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Coordination Chemistry Reviews
148 (1996) 1–17

COORDINATION CHEMISTRY REVIEWS

Armed crown ether complexes in supramolecular assembly

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Received 12 January 1995

Contents

Abstract

Recent advances in macrocyclic chemistry and its applications to supramolecular chemistry are described. We first present concept and examples of "armed crown ethers", which are characterised by a parent crown ether ring and a functionalised sidearm. Their structural variations extend molecular recognition and add new reactivity to the parent crown ether. As a new synthetic approach, the computer-aided design of Li^+ ion-specific armed crown ethers is discussed. The rational design and refined synthesis can offer specific molecular recognition and integrated functions.

We also address two interesting approaches developed in the border regions between macrocyclic chemistry and supramolecular chemistry. Armed crown ethers form unique supramolecular assemblies with membranes and biopolymers. These modify the original functionalities of both the armed crown ether and the membrane–biopolymer and further exhibit supramolecular functions. Combinations of armed crown ether chemistry with computer chemistry, membrane chemistry and biopolymer chemistry provide interesting possibilities in creating new functional supramolecular assemblies.

Keywords: Crown ethers; Supramolecular assemblies

SSDI 0010-8545(95)01151-X

1. Introduction

There are a number of supramolecular assemblies in nature. These biological assemblies often provide highly ordered microenvironments and specifically integrated functions. Enzymes and biomembranes are typical examples which have survived in long-term evolution [1,2]. They include a variety of organic and inorganic components such as proteins, cofactors, lipids, metal cations, ionophores and other functional elements. Their refined and elegant functions are beautifully controlled by precise molecular recognition between more than two active components. These components are specified and organised to work cooperatively in the protein or membrane matrix. Molecular recognition is an important term not only in natural but also in artificial systems [3]. Crown ethers and related macrocycles are known to mimic some parts of biological molecular recognition and to mediate subsequent chemical processes [4,5]. Since crown ethers bring several ions and/or molecules together around the crown ether rings, they can catalyse reactions in an enzyme-mimetic manner and facilitate membrane transport as do biological ionophores.

Artificial supramolecular assemblies may have advantages over biological assemblies: facile synthesis, high physical stability and versatile molecular structure. Although most artificial systems reported still exhibited functions inferior to those of corresponding biological systems, we are in a position to open the door to the supramolecular world in which artificial supramolecules demonstrate potentialities comparable with nature's evolutionary systems [6]. Thus, our next goal is the establishment of general working principles for the design of supramolecular function based on specific recognition. Since crown ether chemistry provides useful strategies for molecular recognition [7,8], its combination with molecular assembly technology offers many opportunities in this new and fascinating field.

Design, synthesis and functions of a new crown ether family applicable to construction of a supramolecular assembly are described in this review. Although a variety of macrocycles have the potential to develop supramolecular assemblies and functions, we deal here with several examples of "armed crown ethers" [9,10]. These have recently been originated and successfully applied in molecular recognition chemistry and biomimetic chemistry. Other interesting approaches towards supramolecular assembly and functionalisation are reviewed in other contributed papers of this special issue. There are notable successes and promising possibilities in chemistry and its applications.

2. Armed crown ethers: concept and examples

Although a variety of crown ethers has been developed, armed crown ethers are of particular interest [11]. These are characterised by a cation binding crown ether ring and a functionalised sidearm. We can design these molecules so that their parent crown ether and sidearm functionalities operate cooperatively and/or independently as schematically shown in Fig. 1. The structural variation of the sidearm groups extends the molecular recognition ability and/or adds new functions to the parent

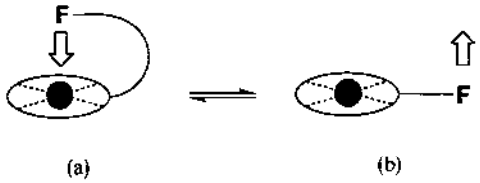


Fig. 1. Cooperative and/or independent action of parent crown ether rings and sidearm functions.

crown ethers. When a potential binding site is introduced on the sidearm, dynamic and three-dimensional complexation can be realised which typically offers a specific ionophore activity. Furthermore the attachment of a catalytic group on the sidearm gives a bifunctional reagent which can catalyse biomimetic reactions.

Double-armed crown ethers, composed of two cation-ligating sidearms and a parent crown ether ring, were originally designed to mimic naturally occurring ionophores [12]. The crown ether ring enforces a rudimentary "hole size" selectivity on the cation complexation, and the sidearm donor provides three-dimensional solvation. Thus, they have flexible molecular structures to wrap guest metal cations completely and dynamically. Since these cation-binding features are closely similar to those of naturally occurring ionophores, double-armed crown ethers are expected to mediate specific cation transport as synthetic ionophores. The carrier-mediated transport, in graphic terms, generally displays a bell-shaped dependence on binding strength: its rate decreases when there is either too weak binding at the entry or too strong binding at the exit of the membrane [13]. Since an effective carrier is required to offer a kinetically fast and three-dimensional complex, with a target species, the armed crown ether is the most appropriate and promising for this purpose.

