

Artificial Multiple-Stranded Molecular Helices

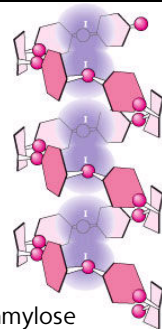
Lit. Seminar D2 Part / 2007.4.25 / Kounosuke Oisaki

<AT THE BEGINNING>

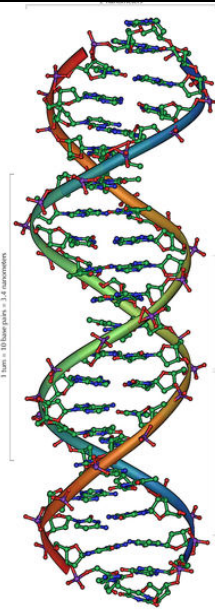
HELIX is one of primordial structures observed from microscopic to living system. Their wide apprance and beautiful structure have long been attracting much scientific and aesthetic interest of people, of course including chemists.

Artificial design of HELIX is one of important approaches to clarify the blackbox of **self-organization process** involving **emergence of macroscopic chirality**. Such reseaches will not only lead us to understand complex natural world, but also build up the basis for development of novel functional materials. However, we have little idea for rational design and synthesis of **MULTIPLE-STRANDED HELICES**, especially.

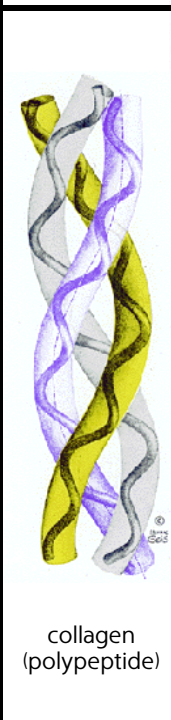
How can we approach such a beautiful strcutures ? Let's consider a little.



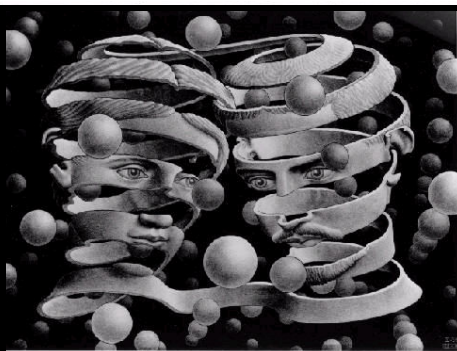
α -amylose (polysacchalide)



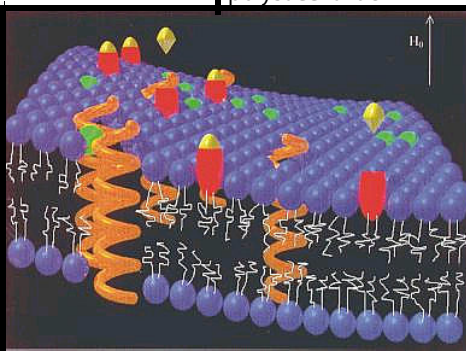
DNA (polynucleotide)



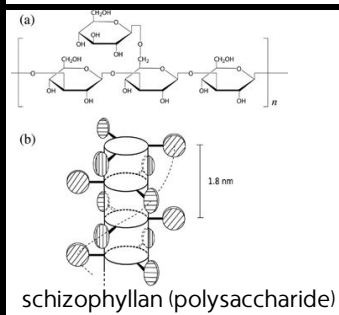
collagen (polypeptide)



"Bond of Union" by M.C. Escher (artwork)



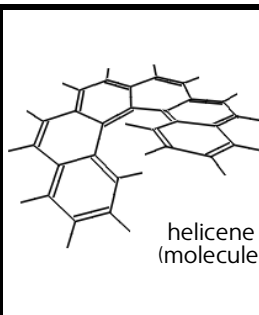
gramicidin (polypeptide)



schizophyllan (polysaccharide)



spring coil (material)



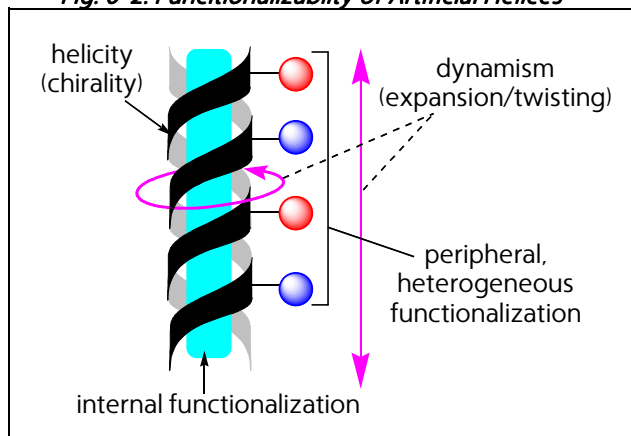
helicene (molecule)



vine of plant (living)

Fig. 0-1. Helices in the world: from molecule to living system

Fig. 0-2. Functionalizability of Artificial Helices



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1. Helicates: Coordination-Based Architectures
2. Acid-Base Interaction-Based Architectures
3. Hydrogen-Bonding-Based Architecture
4. Nanomaterial-Oriented MetalloDNA
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6. Appendix

1 Helicates: Coordination-Based Architectures

Many examples are reported, so far. Review: Piguet, C. et al. *Chem. Rev.* **1997**, *97*, 2005; Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457.

DEFINITION: Helices formed in metal-directed self-assembly process

<Pioneering work by Jean-Marie Lehn>

Lehn, J.-M. et al. *PNAS* **1987**, *84*, 2565, *ACIE* **1988**, *27*, 1095.

Scheme 1-1. Helicate Synthesis

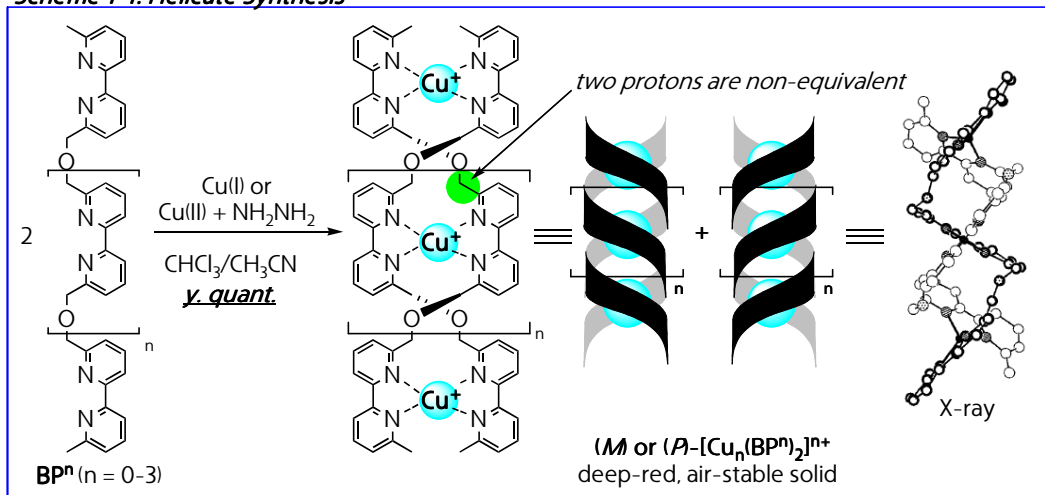
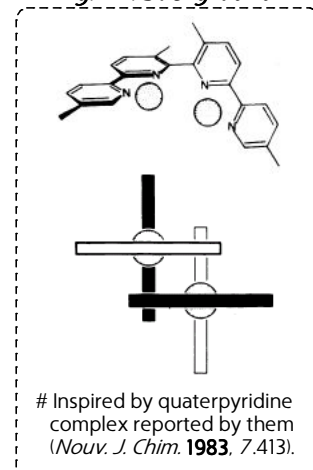
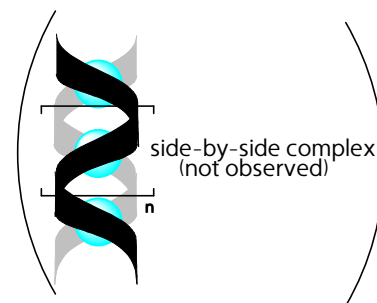


Fig. 1-1. Background



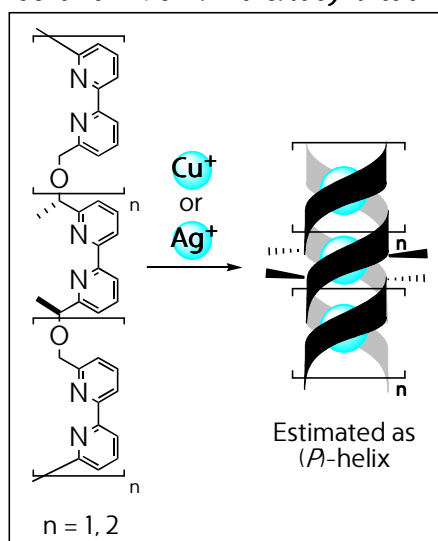
- # The term 'HELICATE' was firstly introduced.
- # Cu^+ has pseudotetrahedral coordination geometry
- # Kinetically stable at $>120^\circ\text{C}$
- # Mixture of *M/P* helicate (confirmed by NMR shift reagent)
- # Solubility depends on the kind of counterion.
- # Only helical structure is obtained. (i.e. side-by-side complex etc. is not observed.)



