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The Many Facets of Adenine: Coordination, Crystal Patterns, and Catalysis[§]

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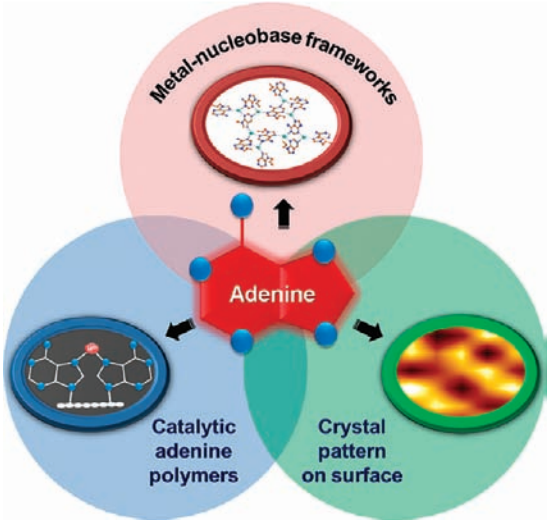

Canonical purine−pyrimidine base pairs, the key to the complementary hydrogen bonding in nucleic acids, are fundamental molecular recognition motifs crucial for the formation and stability of double-helical DNA. Consequently, focused study and modeling of nucleobase hydrogen-bonding schemes have spawned a vast array of chemical and biophysical investigations. The Watson−Crick, reverse Watson−Crick, Hoogsteen, and reverse Hoogsteen hydrogen-bonding schemes stabilize various nucleic acid structures. As a result, numerous modified bases have been designed to maximize such interactions, addressing specific problems related to base pairing and giving rise to supramolecular ensembles in solution or in the solid state. It is also important to realize that suitably predisposed imino nitrogens and other functional groups present in heterocyclic nucleobases present a versatile molecular framework for the construction of coordination architectures, which may be harnessed to mimic base polyads and higher order nucleic acid structures.

Adenine, a purine nucleobase, is an important naturally occurring nitrogen heterocycle present in nucleic acids. It is notable that the adenine unit is also frequently encountered as an inextricable part of enzyme cofactors and second messenger systems, such as NAD^+, $FADH_2$, and cAMP, which are essential for certain catalytic reactions and biochemical processes. In addition, a crucial catalytic role of the adenine moiety is also observed in group II intron catalysis and at the ribosomal peptidyltransferase center. Such versatile functional roles of the adenine framework serve as an inspiration for addressing research problems, ranging from classical coordination chemistry to the development of new materials.

In this Account, we begin by describing the emerging use of adenine nucleobase for the design of metal−nucleobase frameworks. The coordination of metal ions affords a variety of oligomeric and polymeric species; we focus on silver- and copper-based structures and also discuss ferrocenylated adenine tetrads. We then consider the use of supramolecular adenine coordination complexes for transferring molecular properties onto surfaces. This technique is particularly useful for transferring noncovalent interactions, such as van der Waals forces, electrostatic interactions, and hydrogen bonding, to designed architectures in nanoscale applications. Finally, we explore the issue of adenine-based catalytic entities. Here, adenine moieties are first fixed in a polymeric matrix, followed by metalation of the matrix. These metalated adenine-containing polymers are then assayed for catalytic assistance in various chemical and biochemical reactions. Taken together, the versatile coordination abilities and hydrogen-bonding capacity of adenine offer a novel entry point for a natural ligand into materials synthesis.

1. Introduction

Purine and pyrimidine nucleobases are key constituents of nucleic acids, which engender the concept of hydrogen bonding and permit stabilizing stacking interactions.[1] One of the two purine nucleobase, adenine, binds to thymine or uracil with the help of two hydrogen bonds, while guanine specifically recognizes cytosine, with the help

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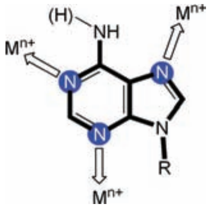


FIGURE 1. Chemical structure of adenine (imino nitrogens important for metal ion coordination are highlighted). The exocyclic amino group may coordinate via deprotonation.

of three hydrogen bonds. The combined effects of these interactions not only provide stability, but also support the remarkable ability of DNA to act as a template for genetic information storage.

The adenine nucleobase contains an exocyclic amino group and four imino nitrogens (Figure 1). The stability of adenine is governed by pH of the medium, temperature, and presence of metal ions. Naturally occurring heterocyclic nucleobases permit versatile metal ion coordination, which is usually invoked for metal ion−nucleic acid interactions.[2]

This Account reflects on our efforts concerning the use of adenine in building metal−adenine coordination frameworks to pattern metal−adenine coordination architectures on surfaces and for metal-catalyzed transformations of some chemical and biochemical reactions.

2. Adenine−Metal Ion Coordination

Nucleic acids have an obligatory requirement for cations (metal ions) owing to their negatively charged backbone. The emergence of stable or quasi-stable nucleic acid conformational ensembles necessitates the presence of cations in order to dissipate the charge repulsion caused by the close proximity of the negatively charged phosphodiester internucleotidic linkage. Thus, the interaction of metal ions with heterocyclic nucleobases plays an important role in nucleic acid structure stabilization and catalysis.[3] It is clear that constituent nucleobases are bestowed with suitably predisposed metal ion binding sites, which can be invoked for the generation of interesting supramolecular structures. As with other coordinating ligands, the metal−nucleobase interaction also critically depends on electronic and chemical properties of the metal ion as well as on the nucleophilicity and accessibility of donor sites.[4]

The adenine nucleobase offers five potential sites for interaction: the N6 amino group and N1, N3, N7, and N9 imino nitrogens.[5] Out of the four imino nitrogens present in purines, the N7 imino nitrogen is most preferred for metal ion binding because it remains exposed in the major groove of the DNA duplex. Several combinations of nitrogen coordination are possible depending on the electronic properties of the metal ion, the pH, and the metal to nucleobase ratio. For instance, N9 is the preferred site for coordination at a 1:1 ratio of N9 deprotonated adenine and CH_3Hg^+ cation,[6] whereas a tridentate coordination via N3, N7, and N9 is invoked when the ratio of adenine to organometallic species is increased to 1:3.[7]

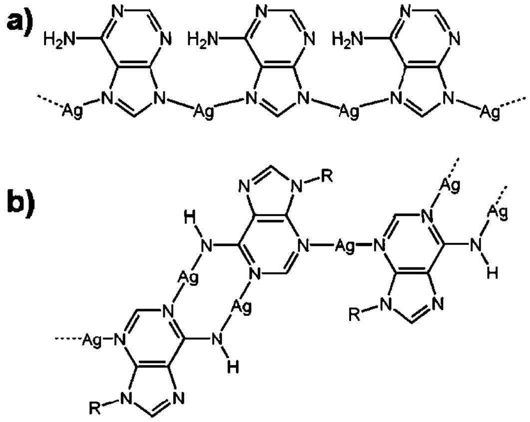


FIGURE 2. (a) Postulated silver−adenine polymer and (b) postulated silver−9-substituted adenine coordination polymer. Adapted with permission from ref 10. Copyright 1964 American Chemical Society.

