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Practical applications of supramolecular chemistry

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This year marks the 50th anniversary of Charles Pedersen's discovery of crown ethers, what is widely considered the birth of supramolecular chemistry. Since then, the field has progressed greatly, winning two Nobel Prizes and seeing the implementation of many practical applications. In commemoration, we are exploring the more recent advances of the field, which have made it past the realm of chemistry, into the real world. Though not a comprehensive review, the topics that we discuss here are supramolecular sensors, imaging for medical applications, metal extraction from ores and nuclear waste, as well as drug delivery.

Introduction

Over the past 50 years, the field of supramolecular chemistry has gone through a massive evolution, branching into so many directions that it has developed its own subcategories. The field has won two Nobel Prizes, beginning with Charles Pedersen, Donald J. Cram, and Jean-Marie Lehn's 1987 award for their development of crown ethers, carcerands, and cryptands, and culminating most recently in the 2016 award to Jean-Pierre Sauvage, Sir J. Fraser Stoddart, and Bernard L. Feringa for their introduction and advance of molecular machines. The chemistry of this field has particularly advanced in the last two decades, giving rise to many real-world applications, a few of which we highlight here.

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In 1967, while working at DuPont, Charles Pederson discovered that cyclic ethylene glycols could bind cationic metals in solution. Furthermore, by tuning the size of his so-called crown ethers he was able to achieve selectivity of binding to specific metals.[1,2] In a biphasic setting, like in the case of water/benzene, it was shown that a salt could be dissociated in the aqueous layer, a resulting cation trapped by a crown ether, and because of its solubility in both solvents, the crown ether could then transfer the cation into the organic layer.[2] Just 2 years later, Lehn and coworkers were able to take the two-dimensional chemistry of crown ethers into three dimensions by synthesizing nitrogen-containing bridged crowns, called cryptands, and using them as host molecules.[3–5] This was later further expanded upon in D. J. Cram's research group with the introduction of cavitands, three-dimensional hollow molecules that can encapsulate guests in their chamber,[6] and carcerands, cage-like host molecules that

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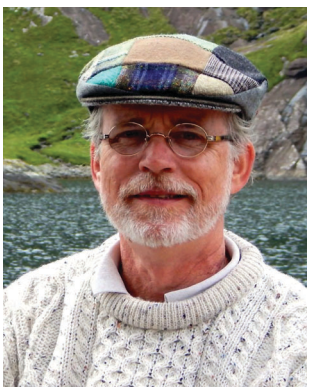

Eric V. Anslyn

Eric V. Anslyn is originally from California and received his BS degree in chemistry from California State University, Northridge. He then moved to the California Institute of Technology do his PhD with Robert H. Grubbs, followed by a postdoc at Columbia University with Ronald Breslow. In 1989 he joined the Organic Chemistry faculty at the University of Texas at Austin. He has made his mark as a physical organic and supramolecular chemist, contributing to both subfields in a career that has spanned almost three decades.

irreversibly bind guests.[7] The advances in this chemistry led to improvements in phase transfer catalysis,[8] where the respective host molecules serve as the phase transfer catalysts, bringing insoluble, charged species from polar solvents into nonpolar, aprotic media.

Supramolecular chemistry in sensing

In the early to mid-1990s, A. P. deSilva was among a group of supramolecular chemists that combined the concepts of host–guest chemistry and fluorescence, leading the field of supramolecular chemistry into the realm of optical sensing. He achieved this by attaching a crown ether to a fluorophore system capable of photoinduced electron transfer (PET). In the presence of sodium the crown would become bound, pulling electron density away from the aromatic ring to which it was attached and interrupting the PET quenching. This would allow fluorescence to be "turned on," and based on its intensity the concentration of sodium present could be calculated (Fig. 1).[9–12] This system was fine-tuned to give distinct responses for other ions, such as calcium and potassium, and is now used to measure blood ion concentrations in both humans and animals in real time.