> Helicity (Chirality) Induction *Helv. Chim. Acta* **1991**, *74*, 1841.

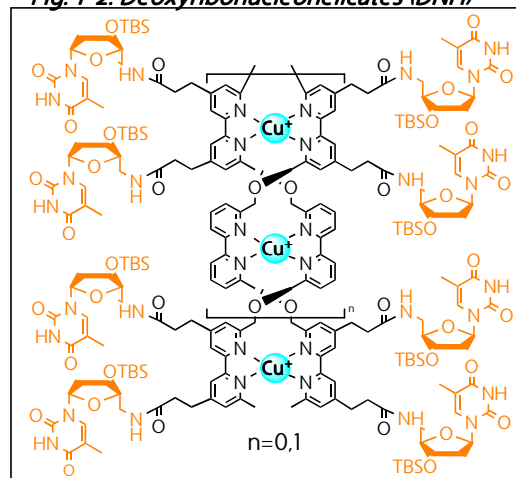
> Functionalization *Nature* **1990**, *346*, 339.

Scheme 1-2. Chiral Helicate Synthesis



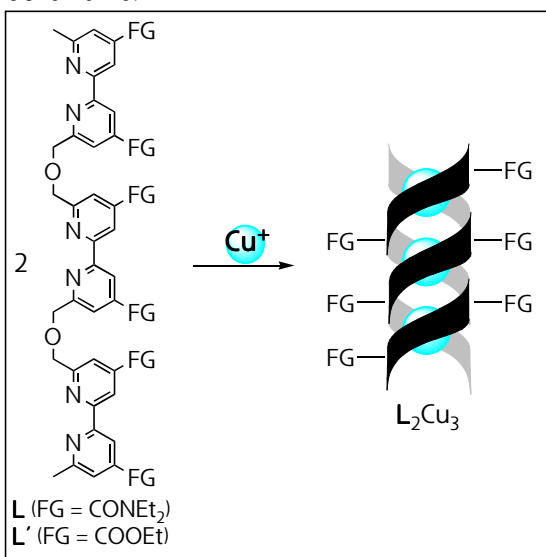
- # Structure is confirmed by $^1\text{H-NMR}$, FAB-MS
- # Only two chiral centers are required.
- # CD shows strong positive Cotton effect

Fig. 1-2. Deoxyribonucleohelicates (DNH)



- # Confirmed by $^1\text{H NMR}$, TOCSY, FAB-MS
- # Interaction with DNA is not investigated

Scheme 1-3.



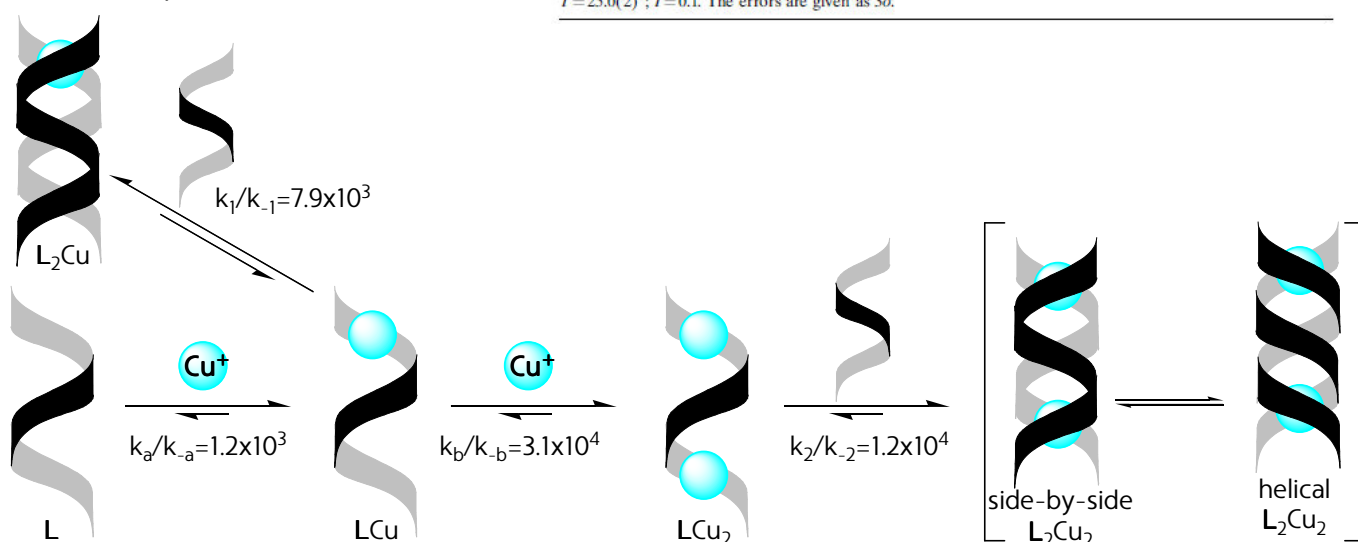
Measured:
Spectrophotometric titration
ESI-MS in various [Cu]/[L] ratio → calculation and fitting with computer program
Kinetics under excess Cu⁺

Table 1-1.

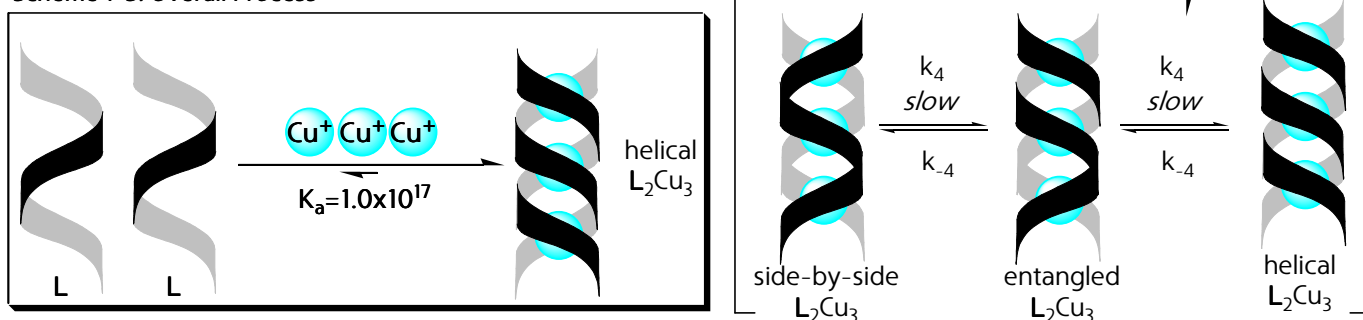
Rate-limiting step		Kinetic results
Step 1		
$L + Cu \xrightleftharpoons{\beta_{LCu^+}} LCu^*$	L	$\log \beta_{LCu^+} = 3.6(4)$
$LCu^* + Cu \xrightleftharpoons{\beta_{L2Cu^{2+}}} L2Cu_2^*$	L'	$\log \beta_{L2Cu_2^*} = 8.1(3)$ $\log \beta_{LCu^*} = 4.0(5)$ $\log \beta_{L2Cu_2^*} = 8.0(5)$
Step 2		
$L2Cu_2^* + L \xrightleftharpoons[k_{-2}]{k_2} L2Cu_3^*$	L	$k_2 = 7(3) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$
	L'	$k_{-2} = 53.0(6) \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_3^*} = 12.2(6)$ $k_2 = 2.0(7) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ $k_{-2} = 0.6(2) \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_2^*} = 13.5(6)$
Step 3		
$L2Cu_3^* + Cu \xrightleftharpoons[k_{-3}]{k_3} L2Cu_4^*$	L	$k_3 = 1.0(1) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$
	L'	$k_{-3} = 7.2(4) \times 10^{-2} \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_4^*} = 16.9(8)$ $k_3 = 45(9) \text{ M}^{-1} \text{ s}^{-1}$ $k_{-3} = 9(2) \times 10^{-2} \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_3^*} = 16.2(8)$
Step 4		
$L2Cu_4^* \xrightleftharpoons[k_{-4}]{k_4} L2Cu_3$	L	$k_4 = 2.0(4) \times 10^{-2} \text{ s}^{-1}$
	L'	$k_{-4} = 1.1(2) \times 10^{-2} \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_3} = 17(1)$ $k_4 = 3(2) \times 10^{-2} \text{ s}^{-1}$ $k_{-4} = 2.7(2) \times 10^{-2} \text{ s}^{-1} \rightarrow \log \beta_{L2Cu_3} = 16.3(9)$
$L'Cu^* + L' \xrightleftharpoons[k_{-1}]{k_1} L_2Cu$		$k_1 = 1.7(9) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ $k_{-1} = 0.22(7) \text{ s}^{-1} \rightarrow \log k_1/k_{-1} = 3.9(5)$

a) Solvent: MeCN/H₂O/CH₂Cl₂ 80 : 15 : 5 (v/v); T = 25.0(2)°; I = 0.1. b) Solvent: MeCN/CH₂Cl₂ 1 : 1 (v/v); T = 25.0(2)°; I = 0.1. The errors are given as 3σ.