Three-dimensional encapsulations of metal cations with double-armed crown ethers have frequently been demonstrated in the crystal state. Typically, Gokel and coworkers reported crystal structures of double-armed crown ether **1** and its Na^+ and K^+ complexes. There are striking differences between these three crystal structures as schematically shown in Fig. 2 [14]. In the free form (see Fig. 2(a)), two sidearms are in an *anti* relationship around the crown ether plane and their carbonyl oxygen atoms are pointed away from the crown ether ring. In the presence of a guest metal cation (see Fig. 2(b) or 2(c)), the carbonyl oxygen atoms are pointed

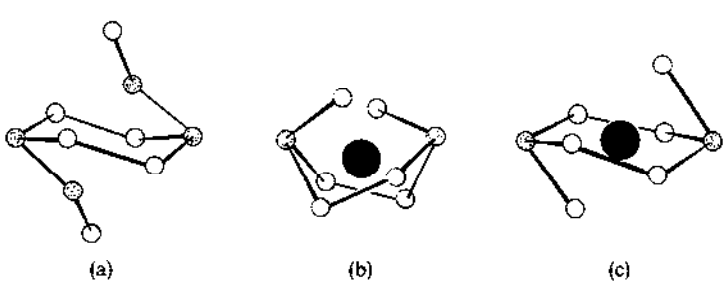
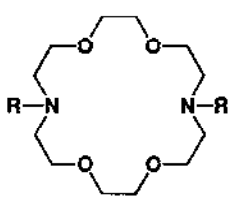


Fig. 2. Skeletal drawings of (a) double-armed crown ether **1** and its (b) Na^+ and (c) K^+ complexes.

into the crown ether ring and are significantly involved in cation coordination. Fig. 2 also reveals interesting structural differences between two metal cation complexes: the Na^+ complex has both of the sidearms on the same side of the crown ether ring while the K^+ complex has one sidearm above and one below the ring. The nature of the guest cation significantly influences the coordination geometry of the armed crown ether **1**. Such crystal structures confirm the "armed crown ether concept" described above and suggest that armed crown ethers have dynamic and three-dimensional ligand topologies usable as effective ionophores.

Depending on the variations of sidearm structures, armed crown ethers bind several cations with varying strength and exhibit interesting transport selectivities. We systematically studied the sidearm effect on the cation binding and transport properties of double-armed crown ethers [5,9,10]. A number of cation-ligating groups have already been attached to the crown ether [15–17], thia crown ether [18,19] and macrocyclic polyamine skeletons [20–22]. Typical examples of double-armed diaza-18-crown-6 derivatives are shown in Fig. 3. In relation to naturally occurring ionophores, double-armed crown ethers **2–4** are notable [23]. They have ester groups at different positions on the sidearms and offer different cation binding behaviours. Fig. 4 illustrates the guest-cation-induced changes in the ^{13}C nuclear magnetic resonance (NMR) chemical shifts of the ester carbons of these armed crown ethers in DMF–D_2O (4:1), together with the optimised structures of their K^+ complexes. Calculations were done using the "extended MM2 program" (CAChe Scientific, version 3.0), although the K^+ ion is not indicated for simplified illustration. Among the ester-armed crown ethers examined, the crown ether **2** appears to have its carbonyl donor groups in the best position to interact with guest cations. Crown ethers **3** and **4** have the ester groups at remote positions and their sidearms may loosely bind guest cations. The carbonyl carbon signal shifts are probably good indications of sidearm coordination and clearly depend on the position of the



	R
1	$-CH_2CONHCH_2CO_2CH_3$
2	$-CH_2CO_2C_2H_5$
3	$-CH_2CH_2CO_2C_2H_5$
4	$-CH_2CH_2CH_2CO_2C_2H_5$

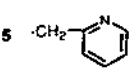
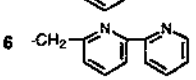
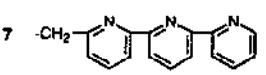
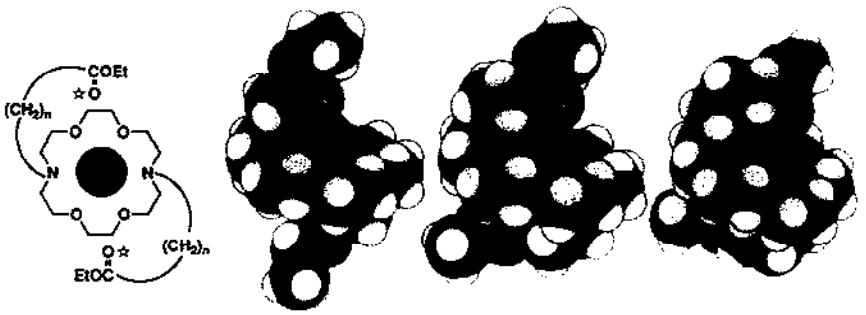
	R
5	
6	
7	

Fig. 3. Typical examples of double-armed crown ether ionophores.