Because the N9 position of purines is connected to a sugar moiety in nucleic acids, many studies of purine−metal ion interaction are conducted on N9-substituted derivatives. Adenine analogues have been explored extensively for imino nitrogen coordination, where N1 and N7 are primarily invoked for transition metal coordination via mono- and bidentate coordination modes. However, several examples involving 3N coordination mode for adenine analogues are also reported.[8] This Account particularly focuses on our research efforts in the area of silver−adenine interaction resulting in interesting coordination geometries and fascinating hierarchical structures.

2.1. Adenine−Silver Interactions. Silver exhibits a preference for heterocyclic nucleobase coordination over internucleotidic phosphate or sugar oxygens.[9] The precipitate obtained by mixing silver salts with adenine was ascribed to polymeric species formed via N7 and N9 coordination (Figure 2a).[10] However, for 9-substituted adenine, simultaneous binding of silver ions to N1, N3, and N6 nitrogens was proposed yielding an insoluble 2D polymeric network (Figure 2b).[10]

We have recently described several examples of 9-modified adenine−silver complexes where a single Ag^+ ion simultaneously coordinates to three adenine moieties via N1, N3, and N7 nitrogens. The formation of an adenine metallamacrocyclic quartet (complex **1**; Figure 3) was achieved by Ag^+ ion coordination to N1, N3, and N7 nitrogens of 9-allyladenine (9-AA).[11] Interestingly, coordination at the N3 position occurred despite an unsubstituted exocyclic amino group.[12]

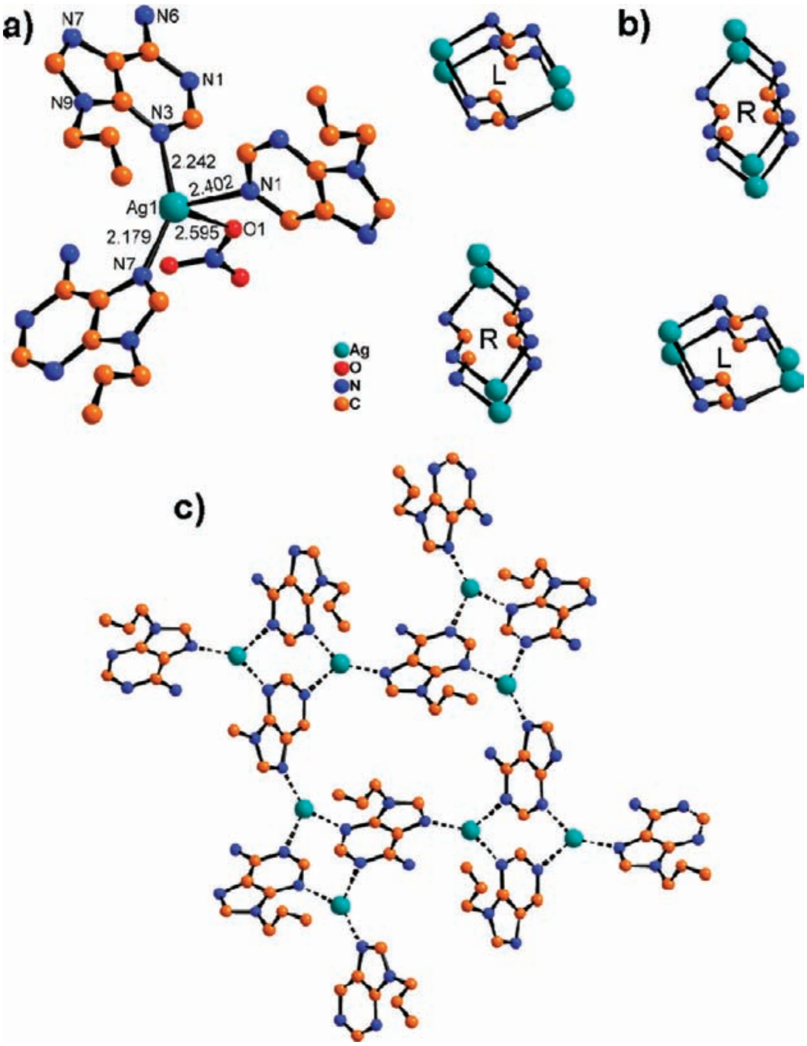


FIGURE 3. 9-Allyladenine-silver complex **1**: (a) coordination around silver center; (b) two right-handed and two left-handed coordination helices; (c) representation of silver-mediated metallamacrocyclic quartet. Adapted with permission from ref 11. Copyright 2006 American Chemical Society.

These results revealed the first example of metallamacrocylic quartet composed of adenine nucleobase with silver as an intervening metal ion (Figure 3c). Interestingly, participating 9-AA ligands in the quartet structure were contributed by two left-handed and two right-handed coordination helices, which were tethered by intervening silver atoms (Figure 3b).

It is recognized that subtle variation in ligand structure and the steric bulk of counteranion may lead to altered coordination structures. Three modifications, primarily designed to probe the tolerance of the adenine–silver metallamacrocylic framework toward substitutions in the individual components of coordination assembly, were introduced in adenine: at N9 position, at C6 position, and by employing silver salts with different counteranions (Figure 4).[13]

X-ray crystallographic evidence confirmed the emergence of persistent metallaquartet structures, involving four silver and four purine molecules, as a dominating feature irrespective of the structural perturbations (Figure 5a,b). As mentioned earlier, these quartets arise by the contribution an adenine ligand from four coordination helices analogous to nucleic acid quadruplexes (Figure 5c).

Analysis of crystal structures revealed the existence of voids in the metallaquartet crystal lattice (Figure 6a), the size of which varied from 4.8% to 8.2% of the total cell volume, after ignoring the presence of solvent molecules.[13] However, it was not possible to predict a pattern of void size variation from this small subset of structures: for example, void size for metallaquartet **4**, where NO_3^- is the counteranion, is 8.2% of the total cell volume, but metallaquartet **3**, containing a comparatively smaller BF_4^- counteranion, exhibited a void size of 4.8% (Figure 6b,c).

Known pH-dependent conformational transitions in polyadenylic acid,[14] were used to extend the investigations of silver–adenine interactions in the basic environment. Crystal growth of 9-allyladenine–silver nitrate complex from ammo-

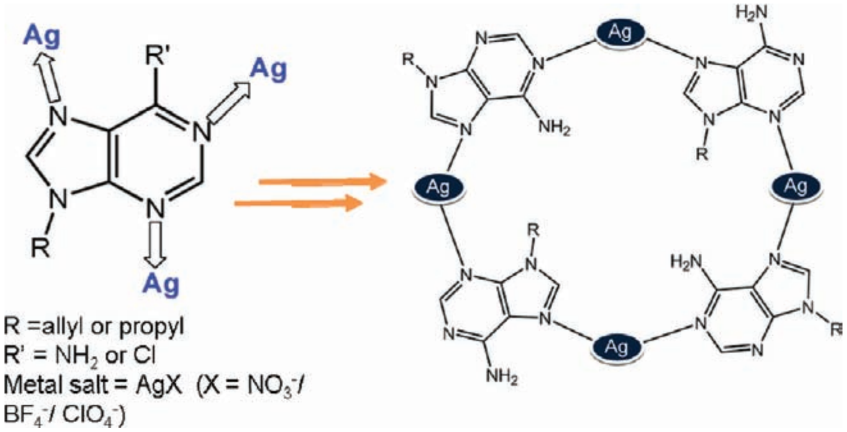


FIGURE 4. Schematic representation of modifications and silver-mediated metallaquartets.