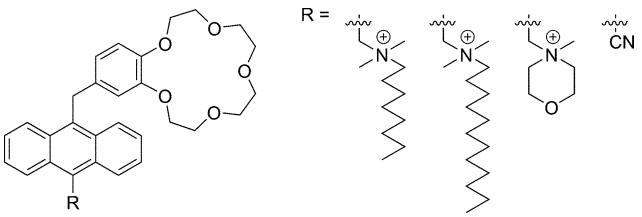

Fig. 1 Structures of various fluorescent sodium sensors.

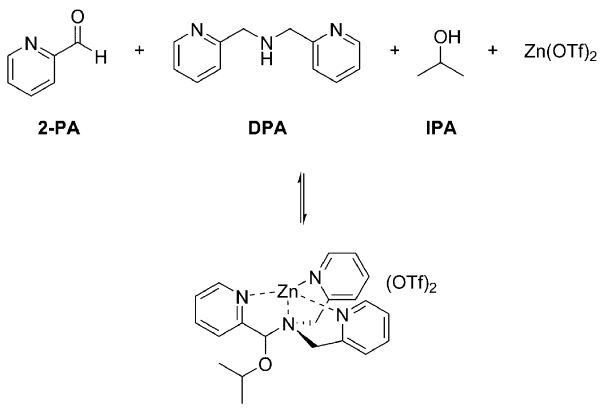

Fig. 2 Reversible addition of a secondary alcohol to an *in situ*-generated iminium from the condensation of **DPA** with **2-PA**.

Furthering the progress of "supramolecular analytical chemistry," a term coined by our group,[13] in 2011 we introduced a dynamic multi-component covalent assembly that set the foundation for chirality sensing of secondary alcohols using circular dichroism (CD). The assembly was completed by the addition of an alcohol to an *in situ*-generated tris(pyridine)-based iminium, allowing the pyridines to bind to a zinc cation in solution (Fig. 2). The resulting helical twist of the assembly could then be used for optical chirality sensing.[14] Similar work was later published on the CD-aided enantiomeric excess (ee) determination of chiral amines using a modified assembly with iron in the place of zinc.[15]

In early 2015, James and coworkers were able to introduce yet another sensor, which made use of supramolecular interactions, to the public. The fundamental chemistry involved was closely based on the science James developed with Seiji Shinkai some twenty years earlier, where a phenylboronic acid with an amino methyl group in the *ortho* position was shown to bind saccharides at physiological pH. When this system was attached to a fluorophore it was postulated to undergo PET quenching, due to the presence of the free lone pair on the amine. However, when the boronic acid would bind a saccharide, the lone pair would become involved in the binding, disrupting the PET, and "turning on" fluorescence.[16–18] This same concept was applied to James's recent GlySure Continuous Intravascular Glucose Monitoring Sensor (CIGMS), but now using two such [*o*-(aminomethyl)phenyl]boronic acids and a six carbon linker between the amines, making the receptor selective for glucose over other sugars (Fig. 3). This chemistry has since been incorporated into central venous catheters (CVCs), which are routinely inserted into the right internal jugular veins (RIJV) of patients in intensive care units. Testing of these has shown a vast improvement in the accuracy of blood glucose monitoring over conventional methods, with the added benefit of continuous, as opposed to intermittent, examination of glucose levels.[19]

Supramolecular chemistry in molecular imaging

Since entering the field of supramolecular chemistry in the early 1990s, Brad Smith has played an important part in many

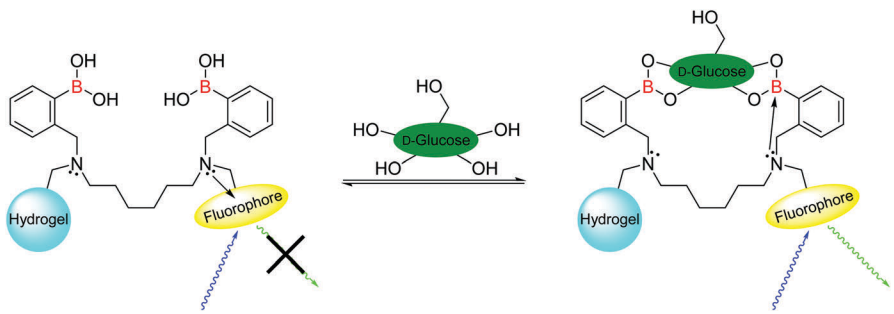

Fig. 3 GlySure CIGMS sensing mechanism.