	$\Delta\delta_{CO}$ (ppm)		
	2 (n=1)	3 (n=2)	4 (n=3)
$+K^+$ (1 eq.)	+0.6	+0.4	-0.1
$+Pb^{2+}$ (1 eq.)	+4.4	+0.3	-0.4

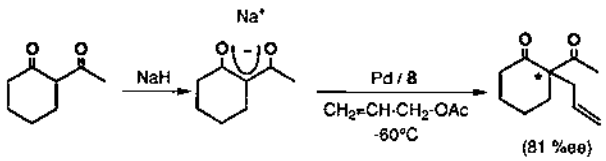
Fig. 4. Optimised structures of ester-armed diaza-18-crown-6 · K^+ complexes and cation-induced values of ester carbon NMR shifts.

carbonyl group as well as the nature of the guest cation. These computer modelling and ^{13}C NMR studies confirm that the ester group of the crown ether **2** provides the most effective coordination with the guest cation. In other words, cooperative binding of the crown ether ring and sidearm can be realised when the arm donor group is sterically disposed to permit coordination with the guest cation trapped in the crown ether ring.

Arm functionalisation successfully modified the transport efficiency and selectivity of the parent crown ether. Typically, ester-armed diaza-18-crown-6 **2** transported Na^+, K^+, Ba^{2+} and Pb^{2+} ions across a chloroform liquid membrane much more effectively than did unsubstituted diaza-18-crown-6. Crown ethers **3** and **4** having ester groups at remote positions, on the contrary, exhibited no enhancement of transport efficiencies. These results are almost parallel to those of computer calculations and ^{13}C NMR binding experiments described above. When the crown ether **2** was employed, cooperative binding of the ester-functionalised sidearms and the diaza crown ether ring produced stable and dynamic complexes and enhanced transport efficiencies for several metal cations. Oligopyridine-armed diaza-18-crown-6s **5**–**7** also exhibited interesting sidearm effects on cation binding and transport profiles [17]. Pyridine-armed crown ether **5** exhibited a larger extraction percentage for K^+ ion than crown ethers **6** and **7**, while bipyridine and terpyridine derivatives **6** and **7** offered the highest extraction abilities for Ba^{2+} and Pb^{2+} ions respectively. A functionalised sidearm of the proper chain length and geometrical arrangement provided for specific encapsulation of the guest cation which was beneficial for recognition and transportation.

Armed crown ethers provide another basis for construction of intelligent molecular

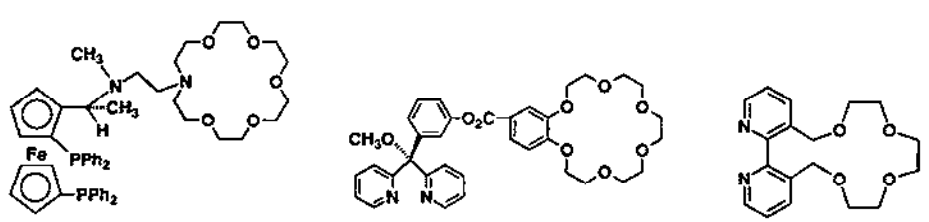
devices if the cation-ligating or reactive sidearm behaves independently of the parent crown ether ring. When a catalytically active group is located on the sidearm, the armed crown ether can catalyse a specific and efficient reaction in an enzyme-mimetic manner. Itoh and coworkers attached chiral ferrocenylphosphine ligand to a crown ether structure (see armed crown ether **8**; Fig. 5) [24]. Its palladium complex greatly accelerated asymmetric allylation of unsymmetrically substituted β-diketones and attained high enantioselectivity:



(1)

Since the crown ether ring accommodates not only cationic guests but also anionic guests which are tightly paired with countercations [25], a ternary complex involving this crown ether and the Na^+ ion of the substrate anion attacked a π-allylpalladium-phosphine intermediate. Such proximity and orientation effects via ternary complexation are frequently observed in biological enzymatic reactions. The complexation of a bifunctional substrate was similarly proposed in a palladium complex with the armed crown ether **9** [26]. Although a limited number of examples have been reported, armed crown ethers have potential as intelligent and smart molecular assemblies exhibiting specific catalytic activities.

Gund and Keppler combined a metal complex with a crown ether for a different purpose [27]. They prepared a platinum complex with bipyridine-functionalised crown ether **10** because *cis*-diaminedichloroplatinum(II) and its bipyridine complexes have been subjects of much attention in cancer therapy. In order to reduce toxic side effects while maintaining therapeutic efficiency, they chose to use the bipyridine-functionalised crown ether **10**. The crown ether structure is bulky enough to suppress the degradation process and to enhance solubility in both hydrophilic and lipophilic media. Thus, the platinum complex with crown ether **10** was expected to have increased membrane permeability and high therapeutic efficiency, although no clinical test has yet been done. These examples demonstrate that the armed crown ether



8 **9** **10**

Fig. 5. Typical examples of armed crown ether reagents.

can be useful as a building block for many purposes such as the development of ionophore, catalyst and other functional devices.