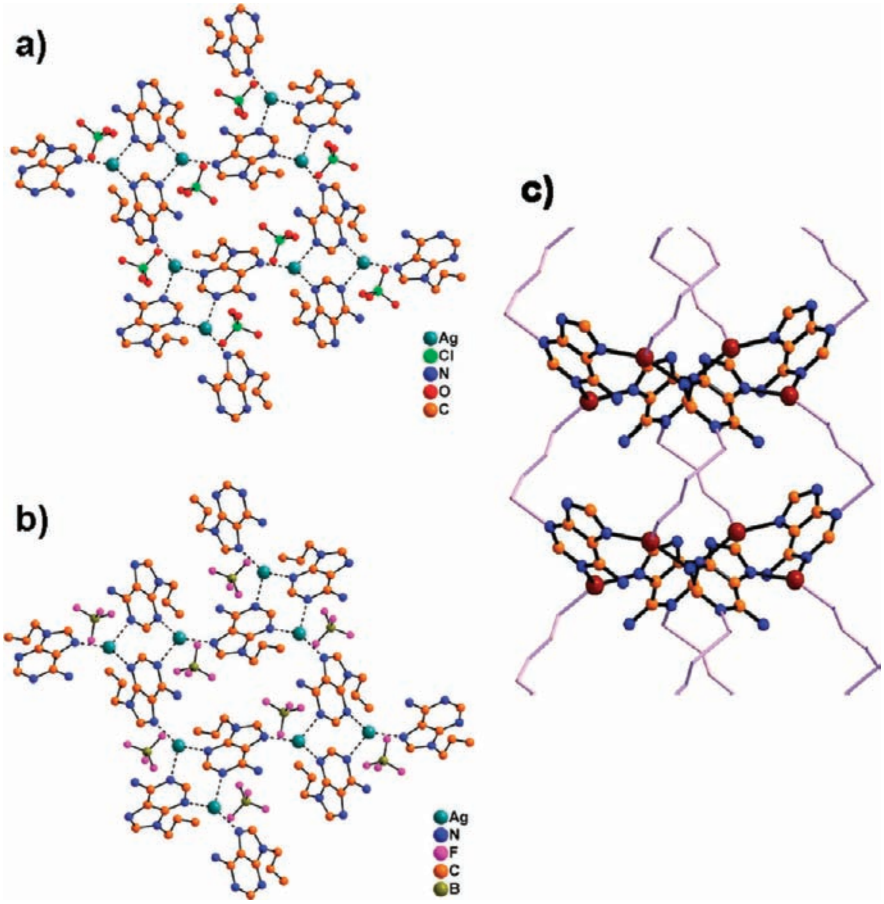


FIGURE 5. Metallaquartet structures of silver-modified adenine complexes: (a) ClO_4^- counteranion, **2**; (b) BF_4^- counteranion, **3**; (c) four-stranded helical wire-frame motif in **3** with two adjacent bowl-shaped quartets. Adapted with permission from ref 13. Copyright 2007 American Chemical Society.

niacal methanolic solution afforded a rare, alternating penta- and tetracoordinated silver ion geometry (complex **5**).[15] One silver ion tetracoordinates to two adenine moieties through N1 nitrogen atoms, while the other two coordination sites were satisfied by the oxygen atoms of the nitrate group. Interestingly, a pentacoordinated mode was exhibited by another silver ion by coordinating to two adenine moieties via N7, oxygen atoms from two nitrate counteranions, and an ammonia molecule (Figure 7a).

The alternate N1−Ag−N1 and N7−Ag−N7 arrangement leads to a zigzag geometry with intervening silver ions. A key stabilizing interaction identified in this zigzag, helix-like structure is a virtual metallamacrocycle composed of coordinated and stacked adenine ligands (Figure 7b).[15] The closure of this

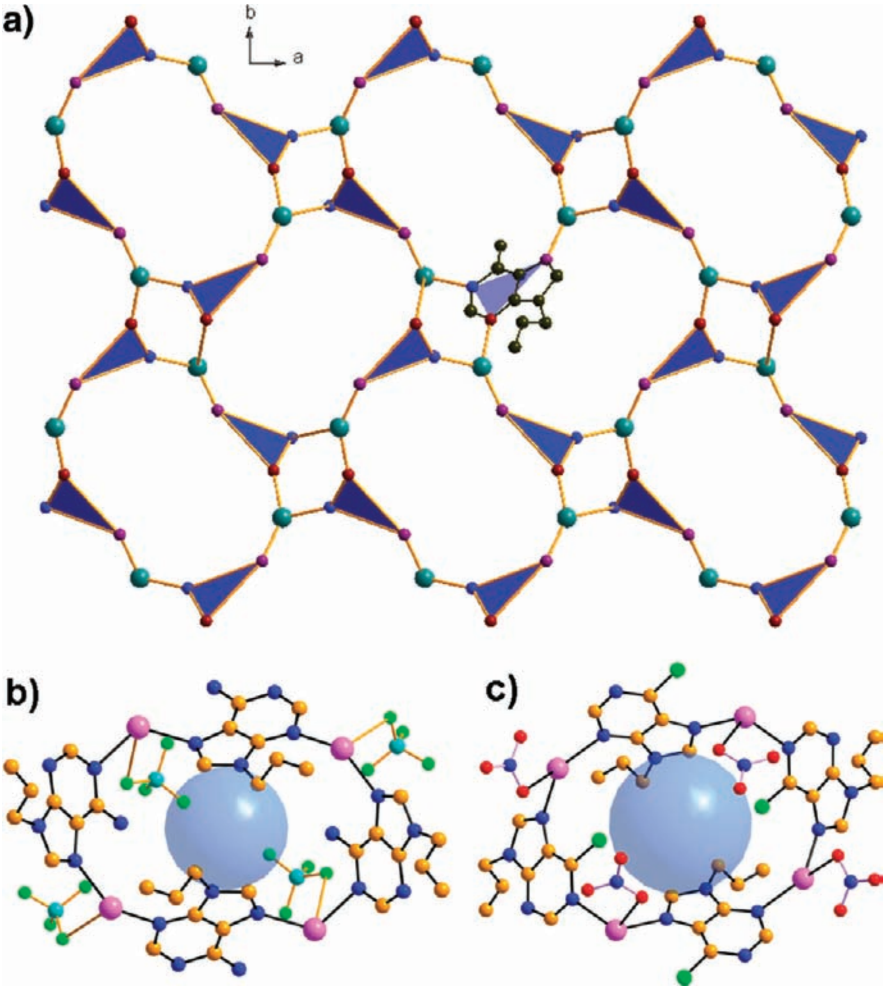


FIGURE 6. (a) Representation of silver−adenine metallaquartets and (b, c) voids within a quartet framework in **3** and **4**, respectively. Adapted with permission from ref 13. Copyright 2007 American Chemical Society.

