electrostatic interactions into molecular frameworks. The discussion of supramolecular chemistry here will emphasize the design of macromolecules using only electrostatic interactions. Specifically, supramolecular structures formed from hydrogen bonding and π-interactions are detailed. Dative-based designs, while offering a number of attractive properties for noncovalent stabilization, have seen limited application for the design of nanoscale architectures. The division between entirely electrostatic assemblies and mixed covalent/electrostatic assemblies is stressed when possible to examine how specific noncovalent interactions can be used as the primary means to define the shape of supermolecular structures. Specific instances of nanostructure formation employing both covalent and noncovalent bonding are addressed subsequently in two sections, where the importance of both structure and function can be considered in context. The interactions between metal centers and organic ligands for the formation of coordination nanostructures is also treated as separate from this general discussion in order to provide emphasis on this particularly well-defined segment of supramolecular chemistry.

16.3.1.1 Hydrogen Bonding in Supramolecular Design

Hydrogen bonding is used extensively in supramolecular chemistry to provide strength, structural selectivity, and orientational control in the formation of molecular lattices and isolated macromolecules. The advantages inherent to hydrogen bonding interactions are universal among the different areas of supramolecular chemistry, whether the application is in the stabilization of base pairs in DNA or the alignment of synthons in infinite crystal lattices. The functional groups most familiar in hydrogen bonding have significant precedent in organic chemistry and are, therefore, readily incorporated into other molecules through chemical methods.[3] The complementary components of a hydrogen bond can be incorporated into molecules with very different chemical and electronic properties. In benzoic acid, for example, a polar carboxylate group is covalently linked to a nonpolar benzene ring to form a molecule with two distinct electrostatic regions (Figure 16.8A). The formation of benzoic acid dimers in solution is strongly directed by the isolation of polar and nonpolar regions in the individual molecules and the stability that comes with forming hydrogen bonds between the highly directing donor/acceptor groups.[34] The predictability of hydrogen bond formation in solution and the directional control that comes with donor/acceptor pairing allows for MBBs incorporating these functionalities to be divided into distinct structural regions based on their abilities to form strong hydrogen bonding interactions. This simplifies

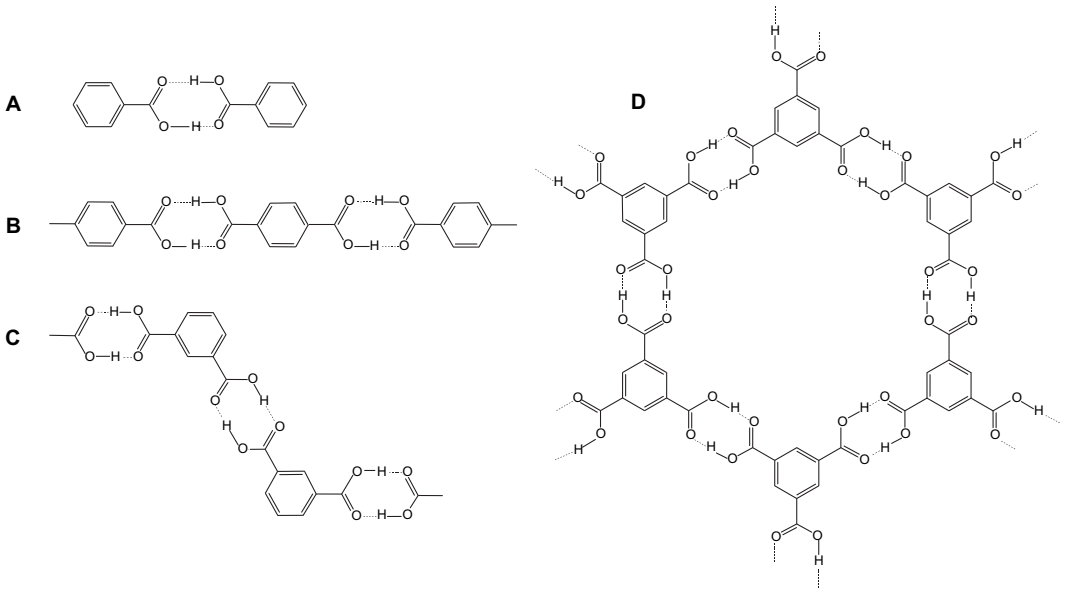

FIGURE 16.8 Hydrogen-bonded aromatic/carboxylic acid assemblies. (A) Benzoic acid dimers. (B) Linear chains of terephthalic acid. (C) Chains of isophthalic acid. (D) Hexagonal arrays of trimesic acid.

the design process in molecules that are tailored to form stable interactions only in specific regions, allowing for the identification of structural patterns in macromolecular formation.[35] The general shape of the nonpolar backbone in benzene, for instance, creates a geometric template from which it becomes possible to predict the shapes of the larger macromolecular structures that result from hydrogen bond formation. To illustrate this template approach with molecular hexagons, a series of examples of both arrays and isolated nanostructures are considered below that use only hydrogen bonding and the shapes of the subunits to direct superstructure formation.

16.3.1.1.1 Crystal Engineering

The hydrogen bond has been used extensively in the design of simple molecular crystals. Crystal engineering has been defined as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desirable physical and chemical properties."[36] Many researchers in the field of crystal engineering have been guided by the very predictable and directional interactions that come with hydrogen bonding in its various forms. The cognizant design of extended arrays of hydrogen-bonded structures in molecular crystals is made possible by the broad understanding of these interactions in other systems, especially from the formation of biomolecules and small guest–host complexes. Among those examples that best demonstrate the rational design of molecular crystals from simple subunits and well-understood interactions are the aromatic/carboxylate structures (Figure 16.8). From the very predictable dimerization of benzoic acid in solution comes a number of similar structures whose geometries are singly dependent on the shape of the hexagonal benzene core. Isophthalic acid[37] and terephthalic acid[38] are simple extensions of the benzoic acid motif that form hydrogen-bonded chains (Figure 16.8B, C). The hexagonal trimesic acid structure[39] stems directly from the placement of strong hydrogen bonding groups on the benzene frame, yielding two-dimensional arrays of hexagonal cavities in the solid state (Figure 16.8D). The same chemical design has also been considered with the amide linkages, in which a higher connectivity is possible through four hydrogen bonding positions (Figure 16.9). Linear chains of benzamide[40] form from each amide linkage, forming four strong hydrogen bonds to three adjacent benzamide molecules. The repeating subunit of these chains is a dimer very similar to that of the benzoic acid dimer, with additional hydrogen bonding groups extending perpendicularly from each dimer to facilitate linear connectivity to other pairs (Figure

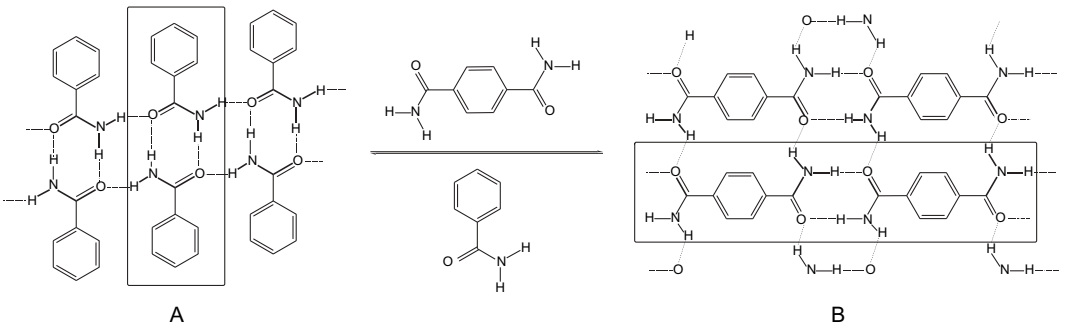

FIGURE 16.9 Hydrogen-bonded structures from amide linkages. (A) Benzamide dimers form linear chains. (B) Terephthalamide forms highly connected sheets. The corresponding aromatic/carboxylate motifs are enclosed in boxes.

16.9A). Planar sheets of terephthalamide[41] form from the same extended linear chain motif found in *para*-substituted terephthalic acid (Figure 16.9B). Again, the perpendicular hydrogen bonding groups direct the connectivity of these linear chains into two-dimensional sheets. The commonality among all of these benzene-based MBBs is the division between the rigid alignment of the functionalities on a covalent framework and the positions of the interaction centers beyond the molecular frame.

16.3.1.1.2 Supramolecular Structures

A number of isolated supramolecular structures are known that use only hydrogen bonding to direct their formation. In some instances, this has been accomplished through modifying the substituents on array-forming MBBs to promote the formation of isolated systems. While unsubstituted isophthalic acid in solution was found to form linear ribbons in the solid state, the addition of bulky substituents at the *meta*-positions of the two carboxylic acid moieties resulted in the formation of isolated molecular hexagons — structures that mimic exactly the hexagonal cavities formed through hydrogen bonding in the trimesic acid arrays[42] (Figure 16.10). For greater control in the formation of complex supermolecules, the engineering of highly directional hydrogen bonding regions is often required. The customization of interactions between MBBs is performed by either attaching more than two hydrogen bonding pairs onto the same framework (to prohibit free rotation when single σ-bonds are used to connect the donor/acceptor assemblies) or by embedding two or more functionalities directly into a covalent framework (Figure 16.11). In both routes, the resulting structures are no longer limited to stable designs based solely on single donor/acceptor pairs or sets of hydrogen bonding fragments isolated to σ-bound molecular fragments.

By fixing the positions of the donor and acceptor groups in a framework, the connectivity of subunits must occur with orientational specificity, creating what are commonly known as *molecular recognition* sites. In hydrogen-bonded systems, each interaction region of the molecular recognition site is clearly identified by the arrangement of the donor/acceptor groups, such as shown in Figure 16.11B. For crystal engineering and nanostructure formation, where stability and the fitting of subunits to one another define the shape of the entire system, both the hydrogen bonding arrangement and the shapes of the molecules are important to the success of a molecular recognition site (Figure 16.11C).

Two specific MBB designs have been extensively used together to illustrate the roles of structure and orientation in the formation of hydrogen-bonded nanostructures. Cyanuric acid and melamine are two highly symmetric molecules with complementary hydrogen bonding regions along each molecular face (Figure 16.12). In solution, 1:1 mixtures of these molecules form insoluble complexes of extended hexagonal cavities[43] (Figure 16.13C). By the removal of a hydrogen bonding interaction from each molecule, two different assemblies have been shown to form. In both instances, cyanuric acid is converted into a barbituric acid-based molecule by the removal of one N-H fragment from the central ring, while the melamine structure is altered by the removal of one nitrogen atom from its central ring (Figures 16.13D and 16.13E). The formation of linear chains has been shown to be favored in the native structures and when the substituents on the MBBs are kept small[44] (Figure 16.13F). The addition

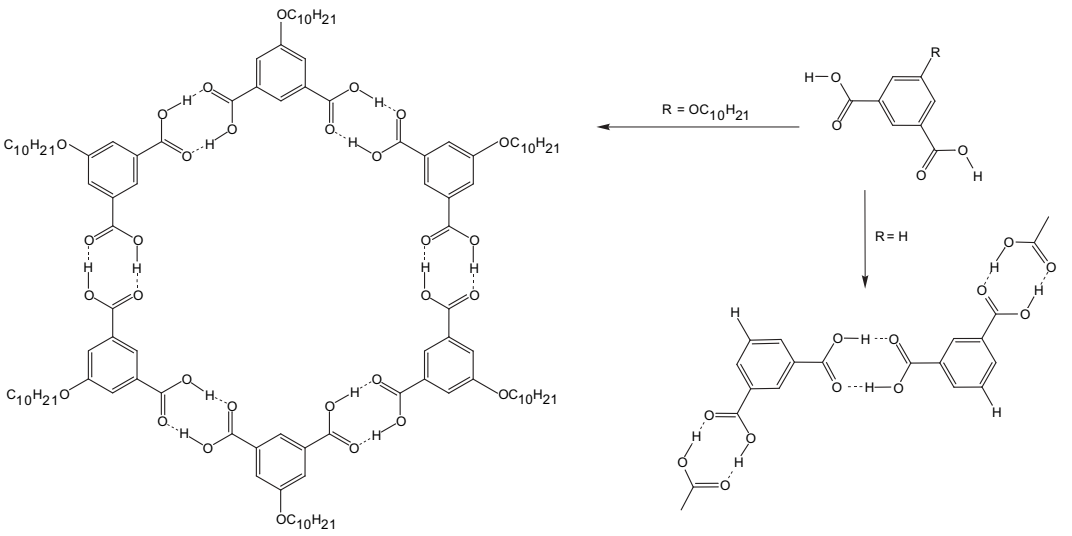

FIGURE 16.10 Isophthalic acid derivatives direct the formation of different hydrogen-bonded networks.

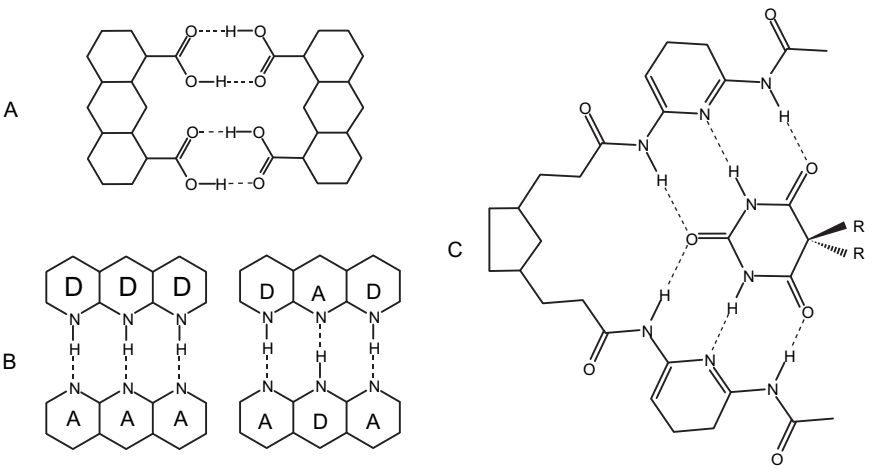

FIGURE 16.11 Engineering orientational specificity into hydrogen-bonded structures. (A) Multiple interaction zones fix the orientation of guest–host complexes by prohibiting rotation. (B) Donor (D) and acceptor (A) interactions between hydrogen-bonded fragments embedded within molecular frameworks. (C) Size and orientation direct the binding of barbituric acid within a molecular recognition zone.

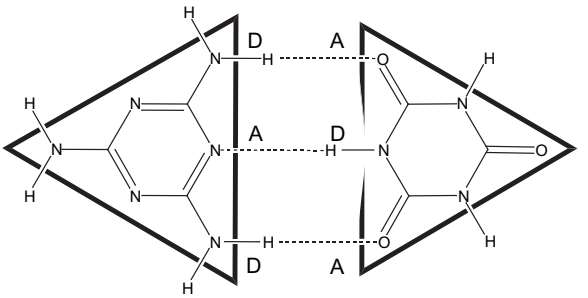

FIGURE 16.12 Complementary DAD:ADA hydrogen bonding in melamine (left) and cyanuric acid (right).

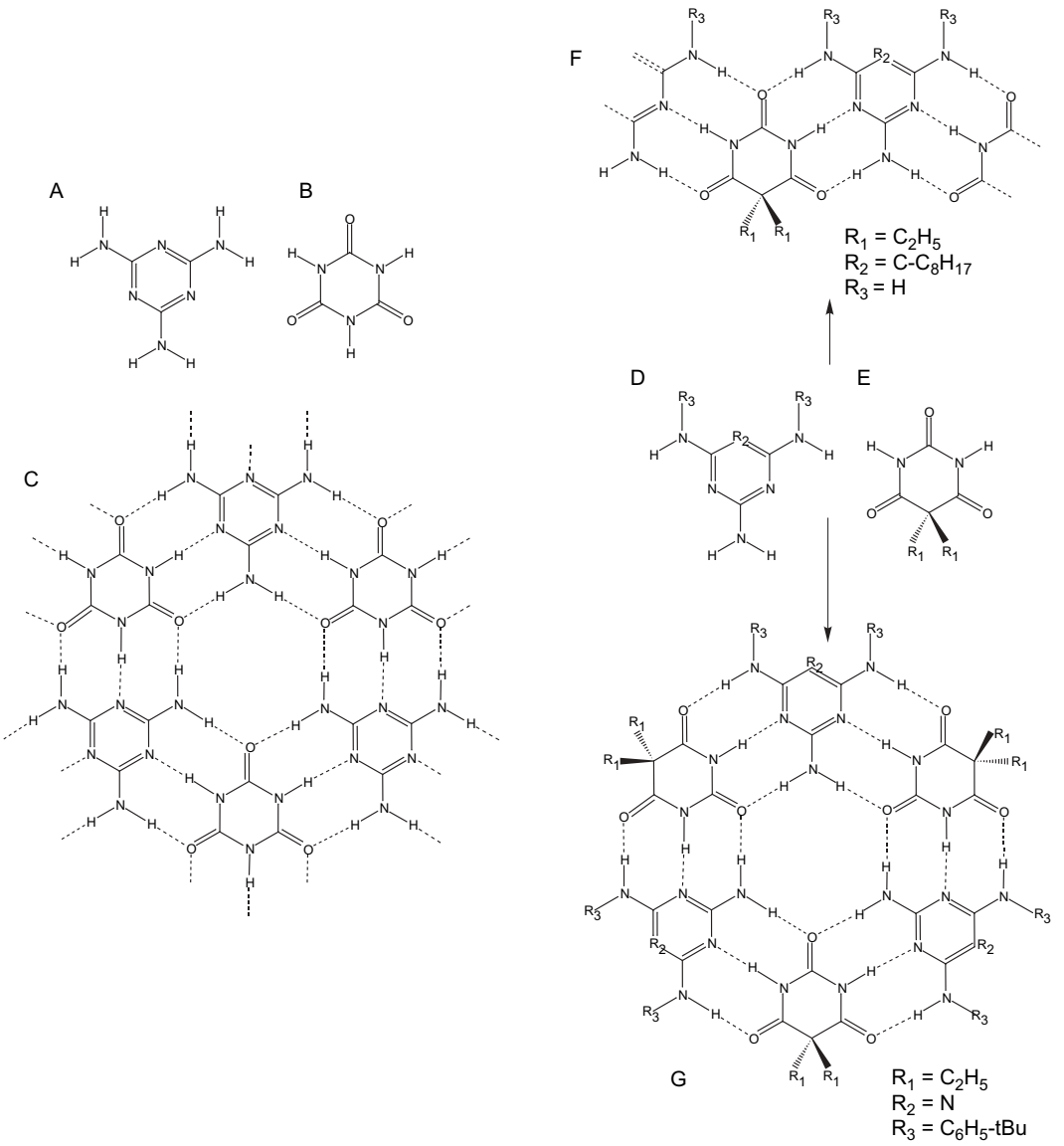

FIGURE 16.13 1:1 mixtures of A and B form extended arrays. Structures utilizing D and E form either linear chains (F) or supramolecular hexagons (G) depending on the choice of R groups.

of bulky substituents to the subunits (similar to the method used to form hexagons of isophthalic acid) directs the hexagonal species shown in Figure 16.13G to self-assemble in solution.[45]

These supramolecular designs are easily rationalized from the shapes of the hexagonal frames to which hydrogen bonding fragments are attached. Hydrogen bonding has been used frequently in the design of smaller guest–host interactions and molecular recognition sites, with much of this work derived from extensive biochemical precedent. Subsequent sections on biomimetic designs and dendrimers illustrate a few of these specific instances of isolated hydrogen bonding interaction in specific MBB designs.

16.3.1.2 π-Interactions

The use of π-interactions has been shown to be important for a number of biological and molecular assembly applications. In biological structures, π-stabilization and the hydrophobicity of the aromatic

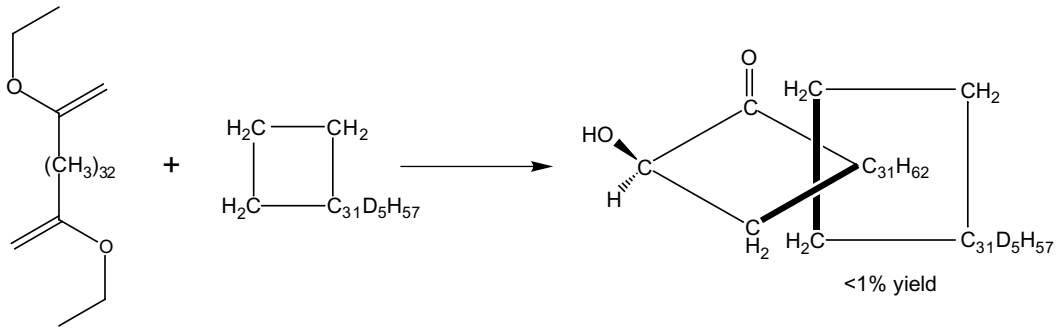

FIGURE 16.14 The first reported catenane.

rings both contribute to the formation of secondary and tertiary (aggregate) structure in DNA and proteins. The stability gained from stacking π-systems with complementary electron densities has been used as a driving force for a number of crystal engineering-based structures. The herringbone stacking pattern of aromatic π-systems with peripheral substituents is a very familiar motif in crystal engineering and has been shown to be responsible for the observed packing of many molecular crystals.[3] For the formation of supramolecular assemblies, however, the role of the π-interaction as a singular driving force is rather limited. Interactions with the π-systems of small aromatic groups are difficult to utilize because the energies of the different orientations can be very similar. Consequently, many supramolecular structures employing π-stacking interactions either use π-stacking in conjunction with other interaction types or use π-π-interactions between highly polarized species to direct the formation of supramolecular structures. Three specific examples are discussed below to illustrate how π-interactions can be employed in the electrostatic-based supramolecular formation of nonbiological structures.

16.3.1.2.1 Catenanes

Catenanes are a unique class of supramolecular structures formed by the interpenetration of two or more macrocycles to form what is often referred to as a *topological bond*. The assembly of interlocked rings has been demonstrated both by statistical and directed techniques. The statistical method used to form the first isolated catenane[46] is shown in Figure 16.14 and gave very poor yields, demonstrating the limitations of self-assembly without direction from electrostatic interactions. The other types of catenanes have been synthesized with far greater success by relying on local stabilization from π-interactions in aromatic rings in conjunction with other electrostatic interaction types.

The formation of two coordination-based catenanes has been proposed to arise from guest–host interactions between π-systems (Figure 16.15). These two structures, identical except for the choice of metal center (either palladium(II) or platinum(II)), form initially as single-ring systems from 1,4-bis(4-pyridylmethyl)benzene. In the palladium(II) complexes,[47] concentration was found to play a key role in determining the relative populations of rings (low concentrations) and catenanes (high concentrations) at ambient temperatures. The equivalent platinum(II) catenane[48] was found to form irreversibly as a function of temperature. Here, raising the temperature of the system to break the strong platinum–nitrogen coordination bond opens the ring systems for monocycle insertion. In both cases, catenane formation is promoted by π-interactions between the ring systems that stabilize the molecular interlocks long enough to allow for the formation of the metal–ligand topological bond.

Perhaps the most familiar catenanes are those composed of paraquat–crown complexes[49] (Figure 16.16). In these systems, the interlocking of a neutral crown ether and a paraquat ring is directed and stabilized by two strong electrostatic interactions. First, strong hydrogen bonding between the crown oxygens and the acidic hydrogens on the aromatic rings of the paraquat serve to fix part of the paraquat within the crown ring. Second, strong π-π-interactions between the crown aromatic rings and the positively charged aromatic rings of the paraquat serve to direct the insertion of the crown ring into the open paraquat assembly prior to its covalent ring closure.