Scheme 1-4. Proposed Mechanism

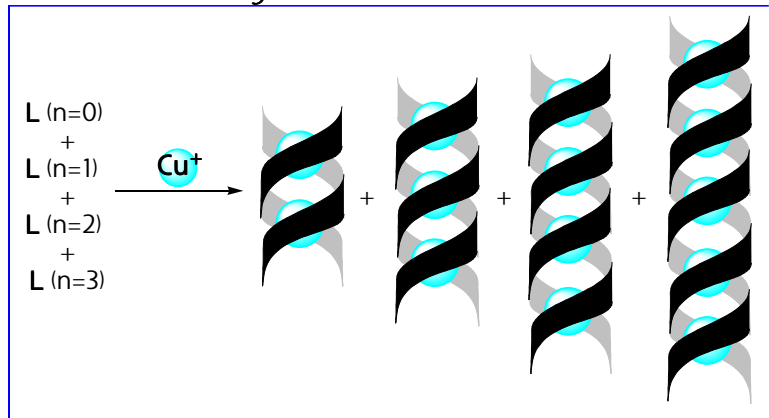


Scheme 1-5. Overall Process



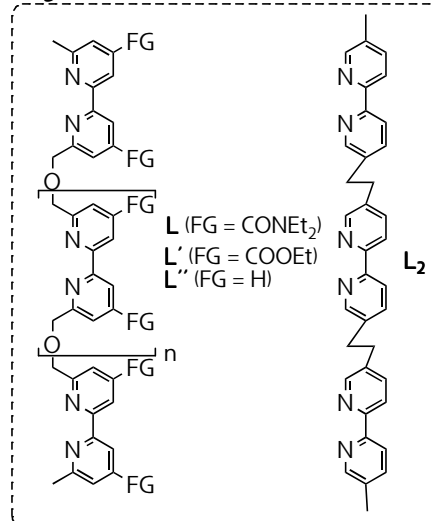
Positive cooperativity for the overall process was demonstrated!

Scheme 1-6. Self-Recognition of Four Helicates

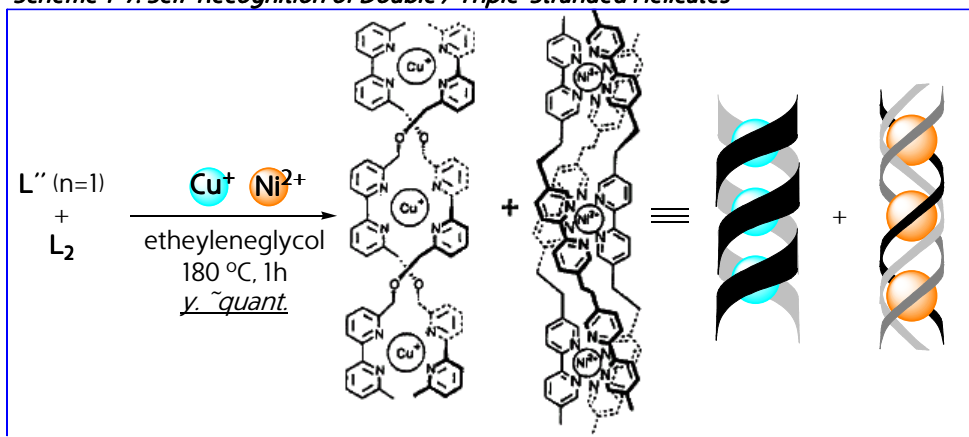


Predominantly four kinds of helices are generated.
(Neither mixed-ligand helicate nor coordination polymer were observed.)

Fig. 1-3



Scheme 1-7. Self-Recognition of Double / Triple-Stranded Helicates



11 components assemble into two higher order structures.
Ni²⁺ has octahedral coordination manner (affording triple-stranded helicate)

all results are supported by ¹H-NMR and FAB-MS

> Anion-Templated Control of Self-Assembly State: Circular Helicates *ACIE* 1996, 35, 1838, *JACS* 1997, 119, 10956.

Scheme 1-8. Circular Helicate Formation

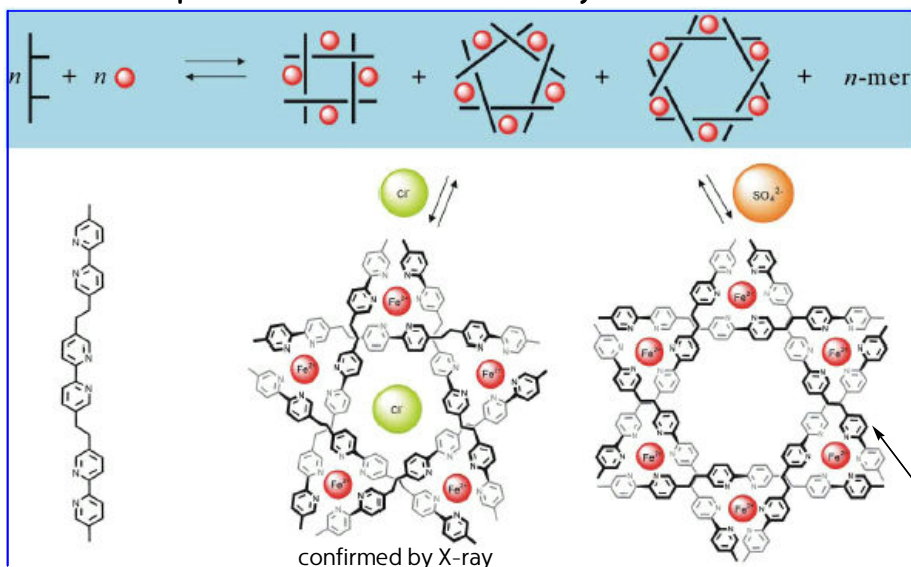


Table 1-2.

iron(II) salt	complex formed
FeF ₂	insoluble
FeCl ₂	[5]cH
FeBr ₂	[5]cH + [6]cH
FeI ₂	insoluble
Fe(BF ₄) ₂	[6]cH
FeSO ₄	[6]cH
FeSiF ₆	[6]cH

Possibly regarded as a primitive case of "Dynamic Combinatorial Chemistry (DCC)" (see my Lit. Seminar in D1)

confirmed by ¹H-NMR, NOE, ESI-MS (X-ray was not taken)

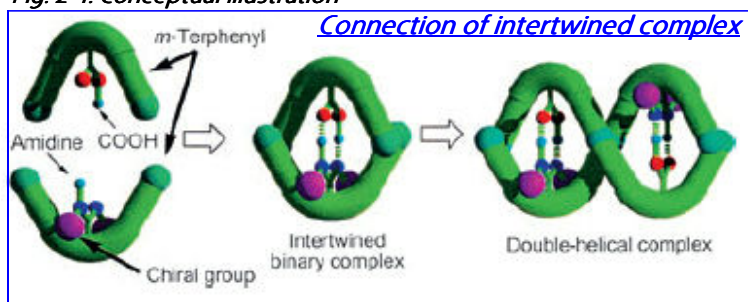
the results described point to the emergence of a new outlook involving a change in paradigm, from "pure compounds" to "instructed mixtures", from "unicity" to "multiplicity + information" (PNAS 1993, 90, 5394.)

2 Acid-Base Interaction-Based Architectures

<Works by Eiji Yashima>

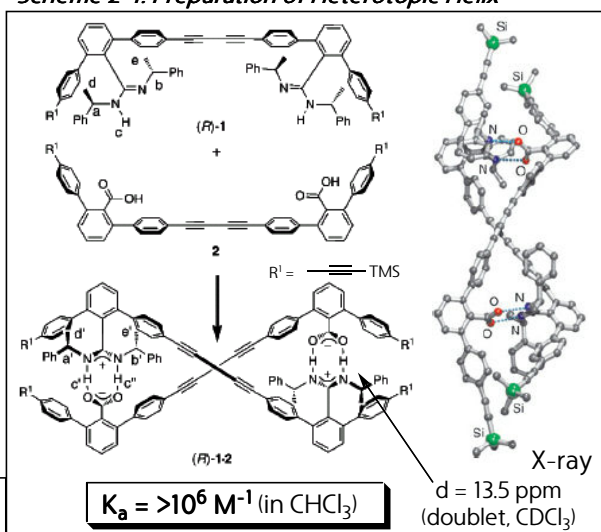
Furusho, Y.; Yashima, E. et al. *ACIE* 2005, 44, 3867.

Fig. 2-1. Conceptual Illustration



- # Use of 'crescent-shaped' *m*-terphenyl derivative.
- # Acid-base interaction is strong enough to predict the structure.

Scheme 2-1. Preparation of Heterotopic Helix



- # *P*-helix was obtained from (*R*)-amidine.
- # Helix formation was confirmed by ¹H and 2D NMR, ESI-MS, X-ray, and CD.
- # Cotton Effect of Helix is much stronger than amidine single strand.
- # Helicity is independent of solvent and temp. (although partial dissociation was observed in polar solvent, DMSO).