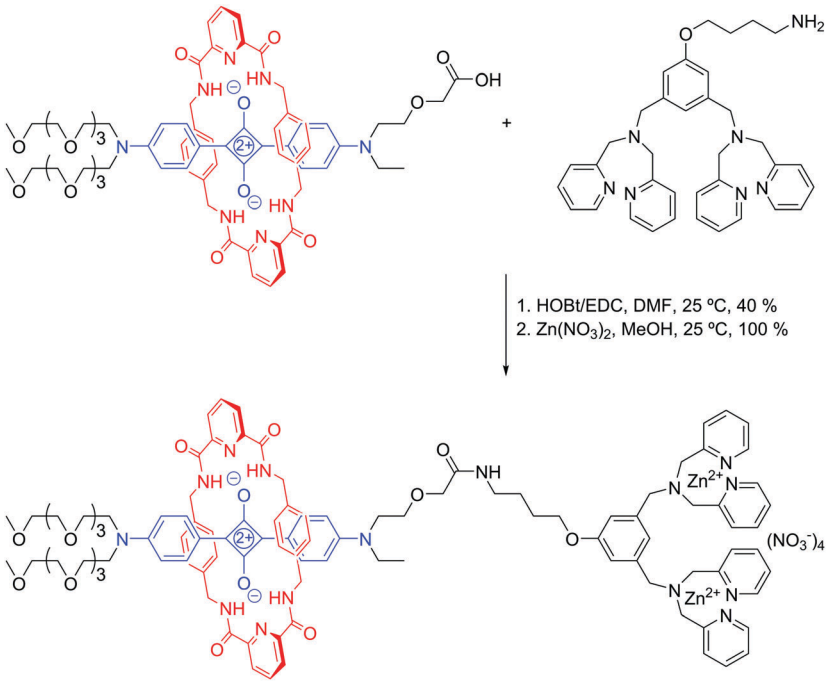

Fig. 4 Bis-ZnDPA conjugated squaraine rotaxane.

of its subcategories, including membrane transport, ion-pair receptors, and rotaxane synthesis, eventually combining the latter with his parallel work in molecular imaging. A rotaxane is an intermolecular complex comprised of a guest that is threaded through a macrocyclic host molecule and capped on both ends with functionalities preventing the macrocycle from falling off. Much of Smith's initial work in imaging was built on fluorescent probes attached to zinc dipicolylamine (ZnDPA) anionic receptors, first introduced by Hamachi and coworkers.[20] While developing new fluorophores with red and near infrared (IR) emissions, Smith's group discovered the improved stability and fluorescent properties of squaraine dyes upon encapsulation in a host, like a tetralactam macrocycle, creating a squaraine rotaxane.[21,22] They showed that the anionic oxygens on the squaraine core formed four hydrogen bonds with the amides in the macrocycle and were also able to tune selectivity for bioconjugation by attaching different moieties, such as the aforementioned ZnDPA receptor, to the ends of the squaraine dye (Fig. 4). While none of these imaging agents have yet found a use in human medicine, many are in preclinical trials and over twelve are now commercially available and used for studies in animal models.[23]