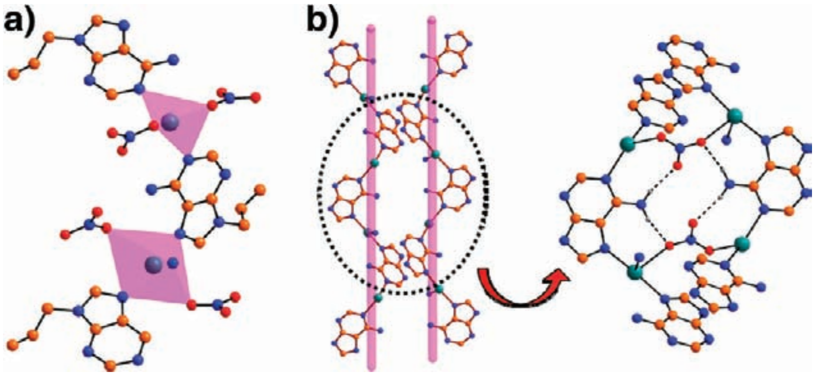


FIGURE 7. (a) Crystal structure of adenine−silver complex **5** and (b) nonintervening helix-like structures and virtual molecular box. Adapted with permission from ref 15. Copyright 2007 American Chemical Society.

virtual metallacycle is achieved via favorable $\pi-\pi$ stacking interactions between the two adenine rings with a separation of ~3.6 Å. Favorable contributions of π-stacking are well-known for metal−organic frameworks and self-assembling supramolecular systems.[16]

2.2. Bisadenine−Silver/Copper Interactions. The formation and mechanistic understanding of cross-link formation at adjacent purine bases in nucleic acids is a process of biological relevance. Study of these structures at the nucleobase level, in the absence of phosphate group and sugar moiety, serve as simple synthetic models where bases are connected by the linkers at appropriate positions.[17]

Intriguing results with 9-substituted adenine−silver complexes encouraged us to investigate complexes with ligands

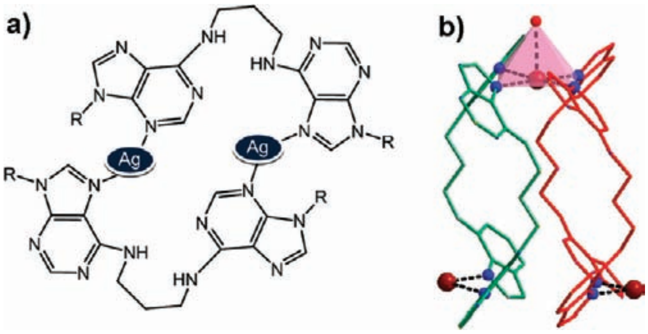


FIGURE 8. (a) Representation of silver-mediated bisadenine molecular box, **6** and (b) molecular structure of two interlinked boxes. Adapted with permission from ref 18. Copyright 2008 Royal Society of Chemistry.

having two adenine units. A symmetric alkyl linker was incorporated at N6 position to tether two adjacent purine bases, while the N9 position was alkylated with a propyl group. This analogue when reacted with silver nitrate afforded a pentacoordinated silver ion (**6**) bound to four adenine moieties and a water molecule in a distorted square-pyramidal geometry.[18] The two adenine bases, within a cross-linked ligand, coordinate via N3 and N7 to two silver atoms, while another ligand complexes in an opposite orientation to form a molecular box (Figure 8a). Interestingly, two molecular boxes are further connected by a silver atom giving rise to a complicated lattice arrangement (Figure 8b).

The crystal lattice, when viewed along the *a*-axis, reveals a series of columnar structures with a porous central part occupying 9.7% of the total cell volume (Figure 9). It should be possible to control the pore size of this columnar architecture by varying the chain length of the polymethylene spacer. Moreover, introduction of rigid connectors or spacers responding to stimuli, such as an azobenzene spacer, may further increase the scope of such molecular boxes for guest entrapment and release.

Copper(II) complexes of N9-substituted adenine exhibit a preference for N7 coordination over N1 or N3 nitrogen, when smaller substituents are present at the N9 position of adenine. A preference for N7 coordination for copper–bisadenine ligand interaction results into an intramolecular foldback structure around the copper ion.[18] This arrangement affords a distorted trigonal-bipyramidal geometry, where N7 and N7′ nitrogens occupy the apical positions, while the equatorial positions are occupied by solvent molecule and counteranions. This geometry is further reinforced by two intramolecular interactions involving N6H···O (from methanol solvent) and N6′H···Cl^- ion (Figure 10a).

A significant feature of this structure is the formation of a virtual box-like structure through in-space hydrogen-bonding interactions of two methanol molecules: one directly bonded to the copper center and the other hydrogen bonded to the N1 nitrogen of the ligand. Notably, an intermolecular $\pi-\pi$ interaction, where a six-membered ring of each adenine moi-

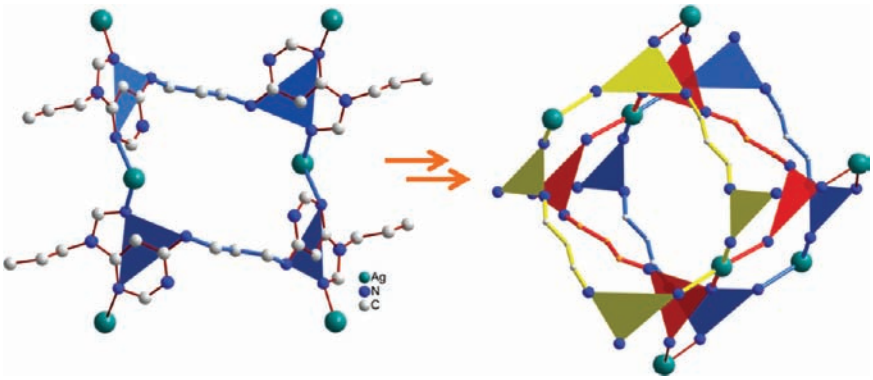


FIGURE 9. Solid-state structure of a bisadenine molecular box **6** and the formation of columnar architecture. Created from data of ref 18.

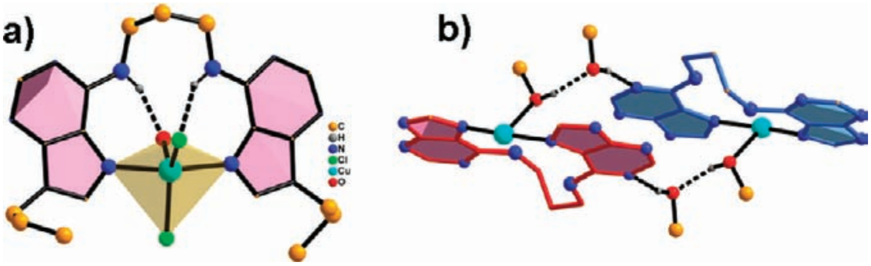


FIGURE 10. (a) Molecular structure of bisadenine–copper complex, **7** and (b) virtual box-like structure formed via hydrogen bonding. Adapted with permission from ref 18. Copyright 2008 Royal Society of Chemistry.