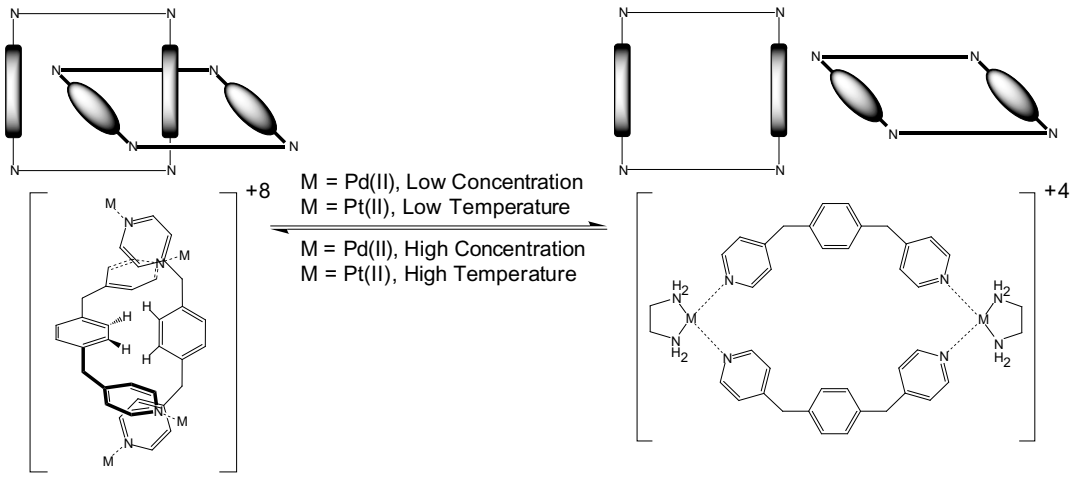

FIGURE 16.15 The effects of metal, concentration, and temperature on the formation of coordination catenanes of palladium(II) and platinum(II).

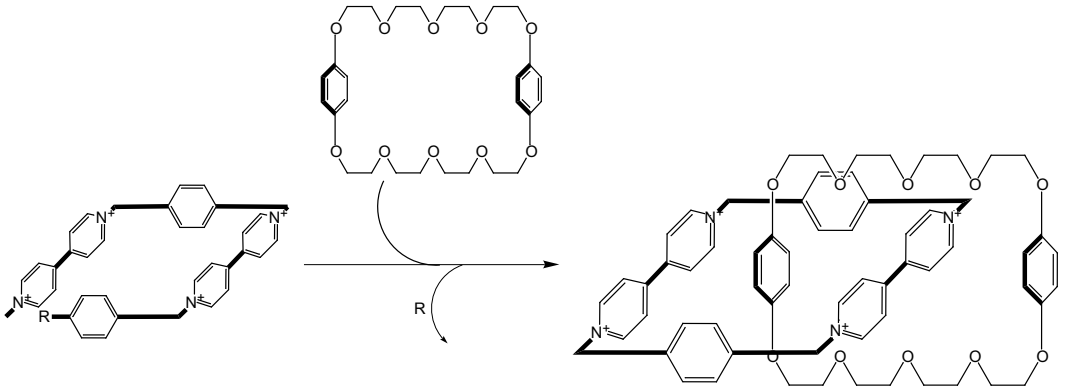

FIGURE 16.16 General crown ether/paraquat catenane and assembly mechanism.

16.3.1.2.2 Molecular Zippers

One of the most interesting pairings of edge-to-face π-π-interactions and hydrogen bonding comes in the form of molecular *zipper* structures formed from amide oligomers[50] (Figure 16.17A). The formation of double strands of the amide oligomers is rationalized based on ^{1}H NMR titration studies in the nonpolar solvent chloroform and the known structural features of oligomer chain pairs used in the dimerization study. In the general design scheme, the oligomer chains A and B have complementary binding regions capable of forming stable A:A, B:B, or A:B dimers. Based on the chain lengths of the two monomers, however, A:A and B:B dimers are found to not maximize the total possible number of π-π-interactions and amide hydrogen bonds (Figure 16.17B). The A:B dimer maximizes the total number of possible interactions along the entire length of the dimer complex, thereby promoting its formation in solution from equal mixtures of both A and B. Among the number of dimer systems examined, the commonalities to all are the increase in stability with increased oligomer lengths (providing more interactions between dimers) and the decrease in stability in polar solvents, such as methanol, which competitively bind to the polar amide functionalities and weaken the zipper structure.

16.3.1.2.3 Aedemers

The preferential face-to-face stacking of aromatic molecules with complementary ring charge densities has been demonstrated in many instances. The application of this phenomenon to nanoscale design

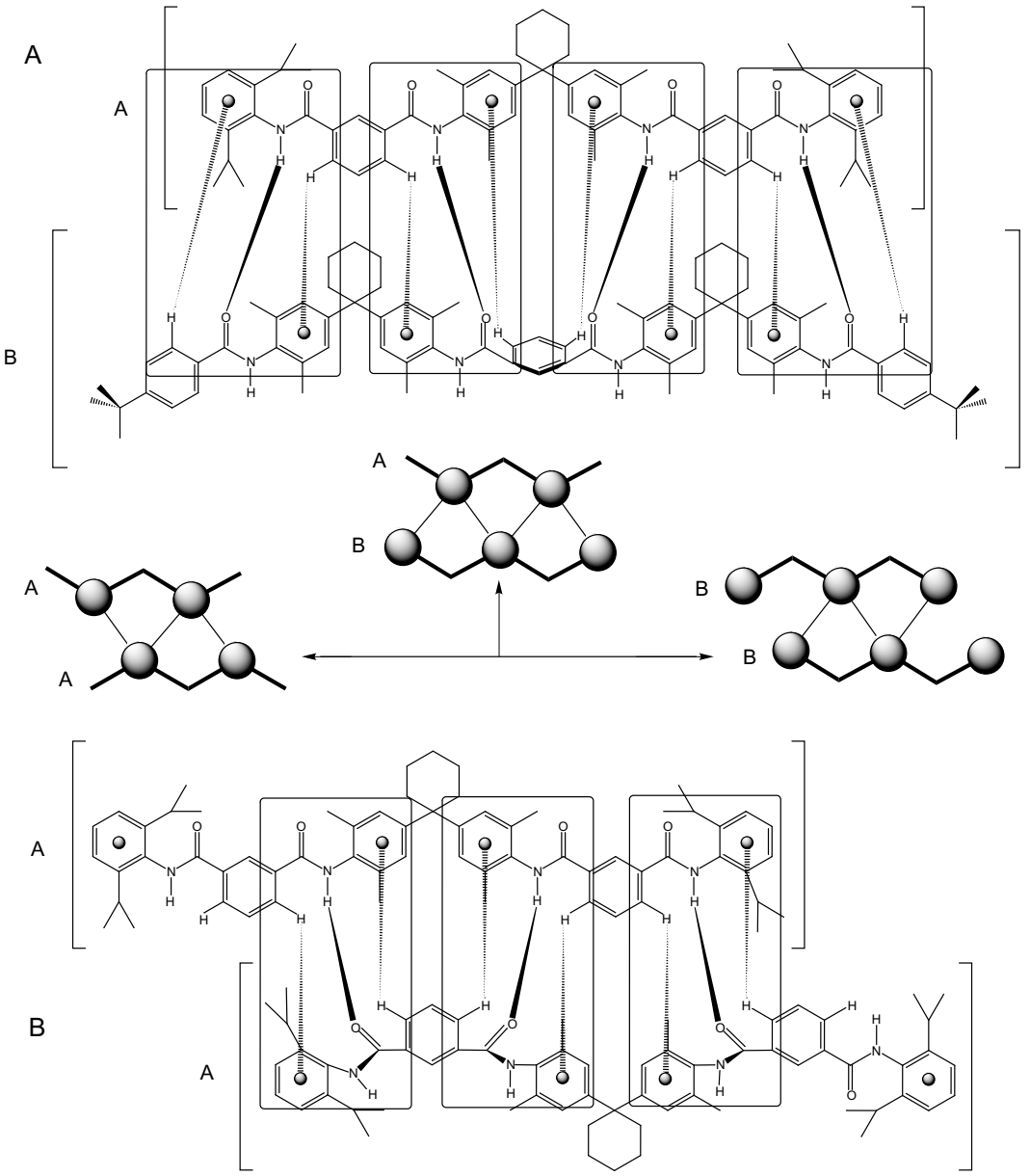

FIGURE 16.17 Molecular zippers from amide oligomers. The number of π-stacking interactions (dashed lines) and hydrogen bonding interactions (bold lines) is maximized with A:B dimers (top).

beyond the alignment of molecules in extended arrays has not, however, been exploited far beyond biological designs. The stabilizing interactions of two complementary π-stacking pairs have been shown to direct the formation of secondary structure in at least one other type of covalently linked macromolecule. The aedemers[51] are synthetic oligomers incorporating π-system donors and acceptors attached by long-chain tethers (Figure 16.18). In aqueous media, the strong π-π-interactions between the donor/acceptor pairs are enhanced by the respective hydrophobicity of the rings and the polar carboxylate groups attached to the tether. In water, the π-systems are found to self-assemble into single stacks of either two or three discrete donor/acceptor pairs.[51]

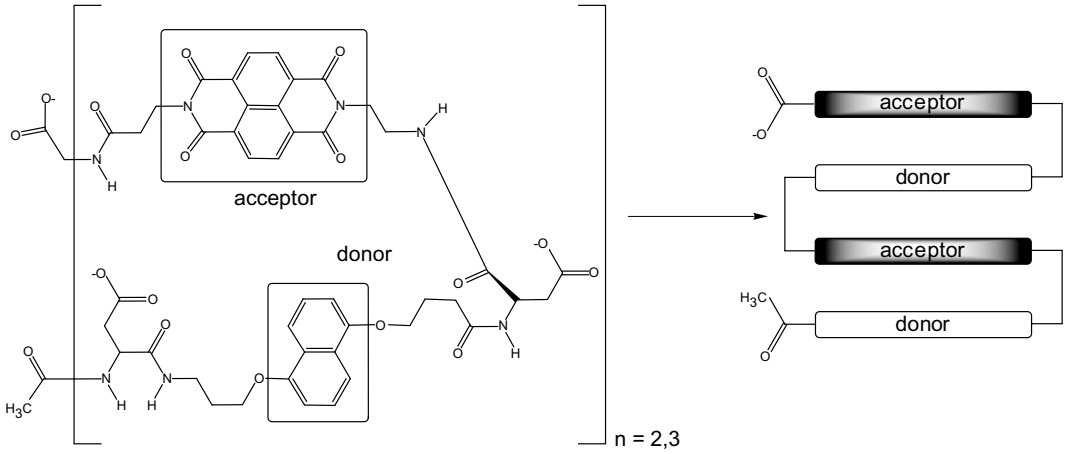

FIGURE 16.18 Aedemer molecules (left) and their directed stacking in water (right).

16.3.2 Covalent Architectures and the Molecular Tinkertoy Approach

The covalent bond is central to all MBB designs. The strength and directionality of these bonds define the shape of the subunits, thereby directing the formation of all larger structures stabilized by covalent bonding or noncovalent interactions. Covalent bonds are typically insensitive to environmental variables, such as the choice of solvent or the ambient temperature. The electrostatic interactions used to stabilize multimolecular structures, in contrast, are often strongly affected by these environmental factors. Covalent bonds offer far greater positional specificity and structural invariance than their noncovalent analogues. The chemical reactions used to form covalent bonds occur preferentially at specific positions on a molecular framework through the placement of suitable functional groups and the control of reaction conditions. Furthermore, covalent bond formation, in contrast with noncovalent interactions, is typically irreversible without concerted efforts to break them. Beyond the formation of the strong connections, the predictability of covalent architectures also allows for control of structure with great accuracy.

The fabrication of larger structures from covalently linked MBBs is based upon the use of individual subunits as rigid building blocks to incrementally build highly stable structures. Covalently linked nanostructures and covalent molecular scaffolding offer the same advantages that stable support structures provide at the macroscale. The shapes of rigidly bound structures are usually reliable over long periods of time. Covalent bond energies for familiar organic structures are an order of magnitude stronger than many of the electrostatic interactions currently employed for the formation of many supramolecular lattices. The continual breaking and reforming of these electrostatic interactions in supramolecular systems, while providing these structures with fault-tolerance and energy-driven self-maintenance, make their interconnectivity very sensitive to their surroundings. Covalently linked structures are themselves structurally stable under similar conditions, and any structural variance comes in the form of deformations instead of bond breaking and reforming. The chemistry involved in forming nanostructures from covalent bonds can be well defined and unidirectional with the correct choices of functional groups and reaction conditions. While the self-assembly methods of supramolecular chemistry provide a means to forming stable structures through the engineering of specific interactions into subunits, covalent connectivity can be directed with great positional control through the rational use of reaction pathways.

The formation of covalently bound nanoscale structures from molecular subunits is common in chemistry and materials science. The most common examples come from polymer chemistry, where small lengths of randomly oriented monomers become long chains of highly interwoven materials as the scale of the system is increased from Angstroms to nanometers and beyond. The formation of highly ordered, covalently bound nanoscale architectures and macromolecules is far less common in chemistry, as the controlled formation of nanoscale structures from covalent bonding is problematic in both of the

routes currently proposed. In the engineering-based, top-down approaches, the positional specificity required for fabricating macromolecules from covalent bonds is simply not available, as the MBBs used for their formation are too small to be controlled and placed with any specificity. One might consider the assembly methodology of these approaches to be "too precise" for the selection of MBBs, as the desired level of control places severe restrictions on the design process and the choices of MBBs. In the bottom-up approaches of solvent-based chemistry and atomic manipulation, the reliability of positional accuracy becomes suspect in assemblies formed from rigid, highly stable connections. Errors in the placement of atoms or MBBs within a given framework, because they are irreversible without a level of chemical manipulation that also jeopardizes the structural integrity of the remaining covalent bonds, can potentially render a fabricated assembly useless with a single misplaced bond. Here, the idealized assembly process of solution-based methods may be considered as "too statistical."

To overcome the limits of both approaches, a fabrication process must successfully address positional control, connectivity, and the chemical manipulation of the reaction centers. The basis of supramolecular chemistry is the formation of a macromolecular assembly from weaker, noncovalent interactions; a wealth of examples demonstrates the validity of the approach.[36,52] The means to covalent supramolecular chemistry need not be dissimilar from this already proven approach to macromolecular formation. A covalent-based approach must, however, rigorously control the reaction conditions and the assembly progress of the larger structures to prohibit the unwanted interactions that are, in supramolecular chemistry, easily removed through the control of the ambient conditions. The scope of synthetic chemistry is narrowed considerably when the discussion is limited to the formation of nanoscale architectures from covalent bonding between MBBs instead of only the manipulation of covalent bonds within a single molecule. To illustrate the considerations and limitations of covalent-based nanostructure design from MBBs, one of the most well-developed chemical approaches is detailed below.

The "Molecular Tinkertoy" approach[53] to nanoscale scaffolding is based upon the treatment of molecules as simple, rigid construction components or *modules*. The features of the modules that are considered most important in this approach are those required for the construction of the assembly, such as the module length and the availability of suitable bonding positions on the module for connectivity to other subunits. Within the Tinkertoy paradigm, all of the required components and critical fabrication issues are based upon only covalent bonding. The engineering kit of the modular chemist consists of (1) rigid rod molecules of variable lengths, (2) connectors to act as corners or intersections for the scaffolding, and (3) a chemical means to control the assembly of the rods and connectors[53] (Figure 16.19). Such a kit at the macroscale is already familiar to any student of organic chemistry in the form of molecular

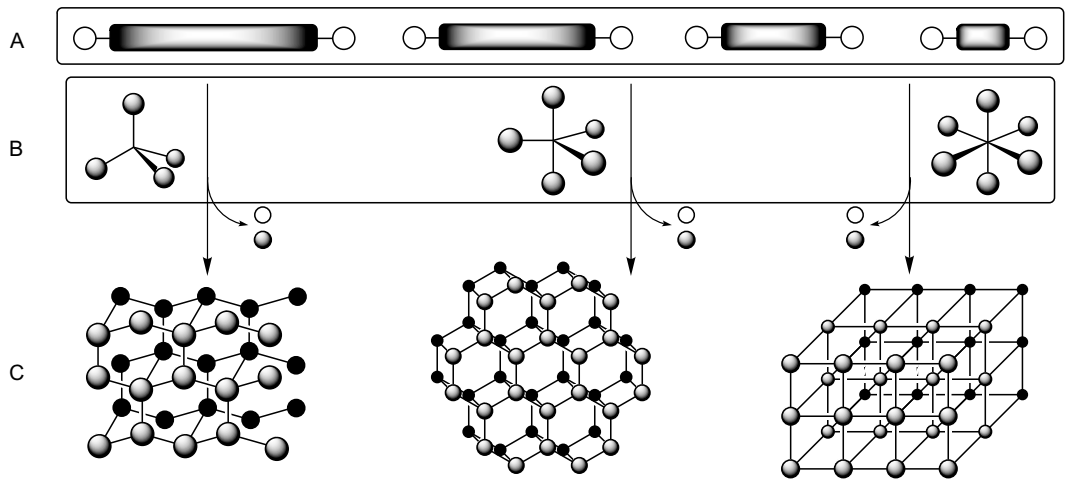

FIGURE 16.19 The engineering kit of the Tinkertoy chemist. (A) Rigid rods of various lengths. (B) Connectors and junctions. (C) A means to covalent assembly to create nanoscale scaffolding.

models, although the construction of scaffolding from the molecular kit is far more challenging than the fitting together of pieces of plastic. Within the context of covalent bonding, each of these three aspects of Tinkertoy design can be treated independently. The fabrication of rigid rods, for instance, can take inspiration from any chemical designs that result in linear structures, regardless of the choice of connectors or the development of the chemical pathways to assemble the nanostructures. The shape of a molecular scaffolding is defined by the connectors; and the engineering of a repeating structural motif, be it a simple cube or a diamondoid-based tetrahedral motif, is accessible based on the choice of the appropriate connector from among the available molecules that allow for the specific connectivity (Figure 16.19). The issue of chemical control becomes the most difficult of the three to handle, as the ordered assembly of extended arrays from simple rods and connectors cannot be controlled from the highly orchestrated procedures used for macroscale scaffolding construction, although the required chemistry is easily applied to the individual connector–junction reactions.

The concepts of the Tinkertoy approach are applicable to all structural features, including the formation of junctions and the assembly of the larger structures in solution. The most exhaustive treatment of the approach thus far has been for the linear, rigid rods used to define the dimensions of the scaffolding. While the number of molecules capable of acting as subunits for linear rods is large, the initial series of proposed subunits has been limited to a select set of twenty-four. The scope of this discussion is limited to the manipulation of these different modules for both the formation of linear rods and the design of molecular junctions. The chemistry of the twenty-four modules has been extensively developed and reviewed in the interest of firmly establishing the precedent for the first components of the engineering kit.[10] These twenty-four linear modules, shown in Figure 16.20, share a number of important characteristics that are briefly described below.

1. Stability
   The most important features to consider with respect to the environment of a nanostructure are the stability and reactivity of its components. Unless chemical functionality is required for an application, the best choices of MBBs are those that will react only during the formation of the covalent architecture. The subunit should, therefore, be inert with respect its chemical environment after assembly.

   The most common structures from among the initial MBBs that provide this level of chemical predictability are the saturated hydrocarbons (Figure 16.20A). These molecules rely exclusively on the use of strong σ-bonding between carbons and hydrogens to form rigid structures and are ideal for rigid rod fabrication. Their interconnected frameworks limit their flexibility while at the same time providing a molecular axis through which linear dimers, trimers, etc., can be formed via single σ-connections. The remaining saturated hydrocarbons (Figure 16.20D) differ from the cage structures by the inclusion of two bonding sites per pair of axial carbons. With these modules, either several σ-bonds can be used to form rigid structures, or both σ- and π-bonding can be used to create single connection points with restricted rotation (Figure 16.20D). The carboranes, a second class of molecules, display extreme stability and unique connectivity within a very small space (Figure 16.20B). The deltahedral framework of the cluster skeleton prohibits appreciable flexibility within the subunit, while the radial bonds of the apical carbons in $C_2B_{10}H_{12}$ and $C_2B_8H_{10}$ provide rigorously linear external linkages. Furthermore, these clusters have been shown in many instances to be remarkably stable compounds under very harsh conditions.[54] The remaining modules contain one or more π-electron systems. While π-systems are more susceptible to chemical reactions than saturated systems, much of this reactivity can be limited through the proper control of the surroundings. The molecules containing π-electrons are the only systems from the original series of subunits that provide a means to form stabilizing electrostatic interactions in solution (e.g., π-interactions, hydrogen bonding, or dative bonds).
2. Size
   Greater control of the size of a nanoscale assembly is possible by using many smaller subunits rather than few larger subunits. The twenty-four initial modules are among the smallest rigid

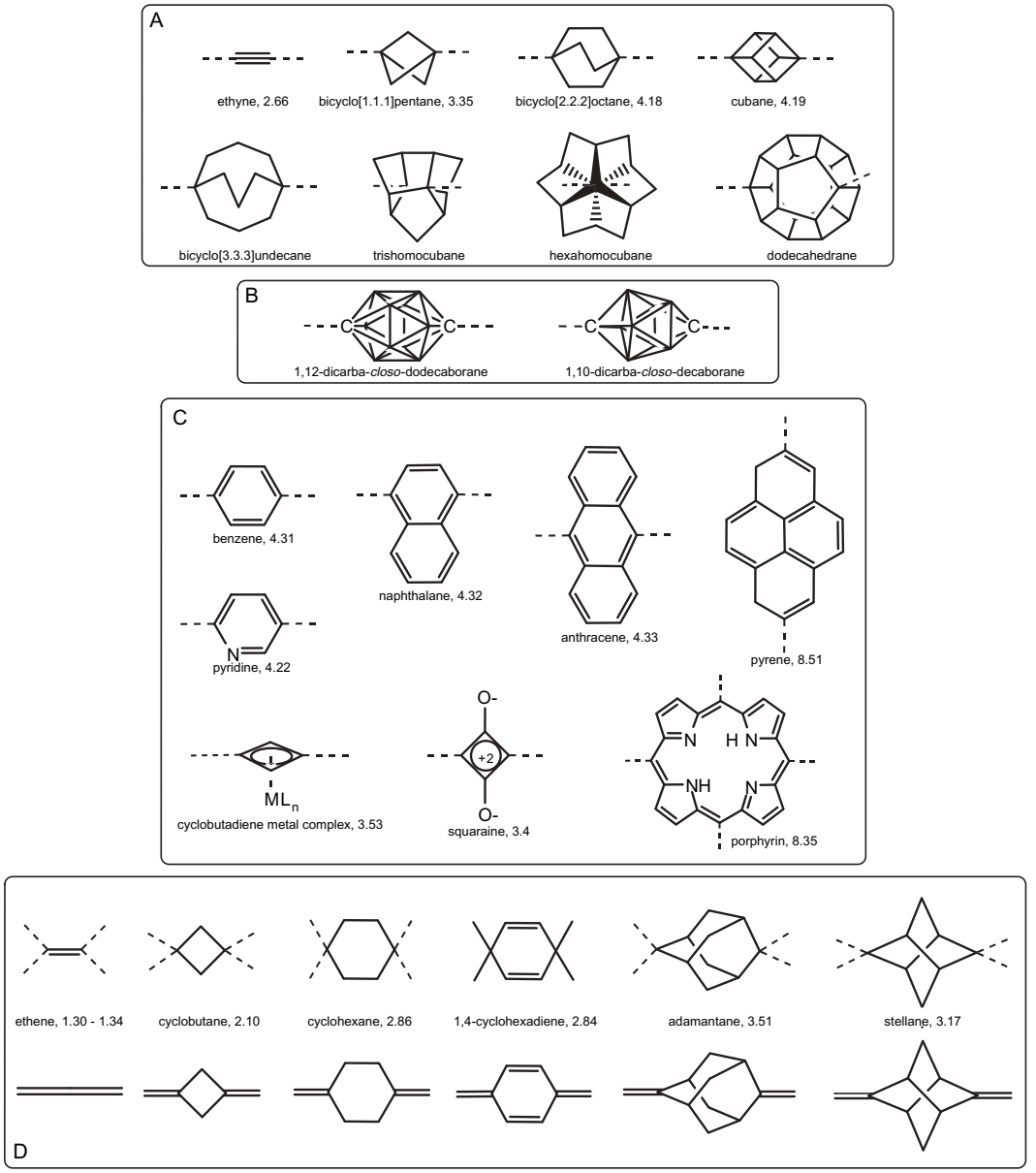

FIGURE 16.20 The 24 original modules. (A) Saturated hydrocarbons. (B) Carboranes. (C) Linear-connecting π-systems. (D) σ/σ and σ/π connectors. As applicable, names and incremental lengths (in Angstroms) are provided.

molecules known, and no single module crosses the nanometer threshold. Ethyne, for instance, is the smallest organic subunit available that provides linear connectivity on both ends through σ-bonding. A linear rod in a nanoscale scaffold can be fabricated from the available modules to "add up" to some required length. The rigid bonding within each module results in the structure having some fixed distance between the axial connection points which, when added to a typical single C-C bond length to account for the extra-module σ-linkage, defines a distance termed an *incremental length* (Figure 16.20). In order to construct a rod of some predetermined length, the only feature that needs to be considered from among the available modules is the incremental length between axial connection points. Having determined which modules are

required to fabricate a rod of some predefined length, a chemical pathway can be employed based upon the known reaction chemistry of each subunit. As necessary, the general approach may be applied to any other molecules or combinations of molecular subunits for the fabrication of rods of an absolute length.

