「形の制御」を機軸とする機能プログラムド分子システムの創製研究

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　天然の機能素子であるタンパク質のアロステリー機構に見られるように，分子レベルで「ほしい時にほしい機能を発現させる」化学プログラミングが，比較的新しい機能開拓の手段として注目されている。特に筆者らの専門分野では、要素（分子）間相互作用の設計に基づいて合目的な組織形態に導く魅力ある機能発現戦略となり得るものである。そこで，当該研究課題においてその具現化をめざし，分子不斉を情報因子に用いる不斉プログラミング（不斉操作）を検討した。いまだ研究途上であるが，新しいキラル材料（絶対配置決定試薬）の開発に結びつく知見を得ている。一方，機能プログラミングを意図した分子間相互作用の開発は，事前構成化にもとづく自己組織材料の創製に寄与する。とりわけ，望んだ状態へ機能システムを誘導するしくみの理解につながるかもしれない。こうした背景のもと，当該研究課題における更なる取り組みとして，構成ユニット（要素）間相互作用を設計し，その高次元（システム）化に取り組むことであると考え，フェニルボロン酸とピロカテコール系色素との可逆的な相互作用を第 3 の化学因子で制御する試みをおこなった。

　本研究成果は，当研究室に所属する埼玉大学大学院生・4 年生諸君の努力の賜であります。またフェニルボロン酸を用いた自己組織化については，Tony D. James 博士（バース大学）との国際共同研究のなかで実施されたことをここに記し，あわせて感謝します。

研究組織

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研究成果

1. 学会誌等

1-1. 研究論文

1) Y. Kubo, Y. Ishii, T. Yoshizawa, and S. Tokita,

   "Effective cation-assisted chirality induction using a dibenzo-diaza-30-crown-10 with bis(zinc(II) porphyrin) units",

   Chem. Commun., **2004**, 1394-1395.

2) Y. Kubo, A. Kobayashi, T. Ishida, Y. Misawa, and T. D. James,

   "Detection of anions using a fluorescent alizarin-phenylboronic acid ensemble",

   Chem. Commun., **2005**, 2846-2848.

3) Y. Kubo, T. Ishida, A. Kobayashi, and T. D. James,

   "Fluorescent alizarin-phenylboronic acid ensembles: design of self-organized molecular sensors for metal ions and anions",

   J. Mater. Chem., **2005**, *15*, 2889-2895.

1-2. 総説

1) Y. Kubo and Y. Ishii,

   "Molecular manipulation based on allosteric crown-appended units and related systems",

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1-3.　特許

1)　久保　由治，石井　佑典，

　　"自己組織型キラルプローブおよびこれを用いた被検査キラル物質の絶対配置決定法"，

　　特願 2006-041991.

2.　口頭発表

1)　久保　由治，

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2)　石井　佑典，吉沢　俊啓，時田　澄男，久保　由治，

　　"ジアザ-30-クラウン-10 誘導型亜鉛(II)ポルフィリンダイマーを用いた協同的不斉誘

　　起現象"，

　　第 17 基礎有機化学連合討論会，1B10，仙台 (2004. 9).

3)　久保　由治，石田　智久，時田　澄男，

　　"フェニルボロン酸の性質を用いる自己組織型蛍光センサーの設計(1)：金属イオンセ

　　ンシング"，

　　日本化学会第 85 春季年会予講集，1F6-43，横浜 (2005. 3).

4)　久保　由治，小林　純，三澤　善大，Tony D. James，

　　"フェニルボロン酸の性質を用いる自己組織型蛍光センサーの設計(2)：アニオンセン

　　シング"，

　　日本化学会第 85 春季年会，1F6-44，横浜 (2005. 3).

5) 石田　智久，小林　純，Tony D. James，久保　由治，

   "フェニルボロン酸の性質を用いた自己組織型アニオンセンシング"，

   第 35 回構造有機化学討論会，1B08，大阪 (2005. 9).

6) Y. Kubo, T. Ishida, A. Kobayashi, and T. D. James,

   "Fluorescent alizarin-phenylboronic acid ensembles: design of self-organized molecular sensors",

   2005 International Chemical Congress of Pacific Basin Societies, Program Number: 130, Honolulu, (2005. 12).

7) 恩田　洋一，石井　佑典，久保　由治，

   "2,2'-ビフェノール架橋型ビスポルフィリンの不斉誘起"，

   日本化学会第 86 春季年会，4K4-09，船橋 (2006. 3).

8) 石井　佑典，二階堂　絵里奈，恩田　洋一，久保　由治，

   "クラウンエーテル-亜鉛ポルフィリン共役体を用いたアロステリック駆動型キラルセンシング"，

   日本化学会第 86 春季年会，4K4-10，船橋 (2006. 3).

3. 招待講演

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研究成果

スマートな化学システムの創製には，多彩な化学的・物理的機能部位を組み合わせるだけではなく，分子レベルにおいてそれらの構造・機能を制御する方法論の開拓が必要である。特に，機能システムを望んだ状態へと誘導するしくみ（機能プログラミング）の理解は，高度機能材料（ナノ材料）の創製に大きなヒントを与えるかもしれない。こうした背景のもと，われわれは，構成ユニット（要素）間相互作用を設計し，機能システムとしての発現を試みた。

1. クラウンエーテルの配座特性を利用したキラル材料の開発

環状ポリエーテルであるクラウンエーテル類は，単純な構造をとりながら様々な環径のものが知られており多彩な配座特性を示す。そこで，形の制御を機軸とする機能プログラミングには都合のよいユニットになりえると考えた。ここでは，金属イオン類との錯体形成時に"U"字型配座を発現するジアザ-ジベンゾ-30-クラウン-10 を共役させたポルフィリン誘導体(1)や 15-クラウン-5 共役型ポルフィリン誘導体(2)を合成し，クラウンエーテルのもつ機能と連携した協働的不斉誘起を検討した結果をまとめる。

1-1. アロステリック駆動型キラルセンシング
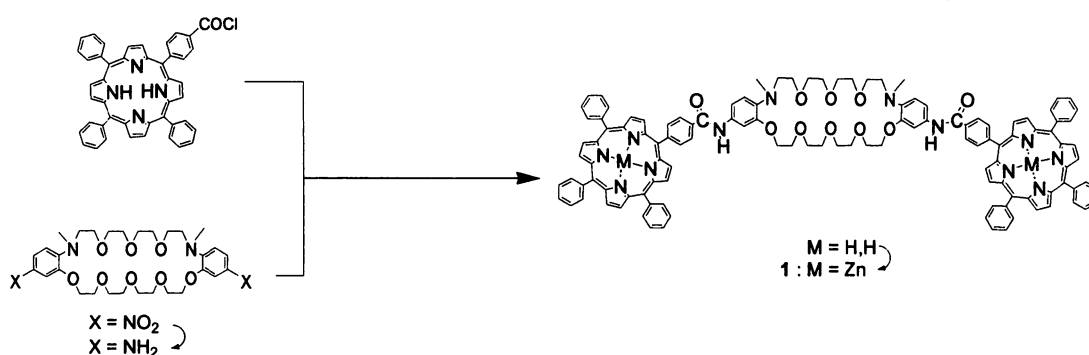
Scheme 1. Reagents and conditions: (i) 10% Pd-C, H₂ (2.5 atm), EtOH, r.t.; (ii) dry CH₂Cl₂ with a few drops of dry Et₃N, 0 °C, under Ar, 48%; (iii) sat. Zn(OAc)₂·2H₂O in MeOH, CH₂Cl₂, r.t.,

Scheme 1 に従い合成された表題化合物 (1) は、二つの亜鉛ポルフィリンが配座柔軟性を有する大環状クラウンエーテルスペーサーにより結ばれた構造をもつ。したがって、キラ

ルジアミン類とのダイトピックな相互作用を介した不斉誘起が可能であり、その検出はポルフィリン間の励起子相互作用に基づく円二色性 (CD) スペクトルによりおこなえた (Figure 1a)。このとき、クラウンエーテル部位に配位し"U"字型配座を誘起させる K^+ を共存させると、その CD 強度を最大で 45%
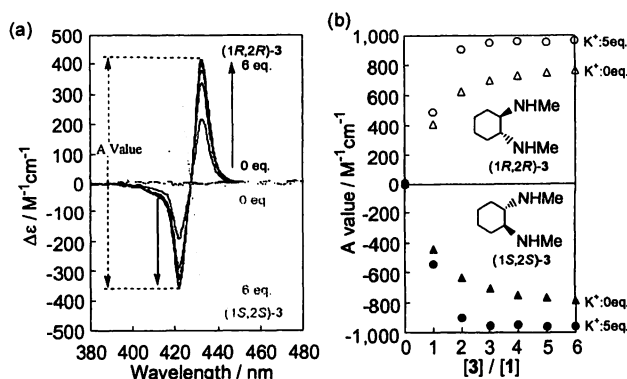

Figure 1. (a) CD spectral changes of 1 upon adding of (1R,2R)-3 (black lines) or (1S,2S)-3 (gray lines). (b) Changes in A value (A = $\Delta\varepsilon_1$-$\Delta\varepsilon_2$) of 1 upon complexation with chiral 3 in the presence or absence of K^+, [1] = 2.0 μM.

増大させた (Figure 1b)。これは、"U"字型への配座変化がビス (ポルフィリン) 反応場の事前構成化を促し、ホスト/ゲスト錯体形成時の不斉配座をより安定化させたためと考えられる。本結果から，大環状クラウンエーテルの配座特性を利用することで，K^+ が存在するとキラル応答場が構成されるようにプログラミングできたものと考察した (*Chem. Commun.*, **2004**, 1394-1395)。

1-2. 水溶液中アミノ酸のキラルセンシング

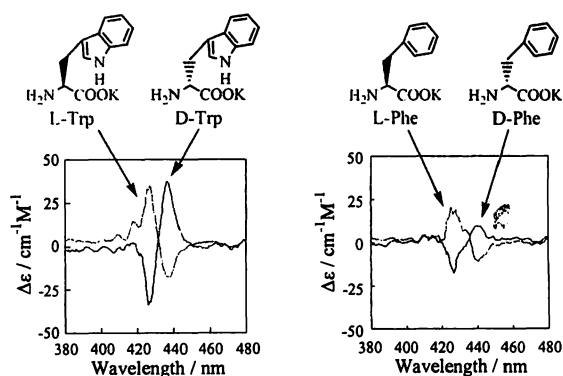クラウンエーテルには本来非極性溶媒に不溶な金属塩を、錯体形成を通じて有機溶媒中に抽出させるイオノフォアとしての特徴がある。事実、1 はキラル有機酸塩を用いた固液抽出法において円二色性 (CD) 活性を示す。そこで、キラルプローブとしての機能追求の観点から、水溶液中に存在するキラルアミノ酸の検出へ展開することを試みた。液

Figure 2. CD spectra of 1 in CH_2Cl_2 after shaking with 1N KOHaq. of chiral amino acids, [1] = 13 μM.

(1 in CH_2Cl_2)－液 (アミノ酸 in 1N KOH_{aq}.) 抽出法による条件検討をおこなったところ、幾つかのアミノ酸のキラリティーを CD スペクトルで簡便に読み出せた (Figure 2)。この結果

は、従来ビスポルフィリン型のキラルプローブでは困難とされた水溶性化学種の検出に対してクラウンエーテルとの機能連携が有効であることを意味しており，ポルフィリンとクラウンエーテルの機能を分子内連携させた協働的不斉誘起の具体的成果となる。

1-3. 自己組織型キラルセンサーとして機能するクラウンエーテル−ポルフィリン共役体

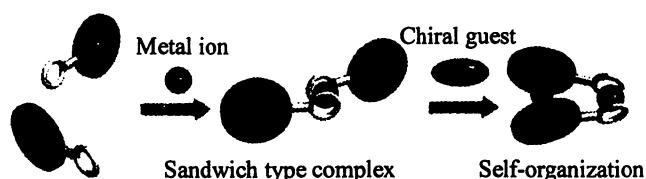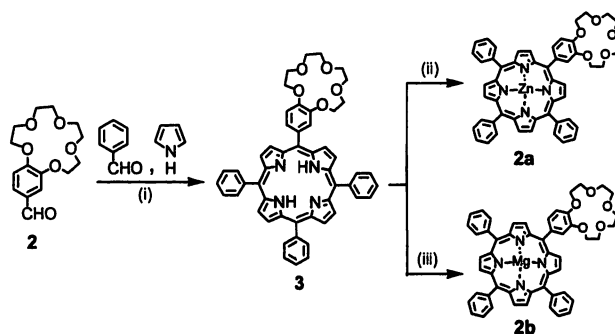われわれは、「形の制御」と連携した不斉操作に取り組んでおり、その機能ユニットとしてクラウンエーテルに注目している。1-3 章では、環径が比較的小さな 15-クラウン-5 が K$^+$ と 2:1 のサンドイッチ型錯体を形成することに着目し、その機構を利用した自己組織型キラルセンサーの検討をおこなった結果を記す。

自己組織型キラルセンサーの動作概念を Figure 3 に示す。クラウンエーテル部位への金属イオンの配位によりサンドイッチ型錯体が形成され、続く被検査キラル物質との協働的な相互作用による自己組織化が促されれば、ポルフィリン間の励起子相互作用を利用した円二色性 (CD) スペクトルによるキラルセンシングがおこなえるかもしれない。当該概念の実現にむけて用い

Figure 3. Schematic images of self-organized chiral sensing.

Scheme 2. Reagent and conditions: (i) propionic acid, reflux, 1h, 6.3%; (ii) sat. Zn(OAc)$_2$·2H$_2$O in MeOH, CH$_2$Cl$_2$, over night, r.t. quant.; (iii) MgBr$_2$·OEt$_2$, CH$_2$Cl$_2$, Et$_3$N, under Ar, 5h, r.t. 33%.

