# Accounts

## Synthetic Incorporation of Metal Complexes into Nucleic Acids and Peptides Directed toward Functionalized Molecules

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Novel synthetic approaches for incorporation of metal complexes into nucleic acids and peptides are described. First, novel artificial $\beta$-*C*-nucleosides bearing a chelator nucleobase (2-aminophenol, catechol, or *o*-phenylenediamine) have been synthesized. These artificial nucleobases were introduced for alternative base pairing through metal coordination instead of the hydrogen bonding in natural DNA. $^1$H NMR and mass spectral studies clearly showed that *o*-phenylenediamine-type nucleoside forms a stable 2 : 1 square-planar complex with a $Pd^{II}$ ion, providing an alternative DNA base pairing through metal complexation. Secondly, an efficient strategy for the liquid-phase synthesis of cyclic metallopeptides having a repeating Gly-L-Cys(terpy$Pt^{II}$) sequence, *cyclo*[-Gly-L-Cys(terpy$Pt^{II}$)-]$_n$Cl$_n$ ($n$ = 3, 4), has been developed. These cyclic metallopeptides were obtained by cyclization of the corresponding linear peptides, $H_2$[-Gly-L-Cys(terpy$Pt^{II}$)-]$_n$OH·$(CF_3CO_2)_{n+1}$ ($n$ = 3, 4), in moderate yields. The former cyclic hexapeptide was found to act as a positively charged anion receptor. This synthetic approach would provide a powerful tool for arraying metal centers on cyclopeptide frameworks.

The field of bio-inspired molecular architectures is a broad and interdisciplinary area of worldwide research that has been growing explosively for more than a quarter of a century. Research in this field is motivated by the belief that the "*bottom-up*" *approach to control or to renew basic building blocks that have been provided by Nature* can lead to an enormous range of possible structures and functions of the final architectures. The self-assembly hierarchy, which is natural in origin, has long been conceptually introduced as a nonbiological approach to self-assembled, nanostructured molecules or materials, and a number of elegant examples are now known.[1] However, the bio-related aspects of molecular architectures, although full of promise, are not as well developed as the nonbiological ones. Although biological systems contain only a limited number of fundamental building blocks, such as nucleosides, amino acids, lipids, and carbohydrates, these molecules are chemically diverse and can be polymerized or assembled in various ways. Owing to recent advances in chemical synthesis and biotechnology, we can combine or chemically modify the biomolecular building blocks to produce novel ones for molecular architectures. In particular, it has been generally accepted that the incorporation of metal complexes into biomolecules is a key design target for the functionalization of biopolymers.[2,3]

In this paper, novel synthetic approaches for incorporation of metal complexes into nucleic acids and peptides are described. First, novel artificial $\beta$-*C*-nucleosides bearing a chelator nucleobase (2-aminophenol, catechol, or *o*-phenylenediamine) have been synthesized. These artificial nucleobases were introduced for alternative base pairing through metal coordination instead of the hydrogen bonding in natural DNA. Secondly, an efficient synthetic method for the liquid-phase synthesis of cyclic metallopeptides has been exploited and their anion binding capability has been examined.

### Metal-Assisted Base Pairing of Artificial DNAs

Nucleic acids are biopolymers consisting of monomeric nucleoside units linked by phosphodiester bonds, which hold genetic information in the cell nucleus. Their unique information codes are converted into proteins and enzymes to control all cellular processes. Despite the complexity of the genetic code, the base pairing process between two complementary DNA or RNA strands is rather uncomplicated and predictable. Nucleosides are *N*-glycosides of two different types of heteroaromatic nitrogen bases, pyrimidines and purines. The pyrimidine bases in DNA are thymine (T) and cytosine (C), the purine bases being adenine (A) and guanine (G). There are two essential rules of complementarity in the Watson–Crick base pair: hydrogen-bonding complementarity (A and G pair with T and C, respectively) and size complementarity (a large purine pairs with a small pyrimidine) (Chart 1). The binding energy of complementary DNA

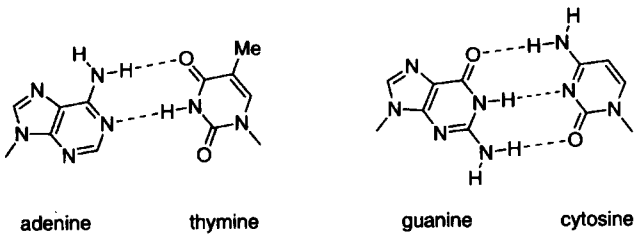



Chart 1.

strands originates from the stacking of the hydrophobic nucleobases in aqueous media, and the specificity of the association arises from the above two fundamental base pairing rules.

Hydrogen bonding is thus a key principle in highly specific interstrand recognition. Alternatively, in our strategy, hydrogen-bonded base pairing is replaced by metal-assisted base pairing, thereby creating a novel binding motif in duplex DNA (Chart 2).[4,5] Although, owing to the vital role of nucleic acid, coordination chemistry has been most extensively studied in the field of bioinorganic chemistry, metal-assisted base pairing by using artificial nucleosides with a "chelator-base" moiety is rare. In this approach, a DNA base itself is directly altered into a chelator-containing nucleobase for the incorporation of metal complexes into oligonucleotides. Such an approach would provide a wide range of applications to functionalized molecules based on its use as the third base pair along with the other two natural base pairs, AT and GC, and based on the metal assemblage through the structural diversity of DNA (e.g., duplex, hairpin, and circle).

The molecules we have synthesized in this study are $\beta$-*C*-nucleosides[6] having a 2-aminophenol (**1**), a catechol (**2**), or an *o*-phenylenediamine (**3**) as a metal-chelating site, which were predicted to form a 2 : 1 square-planar complex with a metal ion such as $Pd^{2+}$, $Pt^{2+}$, $Cu^{2+}$, and $Ni^{2+}$ (Chart 2). These artificial nucleosides are directed toward controlling the net charges of the metal-assisted base pairs bearing geometrical analogies with natural base pairs. For instance, when these nucleosides form a 2 : 1 complex with a divalent metal ion, the complexes of **1**, **2**, and **3** have 0, −2, and

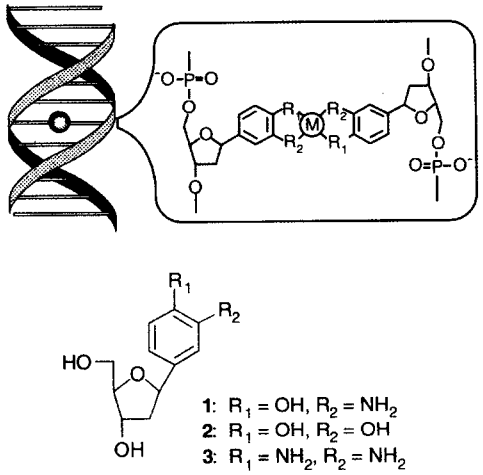



Chart 2.