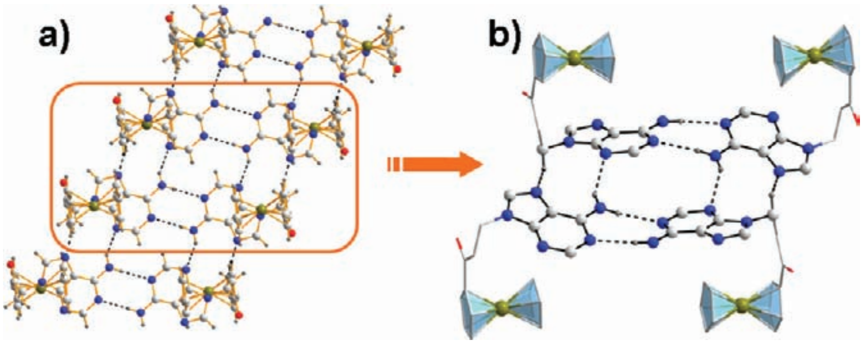


FIGURE 11. (a) Ferrocenylated adenine ribbons in **8** and (b) formation of a ferrocenylated adenine homotetrad. Adapted with permission from ref 22. Copyright 2008 Royal Society of Chemistry.

ety stacks with another one in the adjacent molecule, further stabilizes the crystal lattice (Figure 10b).

2.3. Ferrocenylated Adenine Tetrads. Redox behavior of ferrocene has long attracted its conjugation to biotic molecules catapulting an exciting area of bioorganometallic chemistry.[19] However, ferrocene conjugation to nucleic acids and their components is relatively unexplored[20] compared with similar studies with amino acids and peptides. Because nucleobases offer suitable molecular frameworks in terms of hydrogen bonding and supramolecular assembly, the design and synthesis of ferrocene–nucleobase conjugates offer exciting entry into hybrid molecules.[21]

N9-Ferrocenyl-substituted adenine **8** formed neatly packed ribbon-like structures in the solid state, which were held together by hydrogen bonds and $\pi-\pi$ interactions (Figure 11a).[22] A closer inspection of the crystal lattice revealed an adenine homotetrad structure stabilized with the help of eight hydrogen bonds formed through Watson–Crick and Hoogsteen faces.

The $\pi-\pi$ interactions between the cyclopentadiene (Cp) rings of the ferrocene moiety (Figure 12) and CH–π interaction between the Cp ring and nucleobase were other identified stabilizing interactions, as determined and confirmed by solution NMR studies. Thus, it was possible to realize the notion of decorating directed nucleobase assemblies with redox-active ferrocenyl groups, which may find material applications and aid molecular recognition sensors.

3. Surface Patterning of Adenine Coordination Complexes

The discovery of approaches concerning controlled generation of functionalized surfaces is critical for nanoscale applications in the areas of catalysis, detection, and optoelectronics. Toward this end, supramolecular coordination compounds offer enormous potential in generating novel architectures based on noncovalent interactions such as van der Waals and electrostatic interactions and hydrogen bonding.[23] Given the endless possibilities in ligand design and the extensive choice of metal ions, it is possible to conceive a diverse range of supramolecular coordination polymers, where a set of interesting structures could emerge under the influence of thermodynamic determinants.

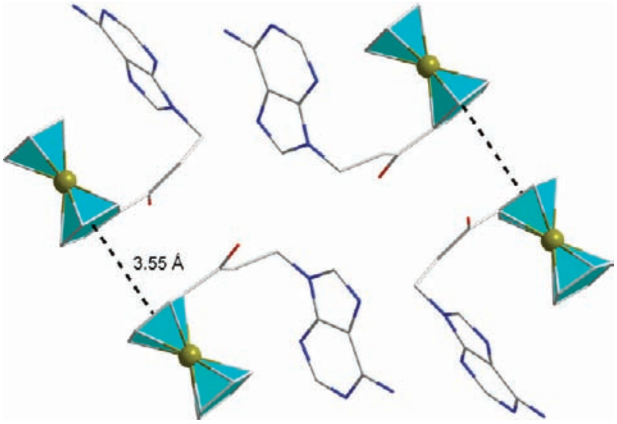


FIGURE 12. Arrangement of ferrocene appendage in **8** showing $\pi-\pi$ stacking interactions. Adapted with permission from ref 22. Copyright 2008 Royal Society of Chemistry.

Designed self-assembly of metal–ligand complexes allows directional control of structure growth, which can be further refined by subtle variations in ligand structures. Physical properties of coordination complexes, such as magnetism and redox and photochemical behavior, can be fine-tuned for desired applications. It has been lately realized that properties of metal-aided supramolecular assemblies can be transferred to surfaces for detailed physical studies.[24] It is worth mentioning that a number of studies have been performed to understand nucleic acid base adsorption on surfaces.[25] When coerced for surface adsorption, the nature of the nucleobase–surface interaction plays a dominant role in determining overall structure of the patterned self-assemblies.[26]

Investigations of adenine adsorption on graphite and other surfaces is primarily driven by the curiosity to model nucleobase self-assembly during prebiotic evolution of biopoly-

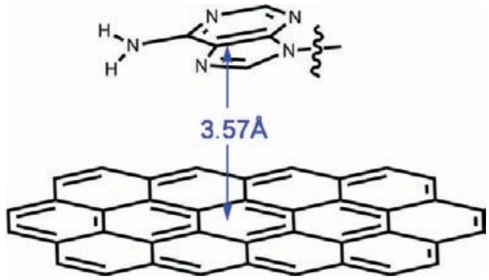


FIGURE 13. Schematic presentation of an N9-substituted adenine molecule interacting with a graphite layer. Adapted from ref 28.

mers.[27] Interestingly, preferential interaction of adenine molecules with highly oriented pyrolytic graphite (HOPG), slightly tilted at a distance of 3.57 Å compared with the graphite plane (Figure 13), is attributed to π-cooperativity arising from exchange and correlation energy of inhomogeneous electrons between adenine and the graphite layer.[28] Adenine forms lateral hydrogen bonds with other adenine molecules to exhibit hexagonal networks on various surfaces.[29]

Interesting solid-state structures of modified adenine−silver complexes prompted us to investigate whether these crystal structures could be transferred and studied on selected surfaces by the help of force microscopy. Surface topological investigations of 9-allyladenine−silver metallamacrocylic complex **1** by atomic force microscopy (AFM) revealed a well-ordered patterned arrangement comprising a repetitive zigzag assembly having a striking resemblance to the crystal structure (Figure 14).[11] The calculated distances from micrographs were found to be ~0.5 and 0.8 nm, which were comparable to the separation between silver atoms in the metallaquartet.

In another example, an admix of 9-allyladenine−copper complex **9** was deposited on the HOPG surface, and the ensuing pattern revealed highly symmetrical features on the nanoscale (Figure 15). The distances from micrographs were comparable to the distance between two copper atoms in the crystal, thus confirming transfer of the solid-state structure on the HOPG surface.[30] It was also possible to correlate an ordered one-dimensional array over 3D representation of the AFM micrograph along the monocrystalline steps of the HOPG surface (Figure 4).