3. New synthetic approaches to armed crown ethers

A variety of armed crown ethers has already been prepared, but their molecular design remains an essentially empirical exercise. Since many trials are required in the refinement of the structure of the armed crown ether, computer-aided molecular design is a promising avenue [28–31]. Metal complexes with crown ethers have been characterised using molecular orbital, molecular mechanic, molecular dynamic, and Monte Carlo calculations. These techniques proved very useful to estimate quantitatively the cavity size of the crown ether ring and the solvation energy of the guest metal cation. Computer calculations can be challenged but may offer new possibilities in "non-empirical" design of a specific armed crown ether.

Li^+ ion specific ionophores are important tools for analysis and separation in biological and environmental systems. Among the many crown ethers examined, 13-crown-4 and 14-crown-4 compounds were recognised as excellent Li^+ ion ionophores for practical uses [32]. Since the diameter of the Li^+ ion is formally size fitted to the 12-crown-4 cavity, we applied a modified neglect of differential overlap (MNDO) calculation to the design of Li^+ ion specific armed crown ethers having 12-crown-4 rings [31]. Fig. 6 illustrates the optimised structures of two different types of complexes between 12-crown-4 and Li^+ ion which have D_{2d} and C_{4v} symmetries [30]. There are interesting structural differences even though the same crown ether and the same guest cation were employed. When D_{2d} symmetry is assumed, the Li^+ ion is completely accommodated in the hole of the 12-crown-4 and looks very comfortable (see Fig. 6(a)). On the contrary, the Li^+ cation is located above the crown ether ring and interacts with a counteranion in the C_{4v} complex (Fig. 6(b)). The stabilisation energy including the anion effect for the C_{4v} complex

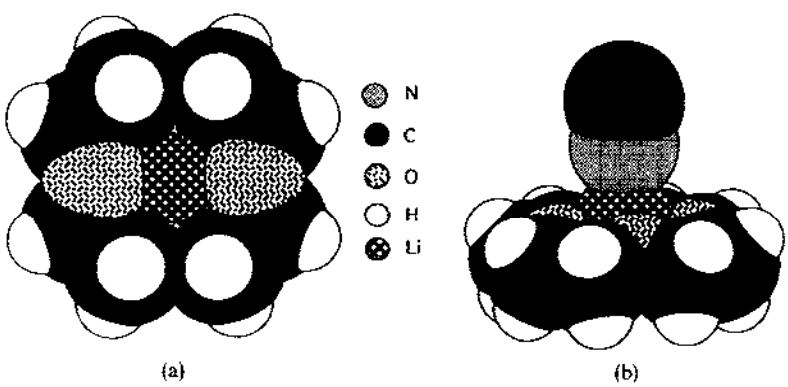


Fig. 6. Optimised structures of (a) the (12-crown-4)·Li^+ complex with D_{2d} symmetry and (b) the (12-crown-4)·Li(NCS) complex with C_{4v} symmetry.

is much larger than that for the D_{2d} complex. The D_{2d}-type complex structure seems to satisfy the "size-fitting concept", but all the solvents and counteranions must be removed before complex formation; these processes involve large energy loss. Thus, our computational studies strongly suggest that the cation-ligating sidearm should be attached to the 12-crown-4 ring to stabilise Li^+ complex as calculated in the C_{4v} complex.

We optimised the Li^+ ion complexes with various armed aza-12-crown-4 derivatives. Fig. 7 displays a typical optimised structure of the Li^+ complex with *N*-aminoethylaza-12-crown-4 in which the amino nitrogen atom on the sidearm acts as an effective binding site. The Li^+ ion was cooperatively coordinated with the amine-functionalised sidearm and the parent aza-12-crown-4 ring. Ether-, ester- and other armed aza-12-crown-4 derivatives were supported to form similar three-dimensional complexes with Li^+ ion, but combined energy estimations of the 6-31G basis set with MNDO optimised geometries demonstrated that the Li^+ complex of the amine-armed crown ether offered the greatest stabilisation energy. Such an encapsulated and stable complexation is ideal as a picture and may offer specific Li^+ ion recognition and transportation.

We prepared a series of armed aza-12-crown-4 derivatives **11–15** which had amine-, ether-, ester-, and nitrile-functionalised sidearms (Fig. 8) and compared their cation complexation behaviours with those predicted [33]. Amine-armed crown ethers **11** and **12** actually exhibited excellent Li^+ ion selectivity while other aza-12-crown-4 derivatives **13–15** diaplayed Na^+ ion selectivity. ^7Li and ^{13}C NMR titration experiments revealed that only an amine-functionalised sidearm provided specific coordination with the Li^+ ion trapped in the aza-12-crown-4 ring, while other ligating sidearms interacted at random with various metal cations. These amine-armed aza-12-crown-4s selectively encapsulated Li^+ ion and specifically transported it, although ether-, ester- and nitrile-armed crown ethers **13–15** transported Na^+ ion more efficiently. Their transport efficiencies were compared with those of 14-crown-4 **16**, which is a commercially available ionophore specific for the Li^+ ion [34]. Interestingly, the amine-armed crown ethers **11** and **12** exhibited higher transport rates for Li^+ ion than 14-crown-4 **16**. Thus, computer chemistry provided an effective guideline for designing ion-specific armed crown ethers.