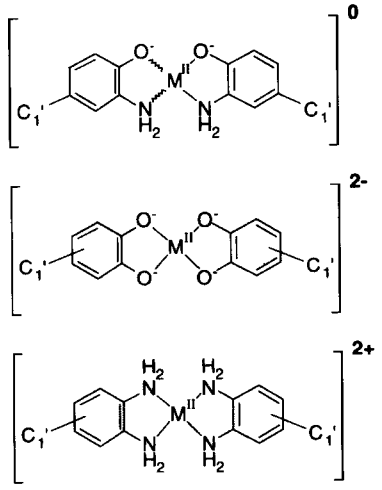
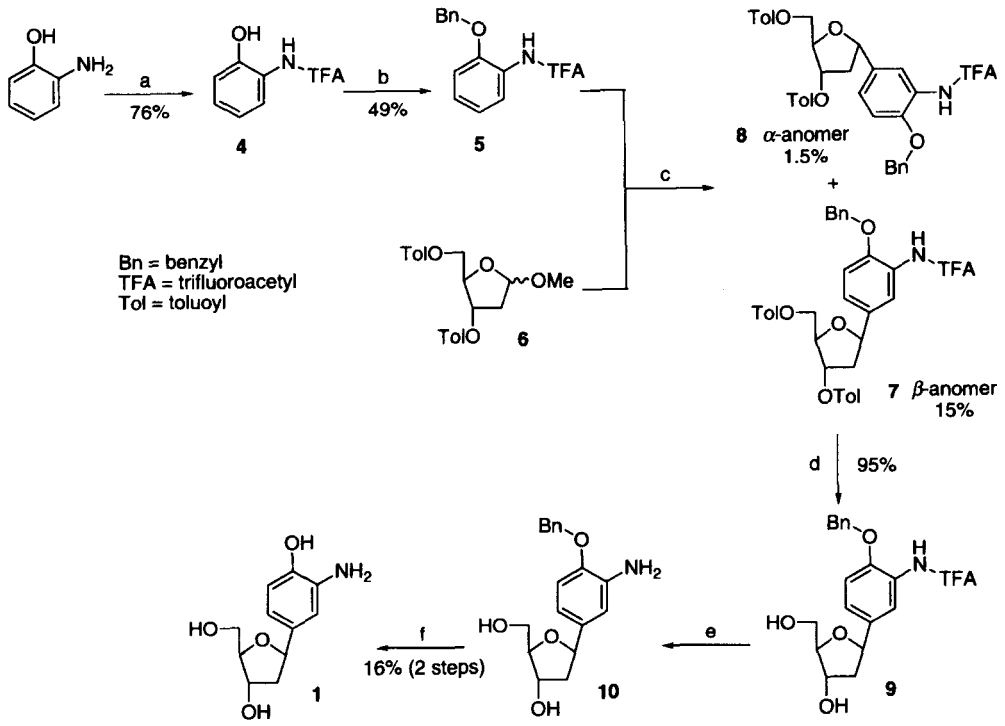


Chart 3.

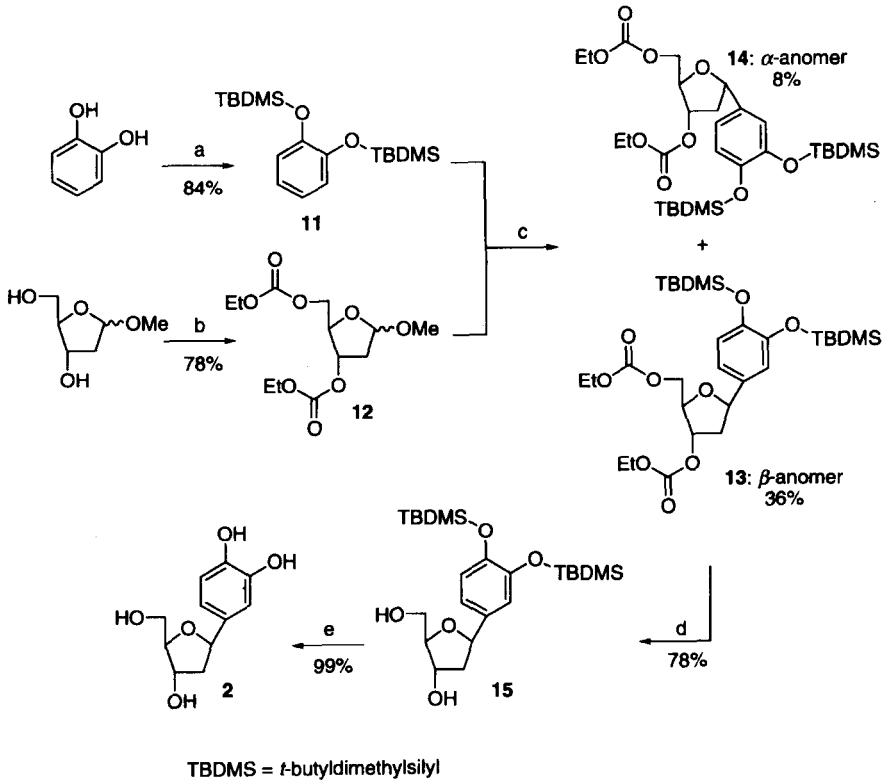
+2 charges, respectively, and therefore might be incorporated together into oligonucleotides at the adjacent positions (Chart 3). The following synthetic methods have been established for these three nucleosides.