Similar experiments with an admix of ammoniacal silver nitrate and 9-allyladenine gave rise to pattern formation on a HOPG surface, while the same mixture on a Si(100) wafer or a mica surface lacked obvious pattern formation.[15] A magnified view displayed a stepladder like arrangement and interestingly, the angle between the two axes of zigzag and

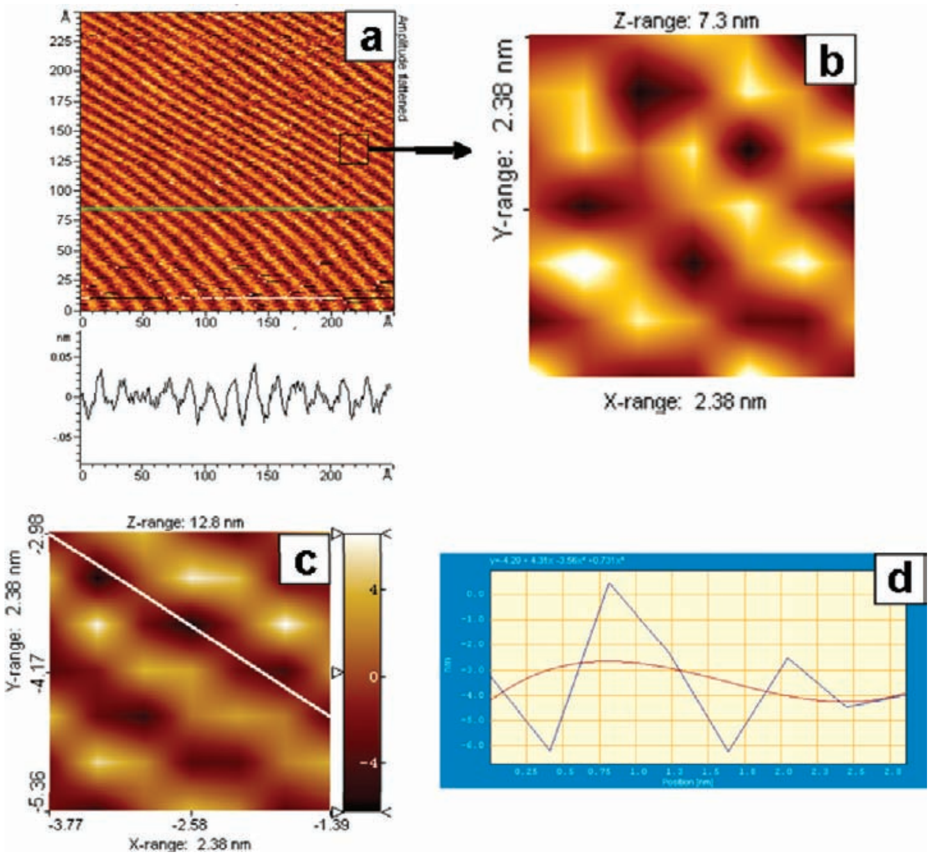


FIGURE 14. (a) AFM image of 9-AA−silver metallaquartet **1** on HOPG surface, (b) magnified image, and (c, d) distance analysis. Reproduced with permission from ref 11. Copyright 2006 American Chemical Society.

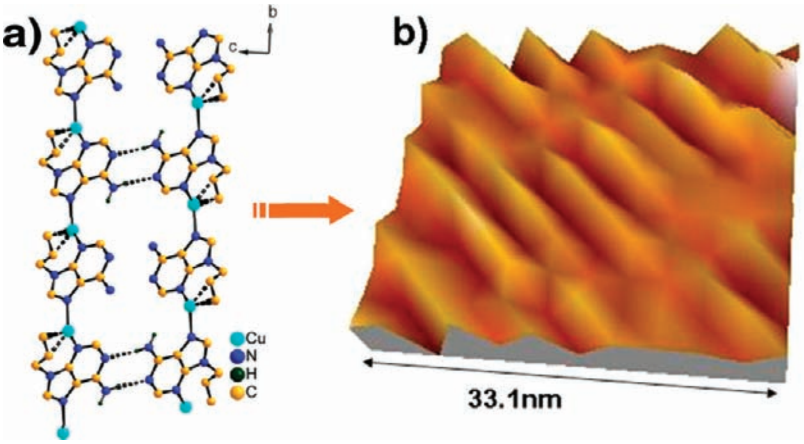


FIGURE 15. (a) Structure of 9-allyladenine–copper complex **9** and (b) 3D representation of AFM micrograph of **9** on the HOPG surface. Adapted from ref 30.

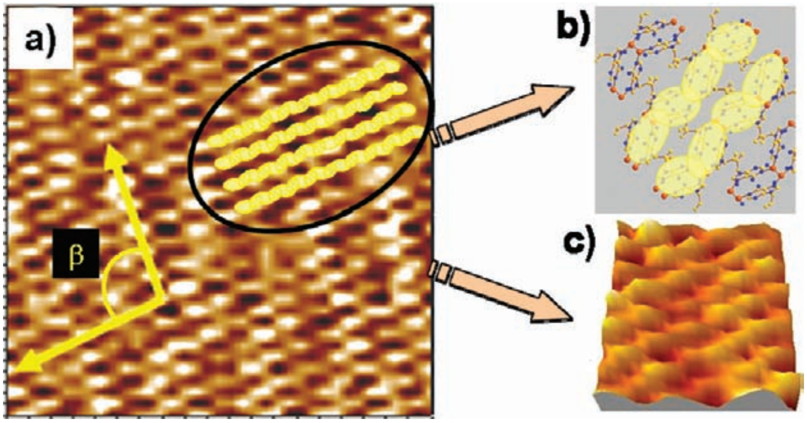


FIGURE 16. (a) AFM micrograph of **5** on HOPG surface and (b) proposed model of coordination complex deposition. Transparent ovals are used to signify similarities between the AFM image and the crystal structure. (c) Three-dimensional contours of the patterned surface. Reproduced with permission from ref 15. Copyright 2007 American Chemical Society.

stepladder patterns was found to be 96° ± 2°, which was nearly equal to the crystal angle $\beta = 96.96°$ (Figure 16). Notably, similarities between the solid-state structure and pattern formation on the HOPG surface reveal persistent silver-adenine interaction.

Thus, we have demonstrated that the structures generated from metal-directed growth and self-assembly of adenine can be patterned onto HOPG surfaces with reasonable control and success. It is surmised that surfaces patterned with porous metal–adenine coordination frameworks may serve as templates for guest positioning as well as for molecular recognition in addition to contributing to the hierarchical control of material organization for bionanotechnological applications.[31]

4. Catalytic Polymeric Adenine Templates

The five-membered imidazole ring harbored in the adenine framework is common to the amino acid histidine side chain where it acts as a general acid–base and a nucleophile in protein enzyme catalysis. It also doubles as an efficient ligand in coordinating metal ions in metalloenzymes.[32] Similar to enzymes carrying histidine residues, certain synthetic adenine derivatives have been shown to exhibit catalytic action possibly via a proton-relay mechanism.[33]

We have explored the issue of adenine-based catalytic entities by fixing the coordination ability of adenine in a polymeric matrix, followed by the use of such metalated adenine-containing polymers for catalytic assistance for various reactions. Vinyl or allyl groups were introduced at adenine N9 position for polymerization and the resulting homopolymer or cross-linked polymer affords an insoluble scaffold consisting of multiple adenine residues for metal ion coordination.