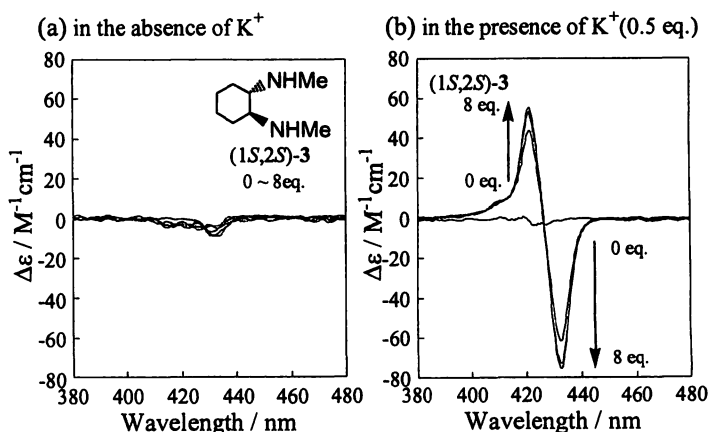Figure 4. CD spectral changes of 2a upon adding of (1S,2S)-3 in the absence (a) or presence (b) of K$^+$ in CH$_2$Cl$_2$-MeCN (8:2 v/v), 25°C, [2a] = 4.0 μM.
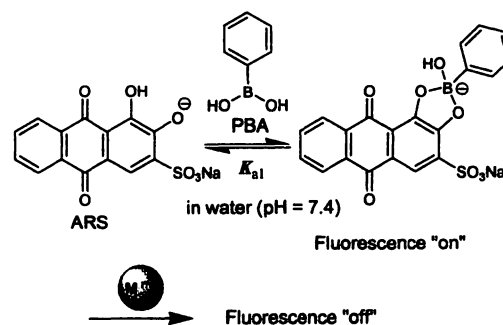
られた 15-クラウン-5 共役型ポルフィリンは、定法を用いて合成され、亜鉛錯体 (2a)、マグネシウム錯体 (2b) へとそれぞれ誘導された（Scheme 2）。亜鉛錯体 (2a) は、キラルジアミン (1S,2S)-3 の添加に対して CD 不活性であった（Figure 4a）が、0.5 eq.の K$^+$ 存在下においてはポルフィリン Soret 帯付近に負の第一、および正の第二 Cotton 効果を観測した（Figure 4b）。すなわち 2a は、それ単体ではキラルプローブとして機能しないが、系中に K$^+$が存在すると Figure 3 に示したような自己組織化が誘起され、被検査物質の不斉に相関した CD 活性を発現した。また 2b においては，K$^+$存在下，キラルアミノアルコール類についてその不斉を CD スペクトルで読み出せた。このように要素間相互作用の設計にもとづく機能プログラミングが新しい自己組織型キラルセンシングの方法論を導いたと考えている（特願 2006-041991）。

2. アリザリン-フェニルボロン酸共役化を利用した自己組織型センシング

ホスト-ゲスト化学で培われた分子間相互作用は，分子認識からナノ集合体を指向した構造プログラミングへ至る多彩な展開に利用されている。われわれは，その相互作用を第 3 の化学因子でコントロールすることに興味がある。そのような試みは，配位金属の酸化状態の変化に伴う金属錯体の構造スイッチ等に用いられているが，化学センサー開発の観点から，「レセプター」と「レポーター」の要素間相互作用を第 3 の化学因子（被検査物質，pH 等）で制御できれば，新しいコンセプトをもつセンサーシステムが提案できるかもしれない。そこで着目したフェニルボロン酸（PBA）は，cis-ジオール体と可逆的な相互作用を起こすだけでなく，顕著な pH 依存性を示す。また，ルイス酸性のホウ素を有するので，塩基性の化合物と反応して環状ボロネートエステル化を促進する性質もある。これらの化学的性質は，ジオール系色素をうまく組み合わせれば，外部刺激応答型の共役体が発現できることを示唆する。本報告書では，ピロカテコール部位をもつアリザリン系色素をレポーター部位として採用し，いくつかのフェニルボロン酸類と共役させることで達成した自己組織型蛍光センシングをまとめる。

2-1. 自己組織型金属イオンセンシング

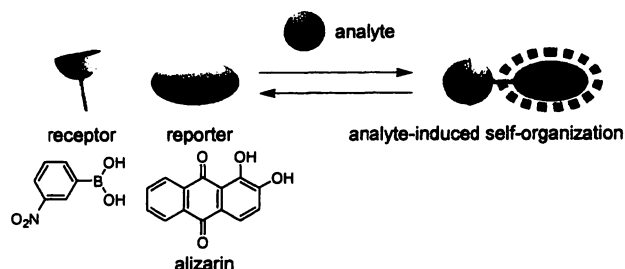アリザリンレッド S（ARS）は単独では蛍光を発しないが，フェニルボロン酸（PBA）存在下中性領域で環状ボロネートエステル化を生じ，[PBA-OH-ARS]$^-$共役体の形成に基づく蛍光発光を示す（λ_{ex} = 478 nm, λ_{em} = 588 nm）。そこで，pH 7.4，ARS と 50 当量の PBA 存在下，Cu^{2+}を添加したところ，効果的な蛍光消光が観測されることを見いだした。UV/Vis スペクトルを用いた Job's plot から ARS : Cu^{2+} = 2 : 1 の錯体形成が示唆され，その結合定数は（1.2 ± 0.14）×10^{12} M^{-2} と見積もられた。この挙動は，水中で組織化した[PBA-OH-ARS]$^-$共役体と Cu^{2+}の競争的相互作用によって，環状ボロネートエステル構造の開裂がおこっていることに起因する。さらに，各種金属イオン（Mg^{2+}, Ca^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Al^{3+}）を用いて蛍光選択性を調査したところ，Cu^{2+}と Al^{3+}に対して効果的に応答した（*J. Mater. Chem.*, **2005**, *15*, 2889-2895）。

2-2.アニオンで誘導されるフェニルボロン酸-アリザリン共役化

メタノール中，アリザリンに 3-ニトロフェニルボロン酸（NPBA）を添加しても反応しない。しかしながら，KF 存在下では蛍光応答を観測した。そこで，アリザリンと 40 当量の NPBA 存在下，KF を添加したところ，蛍光強度の増大を観測し（λ_{ex} = 420 nm, λ_{em} = 586 nm），F$^-$の読み出しが可能となった。この応答挙動は，F$^-$が誘導した NPBA-アリザリン共役体形成を示唆する。各種機器分析データ（^{1}H・^{11}B NMR, FAB MS）にもとづき，メタノール中，NPBA はアリザリンとほとんど相互作用しないが，F$^-$を添加すると *sp^3* 型フェニルフルオロボロネート体が生成し，それがアリザリンと結合した結果，蛍光強度の増加を導くものと考察した（*Chem. Commun.*,

2005, 2846-2848; *J. Mater. Chem.*, **2005**, *15*, 2889-2895）。本研究結果は，要素間相互作用をうまく取り扱うことで，「被検査物質が存在すると，レセプター部位とレポーター部位が共役して応答機能を発現する」という機能プログラミングの実施例とみなすことができよう。

学術雑誌別刷等，ならびに学術研究集会のおける発表の要旨・予稿 (抜粋)

1) Y. Kubo, Y. Ishii, T. Yoshizawa, and S. Tokita,

"Effective cation-assisted chirality induction using a dibenzo-diaza-30-crown-10 with bis(zinc(II) porphyrin) units",

Chem. Commun., **2004**, 1394-1395.

2) Y. Kubo, A. Kobayashi, T. Ishida, Y. Misawa, and T. D. James,

"Detection of anions using a fluorescent alizarin-phenylboronic acid ensemble",

Chem. Commun., **2005**, 2846-2848.

3) Y. Kubo, T. Ishida, A. Kobayashi, and T. D. James,

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J. Mater. Chem., **2005**, *15*, 2889-2895.

4) Y. Kubo and Y. Ishii,

"Molecular manipulation based on allosteric crown-appended units and related systems",

J. Nanosci. Nanotechnol., **2006**, in press.

5) 石井　佑典，吉沢　俊啓，時田　澄男，久保　由治，

"ジアザ-30-クラウン-10 誘導型亜鉛(II)ポルフィリンダイマーを用いた協同的不斉誘起現象",

第 17 基礎有機化学連合討論会, 1B10, 仙台 (2004. 9).

6) 石田 智久, 小林 純, Tony D. James, 久保 由治,

"フェニルボロン酸の性質を用いた自己組織型アニオンセンシング",

第 35 回構造有機化学討論会, 1B08, 大阪 (2005. 9).

7) Y. Kubo, T. Ishida, A. Kobayashi, and T. D. James,

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2005 International Chemical Congress of Pacific Basin Societies, Program Number: 130, Honolulu, (2005. 12).

Molecular manipulation based on allosteric crown-appended units and related systems

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Abstract: Synthesis of many potentially useful molecular units by chemists promotes the development of methods for constructing supramolecular architectures. Indeed, programmed supramolecular interactions play crucial roles in the preparation of well-defined nanoscale assemblies. This review highlights successful approaches in designing for specific functions systematically. The incorporation and synergistic communication of conformation-switchable segments into molecules bears great promise. Allostery, which is often observed in naturally occurring proteins, provides a hint for molecular manipulation. In supramolecular chemistry crown ethers can serve not only as substrate-binding sites but also as function-tuning sites. With the combination of synthetic versatility and well-tailored design, diverse capabilities (molecular recognition, catalytic properties, chirality, actuation, and so on) become possible at the molecular or mesoscopic level. The synthetic preparation of advanced molecular units allows the systems to become smarter, and promise nanosystems with programmable functions. This review considers mainly the use of crown ethers which act as anchoring as well as allosteric sites, from the standpoint of design for molecular manipulation. It also gives a brief discussion of recent progress in molecular manipulation, based on related systems. The "synthetic systems" described in the present review should contribute to not only to more elaborate "chemical systems", but also to the evolving field of "molecular machinery", that can utilize these systems.

CONTENTS:

1. Introduction: bottom-up approach toward nanosystems

A bottom up approach is a promising strategy in nanoscience and nanotechnology,[1-9] which starts from atoms or molecules and then builds up to nanostrutures. In current progress in molecular electronics, which can be defined as technology utilizing single molecules, small groups of molecules, carbon nanotubes, or nanoscale metallic or semiconductor wires to electronic functions,[10,11] miniaturization of devices is crucial. This trend accords not only with energy- and resource-savings but also recyclability. The situation has inspired supramolecular chemists to perform fabrication, because they are expert at handling molecules and understand how the molecules can be organized to develop the desired entities through appropriate intermolecular interactions (the supramolecular bottom up approach).[12] In particular, chemists who are able to perform sophisticated synthesis play a significant role in this approach, since the built-up systems would be more smart as the molecular components become more elaborate. The basic concept is depicted in Fig. 1, in which the x-axis and y-axis respectively represent the size of materials and the design of integration of interactions. The correlation between the size and the integration of interactions roughly relates to the complexity of function. Thus, the steeper this slope is, the greater the degree of complexity per size increases. Down sizing of systems may be possible, leading to a smart miniaturization. The principle motivates chemists to synthesize smart molecules as components. Such chemists are in a good position to develop bottom-up strategies for constructing nanoscale devices and machines.[13]
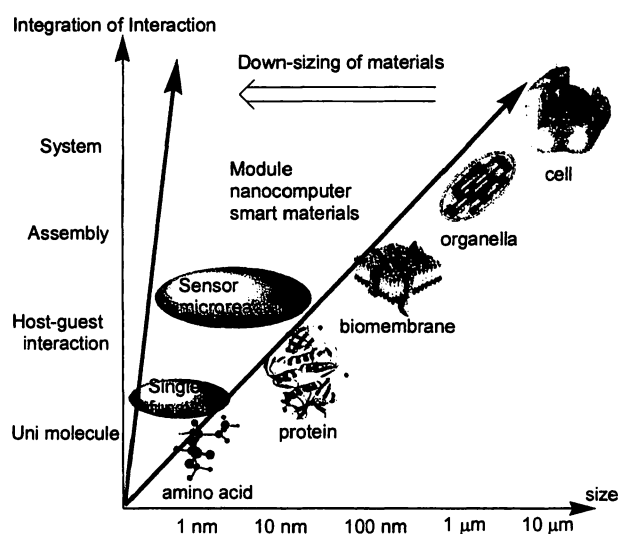

Fig. 1. Concept of integrated smart materials.

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Well-tailored systems useful in nanoscience require a machinery for regulating molecular functions. Much attention has been focused on the development of molecular systems possessing the "dynamic" function of molecular recognition in the development of methodologies for controlling functions. The controlled organization of functional systems is crucial in developing chemical systems having both structural and reactional complexity. Such regulatory systems are essential in biological processes in (a typical example is allosteric proteins[14-16]), and would relate to the organization of systems with molecular programming.[17-20] This approach would also explore the basic design of molecular machines with a smart function, the ultimate target being bio-molecular motors in which chemical energy is transferred into kinetic energy (Fig. 2).[21] Since bio-molecular motors have molecular recognition, enzymatic, energy-conversion, and self-organization functions, a systematic understanding of molecular motors would allow us to design nanomaterials. The design of allostery-based molecular manipulation should be a potent strategy toward this end, and chemists can synthesize desired molecular components. Programmable nanoarchitecture is a future feasible goal.

This review mainly illustrates intriguing results in the field of molecular manipulation.

Fig. 2. Examples of motor proteins. H. Hess et al., Reprinted with permission from [21], *Chem. Eur. J.*, 10, 2110 (2004). © 2004, Wiley-VCH.