Scheme 1 depicts a synthetic route for the synthesis of a $\beta$-*C*-nucleoside **1** which has 2-aminophenol as a nucleobase.[5] The most common method for C–C bond formation at the anomeric carbon involves nucleophilic attack on this naturally electrophilic center.[6] The Friedel-Crafts approach proceeding via electrophilic aromatic substitution was used to build up the carbon skeleton of the nucleoside **1**, where $SnCl_4$ was used as the Lewis acid promoter. In the synthesis of the nucleoside **1**, *o*-benzyloxy-trifluoroacetanilide **5** was used as the aromatic nucleophile. The reaction of **5** with 1-*O*-methyl-3,5-*O*-ditoluoyl-2-deoxy-D-ribofuranose **6**[7] was examined at 0 °C in $CH_2Cl_2$ in the presence of $SnCl_4$, and the $\beta$-*C*-nucleoside **7** was found to be produced with high selectivity ($\alpha$-**8** : $\beta$-**7** = 1 : 10), albeit in low yield. The $\beta$ configuration of the epimer **7** was clearly determined by X-ray analysis (data not shown). Its $^1$H NMR spectrum in $CDCl_3$ showed the signal for H-1′ which is a nearly evenly spaced doublet of doublets with the coupling constants $J_{1'-2'\alpha}$ = 5.1 and $J_{1'-2'\beta}$ = 11.0 Hz. This 1′–2′ coupling constant trend is consistent with the trends reported for related $\beta$-*C*-nucleosides,[8,9] while the H-1′ resonance for $\alpha$-*C*-nucleoside **8** appeared as a pseudo-triplet. The corresponding dihedral angles from the X-ray structure of **7** were found to be 36.7° and 158.9°. Application of the Karplus relationship empirically adjusted for nucleosides[10] predicts $J$ = 5.9 and 9.6 Hz, respectively, indicating that the ring conformation in solution is similar to that in the crystal. $^1$H NOE differentiation experiments also provided clear evidence for the anomeric configuration for **7**.[5b] Removal of toluoyl groups of **7** with NaOMe in MeOH provided **9** quantitatively; this was then converted into the desired $\beta$-*C*-nucleoside **1** by treatment with $MeNH_2$ in MeOH and subsequent hydrogenation.

As for the synthesis of catechol nucleoside **2** (Scheme 2),[5] *O*-protected catechol **11** was used for the Friedel–Crafts coupling reaction with 1-*O*-methyl-3,5-protected 2-deoxy-D-




Scheme 1. Reagents and conditions: (a) trifluoroacetic anhydride, pyridine, $CH_2Cl_2$, 0 °C, 76%; (b) benzyl chloride, *i*-$Pr_2EtN$, 1,2-dichloroethane, reflux, 49%; (c) 1-*O*-methyl-3,5-*O*-ditoluoyl-2-deoxy-D-ribofuranose, $SnCl_4$, $CH_2Cl_2$, 0 °C, 15% ($\beta$-anomer), 1.5% ($\alpha$-anomer); (d) MeONa, MeOH, r.t., 95%; (e) $MeNH_2$, MeOH, r.t., (f) $H_2$, Pd-C, MeOH, r.t., 16% (two steps).



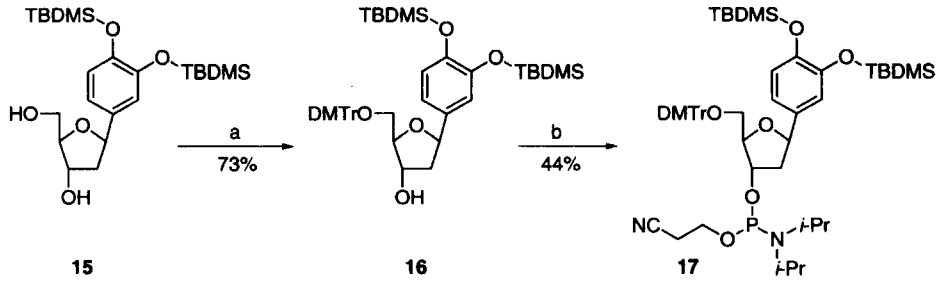

Scheme 2. Reagents and conditions: (a) *t*-butyldimethylsilyl chloride, pyridine, 80 °C, 84%; (b) HCl, MeOH, r.t., 78%; (c) $SnCl_4$, $CH_2Cl_2$, 0 °C, 36% ($\beta$-anomer), 8% ($\alpha$-anomer); (d) $K_2CO_3$, MeOH, r.t., 78%; (e) *n*-$Bu_4NF$, THF, r.t., 99%.

ribofuranose **12** in the presence of $SnCl_4$ as the Lewis acid promoter to afford fully protected nucleosides **13** (36%) and **14** (8%). The anomeric configurations for these compounds, **13** and **14**, were determined to be $\beta$- and $\alpha$-anomers, respectively, from the $^1H$ NMR coupling constants between H-1′ and H-2′ resonances. Epimer **13** showed two distinct H-1′ to H-2′ coupling constants ($J$ = 4.6 and 11.2 Hz), while epimer **14** exhibited a pseudo-triplet for H-1′. Ethoxycar-