3. Chemical Precedent
   The design of linear rods from the available modules is both flexible and straightforward. With few exceptions, chemical precedent exists for the syntheses and linking of all twenty-four modules.[10] Furthermore, the chemistry required for linking together different modules has also been demonstrated. Co-oligomers, chains of subunits composed of two or more different modules, are important both for customizing the lengths of the linear rods and for altering the solubility properties of the larger structures. Of particular importance in the linear rod treatment is the ethyne bridge. Ethynyl linkages are ideal for improving the solubility of molecular rods while minimizing the increase in chain length. A great deal of chemical precedent also exists for their inclusion into a number of modular structures.

Many linear molecular rods have been synthesized from the collection of modules. Beyond the formation of the rods is their connection to either two-dimensional junctions to form planar molecular grids or three-dimensional junctions to form molecular scaffolding. While covalent junctions have not been fully addressed, a number of the original twenty-four modules offer both structural flexibility and chemical precedent beyond their useful axial bonding. Specifically, the symmetry and connectivity of certain modules are appropriate for the formation of diamondoid, honeycomb (hexagonal), and cubic molecular lattices through familiar chemical manipulation. These lattices and the modules appropriate for their juncture are discussed below.

16.3.2.1 Diamondoid Scaffolding

Diamondoid structures are networks of tetrahedra in a molecular or macromolecular lattice (Figure 16.21). Within the lattice are two basic structural features. The first and most fundamental feature is the tetrahedral center (Figure 16.21A), to which four adjacent tetrahedra are attached. The smallest tetrahedral-based structural motif in the diamondoid lattice is the adamantanoid framework (Figure 16.21B). In the actual diamond framework, the tetrahedral centers are sp^3-hybridized carbon atoms, and the

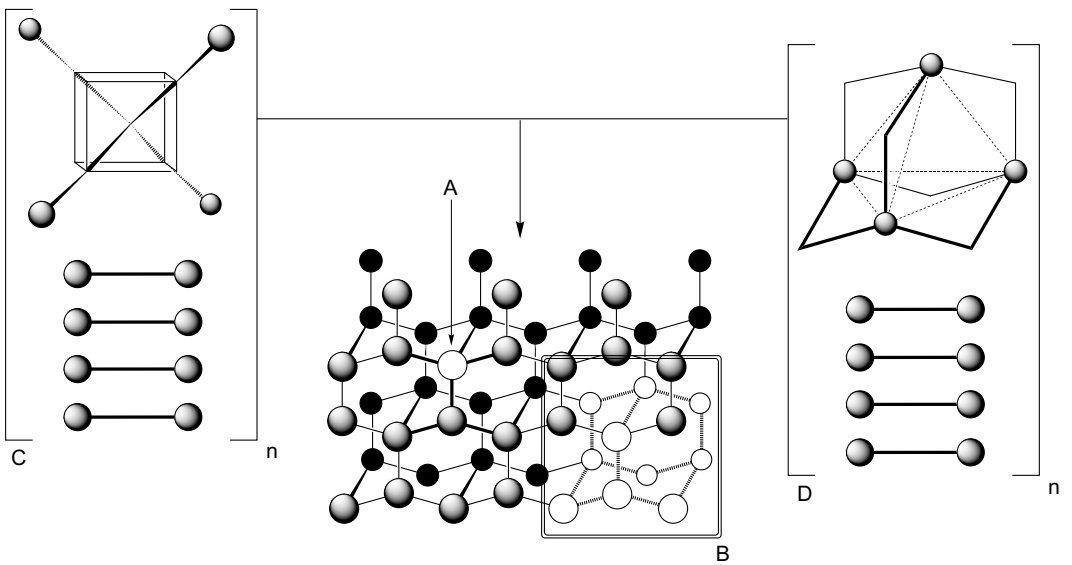

FIGURE 16.21 Diamondoid nanoscaffolding. (A) Tetrahedral module. (B) Adamantyl subunit. (C) Cubane assembly. (D) Adamantane assembly.

repeating motif is the adamantyl frame. The strength of diamond at the macroscale stems from the strength of the carbon–carbon σ-bonds and the extensive connectivity of the carbon atoms within the diamond network. The formation of MBB-based diamondoid frameworks has been explored in a number of coordination and supramolecular designs.[55–57] The noncovalent interactions within these diamondoid lattices offer reasonable strengths, the same high connectivities, and the spontaneous self-assembly of the subunits into rigid lattices. For the fabrication of extended arrays of diamondoid lattices, this self-assembly feature is particularly attractive, because the synthesis of molecular diamond has been limited to small molecules based more on incremental growth of adamantane frames[58] than the actual formation of rigid, covalent arrays.

Covalent diamondoid structures offer structural rigidity and controllable assembly intermediate between molecular diamond and the noncovalent MBB designs. The Tinkertoy approach offers a plausible means to the formation of such covalent diamondoid arrays. To construct these arrays with linear rods, the required molecular junctions must have tetrahedral symmetry elements that can connect through σ-bonds at the tetrahedral centers. Adamantane and cubane provide both the required tetrahedral symmetry elements for the placement of the linear rods and the synthetic precedent for their covalent attachment. Among the modules bicyclo[2.2.2]octane, bicyclo[1.1.1]pentane, bicyclo[3.3.3]undecane, trishomocubane, hexahomocubane, and dodecahedrane, structures with either tetrahedral centers or quasi-tetrahedral bonding positions (threefold rotation axes exist that include the axial connection points for the linear rods), either the chemistry has not been developed for tetrahedral assembly or the structures are too flexible to adequately control the diamondoid assembly. The control of functional group placement at the tetrahedral corners of both adamantane and cubane has been well developed, with many of these same functional groups employed for the syntheses of linear rods from these two modules. The control of tetrahedral adamantane functionalization has already been exploited for the formation of supramolecular building blocks in diamondoid lattice formation. In these MBBs, carboxylate groups are used to form strong hydrogen bonding interactions with neighboring adamantane frames, effectively extending the connectivity of the trimesic acid complex into a third dimension.[55] The covalent attachment of linear rod modules has also been demonstrated by way of a tetraphenyl adamantane derivative (Figure 16.22) that has been used as an MBB for subsequent macromolecular syntheses.[59]

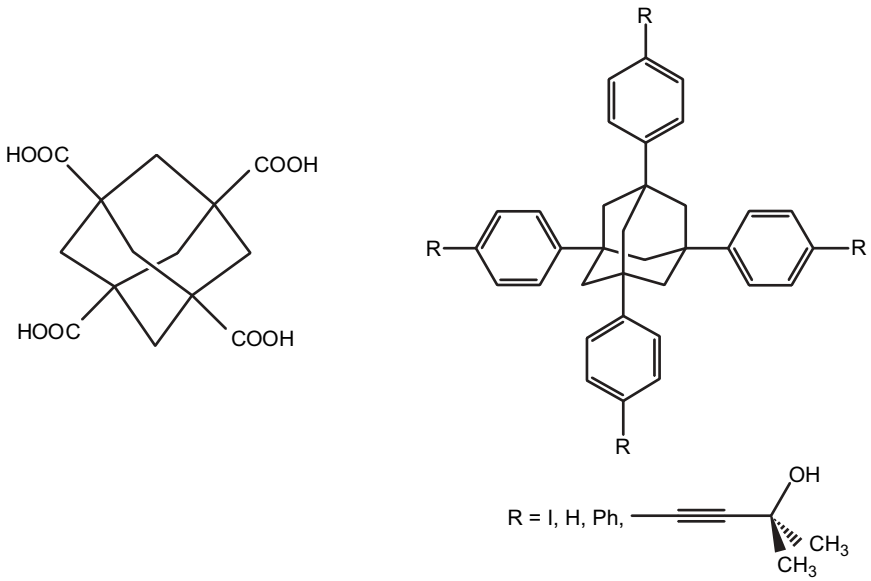

FIGURE 16.22 Adamantane-based MBBs for supramolecular design. (A) Adamantane-1,3,5,7-tetracarboxylic acid for supramolecular designs from hydrogen bonding. (B) Adamantane-based fragment with module linkages and known substituents.

16.3.2.2 Honeycomb Lattices

Macromolecular honeycombs require two different modes of connection (Figure 16.23). The hexagonal planar array is formed by the connection of linear molecules to triangular junctions. With the hexagonal plane formed, the vertical stacking of these structures is performed by attachment of the triangular junctions through chemical bonds perpendicular to the hexagonal plane. The ideal junctions for honeycomb designs are then molecules with trigonal bipyramidal symmetry, providing the ideal connectivity for linear rod structures in all directions. Such junctions are readily available from familiar coordination compounds. These structures, however, do not provide the structural stability of covalently bound junction/rod linkages. Although no single module addresses all of the design issues entirely, three are available that individually account for specific aspects of the honeycomb design.

Planar hexagonal scaffolding has already been addressed in the structure and chemistry of benzene. The placement of functional groups at the 1,3,5-positions of the benzene ring (Figure 16.24) yields the required triangular connectivity for the junctions, while an extensive chemical precedent for benzene functionalization makes the ring ideal for such applications. The propensity of trimesic acid to form

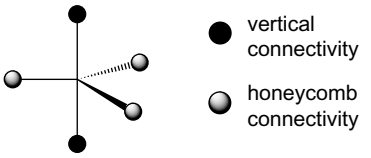

FIGURE 16.23 Honeycomb/vertical stacking connectivity in D_3-symmetric modules.

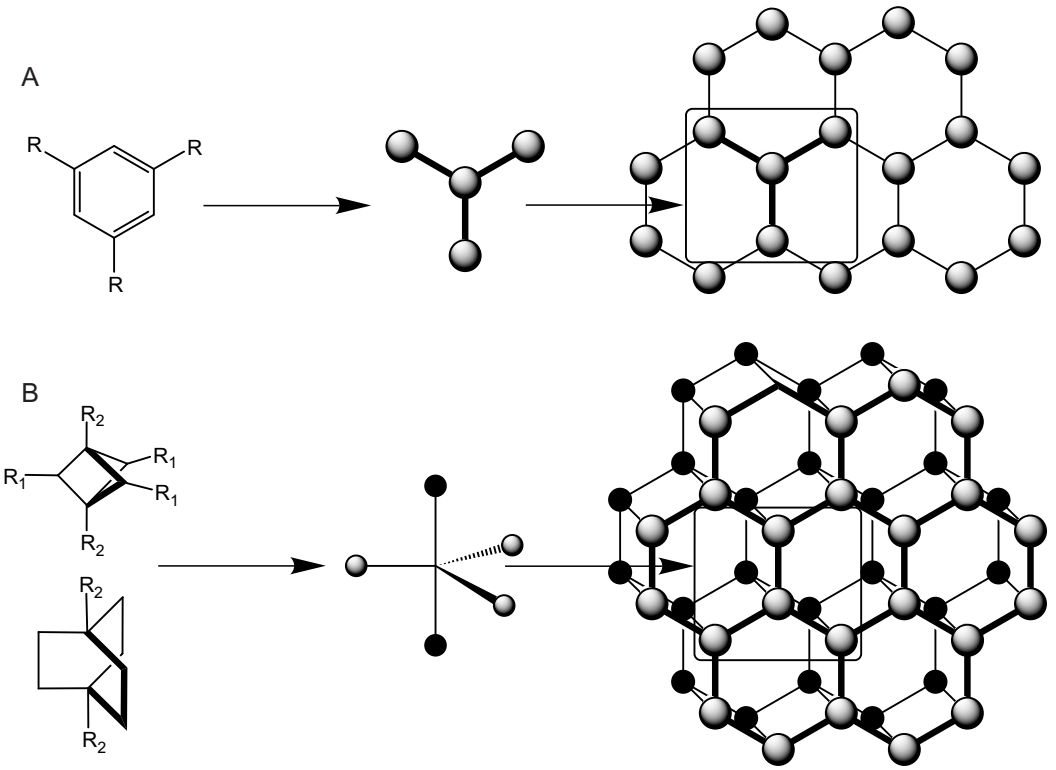

FIGURE 16.24 Examples of honeycomb scaffolding. (A) Planar structures formed from 1,3,5-substituted benzene rings. (B) bicyclo[1.1.1]pentane and bicyclo[2.2.2]octane modules as potential subunits for three-dimensional honeycomb structures.

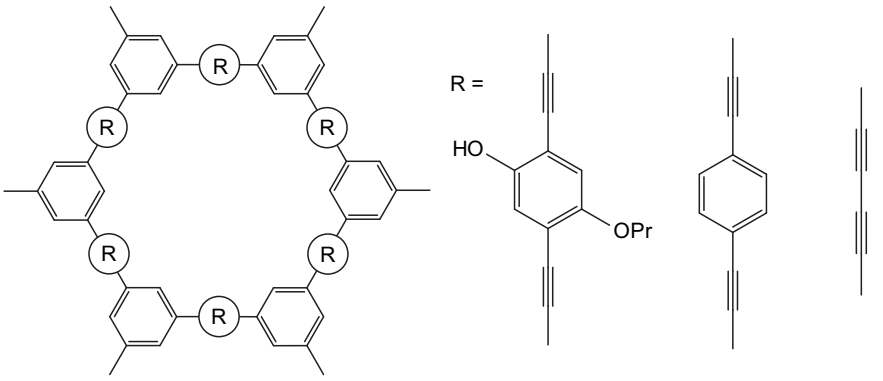

FIGURE 16.25 Isolated hexagonal macromolecules from benzene junctions.

extended arrays of hexagonal cavities from carboxylate-based hydrogen bonding interactions clearly demonstrates the importance of the geometry of the junction in directing the formation of the larger structures in solution (Figure 16.8). This same chemical design can be and has been employed successfully in a number of isolated benzene-based systems employing linear rods (Figure 16.25). Among the many known hexagonal macromolecules employing benzene junctions, many incorporate linear structures similar or identical to rod designs from the selected modules.[60–62]

The limitation of the benzene ring for scaffolding design is its planarity. While π-stacking interactions might be employed to form vertical honeycomb scaffolding, the covalent connection of hexagonal arrays into the third dimension is impossible with the benzene ring alone. From a structural standpoint, however, it is important to note that the only function of the benzene junction is to provide a triangular framework. Any other modules that incorporate equilateral triangles within their covalent frames will perform the same task. From among the remaining modules, the bicyclo[1.1.1]pentane and bicyclo[2.2.2]octane cages provide the correct symmetry and structural elements for the formation of planar arrays and vertical stacking through covalent bonds (Figure 16.25). The bicyclo[1.1.1]pentane is the better choice for designing such systems, as the structure is less flexible than the octane cage, and the carbons used for forming the hexagonal array from the linear rods have their available σ-bonds oriented in the hexagonal plane. The current limitation with the pentane cage for hexagonal designs is the synthetic precedent for the functionalization of the equatorial carbons, although these issues have recently received significant attention.[63]

16.3.2.3 Cubic Scaffolding

Idealized cubic lattices from the molecular Tinkertoy approach share a number of similarities with both the diamondoid and honeycomb designs. Structural connectivity in cubic lattices begins with octahedral junctions (Figure 16.26). Provided the junctions have ideal octahedral symmetry, the cubic lattices appear uniform with respect to all perpendicular sets of axes. The high symmetry of the idealized junction, as was found in diamondoid structures, permits the outward growth of the lattice from a single point by the addition of quantities of junction and linear rod without orientational preference. This simplifies the required control of the growth process relative to honeycomb structures, which have two different types of covalent connectivity that must be considered. Unlike the diamondoid structures, however, lattices formed from octahedral junctions have a very well-defined layering scheme along each axis. Therefore, a plausible growth process for the entire cubic lattice can mimic the same processes used for honeycomb growth, where a single layer is formed from two orthogonal sets of connections, while a third set perpendicular to the growing lattice plane remains unused until vertical connectivity is required. In instances where the growth process is selected to mimic the honeycomb methodology, the idealized octahedral junction can be separated into a square planar component and a perpendicular axial component. The selection of planar or vertical connectivity can be controlled during the growth process by chemical manipulation of the two distinct growth directions (Figure 16.26B).

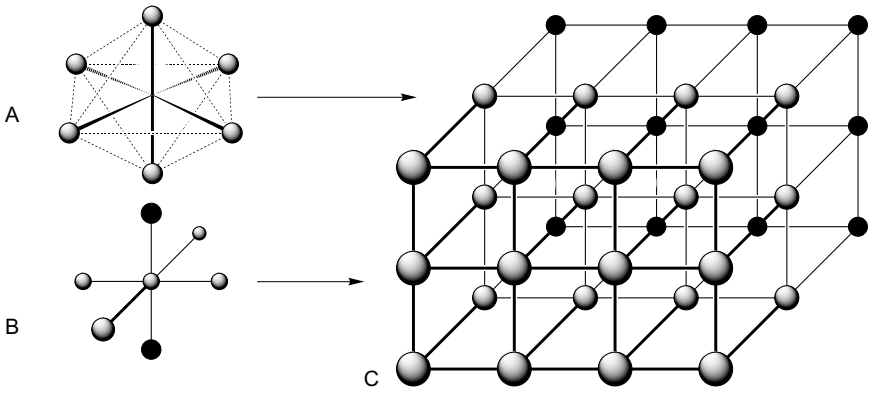

FIGURE 16.26 Cubic scaffolding. (A) Octahedral subunits for uniform structure growth. (B) Square-planar connectivity and vertical stacking connections for deformed cubic lattices. (C) A cubic lattice.

No single module provides the idealized octahedral connectivity required for uniform lattice growth in all directions. The design of two-dimensional square planar lattices can be readily designed from single σ-bond connectivity using porphyrins and cyclobutadiene metal complexes or double σ-bond/mixed σ–π connectivity using cyclobutane rings, stellanes, or adamantanes. Beyond the initial designs, however, the limited chemical precedent of a number of these modules prohibits their current usability. From these initial five modules, the porphyrins have been successfully employed in a number of rectangular and square planar arrays because of their extensive synthetic precedent and the availability of subsequent vertical connectivity through slight structural modification[64–65] (Figure 16.27). A number of linear rods have been used to connect porphyrins together, including ethynyl chains,[66] benzene chains,[67,68] chelating ligands,[69–72] and other porphyrins.[73–75] While the square planar framework has also been demonstrated

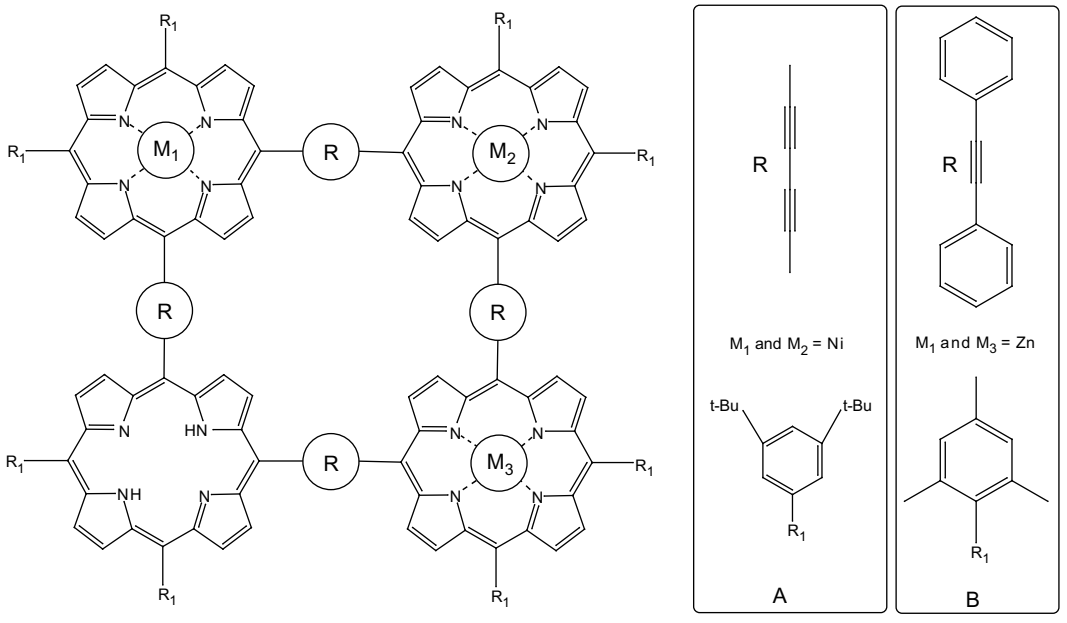

FIGURE 16.27 Porphyrin squares, connecting linear rods, and peripheral substitutions. (Set A from Sugiura, K., Fujimoto, Y., and Sakata, Y., A porphyrin square: synthesis of a square-shaped π-conjugated porphyrin tetramer connected by diacetylene linkages, *J. Chem. Soc., Chem. Commun.,* 1105, 2000; Set B from Wagner, R.W., Seth, J., Yang, S.I., Kim., D., Bocian, D.F., Holten, D., and Lindsey, J.S., Synthesis and excited-state photodynamics of a molecular square containing four mutually coplanar porphyrins, *J. Org. Chem.,* 63, 5042, 1998. With permission.)

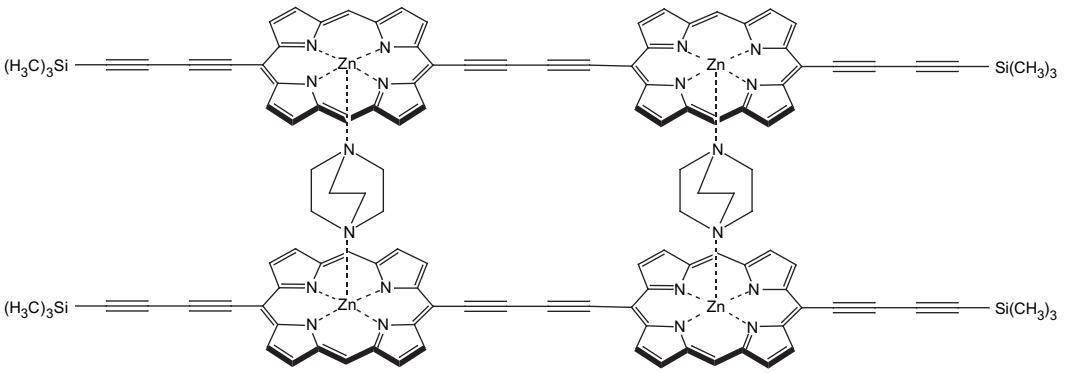

FIGURE 16.28 Metal–ligand coordination stacking design from porphyrins subunits.

with the cyclobutadiene metal complexes, the extension of these arrays into the third dimension is prohibited by the use of metal complexation to stabilize the highly reactive four-member ring.