4.1. Phosphate Ester Hydrolysis. This hydrolytic pathway is a crucial step for key biochemical processes such as synthesis and processing of nucleic acids, release of chemical energy stored in ATP, signal transduction, and regulation of protein function. Inevitably, a large number of protein enzymes, like phosphatases, diesterases, triesterases, and nucleases, are recruited to catalyze phosphate ester (P-ester)

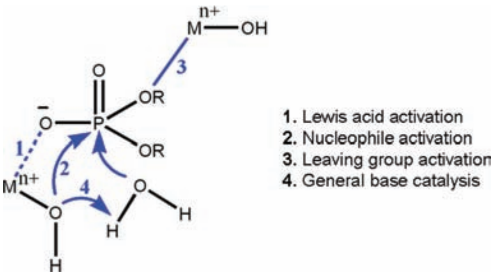


FIGURE 17. Various pathways of phosphate ester activation by metal ions.

hydrolysis under physiological conditions. These enzymes also require a number of metal ion cofactors, such as Ca^{2+}, Zn^{2+}, and Fe^{3+}, for the desired activity.[34] Consequently, synthetic phosphatase and nuclease model systems employ a wide range of metal ions and mimic native enzyme reactivity.[35]

It is generally agreed that metal ions can accelerate P-ester hydrolysis by four distinct activation pathways: Lewis acid activation, nucleophilic activation, leaving group activation, and general base catalysis (Figure 17).[36] Stronger Lewis acidic nature of coordinated metal ions (M^{n+}) can activate the phosphodiester bond by neutralizing negative charge at the phosphorus center, thus making it more susceptible for nucleophilic attack (pathways 1 and 3). In addition, water molecules coordinated to metal ions can also be substantially more acidic compared with free water molecules due to polarization effects. Thus, the generation of metal-bound hydroxide ion is possible at neutral pH,[37] which in turn can act either as a general base (pathway 4) or as an intramolecular nucleophile (pathway 2).

Allyl or 4-vinylbenzyl adenine polymerizable fragments were introduced at N9 position, followed by their polymerization in the presence or absence of cross-linkers, such as 1,4-divinylbenzene or ethylene glycol dimethacrylate (Scheme 1), to yield matrices containing a number of adenine residues.[38] Subsequent to synthesis and characterization, adenylated polymer was subjected metalation with copper, ruthenium, or uranyl cations. Thus, the polymeric backbone allowed creation of a constellation of adenine residues within a rugged coordination network. As expected, cross-linked nucleobase polymers were insoluble, hence all cleavage reactions catalyzed by such metallopolymers can be considered as examples of heterogeneous catalysis. Significant rate enhancements were obtained for activated substrates, and as expected these reagents displayed highly efficient catalyst recycling.

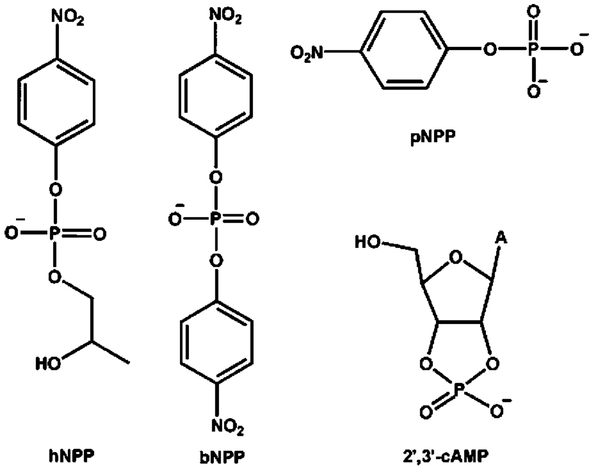
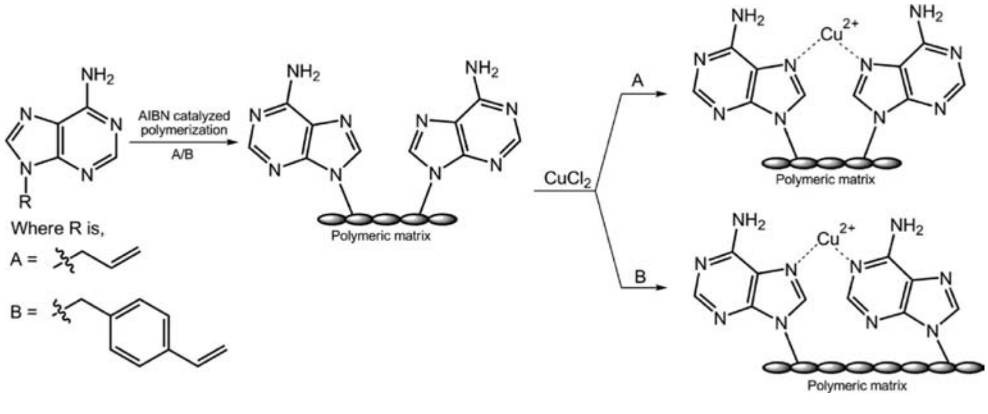


FIGURE 18. Type of P-ester substrates used for hydrolysis studies.

The hydrolysis of model phosphate ester substrates like *p*-nitrophenyl phosphate (pNPP), bis-(*p*-nitrophenyl) phosphate (bNPP), and 2-hydroxypropyl-*p*-nitrophenyl phosphate (hNPP) was studied with the help of metalated adenylated polymers. While bNPP acts as a phosphodiester substrate for an intermolecular hydrolytic reaction, hNPP acts as a RNA-like substrate containing a phosphodiester linkage for an intramolecular hydrolytic reaction owing to the presence of an internal hydroxyl group (Figure 18).

Rate accelerations approaching two-million-fold were observed for bNPP phosphodiester hydrolysis by employing

SCHEME 1. Schematic Representation of Metalated Adenylated Polymeric Matrices Showing Two Possible Scenarios for Metal Ion Coordination in the Polymeric Network



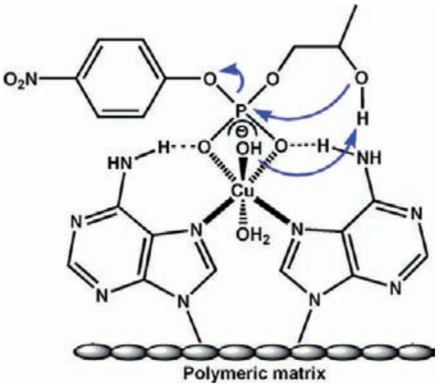


FIGURE 19. A proposed model for the hydrolysis of a model substrate by metalated polymers. Adapted from ref 38b.

metalated adenine-containing polymeric templates.[38b] Analogous to classical protein enzymes, these catalysts displayed Michaelis–Menten kinetics, and their activity was found to be modulated by pH and temperature variations.[38b] Notably, unmetalated cross-linked polymers and direct addition of metal ions failed to promote phosphate ester hydrolysis.