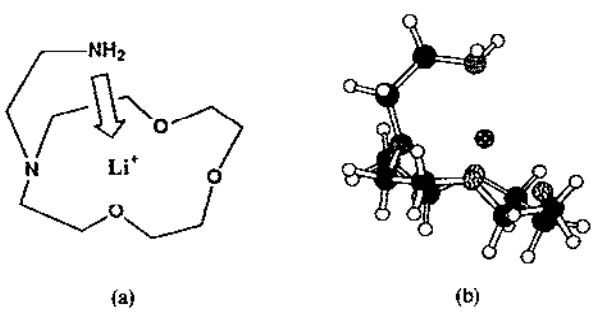


Fig. 7. Optimised structure of the *N*-aminoethylaza-12-crown-4 · Li^+ complex.

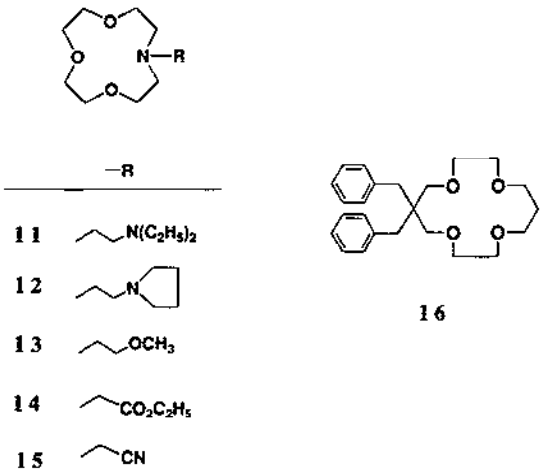


Fig. 8. Li^+ ion specific armed crown ethers as ionophores.

4. Armed crown ether complexes in membrane assemblies

Both natural and artificial surfactants form micelles, bilayer vesicles, liquid crystals and related membrane-type assemblies. These are oriented arrays of molecules and useful vehicles for the ordering of functionalised components in a supramolecular fashion [2]. As proposed in the fluid-mosaic model, biomembrane assembly is composed of phospholipids and glycolipids as a matrix, and incorporates proteins, receptors, ionophores and other functional elements either on the surface or in the interior. There is a variety of molecular motions: lipids undergo rotation and segmental motion, kink formation and transverse flip-flop motion; functional molecules diffuse laterally in the plane of the membrane; selective ordering and segregated domains are often produced. Lipid–protein and lipid–ionophore interactions have been extensively investigated. These sometimes lead to denaturation and/or conformational changes of protein and ionophore, which substantially control membrane permeabilities of proton, ion and small molecules.

A synthetic membrane assembly can solubilise, concentrate, compartmentalise, organise and localise several active species in a similar fashion to a biomembrane. Since this may provide a specific microenvironment for molecular recognition, armed crown ethers can offer different cation recognition and subsequent chemical functions in the membrane assembly. Two ambitious approaches have already begun along this line: (i) self-assembly of an armed crown ether surfactant (Fig. 9(a)) and (ii) hybrid assembly of an armed crown ether with a membrane-forming surfactant (Fig. 9(b)). We can construct a variety of structurally organised and functionally integrated supramolecular systems by combining armed crown ethers with membrane-type assemblies [5,35].

Echegoyen and Shinkai independently prepared cholesteryl-armed crown ethers which formed vesicle and liquid crystal respectively (Fig. 10). Crown ether **17** aggre-

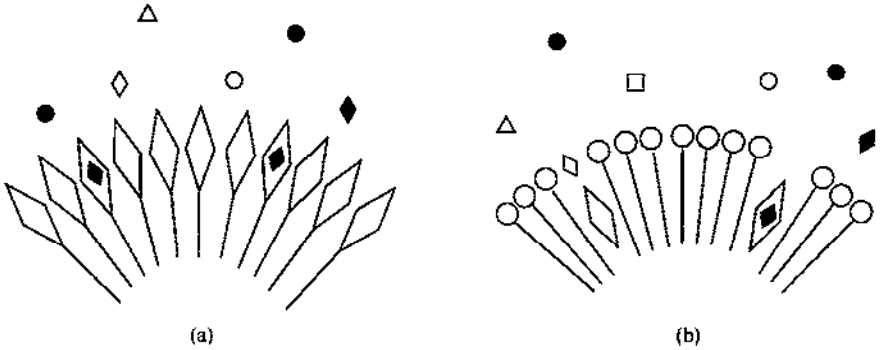
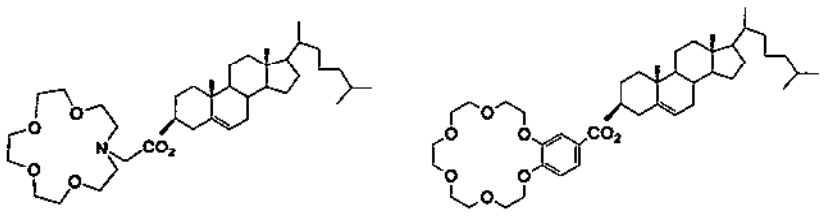


Fig. 9. Schematic illustration of supramolecular assemblies with membranes.