The article begins by addressing allosteric action, as a bio-inspired system; this is readily applicable to information transmission to a remote site and in catalytic action. In particular, crown ether-derived allosteric compounds are fully described. A large-ring sized crown ether is a handy platform, and an activity-controllable artificial enzyme system has been created using the crowned compound. Such supramolecular allosteric catalysts have more recently received attention as nascent models of modules. The concept is not limited to crown-appended systems; related systems have been developed based on transition metal-induced coordination models, and are also reviewed in this article. Also, chirality communication between compounds is essential in biological systems. Thus, the design of systems driven by chirality information is a further important issue in chemical systems. Chirality manipulation (helicity induction, chirality amplification, and chirality memory) at the molecular or mesoscopic level is described below as an interdisciplinary area between supramolecular chemistry and chiral chemistry. Finally, molecular manipulation is clearly concerned with motion generation; based on examples of molecular actuators we discuss how to develop dynamic nanosystems.
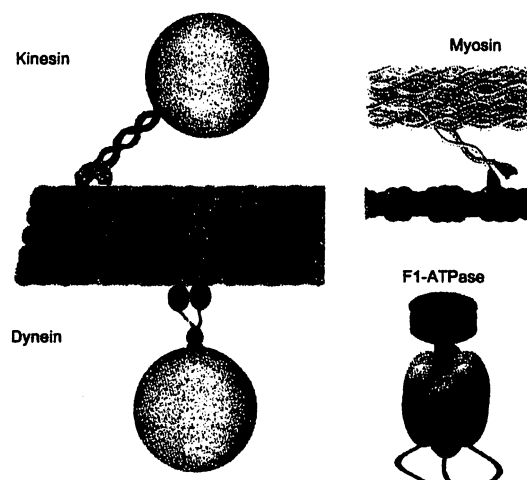
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2. Allostery

Shape control of molecules that respond to an external stimulus is important in the design of funtion-switchable systems.[2] Indeed, allosteric modulation of activity is common feature in proteins. For example, a prototype hemoglobin is active only in its tetrameric form, and even allows allosteric regulation for binding O_2 molecules where a cooperative effect exists between four subunits.[22-25] As a further example, cooperative interactions play a crucial role in gene transcription. Cyclic AMP, for instance, has a strong cooperative effect upon the binding of gene-transcription-regulating cAMP receptor protein (CRP) to DNA.[26] Oxygen binding in hemoglobin, is positively homotropic, whereas the allosteric interactions in cAMP/CRP/DNA can be described as positively heterotropic in their action in which two differential sites communicate positively with each other. Allostery is thereby classified into four different categories: positive homotropic, negative homotropic, positive heterotropic, and negative heterotropic modes.[27-32] Although transmission of homotropic effects between subunits is an important aspect of cooperative effects,[33-44] dynamic action based on heterotropic allostery (*vide infra*) should be easier to handle than that of homotropic allostery from molecular manipulation point of view. Fig. 3 shows the operation of heterotropic allosterism, for example, in which a guest binding at one site should cause a positive or negative effect on a different guest binding site through appropriate topological changes.
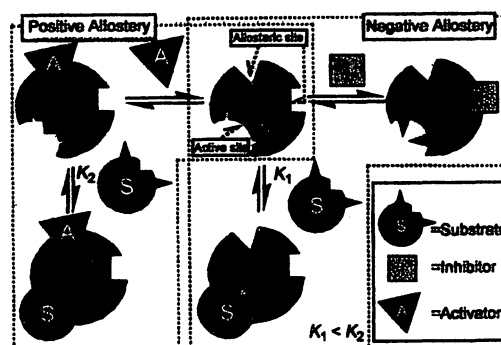
Fig. 3. The schematic drawing of heterotropically allosteric modes.

2-1. Crown ether-appended heterotropic allostery systems

Crown ethers[45-49] are macrocyclic oligomers of ethyleneoxy units, and are a powerful tool for constructing desired systems because of their structural topology and superior synthetic susceptibility.[50] As Fig. 4 makes clear, the flexibility increases with larger ring size. The crown ligands (e.g., 30-crown-10) tend to wrap cations of small size. The wide variety of structural topology of crown ligands has motivated us to introduce them into artificial receptors. Since the pioneer work of an allosteric receptor was reported by Rebek in 1979,[51] allosteric control based on host-guest interaction has become a major subject; in particular, synthetic architectures with crown ether segments have been widely offered because their versatile synthetic susceptibility has allowed chemists to use them as scaffolds for bio-inspired materials. The initial model of crown-appended allosteric systems is adapted to control the cation binding properties of crown segments.

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Fig. 4. Versatile complexation modes of crown ethers with cations.

3

Rebek's model **1** has a 2,2'-bipyridine moiety as an allosteric site which connects with crown ethers to provide cation-binding sites.[52] A suitable metal ion capable of efficient binding at the bipyridyl moiety, $W(CO)_4$, can control the cation-binding property of the crown ether thr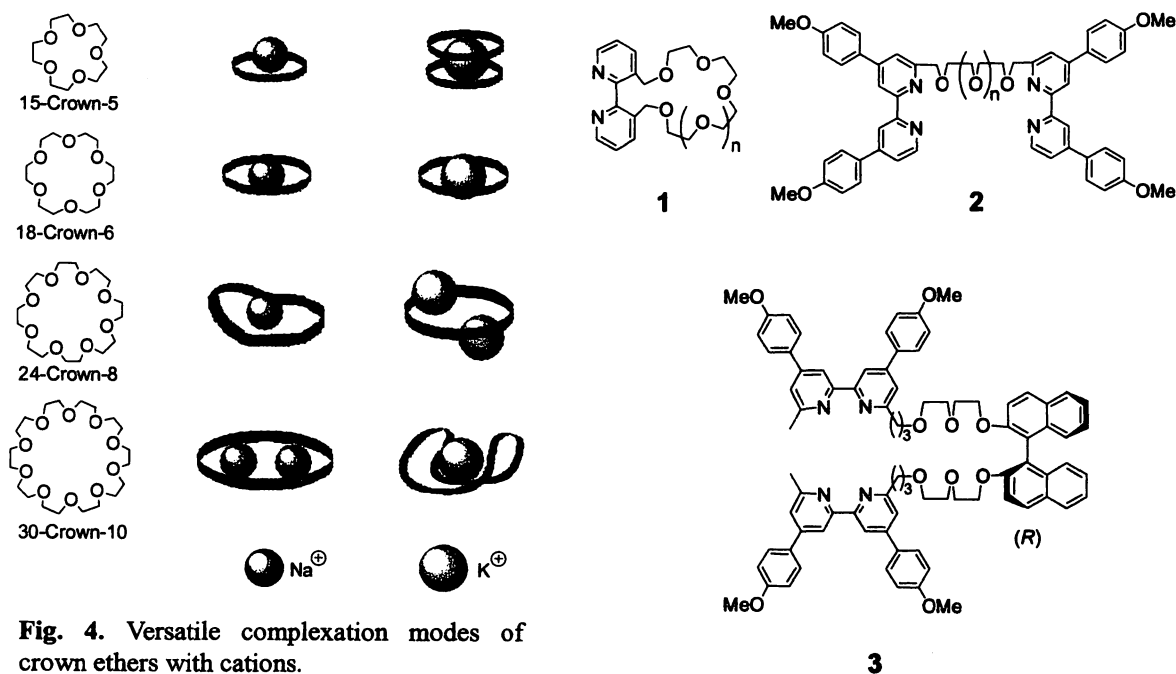ough tungsten-induced conformational changes of the crown ether rings. By replacing the crown ring by an acyclic analogue (potand), more dynamic conformation change occurred (see compound **2**)[53] in which an allosteric effector (Cu^+) bound in the bipyridyl moiety can induce pseudo cyclic polyether formation to efficiently bind alkali metal ions based on the macrocyclic effect.[54] The change in selectivity was elucidated in terms of a transport experiment across a CH_2Cl_2. When $n = 4$ in the structure of **2**, K^+ as a picrate salt can be transported 10-fold faster in the presence of Cu^+ than under Cu^+-free conditions. Similar considerations were applied to the allosteric transporter **3** for the amino acid tryptophane through a liquid membrane.[55] Recently, Nabeshima et al. have expanded the system into a novel pseudocryptand.[56] Complexation of the tripodal polyether-bipyridine conjugate **4** with Fe^{2+} yields the pseudocryptand Fe^{2+}-4, possessing a cavity which is surrounded by three polyether chains in a helical fashion (Fig. 5). The combination of the macrocyclic effect and the intramolecular interchain interactions
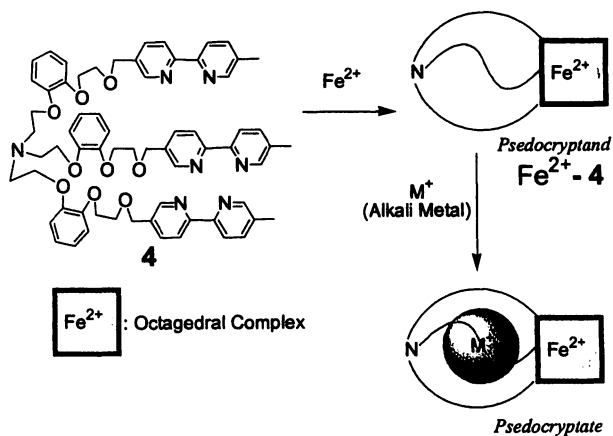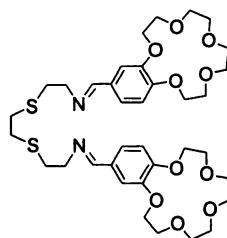

Fig. 5. Pseudocryptand Fe^{2+}-4 as an allosteric host.

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finely controls the positive and negative allosteric effects, depending on the size of the guest. Alternatively, Kobuke et al. proposed potand derivatives with catecholate groups as ligand. Addition of boric acid to a solution of the ligand produced a metal-assisted coronand structure with a C_2 symmetric (compound 5). ^{1}H NMR and FAB MS spectrometry indicated that alkali metal ions (Na^+ and K^+) were entrapped in the boron-monoanionic crown-like cavity.[57]
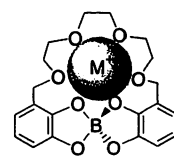
M$^+$-5 (M = K or Na)

The same strategy has been applied in bis(crown ether) systems; Beer et al. have synthesized a schiff base-linked bis(crown ether) 6.[58] The cation-binding properties of the bis-crown segment is influenced by allosteric metal ions accommodated by the tetradentate S_2N_2 site. It has been reported that Cu^{2+}-binding of a square planar fashion at the S_2N_2 site favors a sandwich-like complexation with K^+, whereas Ag^+-binding at the S_2N_2 site causes the crown segment to be further away. Furthermore, pre-organized bipyridine-bis(crown ether) system 7 exhibited an enhanced binding property toward Na^+ and cationic bipyridine upon interaction with $Ru(bpy)_2^{2+}$ in the allosteric bipyridine site.[59] On the other hand, Rodríguez-Ubis and Brunet et al. have prepared a bis(crown ether) receptor derived from bispyrazolylmethane 8 as a model of negative heterotropic allostery; transport experiments of alkyl di- or monoammonium cations using a liquid membrane in the presence or absence of Zn^{2+} in the receiving phase evidenced negative allosteric effects of the metal ions toward the ammonium complexation events.[60] The biphenyl-derived bis(crown ether) 9 was prepared by Costero et al..[61] Complexation and transport studies indicate that 9 shows a negative allosteric cooperativity in Na^+ transport when Hg^{2+} is complexed by the benzylic cavity which serves as an allosteric crown segment. Castero has also reported the related allosteric carrier consisting of three crown ether subunits 10.[62]
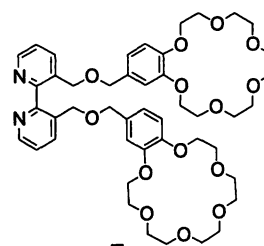
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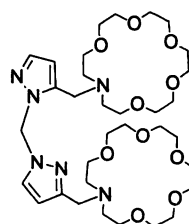
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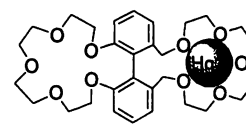
Hg^{2+}-9
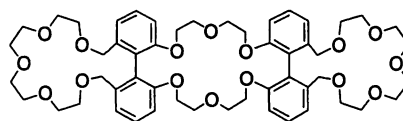
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Bis(crown ether) with an azobenzene linker 11 showed photochemical switching for binding metal ions, although the system is not defined as allosteric. Light-controlled molecular-level tweezers are well-known as the earliest example of a molecular machines.[63]

The use of crown ethers is not limited to receptor binding sites; efforts have been made to use crown ether as a remote site to control complexation strength, a so-called heterotropically allosteric

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11

UV light ↕ visible light

K⁺-11

12

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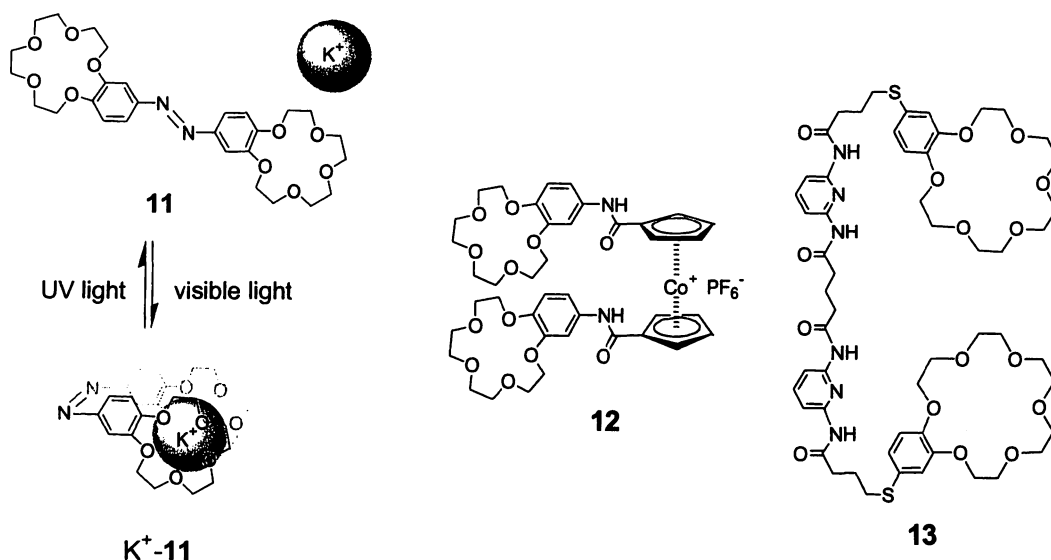
site. A number of examples have been investigated. A cobalticinium bis(benzo crown ether) 12 was synthesized by Beer et al, with a K⁺-induced negative allosteric effect for binding simple anions (Br⁻, Cl⁻) at amide sites of the molecule. K⁺ coordination to the crown moieties seem to disturb a favorable binding geometry for the anions.[64] Another example of crown ether-derived allosteric systems for anion-binding comes from bis (crown)-substituted hydrogen-bonding receptor 13.[65] Although receptor 13 shows a moderate affinity for Cl⁻ and Br⁻ in CDCl₃/CD₃CN (4:1 v/v), which was employed in an NMR study, addition of Cs⁺ as an allosteric effector could organize anion binding sites, resulting in 10-fold enhancement of Br⁻ affinity and 45-fold enhancement for Cl⁻.