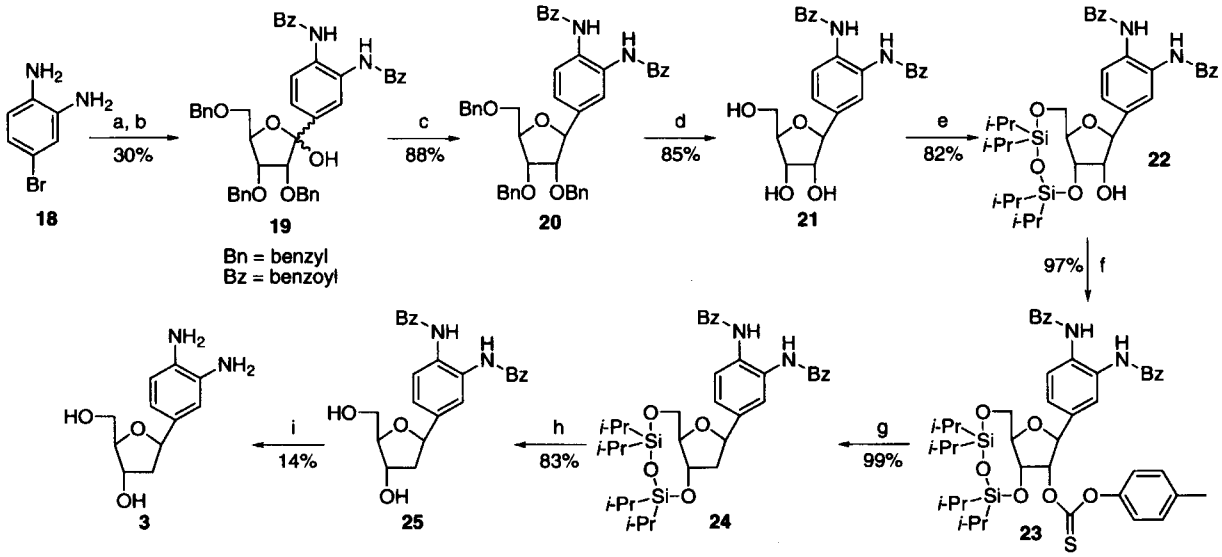
bonyl groups of **13** were removed by treatment with $K_2CO_3$ in MeOH in 78% yield, followed by deprotection of *t*-butyldimethylsilyl groups with tetrabutylammonium fluoride to afford nucleoside **2** quantitatively.

Owing to recent developments of automated DNA synthesizers, artificial diol compounds can be readily introduced into DNA oligomers having a designed sequence. Most such systems adopt the 3′-phosphoramidite method. Hence, a phosphoramidite derivative of nucleoside **2** was synthesized with the aim of incorporating it into DNA oligomers (Scheme 3). 5′-Hydroxy group of nucleoside **15** was protected with 4,4′-dimethoxytrityl group in 73% yield, and then converted into cyanoethyl phosphoramidite derivative **17** in 44% yield.

In contrast with the nucleosides **1** and **2** which could be efficiently synthesized via Friedel–Crafts coupling reactions as the key step between the aromatic ring and ribose moiety, *o*-phenylenediamine nucleoside **3** was prepared in rather longer steps through an RNA type intermediate followed by the removal of 2′-hydroxy group (Scheme 4).[4] Initially, we tried to prepare **3** via a coupling reaction of organocadmium species of an *N*-protected *o*-phenylenediamine derivative with 2-deoxy-3,5-di-*O*-*p*-toluoyl-$\alpha$-D-*erythro*-pentofuranosyl chloride (Hoffer's $\alpha$-chloro-2-deoxyribose). However, the preparation of organomagnesium species before transmetallation was not successful. Then as starting material for the synthesis of **3** the readily available ribonolactone, 2,3,5-tri-*O*-benzyl-D-1,4-ribonolactone[11] and the STABASE (*N*-1, 1,4,4-tetramethyldisililazacyclopentane) adduct of 4-bromo-*o*-phenylenediamine,[12] **18**, were used. The coupling reaction and the succeeding conversion to deoxyribonucleoside followed the synthesis of *C*-nucleosides developed by Leumann et al.[9] Lithiation-substitution methodology was applicable to the STABASE adduct of **18**. Treatment of this adduct with *n*-BuLi at −78 °C and in situ reaction with ribonolactone and the subsequent benzoyl protection of the two amino groups furnished a mixture of hemiacetals **19** in 36% yield in two steps. The reduction of **19** with excess $Et_3SiH/BF_3{\cdot}Et_2O$ provided *only* the naturally configured $\beta$-epimer **20**. The anomeric configuration of **20** was determined in a close connection with the structural assignment for **25**, as will be mentioned afterwards. Debenzylation of **20** with $BBr_3$ pro-




Scheme 3. Reagents and conditions: (a) 4,4′-dimethoxytrityl chloride, pyridine, 0 °C, 73%; (b) 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite, *N*,*N*-diisopropylethylamine, MeCN, r.t., 44%.




Scheme 4. Reagents and conditions: (a) 1,2-bis(chlorodimethylsilyl)ethane, DBU, DMF, 120 °C, 82%; (b) (i) *n*-BuLi, 2,3,5-tri-*O*-benzyl-D-1,4-ribonolactone, THF, −78 °C, 0 °C; (ii) benzoyl chloride, triethylamine, $CH_2Cl_2$, 0 °C, r.t., 36% (two steps); (c) triethylsilane, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −78 °C, r.t., 88%, (d) $BBr_3$, $CH_2Cl_2$, −78 °C, r.t., 85%, (e) $TIPDSCl_2$, pyridine, 0 °C, r.t., 82%; (f) *O*-*p*-tolyl chlorothionoformate, DMAP, MeCN, r.t., 97%; (g) AIBN, *n*-$Bu_3SnH$, toluene, 80 °C, 99%; (h) *n*-$Bu_4NF$, THF, r.t., 83%; (i) NaOH, $H_2O$, 80 °C, 14%.

vided the *N*-protected ribo-*C*-nucleoside **21** in 85% yield. Selective protection of the 3′- and 5′-hydroxyl groups with $TIPDSCl_2$ (1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane) in pyridine gave **22** in 82% yield. Treatment of **22** with *p*-tolylchlorothionoformate, followed by homolytic reductive cleavage of the C–O bond with AIBN and $n$-$Bu_3SnH$ afforded 2′-deoxy derivative **24** quantitatively. Desilylation of **24** with tetrabutylammonium fluoride provided the *N*-protected phenylenediamine 2′-deoxy-*C*-nucleoside **25**, which was then converted into the desired *C*-nucleoside **3** by treatment with aqueous NaOH.

The anomeric configuration of **25** was determined by $^1H$ NOE experiments and by examining coupling constants in $CDCl_3$ for H-1′ and H-2′. In $\beta$-anomers, H-2′$\alpha$ is only near H-1′. When H-1′ was irradiated, we observed a 4% enhancement at H-2′$\alpha$. The epimer **25** exhibited an H-1′ resonance as a nearly evenly spaced doublet of doublets ($J$ = 6.4 and 10.7 Hz). This result is comparable to that of the related $\beta$-nucleoside **9** in $CDCl_3$ ($J$ = 5.9 and 10.3 Hz).

