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Oligopyrrole Macrocycles: Receptors and Chemosensors for Potentially Hazardous Materials

Brett M. Rambo[a,b] and **Jonathan L. Sessler**[a,c]

Brett M. Rambo: brambo@signaturescience.com; Jonathan L. Sessler: sessler@mail.utexas.edu

[a]Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-0165 (USA), Fax: (+1) 512-471-7550

[b]Signature Science, LLC, 8329 North MoPac Expressway, Austin, TX 78759 (USA), Fax: (+1) 512-533-9563

[c]Department of Chemistry, Yonsei University, Seoul 120-749 (Korea)

Abstract

Oligopyrroles represent a diverse class of molecular receptors that have been utilized in a growing number of applications. Recently, these systems have attracted interest as receptors and chemosensors for hazardous materials, including harmful anionic species, high-valent actinide cations, and nitroaromatic explosives. These versatile molecular receptors have been used to develop rudimentary colorimetric and fluorimetric assays for hazardous materials.

Keywords

explosives; macrocycles; oligopyrroles; radiation; sensors

Introduction

Oligopyrrolic species have grown in popularity since they became recognized targets for synthesis early in the 20th century.[1] This diverse class of molecules includes polypyrrole,[2] as well as macrocycles such as porphyrins,[3] expanded porphyrins (i.e., larger analogues of porphyrins),[4] and calixpyrroles (stabilized porphyrinogen analogues).[5] Naturally occurring oligopyrroles, such as porphyrins and related tetrapyrrolic macrocycles, are time-honored systems that have proved amazingly versatile as ligands for cation complexation. Recently, however, these and other oligopyrroles, particularly expanded porphyrins and calixpyrroles, have received attention as molecular receptors for anions and neutral substrates,[6] as well as complexants for cations that are typically too large to form stable 1:1 complexes with porphyrins. Whereas cation coordination generally relies on the donor ability of the pyrrolic nitrogen, neutral substrate and anion recognition is typically achieved through hydrogen bonding through the pyrrolic N−H moiety. The selectivity of the pyrrolic macrocycle in question can be readily tuned by altering the shape and/or size of the binding cavity. Further, many (but not all) expanded porphyrins possess extended π-conjugation pathways, which results in unique optical features. This has made these systems attractive for use as colorimetric and fluorimetric sensors.[7]

Correspondence to: Brett M. Rambo, brambo@signaturescience.com; Jonathan L. Sessler, sessler@mail.utexas.edu.

This Concept article focuses on the use of oligopyrrolic compounds as receptors and chemosensors for potentially hazardous materials. While attempting to illustrate the promise of the generalized oligopyrrolic approach by noting the work of others, we will concentrate on contributions from our own laboratory. Specifically, we highlight the binding and detection of high-valent actinides[8] (e.g., uranium, plutonium, and thorium), harmful anionic species[9] (e.g., pertechnetate, perrhenate, and sulfate), as well as nitroaromatic explosives[10] (e.g., trinitrotoluene (TNT), trinitrobenzene (TNB), and trinitrophenol (picric acid; TNP)).

The ability to capture and detect hazardous materials (i.e., radioactive and high explosive compounds) relates to several issues of paramount importance in today's society. Among these are the current push towards "cleaner" energy sources,[11] concerns associated with nuclear power, as well as forensic analysis[12] and national security.[13] The diverse molecular recognition capabilities and optical properties of oligopyrroles have led to several preliminary findings that lead us to suggest that this class of compound could be applied to remediation and sensing of multiple classes of hazardous materials. As implied above, other groups have made important contributions to this field. A number of these are specifically noted at appropriate places in the text.