Fig. 2-2. CD Spectra of Amidine and Helix

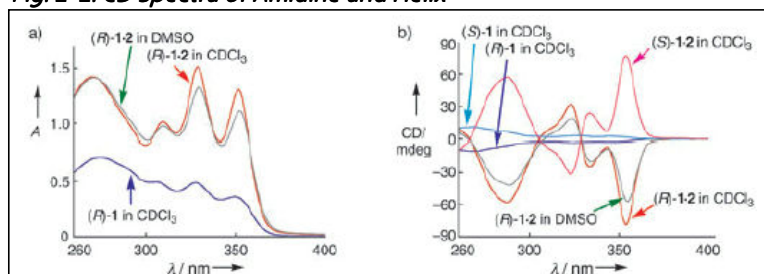
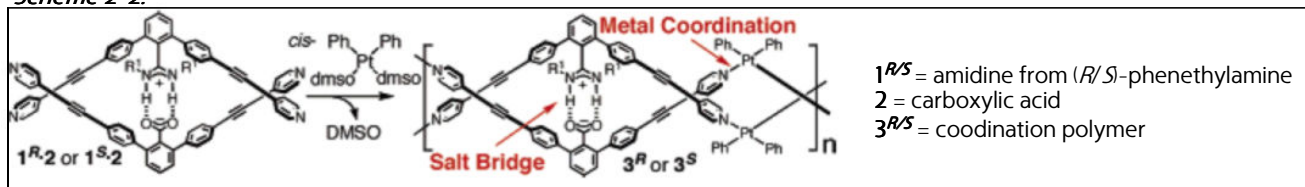


Figure 4. a) UV/Vis spectra (0.1 mM, 20°C) of amidine (*R*)-1 in CDCl₃ (blue), and complex (*R*)-1-2 in CDCl₃ (red) and in DMSO (green). b) CD spectra (0.1 mM, 20°C) of (*R*)-1 (blue), (*S*)-1 (light blue), (*R*)-1-2 (red), and (*S*)-1-2 (pink) in CDCl₃, and (*R*)-1-2 in DMSO (green).

> Extension to Helical Coordination Polymer

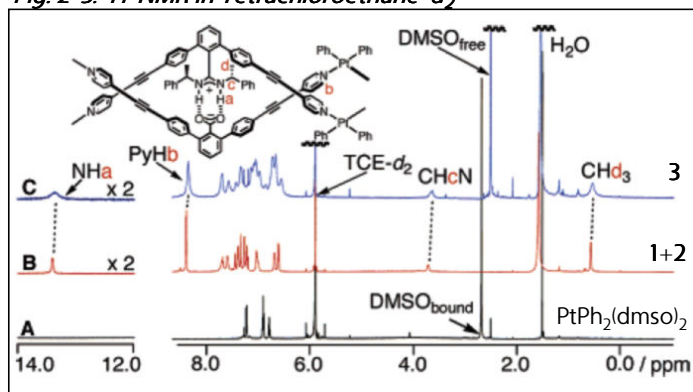
JACS 2006, 128, 6806.

Scheme 2-2.



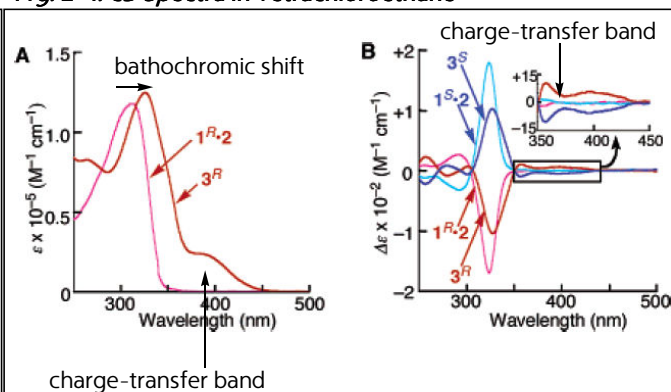
- # First example of double-stranded helical coordination polymer stable in solution

Fig. 2-3. ¹H-NMR in Tetrachloroethane-d₂



- # Structure is confirmed by NMR (¹H-DOSY) dynamic light scattering experiment, CD and AFM

Fig. 2-4. CD Spectra in Tetrachloroethane



- # These data suggested that **3** has a nature of **large π-conjugated system** with helicity.

Scheme 2-3. Fomation of 3:2 Complex

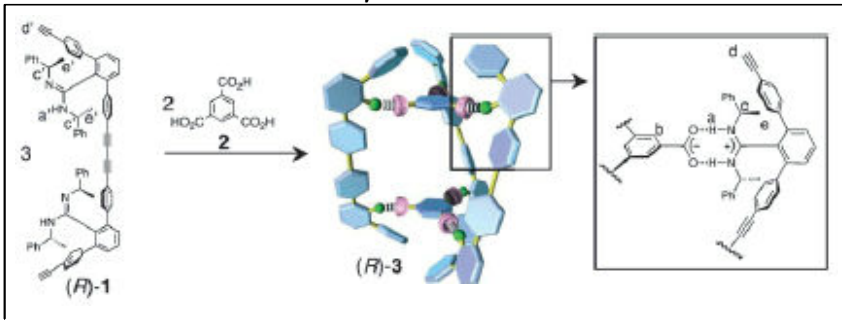
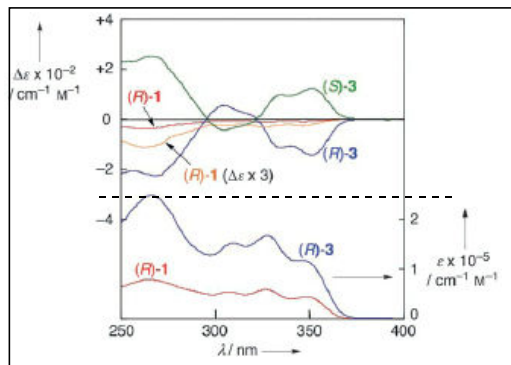
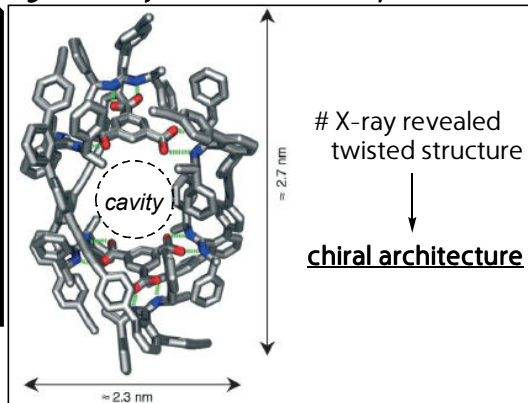


Fig. 2-5. X-ray structure of 3:2 Complex



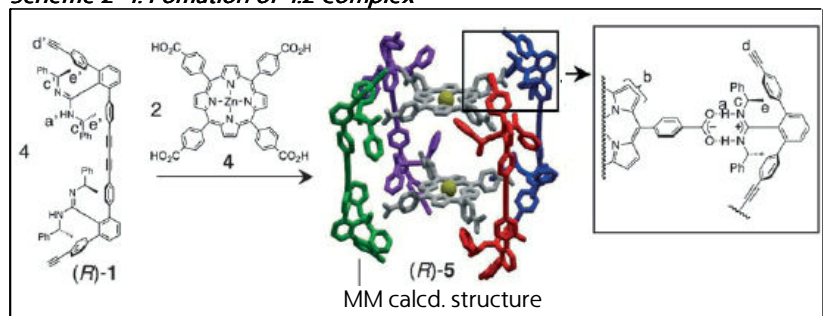
CD spectra unambiguously clarified the enantioselective formation of higher order structures.

Cotton effect is much stronger at lower temperature.

Dynamic character of architecture is implied.

Fig. 2-6. CD Spectra of 1 and 3

Scheme 2-4. Fomation of 4:2 Complex



Variation of modules is advantageous.

CSI-MS, ¹H NMR agreed with the speculated structure.

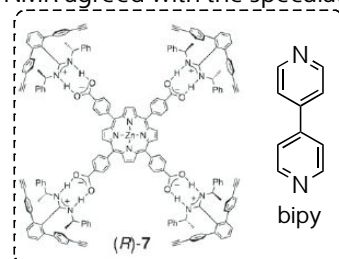


Fig.2-7. CD Spectra

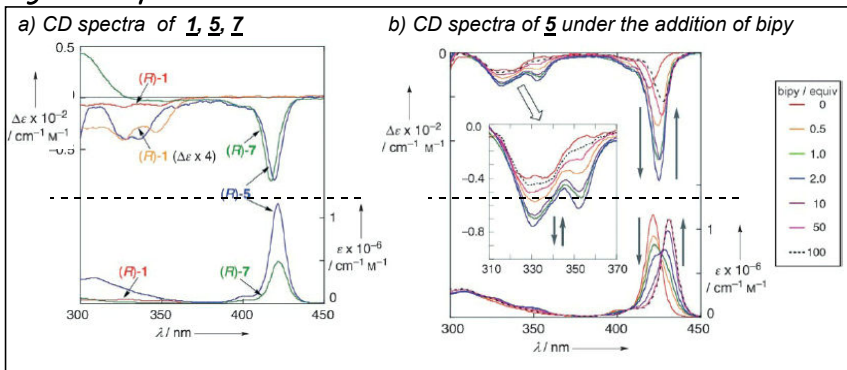
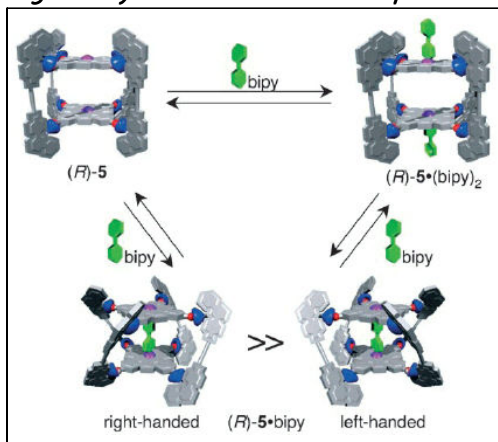


Fig. 2-8. Dynamic Nature of 4:2 Complex



MM calc and CD spectra suggested relatively untwisted structure of 6.
Cotton effect on Soret band (420nm) is due to close amidine chirality. (Temperature-independent, and 7 showed similar tendency)

Addition of bipy induced Cotton effect on 300–370 nm and red shift of Soret band
Bipy NMR peaks shifted upfield.
More than 1.0 eq. of bipy weakened the Cotton effect.