Complexation between the nucleoside **3** and $Pd^{2+}$ in $D_2O$ was investigated by $^1H$ NMR spectroscopy (Fig. 1). Proton resonance in the aromatic region, as well as the resonances in the ribose moiety, shifted to lower field almost in proportion to increasing concentration of $Pd^{2+}$, and the complexation was completed when the concentration of $Pd^{2+}$ reached half the concentration of **3**. This result shows that **3** and $Pd^{2+}$ form a stable 2 : 1 complex **26** with a high binding constant. Although there are two possible structures (*cis* and *trans*) for the complex **26**, we observed only one species in the

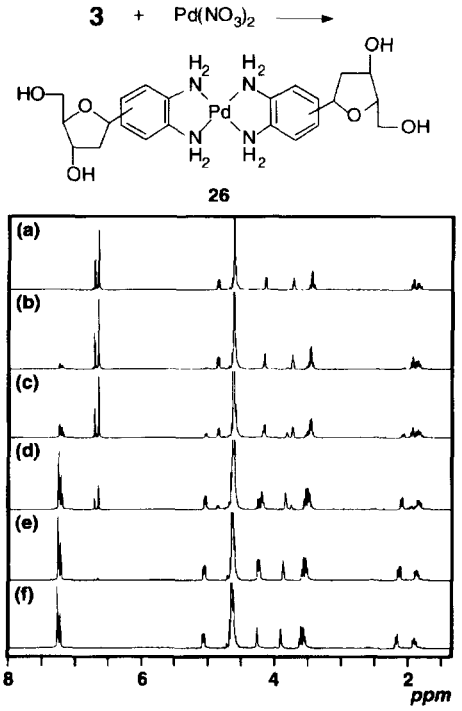



Fig. 1. 500 MHz $^1H$ NMR spectra of nucleoside **3** with increasing amounts of $Pd^{2+}$. [**3**] = 26 mM in $D_2O$ (1 M = 1 mol $dm^{-3}$). $[Pd^{2+}]/[\mathbf{3}]$ = (a) 0.00, (b) 0.08, (c) 0.19, (d) 0.38, (e) 0.49, and (f) 0.57.

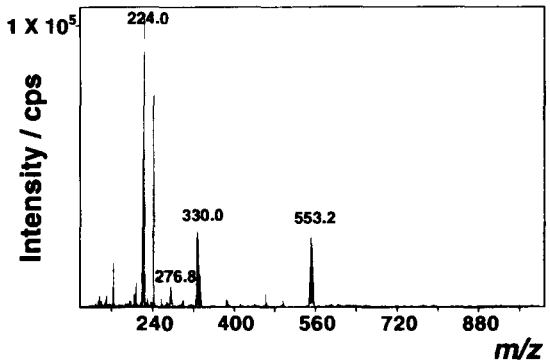



Fig. 2. ESI mass spectrum of $Pd^{2+}$ complex **26**: 553.2 ($[ML_2 - H^+]^+$; calcd for 553.13), 330.0 ($[ML]^+$; calcd for 330.02), 276.8 ($[ML_2]^{2+}$; calcd for 277.07), 224.0 ($[L]^+$; calcd for 224.12), where M = $Pd^{2+}$, L = nucleoside **3**.

NMR spectra. The electrospray ionization (ESI) mass spectrum also provided clear evidence for the 2 : 1 complexation (Fig. 2).

This work demonstrated the syntheses of three types of artificial $\beta$-*C*-nucleosides with a metal coordination site as a nucleobase providing an alternative DNA base pairing through metal complexation. The structure, thermodynamical stability, and kinetical behaviors of double-stranded DNAs including these nucleosides could be controlled by the coordination geometry, oxidation state, and ligand exchange rate of the metal ions lying at the center of base pairs. The methodologies developed in this study would be widely applicable to this type of nucleosides for DNA nanotechnology as well as artificial gene control. The site-specific incorporation of the newly synthesized nucleosides into oligonucleotides will be reported elsewhere.

## Cyclic Metallopeptides

Cyclic peptides are a particular class of compounds that have long attracted our attention in terms of their biological activity[13] and great potential as functional molecules.[14] The development of synthetic strategies for functionalized cyclic peptides is a fundamental challenge in the emerging field of bio-related molecular architectures. One of the most exciting recent examples in this field is self-assembling nanotubes made from cyclic D,L-$\alpha$-peptides and from cyclic $\beta$-peptides.[14] As another advantageous tool for the peptide design, metal binding sites have been engineered into peptides and proteins using the side chains of naturally occurring amino acids or unnatural metal coordination sites incorporated at the residues, for model studies of protein folding and enzymes, biosensors, and molecular architectures.[3]

There are twenty common $\alpha$-amino acids throughout nature, each of which contains an identifying side chain, at the asymmetric carbon center, possessing a specific chemical structure, hydrogen bonding capability, hydrophobicity or hydrophilicity, charge, and reactivity. From a coordination chemical point of view, the most significant amino acids for the purpose of modification or conjugation are the ones that are readily linked with metal complexes at the side

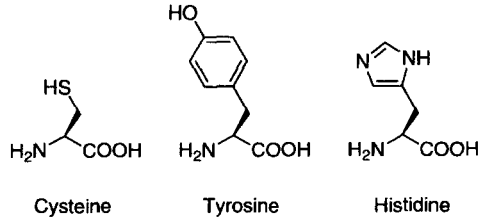



Chart 4.

chain: cysteine, tyrosine, histidine, aspartic acid, glutamic acid, and lysine (Chart 4). Each of these side chains, in the unprotonated form, can act as a metal coordination site. Among them, cysteine is the only amino acid containing a thiol group which is negatively charged with simultaneous deprotonation only at high pH or when it binds to a metal ion. Our approach is thus based on the use of L-cysteine (L-Cys) as a component of cyclic peptide–metal complex conjugates.

Recently, we reported an efficient strategy for the liquid-phase synthesis of cyclic peptides having a repeating Gly–L-Cys(terpyPt$^{II}$) sequence, *cyclo*[–Gly–L-Cys(terpyPt$^{II}$)-]$_n$Cl$_n$, **28** ($n$ = 3) and **29** ($n$ = 4) (Fig. 3).[16] Interest in the incorporation of a terpyPt$^{II}$ complex onto L-Cys was initially aroused by its binding to DNA and antitumor properties.[17] These peptides were designed so that positively charged Pt$^{II}$ complexes can be aligned periodically on the periphery of the macrocyclic peptide framework. We have also found that these cyclic metallopeptides provide a novel structural motif of the receptor site for anionic guest species.