Because no single module provides a chemically feasible route to vertical stacking after the formation of the square planar array, alternative stacking interactions must be employed for the formation of quasi-octahedral complexes. The porphyrins provide this added functionality by way of metal complexation within the central core. The coordination center within the porphyrin core then requires the use of metal–ligand complexation to form the vertical stacking interactions. The same directionality provided by covalent σ-bonding is still available from metal–ligand coordination, however, and the relative strengths of these stabilizing interactions can be controlled by the choice of metal. While a module-derived dipyridine structure is plausible based on the axial positions of the nitrogen lone pairs, the known vertical stacking motif has been performed with 1,4-diazabicyclo[2.2.2]octane,[76] the axial coordination analogue of bicyclo[2.2.2]octane (Figure 16.28).

The exclusive reliance on covalency for the fabrication of a nanostructure is not without important limitations. One limitation stems from the essentially irreversible formation of covalent bonds. In the formation of larger systems, extreme care must be taken to make chemical reactions as predictable and unidirectional as possible. The thermodynamically driven self-correction mechanisms of biological systems and supramolecular crystals cannot be used to repair an "incorrect" covalent bond without jeopardizing the structural integrity of the remaining structure. When an unwanted covalent bond forms, the means to correcting the error often involves harsh chemical manipulation. Thus, when a chemical route is chosen to correct some structural error, the pathway must be tailored to avoid reacting with any other part of the molecular superstructure. Also, because a chemical reaction is required to form a covalent bond, any structures employing a covalent bond are not strictly self-assembling. In a hydrogen-bonding network, for instance, the lattice forms due to electrostatic interactions between donors and acceptors. The stability that comes with these weak interactions may be small, but the formation of the larger network provides significant stabilization and the structure spontaneously forms. The formation of covalent architectures typically requires control of environmental conditions and subsequent purification of the desired product from the remainder of the reaction mixture.

A variety of chemical considerations associated with the synthesis and characterization of these structures has also been considered within the context of the Tinkertoy approach.[10] First among these considerations is the solubility of the progressively larger structures. The growth of larger structures is often limited by the ability to keep the assembly in solution. The chemical methods most likely to keep a larger structure in solution, such as the addition of side chains or the use of charged species, often have their own drawbacks. For instance, the application of these solvation techniques can affect the function of the nanostructure in unpredictable and undesired ways. With issues of solubility come problems of separation and purification. Such issues are familiar to biochemists, however, and many of the same techniques that have permitted the separation of biomolecules can also be applied to nanostructures.

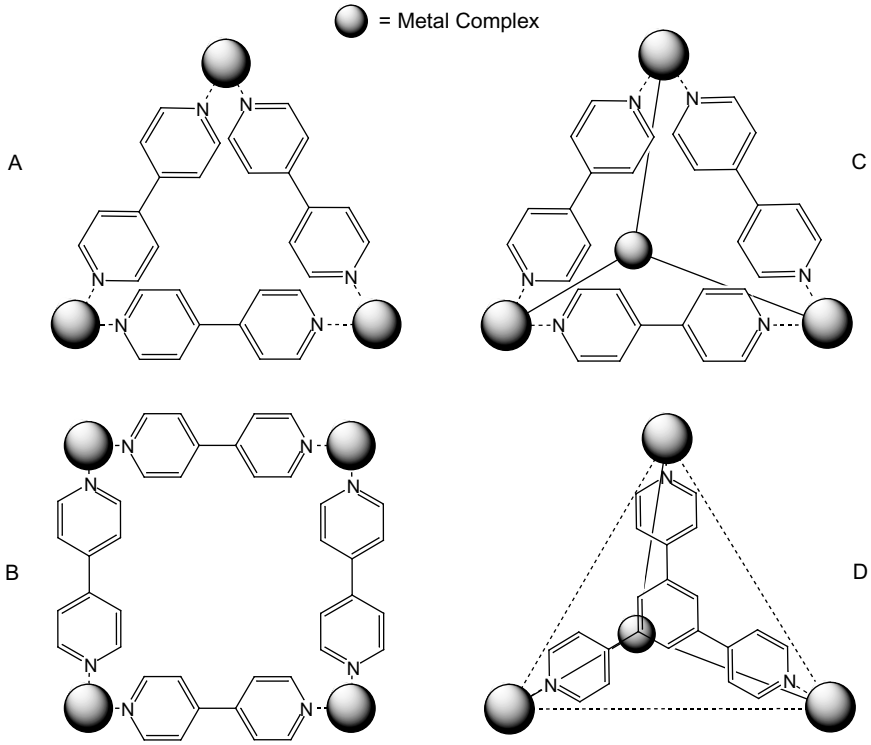

FIGURE 16.29 Metal–ligand structural motifs. A (triangle) and B (square) are two-dimensional structures with the ligands defining the sides. C and D (tetrahedrons) are three-dimensional structures with the ligands defining either the sides (C) or the faces (D).

16.3.3 Transition Metals and Coordination Complexes

One of the great advances in macromolecular design has been in the development of a variety of metal complexation motifs for the formation of two- and three-dimensional nanostructures. The design features here are based on the chemistry of small metal–ligand compounds, where the coordination requirements of the metal direct the attachment and orientation of ligands. The formation of larger geometric structures from metal–ligand compounds typically comes through the use of ligands with two or more separate metal-coordinating regions (Figure 16.29). In two-dimensional designs, the ligands typically constitute the sides of the structure while metal complexes define the corners. In three-dimensional designs, the ligands delineate the faces of the structures with the metals occupying the vertices. The chemistry involved in the formation of these nanostructures is often straightforward. The nanoscale assembly of coordination complexes is typically accomplished by the removal of labile ligands from some coordinately saturated metal complex in solution, a process greatly simplified by the relatively weak strengths of many metal–ligand bonds.[77] Coordination-based methods not only allow for the formation of symmetric molecular nanostructures but also provide for the formation of molecular cavities through ligand encapsulation pathways[78–80] (Figure 16.30).

The vast majority of coordination nanostructures have been based upon the use of chelating organic ligands, with either nitrogen atoms as the lone-pair donors or cyclic ligands with hydroxyl (-OH) groups used to provide metal connectivity through relatively weak covalent metal–oxygen bonds. Nitrogen-based ligands have been used far more often in coordination-based nanostructure design and are preferred among other ligand types for a number of structural reasons. The nitrogen atom is a close structural analogue and is isoelectronic with a covalent C-H fragment, making it quite versatile in the modification of organic ligands for metal complex formation (Figure 16.31). Whether incorporated into a saturated

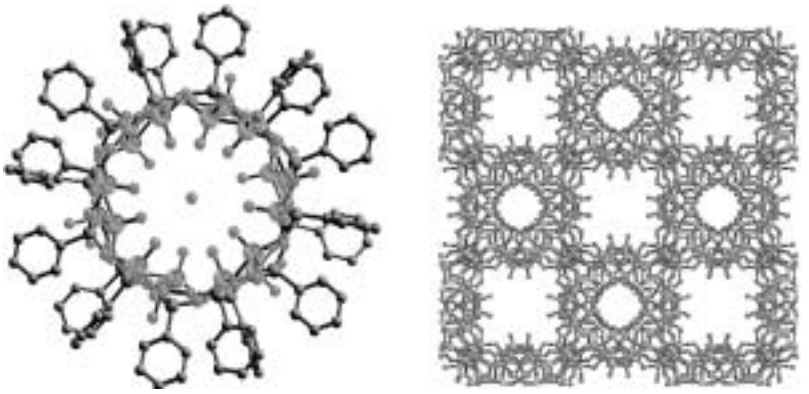

FIGURE 16.30 Structures with metal–ligand coordination cavities and channels.

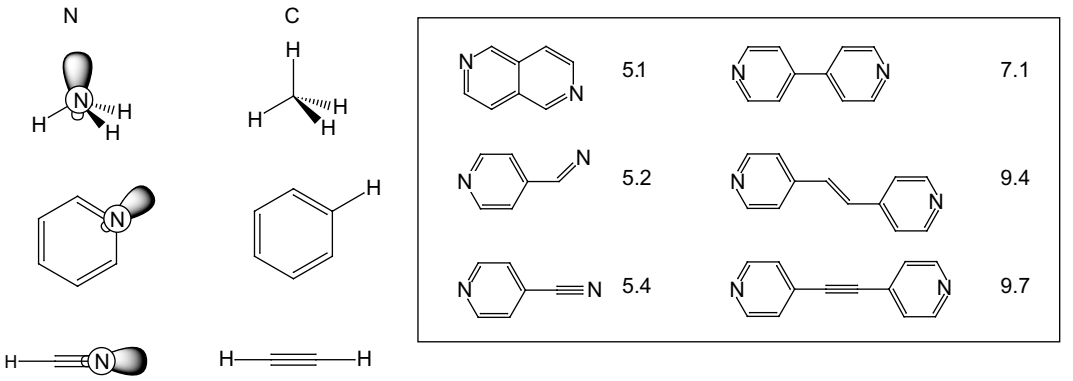

FIGURE 16.31 The inclusion of nitrogen (left) lone-pair donors into simple organic frameworks and a selection of N-N distances (in Angstroms) in common organic ligands.

aliphatic framework or directly into an aromatic ring to form a heterocycle, a nitrogen atom and a C-H fragment are nearly identical in terms of hybridization and geometry except that a hydrogen atom is required to form a complete electronic octet for carbon. The radial orientation of the lone pair from the backbone of many ligands provides accessibility to coordinating metals, while the σ-bond quality of the lone pair provides predictable, unidirectional coordination based on the geometry of the nitrogen atom in the ligand. These organic ligands can be designed such that the nitrogen lone pair is the only site on the ligand available for coordination to the metal center in nanostructure formation. The nitrogen lone pair, in the absence of a Lewis acid, becomes the reaction center for complexation only when the metal center becomes coordinatively unsaturated, typically by chemical methods too gentle to affect the ligand framework. This predictability in nitrogen–metal coordination comes from a vast synthetic precedent, ranging from the simple coordination of NH_3 to the complexation of multidentate ligands that serve to singly saturate the metal coordination sphere. Furthermore, the dissociation of the nitrogen-based ligand from the metal center has little effect on the stability of the ligand itself, providing a thermodynamic means for controlling the formation and self-maintenance of these systems. The chemical modification of these ligands also has significant structural implications for the resulting assemblies. Simple modification to the organic framework of these ligands can target macromolecular structures to within a few Angstroms of some specified size (Figure 16.31). Similar to the molecular Tinkertoy approach, ligands can be modified either step-wise through the addition of linear linkers (such as acetylene) or more subtly using nonlinear linkers, such as either flexible ring systems or saturated organic chains.

Similar to the study of structure and function in biomolecules (*vide infra*), much of the initial work in metal complexation involved the modification of known structures to create new structures. As the

field has progressed, the catalogue of structures and reactions has increased to the point where trends and designs have been focused into general strategies for fabricating new structures. The two most actively investigated approaches to designing coordination architectures are discussed below.

16.3.3.1 Molecular Library Model

The molecular library model,[81] also known as the *directional-bond approach*,[77] is the metal–ligand analogue to the molecular Tinkertoy approach. The model addresses the design of nanostructures by using a set of molecular fragments encompassing a wide range of geometric patterns for the fabrication of two- and three-dimensional structures. In this approach, a *geometric fragment* is simply some subunit of a larger structure, such as a corner, a vertex, or a side. To classify a ligand or metal complex into a particular fragment category, a structural analysis is performed to determine the angles among all available coordination sites in the molecular framework. The choice of ligands is typically limited to rigid molecules with monodentate coordination modes (single lone pairs) in order to improve the predictability of the method for nanoscale design.[82] The number of candidate ligands is very large, however, and the restriction to molecules with limited degrees of freedom does not significantly affect the flexibility of the method. The rigidity of both the ligands and the metals is used only to restrict the choices of geometric fragments for particular designs, and a small amount of flexibility in the ligands and metal coordination sphere is expected in the assembly process. An important aspect of this approach is that both ligands and metals can be used as the fragments to form a structural feature. A nonlinear or multi-branched ligand, for instance, can be used as a corner or a vertex just as a metal with axial coordination sites can be used as a side. It is the higher coordination of ligands to a metal center that sets the metal apart from organic systems, however, and the metal is most frequently employed as the more complicated geometric fragment.

The range of available ligands and metal complexes has been divided into two libraries based on the dimensionality of the desired structure[81] (Figure 16.32). For the design of two-dimensional nanostructures, such as regular polygons or polycyclic assemblies, the classification of doubly connecting, or *ditopic*, geometric fragments requires only three points. In the ligand, these points are composed of two lone-pairs and the center of the covalent framework of the ligand (Figure 16.33). In the metal complex, these three points are the two coordination sites for the connected ligands and the metal atom (Figure 16.33). The internal angles of the desired nanostructure then determine which fragments can be used for its fabrication. For the fabrication of cyclic polygons with three to six sides, the internal angles and combinations of geometric fragments required are summarized in Figure 16.32 (A–I). It is important to note that these ditopic classifications define only individual sets of binding angles within a molecule. Within a molecule used as a geometric fragment in a larger structure, it is possible to have independent sets of binding angles. Consequently, structures with multiple planar rings are possible (Figure 16.33).

Three-dimensional nanostructures are fabricated from combinations of tritopic and ditopic geometric fragments. Symmetric three-dimensional structures resulting from various combinations of tritopic and ditopic fragments are shown in Figure 16.32 (J–M). The design strategy for new nanostructures is the same in both two- and three-dimensional systems, except the additional level of complication of three-dimensional structures requires more elaborate geometric fragments for the assembly. In both library sets, the linear linkage serves the important roles of length extender and coupler for identical fragments. It should be noted that length is not a factor considered in the classification process. Modifying the length of a structure is a matter of either modifying the molecular bridge between coordinating regions of a ligand or using linear subunits of the appropriate length with metal complexes at the corners (two dimensions) or vertices (three dimensions).

16.3.3.2 Symmetry Interaction Model

The symmetry interaction model[80,83] is founded in the understanding that many highly symmetric, naturally occurring structures are formed as a consequence of incommensurate lock-and-key interactions between the subunits.[84] The method, as applied to metallocycles, is then retrosynthetic in principle, using

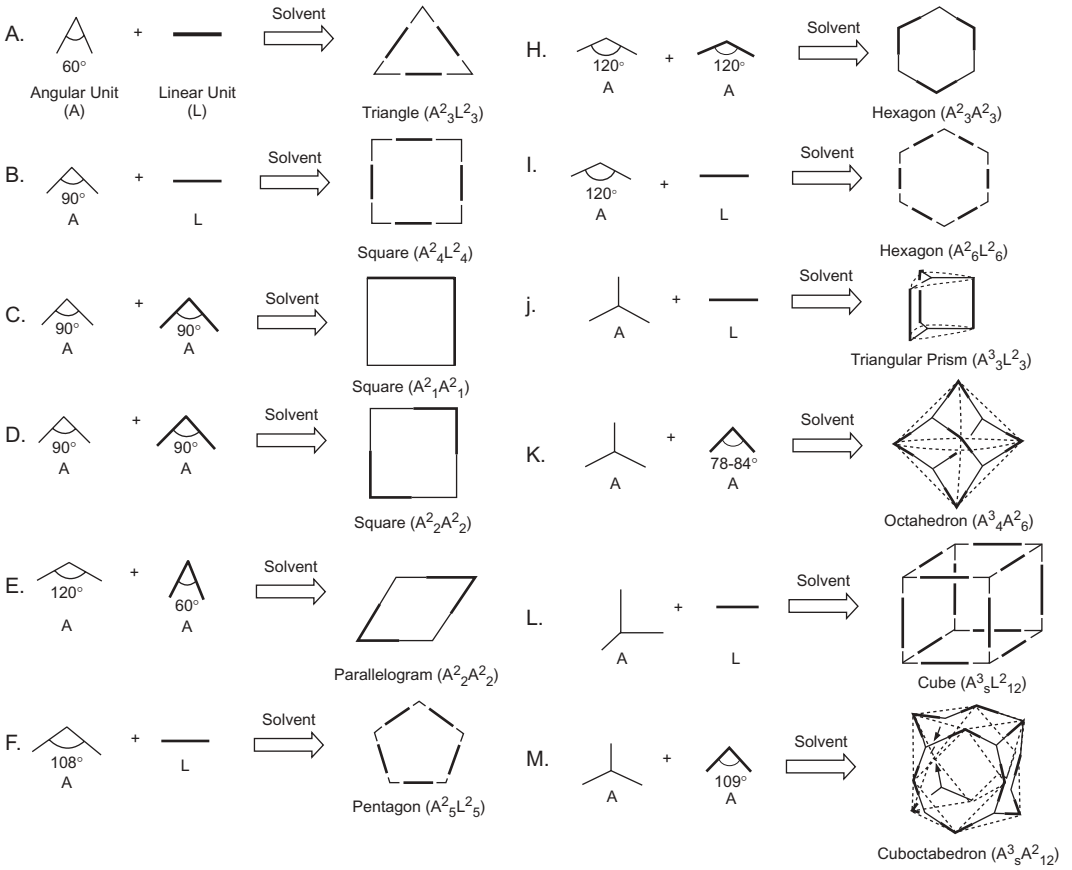

FIGURE 16.32 Metal complex and ligand classifications for two- and three-dimensional coordination nanostructures in the molecular library approach. (From Stang, P.J. and Olenyuk, B., Self-assembly, symmetry, and molecular architecture: coordination as the motif in the rational design of supramolecular metallacyclic polygons and polyhedra, *Acc. Chem. Soc.*, 30, 502, 1997. With permission.)

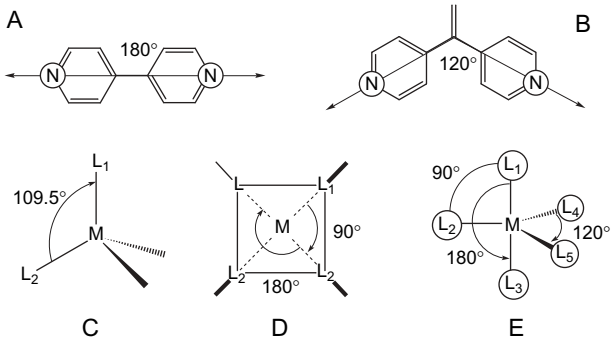

FIGURE 16.33 Binding angles in a selection of ligands (A, B) and metal complexes (C–E). Note that two unique angles are available in square planar structures (D), and three unique angles are available in trigonal bipyramidal structures (E).

the known geometric features of highly symmetric polyhedra to direct the formation of new metal–ligand assemblies. This model differs from the molecular library model in two important respects. First, there is a definite division between the role of the metal and the role of the ligand in the symmetry interaction

model. This is in contrast to the molecular library, where both ligands and metal complexes can be used anywhere within the skeleton of a nanostructure to create corners, vertices, or sides. Second, through the selection of geometric fragments in the molecular library approach, the binding angles within each metal are determined by the orientation of the leaving groups on the metal. The remainder of the metal coordination sphere is saturated with other ligands that retain their coordination positions during the nanostructure fabrication process. The symmetry interaction model relies on the strong binding of chelating ligands to saturate the entire coordination sphere of the metal ion.[82] The coordination sphere of the metal, then, is responsible for defining the orientation of the ligands in the final structure, while the ligands are responsible for forming the sides (between metal–metal pairs) or faces (binding three metals) of the structure (Figure 16.29). The use of chelating ligands in the symmetry interaction model has the benefit of increased stability in the final structures through the formation of multiple coordination bonds per ligand and the inherent kinetic stability that comes from the chelate effect.[8] The important components in the symmetry interaction model are the orientation of the lone pairs of the chelating ligands within the organic framework and the geometry of the coordination sphere of the main group or transition metal atoms.

The development of a rational design strategy for the symmetry interaction model is more complex than for the molecular library model. In the symmetry interaction model, a library of angles and interactions based solely on the choice of metal or ligand is not employed. Instead, the design of nanostructures from this approach requires an understanding of the chelating ligands and the coordination sphere of the metal ion. Among the coordination nanostructures, most of the designs applicable to the symmetry interaction approach are based on the use of tetrahedral (4-coordinate), square planar (4-coordinate), and octahedral (6-coordinate) structures (Figure 16.34). As the ligands themselves are not responsible for imparting dimensionality to these designs, polyhedral coordination nanostructures based on the symmetry interaction approach employ metal ions with octahedral coordination spheres. This limitation does simplify the design process because it is possible to classify the available metal ions according to their coordination numbers. Because this methodology requires that the metal be stripped of ligands prior to nanostructure formation, it is also possible to select metal–ligand starting materials based on the lability of the metal complex ligands under certain reaction conditions.

A means has been developed to understand the spatial relationships between the metal coordination sphere and the attached ligands by defining common geometric features and determining their importance in the fabrication process.[80,84] Because the method relies heavily on the use of symmetry to define the geometric features of both the interactions and the assemblies themselves, highly symmetric structures, such as Platonic solids, can be fully analyzed by considering their vertices. The coordination sphere of the metal, where all of the connectivity and structural determination occurs, is divided into a *Coordinate Vector*, a *Chelate Plane*, and an *Approach Angle* (Figure 16.35). The coordinate vector is defined as the vector between the coordinating atom(s) of the ligand and the metal. In chelating ligands, the bisection point of the lone pairs and the metal atom forms this vector. In monodentate ligands, this vector is simply along the lone pair–metal bond. The coordinate vectors and the rotation axis of the metal that would

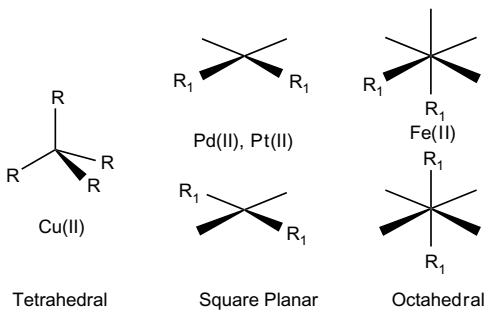

FIGURE 16.34 Coordination geometries for common metal ions.

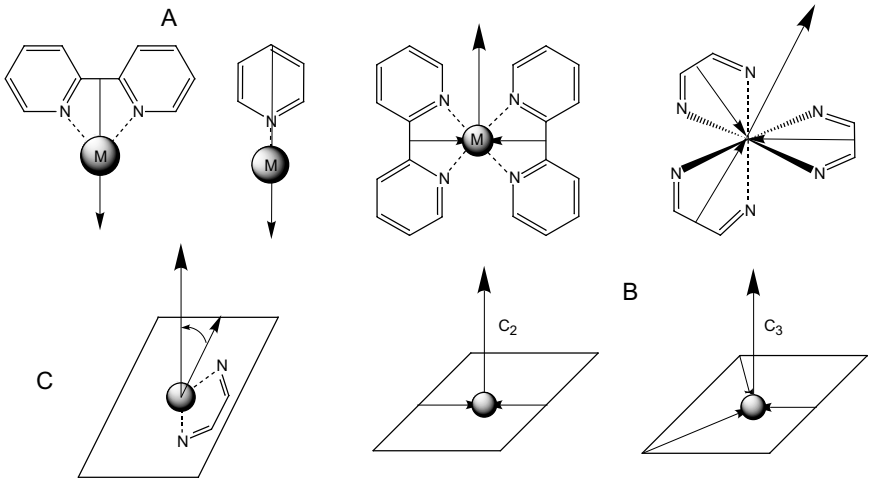

FIGURE 16.35 (A) Coordinate vectors. (B) Chelate plane. (C) Approach angle.

transform one ligand into an adjacent ligand then define the chelate plane. In metals with three ligands, only the three coordinate vectors of the ligands are required to define the chelate plane. In metals with two ligands, defining a third axis perpendicular to the coordinate vectors and the major rotation axis of the metal–ligand complex designates the chelate plane. The approach angle is defined as the angle between the major axis of the metal center and the plane of the chelating ligands in the final structure.