Crown-appended allosteric receptors for binding organic guests have been also reported; molecule 14 is the first controllable saccharide-binding system.[66] It is well known that a boronic acid group reversibly forms covalent bonds with a variety of sugar molecules in water, so that artificial receptor systems with a boronic acid moiety have been proposed in sugar recognition.[67] Thus, conformational regulation coupled with metal ions accommodated in the crown unit cause a reduction in the amount of a 1:1 saccharide-diboronic acid complex, being easily monitored from the circular dichroism (CD) intensity. Similarly, the allosterically bis(crown ether)-coupled diboronic acid "Glucose Cleft" 15 has been synthesized.[68] When a metal ion-induced sandwich-like complexation mode is formed by two 15-crown-5 rings, glucose is released from 15. The third example of negative allostery for

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16

17

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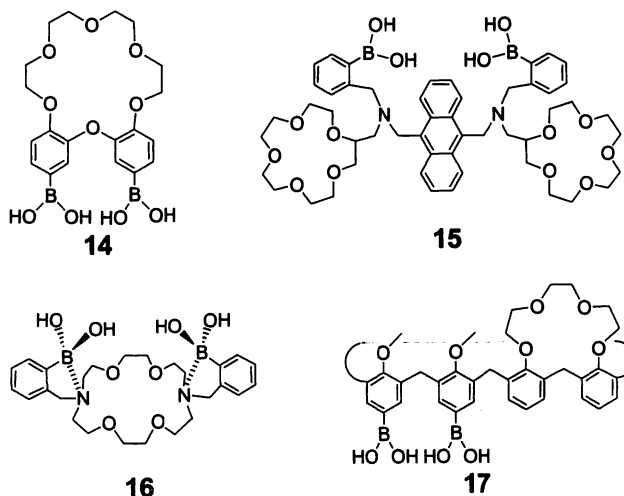
sugar-binding involves has been made in terms of more direct coupling between a diazacrown ether and a diboronic acid function (compound **16**).[69] Compound **16** forms a 1:1 complex with D-fructose or D-glucose with the aid of the intramolecular B---N interaction. However, adding Ca^{2+} as an allosteric metal ion gives rise to a competitive interaction with the nitrogen that reduces the B---N interaction. As a result, the binding ability of **16** with the saccharides was weakened. Further, Shinkai et al. synthesized a unique calix[4]arene system **17** in which the crown-strapped segment was incorporated at the lower rim, whereas two boronic acids were attached to the upper rim.[70] D-Glucose and the related monosaccharides as guest molecules can bind to the boronic acids. Binding of small metal ions (Li^+, Na^+, Mg^{2+}, and Ca^{2+}) gives rise to a negative allostery for the saccharide-binding, whereas positive allostery was obtained with larger alkali ions such as K^+, Rb^+, and Cs^+. Fine tuning of the calixarene conformation with the metal ions could control the receptor function for monosaccharides drastically.

Alternatively, allosteric hydrogen bonding-type receptors for organic guest-binding have been proposed; for example, thymine receptors **18**, 2,6-diamidopyridine derivatives tethered to an anthracene ring by a polyoxyethylene spacer, were synthesized.[71] On interaction with Na^+, the binding ability with 1-butylthymine was enhanced by a factor of 4-6 by through-space interaction of the anthracene ring. Again, the use of conformational regulation of flexible calixarene platforms allows the development of allosteric hydrogen-bonding receptors; monodeoxycalix[4]arene–crown ether conjugate **19** was synthesized by Fukuzawa et al., and exhibited a positive heterotropic allostery for binding neutral guest molecules when alkali metal ions (Na^+ and K^+) were accommodated in the crown moiety.[72]

Use of the crown ether unit as an allosteric segment in this way provides a potent method for pre-programming in molecular systems. Recently, Rice et al. synthesized the crown-appended pyridyl-thiazole ligand **20**.[73] In the presence of Hg^{2+} and Na^+, the ligand **20** forms a dinuclear double helicate complex, whereas, the addition of Hg^{2+} and Ba^{2+} leads exclusively to a mononuclear species. As a result, allostery-based control of self-assembly has been achieved, which is handled as "reprogrammed" approach.

The heterotropic allostery referred to above is used for control of the binding or release of guest

Na$^+$-**18**-(1-butylthymine)   **19**   **20**
(Y = H, OMe, CN)

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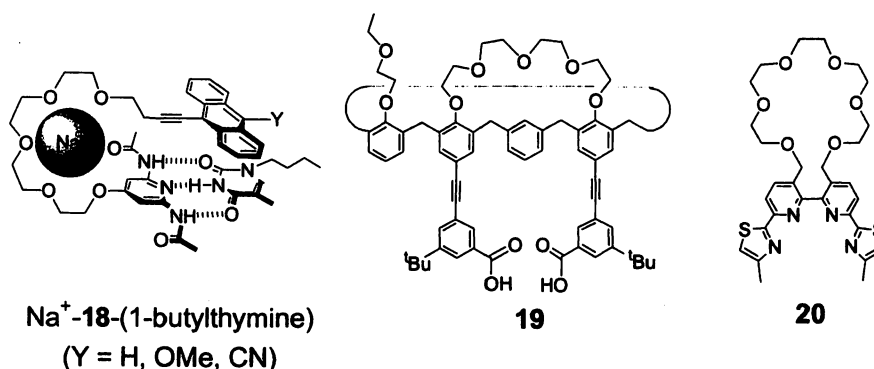
species. Recently, a unique approach has been taken by V. W.–W. Yam et al. in which *trans-cis* isomerization of palladium(II) phosphate complex **21** was efficiently controlled by an allosteric metal ion (Scheme 1).[74] This could lead to design programming for self-organized molecular capsules, since a number of insights have been obtained for large three-dimentional assemblies through metal (Pd^{2+}, Pt^{2+})-coordination.[75]
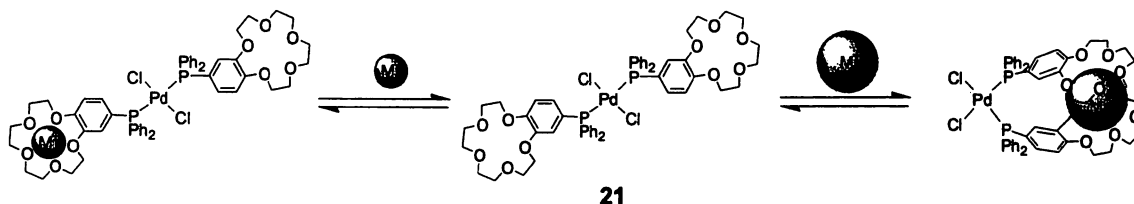
Scheme 1. Schematic presentation of the *trans-cis* isomerization of **21** in the presence of different metal ions.

2-2. Large-ring sized crown ethers

As part of our aim developing conformationally function-programmable systems, we have noted topological aspect of dibenzo-30-crown-10, with a larger ring size and greater flexibility.[76-79] On wrapping cations of small size, a dramatic change in conformation takes place in the ring. For example, it is well known that unique complex structures can be made of dibenzo-30-crown-10 with K^+ [80] and electron-deficient pyridinium derivatives.[81,82] Dynamic conformational regulation of the highly flexible dibenzo-30-crown-10 macrocycle *via* host-guest interaction has spurred us to design function-tunable (allosteric) systems in supramolecular chemistry. Although much effort has been devoted to the development of synthetic receptors possessing crown ethers (*vide supra*), studies of dibenzo-30-crown-10-derived systems have been limited,[83] possibly due to the difficulty of modifying the skeleton.[84] Nevertheless, their great potential as building blocks for conformationally tunable molecular systems make it worthwhile to search for a convenient synthetic path. Thus, from
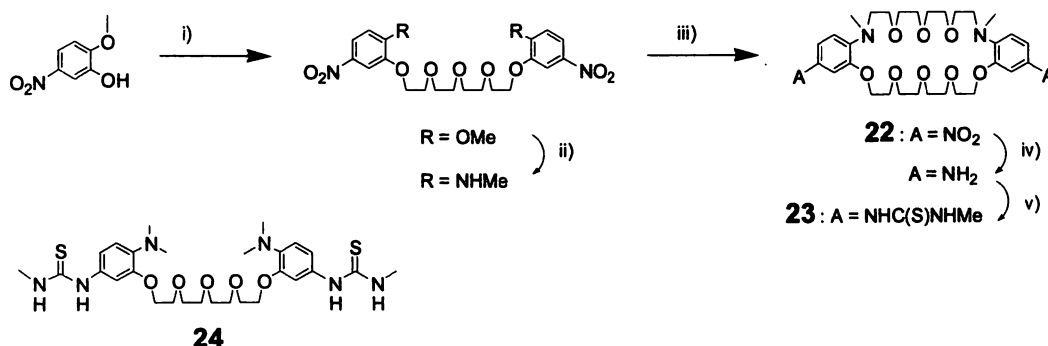
Scheme 2. *Reagents and Conditions*: (i) 3,6,9-trioxaundecane-1,11-diyl bistosylate, K_2CO_3, dry Acetone, reflux, quant.; (ii) methanolic solution of $MeNH_2$ (40 % v/v), in a sealed tube, 100 °C, quant.; (iii) 3,6,9-trioxaundecane-1,11-diyl bistosylate, NaH, dry DMF, 80°C, 22 %; (iv) 10 % Pd/C, H_2 (2 atm), EtOH, rt; (v) MeSCN, CH_2Cl_2, 40 °C; 40% (from **22** to **23**).

9

retro-synthesis, it has proved possible to synthesize regioselectively a dinitro-substituted diaza-congener **22** from a commercially available material, 5-nitroguaiacol, in only three steps (Scheme 2).[85]

Dynamical conformational change of the skeleton by cation complexation motivates us to develop a well-tailored receptor with a heterotropic allostery. Accordingly, we have synthesized system **23** with bis(thiourea) units in the terminal positions through reduction with H_2, followed by the reduction with MeSCN, from **22**. Thiourea and related molecules have attracted considerable attention for their potential as binding units in anion receptors,[86-90] because of their characteristic behavior based on Lewis acid and strong hydrogen-bond donors.[91-105] The topological arrangement of thiourea units generates an allosteric anion binding ability. As expected, K^+-assisted diphenylphosphate binding coupled with a dynamical conformational change was observed, in which a cleft-type geometry is organized to create a bis(thiourea)-based microenvironment. Indeed, Fig. 6(a) shows the results of titrations in which the shifts of Ar-NH-C(S) resonances were monitored as a function of the incremental amounts of $(PhO)_2P(O)O^-$ as a Et_4N^+ salt, both in the absence and presence of K^+ (3 equiv.). The presence of K^+ causes a much more rapid shift in the resonance than K^+-free **23**. Analysis of the binding curves suggests two stepwise complexations, as follows: H + G $\rightleftharpoons$ HG (K_1), HG + G $\rightleftharpoons$ HGG (K_2), $[H_0]$ = [H] + [HG] + [HGG], where [H] and [G] respectively refer to **23** and the anion. Table 1 summarizes the estimated values (K_1 and K_2) as well as the result with I^-. System **23** shows high selectivity for an oxoanion such as $(PhO)_2P(O)O^-$, as compared with $K_1 \times K_2$, and suggests significant binding by the thiourea units. It follows that an efficient cooperative complexation of K^+ and $(PhO)_2P(O)O^-$ takes place; the K_1 value of the phosphate ion increased by a factor of 19 in the presence of K+, to 9,200 M^{-1}. Addition of the cation gave a considerable increase in 1:1 stoichiometric recognition with $(PhO)_2P(O)O^-$ over I^- with a selectivity of 130-fold. This result is unique, because in principle the cooperative factor due to the cation for anion binding increases with decreasing anion basicity.[106] Thus, the greatly enhanced binding of $(PhO)_2P(O)O^-$ with a relatively high basicity is attributed to a particular K^+-assisted organization of **23** which favors ditopic binding with the phosphate ion, accompanied by an increase in acidity of the thiourea protons. The titrations were repeated with both Na^+ and Cs^+. Although the cooperative binding for Na^+ and $(PhO)_2P(O)O^-$ could not be estimated, because of a precipitation problem, the binding capability toward $(PhO)_2P(O)O^-$ could also be accelerated by Cs^+ added as a phenylborate salt (CsTPB). However, the greater ionic size of Cs^+ allowed for less complementarity between the cation and **23**, so that the cooperative effect was not as strong as with K^+. As a control experiment, similar titrations using **24**, which lacks the crowned cavity, were carried out to study the role of the crowned segment; **24** has association constants K_1 = 210 M^{-1} and K_2 = 62 M^{-1} with $(PhO)_2P(O)O^-$ in K^+-free conditions, which are lower than those of **23**. The cooperative binding behavior was less clear in the presence of 3 equiv. of K^+ (Table 1). The presence of a crowned segment which can

10

efficiently accommodate K^+ plays an important role in phosphodiester binding.

Table 1 Association constants (K_1 and K_2/M^{-1})[a] for **23** and **24** with anions in the absence and presence of metal ions in CD$_3$CN at 24 °C

	(PhO)$_2$P(O)O^{-b}		I^{-c}	
	K_1	K_2	K_1	K_2
23	490	110	< 10	< 3
23 (+ K$^+$)[d]	9,200	15	69	31
23 (+ Cs$^+$)[d]	3,200	24	-^{e}	-^{e}
24	210^f	62^f	-^{e}	-^{e}
24 (+ K$^+$)[d]	300^f	100^f	-^{e}	-^{e}

[a]The data were averaged over at least three runs (error < 20 %). [b](Et$_4$N) salt. [c](n-Bu$_4$N) salt. [d]Titrations were carried out in the presence of 3 equiv. of KTCPB and CsTPB, respectively. [e]Values not determined. [f]At room temperature.

A molecular force calculation was carried out to evaluate the complex structure formed by **23** with K$^+$ and (PhO)$_2$P(O)O$^-$. Energy minimization (ESFF force field) with the quasi Newton-Raphson algorithm was performed using Insight II version 2000 / Discover Release 3.0.0 version 98.0 (Accelrys) on a Silicon Graphics COMTEC 4D O2 workstation. The modeling approach (Fig. 6(b)) implies that **23** binds K$^+$ and (PhO)$_2$P(O)O$^-$ cooperatively in an induced fit fashion, where the crowned segment of **23** wraps around K$^+$ to generate a U-shaped conformation. The result motivated us to use heterotropic allostery in considering programmable microenvironments.
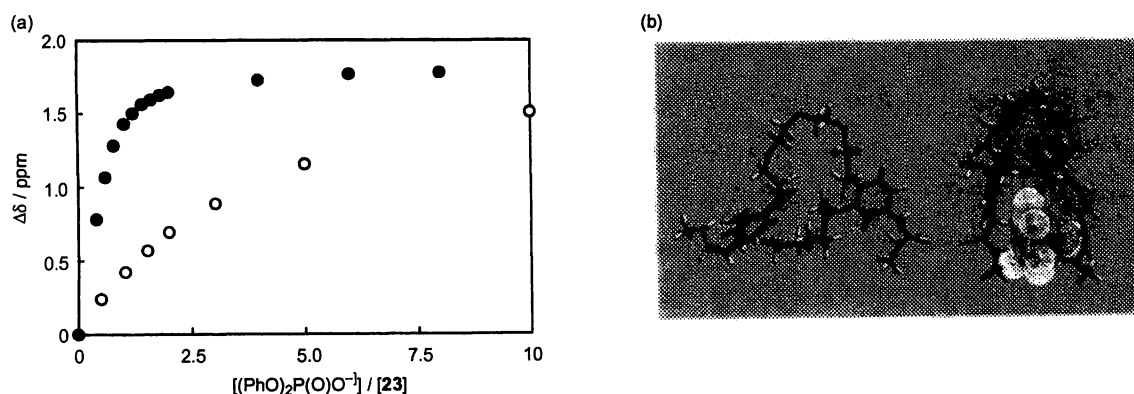

Fig. 6. (a) Titration plots of the Ar-NHC(S) resonances of **23** following addition of (PhO)$_2$P(O)O$^-$ in CD$_3$CN: (●) **23** + K$^+$ (3 equiv.); (○) **23**; [**23**] = 2.0 mM at 24 °C. (b) An energy-minimized *complex* structure of [K$^+$-**23**-(PhO)$_2$P(O)O$^-$].