The synthetic route for the linear metallopeptides is shown in Scheme 5. Treatment of TFA·H–(Gly–L-Cys)$_n$–OH ($n$ = 3 and 4) with 1.2$n$ equivalent [(terpyPt$^{II}$)Cl]Cl·2H$_2$O in H$_2$O at room temperature afforded TFA·H-[Gly-L-Cys(terpyPt$^{II}$)]$_n$-OH·(CF$_3$CO$_2$)$_n$, **27a** ($n$ = 3) and **27b** ($n$ = 4), in high yields, respectively. Linear hexapeptide **27a** was well cyclized at the concentration of ca. 0.50 mM in H$_2$O–MeCN (7 : 3) at 25 °C for 48 h in the presence of excess EDC·HCl (1-(3-

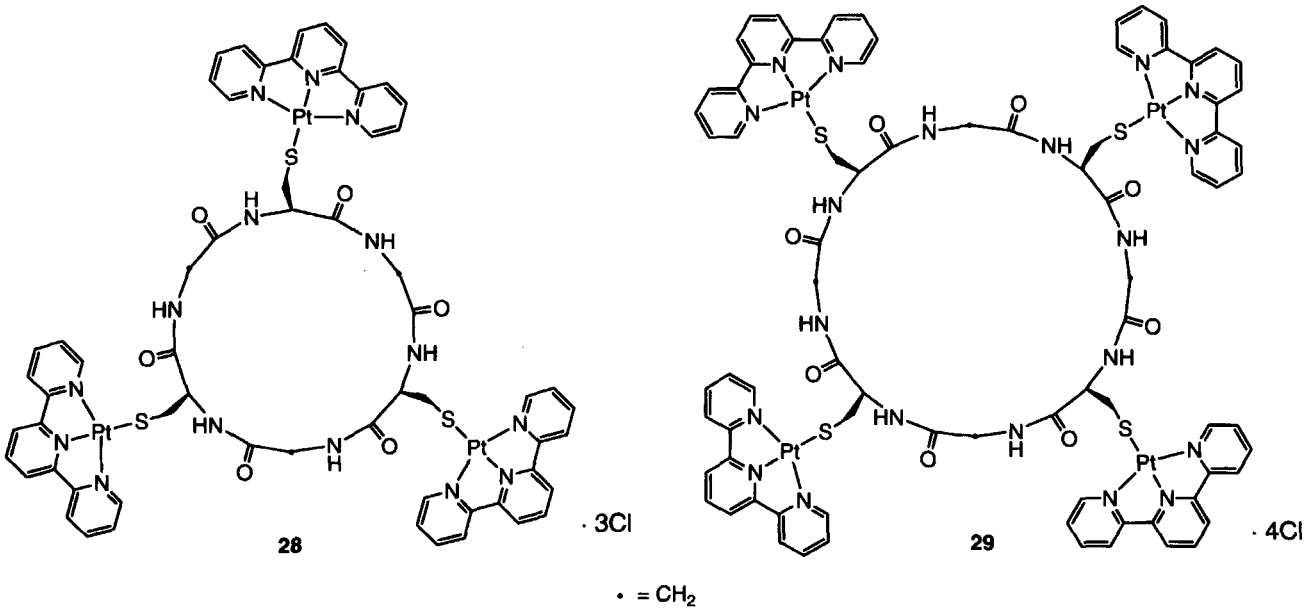
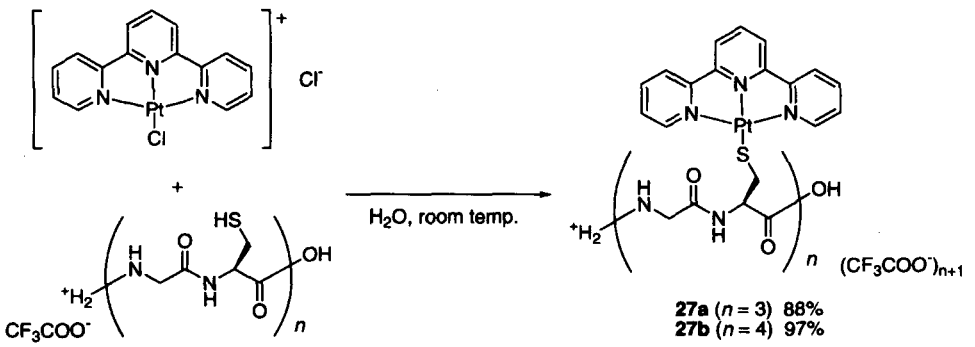
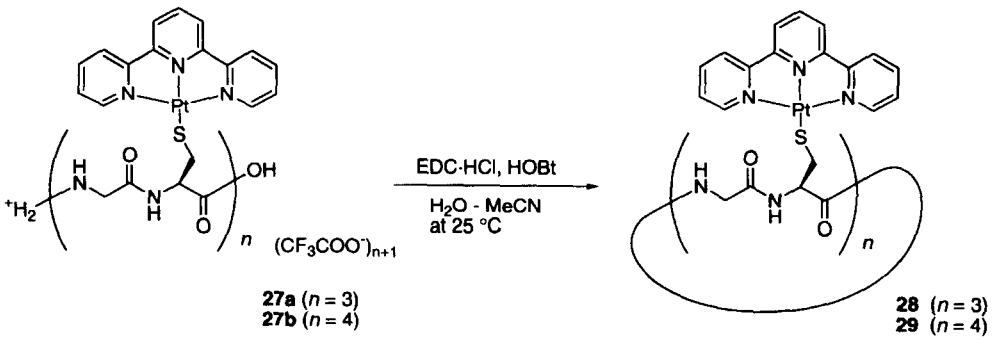



Fig. 3. Chemical structures of the cyclic metallopeptides newly synthesized in this study.




Scheme 5. Synthetic route for the linear metallopeptides, **27a** and **27b**.




Scheme 6. Cyclization of **27a** and **27b**.