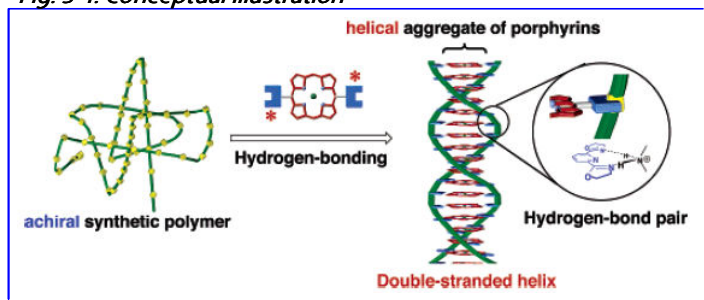
bipy is encapsulated in the cavity and induced supramolecular chirality via dynamic structural change.

3 Hydrogen-Bonding-Based Architectures

<PyBOX-Ammonium Cation System by Seiji Shinkai>

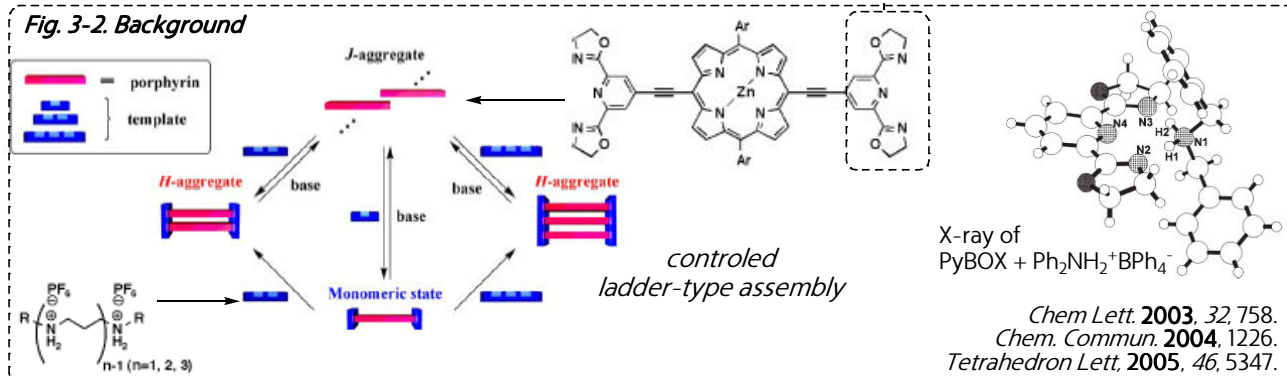
Sada, K.; Shinkai, S. et al. *JACS* 2007, 129, 270.

Fig. 3-1. Conceptual Illustration



Introduction of chirality to ladder architecture will twist the structure to give helix!

Fig. 3-2. Background



Scheme 3-1.

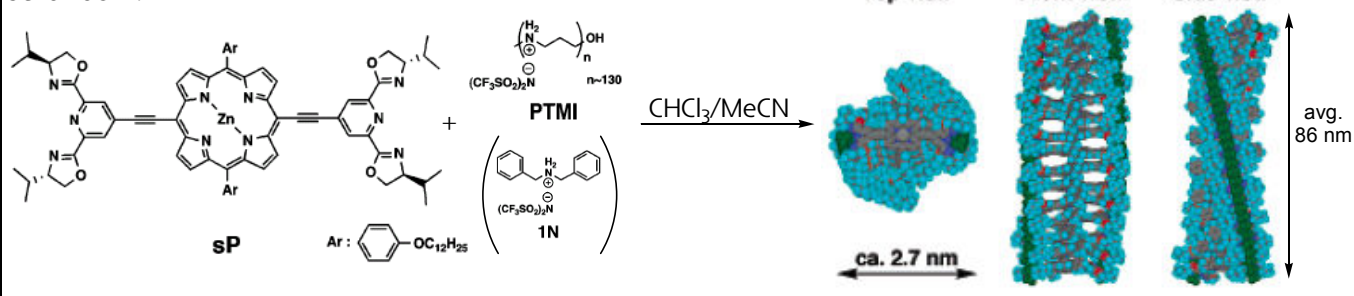
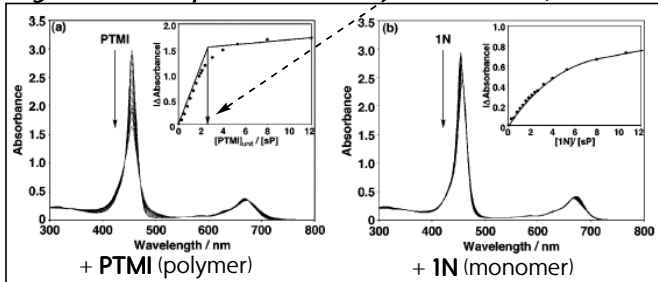
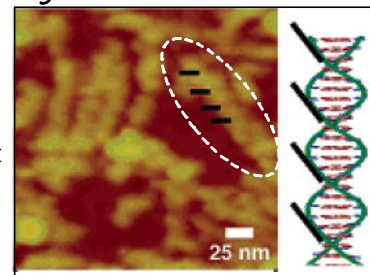


Fig. 3-2. UV/Vis spectra of sP



ca. 2:1 complexation
Decrease of Soret band (455nm) absorbance is attributed to the stacking of porphyrin. Monomer didn't induce such stacking.

Fig. 3-4. AFM Visualization



Direct observation of discrete helical structure was possible.

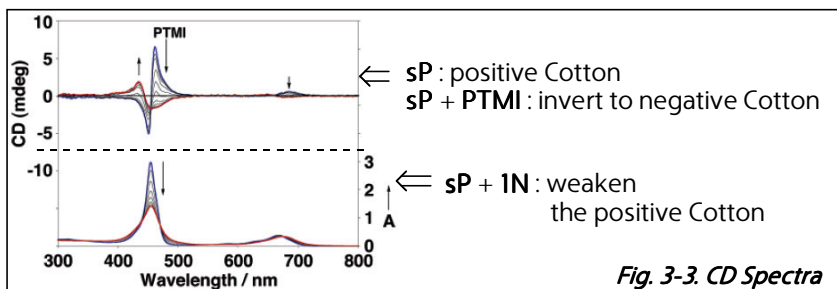


Fig. 3-3. CD Spectra

macromolecular helicity is induced!

Fig. 3-5.

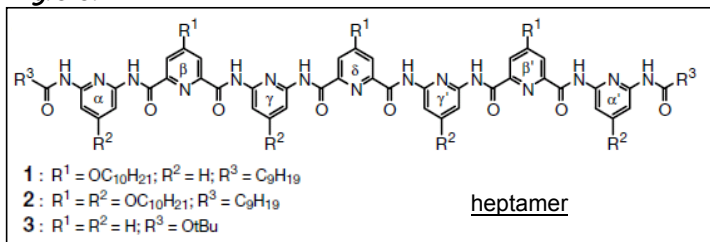
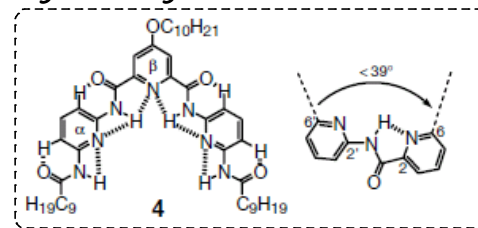
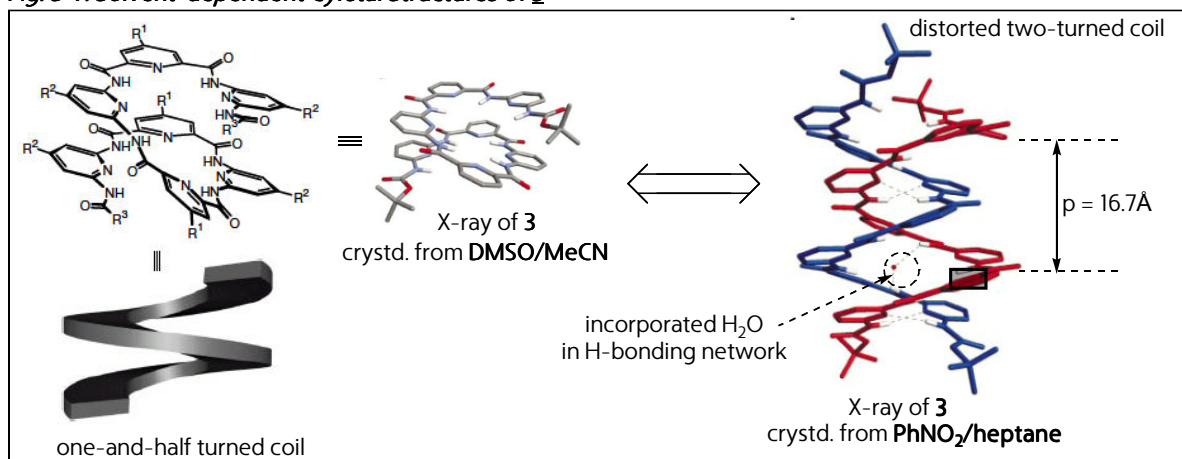