11

3. Allosteric enzyme models

3-1 Crown-appended systems

The development of artificial enzymes is one of the most exciting subjects in supramolecular chemistry.[107-111] The aim is to attain a "supramolecular catalyst" beyond natural enzymes. A modular approach based on potent combinations of reaction and receptor units has mainly been employed, both units being complementary to a substrate in the molecule. In particular, natural enzymes often possess two or three metal ions in their activation sites.[112-117] Crown ethers can thus serve as the receptor units. Canary reported a heterodinuclearting ligand **25** which can bind an alkaline earth metal ion and a zinc(II) ion at the crown and terpicolyl sites, respectively.[118] A Ba^{2+}-Zn^{2+} dinuclear complex with **25** was applied for the catalytic cleavage reaction of the phosphate diester (DPNP), which showed a rate enhancement of 1120-fold over background DPNP hydrolysis. Saturation kinetics studies suggest that the dinuclear Ba^{2+}-Zn^{2+} complex has a higher affinity to the substrate. The homoditopic ligand **26** in which two aza-18-crown-6 units are connected by an m-xylene spacer catalyzed ethoxide-induced cleavage reactions of ester and amide.[119] In this system, Ba^{2+} is accommodated in each aza-18-crown-6 unit to form a $(Ba^{2+})_2$-**26** complex. One of the metal ions can bind and activate the ethoxide ion nucleophile, and the other can serve as an anchoring group for the distal carboxylate of the substrate. The synergistic action of the two metal centers is exploitable in successful attempts to develop bifunctional enzyme models. Indeed, $(Ba^{2+})_2$-**26** showed a 865- and 1250-fold rate enhancement over the background basic ethanolysis of amide **27** and the ester congener, respectively. The same research group has improved the bis-barium complex toward a phototunable supramolecular catalyst.[120] The bis-barium complex **28**, being composed of azobis-(benzo-18-crown-6) ether ligand, adopts photoswitchable *cis* and *trans* forms, so-called "butterfly crown ethers". Kinetic experiments for the basic ethanolysis of **27** have indicated that the catalytic properties $(Ba^{2+})_2$-**28** can be reversibly activated-deactivated by light-induced changes in molecular geometry.

In this way, crown ether has acted as an anchoring site of artificial enzymes by incorporating a suitable metal ion. However, if dynamic conformation-regulation by chemical stimuli could communicate to the reaction-microenvironment

Ba^{2+}-Zn^{2+}-**25**

DPNP

$(Ba^{2+})_2$-**26**

28

12
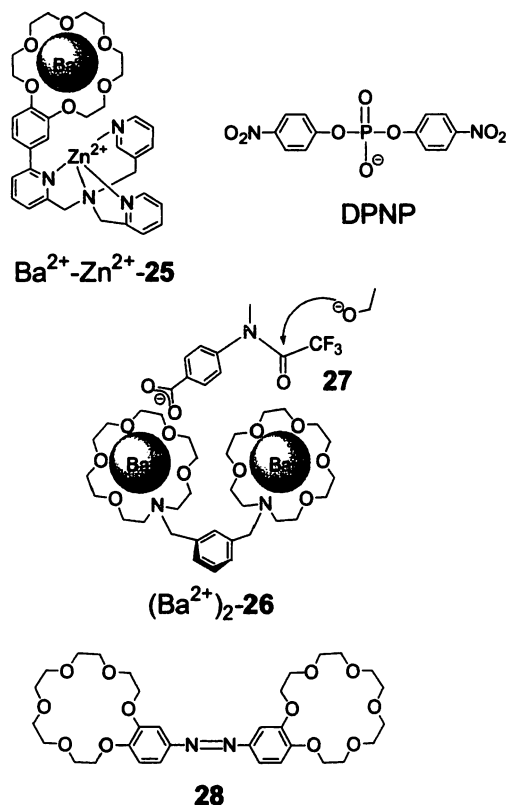
an allosteric enzyme model could be developed. The first simple synthetic model of an allosteric effect applied to a chemical reaction was reported by Pierre et al. in 1992.[121] An acyclic polyether ligand **29** with both a quinone and a dimethoxybenzene as terminal groups is allowed to react with NADH model, 1-propyl-1,4-dihydronicotineamide, **30**. Reduction of the quinone exhibited 30-fold kinetic enhancement in the presence of K^+. An effective charge transfer interaction in the transition state of the reduction may be brought about by a K^+-induced conformational change (Scheme 3).

Furthermore, a highly flexible conformation in a large ring-sized crown ether (*vide supra*) led us to consider an alternative design of activity-tunable enzyme models. We
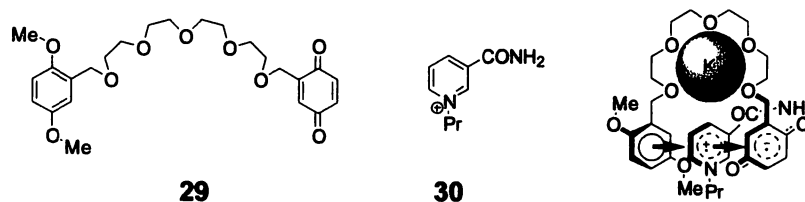
Scheme 3. Proposed mechanism of allosteric activation of the reduction of **29** with **30**, mediated by K^+.

investigated whether the bis(thiourea)-based microenvironment created by an allosteric cation in **23** could be a feasible activity-controllable catalytic model.[122] The trial was applicable for allosteric control of phosphodiester bond cleavage, where we used 2-hydroxypropyl-*p*-nitrophenyl phosphate (**HPNP**) as a tetraethylammonium salt, being a RNA model substrate. Phosphodiester cleavage of **HPNP** (0.85 mM) was carried out in MeCN under basic conditions by adding excess NEt_3 (0.1 M) at 25°C, and was monitored by increasing the absorption intensity at 400 nm caused by release of the ionized *p*-nitrophenol *via* the transesterification mechanism; the reaction then followed pseudo-first-order kinetics. The kinetic data were estimated from the initial rates (< ca. 15% conversion). Fig. 7 shows that, in contrast to the much lower cleavage reactivity of **HPNP** under uncatalyzed conditions, addition of **23** (4.5 mM) and 1 equiv. K^+ to the solution allowed the cleavage reaction to proceed significantly (k_{obs} = (8.0± 0.7) × 10^{-5} s^{-1}). Under identical conditions using K^+ free-**23**, the cleavage rate was 400 times less than for the 1:1 mixture of K^+ and **23**. On the other hand, use of other monovalent metal ions [Na^+ and Cs^+ as tetraphenylborate salts] in similar conditions gave slower reaction rates than in the presence of K^+. These observations suggest that K^+ is an efficient allosteric effector of the catalytic reaction. However, no acceleration of the reaction occurred for *N*-methyl-*N'*-phenyl thiourea in the presence of K^+, or with dibenzo-30-crown-10 as a macrocyclic control compound in the presence of K^+. The latter case in particular suggests that two

thiourea "arms" incorporated in **13** are organized by K^+ to contact **HPNP** complementarily, enhancing the cleavage rate; a ca. 270-fold rate enhancement occurred with K^+-**23** rather than K^+-coordinated

HPNP

13
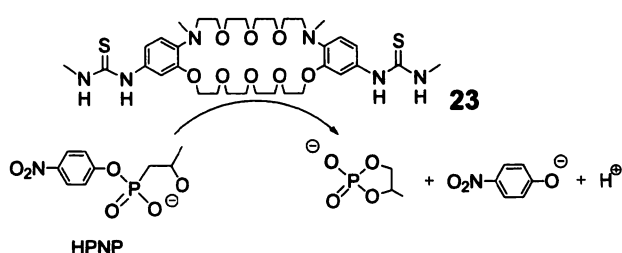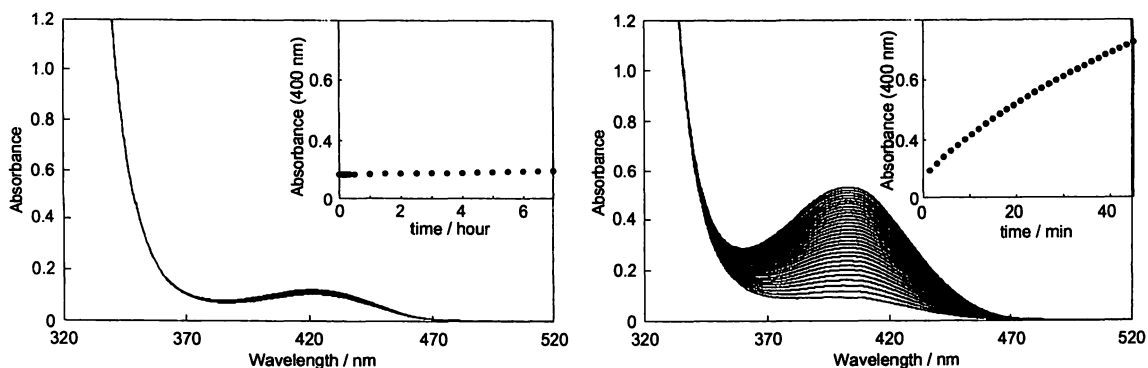
Fig. 7. Time-course of the spectral changes for the cleavage of HPNP (0.85 mM) in the presence of 23 (4.5 mM) (left), and in the presence of 23 (4.5 mM) as well as K⁺ (4.5 mM) (right) in a MeCN solution involving 0.1 M Et₃N.

K⁺-23-HPNP complex
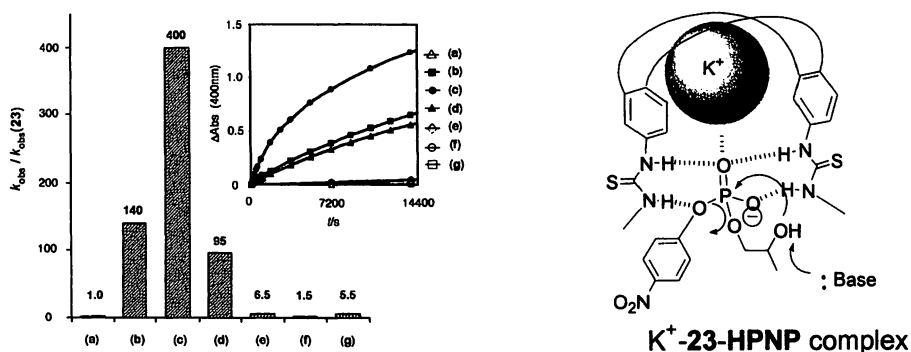
Fig. 8. Acceleration effects k_{obs} / k_{obs} (23) on the cleavage of HPNP (0.85 mM) in a MeCN solution (a) with 0.1 M NEt₃ at 25 °C. (a) 23 (4.5 mM); (b) 23 (4.5 mM) + Na⁺ (4.5 mM); (c) 23 (4.5 mM) + K⁺ (4.5 mM); (d) 23 (4.5 mM) + Cs⁺ (4.5 mM); (e) N-methyl-N'-phenyl thiourea (9.0 mM) + K⁺ (4.5 mM); (f) dibenzo-30-crown-10 (4.5 mM) + K⁺ (4.5 mM); (g) K⁺ (4.5 mM); Insertion data: time course of the reaction in above conditions, (a) (△); (b) (■); (c) (●); (d) (▲); (e) (◇); (f) (○); (g) (□). The kinetic data are averaged over at least individual three runs. Y. Kubo et al., Reprinted with permission from [121], *Tetrahedron Lett.*, **43**, 3455 (2002). © 2002, Elsevier.

dibenzo-30-crown-10. Fig. 8 summarizes the results of rate acceleration with a plausible mechanism in which the cooperative association of K⁺ with 23 gives rise to a suitable microenvironment for cleavage of the phosphodiester bond. In this way, dynamic control with conformationally flexible crown ether leads us to use it as a simple programmable scaffold. Clearly the right combination of metal-induced allostery and enzyme function could give rise to a "supramolecular catalyst".[31]

3-2 Polytopic ligand systems

Since many hydrolytic enzymes have two or three metal ions in their active sites (e.g., metallo-phosphodiesterase),[112-117] a common strategy in artificial models leading toward such enzymes is to synthesize systems possessing plural ligated metal ions.[123,124] The design of activity-tunable multinuclear metallocatalysts is therefore also important in molecular manipulation. This review deals with supramolecular allosteric enzymes utilizing a transition metal as an allosteric segment, although these systems do not have any crown ether units. Krämer et al. have reported allosteric synthetic catalysts, specifically trinuclear metal complexes with a polypyridyl ligand, 31, used for metal ion induced activity tuning of an artificial phosphodiesterase. The complexes consist of two functional Cu^{2+} ion which serve as a catalytic site as well as (Ms: Cu^{2+}, Ni^{2+}, Pd^{2+}, Co^{2+}, and Co^{3+}) as an allosteric site.[125,126] The reaction was monitored via UV/Vis spectroscopy according to release of

catalytic site

allosteric site

$[(L-H)M_sCu_2]^{5+}$ (L = 31)