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole) (Scheme 6). In this cyclization reaction, HOBt was essential and plays a role to reduce steric hindrance of an activated intermediate. *Cyclo*[-Gly-L-Cys(terpyPt$^{II}$)-]$_3$Cl$_3$, **28**, was obtained as a highly pure red precipitate in 58% yield. Its cyclic structure and ring size were clearly determined by high-resolution ESI-TOF mass spectroscopy (Fig. 4a). Isotopic distribution of the spectrum showed good agreement with theoretical simulation (Fig. 4b). $^1$H NMR spectra for **27a** and **28** are compared in Fig. 5. Whereas the $^1$H NMR spectral pattern of the linear **27a** was complicated (Fig. 5a), that of the corresponding cyclic peptide **28** was highly symmetrical and only one set of signals assignable to a Gly–L-Cys(terpyPt$^{II}$) subunit was observed (Fig. 5b). Similarly, the octapeptide **27b** was well cyclized to afford cyclic peptide **29** in 58% yield (Scheme 6). Its cyclic structure and ring size were also determined by ESI-TOF mass and $^1$H NMR spectroscopies (Figs. 4c, 4d, and 6). The steric hindrance and electrostatic repulsion which would occur intramolecularly between the positively charged Pt$^{II}$ complexes may complicate the solvent-dependent prefolding of the linear starting peptides, and may possibly facilitate the intramolecular cyclization.

The terpyPt$^{II}$ complex moieties of **28** were readily removed

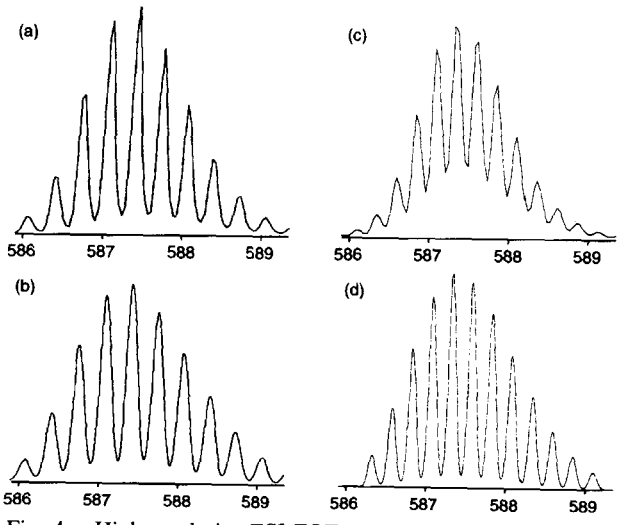



Fig. 4. High-resolution ESI-TOF mass spectra for (a) **28** and (c) **29** and their theoretical isotopic distribution for (b) **28** and (d) **29**.

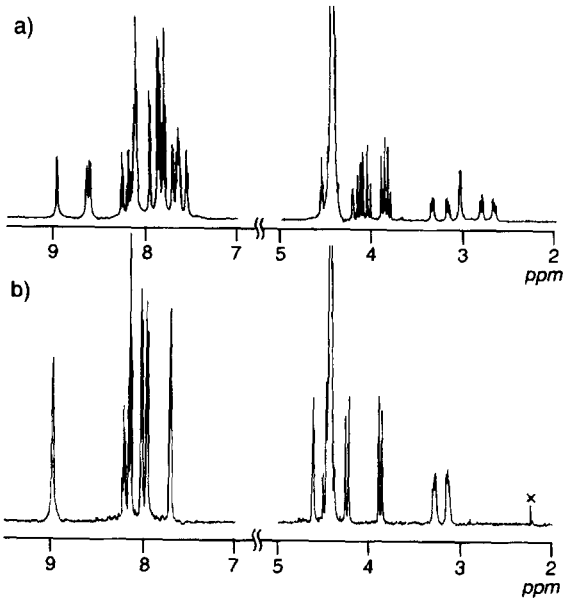
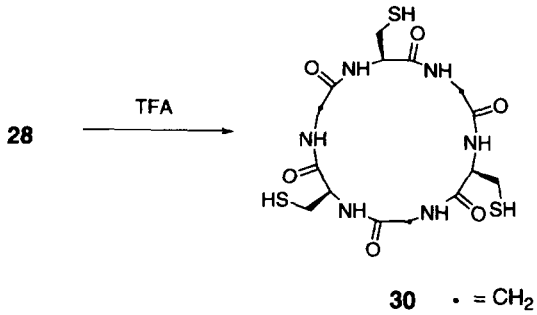



Fig. 5. $^1$H NMR spectra of a) TFA·H–[Gly–L-Cys-(terpyPt$^{II}$)]$_3$–OH·(CF$_3$CO$_2$)$_3$, **27a**, and b) *cyclo*[–Gly–L-Cys(terpyPt$^{II}$)–]$_3$Cl$_3$, **28**, in D$_2$O at 60 °C referred to external TSP.




Scheme 7. Removal of Pt$^{II}$ complex moieties from **28** by acid treatment.

by treatment with trifluoroacetic acid to afford the corresponding cyclic peptide, *cyclo*[–Gly–L-Cys-]$_3$ **30**, as indicated by its ESI mass data (*m/z* 479 [M – H$^+$]$^-$) (Scheme 7). Consequently, terpyPt$^{II}$ complexes can be regarded as both protecting and promoting groups for peptide cyclization.