A demonstration of the geometric features in assembled macromolecules is provided here for two structures (Figure 16.36). In a helical, D_3-symmetry structure composed of two metals and three chelating ligands (simplified to M_2L_3), the orientation of the ligands in the coordination sphere of the two metals requires that the two chelate planes be parallel to one another. The C_3-rotation axes and the C_2-rotation axes that bisect each shared ligand of the two metals are then automatically aligned. Within any such helical or rod-like structure of D_{3h} symmetry, the local features of the metal coordination sphere are consistent. The selection of metal–ligand sets can be directed by the known geometric requirements of the structure. The formation of a molecular tetrahedron from chelating ligands and metals can be completed by either an M_4L_6 combination, where six ligands are required to form each of the skeletal components, or an M_4L_4 combination, where each ligand consists of the three chelating sites related by a C_3-rotation axis through the plane of the ligand (Figure 16.36). Each metal is bound to three chelating

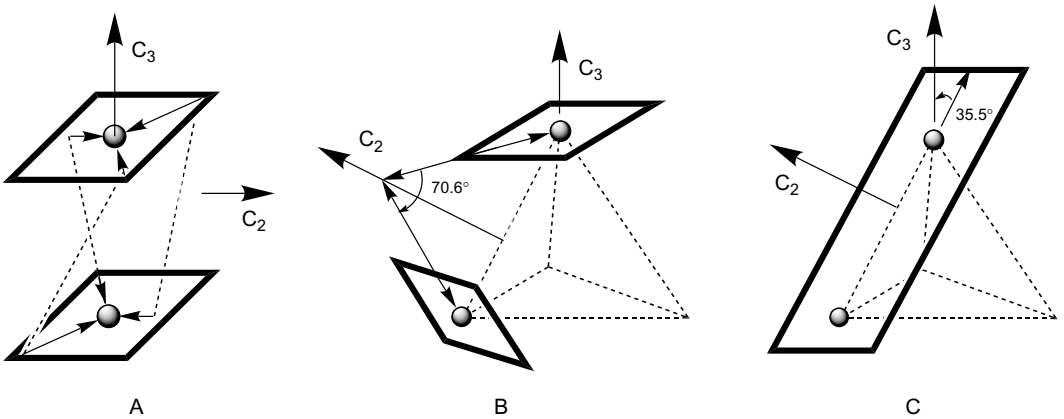

FIGURE 16.36 Structural examples of the symmetry interaction approach. (A) D_3-symmetry helix. (B) Tetrahedron from coordinate vector description. (C) Tetrahedron from approach angle description.

ligands, with the chelate plane defined by the coordinate vectors at each vertex. In the M_4L_6 case, the C_2-rotation axes bisect the ligands along the tetrahedral skeleton. The C_2-rotation axes in the M_4L_4 case are at the same positions in the tetrahedral frame, although the skeletal framework of the tetrahedron is only inferred because all ligands are now facial. The idealized tetrahedron is defined from the coordinate vectors of two coordination centers along a single C_2-axis, making a theoretical angle of 70.6° with respect to the relative orientations of the chelate planes (Figure 16.36). In cases where the chelating ligands are held planar to one another and are orientated antiparallel, the approach angle can be used as the defining feature of the metal–ligand interaction. In a tetrahedron, the use of these ligands requires that the approach angle be 35.3°. Given a coordination nanostructure, all of the isolated metal–ligand complexes can be treated by similar symmetry descriptions. From the geometric relationships of the metal–ligand interactions and the structural features of the isolated metal–ligand complexes, an understanding of many macropolyhedral structures made from metal–ligand interactions becomes possible.

16.3.3.3 Two-Dimensional Structures

Two-dimensional polygons fabricated from metal–ligand interactions have extensive synthetic precedent, and there is virtually no limit to the possible structural combinations that can be made from very simple synthetic modifications.[82] As systematized in the molecular library approach,[81] the specific structural features (side lengths and internal angles) of many regular polygons are chemically accessible by employing bis-monodentate ligands (although bis-bidentate ligands are also appropriate with certain metal centers) and coordinatively unsaturated metal centers. While the control of structural features may not be absolute compared to proposed atomistic[6] or molecular Tinkertoy[53] methods, the approach and the many available structures provide the means for controlling size and shape well below the nanometer threshold in a highly predictable manner. This control over structural features is incorporated both within the extensive synthetic precedent for the organic ligands and the selectivity for coordination number and ligand type among the available metal complexes. With the structural variety of geometric fragments in the molecular library also comes the ability to select for chemical reactivity.

The flexibility of the metal–ligand bond in polygon formation is highlighted here by a selection of palladium- and copper-based systems below (Figures 16.37 and 16.38). The commonly employed palla-

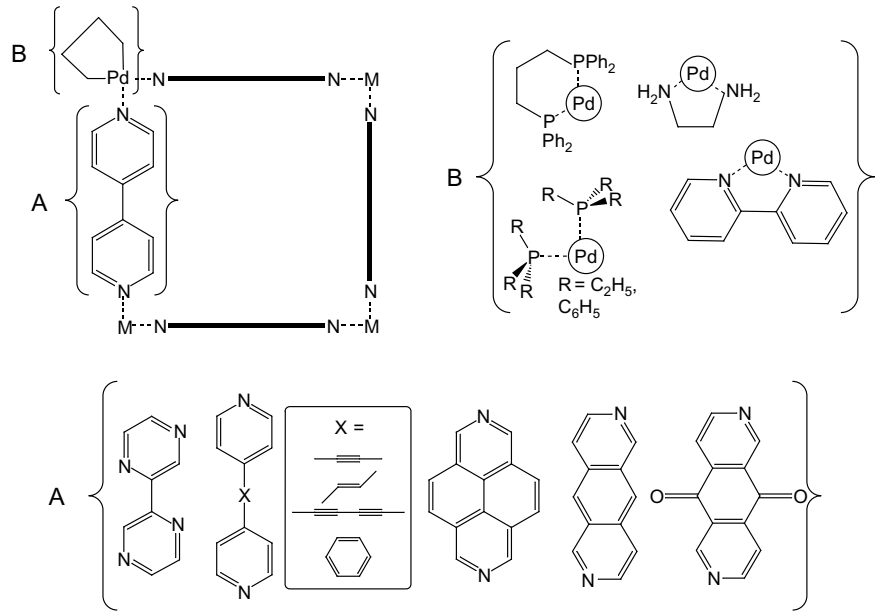

FIGURE 16.37 A selection of known square planar palladium(II) coordination structures. (A) Coordinating ligands. (B) Metal centers with auxiliary ligands.

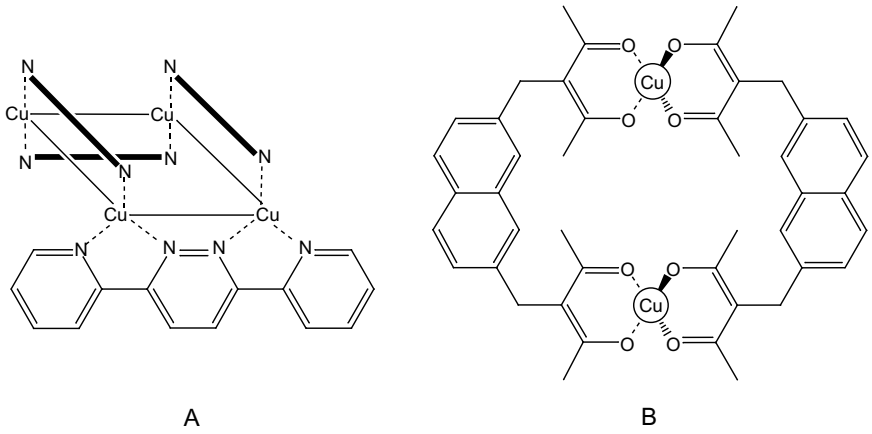

FIGURE 16.38 Tetrahedral metal–ligand centers for copper(I) complexation structures.

dium(II) ion (as well as platinum(II)) is square planar, providing a perpendicular pair of coordination sites for monodentate ligands. Consequently, molecular squares are a familiar result of their use. The copper(I) ion, as a tetrahedral coordination center, is useful for connecting bidentate ligands perpendicular to one another.[85–89] Besides the obvious differences in ligand placement and orientation come the differences in ligand mobility. In the palladium-based nanostructures, single metal–ligand σ-bonds provide free rotation about the coordination site and greater structural flexibility. With bidentate coordination in the copper complexes, structural flexibility is greatly limited.

A selection of known palladium–nitrogen coordination combinations is shown in Figure 16.37. Although polygons with more sides are possible, structures usually contain from three to six sides.[82] In the structures where the palladium is used as a corner, the metal is delivered to the reaction mixture with one bidentate ligand (typically diamine [H_2N-R-R-NH_2] or diphosphine [Ph_2P-R-R-PPh_2]) and two labile ligands. Many nanostructures based on the molecular library model incorporate both strongly binding and weakly binding ligands in the same metal complex to allow for greater control over the ligand coordination position.[82] In tetrahedral metal complexes, where the two labile ligands are always next to one another, the difference in metal–ligand bond strengths serves to control which ligands are removed during nanostructure formation (Figure 16.34). In the square planar and octahedral cases, different isomers place the labile ligands at nonadjacent positions. Both the bond strengths and the ligand positions must be accounted for in the selection of the metal complex. When labile ligands are oriented 180° to one another in the palladium systems, these complexes become linear linkages suitable for use as the sides of polygons.

The formation of the palladium(II) nanostructure begins with the removal of the labile ligands. Two common labile ligands in palladium(II) complexes are triflate (OTf^-) and nitrate (NO_3^-) anions. Their removal leaves both an open coordination site and a positive charge on the metal. The oxidation state of the metal changes as a result of the loss of an unpaired electron to a highly electronegative atom. In OTf^- and NO_3^-, the two electrons are lost to form the palladium(II) ion due to the electron-withdrawing oxygens on each ligand. Coordination of bis-monodentate ligands then leads to the formation of the polygon sides. The process is repeated until each metal has lost its labile ligands and coordinated an equal number of nitrogen ligands.

The square planar geometry of the palladium(II) does not limit its applicability to polygons with more or fewer than four sides. The otherwise disfavored formation of strained complexes, such as molecular triangles from square planar palladium(II) cations, can be forced to occur in a system by steric[90] concentration (enthalpy/entropy arguments),[91,92] or guest–complexation effects.[92] For instance, the replacement of the small bidentate ethylenediamine ligand with 2,2′-bipyridine results in the formation of both squares (the preferred structure with the smaller ligand) and triangles in solution from steric effects[92] (Figure 16.39). Both concentration–dependence and guest–complexation were found to play important

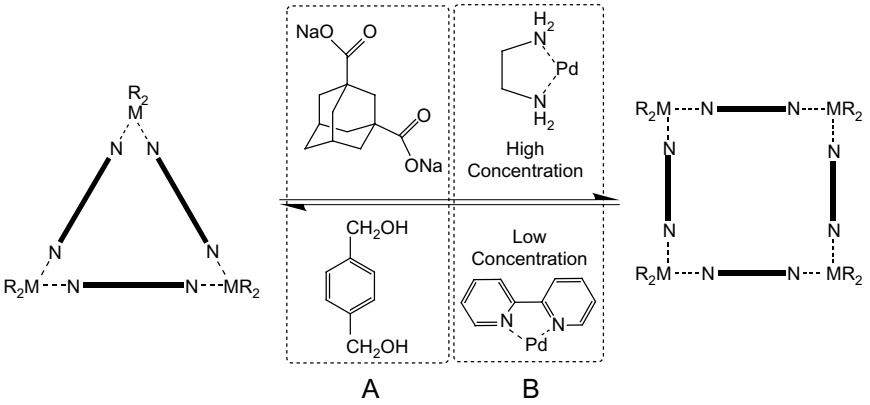

FIGURE 16.39 The direction of triangle or square formation in solution. (A) Steric bulk of polar groups within the nanostructure. (B) Steric bulk of auxiliary metal–ligands or concentration of the coordination nanostructures in solution.

roles in controlling the equilibrium of one palladium(II)-based assembly[47,48] (Figure 16.39). By varying the concentration of palladium(II) complexes (salts of ethylenediaminepalladium with either triflate or nitrate) and bidentate ligands (trans-1,2-bis(4-pyridyl)ethylene), the formation of triangles or squares could be directed.[92] At low concentrations (0.1 mM), triangles were favored due to entropic effects. At higher concentrations (10 mM), the more stable molecular squares were favored. Guest–complexation was found to affect the concentrations of trimer and tetramer in solution by directing either the triangle or the square to form with the addition of *p*-dimethoxybenzene or a disodium salt of 1,3-adamantanedicarboxylic acid, respectively[92] (Figure 16.39). Alternately, the incorporation of flexible bis-monodentate ligands can be used to form triangles from the square planar palladium(II) ion.[93] In instances where the labile ligands of the palladium(II) complex were oriented 180° from one another, coordination polygons with various numbers of sides were fabricated by altering the binding angle of the ligands. This is the method employed in one instance for forming molecular hexagons and pentagons in solution.[82,94]

Copper(II) has been used as the coupling element for a number of both two- and three-dimensional nanostructures.[85–89] The formation of small molecular squares using four copper(I) ions was made possible by the use of 3,6-bis(2′-pyridyl)pyridazine and copper(I) triflate.[88] In this design, the tetrahedral coordination center of the copper(I) ion fixes two pairs of bidentate ligands perpendicular to one another on opposite sides of the coordination plane of the four metal centers (Figure 16.38A). The characterization of this molecule indicated that the close proximity of the ligand rings to one another allows for a favorable π-stacking interaction, increasing the overall stability of the entire molecule.[88] Two copper(I) ions can also be used with ligands containing flexible bidentate regions to form molecular squares.[89] The free rotation of the bidentate branches in a bis-dione allow for one such dinuclear copper(I) complex[90] (Figure 16.38B). As will be discussed below, the copper(I) ion is very well suited to using the same types of bidentate coordination to form three-dimensional structures.

16.3.3.4 Three-Dimensional Structures

The spontaneous formation of three-dimensional architectures from noncovalent self-assembly is a common occurrence in biological systems. In proteins, the spontaneous formation of structure and function occurs at the most basic level, with hydrogen bonding along the polypeptide chain to form the secondary structure, and also among the largest of the aggregate protein interactions, such as in many viral and bacterial capsids. The tetrahedral bonding in carbon places significant restrictions on the geometric flexibility of the designs. This requires organic systems to use larger molecular subunits, such as amino acids and nucleotides, in order to gain enough structural flexibility to create complex structures. In contrast, the use of metals in the design of nanostructures, especially in smaller nanosystems, offers far greater flexibility for the formation of structurally complex macromolecules from

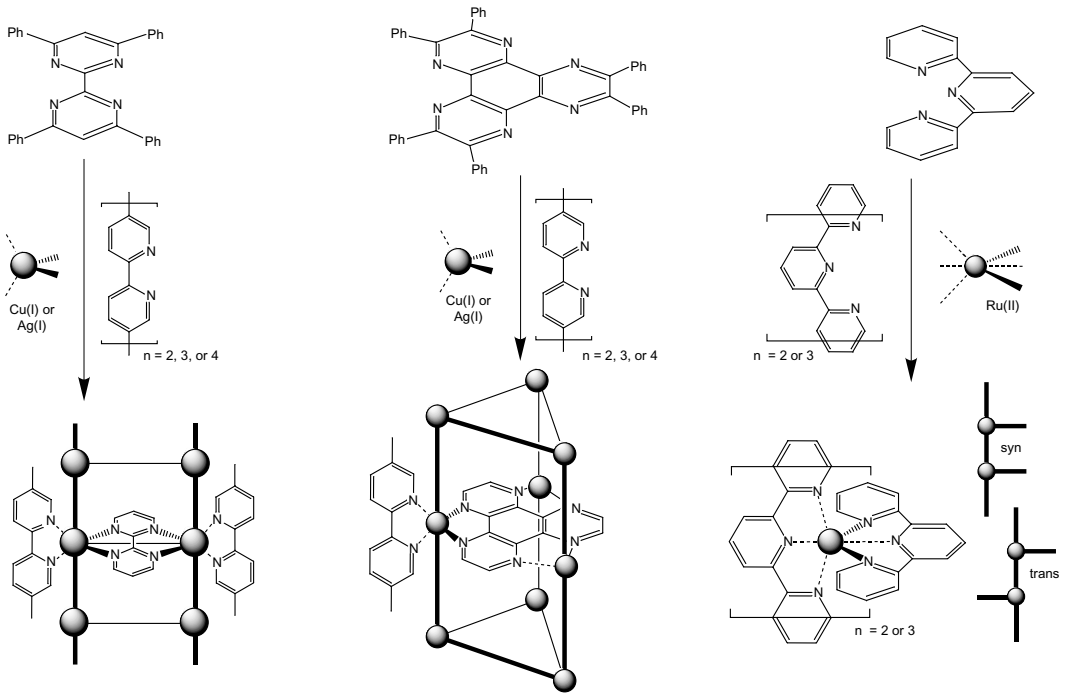

FIGURE 16.40 Ladders (left), rods (middle), and racks (right) formed from metal–ligand coordination.

controllable chemical and electrostatic interactions. The same advantages for creating two-dimensional structures from metal–ligand interactions are also realized in the third dimension, and both monodentate and bidentate (chelating) ligands have been used prominently in the formation of three-dimensional nanostructures.

The synthetic precedent for three-dimensional architectures can be divided into two broadly defined categories. The first of these categories includes linear coordination complexes such as ladders, racks, rods, and helices. Such systems are based on the vertical stacking of identical ligand–metal coordination regions and are extendable by modifying the lengths of the subunits that define their walls (Figure 16.40). The second category encompasses the polyhedral macromolecules. These systems confine the coordination regions to vertices instead of linear arrays, resulting in unimolecular architectures with dimensional customizability confined to modification of the ligands that define the sides (bis-chelating ligands) or faces (tri-chelating ligands) (Figure 16.41).

Ladders and rods are fabricated using tetrahedral-coordinating metals that act as *spiro*-centers between two different ligands to lock them in place and perpendicular to one another (Figure 16.40). Both ladders and rods utilize the same coordination center and a repeating sequence of covalently bound bidentate ligands to act as the vertical stabilizers (walls). Two such ladder structures employ a tetraphenyl derivative of the tetradentate bipyrimidine as the horizontal ligands, or rungs, and copper(I) as the metal centers to coordinate the rungs to 2,2′-bipyridine chains[95] (Figure 16.40). Three known rods were fabricated similarly, utilizing tetrahedral metal centers (copper(I) or silver(I)) and the same ligand chains of 2,2′-bipyridine as the vertical supports. These rod structures, however, employ hexaphenyl derivatives of hexaazatriphenylene as the tridentate ligands for the horizontal supports.[86] Molecular racks are based on the same basic ideas. These systems, however, employ tridentate ligands and six-coordinate metal centers to form rigid arrays. Because only one extended vertical chain is required to form these structures, racks can be formed from isomers of the same repeating tridentate motif.[96] A variety of *syn*- and *trans*-isomers of ruthenium(II) racks have been synthesized through thermodynamic self-assembly using vertical chains with both two- and three-tridentate subunits[97,98] (Figure 16.40).

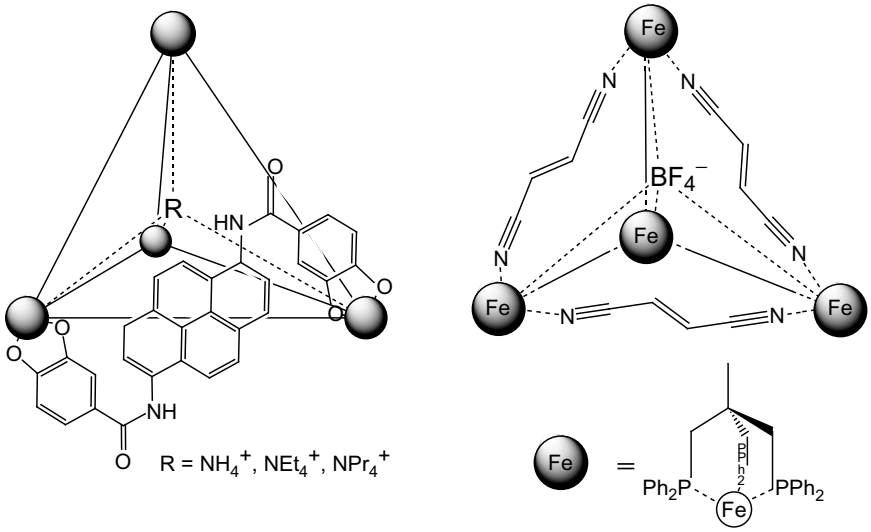

FIGURE 16.41 Coordination tetrahedra and encapsulation of guest molecules. (A) Symmetry interaction-based coordination tetrahedra and a series of encapsulated cations. (B) Molecular library-based tetrahedra and encapsulated boron tetrafluoride ion.

The symmetry interaction approach has been used extensively in the design and study of homodimetallic helicates.[77] The majority of these structures share the same design features, including the utilization of two octahedral coordination centers and three ligands composed of two bidentate regions and various organic bridges that provide unrestricted rotation about the bridge–bidentate bond. The chelate planes of the octahedral metal pairs are held parallel, requiring that each set of three bidentate ligands be provided with enough rotational flexibility to orient themselves along the C_3 rotation axis of the coordination spheres (Figure 16.42). The customization of the helicate shape is limited to modification of the ligand lengths. From among a set of common bidentate motifs, including those shown in Figure 16.42, any of a number of organic structures have been employed as bridges to vary the helicate length.[80]

It is remarkable that often the only requirements for the formation of macromolecular polyhedra are highly coordinating metal centers and multi-branching ligands. Many of the resulting macromolecular polyhedra, because their formation and stability are based only on metal–ligand coordination along the periphery, are skeletal structures with hollow cavities. Because the exteriors of these hollow polyhedra can be often deformed or broken through thermodynamic manipulation, it becomes possible to incor-

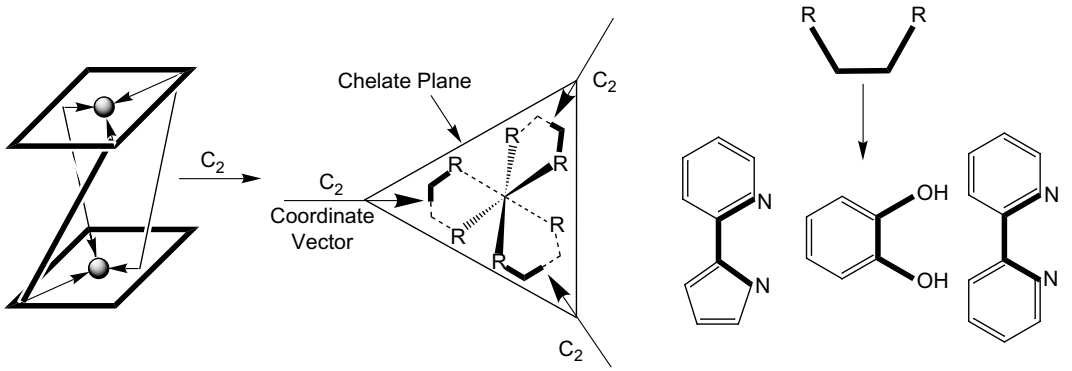

FIGURE 16.42 Helicate formation from the symmetry interaction model. At right is a selection of employed chelating ligand fragments.

porate smaller molecules into the polyhedral cavity in solution. Consequently, these macromolecular coordination polyhedra can act as large host molecules for the incorporation of single-guest molecules or collections of molecules for isolated chemical or structural studies.