Oligopyrrolic Receptors and Colorimetric Sensors for Actinides

Actinides, used for defence purposes, energy production, and medicine, have provided the chemical foundation for some of the most transformational technologies of the last century. However, the use of actinides has led to growing concerns regarding waste management and potential environmental impact.[14] The United States and Russia have combined to produce nearly 200 metric tons of purified plutonium for their respective weapons programs.[15] Additionally, nuclear energy currently accounts for 25–30% of the world's electrical power supply, a percentage that is expected to increase with the global push for CO_2-free energy sources. Nuclear energy production has resulted in the generation of roughly 700 metric tons of plutonium and uranium, a large portion of which is found in the form of spent reaction fuel.[15] Radioactive waste presents its own particular set of problems (relative to most other hazardous materials), with those involving storage, transportation, and stockpiling being particularly well recognized. Apprehension due to nuclear proliferation serves to exacerbate these concerns, as do the prospects of nuclear arms smuggling between countries and the creation and use of improvised radiological weapons (so called 'dirty bombs'). The March 2011 tragedy in Japan has only served to highlight these concerns.

As underscored by these recent events, after a nuclear spill or accident, it would be useful to have fast and accurate methods of detecting early actinide species, such as uranium, neptunium, and plutonium. To do this effectively, it will be important to 'sense' these species in their most stable dioxo forms (or 'yl' cations). This sensing ability could also prove useful under less catastrophic conditions. The pentavalent actinyl ions AnO_2^+ (An=Np and Pu) are stable, relatively mobile in the environment, and are typically hard to complex using ligands containing soft donor sites, as typically found in common chromophoric materials. Also of concern is Pu in the VI oxidation state. Common forms of this cation display high solubility and mobility in water, making them potential environmental hazards.

Currently, detection of plutonium and uranium is mainly done using α-scintillation counting methods.[16] These detection methods typically rely on the use of Geiger counters, and thus may not be suitable in all foreseeable instances. Thus, we believe that there is a need for systems that are not only capable of selectively recognizing but also reporting the presence of actinyl species through, for example, a change in the optical signature upon complexation.

Porphyrins are a well known class of pyrrole-derived macrocycles that stabilize complexes with many metal cations.[17] In fact, structurally characterized examples of U^{IV} and Th^{IV} porphyrin complexes are known.[18] However, as a general rule expanded porphyrins have proved to be more effective ligands for the stabilization of 1:1 complexes with the actinyl cations (i.e., MO_2^{n+}; M=U, Np, and Pu; n=1 or 2). These latter complexes typically exploit the larger cavity size and greater number of nitrogen donor atoms present in expanded porphyins (relative to the porphyrins). In early studies, uranyl complexation was observed in the case of Alaskaphyrin,[19] oxasaphyrrin,[20] pentaphyrrin,[21] and amethyrin.[22] In 2001, the Sessler group reported the synthesis and characterization of hexaphyrin(1.0.1.0.0.0) (isoamethyrin; **1**; Scheme 1) and its ability to complex the actinide ions uranyl (UO_2^{2+}) and neptunyl (NpO_2^{+}).[23] The actinide complexes in question were both characterized by single-crystal X-ray diffraction analysis. Further, these complexes were shown to be stable over a period of weeks, as inferred from UV/Vis spectroscopic studies.

In a follow-on study published in 2004, it was reported that isoamethyrin undergoes colorimetric changes upon exposure to the UO_2^{2+}, PuO_2^{2+}, and NpO_2^{2+} ions. These complexation-dependent color changes are detectable with the naked eye,[24] and are ascribed in part to a change from a formally antiaromatic or nonaromatic form to a formally aromatic complex containing a 22 π-electron periphery.