These cyclic metallopeptides were predicted to serve as positively charged anion receptors.[18] In these receptors, coulomb interaction may be an attractive force for anion

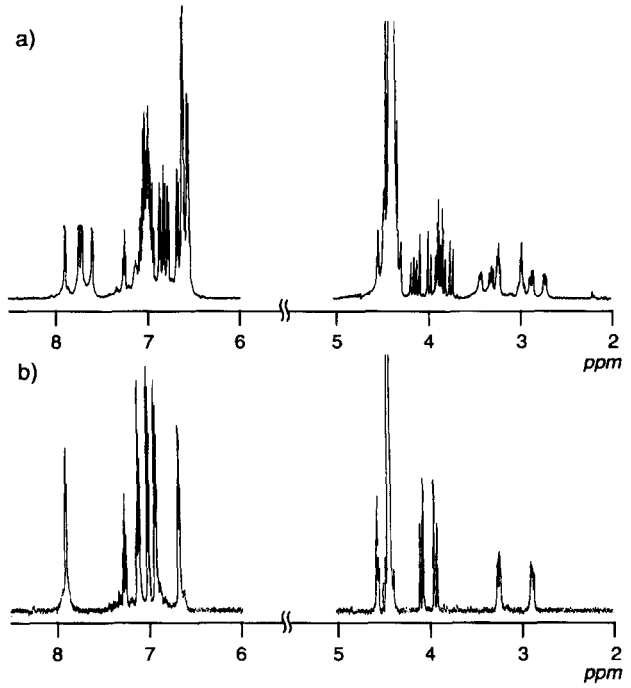
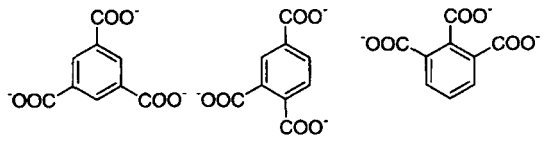



Fig. 6. $^1$H NMR spectra of a) TFA·H–[Gly–L-Cys-(terpyPt$^{II}$)]$_4$–OH·$(CF_3CO_2)_4$, **27b**, and b) *cyclo*[–Gly–L-Cys(terpyPt$^{II}$)-]$_4$Cl$_4$, **29**, in $D_2O$ at 60 °C referred to external TSP.




**31** **32** **33**

Fig. 7. Tricarboxylates used as anionic guest molecules.

binding. We have examined the binding of cyclic hexapeptide **28** to tricarboxylate anions (Fig. 7). We first tried to estimate its binding affinity to a series of carboxylate anions in solution. However, the binding constants could not be determined accurately due to the low solubility of the complex in general solvents. As a result, the cyclic hexapeptide **28** selectively separated benzene 1,3,5-tricarboxylate **31** from an equimolar mixture of three tricarboxylates (**31** and its 1,2,4- and 1,2,3-isomers, **32** and **33**, respectively) in neutral water at room temperature. The $^1$H NMR spectrum of the red precipitate (yield 85%) from the solution exhibited the 1 : 1 complexation between **28** and **31** in the neutral form, as shown in Fig. 8. Even in acidic solution ($D_2O$ containing 20% $CD_3CO_2D$) the signal assignable to the substrate **31** indicated a significant up-field shift, suggesting the high stability of the ternary complex of **28** with **31**. This was also firmly supported by its ESI mass data (*m/z* 1970 [peptide$^{3+}$ + tricarboxylate$^{3-}$ + H$^+$]$^+$, 986 [peptide$^{3+}$ + tricarboxylate$^{3-}$ + 2H$^+$]$^{2+}$). According to molecular modeling, terpyPt$^{II}$ moieties are expected to be conformationally flexible. We propose that, as shown in Fig. 9, three terpyPt$^{II}$ complexes surround the opening to the binding cavity of **28** and these three are all well positioned to bind the anionic substrate **31** through electrostatic interactions with the positively charged Pt$^{II}$ centers.

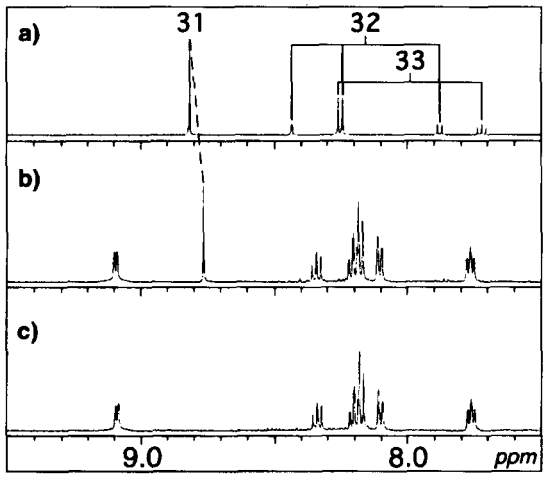



Fig. 8. Selected portions of $^1$H NMR spectra (20% $CD_3CO_2D/D_2O$, 60 °C, 500 MHz) of a) a mixture containing equimolar amounts of sodium 1,3,5-, 1,2,4-, and 1,2,3-benzene tricaboxylates, **31**—**33**, b) the resulting precipitate obtained from an aqueous solution containing an equimolar mixture of *cyclo*[–Gly–L-Cys(terpyPt$^{II}$)–]$_3^{3+}$, **28**, and sodium benzene tricarboxylates, **31**—**33**, and c) only *cyclo*[–Gly–L-Cys(terpyPt$^{II}$)-]$_3^{3+}$, **28**.

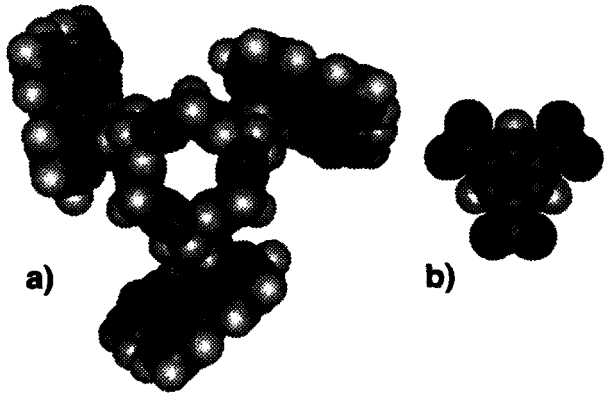



Fig. 9. Computer-generated models of *cyclo*[–Gly–L-Cys-(terpyPt$^{II}$)-]$_3^{3+}$, **28**, and 1,3,5-benzene tricarboxlate, **31**.

We have demonstrated an efficient strategy for the liquid-phase synthesis of cyclic peptides containing a repeating Gly–L-Cys(terpyPt$^{II}$) sequence. The subject in hand is to enhance the generality of this cyclization method by changing the ring size and/or the sequence.

## Summary

In this work, novel synthetic strategies for reconstruction of nucleic acids and peptides using metal complexes have been developed. These results raise the appealing possibility that this approach will lead not only to understanding or controlling bio-related events in which nucleic acids and proteins participate, but also to providing a novel molecular architecturing method for arraying metal centers on the skeletons of biomolecules in different ways.

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