Coordination tetrahedra are the smallest of the polyhedral structures to be formed both through the use of monodentate ligands and chelating ligands. The chelate-based systems are ideally suited to formation based on the principles of the symmetry interaction model, and their formation and structural features have been extensively studied.[80] Two basic motifs in coordination tetrahedra exist: those utilizing four metal centers and six ligands to form the edges of the structure (M_4L_6, Figure 16.A1.C) and those using four metal centers and four tridentate ligands to form the faces (M_4L_4, Figure 16.A1.D). It has been shown that small tetrahedral coordination structures can be used as a way of isolating small molecules in solution[99] (Figure 16.41). This work demonstrated two important features of coordination polyhedra. First, it showed that these coordination polyhedra are dynamic, with their metal–ligand bonds continually being broken and reformed in solution in order to establish an equilibrium with the guest molecules. Second, it showed that guest molecules can be preferentially selected and encapsulated within a tetrahedron (in the order $NEt_4^+ > NPr_4^+ > NMe_4^+$). In an example of the molecular library approach to three-dimensional nanostructure formation, the linear bidentate molecule fumaronitrile was used as the linking ligand to form the sides of a tetrahedron employing iron(II) vertices[100] (Figure 16.41). The remainder of the iron(II) coordination sphere was saturated using a tridentate phosphine ligand. Again, the tetrahedron was shown to encapsulate a counterion guest (BF_4^-). In this system, however, the tetrahedral symmetry elements are aligned in conjunction with the symmetry elements of the macrostructure. It is believed that the anion may be acting as a template over which the assembly of the cluster proceeds.[100]

16.3.4 Biomimetic Structures

The most versatile and, arguably, most important use of the MBB approach for the formation of nanostructures occurs in biochemistry, where intricate and highly specialized molecular "machinery" controls the manipulation of simple molecules to create functional structures. Biochemistry, as applied to the synthesis of nanostructures, is a special case of supramolecular chemistry. In these biomolecules, the covalent and electrostatic interactions of individual MBBs are used in concert with their aqueous surroundings to impose a sequential order and preferred orientation in the self-assembly of complex structures. The mechanisms and the raw materials of biochemical nanotechnology are not only self-sustaining, where the means for synthesizing and modifying the subunits are internally available to the system, but also self-regulating, where enzymatic activity controls such features as the availability, degradation, and reconstitution of materials into new macromolecules. The MBB approach, when considered from a biomimetic or biochemically inspired perspective, provides both an extensive background from which to understand design- and preparation-related issues at the nanoscale and a wealth of elegant examples from which to conceive novel structures. By studying the dynamics of biomolecular interactions, the role of the subunit in the formation of larger systems and the effects of environment on the formation and operation of these nanostructures may be better understood within a very important context.

Apart from the structural beauty of biomolecular systems, the greatest advantage of relying on biomimetic approaches to form nanostructures is that entire classes of functional structures already exist for study and modification. Nature has provided both a conceptual scaffolding from which to study structure/property relationships on chemically massive structures and a wealth of example systems that are often easily obtained. The biomimetic approach also has the unusual quality of being based upon a "finished product." The goals of biomimetic design are then achieved through retro-analysis, working from a known model to construct a new system based in biochemical precedent through chemical derivitization of the known subunits, environmental manipulation, or the application of biomimetic principles to other non-biological subunits.

The foundations of biochemical design are well understood from an MBB perspective. A great deal of knowledge of the structure and function of the subunits and a detailed understanding of the electrostatic interactions responsible for imparting secondary structure is available for these systems. The literature

on this subject is vast, and more detailed discussions are presented elsewhere.[28,101] A great amount of biochemical detail has been omitted from this discussion in order to focus on the actual MBB aspects of these structures and how the biomimetic approach can be readily applied to new systems. While the intricacies of protein folding, enzymatic activity, and tertiary structure are all important aspects of biochemistry, the fundamental understanding of molecular interactions at the macromolecular level are available from even small segments of DNA or small peptide chains in a protein.

16.3.4.1 DNA

Each nucleic acid molecule, the MBB of DNA, can be divided into three parts, with each portion of the molecule contributing significantly to the structure and electrostatic properties of the resulting DNA double helix (Figure 16.43). The covalent architecture of each helix, the primary structure responsible for maintaining the order of the nucleic acids, is composed of a phosphodiester and a 2′-deoxyribose residue in each subunit. The primary structure of the helix is formed via a condensation reaction between a phosphodiester and the 2′-hydroxyl group of a deoxyribose sugar, resulting in the elimination of one water molecule for each nucleotide linkage. Attached to each deoxyribose is either a monocyclic pyrimidine or dicyclic purine nitrogen base. Base pairs are then stabilized through hydrogen bonding interactions between a purine (adenine or guanine) and a pyrimidine (cytosine or thymine) on different (complementary) helices (Figure 16.44). For the purposes of encoding genetic information, two different purine/pyrimidine pairs (A with T and C with G) occur naturally. It is, however, sufficient to simply define the pyrimidine/purine pairing sequence in order to form the double helical structure of DNA. The complete secondary structure of DNA is a product of two types of electrostatic interactions. First, the formation of the double helix results from the correct hydrogen-bonded pairing of complementary bases between helices. Second, a π-stacking interaction, largely isolated within each helix between adjacent bases, further stabilizes the structure. This stacking is not completely isolated within a single helix, however, as the twisting of the double helix creates a slight overlap between bases on opposite strands.[102]

16.3.4.2 Proteins

Amino acids, the building blocks of proteins, are also composed of three structurally and electrostatically important parts. This division of structure begins with the covalent framework of the amino acid sequence, which is limited to the repeating peptide linkage (N-C-C) formed through rotationally unrestricted σ-interactions (Figure 16.45A). Directly attached to the N-C-C backbone are alternating donor (N-H) and acceptor (O = C) pairs for the formation of hydrogen bonds (Figure 16.45B). Any of a number of possible pendant (R) groups may be incorporated into the structure (Figure 16.45C). These functional substitutions on each amino acid are responsible for some of the secondary structure stabilization and enzymatic activity of the protein. The naturally occurring side-groups fall into four major categories based on their behavior in aqueous media.[101] These categories are (1) hydrophobic, (2) polar, (3) positively

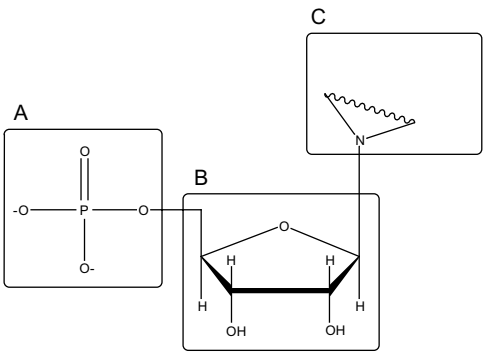

FIGURE 16.43 Structural components of DNA nucleotide bases. (A) Phosphodiester linkage. (B) 2′-ribose sugar. (C) Purine or pyrimidine nitrogen base.

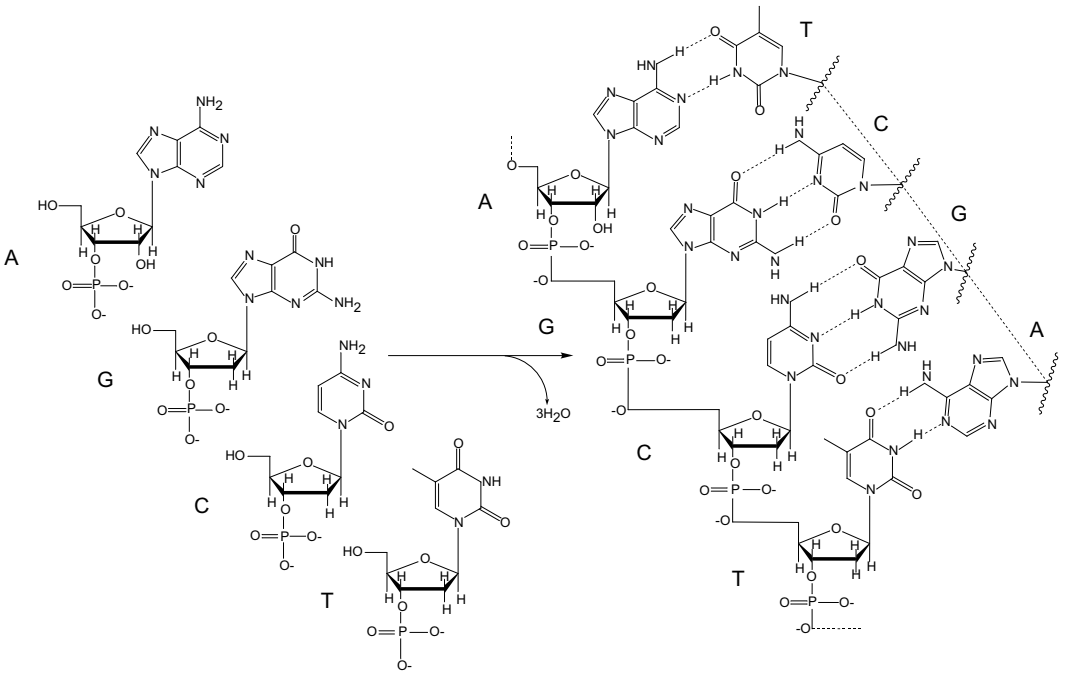

FIGURE 16.44 Connectivity and hydrogen bonding among nucleotide sequences in DNA.

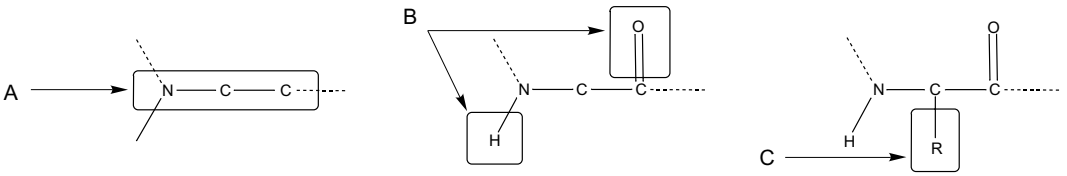

FIGURE 16.45 Structural features of amino acids. (A) N-C-C backbone. (B) Hydrogen bonding regions. (C) Pendant group.

charged, and (4) negatively charged. Since these are all neutral molecules in their isolated forms, their charge is a function of the pH of the intracellular environment.[101] For the general discussion, the R groups can be temporarily neglected, although their importance in imparting function to these structures cannot go unnoticed. As with DNA, the protein backbone is formed through a condensation reaction. The formation of secondary structure then occurs within small sequences of the polypeptide chain through intrachain hydrogen bonds between a N-H hydrogen and a C=O oxygen (α-helices) or between pairs of longer polypeptide chains through intrachain hydrogen bonding between the N-H hydrogens of one chain and the C=O oxygens of another (β-sheets) (Figure 16.46). The twists and bends responsible for the overall three-dimensional structure of proteins are a result of local breaks in the α-helices and β-sheets. The sequences responsible for these local breaks typically extend over many fewer amino acids than do the more regular helices and sheets.[28]

Nucleotides and amino acids share important similarities in subunit design. The formation of polypeptide chains and single helices occur through the removal of water, by far the most prevalent molecule in the intracellular matrix. The availability of subunits for macrostructure formation is regulated by either direct synthesis or modification of externally acquired subunits. In both nucleotides and amino acids, the subunits contain a covalent framework through which to interact with adjacent subunits and a highly directed noncovalent framework capable of stabilizing arrangements of subunits through electrostatic interactions. The majority of all superstructure formation occurs through hydrogen bonding, electrostatic

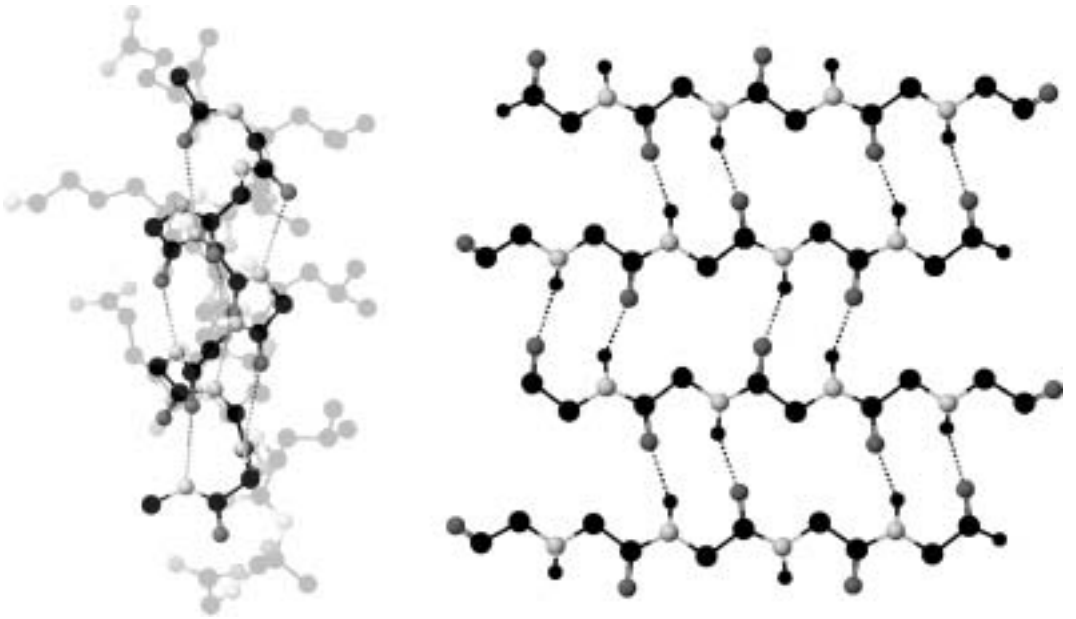

FIGURE 16.46 α-Helix (left) and β-sheet (right) secondary structures from amino acid sequences.

interactions that are easily broken in aqueous solutions. Hydrogen bonding promotes added functionality by allowing for the low-energy error correction of structural mismatches. Both π-π-interactions and the hydrophobic environment promote the π-stacking of the nucleotides, where this stacking serves to minimize the total surface area of the rings in contact with the polar aqueous surroundings. The anionic nature of the phosphodiester backbones at typical *in vivo* pH promotes the solvation of the exterior of the helices and increases stabilization in solution. The aqueous environment also has a destabilizing effect, since broken base pairs can hydrogen-bond to nearby water molecules. The similar strengths of hydrogen bonds between either amino acids or nucleotides and water means that rearrangements of the structures can and do occur dynamically, driving these structures to their energetic minima during their formation and allowing these structures to readily change shape or to be disassembled. While hydrogen bonding with the solvent can occur in the unpaired bases, their correct base pairing pattern provides greater stability, both through entropic affects and the proper alignment of π-stacking pairs. The effect of solvent on structure and biological function is best demonstrated by considering the folding and enzymatic activity of proteins in other solvents. In such nonaqueous instances, significant structural deformations from the aqueous structure and limited function are often observed, which result from improper folding.

This biochemical precision in design and function provides a very complete model from which to design similar macromolecules. Approaches to nanoscale design based on biomimicry begin with the realization that the possible variations of structure and function are enormous. The structures and functions of many of the naturally occurring biomolecules are still being investigated, and much more work still needs to be done to understand how these molecules interact with one another in the intracellular matrix. The extension of the biomimetic approach beyond biochemistry provides researchers with both a synthetic framework and a familiar nanoscale motif from which to design new structures. Two very broad methodologies based on the current understanding of structure and function in biochemistry have emerged in recent years. In one methodology, the known chemistry of nucleotides and amino acids are being exploited to develop novel, nonbiological nanostructures. In this approach, the *biochemical properties* of the subunits are being applied in new ways to form structures based in biochemistry but without any direct biological relevance. In the other methodology, the fundamental principles of biomolecular formation are being applied to new synthetic subunits. The emphasis on biomimetic design leads to the use of molecular subunits that are designed to behave like nucleotides and amino acids based

on covalency and electrostatic stabilization features. In these designs, the choice of subunit can include anything from nucleotides that have been slightly altered from their naturally occurring forms to completely novel molecules applied in a biomimetic fashion. It is important to note here that the design approach from the synthetic subunits is directed specifically toward biomolecule mimicry, even when the subunits are ideal for other designs. These two approaches are closely related within the biomimetic context, as both approaches are founded directly from the guiding principles of biochemistry.

16.3.4.3 New Designs from Old Subunits

Nucleotide sequences and polypeptide chains are simply large molecules made up of a series of connected, structurally similar subunits. A particular order of nucleotides in DNA leads to the complementary pairing of bases and the storage of genetic information for the formation of specific polypeptide sequences. A specific order of amino acids in polypeptide chains is responsible for directing the spontaneous formation of a secondary structure by way of hydrogen bond-directed folding. From the final product of this protein formation comes a macromolecule with biological activity. In both DNA and proteins, a limited number of different combinations of nucleotides and amino acids control every biochemical process that occurs in an organism. In all other possible combinations of these MBBs, the potential exists to form a macromolecule with some unique nonbiological structure or function. In instances where a new sequence is nearly identical to a natural sequence, one might expect the structures and functions of both to be very similar. This is often the case, although examples exist where the substitution of one key subunit by another leads to the complete loss of biological activity. As more deviations from a natural sequence are incorporated into a synthetic sequence, the new structure loses these similarities. As a new structure, however, its properties may prove ideal to some other function. As general MBBs, there is essentially no limit on their application to the creation of other macromolecules or nanoscale materials.

Great structural variety and chemical function are available from different combinations of amino acids. The current limits on our ability to understand their interactions, however, prohibit the design of very complex structures. In contrast, the interactions responsible for the formation of DNA double helices are well understood because the separation of covalent backbone and electrostatic moieties is pronounced in the nucleotides. Our understanding of the noncovalent interactions of nucleotide bases with one another are specifically relevant in this respect. Consequently, the cognizant design of new structures from naturally occurring nucleotides has proven to be far more manageable than similar efforts from amino acids. Among the many nanostructural designs employing DNA as a key structural element, the most intriguing of these designs uses DNA as a construction element in the same way that molecular Tinkertoy approaches use linear molecules as components in skeletal frameworks. Many complex supermolecular structures from simple DNA fragments have been synthesized by relying on the strength of the double helix and the very predictable interactions of nucleotide bases. In these approaches, the DNA strands are divisible into rigid sections of stable base pairs and sticky sections of unpaired bases (Figure 16.47). In the fabrication of materials, rigid sections are responsible for defining the sides of structures while the manipulation of the sticky ends are responsible for forming and stabilizing corners.

One of the first structural applications of rigid/sticky nanoscale assembly was in the formation of tetravalent DNA junctions[103] (Figure 16.48). Each junction is composed of three regions which facilitate the self-assembly of two-dimensional lattices in solution. The formation of one base-paired arm exposes

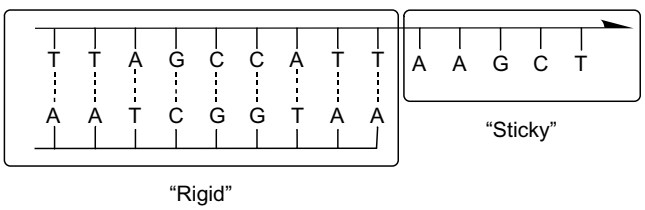

FIGURE 16. 47 *Rigid* (paired) and *sticky* (unpaired) regions of DNA building blocks.

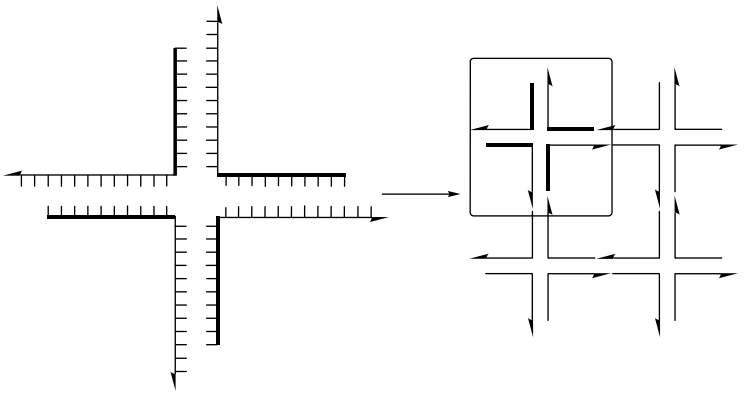

FIGURE 16.48 Two-dimensional DNA junctions from *rigid* and *sticky* engineering.

a sticky region and aligns two single sequences that will become a perpendicular set of arms. The perpendicular arms have identical base sequences and are unable to pair with each other. An arm/unpaired fragment with complementary bases to the unpaired arms of another fragment then pair to form the remainder of the rigid portion of the junction. Self-assembly of these junctions into a two-dimensional lattice occurs with the pairing of the extended sticky ends at each junction corner.

This same DNA design strategy of engineering strongly binding regions within junctions and incorporating unpaired strands to the ends of these junctions has been used for the formation of corners or vertices in a number of complex geometric structures, including isolated polygons and a number of polyhedral nanostructures.[104,105] All cases thus far demonstrate the importance of a rational design approach to the formation of DNA-based structures, because the extension of base pairing beyond two dimensions requires that base-pair complementarity be precisely controlled in order to direct structural formation beyond simple linear sequences. Most recently, a nanomechanical rotary device has been shown to operate by way of conformational changes between the device DNA strands and a second set of strongly binding DNA fragments.[106] The strong noncovalent binding of trigger fragments to the device strands causes conformational changes in regions that find new energetic minima through rotation. In effect, a DNA device has been created which is powered by a very site-specific kind of DNA "fuel."[106] Among other applications of DNA for nanostructural formation are those that rely solely on the complementary binding of strands to direct and stabilize other structures. For instance, complementary binding has been used as the noncovalent stabilizer to direct the formation of simple polygons from oligonucleotide/organic hybrid[105] (Figure 16.49).

16.3.4.4 Old Designs from New Subunits

The reproduction of biomolecular structures by synthetic subunits provides chemists with both an interesting challenge in supramolecular chemistry and a well-established set of guiding principles. The emphasis on designing subunits for the sole purpose of reproducing bioarchitectures is founded in our increased understanding of structural interactions within DNA and proteins. In both DNA and proteins, the vast majority of this structural precedent is based at the subunit level. Much of the work has been based on the use of subunit modification for the purpose of understanding the formation of secondary structures.