As seen in Figure 1, the addition of uranyl acetate results in distinct color changes in methanol–dichloromethane solutions (3:4; v/v) containing isoamethyrin The acid salt of isoamethyrin exhibits three prominent bands at 384 nm (ε = 24 000 $_{M}^{-1}$ cm^{-1}), 497 nm (ε = 54 000 $_{M}^{-1}$ cm^{-1}), and 597 nm (ε = 25 000 $_{M}^{-1}$ cm^{-1}), respectively. In contrast, the uranyl complex **2** is characterized by a Soret-like transition at 530 nm (ε = 330 000 $_{M}^{-1}$ cm^{-1}) and two smaller Q-like bands at 791 nm (ε = 56 000 $_{M}^{-1}$ cm^{-1}) and 832 nm (ε = 81 000 $_{M}^{-1}$ cm^{-}). The free-base form of **1**, the starting species used to coordinate the uranyl cation, has a molar absorptivity of 50 000 dm^3 mol^{-1} cm^{-1} (472 nm), which is six times lower than that of complex **2**. These distinct spectral differences led to the further study of this isoamethyrin as a potential chemosensor for high valent actinide cations.

Similar colorimetric changes were observed when **1** was exposed to the PuO_2^{2+} and NpO_2^{2+} ions in MeOH–CH_2Cl_2 solution (1:1; v/v). The molar absorptivities of these complexes were not recorded due to the highly radioactive nature of these species. However, the authors noted the facile nature of complex formation. The addition of Pu^{VI} or Np^{VI} to a solution of **1** containing Et_3N resulted in an instantaneous color change, whereas about 24 h was required to produce a visible color change after the addition of UO_2^{2+} salts. The increased rate of colorimetric response was attributed to the stability of the neptunyl and plutonyl cations in the V oxidation state, where uranyl typically prefers the VI state.[25] Specifically, it was suggested that addition of the former cations results in reduction of the Np^{VI} and Pu^{VI} actinyl cations to the corresponding V oxidation state, thus facilitating oxidation of the isoamethyrin ligand. Support for this notion came from the fact that although the Np^{V} complex is obtained independent of the oxidation state of the metal before addition (V or VI), the rate of metal complex formation differs.

To determine the effective ‘dynamic range’ associated with the formation of actinide complexes of **1**, quantitative studies were conducted with depleted uranium acetate. This choice of substrate reflects an effort to avoid the complications inherent in working with radioactive materials. In these studies, a solution of isoamethyrin in methanol–dichloromethane 95:5 (v/v), containing four equivalents of Et_3N, was titrated with the uranyl cation dissolved in the same solvent system. On this basis, a detection limit of 5.8 ppm was calculated for naked-eye detection. In a separate study, a detection limit approaching 28 ppb was determined by using UV/Vis spectroscopy. These detection limits are competitive with

those for two commonly used metal indicator systems, namely 2,2′-(1,8-dihydroxy-3,6-disulfonaphtylene-2,7-bisazo)bisbenzenearsonic acid (AzIII)[26] and 2-(5-bromo-2-pyridylazo)-5-(diethylamino)phenol (BrPA-DAP),[27] both of which have been used as colorimetric sensors for this actinide cation (detection limits of 46 and 200 ppb, respectively). Further studies revealed that isoamethyrin is not as sensitive as these classic dyes to other metals (e.g., Gd^{III}, Zn^{II}, Ce^{IV}, and La^{III}) that may be present in actinide-rich samples. It was thus proposed that the use of isoamethyrin for actinide sensing could lower the risk of 'false positives' relative to alternative color-based approaches.

To exploit further the ability of isoamethyrin to recognize and sense actinides, efforts were made to immobilize this system onto a solid support. Immobilized sensors are attractive because they are generally more convenient to work with than solution-based indicators or chemosensor systems. They can also be incorporated readily into multiple sensor arrays. In an effort to develop such a system Melfi, et al., attached a functionalized isoamethyrin to a TentaGel bead consisting of an amino-terminated polystyrene-poly(ethylene glycol) graft co-polymer resin (90 μM, 0.30 mmol g^{-1} NH).[28] To take advantage of the amine-functionalized resin, a carboxyl-functionalized derivative of isoamethyrin (i.e., **7**) was prepared. This was done by condensing bipyrrole **3** with two equivalents of ethyl methyl bipyrrole, **4**, resulting in the formation of an open chain hexapyrrolic precursor **5** (Scheme 2). Exposing a solution of **5** to $FeCl_3$ in 2 M aqueous HCl resulted in the formation of bis-carboxyester-functionalized isoamethyrin **6**. The resulting macrocycle displayed an antiaromatic ring current in its ^1H NMR spectrum in analogy to what was seen for **1**. Further, **6** was found to react with $UO_2(OAc)_2$ in solution (CH_2Cl_2–CH_3OH; 1:1; v/v) over the course of 48 h. The UV/Vis spectrum and a single-crystal X-ray analysis of the resulting uranyl complex revealed only slight differences from what was observed in the case of **2**.