Fig. 3-6. Background



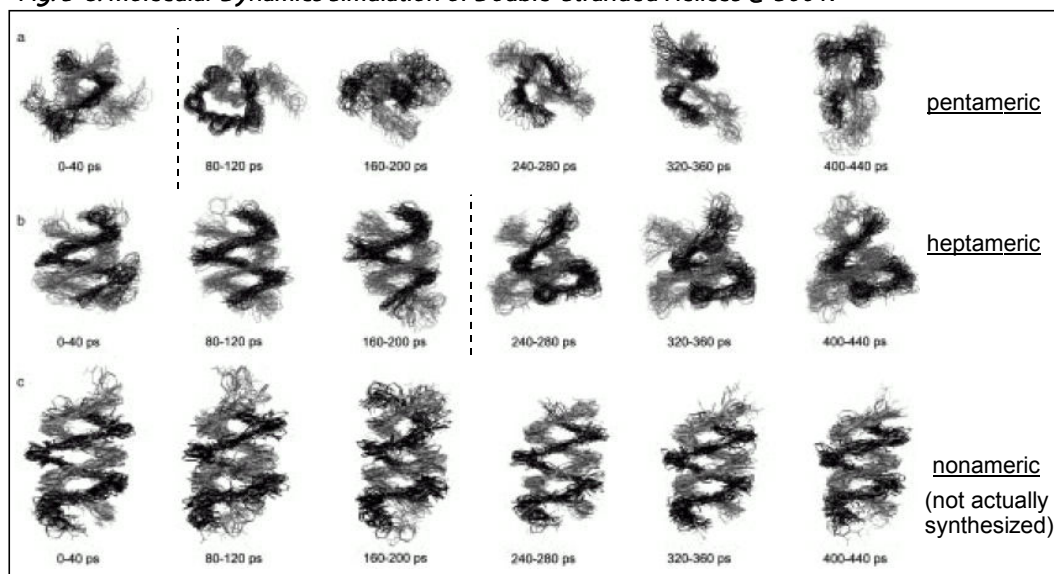
Oligopyridine carboxamide has curved conformation through intramolecular hydrogen-bonding.

Fig. 3-7. Solvent-dependent Crystal Structures of **3**



- # Helix is stabilized by both H-bonding and π - π stacking.
- # Duplex formation in solution phase was also detected by NMR and MS analysis.
- # Addition of polar solvent destabilize the double-helix.
(solvation on functionality would disturb helix formation)
- # Variable Temperature NMR measurement suggested inter-exchange of strands of duplex (**2**)₂ is slow up to 55 °C, and dissociation of (**2**)₂ is slow up to 105 °C.

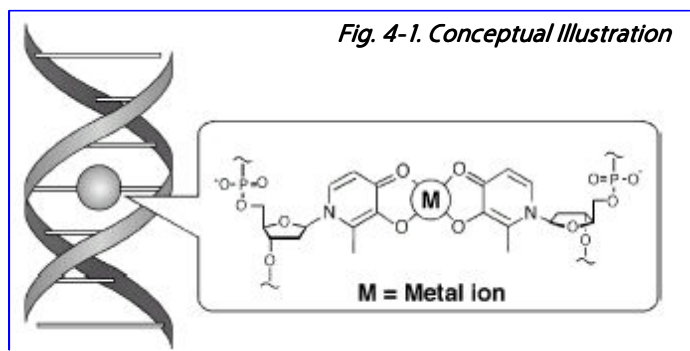
Fig. 3-8. Molecular Dynamics Simulation of Double-Stranded Helices @ 500 K



- # During the simulation at lower temperature (300K), duplex was stable.
- # At higher temperature, (700K), duplex was dissociated.
- # The stability of the double helices increases with strand length.

4 Nanomaterial-Oriented MetalloDNA

Review: Tanaka, K.; Shionoya, M. *Curr. Opin. Chem.* **2004**, *8*, 592, *Chem. Lett.* **2006**, *35*, 694.



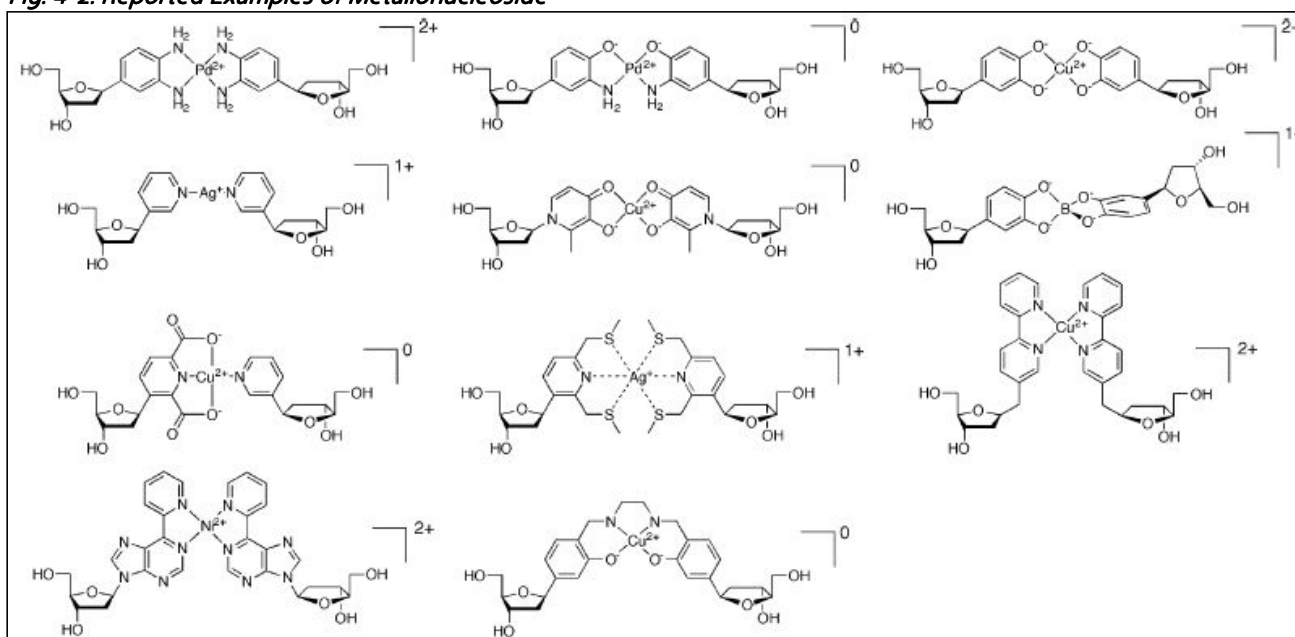
- # Artificial DNA is easily preparable by automated DNA sequencer.
 - > Very finely tuned, pure compound is available
 - > Inclusion of unnatural nucleotide is possible
- # Metal complexes provide various properties. (redox/magnetism/opticity/radioactivity/Lewis acidity etc.)



Easily applicable to novel nanomaterial

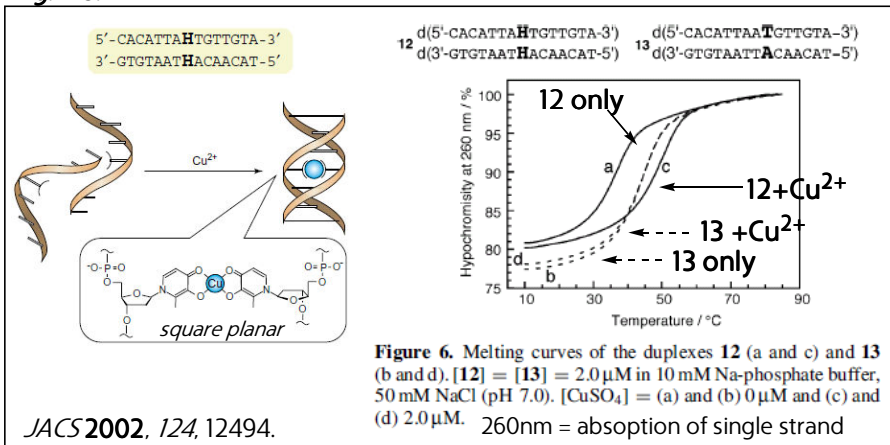
(electric nano-wire, molecular magnet, luminescent material, multinuclear chiral catalysis, gene-regulative tool, drugs etc.)