$2Cu^{2+}$
M = Pt^{2+}

$2Cu^{2+}$
M = Pd^{2+}

33   32

= Zn^{2+} or Cu^{2+}

34
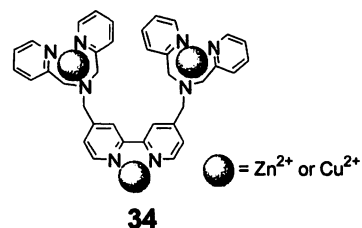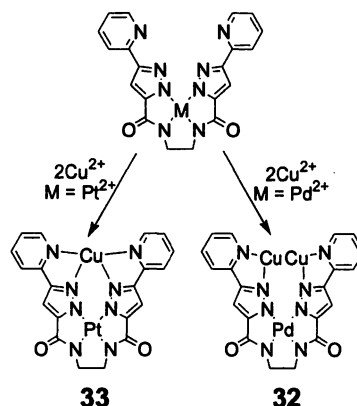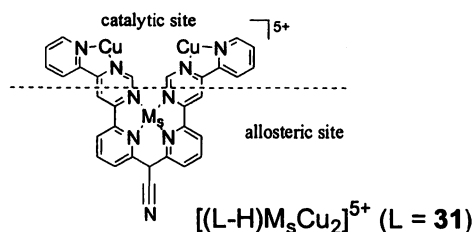
nitrophenolate produced by intramolecular transestification of **HPNP**. The substrate-binding constant (K_{HPNP}) and the catalytic rate constants (k_{cat}) have been determined from Michaelis-Menten kinetics. The characters of the Ms has a significant effect on the catalytic rate constant, k_{cat}; Indeed, when using Cu^{2+} or Co^{3+} as the Ms, k_{cat} is 70-fold larger than with Pd^{2+}. The details were elucidated by an X-ray study of $[(L-H)Cu(MeOH)]ClO_4$ (L = 31). A subsequent study allowed on/off regulation of the catalytic action.[127] Whereas $[Cu_2Pd(L-4H)^{2+}]$ **32** is a highly active catalyst for phosphodiester cleavage, $[CuPt(L-4H)]$ is inactive. The metal ion, coordinated to an allosteric site, can control the nuclearity (mono- or dicopper) of a catalytic site; this corresponds to on/off regulation of catalysis for phosphodiester cleavage, since only the dicopper species is catalytically active. A further example of an allosteric model of an artificial phophodiesterase, **34**, was generated using a regulatory bipyridine site.[128]

Mirkin et al. have recently designed and developed a novel catalytic system with a sensor function.[129] The designed system contains two structural domains having Rh^+ metal centers, and a catalytic domain containing two zinc(II) metal centers (Zn^{2+}-salen). The macrocyclic cavity (Fig. 9) of **35-T** can be opened to **35-R** by the insertion of CO gas (1 atm) in the presence of Cl^- as a benzyltrimethylammonium salt in CH_2Cl_2, corresponding to a significant change of the molecular

15

shape. In **35-R**, a bimetallic reaction took place in which acetic anhydride is activated by one Zn^{2+}-salen moiety, and is in proximity to a pyridyl carbinol bound to the other zinc(II) center. The Cl^- acts as an "on" switch for the catalysis; rate enhancement by about 25 times can be achieved upon activation. Interestingly, when the acyl transfer reaction between acetic anhydride and pyridyl carbinol was used the acetic acid produced allows coupling of the amplification step to a pH-sensitive fluorophore. As a result, the fluorescence signal could be amplified *via* the Cl^- switched-on catalytic cycle. This provides an interesting novel approach to the design of molecular sensor systems.

4. Chirality manipulation

4-1. Helicity induction

Chirality manipulation is one intriguing challenge in supramolecular chemistry. Biological self-assembly often involves helical structures, such as DNA or α-helix, which play an important role in living systems. Several ways of producing artificial helical structures have been pursued. Lehn has strongly promoted that the control of self-assembly through adequate

Fig. 9. Supramolecular allosteric catalytic signal amplifier. Analyte (Cl^- or CO) binding opens the cavity and allows substrate molecules to enter, where they undergo a fast intramolecular reaction to generate acetic acid, which protonates a pH-sensitive fluorescence probe. C. A. Mirkin et al., Reprinted with permission from [129], *J. Am. Chem. Soc.*, **127**, 1644 (2005). © 2005, American Chemical Society.

programming by combing ligand strands and specific metal ions has led to the formation of double helicates.[130-134] This metal-template approach has been developed by several research groups.[135] Interestingly, some metal complex helicates show helicity switching induced by external stimuli.[136] An alternative approach based on hydrogen-bonding interaction has been investigated.[137-141] Also, synthetic polymers are promising candidates for inducing helicity, and extensive efforts have been made to explore novel functions of materials.[142-149] Here, we emphasize helicity induction through · noncovalent interactions using crown-appended supramolecular systems. For instance, the covalent introduction of a crown ether moiety into a heterobicyclic base (compound **35**) allows the generation of self-assembled helical rosette nanotubes by the binding of a chiral amino acid in its zwiitterionic

16

form to the crown ether.[150] Fenniri et al. found that chiropotical properties at the macromolecular level could be tunable. The proposed supramolecular pathways are summarized in Fig. 10. On the basis of transmission electron microscopy (TEM), dynamic light scattering (DLS), small-angle X-ray scattering (SAXS), and circular dichroism (CD) studies, at high concentrations ($\geq$ 1 mM in MeOH) a "fast pathway" proceeds preferentially; **35** undergoes hierarchical self-assembly to generate rosette nanotubes of diameter ~ 4 nm, which upon adding chiral amino acid, L-Ala, as a promoter, rapidly form M-helix nanotubes. At low concentrations ($\leq$ 0.04 mM in MeOH) **35** exists mainly in a nonassembled state. However, addition of L-Ala then triggers a "slow pathway" to set up a hierarchical self-assembly of rosette nanotubes having a M-helix. In both cases, the kinetic data indicate autocatalytic formation of the nanotubes.

A distinct approach for helical aggregation has been developed by Shinkai et al..[151] They synthesized crown-appended cholesterol-based organogelator **36**, which has two cholesterol segments at the terminal as chiral aggregate-forming sites, two amino groups as an acidic
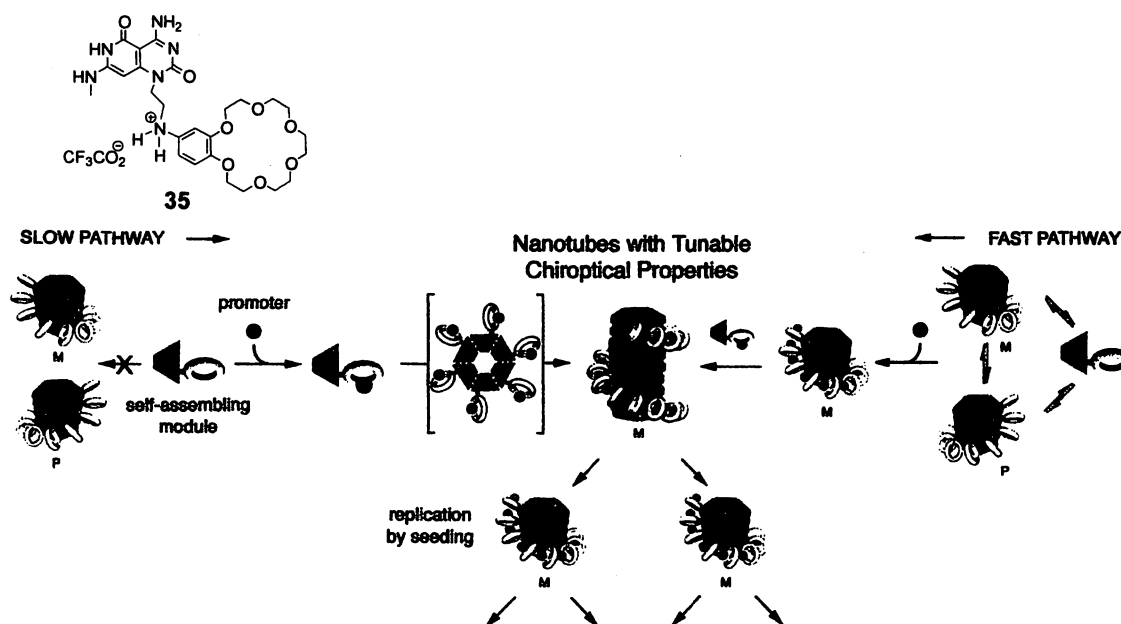
Fig. 10. Supramolecular pathways and their proposed autocatalytic nature for the formation of helical rosette nanotubes with predefined properties. Reprinted with permission from [150], H. Fenniri et al., *J. Am. Chem. Soc.*, **124**, 11064 (2002) © 2002, American Chemical Society.

proton-binding site, and one crown moiety as a cation-binding site. Subsequently, it can gelate various organic solvents. The silica obtained from the **36**-acetic acid gel, upon sol-gel polymerization of tetraethoxysilane, has a helical ribbon with 1700 – 1800 nm pitches and a tubular silica structure of

17
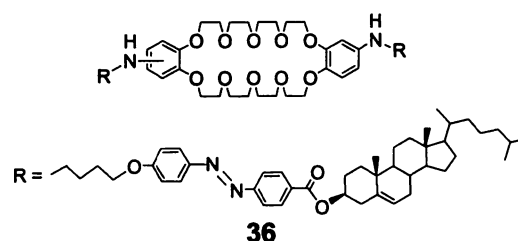
outer diameter with ~ 560 nm.

The use of synthetic polymers offers great advantages in providing chilarity amplification. Yashima et al. have designed and synthesized a stereoregular poly(phenylacetylene) with a bulky crown ether as a pendant (poly-37).[152] Upon complexation with L-amino acid perchlorates in MeCN, helicity induction on poly-37 has taken place sho⌐ et al. report that by taking advantage of a signific the polymer through a cooperative nonbonding i can be detected (Fig. 11). Further, by copolymeri crown ether pendant, the same research group has They have also successfully produced of a helica non-covalent interaction with L-Ala at the crown

As mentioned above, chirality manipulation which a simple crown ether unit plays a signifi promoters. The motivation for investigating chirality manipulation is that chiroptical outcome is spontaneous and predictable, and immediately   applicable   in chirotechnology.[154]   It   leads   to

Fig. 11. Schematic representation of macromolecular felicity induction on poly-37 upon complication with L-alanine. Reprinted with permission from [152], E. Yashima et al.. J. Am. Chem. Soc., 125, 1278 (2003), © 2003, American Chemical Society.

sensors,[149,155-161] asymmetric catalysis,[162,163] actuators such as molecular motors,[164,165] photochromic materials,[166,167] nonlinear optical materials,[168] liquid crystalline systems,[169] and others valuable products.

4-2 Allostery-based chirality induction

At the molecular level, a common methodology of chirality induction (chirogenesis),[170] in which a chiral-orientated conformation is created by the transfer of chiral information from an external species by noncovalent interaction, has great potential for chirality manipulation. As a result, chirality induction associated with allosteric control has become an intriguing topic and relating to chirality manipulation viewed as molecular programming. In 2000, Mizutani et al. reported allosteric chirality amplification

Fig. 12. Possible mechanism of chirality amplification in zinc(II) bilinone dimer. Reprinted with permission from [171], T. Mizutani et al., J. Am. Chem. Soc., 122, 748 (2000), © 2000, American Chemical Society.

using a zinc bilinone dimer.[171] The zinc bilinone **38** is a helical molecule which undergoes racemization between right-handed (*P*) and left-handed (*M*) conformers in a solution. Since coordination of a chiral guest (e.g., L-Asp(OMe)-OMe) to the zinc can induce helical chirality due to the shift *P-M* equilibrium, chirality has been amplified allosterically in the zinc bilinone dimer; addition of the chiral guest to induce M-helicity in the bilinone can convert the *PP* conformer to the *MM* conformer in a stepwise fashion (Fig. 12). The enantiomeric excesses of helices were estimated using ee = ([MM] − [PP]) / ([PP] + [PM] + [MM]) in the presence of the guest. When **38** and L-Asp(OMe)-OMe were used, 86 % enantiomeric excess was obtained with increasing ICD magnitude. The allosteric effect clearly provides a potent way to amplify chiral induction in the zinc bilinone dimer. The enantiomeric excesses were consequently found to be higher in **38** than in monomer **39**.
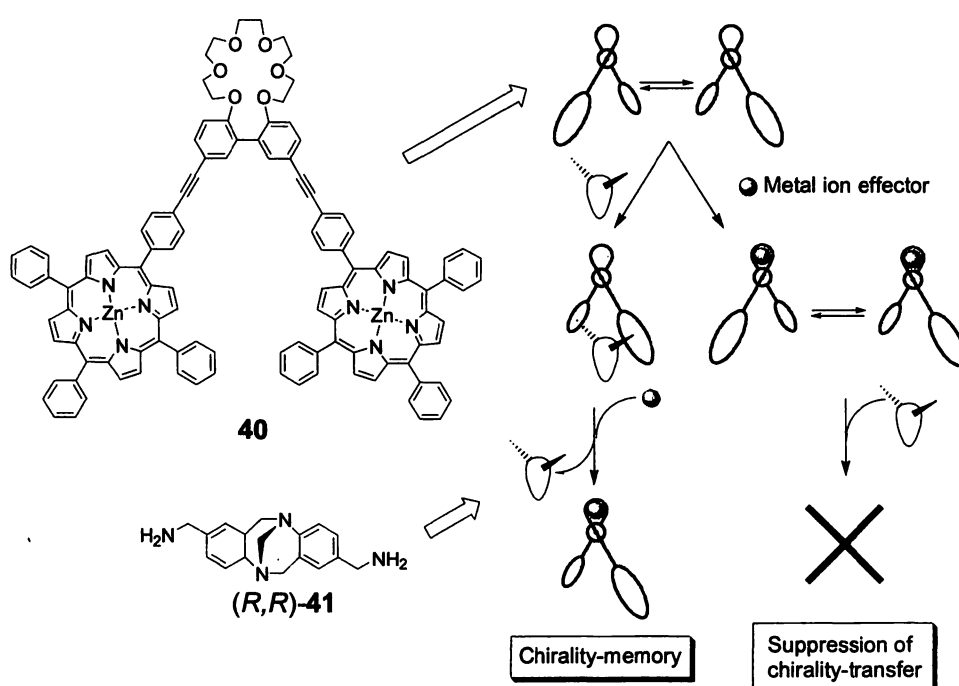
Fig. 13. Design of chirality-transfer control using an anti-cooperative binding motif.