Metal extraction

Although not strictly-speaking an organic technique, hydrometallurgy, a subset of extractive metallurgy which involves using aqueous extractions for obtaining metals from ores, has even found a very important use for host–guest chemistry. When an ore is first exposed to a highly acidic aqueous solution, the different metals contained are leached out as salts of the acid used. This aqueous solution is then exposed to an immiscible organic solvent containing ligands that bind to specific metals in the mixture. Once the cationic metal of interest is extracted into the organic phase it is again exposed to an acidic aqueous solution to "strip" the metal from the ligand, allowing the organic phase to be recycled as an extracting solvent, while the metal is reduced by electrolysis and isolated.[24,25] For the past twenty years Peter A. Tasker, at the University of Edinburgh, has been developing ligands to specifically bind copper for hydrometallurgical extraction. He has shown that phenolic oximes are particularly selective for copper over other metals at low pHs because the cavity formed between two such oximes is an exact fit for the copper.[26] The strength of binding can be further tuned by flanking the oxime with different functional groups to "buttress" the ligands' hydrogen bonding, with hydrogen bond acceptors increasing the binding affinity (Fig. 5).[24] As of 2013, these oximes and the methods described above were accounting for about 25% of the world's copper recovery from crude ores.[25]

In similar fashion, host–guest chemistry has been used to extract radioactive cesium out of high-level nuclear waste. Pioneered by Bruce A. Moyer of Oakridge National Lab, the caustic-side solvent extraction (CSSX) process has been in use for this purpose since 2008, particularly at the Savannah River Site (SRS). Moyer's research group began developing ligands, based on calixarenes with appended crown ethers, to bind cesium in the late 1990s and early 2000s. By adjusting the lipophilic groups on the crowns they were able to control the solubility of the ligands in alkane solvent mixtures without greatly affecting the affinity of the ligands for cesium. As a result, when extractions were performed on industrial scale, the newly developed calix[4]arene-bis-(*tert*-octylbenzo-crown-6)

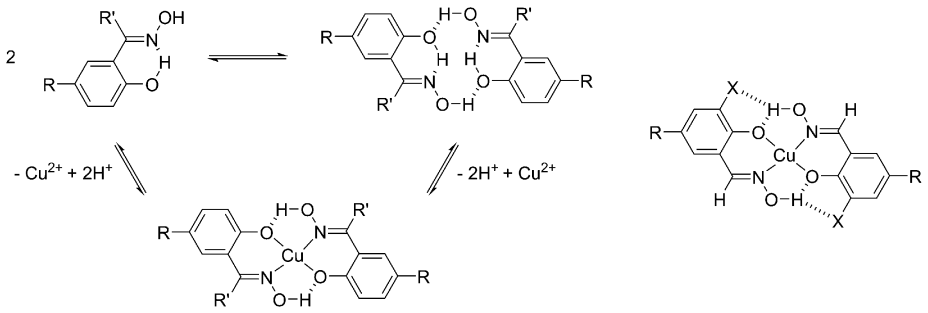

Fig. 5 (left) Copper binding into the cavity between two phenolic oximes. (right) "Buttressing" of ligand hydrogen bonding.

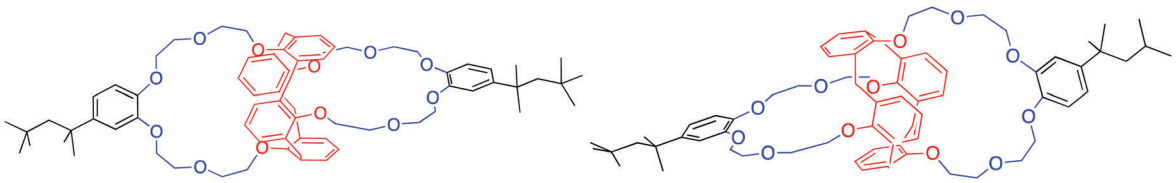

Fig. 6 Two views of calix[4]arene-bis-(*tert*-octylbenzo-crown-6) Cs extractant. The colors are meant to emphasize the 3-dimensionality of the host, with the red portion highlighting the calix[4]arene core structure and the blue representing the crown ethers.

hosts showed an improved ability to prevent emulsion formation between the aqueous and alkane solvents (Fig. 6).[27] With the development of certain additives, Moyer and coworkers were able to fine-tune the binding of cesium in the waste streams, while also improving the tolerance of the extracting solvent to lipophilic anion impurities from the waste and resistance of the solvent to thermal and radioactive decay.[28]

One of the most readily available and widely used families of supramolecular host molecules is cyclodextrins (CDs). These toroid-shaped macrocyclic rings, consisting of α-1,4-linked sugar molecules in an arrangement that gives two hydrophilic portals around a single hydrophobic cavity, are both inexpensive and environmentally benign. Over the last 40 years they have been used to encapsulate a broad range of different organic,[29–31] organometallic,[32–34] and inorganic[35,36] guests.