Fig. 4-2. Reported Examples of Metallonucleoside



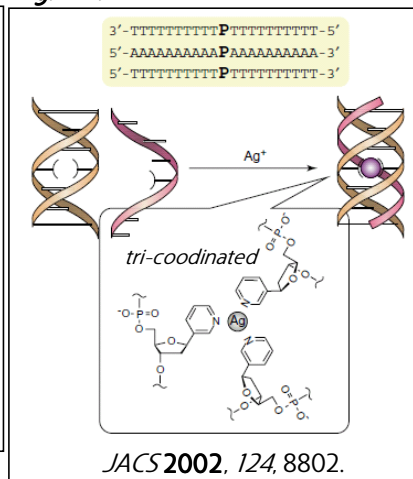
Strength: **hydrogen bond** (ca. 5 kcal/mol) < **coordinative bond** (10–30 kcal/mol) < **covalent bond** (ca. 100 kcal/mol)
 ⇒ tunable stability of DNA multiple strand with high variety

Fig. 4-3.



Thermal stability of DNA duplex is increased.

Fig. 4-4.



Triple-stranded DNA is available.

Fig. 4-5.

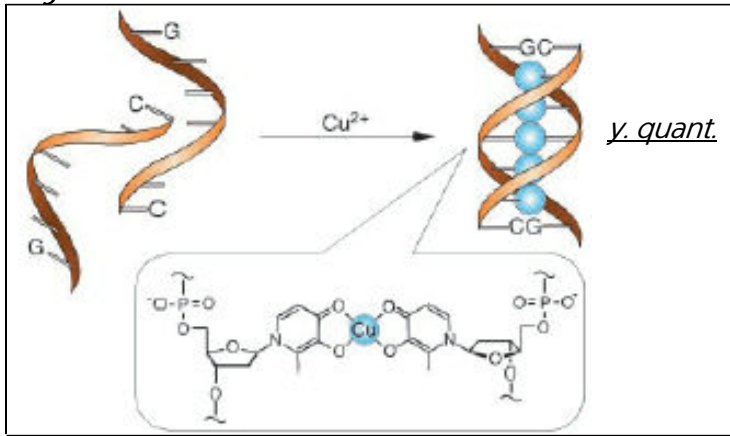


Fig. 4-6.

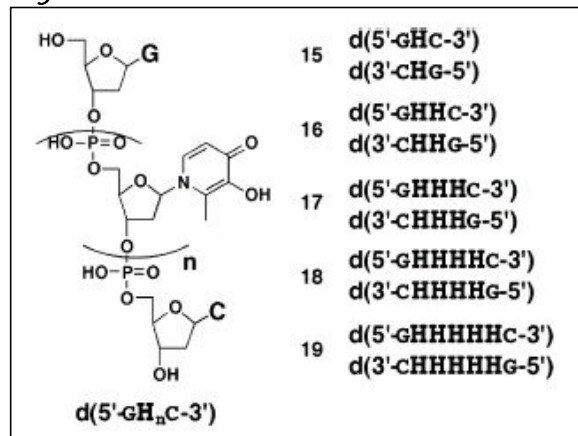


Fig. 4-7. UV Spectra in pH 7.0 buffer

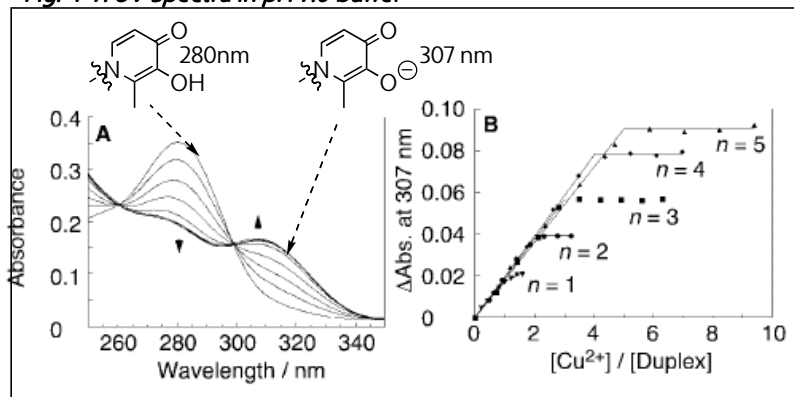
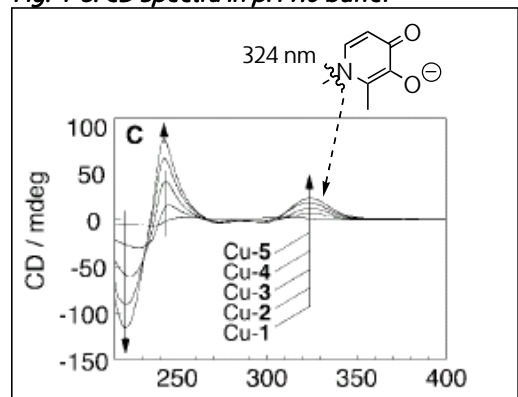


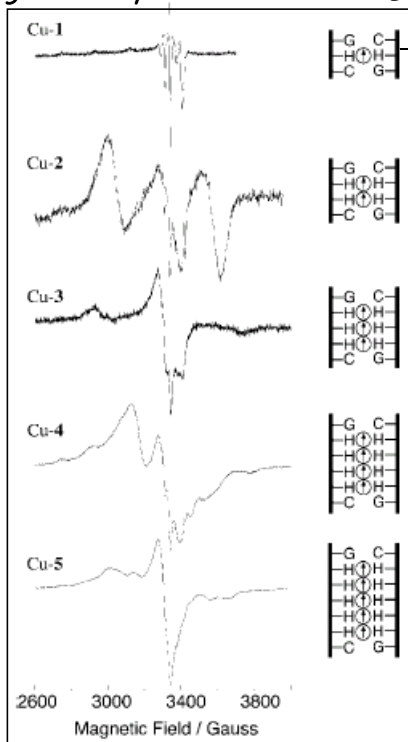
Fig. 4-8. CD Spectra in pH 7.0 buffer



Stoichiometry of Cu corresponds to the number of artificial nucleotide.

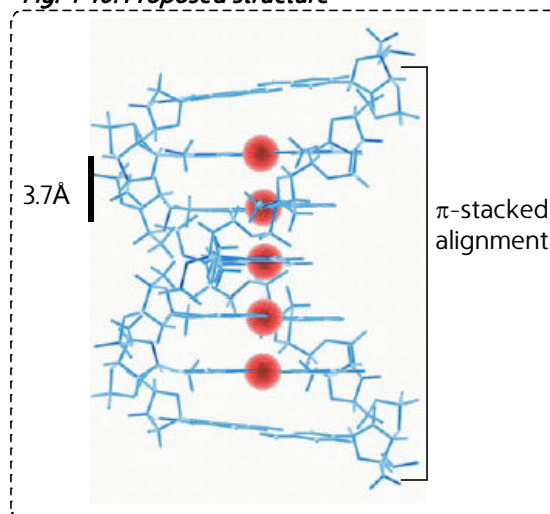
Helicity is independent of Cu number

Fig. 4-9. EPR spectra in frozen water (@1.5 K)



Each Cu^{2+} electron spin is **ferromagnetically coupled** (all spins are parallel) through d-d orbital interaction.

Fig. 4-10. Proposed structure



ESI-TOF-MS also agreed with this structure.

Fig. 4-11. Sequential Incorporation

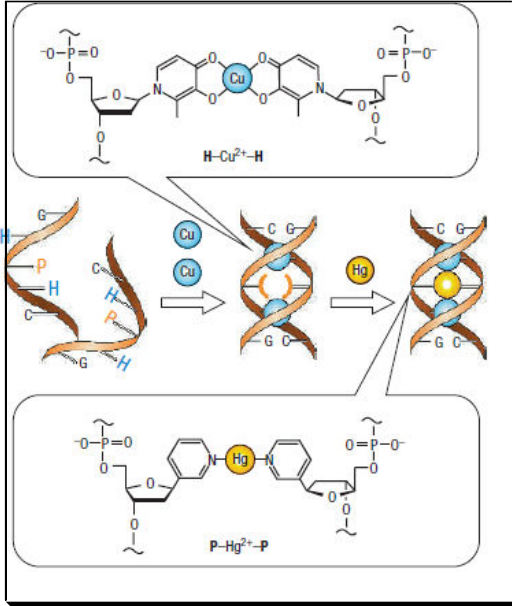
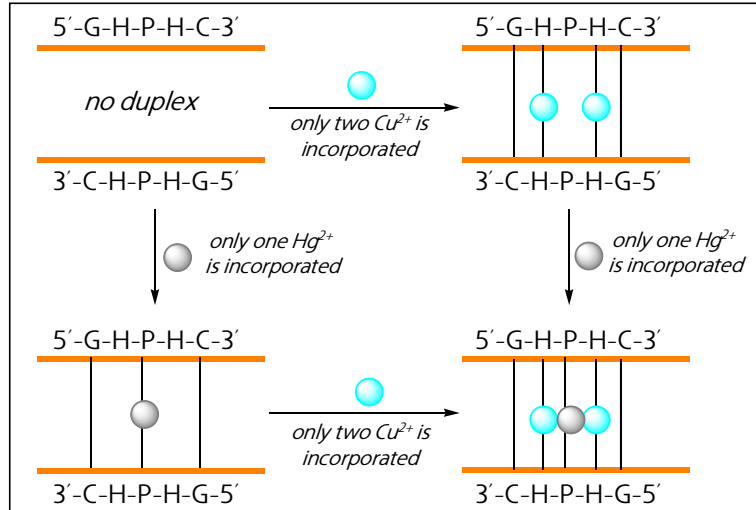
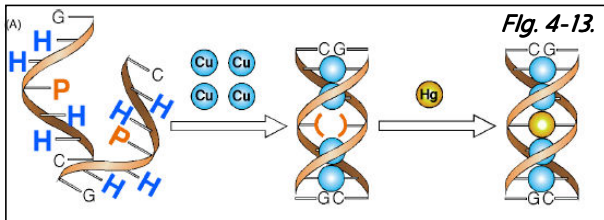