At one end of the biomimetic design regime is the use of synthetic nucleotides and amino acids to alter the properties of familiar biomolecules and to make novel structures based on the known interactions of these subunits.[107–111] The modification of amino acids in peptide sequences has been extensively used as a means to study protein folding, the enzymatic processes of these structures, and novel molecular scaffolding designs based on common supramolecular protein motifs, such as artificial α-helices and β-sheets. The design advantages responsible for the proliferation of nanostructures based on nucleotide interactions have also been responsible for the extensive modification of nucleotides as a direct means

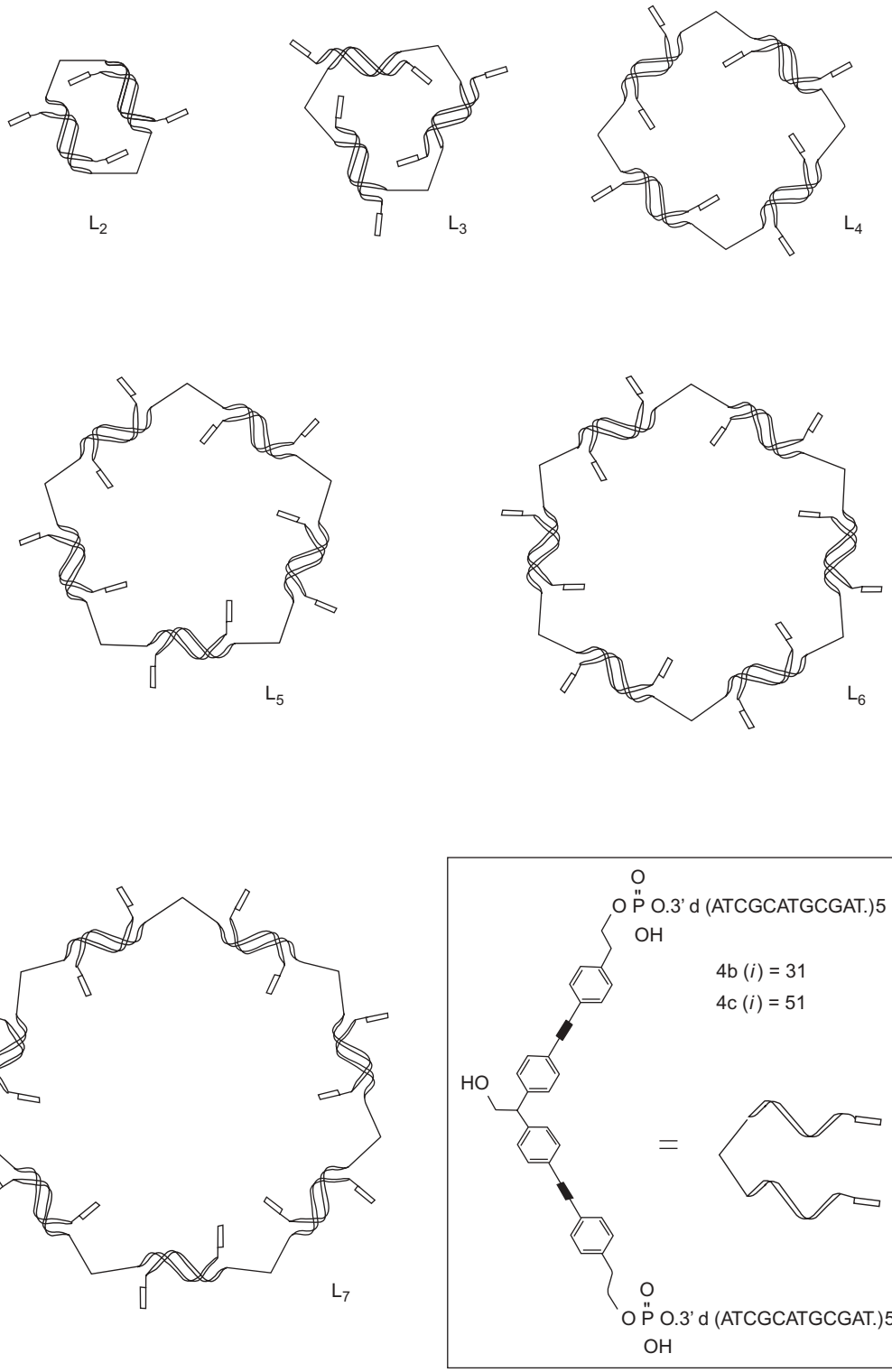

FIGURE 16.49 Polygons from DNA/organic hybrids. (From Shi, J. and Bergstrom, D.E., Assembly of novel DNA cycles with rigid tetrahedral linkers, *Angew. Chem. Intl. Ed. Engl.*, 36, 111, 1997. With permission.)

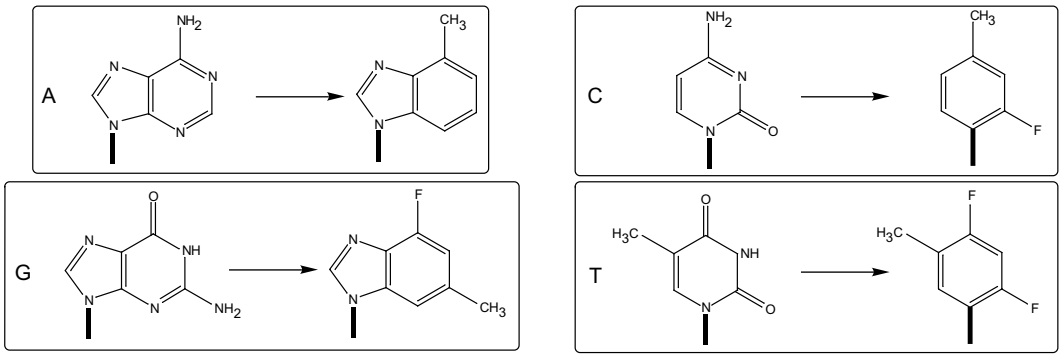

FIGURE 16.50 Nucleotide mimic structures without hydrogen bonding groups (right) from native structures (left).

to study the structure and function of DNA. A selection of synthetic nucleotides and their corresponding natural nucleotides is provided in Figure 16.50. Among these particular designs, the modifications have involved the removal of hydrogen bonding from the nitrogen bases, and they were used specifically to demonstrate the importance of aromatic stacking in the stabilization of the DNA double helix and to provide key insights into the importance of hydrogen bond stacking stabilization in the formation of DNA double helices and the molecular recognition events of DNA replication.[107]

Much of this work, which has emphasized altering the interactions between individual base pairs while causing minimal deformations in the double-helical structure, is also directly applicable to the novel DNA-based design strategies described above, as the modifications are typically rather subtle and the integrity of the nucleotide architecture remains intact. With the structural benefits of artificial MBBs in biomimetic design come many potential biomedical applications, as these synthetic subunits are generally not degraded by enzymatic processes, making them interesting candidates for the synthesis of novel therapeutics and biomaterials.[107]

At the other end of this biomimetic design regime is the reliance on only the biomimetic design strategy for the creation of biomolecular architectures. Such structures follow directly from the implementation of the structure–property relationships found in nucleotides and amino acids as the guide for the synthesis of new MBBs. These new subunits then share many of the same important design features as nucleotides and amino acids but have marginal structural similarities to the native subunits. The design features most important in the biomimetic design of novel subunits include consideration of primary and secondary structural features.

1. Primary Structure
   The covalent backbones of DNA and proteins define the order of the subunits while also providing some degree of structural flexibility to allow the noncovalent assembly of the larger structures. Within each subunit and in the subunit–subunit connections in both structures, this flexibility is incorporated by way of σ-bonding. Positional control is a function of rotation at specific points in the nucleotide/amino acid framework. As one limiting case, the covalent framework of a subunit can be designed to have no structural flexibility except for freedom of rotation at the subunit–subunit connection points and at the point of attachment for the fragment responsible for electrostatic stabilization (Figure 16.51A). This is similar to the freedom of movement in DNA, as the deoxyribose ring does strongly limit the positional freedom of the attached nitrogen base and the phosphodiester linkage. As a second limiting case, only freedom of movement at the subunit–subunit connections is allowed; and the remainder of the structure is rigid with respect to reorientation about the subunit–subunit bond (Figure 16.51B).
2. Secondary Structure
   Secondary structure is determined by the electrostatic stabilization introduced in the subunits and the positional freedom of these subunits as defined by the subunit–subunit connectivity. In DNA, not only are the nitrogen bases connected through a rotationally unrestricted bond to

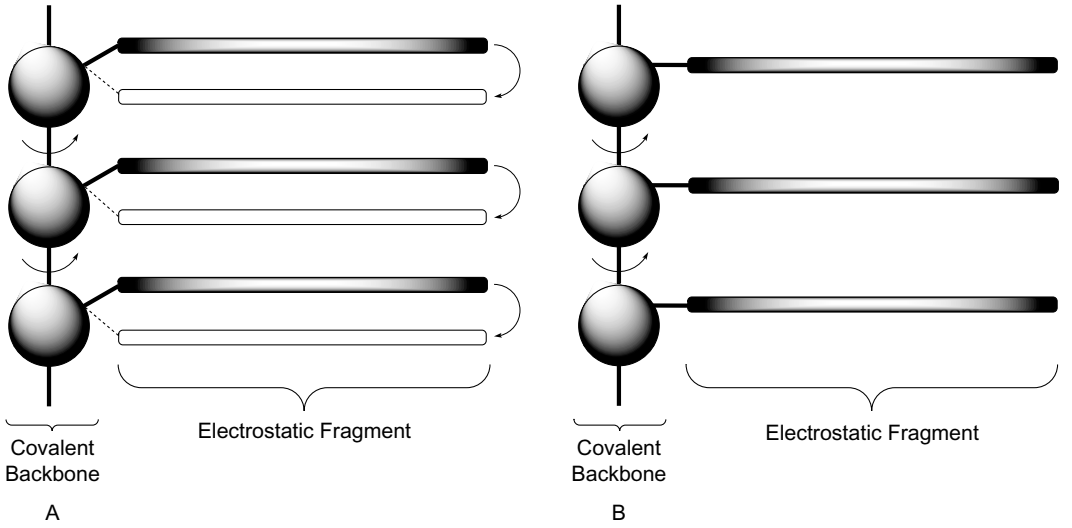

FIGURE 16.51 Limiting cases of MBB flexibility in biomimetic design. (A) Rotational freedom in both the covalent backbone and electrostatic regions. (B) Rotational freedom only in the covalent backbone.

the deoxyribose ring, but a number of pivot points are available for further orientational control. This flexibility is limited, however, by the use of ring structures in both the electrostatic component and the covalent framework. In amino acids, considerable rotational flexibility is available within the covalent backbone, allowing for different structural motifs to form from the subunits (α-helices, β-sheets).

The choice of electrostatic stabilization is also a factor to be considered. In both DNA and proteins, hydrogen bonding predominates. From an engineering perspective, the use of hydrogen bonds is ideal for both the degree of stability required of these structures and the environment in which these structures must function. The interactions of the subunits with the aqueous surroundings are the fundamental means by which all secondary structure formation occurs. Water plays the role of the medium, as it is the solvation of the larger structures that allows for electrostatic interactions to form and reform on the way to a stable minimum. Water, as a small molecule capable of forming stable hydrogen bonds with the noncovalent framework of DNA and proteins, is also responsible for the local destabilization of the larger structures. This local instability is responsible for the structural dynamics of proteins and DNA in solution and can be viewed as an integral part of the function of enzymes in all intracellular processes.

The design of a structural analogue to proteins or DNA from these guidelines must begin with the design of subunits that embody the same fundamental properties as nucleotides or amino acids. While the predictability of protein folding is still difficult, structure and enzymatic activity can be rationalized based on the final structure. DNA, however, has been found to be very amenable to structural manipulation. The predictability of the double helix from naturally occurring sequences has become familiar enough that DNA has been used to build artificial scaffolding and simple devices. Based on the ability to rationally design structures from the familiar structure–property relationships of the DNA nucleotides, alternative helical and double-helical structures based on novel subunits should also offer a certain degree of macromolecular predictability. One example of this approach is provided below.

The design of a new structural subunit employing the limiting cases in bonding and interactions is shown in Figure 16.52. Here, the covalent framework that defines the macromolecular backbone is based on rigid carboranes that are held together through a structurally inflexible five-member ring. By fixing the two inflexible carboranes to one another through the small ring system, structural flexibility within the subunit is greatly diminished. Connectivity between subunits is made by way of either a direct subunit–subunit linkage or through the use of some small, flexible spacer. As a consequence of the design, large-scale flexibility

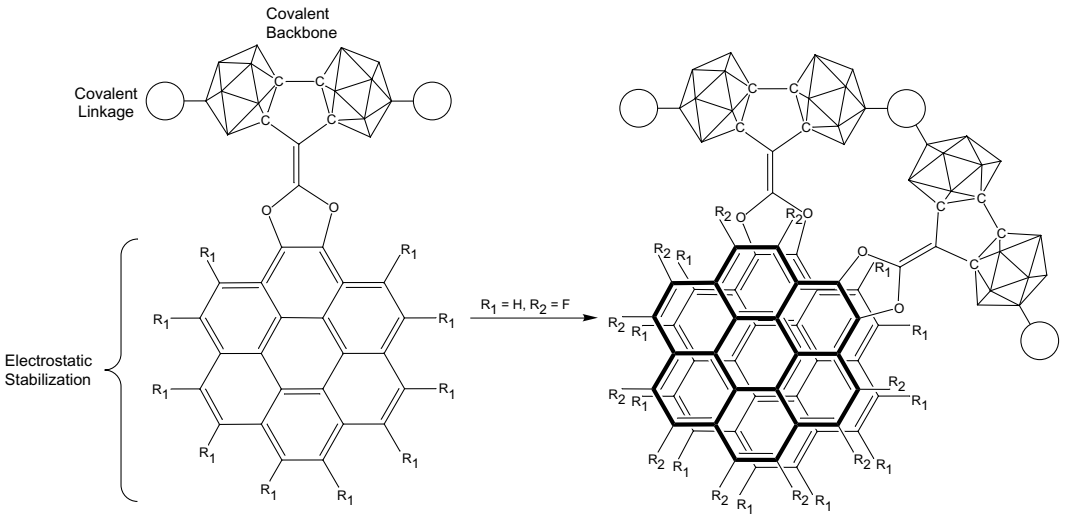

FIGURE 16.52 Synthetic bis-*ortho*-carborane MBB for biomimetic design. Cage boron–hydrogen bonds, oriented in the eclipsed conformation, are shown as unlabeled vertices.

is limited to rotation at a single point in the covalent backbone. All secondary structure formation, therefore, must occur through the rotational reorientation of subunits with respect to one another.

The means to secondary structure stabilization occurs through the interaction of functional groups pendant on the subunit frame. In these structures, the functional groups are placed at the noncarborane-substituted position of the five-member ring. The removal of rotational flexibility in this structure is by way of σ- and π-bonding between the covalent framework and the functional group. With both the interior of the subunit and the functional group held fixed through covalent bonding, interactions between subunits can only occur through rotational interactions.

The reliance on direct interactions, like hydrogen bonding, requires additional degrees of orientational flexibility within the subunit framework in order to form the most stabile interactions when the positions of the subunits themselves are not ideally arranged spatially. The reliance on rigorously directional interactions in solution can be removed by the selection of functional groups that do not interact through directed interactions. This route requires the removal of polar interactions as the means to forming stable interactions. The use of π-stacking interactions in the DNA double helix provides both significant stability and direction for the formation of a helical network with unfavorable interactions with the aqueous surroundings. As π-stacking can be engineered to be most favorable with actual stacking of the π-electrons between rings, the use of this type of interaction for the formation of helical structures should be possible. This helical stacking can be accomplished by limiting the positional flexibility of the π-systems to motions that align them in a vertical manner with limited opportunity to form other stable π-stacking arrangements. The rotational limitations of the carborane subunits allow such limited flexibility. Within the subunit formed from the linking of carborane-based MMBs to one another through bonds that only provide rotation and stable π-stacking interactions, the helical structure is both controllable and favored (Figure 16.53A). This preferential formation can be enhanced by the inclusion of polar functionalities on the exterior of the carborane subunits, forcing the π-stacking alignment within the helices by hydrophilic/hydrophobic interactions. Furthermore, the formation of double helices from the same stacking arrangement can be enhanced by the use of π-stacking pairs with alternating ring-periphery electron densities (Figure 16.53B). From the stability shown for benzene–perfluorobenzene pairs, similar MBB designs based on the same covalent subunit framework and π-system containing modified substituents becomes an interesting possibility for directing the formation of such designs. With the exclusive use of π-stacking for the formation of secondary structure, however, a larger space must be employed between stacking moieties.

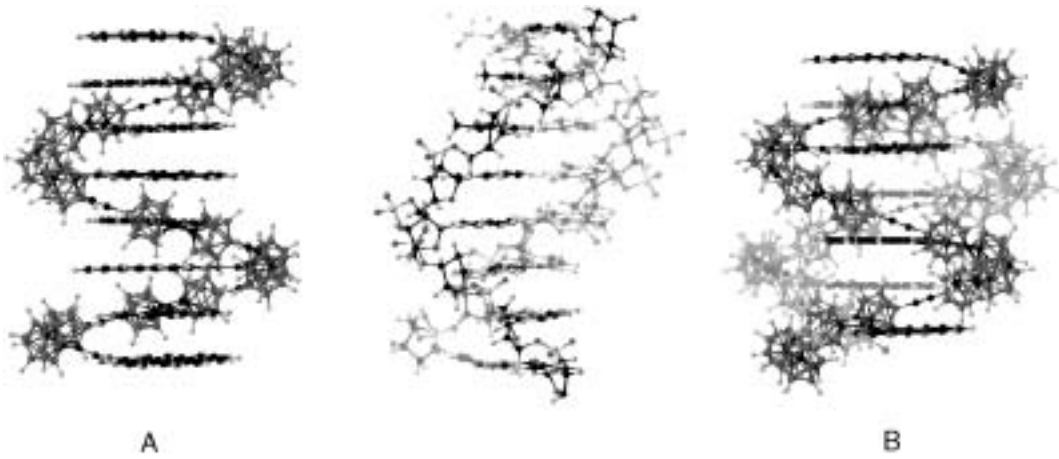

FIGURE 16.53 Helical (A) and double-helical (B) designs from synthetic MBBs. DNA provided at center (all structures to the same scale).

In carborane-based subunit designs, a double-helical structure can be designed by alternating the covalent backbone of each helix with subunits containing π-stacking functionalities.

16.3.5 Dendrimers

Dendrimers, also commonly referred to as *starburst polymers, cascade polymers*, or *arborols*, compose a special subset of supramolecular chemistry[112–115] that employs an MBB methodology in their formation. Dendrimers can be defined as "highly ordered, regularly branched, globular macromolecules prepared by a stepwise iterative fashion."[116] While the growth process of these structures is based in polymer chemistry, dendrimers offer exceptional control of structural and chemical properties within a predictable, unimolecular architecture. Further, the control of chemical functionality is available both within and along the periphery of dendrimers at any step in the growth process. Consequently, dendrimers can be either synthesized for a specific function or can be designed to behave as a nanoscale chemical environment itself for a number of applications (*vide infra*). With increasing interest in the use of dendrimers in materials science, biomedical applications, and in nanoscale laboratory applications,[114–117] the rapid progress in their development has emphasized both the basic methods for their fabrication and selective methods for the incorporation of function.

A number of structural and synthetic features separate dendritic polymers from the two remaining classes in polymer chemistry: hyperbranched polymers and linear polymers.[116] First, the dimensionality of a dendrimer is controllable from the very beginning of its growth. Linear polymers, while their random assembly in solution is three-dimensional, are formed through one-dimensional bonds. Because their orientation is statistical during this linear assembly process, there is little control over their secondary structure. The dimensionality of a dendrimer is determined from the shape of its structural core, which then directs the polymerization process over a length (one-dimensional), an area (two-dimensional), or a volume (three-dimensional). Because the growth of a dendrimer occurs radially from the inner core, the initial branching of the structure must take on the dimensionality of the inner core. Second, dendrimers are formed through a controllable, iterative process. Both linear and hyperbranched polymers, in contrast, are formed through chaotic, noniterative reactions, limiting both the control of their shapes and the degree of their polymerization. A dendrimer can be grown with no polydispersity, yielding a single, uniform structure of chemically massive unimolecular proportions. The largest of these unimolecular dendrimers have been shown to grow to sizes of up to 100 nm and molecular weights of 10^3 kDa.[117] Third, and perhaps most useful for nanoscale fabrication, is that the growth of a dendrimer can potentially be designed to be self-limiting regardless of the availability of monomer or reaction conditions. This is possible because the

exponential addition of monomers to the dendrimer periphery rapidly surpasses the increase in the volume of the final structure, which only increases as the cube of the radius. Consequently, a dendrimer will eventually reach a steric limit past which monomer addition is impossible, a condition known as *De Gennes dense packing*[116] or the more general term *starburst limit*.[118] This steric limitation is based on a theoretical limit, however, and the understanding of dendrimer shape is still an area of significant research interest.

Dendrimers are, perhaps, the most controllable of the covalently bound supermolecular structures because the reactions involved in their formation are both self-directing and statistical in solution. The preparation of dendrimers is based in linear polymer chemistry, where a simple A/B copolymer motif is used to create covalent bonds between complementary reaction pairs. In dendrimers, this reaction pair strategy utilizes both a small molecule from which polymerization begins and an A monomer onto which multiple bonding sites for B monomers are incorporated. The initial A monomer or some other template molecule then becomes the seed, or *focal point*, from which *n* (typically 2 or 3) branches extend. By defining a dendritic focal point, it is not required that the point from which the growth process occurs be the absolute center of the dendrimer. In fact, dendrimers can be formed with the focal point on almost any type of molecule at almost any position, and a number of structures have been synthesized using aspects of the dendritic growth for purely functional purposes.

The structure of a dendrimer may be divided into a focal point and branched generations (Figure 16.54). A *generation* is simply a shell of B monomers around either the focal point (then referred to as the *inner core*) or a previous growth generation. Uniform dendritic growth then requires the addition of a stoichiometric quantity of B monomers for the number of A regions available along the dendrimer periphery. Uniform dendrimer growth is then most directly limited by the availability of monomer, steric constraints, and solubility.

While few alternative routes are known, the vast majority of all dendrimer syntheses is based on either *divergent* or *convergent* strategies. In the divergent approach,[119–121] the site from which dendritic growth begins becomes the focal point of the entire dendrimer framework (Figure 16.54). Each additional generation of monomer adds such that *n* of these monomers covalently bond to the dendritic periphery at the tail of each previous generation (which then becomes a local focal point in the growth process). The uniformity of each generation is controllable by the inclusion of chemical functionalities onto the ends of each monomer, rendering the newly added generation incapable of undirected growth. The growth process is then continued by the removal of these chemical functionalities. This control of the periphery during the growth process results in divergent-based dendrimers having limited polydispersity in the final structures. Uniform dendritic growth is halted with the depletion of available monomer or the steric congestion of branches along the periphery. It is important to note that only uniform dendritic growth is stopped due to steric congestion. Irregularities in the peripheral branches result from continued addition of

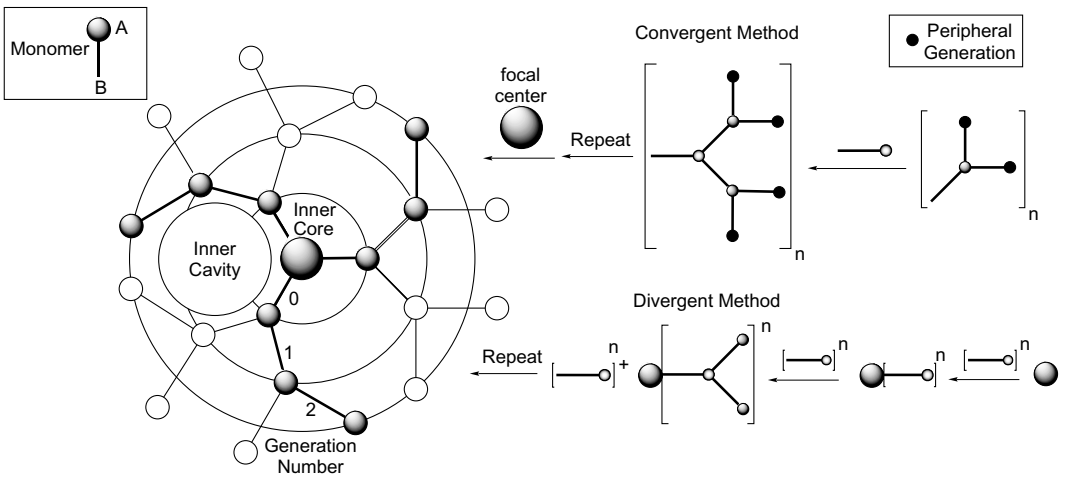

FIGURE 16.54 Dendrimer framework and convergent and divergent synthetic methods.

monomer beyond the starburst limit. Consequently, the control of the absolute size and packing in these structures is difficult to predict with great accuracy beyond a certain generation. It is because of the number of defect structures possible with the radial growth mechanism beyond a certain peripheral steric bulk that the divergent methods have some uncontrollable degree of polydispersity in the final structures.[116]

The convergent approach[116,122,123] to dendrimer formation begins with the peripheral generation and builds inward to a focal point by the coupling of progressively larger branches (Figure 16.54). This reversal from the divergent approach has the effect of switching the important advantages and limitations of the two methods. The fabrication of larger dendrimers is possible by divergent methods, as smaller monomers are added to the periphery of an otherwise sterically congested structure. In convergent methods, large branches are combined with one another, making the proximity of the reaction centers a critical factor in controlling the synthesis of larger structures. Convergent methods lead to greater uniformity of macromolecules, however, as the physical separation of defect structures is a far easier task.[116]

By the divergent method, two dendrimers might have identical molecular weights but great variability in branch lengths due to misdirected polymerization in larger structures. In the convergent methods, large branches either connect together to form a much larger branch or remain unconnected. The resulting increase in mass of bound branches then provides a direct means for separating structures. While the ultimate connection of these branches to the focal center may be a difficult task due to steric crowding, the completed structures are far more massive than any other components left in the reaction mixture and are therefore easier to isolate. The coupling of progressively larger branches, however, does ultimately limit the size of the dendrimers possible by the convergent method.[117]

The design of dendrimers and dendritic structures has begun to move beyond the polymerization chemistry of the branches and into the regime of structure- and application-specific modifications. The design of these functional dendrimers begins with the choice of the inner core. Among the synthesized dendrimers with functionalized cores, some of the most useful interiors for nanoscale applications include those with guest–host binding sites,[124,125] "dendritic probe" potential,[126,127] catalytic activity,[128–130] redox activity,[131–134] and those which employ dendrons, or larger dendritic branches, to act as stoppers for molecular assemblies.[135] A number of these applications are discussed below.