17 18

Fig. 10. Typical examples of cholesteryl-armed crown ethers.

gated in water and formed a nonionic liposome in which the crown ether ring acted as an amphiphile and the cholesteryl arm gave high lipophilicity [36]. This crown ether bound Na^+ and K^+ ions in homogeneous solution but Na^+ or K^+ ion only slightly influenced the size of its liposome. Different factors may be involved in membrane assembly from in a solution. A mixture of crown ether **18**, cholesterol nonanoate and cholesterol formed cholesteric liquid crystals. Addition of an amino acid ester salt interestingly changed the helical pitch of the resulting liquid crystals and remarkably induced colour changes in an enantioselective manner [37]. The binding of a chiral ammonium salt with the 18-crown-6 ring was thought to act as an effective trigger for structural change in the liquid crystal assembly. This may lead to colour detection of the chirality of amino acid derivatives.

Hybrid assemblies of armed crown ethers and membrane-forming surfactants have been made to mimic biological cation transport processes: ionophore and channel. In addition to many examples of ionophore models [38], Fyles et al. [39] and Lehn et al. [40] presented cation channel models based on 18-crown-6 derivatives **19** (Fig. 11). When these armed crown ethers were incorporated into the closed vesicle of phospholipid, a molecular channel was spontaneously formed across the vesicle. A metal cation permeated through the channel composed of crown ether **19**. Several types of armed crown ethers and related macrocycles were designed further to construct cation-conducting channels [41].

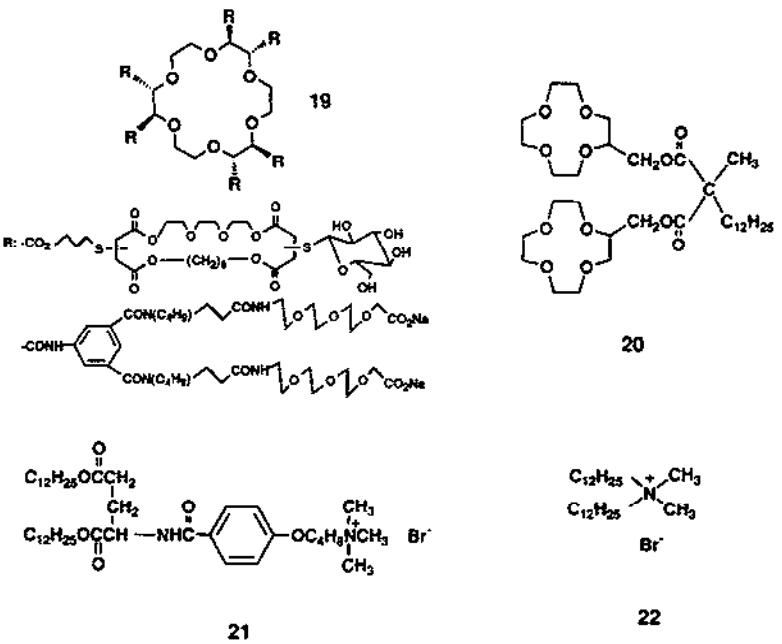


Fig. 11. Armed crown ethers and synthetic surfactants for membrane assembly.

Some armed crown ethers exhibited different cation recognition abilities in hybrid membrane assemblies from those in solution systems. Nakashima et al. reported a highly Na^+ ion selective membrane assembly which was composed of lipophilic bis-12-crown-4 **20** and chiral lipid chromophore **21** [42]. Its cation extraction process from bulk aqueous to membrane assembly phases was monitored by circular dichroism spectroscopy. This bis crown ether **20** demonstrated greatly amplified Na^+ ion selectivity in the hybrid membrane assembly, although it exhibited modest Na^+ ion selectivity in homogeneous solution [43].

Tsukube et al. introduced several armed crown ethers into a membrane assembly composed of quaternary ammonium surfactant **22** [44]. The membrane assembly was easily prepared by dispersing an aqueous solution of lipophilic armed crown ether **7** and membrane-forming surfactant **22**. When metal salt was added, Cu^{2+} ion was very effectively extracted by the armed crown ether **7** from bulk aqueous into the membrane phases. The resulting Cu^{2+} complex was immediately precipitated with membrane aggregate by addition of $Mg(ClO_4)_2$ salt and easily separated from the aqueous solution by filtration. Although the armed crown ether **7** bound various transition metal cations in homogeneous solution [17], Ni^{2+}, Co^{2+}, and Zn^{2+} ions were poorly extracted by this membrane assembly. The hybrid membrane assembly may provide an effective microenvironment for specific metal extraction and recognition.