In 2013 Stoddart and coworkers reported the first example of using a cyclodextrin to capture a gold species.[37] In this first instance the group tested the abilities of α-, β-, and γ-cyclodextrins (6-, 7-, and 8-membered macrocycles of glucose, respectively) to separately bind $KAuCl_4$ and $KAuBr_4$. While they found that complexation occurred in all 6 of these cases (single crystals were grown and solved for all combinations of hosts and guests), they noticed that the $KAuBr_4$ combination with α-cyclodextrin (α·Br) was quite different from the rest. Unlike the other five cases, the α·Br complex showed a 1:2 binding stoichiometry of $KAuBr_4$ to α-CD, with the square planar $[AuBr_4]^-$ anion being sandwiched between the primary hydroxyl faces of two separate α-CDs and the octahedral hexahydrate of the potassium counter-ion $[K(OH_2)_6]^+$ fitting between the two α-CDs' corresponding secondary hydroxyl faces (Fig. 7). This highly ordered packing of face-to-face CDs around the described counter-ions allows for the formation of needle-like nanowire crystals with lengths exceeding 20 nm.[37] When aqueous solutions of $KAuX_4$ (X = Cl, Br) were independently combined with aqueous α-, β-, and γ-CD solutions the α·Br complex displayed yet another distinctive property in the formation of a precipitate within 1–2 minutes of combining the two components of the mixture, while the other solutions remained homogeneous. This characteristic opened up the possibility of using α-CD for the

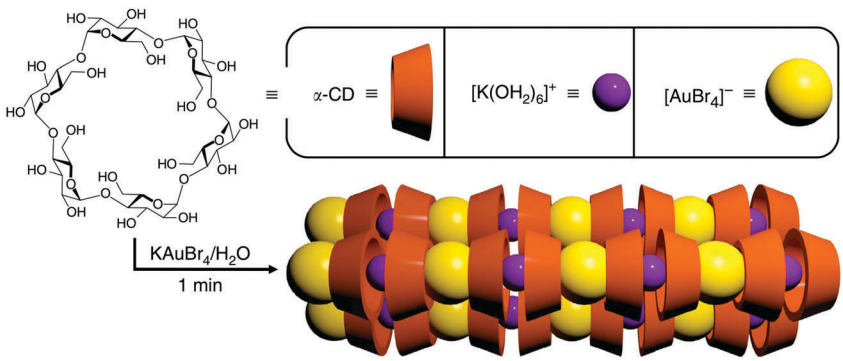

Fig. 7 Highly ordered packing of the α·Br complex. Reproduced with permission from ref. 37. Copyright 2013, Nature Publishing Group.

"green" recovery of gold from crude ores, which the Stoddart group quickly realized, developed a full method for achieving, and patented in 2014.[38] Since developing the patented methodology, the Stoddart group has extended the binding studies to similar gold species, with varied Na^+, Rb^+, and Cs^+ cations, while keeping the assortment of Cl^- and Br^- anions and α-, β-, and γ-CDs constant. While the assay showed that co-precipitates of α-CD could form with $RbAuBr_4$ and $CsAuBr_4$ in addition to $KAuBr_4$, the most efficient and high-yielding crystallization was afforded by the already established α·Br complex.[39]