We focus on chirality manipulation using allosteric crown-appended systems in which the crowned segment is able to contribute to the key dynamic process of conformational regulation associated with a non-covalent interaction. The design strategy is shown in Fig. 13;[172] we have taken advantage of negative heterotropic allostery to tailor the molecular system for this approach. This designed molecule, the crown-strapped biphenyl-derived zinc(II) porphyrin dimer **40**, exists as an equal mixture of enantiomeric twisted conformers based on the biphenyl unit, which are in rapid equilibrium. However, on complexation with a suitable chiral guest, the equilibrium shifts to just one of the enantiomeric conformers. If an allosteric effector could induce a conformation change to dissociate the chiral guest while maintaining the enatiomeric conformation, an allosteric effector can

19

cause the system to memorize an induced chirality.[173-186] On the other hand, under alternative conditions, if the same effector acts as a negative allostery for binding the chiral guests, the effector also suppresses transfer of the induced chirality to the system. System **40** contains paired porphyrin-chromophores that allow us to easily monitor an induced chirality in terms of circular dichroism (CD) spectroscopy, and the center metal allows the coordination of chiral ligands. The binding of a chiral inducer which can ditopically interact with the concave porphyrins accompanying a preferential orientation then efficiently transfers the chirality to **40** through complexation. We must also design a suitable chiral inducer which allows a metal accommodated in the crown segment to give rise to a negative allostery. The Tröger's base analogue **41** used has a chiral "V" shaped geometry as well as the amine N-N distance of 12 Å. We therefore expect that **41** will bind bidentately to **40** in the concave cavity of the bis(porphyrin) with an induced-fit fashion since the optimized porphyrin center-to-center distance of **40** is ca. 21 Å. The geometrical features could lead to an anti-cooperative binding mode between an allosteric effector (metal ion) accommodated in the crowned spacer and the chiral inducers. Fig. 14 shows the results of chirality manipulation on the porphyrin dimer **40** from monitoring the changes in CD amplitude. The amplitude of **40** induced by

1.5 equiv. of (R,R)-**41**, where the ratio of complexation between **40** and (R,R)-**41** is ca. 70 %, decreased progressively up to 4 equiv. of Ba^{2+} addition (8 µM), but there still remained CD active with A = 52.3 $M^{-1}cm^{-1}$ even in the presence of excess Ba^{2+} (100 µM). The reduced CD intensity might be due to conformational flexibility involving the competitive binding event between **40**·(R,R)-**41** and **40**·Ba^{2+} complexes. Thus, to remove (R,R)-**41** from the complexation event completely, as well as to fix the conformation of **40**, we added achiral 1,10-diaminodecane **42**. The CD amplitude was found to increase again, clearly indicating that the added **42** fixed the chirality induced by (R,R)-**41**. This result is striking since addition of **42** to a Ba^{2+}-free solution of **40** and (R,R)-**41** resulted in silence CD. This assessment is also supported by ^1H NMR spectra. In this way,

Fig. 14. (a) Changes in CD amplitude induced by (R,R)-**41** addition and subsequent Ba^{2+} and **42** addition; (b) Changes in CD amplitude induced by (R,R)-**41** addition and subsequent **42** addition; (c) Changes in CD amplitude induced by (S,S)-**41** addition and subsequent Ba^{2+} and **42** addition; (d) Changes in CD amplitude induced by (S,S)-**41** addition and subsequent **42** addition: the CD amplitude represents the total amplitude of CD couplets [A (= $\Delta\varepsilon_1$ - $\Delta\varepsilon_2$)]. These data were collected in CH_2Cl_2-MeCN (9:1 v/v) at 25 °C when the concentration of **41** is 2.0 µM.

20

— 44 —

the simple metal ion, Ba^{2+}, shows high memory efficiency. On the other hand, when (S,S)-**41** was used, the CD spectra showed mirror image behavior (Fig. 14). Furthermore, the allosteric metal ions can suppress chirality induction by **41**; upon adding 50 equiv. of Ba^{2+} to a solution of **40** prior to complexation with **41**, with appearance of the CD band with incremental amounts of (R,R)-**41** was significantly suppressed. With combined chiral induction and allostery, we can manipulate chirality at the supramolecular level.

The control of chirality transfer using a pseudocrown ether system has been reported by Nabeshima et al..[187] The pseudocrown ether **3** consists of two polyether chains that connect (R)-1,1'-binaphthyl and 2,2'-bipyridine moieties. The Cu^+-complexes, Cu^+-**3**, are two diastereomers: helical and nonhelical structures (Scheme 8). Indeed, the ratio of the two signals for the picolyl methyl protons in ^1H NMR indicates that one diastereomer is formed with slight preference (42:58) (Fig. 15). However, the presence of Na^+ (4 equiv.) altered the distribution of the
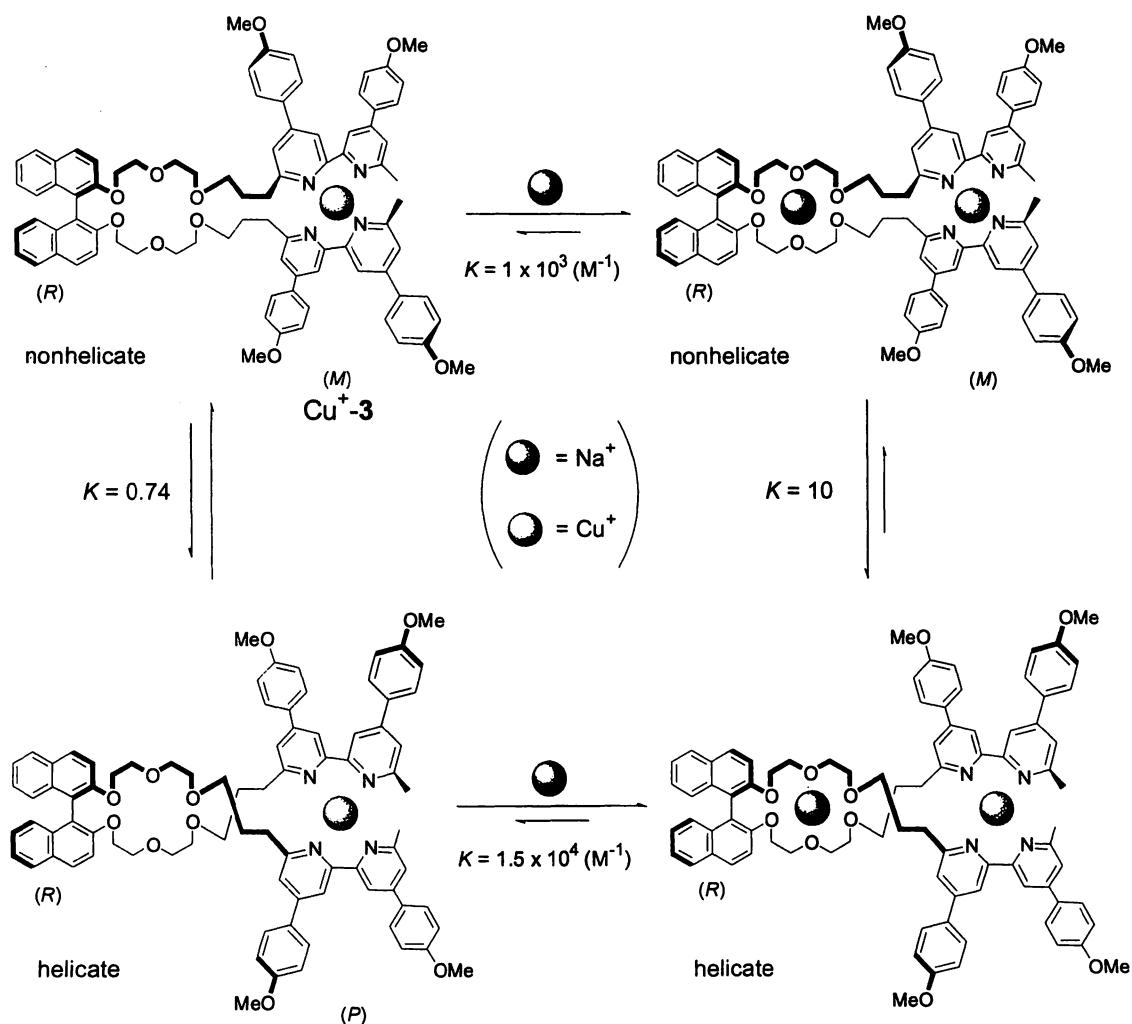
Scheme 4. Transfer of chiral information from the binaphthyl moiety to the $[Cu(bpy)_2]^+$ complex of **3**, bpy = 2,2'-bipyridine.

21

diastereomers, so that the other isomer was predominantly formed (89:11). The Na$^+$-induced preferential formation of one diastereomer of Cu$^+$-3 exhibited a significant CD sign, suggesting a helical structure. Enhancement of the diastereomeric excess (77 %) in Cu$^+$-3 upon adding Na$^+$ implies that the chirality of the (R)-1,1'-binaphthyl unit is transferred to the tetrahedral Cu$^+$-bipyridine complex upon complexation with Na$^+$. The Na$^+$ acts not only as an achiral guest but also a mediator of chiral information.
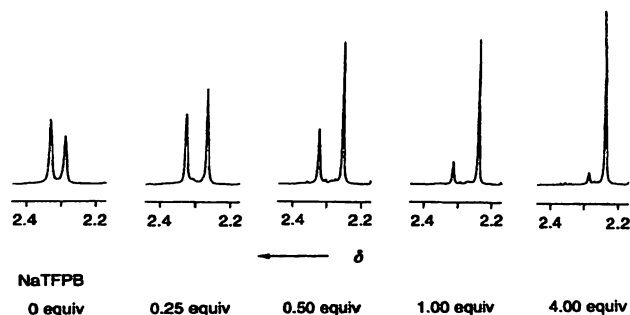

Fig. 15. ^{1}H NMR spectra of Cu$^+$-3 in a mixture of CDCl$_3$ and CD$_3$CN (95:5). a) [Cu$^+$-3]TFPB; b) [Cu$^+$-3]TFPB and 4 equiv. of NaTFPB; (c) The signals for the picolyl methyl groups in the absence and presence of NaTFPB (0.25 – 4 equiv.). T. Nabeshima et al., Reprinted with permission from [187], *Angew. Chem. Int. Ed.*, 41, 481 (2002). © 2002, Wiley-VCH.

In our continuing project for chirality manipulation at the molecular level, exploitation of the conformation-flexibility of large ring-sized crown ether is interesting; we found that a novel achiral-to-chiral transformation of bis(arylthiourea)-derived dibenzo-diaza-30-crown-10 43,[188] which was obtained through K$^+$ and I$^-$ coordinated self-assembly in the solid state. This self-assembly has the space group $P\bar{1}$ and forms a crystallographic centro-symmetric structure in which the U-shaped diaza-crown segments are located at opposite sites to each other. In Fig. 16,[189] it is clear that K$^+$ is enwrapped to give eight K-O distances in the range 2.7870(9) – 3.0363(12) Å and two K-N distances of 3.0475(10) and 3.5094(10) Å, whereas the arylthiourea units of 43 were found to have a different orientation to each other in the self-assembly (*vide infra*); this could explain the differing K-N distances.

43
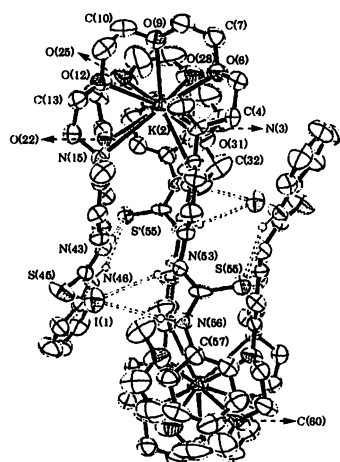
Fig. 16. ORTEP drawing of self-assembled (K$^+$-43)I$^-$, showing the numbering scheme. The intermolecular hydrogen bonds are marked as dashed lines. Hydrogen atoms which are not involved in hydrogen bonding interactions have been omitted for clarity.

(K$^+$-43a)I$^-$ (K$^+$-43b)I$^-$
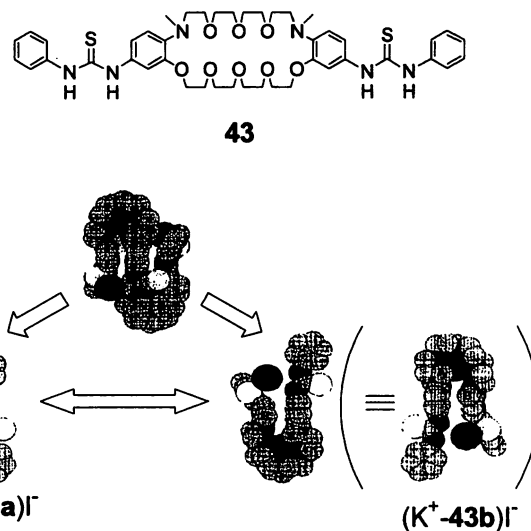
Fig. 17. Chirality induction of the diaza-crown segment through self-assembled (K$^+$-43)I$^-$. Symbols "A" and "B" denote methyl carbons attached to N(3) and N(15) respectively.

22

The iodide ion interacts with one thiourea segment [I(1)-N(53) 3.5364(9) Å, I(1)-N(56) 3.6109(9) Å]. However, the further thiourea unit does not bind to I$^-$, but participates in an intermolecular hydrogen bonding interaction with a thiourea of a second **43** to assist in the self-assembly of the (K$^+$-**43**)I$^-$ complex. This systematic hydrogen bonding network constitutes a head-to-tail binding mode between thiourea units. The ORTEP drawing of Fig. 17 shows a further remarkable feature: the self-complementarity of (K$^+$-**43**)I$^-$ implies that the ligand concerned became enantiomers **43a** and **43b**, which refer to the chirality at the nitrogen (N(3) and N(15)) being considered to coordinate to the K$^+$. This is a unique example of an achiral-to-chiral transformation caused by ion pair-coordinated self-assembly. The fascinating insight that chirality can be induced in the highly flexible crown ether congener motivated us to synthesize 30-crown-10-derived bisporphyrin **44**.[190] Further the cation-binding property of the crown segment is capable of allostery-based chirality induction, because the terminal porphyrins would bind chiral amines ditopically. Upon complexation with (1R,2R)-**45**, the conformational flexibility of the crowned spacer allows for switching of the porphyrin orientation into the tweezers, giving rise to a positive exciton coupled CD spectra (Fig. 18). This follows from the generation of a chiral screw structure of **44** *via* a steric repulsion mechanism between the coordinated **45** and the neighboring porphyrin rings, as shown in Fig. 18b. A further feature of **44** is that a suitable metal ion accommodated in the crown segment can induce a tweezers-like structure. UV/Vis titration to monitor the Soret band of **44**, upon adding KClO$_4$ in CH$_2$Cl$_2$-MeCN (8:2 v/v), showed a hypsochromic shift by 2 nm, along with significantly decreasing absorption intensity (Fig. 19a). The spectral change suggests that cofacialization of the porphyrin units takes place effectively in these conditions. This phenomenon assist in chirality induction; as shown in Fig. 19b, the presence of K$^+$ gave a steep ascending behavior in the CD amplitude, compared to K$^+$-free conditions. The amplitude approached a plateau at a [(1R,2R)-**45**]:[**44**] ratio of 2:1, where a 45% enhancement of the amplitude of the CD spectra was observed. This result is supported by the fact that the apparent association constant of **44**-(1R,2R)-**45** complex under K$^+$-coordinated conditions is twice as great as without K$^+$, so that the allosteric effect in which the K$^+$-binding in the crowned moiety tunes the conformation to bind (1R,2R)-**45** can assist chirality induction in **44**. A similar enhancement was obtained in the case of (1S,2S)-**45**. K$^+$-assisted chirality induction was found to be remarkable for the chiral diamine **46** with bulky substituents at the amino groups. This result suggests that chirality amplification, coupled with positive heterotropic allostery, allows a new type of chiral probe capable of determining the absolute configurations of various kinds of substrates. Further investigation to tailor this to the applications is underway in our laboratory.