Recently many types of monolayer assemblies were investigated which were composed of armed crown ether, cyclophane, calixarene and other ligand surfactants

[45]. Since monolayers are not as rigid as bilayers, most of them exhibited parallel guest recognition behaviours to those observed in the solution systems. In contrast, bilayer membrane assemblies were confirmed to provide highly specific microenvironments for unique molecular recognition. Armed crown ethers vary widely in structure and offer interesting guest recognition abilities in both solution and membrane assembly. Many kinds of applications may be envisaged in biomimetic, separation and related chemistry.

5. Armed crown ethers in biopolymer assemblies

Proteins, nucleic acids and other functional biopolymers can be good guests for armed crown ethers. Although these are too large to form 1:1 complexes, the crown ether can bind $-NH_3^+$, $-CO_2^- M^+$, $-PO_4^- M^+$ or other functional moieties exposed on the biopolymer surface and form supramolecular complexes (Fig. 12(a)). When the biopolymer is wrapped by a number of crown ethers and forms a hybrid supramolecular assembly, its solubility, stability, reactivity and further functions are modified.

Some proteins are known to form this type of supramolecular assembly with crown ethers. Odell and Earlam reported that 18-crown-6 and cryptand [2.2.2] were excellent complexing agents for various proteins [46]. The crown ether complexed with the polar surface of the protein and allowed its dissolution into non-aqueous media. For example, cytochrome c, water-soluble haem protein, contains 19 lysine groups to be complexed with crown ether and cryptand. When 120 equivalents of 18-crown-6 were added to a suspension of cytochrome c, the cytochrome c was immediately solubilised in methanol and a clear solution was readily obtained. Bovine serum, lysozyme and other proteins were similarly solubilised in organic media via supramolecular complexation with a crown ether. Since a dendrimer type of crown ether oligomer was recently reported to solubilise myoglobin in DMF [47], the crown ether can coat a variety of hydrophilic biopolymers and form lipophilised supramolecular assemblies.

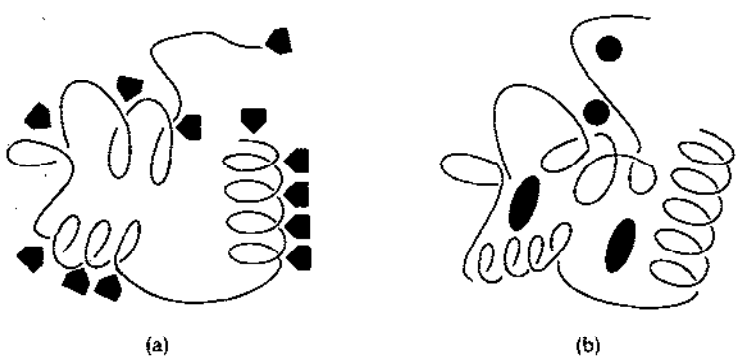
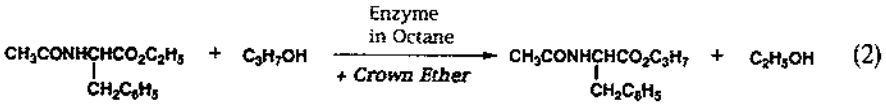


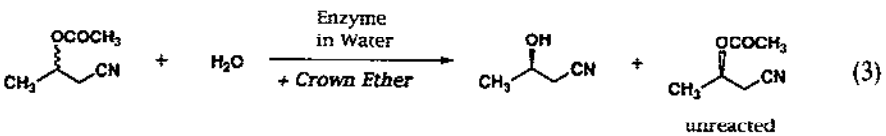
Fig. 12. Schematic illustration of supramolecular assemblies with biopolymers.

Crown ether–biopolymer assemblies have broad applications in bioscience and biotechnology because they may exhibit activities different from those of the native assemblies [48]. Enzymes are effective biological catalysts but promote reactions of various non-biological substrates in organic solvents [49]. Enzymatic reactions in organic solvents generally have many advantages: high solubility of organic substrates; enhanced thermal stability of enzymes; elimination of undesired side reactions; protection from water. Since their reaction rates and stereoselectivities are largely dependent on the nature of the solvent employed, several media other than water have been investigated. Reinhoudt et al. reported the effect of crown ether on enzyme-catalysed reactions in apolar organic solvents [50]. The transesterification of *N*-acetyl-L-phenylalanine ethyl ester with propanol was examined in octane:



(2)

Addition of 18-crown-6 increased rates of α-chymotrypsin- and subtilisin-catalysed reactions 4.1- and 2.0-fold. They proposed that the crown ether enhanced solubilities of these enzymes in the octane used and accelerated the reaction rates. Itoh et al. demonstrated that crown ethers enhanced the reactivity of hydrolytic lipase [51]. In the hydrolysis of β-acetoxybutyronitrile, several crown ethers accelerated both rate and enantioselectivity:



(3)

Although the detailed mechanism is not clear, the reactivity of the lipase was controlled by supramolecular complexation. Thus, a biopolymer assembly with a crown ether can be considered a promising supramolecular catalyst in organic synthesis.