Drug formulation and delivery

The straightforward synthesis and derivatization, along with the inherent biocompatibility of certain cyclodextrins, lends this family of supramolecular hosts to yet another use: in drug delivery. Though cyclodextrins have an inherent hydrophilicity, among the natural α-, β-, and γ-CDs, β-CD is relatively insoluble in water, unless it is bound to a guest. The root cause of this is likely the strong intermolecular forces between its molecules in the crystal state, so to mitigate these and improve the aqueous solubility the pharmaceutical industry generally uses substituted β-CDs, such as 2-hydroxypropyl-β-cyclodextrin (HPBCD), sulfobutylether β-CD sodium salt (SBEBCD), and randomly methylated β-cyclodextrin (RAMEB).[40,41] As a demonstrative example of CDs being used for the purpose of drug delivery, ziprasidone is an antipsychotic drug, which has a water solubility of 0.003 mg mL^{-1} in its free base form, but formation of a complex between this free base and a 40% (w/v) aqueous solution of SBEBCD increases the solubility to 0.35 mg mL^{-1}. The mesylate salt analog of ziprasidone further increases the solubility of the parent drug to 1 mg mL^{-1} and that of its SBEBCD complex to 44 mg mL^{-1}, making the latter the formulation of choice used for intramuscular injections.[41] Alternatively, CDs have been used for a variety of purposes in their unbound forms. For example, a substituted γ-CD, commercially marketed as Sugammadex, has been used in medical settings for over a decade to bind an anesthetic drug called rocuronium inside the body, reversing its effects.[42] Worldwide, the use of CDs as drug delivery excipients has been on an upward trend over the last 20 years, with the number of marketed drugs containing CDs reaching about 35 in 2010,[41] and will unquestionably remain a central focus of drug delivery research in the future.

A similar family of hosts that has recently begun garnering the attention of the drug delivery community is that of the cucurbit[*n*]uril-type. Cucurbit[*n*]urils (CB[*n*]s) are macrocyclic cavitands consisting of glycoluril repeat units connected by methylene group linkers between the urea nitrogens (Fig. 8). They contain hydrophobic cavities flanked by polar carbonyl groups at the two portals and the different ring sizes (n = 5, 6, 7, 8, 10) have been shown to encapsulate either one, or in the case of CB[8], two guests.[43,44] Because of its substantially higher solubility in water than most cucurbiturils, CB[7] has been recently examined by many groups for its biocompatibility[45,46] and potential as a drug host, showing in several cases improved solubility of the parent drug.[47,48]

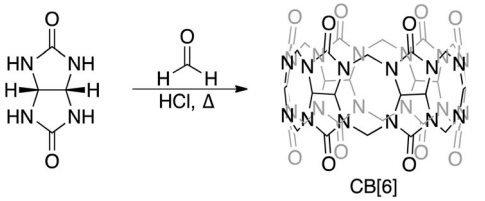

Fig. 8 Condensation of glycoluril with formaldehyde to yield cucurbit[6]uril.

Even more promising for the purpose of drug delivery are the acyclic cucurbiturils recently pioneered by Isaacs and coworkers. In 2010 a proof-of-principle study of the toxicity and cellular uptake of CB[5], CB[7], and three acyclic CB[*n*]s showed ample biocompatibility and ability to cross the cell membrane.[46] This was soon followed up with an expansion of the library of acyclic CB[*n*] variants and a demonstration of their ability to substantially improve the water solubility of an array of clinically prevalent, poorly soluble pharmaceuticals (up to a 2750-fold increase).[49] These complexes exhibited *in vitro* compatibility with human kidney and liver cells, showed no ill effects from high dose *in vivo* studies on mice, as well as an increased potency of some anti-cancer drugs when first encapsulated in the hosts.[49] Given the recent developments in CB[*n*] research, they are likely to gain usage in drug formulation, and may eventually supplant CDs as the drug delivery excipient of choice.

While these are merely a few examples of how supramolecular chemistry has impacted the real world, many others have found uses in more niche chemical applications,[50] helping the overall progress of science. It is clear that host–guest interactions have become a mainstay in the organic and organometallic subdivisions, even governing some inorganic equilibria, and are at the center of development of new uses in a wide range of fields, from drug delivery and pharmaceuticals to sensing. To a field that was born 50 years ago with the development of the world's first applied supramolecular hosts, an innovation that eventually won a Nobel Prize, it is a fitting celebration that it most recently was once again the recipient of the highest honor in science.

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