Hydrolysis of natural and unactivated substrate such as 2′,3′-cAMP was also achieved by metalated adenine polymers with appreciable rate enhancement and regioselectivity. Rate enhancements of ~1600-fold, relative to the uncatalyzed reaction, were observed with a preferential formation of 3′-AMP as the major regioisomer.[38c] Therefore, the catalytic potential of metalated polymeric templates was not limited to activated substrates but was also readily applicable to natural, biologically relevant substrates.

In order to determine preferential activation of attacking nucleophiles by metalated resins, P-ester solvolysis experiments were performed in water, 50% aqueous ethylene glycol, and ethylene glycol. Analysis of pseudo-first-order rate constants reflected a 2-fold increase in k_{obs} for 50% aqueous ethylene glycol over pure ethylene glycol, while the rate enhancement was over 5-fold if the reaction was performed in water alone.[38b] These observations confirm efficient generation of metal-bound hydroxide ion for bNPP hydrolysis, when compared with the metal-bound alkoxy intermediate (Figure 19).

The heterogeneous nature of polymeric catalyst offers considerable advantage as it is easy to remove the catalyst from the reaction mixture. Recycled polymeric templates retained their catalytic activity over several cycles of hydrolysis of activated phosphate esters and natural substrates.[38b,c] The initial velocities observed in recycling experiments were similar to those observed for fresh polymeric catalyst, thus demonstrating their rugged and truly catalytic nature. In a typical example, metal ion content of the metalated polymer was determined after a few cycles of hydrolytic reaction by atomic absorption spectroscopy. No significant loss in the concentration of metal ion was observed confirming robust molecular structure and stable adenine metal ion coordination within the polymeric matrix.

4.2. DNA Photocleavage by UO_2^{2+}–Adenine Polymer.

Photoinduced nucleic acid cleavage complements the more widely used hydrolytic or oxidative DNA cleavage pathways. As discussed in the previous sections, the latter methodologies generally require involvement of metal ions for nucleophile activation or for the generation of reactive species via redox cycling. In contrast, photocleavage relies on controlled photophysical characteristics of metal–ligand complexes, which are tuned to cleave DNA when excited by a specified wavelength of light (Figure 20).[39]

We applied atomic force microscopy (AFM) to follow controlled DNA cleavage by an adenine–copper couple. This approach allowed for in-depth probe of various conformational ensembles and topological intermediates arising out of the treatment of a synthetic nuclease.[40] Controlled reaction of synthetic nucleases with plasmid DNA resulted in the formation of circular relaxed and linear products suggesting a possibility of both single- and double-strand plasmid cleavages. Arguably, nondestructive surface trapping and AFM detection

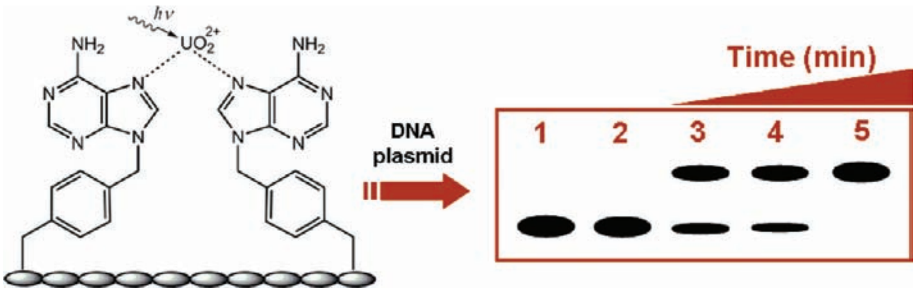


FIGURE 20. Photoactivation of uranylated adenine-containing polymer and representation of electrophoretic analysis of DNA plasmid cleavage (lane 1, DNA plasmid; lane 2, plasmid in presence of light without catalyst; lanes 3–5, time-dependent DNA cleavage in presence of adenylated catalyst and light). Adapted with permission from ref 39. Copyright 2003 Royal Society of Chemistry.

of nucleic acid topological intermediates provide an attractive alternative toward visualization of DNA structural modifications.

4.3. Phenol Oxidation by Metalated Adenine Polymers. Interestingly, copper−metalated adenine polymers were found to exhibit tyrosinase-like phenol oxidation activity. Naturally occurring tyrosinase is a copper-containing oxidase, which converts mono- and diphenols to quinone products. This reaction is significant for the melanogenesis pathway where the *o*-quinone product undergoes autopolymerization giving rise to colored pigments, such as melanin.

Copper-metalated adenine polymer oxidized catechol, 4-*t*-butylcatechol, and 4-hydroxyanisole phenolic substrates in the absence of any added co-oxidant such as H_2O_2. The catalytic oxidation of phenols was monitored via generation of colored adducts from the penultimate phenol oxidation product, the *o*-quinone. It was equally effective in oxidizing monophenols and diphenols and followed classical Miachelis−Menten kinetics.[41]

Facile recovery and reusability of polymeric catalyst is an important feature of this system. Recovered polymer from an oxidation reaction was recycled four consecutive times with different phenol concentrations. The initial velocities for different catechol concentrations using fresh and recycled polymeric catalyst were similar to the fresh catalyst, confirming the rugged nature of the polymeric catalyst and its superiority over conventional catalysts.[41] This approach has been extended to other nucleobase polymers, which afford controlled oxidation of 2,6-dimethoxyphenol and other substrates. It was proposed that multiple copper(II) centers in the polymeric matrix exert their catalytic potential presumably by activating dioxygen molecules for phenol oxidation.[42]

5. Outlook

The hydrogen-bonding capacity and versatile coordination ability of adenine toward a variety of metal ions is a remarkable feature of this heterocyclic nucleobase. The former is responsible for correct DNA base-pairing and structure stabilization, while the latter not only is manifested on charge dissipation but also influences pK_a of the exocyclic nitrogen, thus making adenine effective for biochemical catalysis. With these inspirations, we have exploited silver−adenine interactions to discover newer paradigms of metal−nucleobase interaction, and in the process, we have described novel luminescent nucleobase metallaquartets and other structures.

Interestingly, the transfer of adenine metallaquartets and other crystal structures onto graphite surfaces was also achieved and carefully studied with the help of force microscopy. Taken together, design of metallaquartets and other higher order structures and the catalytic activity of metal−adenine systems present a novel entry point into material synthesis from a natural ligand, adenine. Future studies are directed toward the generation and mimicry of nucleic acid superstructures by metal-mediated adenine architectures, design of custom surfaces by transferring crystal information onto surfaces, and discovering focused applications concerning chemical and biochemical catalysis.[43]

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Jitendra Kumar was born in 1982 in Gonda, India. He received his B.Sc. in 2002 and M.Sc. (organic chemistry) in 2004 from Avadh University (Faizabad, India). After receiving a Shyama Prasad Mukherjee Fellowship in Chemical Sciences from CSIR (2006), he joined IIT Kanpur for doctoral research. His research interest includes adenine functionalization and its interaction with transition and non-transition metal ions.

FOOTNOTES

[§] Dedicated to Prof. C.N.R. Rao on the occasion of his 75th birthday.

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