A biopolymer can also act as a host for an armed crown ether. Enzymes and other proteins have binding sites for specific substrates around the active centres and for effectors at the allosteric sites (Fig. 12(b)). When a crown ether is accommodated in these binding sites, the activity of the host biopolymer is strongly influenced and modified. Inhibition and/or activation of the enzyme is a typical example [52].

Tsukube et al. first attempted to use armed crown ethers **23–27** as substrates in lipase-catalysed hydrolysis (Fig. 13) [53]. The lipase hydrolysed these non-biological esters, and the reaction rates were largely dependent on the natures of the parent crown ether and the metal salt added. Among them, 12-crown-4 ester **23** offered the most enhanced reactivity and the highest enantioselectivity in the presence of an Na^+ salt, while Li^+ and K^+ salts influenced only reaction rates. Fast atom bombardment mass spectroscopy, ^{13}C NMR and computational studies revealed that this crown ether substrate formed a diastereomeric 2:1 Na^+ complex: the Na^+ ion was

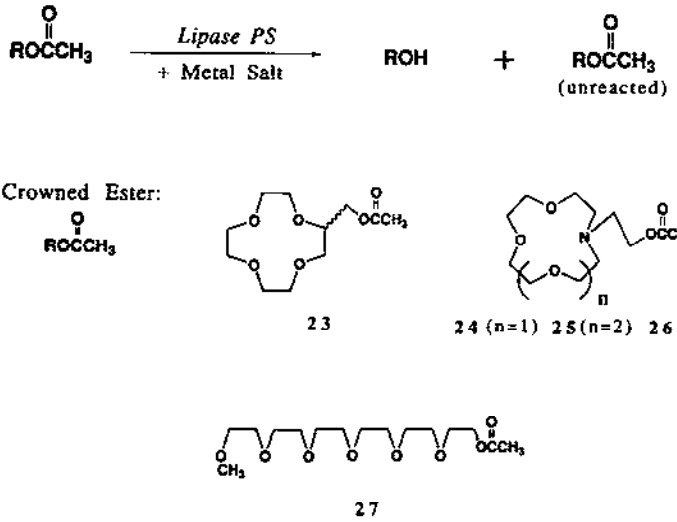


Fig. 13. Lipase-catalysed hydrolysis of crown ether substrates.

sandwiched between two chiral crowned substrates. The lipase employed has a relatively large cavity for substrate binding and may recognise the chirality of the diastereomeric 2:1 complex in the reaction course. In other words, the armed crown ether–Na^+ complex can be a specific substrate for the lipase.

RNA and DNA themselves form supramolecular assemblies. They have effective pockets between cumulated nucleic acid bases and polyanionic backbones as cation-binding sites [54]. Although a number of drugs have been synthesised to interact specifically with nucleic acids, Takagi and coworkers designed armed crown ether **28** (Fig. 14) as a DNA binder. This has a 15-crown-5 ring and an acridine-functionalised sidearm [55], and exhibited interesting DNA-binding affinity in the presence of K^+ or Na^+ cations. They proposed cooperative actions of the crown ether ring and the acridine sidearm; the crown ether–M^+ complex interacts with phosphate anion on the polymer backbone and acridine inserts between the cumulated bases. Kerwin synthesised crown ether **29** including a DNA-cleaving propargylic sulphone [56]. Since the crown ether moiety interacts with the polyanionic DNA as a metal cation complex, the propargylic sulphone is expected to be fixed on the DNA chain and to exhibit increased activity in the presence of Na^+ and K^+ cations. These

Fig. 14. Typical examples of armed crown ethers for binding of nucleic acids.

examples demonstrate that the introduction of crown ether structure into a DNA-detecting or cleaving reagent enhances its affinity and reactivity. Therefore, crown ethers are unique and useful chemical tools in diverse areas of bioscience and biotechnology.

6. Concluding remarks

Armed crown ethers are particularly interesting molecular elements in supramolecular science and technology. They can exhibit specific cation recognition properties and also mediate ion transport and catalytic reactions. The synthetic strategies for this class of compounds have been established and a variety of functionalities have been successfully introduced via molecular architecture. We also demonstrated here that armed crown ethers formed unique and interesting supramolecular assemblies with membranes and biopolymers. These modified the original functionalities of both the armed crown ether and the membrane–biopolymer and further exhibited supramolecular functions. In this review we have therefore described good examples of supramolecular functions based on molecular recognition. Although the number of investigations to date is limited, combinations of armed crown ether chemistry with membrane chemistry, biopolymer chemistry and related knowledge will undoubtedly allow us to evolve a more intelligent and smart supramolecular assembly and to expand our horizons of supramolecular chemistry.

Acknowledgements

The author is grateful to Professors Jun-ichi Uenishi of Okayama University of Science and Toshiyuki Itoh of Okayama University for their valuable discussion. He also thanks the American Chemical Society for granting permission to reproduce Fig. 2. This work was partially supported by the Nishida Research Fund for Fundamental Organic Chemistry.

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