In the design of a dendrimer with an application-specific focal core, the method of dendrimer formation must be chosen carefully. Because dendrimer growth begins at the focal point in divergent methods, the application of a divergent growth scheme requires that the active portion of the core be chemically inert to the polymerization process and that this inertness continue over subsequent polymerization cycles. The convergent method, however, directs the growth of uniform branches until the focal core is ultimately added to the system. As the final formation of the dendrimer in the convergent method requires a chemical step that need not be a polymerization reaction, it is possible to add functional cores with far greater control. Consequently, a number of the discussed functional structures have been synthesized based on convergent approaches.[116]

Beyond the core, the customizability of both the monomers and the periphery has been used to engineer large-scale structural features and functionality into dendrimers. Between the core and the periphery, the inner-branching structure of dendrimers has been found to be highly customizable both for the formation of microenvironments within the cavities formed during the dendrimer growth process and for the inclusion of a number of host–receptors for the selective binding of guest molecules. The chemical modification of the periphery has proven to be a critical feature in the application of dendrimers. The exponential increase in dendrimer growth results in the rapid increase of peripherally bound substituents. As the dendrimer grows, the interactions between the periphery and the environment become the principle features governing dendrimer solubility and morphology. A number of studies have demonstrated that dendrimers incorporating either polar or nonpolar moieties along their periphery have significantly different solubility properties.[136,137] Furthermore, it has been shown that incorporating both highly polar and nonpolar regions into the dendrimer framework gives these structures unique yet controllable molecular encapsulation behavior.[137,138]

Combinatorial strategies have also been used in the dendrimer polymerization process as a means to alter the properties of both their interiors and periphery. A combinatorial approach to dendrimer

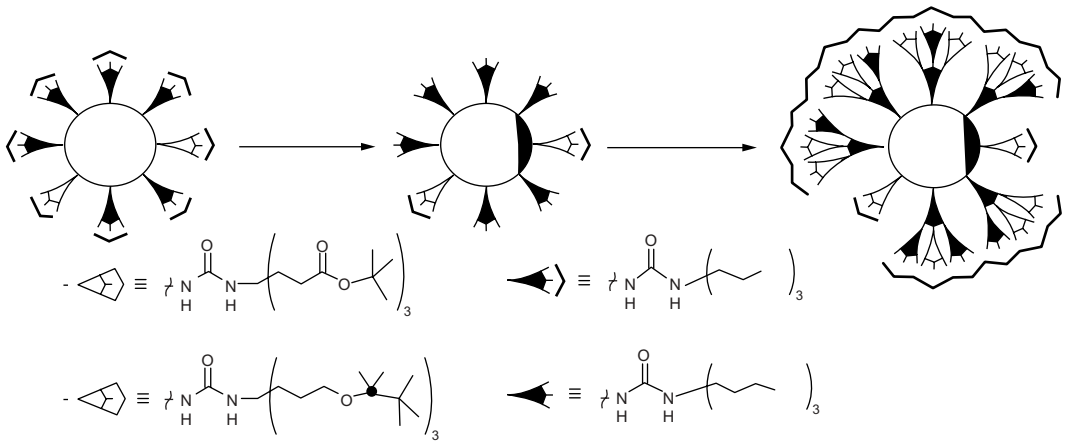

FIGURE 16.55 Dendrimer polycelles from the inclusion of heterogeneous monomers. (From Newkome, G.R., Supra-supermolecular chemistry: the chemistry within the dendrimer, *Pure App. Chem.*, 70, 2337, 1998. With permission.)

synthesis is one in which different monomers are made available during polymerization at various steps in the growth process. In this process, the incorporation of different chemical branches during dendrimer growth can be accomplished either from the very beginning of the dendrimer formation, where the entire dendrimer is then made up of structurally unique branches, or after some number of identical generations have been added. Both approaches result in different local environments within the dendrimer, because the internal cavities typically span multiple generations. These heterogeneous structures, formed by altering the concentrations of different monomers during the growth process, have been termed *polycelles*. The first instances of polycelles employed a selection of isocyanate-based monomers with either reactive or chemically inert ends[139] (Figure 16.55). Not only was it shown that different monomers were readily incorporated into the same dendritic framework, but the combination of reactive and unreactive monomers demonstrated the ability to form dendritic branches with different generation numbers and chemical functionalities.[140] By this method, both the internal cavities and the dendritic periphery form molecular-sized pockets within which encapsulation, trapping, or noncovalent binding can occur.

As a class of supermolecules, dendrimers share similarities in MBB design methodology with both the biomimetic and molecular Tinkertoy approaches. A repeating subunit is connected covalently to other subunits to define a stable, although flexible and highly branched, skeleton. The shape of the final structure is then determined by the interactions of the subunits as constrained by the covalent framework. The reliance on covalency as the principle means of structure formation and the application of covalency within the context of a controlled-growth approach is what gives dendrimers a molecular Tinkertoy quality. Also, the many finger-like projections of the branches that give dendrimers their random, dynamic morphology are still anchored at structurally well-defined focal centers, as in the skeletal framework of rigid architectures. Finally, it is possible to impart structural rigidity to both sets of structures beyond any local stability that comes with noncovalent interactions, although this rigidity in dendrimer design must come at a cost of significant steric congestion, which can make a predictable, uniform growth process difficult.

The MBB similarities between dendritic methods and the biomimetic approach come from the use of subunit properties and interactions to define the secondary structure of the macromolecule, including the customization of both classes of macromolecules to control such features as solubility and aggregate interactions (tertiary structure). Dendrimers, because they are made from simple subunits in solution, can be grown specifically for particular environments. Similar to biomolecules, the electrostatic properties of the monomer can give rise to local environments within the dendrimer itself, as has been demonstrated in many instances by the incorporation of nonpolar/polar functionalities into polar/nonpolar monomers. For example, water-soluble, unimolecular micelles and other large

dendritic structures have been synthesized with nonpolar centers by incorporating charged functional groups, such as carboxylate anions, into the periphery.[141] Biomimicry is taken further in dendrimers with the use of redox-active porphyrin focal centers and dendritic outgrowth to model the enzymatic behavior of some proteins.[131,142] By engineering hydrophobic/hydrophilic regions into a macromolecule to direct the formation of secondary structure in solution, this approach is similar to the chemical design of DNA and proteins.

The interactions between subunits that define the final structure in dendrimers are not necessarily based upon the formation of a directed secondary structure (biomimetic approaches) or by fixing the subunits within a larger covalent framework (Tinkertoy approaches). There are no intramolecular features governing the absolute size of the DNA double helix. This holds for proteins to a lesser extent, as it is the intramolecular interactions between the larger subunits (α-helices and β-sheets) in the protein that direct the formation of a localized, three-dimensional structure. Uniform dendrimer growth will, however, eventually succumb to steric crowding along the periphery. Also, the study of dendrimer formation for specific structural applications beyond the radial growth mechanism is still in its infancy. The formation of dendritic superstructures, including monolayer and multilayer formations on surfaces, has been demonstrated as a function of aggregate interactions and general molecular packing. The applicability of these designs, however, are currently limited to "bulk material" uses, such as chemical sensors,[143] catalysis, and chromatographic applications.[144,145]

Dendrimers are not just an interesting class of macromolecular structures. They can be synthesized to include the properties and functions of many customizable monomeric subunits and focal centers. Furthermore, this functionality can be wholly incorporated into a growth generation *via* stoichiometric control of the monomers, introduced statistically by the addition of dissimilar monomers, or performed by post-synthetic modification. Both the *microenvironment* and *functionalization* possibilities of dendrimers have been studied with great success. A brief discussion of two of the applications is provided below.

16.3.5.1 Guest–Host Interactions

One of the functional similarities between dendrimers and nanostructures employing electrostatic interactions, such as molecular crystals and biochemical structures, is the ability to integrate guest–host regions into the covalent skeleton through direct modification of the MBB subunits. A monomer generation can have incorporated into it a region customized to bind a specific molecule or type of chemical functionality. One benefit to introducing chemical functionality by way of monomer-based methods is that the tailoring of noncovalent interactions can be accomplished prior to the incorporation of the monomer into the dendritic framework. Furthermore, as has been demonstrated in the design of dendrimers with polar/nonpolar regions, it is possible to selectively exclude intramolecular or aggregate interactions between the guest–host binding regions from the remainder of the macromolecule simply by the exclusion of certain chemical functionalities from the remaining monomer generations. A dendrimer synthesized with a host interaction designed from strong hydrogen bonds, for instance, can be grown to include large pockets of nonpolar regions (such as long-chain alkanes) in subsequent generations.

The ability to bind molecules in solution by these engineered guest–host interactions depends upon the size of the dendrimer, the amount of branching, and the generation to which the guest–host region is added. In dendrimers with regions of limited steric congestion, it becomes possible to form stable guest–host interactions with many types of molecules. The applications here range from the trapping of molecules in solution by guest–host interactions to the formation of dendrimers themselves by noncovalent means. In both instances, the orientation of the host-binding region with respect to the focal point provides a means for controlling the exact orientation of the bound guest. In the case of dendrimer formation by guest–host interactions, the relative orientation of one branch to another can be controlled. In both cases, however, it is important to note that the size of the dendrimer is a critical feature, as the formation of stable guest–host interactions requires that the guest bind in the absence of steric strain. A number of studies have shown how the steric bulk of the

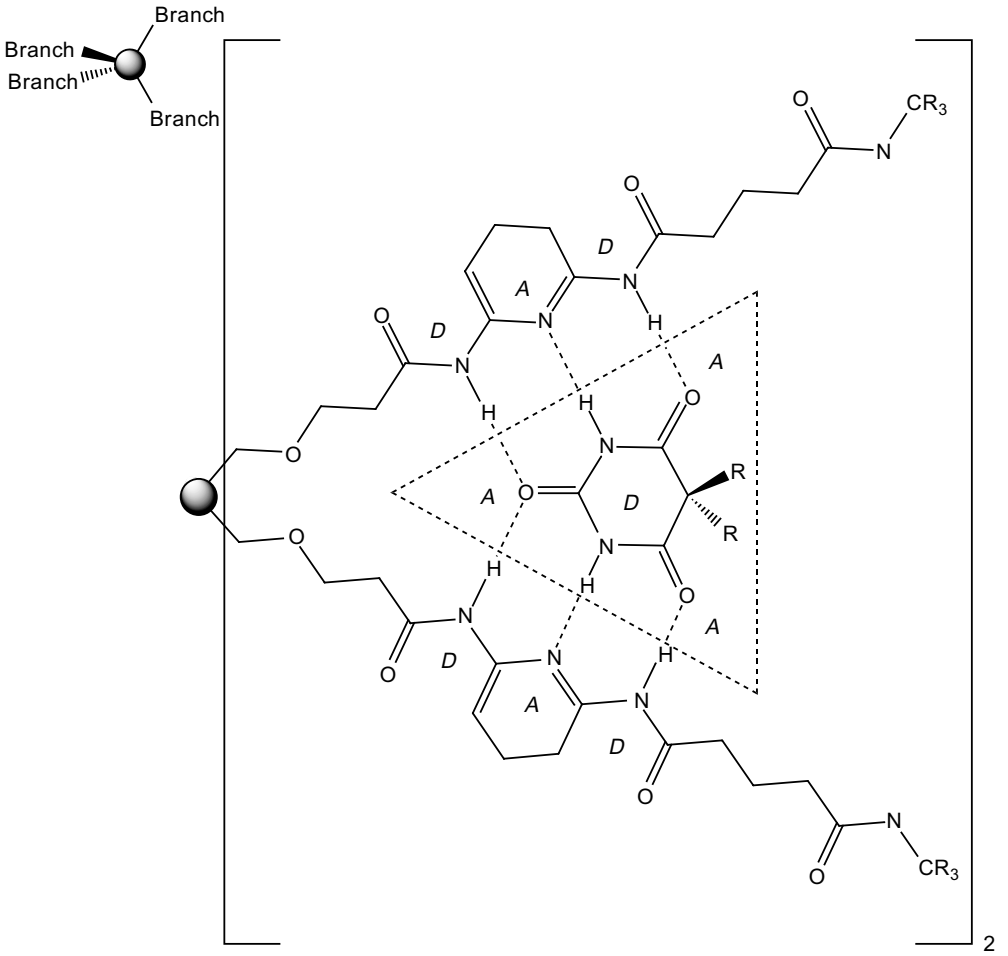

FIGURE 16.56 Guest–host assembly from dendrimer engineering (barbituric acid at center).

dendrimer can affect both the orientational specificity of the guest binding region and the strength of the host–guest interaction.[146–148]

The use of hydrogen bonding within a dendrimer framework for forming stable guest–host interactions with small molecules has been demonstrated.[140] In a series of dendritic motifs, a hydrogen-bonding region composed of diacylaminopyridine was introduced early in the growth process (Figure 16.56). The binding pocket of the dendrimer with the inclusion of diacylaminopyridine is then donor–acceptor–donor (DAD) in nature, which can be used to bind selectively to guest molecules with a complementary acceptor–donor–acceptor (ADA) arrangement (Figure 16.56). The molecule selected for studying the guest–host binding interaction in these dendrimers was barbituric acid, which contains two such ADA structures. NMR (^{1}H) titration methods were used to show that pairs of dendrimer arms were able to form stable interactions with a barbituric acid molecule. The assembly of large dendrimers from noncovalent interactions has also been elegantly demonstrated.[149] The focal centers of dendritic branches were engineered with two isophthalic acid fragments incorporated into a small aromatic spacer, providing four hydrogen bonding regions (or eight possible hydrogen bond pairs) per core fragment. Hexameric dendrimers were found to form preferentially in solution by way of strong hydrogen bonding between donor–acceptor pairs at the focal centers of each branch (Figure 16.57).

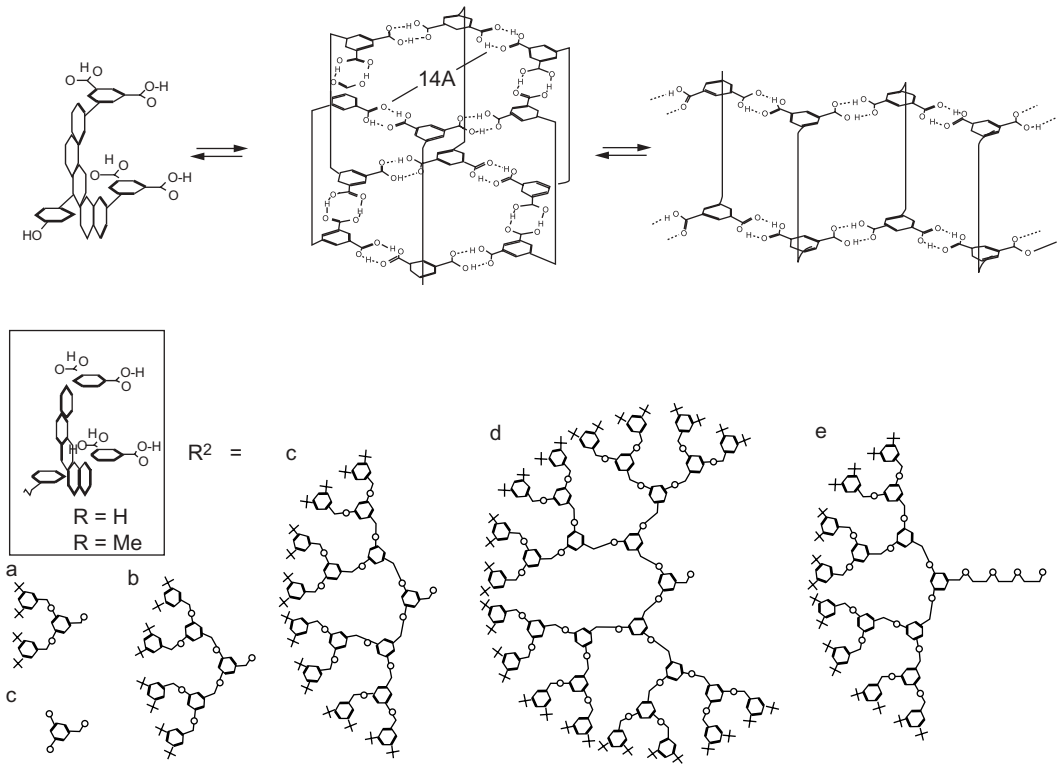

FIGURE 16.57 Dendrimer formation from hydrogen bonding interactions. (From Zeng, F. and Zimmerman, S.C., Dendrimers in supramolecular chemistry: from molecular recognition to self-assembly, *Chem. Rev.*, 97, 1681, 1997. With permission.)

16.3.5.2 Microenvironments

In much the same way that transition metal nanostructures have been shown to encapsulate small molecules, the cavities formed by the overgrowth of generations along the periphery of large dendrimers have been shown to create microenvironments within which molecules can become trapped and bound. The isolation of single molecules or small ensembles of molecules within macromolecular enclosures has obvious utility in nanoscale laboratory applications, a field of chemistry just beginning to develop as an outgrowth of supramolecular chemistry. Molecular cavities within larger dendritic structures benefit from the variety of available monomers, the reproducibility of the cavities using dendritic growth methods, and the wide variety of polar and nonpolar solvents by which to promote solubility and encapsulation. For instance, a macromolecule can be synthesized with multiple regions that behave very differently in different solvents. In dendrimers large enough to encapsulate molecules, the properties of the cavity interior can be very different from the environment at the dendrimer periphery. One notable example of how molecules can be preferentially separated from solution based on polar/nonpolar interactions is provided in the encapsulation of Bengal Rose or 4-nitrobenzoic acid within the nonpolar cavities of a unimolecular micelle composed of long-chain alkane interiors and hydrophilic aliphatic acid exteriors[150,151] (Figure 16.58). Aqueous environments promote the encapsulation of the molecules in the nonpolar interior, while nonpolar solvents, such as toluene, were found to promote their release. Differences in local hydrophilicity/hydrophobicity are easily controlled in dendrimers by either the choice of the initial monomer or the post-synthetic functionalization of the dendrimer periphery. The differences in the spectroscopic properties of many molecules that come with different solvent shells have been the key to studying many encapsulated molecule/dendrimer systems.[117]

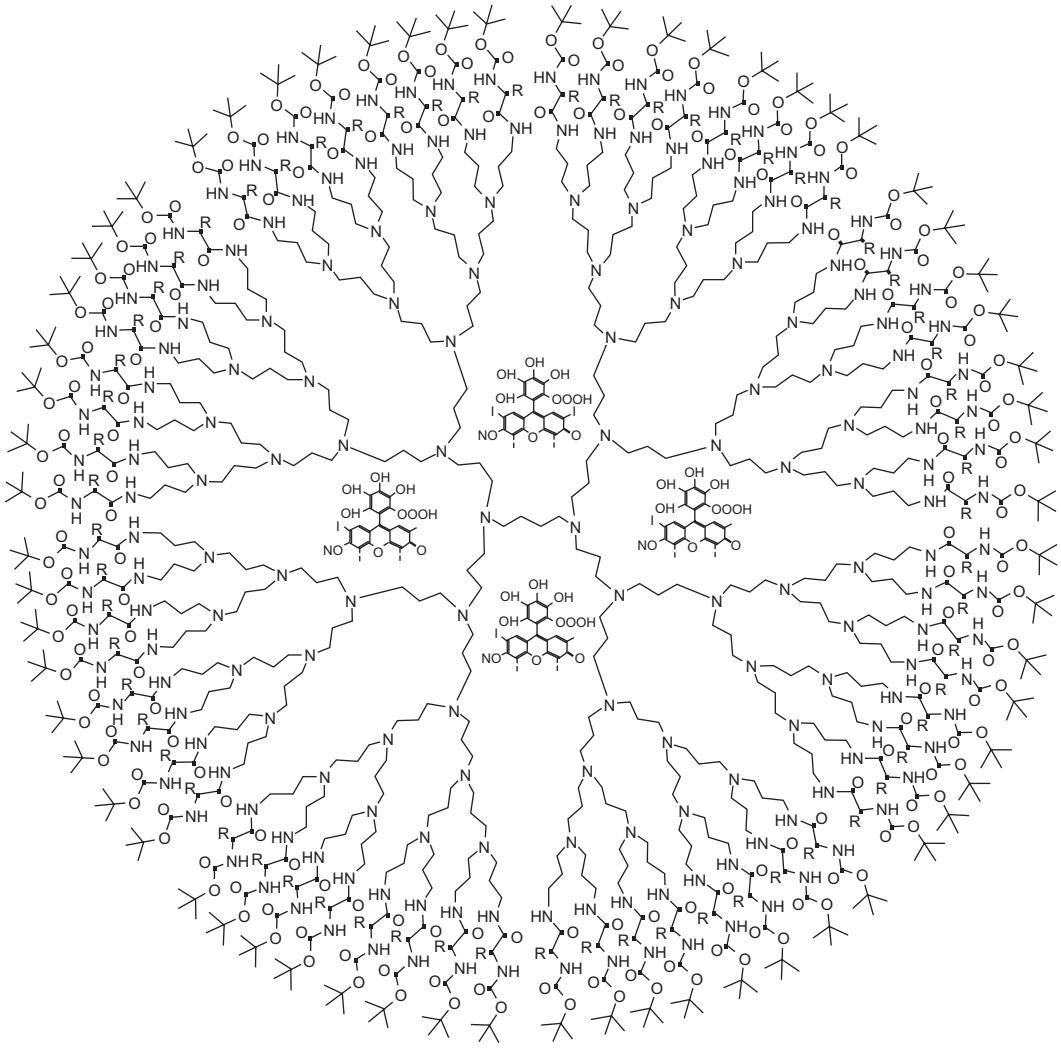

FIGURE 16.58 Bengal Rose encapsulation in dendrimer center. (From Zeng, F. and Zimmerman, S.C., Dendrimers in supramolecular chemistry: from molecular recognition to self-assembly, *Chem. Rev.*, 97, 1681, 1997. With permission.)

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