Fig. 4-12. Control Experiments

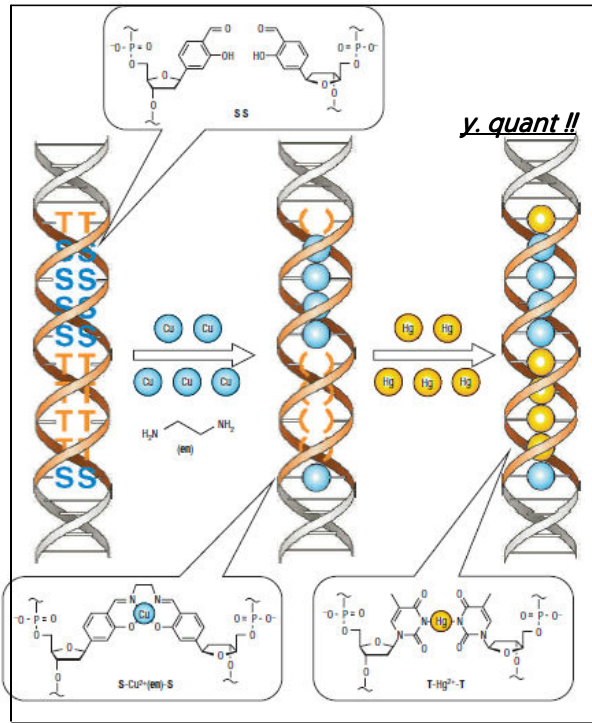


- # Sequence of incorporation is not important.
(P-Cu-P or H-Hg-H is mismatched no metal exchange occurred)
- # These phenomena were confirmed by UV photometric titration, CD, and ESI-TOF-MS



- # They also synthesized Cu-Cu-Hg-Cu-Cu duplex.

Fig. 4-14. Templating Approach toward Multimetallic DNA



- # Templating cross-linking method afforded rather stabilized duplex and make more numbered metal-inclusion possible.

S-S pair: Cu^{2+} , Ni^{2+} , Mn^{3+} , Fe^{3+} , VO^{2+}
T-T pair: Hg^{2+}

- # Incorporation is confirmed by CD and ESI-ICR-MS

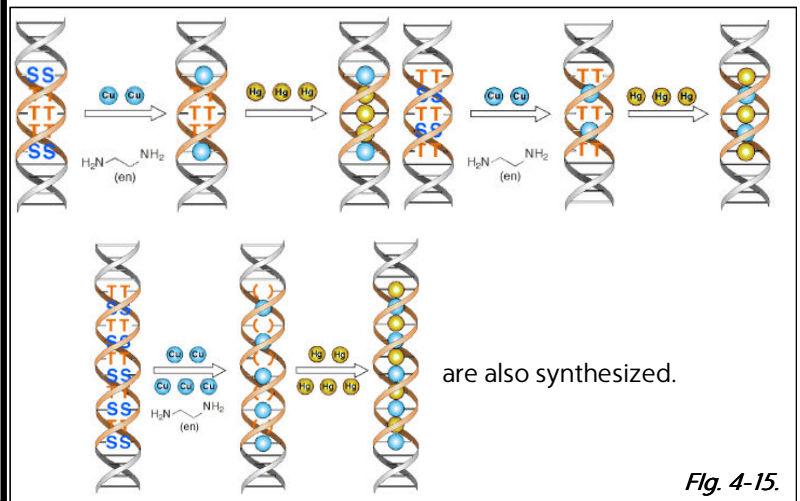
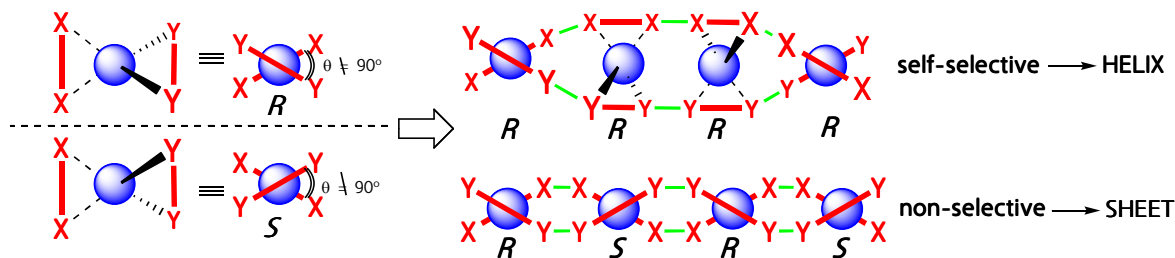


Fig. 4-15.

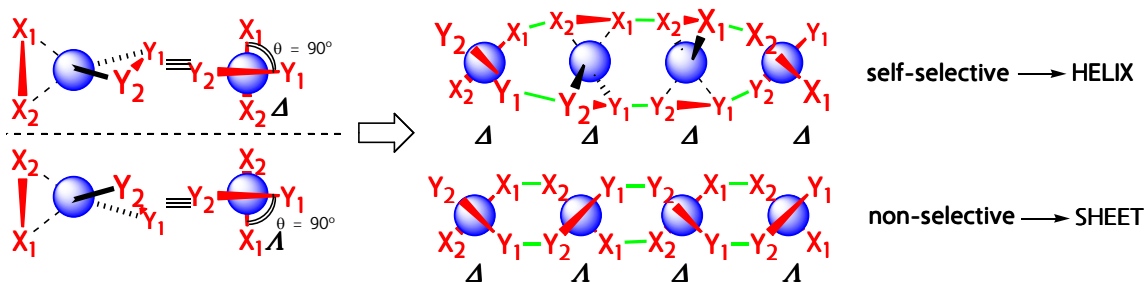
5 How can we design multiple-stranded helices?

簡単な構成ユニットを混ぜて多重らせんを作りたい。どうすればよいか？ 以下、抽象化による個人的立案。

A. asymmetrical interaction + symmetrical strand helicate, *m*-terphenyl, pybox-ammonium



B. symmetrical interaction + asymmetrical strand DNA etc.



X-XおよびY-Y(もしくはX₁-X₂およびY₁-Y₂):モノマー
 ●:X-XとY-Yが持つ機能部位間の相互作用(可逆/不可逆)
 —:モノマー間相互作用(可逆/不可逆)

<Explanation in Japanese>

<1. モノマーX-X, Y-Yのデザイン>

XはX同士、YはY同士でしか相互作用しない。

下付番号のものはヘテロで相互作用する(X₁はX₂とだけ結合。X₁とX₁は結合しない。Y₁, Y₂も同様)

<2. 機能部位間相互作用●のデザイン>

(A)方向性をもたないモノマーの場合 → ねじれ位置(ねじれ角≠0,90度)になるような相互作用

(B)方向性を持つモノマーの場合 → ねじれ位置(ねじれ角≠0度)になるような相互作用

<3. モノマー間相互作用(—)のデザイン>

・ユニット内相互作用がユニット間のそれに優先するような、結合方向性を持つ。

・モノマーX-X, Y-Y(もしくはX₁-X₂およびY₁-Y₂)が相互作用●を経て結合した複合体には、

鏡像関係(R/S or Δ/Λ)が考えうる。一方の鏡像関係だけを選択的に作り上げるか、

同じ鏡像関係のものだけ自己選択的に重合(R-R-RやΔ-Δ-Δ...)させることができればHelix構造が作れる。

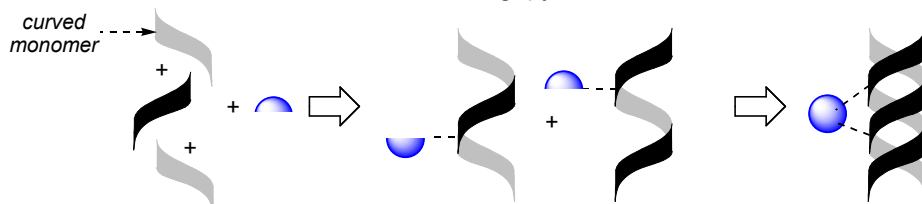
(鏡像関係のものが混在重合(R-S-RやΔ-Λ-Δ...)すればSheet構造になる。)

1. 2. 3. の条件をすべて満たすモノマー種を設計できれば、ヘテロ二重らせん構造へのボトムアップ的アプローチができるはず。

現在のところ実験的知見に乏しく、設計上の最大のポイントになるのは3でしょう。

この設計指針は、本質的に3重/4重...らせんへも拡張可能です。

C. entanglement of single-stranded helices Oligopyridine carboxamide



A,Bにおいては、モノマー間相互作用(—)を共有結合にしたときにらせんを巻くこと前提していません。つまりCはA,Bの特殊な場合と考えられそうです。一重らせんをどうやって設計するかが最大のポイントでしょう。