23

44

(1R,2R)-45 : R = Me
(1R,2R)-46 : R = CH₂CH₂ᵗBu

(1S,2S)-45 : R = Me
(1S,2S)-46 : R = CH₂CH₂ᵗBu

(a)

(a)

(b)
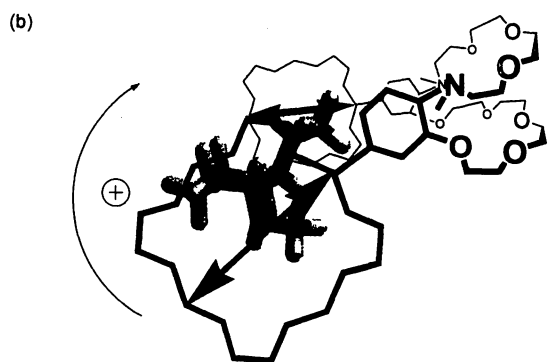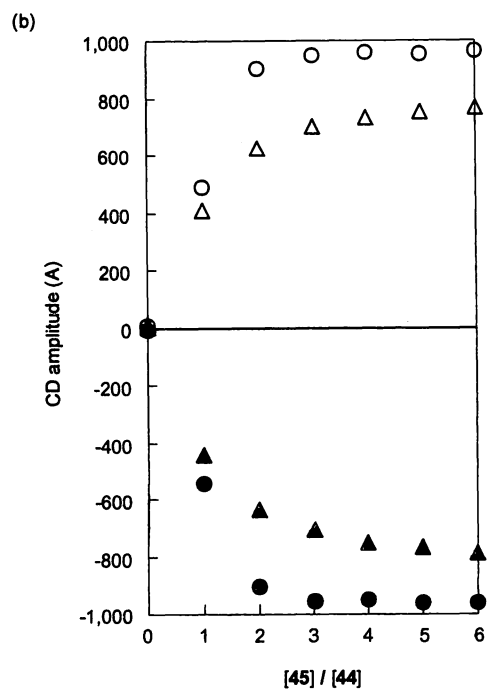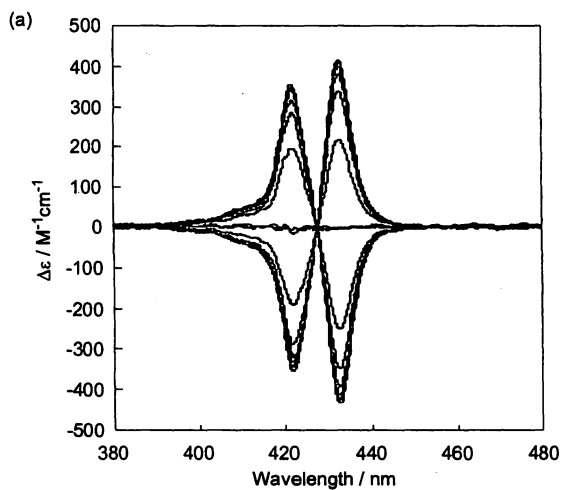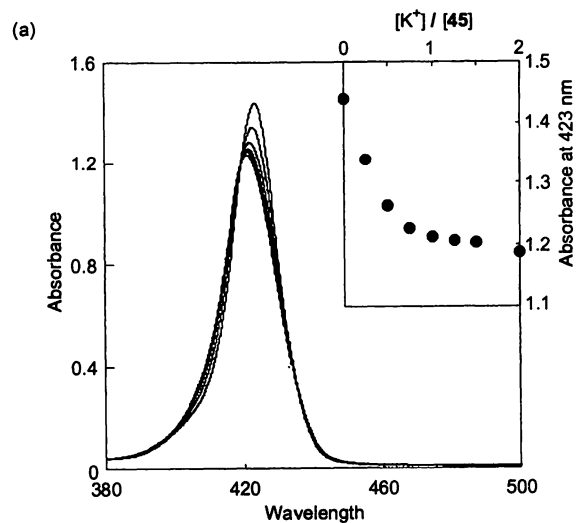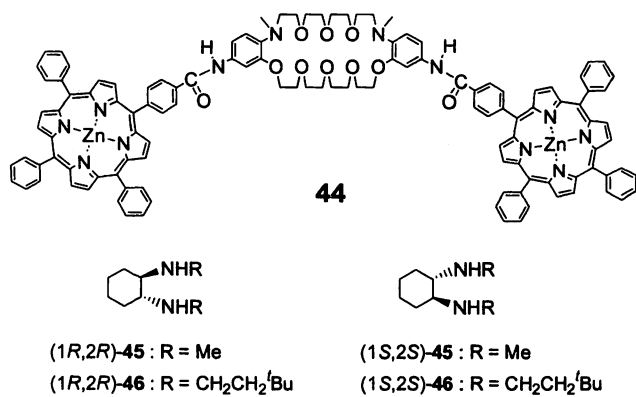
Fig. 18. CD spectral changes of **44** upon adding (1R,2R)-**45** (red line) or (1S,2S)-**45** (blue line) in CH₂Cl₂-MeCN (8:2 v/v) at 25 °C, [**44**] = 2.0 μM; [**45**] = 0, 2.0, 4.0, 6.0, 8.0, 10, 12 μM: (b) A plausible binding motif of the **44**-(1R,2R)-**45** complex.

(b)

Fig. 19. UV/Vis spectral changes of **44** upon adding K⁺ in CH₂Cl₂-MeCN (8:2 v/v) at 25 °C, [**44**] = 2.0 μM; [K⁺] = 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 μM. (b) Changes in CD amplitude [A (= Δε₁ - Δε₂)] of **44** (2 μM) upon complexation with chiral **45** in the presence or absence of K⁺ (5 equiv.) in CH₂Cl₂-MeCN (8 :2 v/v) at 25 °C: (○) (1R,2R)-**45** with K⁺; (Δ)(1R,2R)-**45** without K⁺; (●) (1S,2S)-**45** with K⁺; (▲) (1S,2S)-**45** without K⁺.

24

5. Molecular actuator

One of goals of molecular programming is motion generation at the supramolecular level by means of chemical, electrochemical, photochemical stimuli, or others. The insight of motion generation provides a structural hint for developing molecular machines.[2,4,191-194] At present the best tool is to use movement properties involving interlocking rings (catenanes) or rings threaded by molecular string like components (rotaxanes and pseudorotaxanes).[195] Crown ethers have been widely utilized as ring units of the systems.[196] We now briefly consider related elegant examples. Stoddart et al. synthesized [2]rotaxanes in which a dibenzo-24-crown-8 (DB24C8) ring is threaded by components at a dialkylammonium and a dipyridinium anchor site; see 47.[197] The presence of the crown ether allows the binding of an ammonium segment. Upon adding excess iPr$_2$NEt to a solution of the [2]catenane, however, deprotonation of the ammonium binding site takes place and destroys the intercomponent hydrogen bonds, so that the crown ether shuttles to the bipyridinium moiety. On the other hand, the original conformation is restored by adding CF$_3$COOH (Fig. 20). This shuttling process has been followed by ^{1}H NMR spectroscopy, monitoring the bipyridium protons as probes.

As improved nanoactuators, in 2004, a more complex and better organized system was reported by the same research group, and designed as a molecular elevator.[198] The tritopic host **48** that was used consists of three DB24C8 rings fused together within a triphenylene core. A trifurcated guest **49**, in which three dibenzylammonium ions are linked to a central benzenoid core, is interlocked by **48** (Fig. 20). The energy needed to raise and lower the host platform between the two levels on the legs of the rig is supplied by an acid-base reaction. The distance traveled by the platform is about 0.7 nm, and the research group estimated that the elevator movements from the upper to lower level could generate a force of up to 200 pN.

Fig. 20. An acid-base controllable molecular shuttle. Reprinted with permission from [197], J. F. Stoddart et al., *J. Am. Chem. Soc.*, **120**, 11932 (1998), © 1998, American Chemical Society.

Returning to the main subject of this review, Blanchard et al. have reported some molecular actuators based on a dynamic nanosystem driven by cation-binding.[199] Crown-appended quater- and sexithiophenes **50** have been synthesized, in which the complexation with several cations leads to a geometrical change in the conjugates chain. Detailed investigations (^{1}H NMR, UV/Vis, and cyclic voltammetry) together with crystallographic and theoretical studies indicate that the cation binding

25

induces large conformational transitions in the π-conjugated chain, so that the systems are interesting models of molecular actuators. This study suggests that an allosteric method can be fully combined with the dynamic operation of molecular machinery.
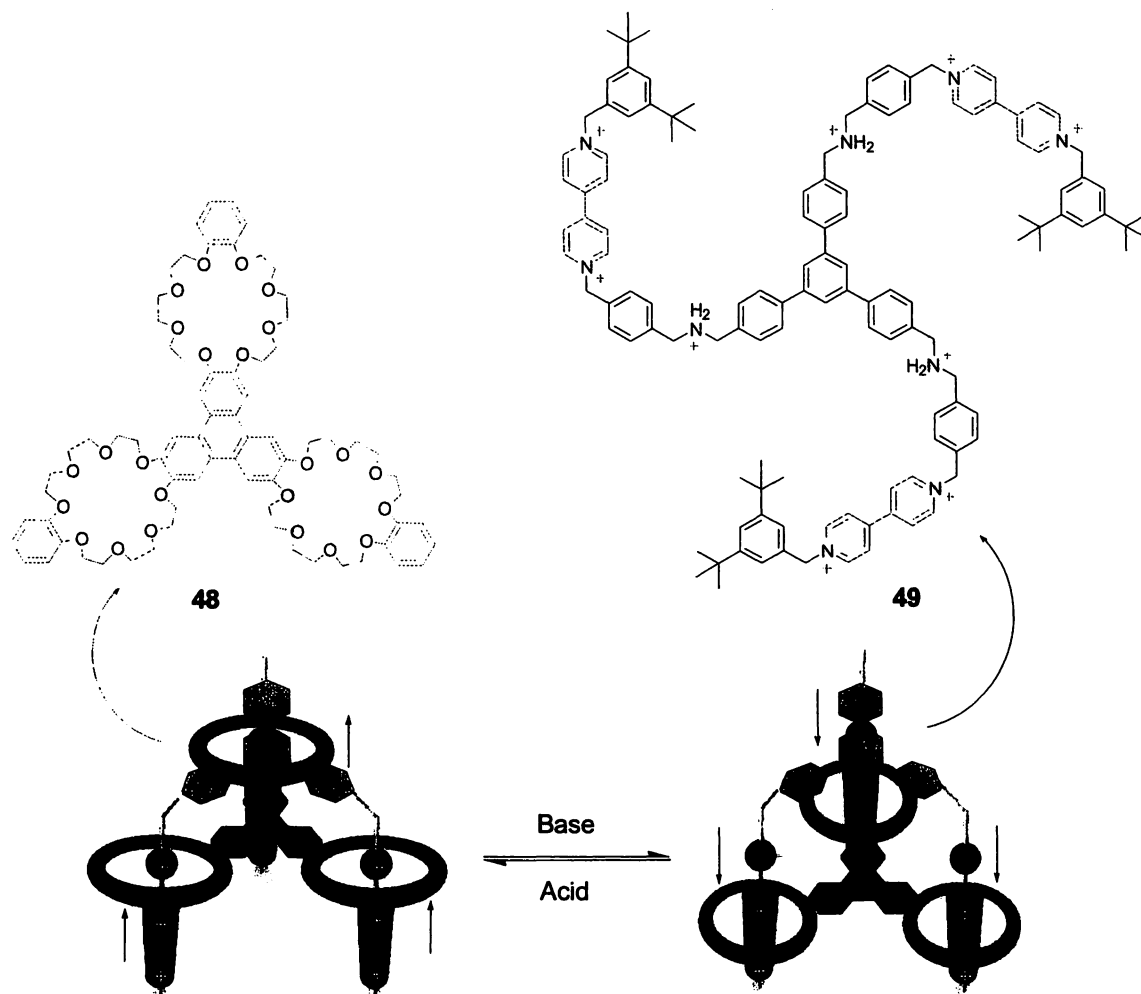
Fig. 21. Rotaxane-based molecular elevator.

6. Summary

Since the discovery of crown ether complexes by Pedersen, many efforts have been devoted to developing synthetic receptors possessing crown ether units. Their structural topology and superior synthetic susceptibility provide a powerful tool that serves as host-guest binding units. Indeed, taking advantage of such properties, a number of artificial systems ranging from the molecular level to macromolecular level use crown ether units as anchoring units to provide non-covalent interactions

50 : n = 1 or 3 M^{2+} = Ba^{2+}, Sr^{2+}, Pt^{2+}

26
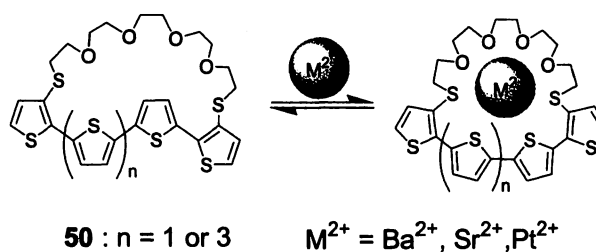
as well as allosteric sites for function-controllable units. Since it seems that dynamic action based on heterotropic allostery is feasible viewed as a design problem in molecular programming, the earlier part of this article mainly described heterotropically allosteric systems based on crown ethers. This review has argued that shape-regulation based on dynamic ion or molecular recognition is a powerful way to develop advanced "chemical systems". Activity-tunable enzyme models, chirality manipulation, and molecular actuators are fully overviewed as well as the functions of related systems involved. The synthetic preparation of advanced molecular units allows systems to be smarter, pointing to the development of nanosystems having programmable functions. Recently, nanoscale assemblies programmed by supramolecular interactions has become of interest topics.[200,201] Further exploration coupled with dynamic ion or molecular recognition warrants well-tailored programming to develop novel nanosystems with the ultimate aim of creating molecular machines.

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34