Immobilization of **6** onto the amino-terminated TentaGel resin was accomplished by subjecting the ester groups to hydrolysis; this gave the corresponding diacid **7**, which was attached to the bead using standard amide-coupling procedures.[29] The highly colored nature of isoamethyrin made resin functionalization easily discernable by naked-eye detection. Since 100% functionalization of the amino sites resulted in a dark/opaque bead, typically 5–20% coverage levels (0.0015–0.006 mmol g^{-1}) were used so that any uranyl cation-induced color changes could be visualized. It was determined that each bead had an approximate diameter of 220 μm and acted as a miniaturized cuvette ensemble. The 'free-base' form of **7** (on the resin) was generated by washing the beads with a 10% aqueous NaOH solution. Subsequent to exposure to uranyl acetate (0.024 M in methanol), the bead changed from a golden yellow color to a pinkish-red. The authors noted that a color change was observed after one day, but the reaction was allowed to go for nine days to ensure complete coordination of the uranyl cation. On the basis of the earlier studies (vide supra), this color change was attributed to a shift in the Soret band λ_{max} by about 40 nm.[22,30]

The resulting beads were analyzed by using a custom designed flow cell, and the substrate-induced color changes in the receptor functionalized TentaGel beads were quantified into red, green, and blue channels (Figure 2). The color intensities were extracted by using a CCD video chip before and after exposure to the uranyl cation. The images of blank beads were used to establish a reference light intensity, and those of the functionalized beads were used to determine the absorbance values of the three color windows. The isoamethyrin-functionalized beads displayed a distinct increase in intensity in the red channel upon treatment with the analyte. The changes in the green and blue channels were found to be less intense by comparison. The authors postulated that the changes in the red channel are a direct result of macrocycle oxidation and coordination of the uranyl cation to the oxidized macrocycle. While the response time proved too slow to make this approach of practical

utility, this bead-supported sensor served to establish that isoamethyrin could be used to detect the uranyl cation even after being attached to a solid support.

A separate study by Hayes, et al., detailed the use of isoamthyrin attached to a different solid support, namely a plastic fiber optic.[32] This platform was functionalized with dihydroxy isoamethyrin (DHI) to form a chemophotonic sensor.[32] The resulting ensemble, which was designed to signal the presence of the uranyl cation by modulation of surface evanescent waves, takes advantage of a unique condition present at the silica–water interface of glass fiber optic arrays, namely the presence of excess negative charges.[31] The resulting surface potential, resulting from ionized SiOH groups, was expected to attract positive ions to the fiber. Meanwhile, other silanol groups served as the point of attachment for the DHI.

The actual device was generated by tethering DHI to the sensor region of an optical fiber that contained poly(methyl-methacrylate) (PMMA) functionalized with glycidoxypropyltrimethoxysilane (GPS). The nucleophilic groups on DHI were used to open the epoxide ring in accord with reported literature procedures.[33] The fiber was then coupled to a source-detector module and irradiated using a single color LED or a white light source. An optical sensor node was used to either record the spectrum or monitor the optical loss in the fiber over three basic wavelength channels, namely blue (400–500 nm), green (500–600 nm), and red (600–700 nm) upon exposure to the uranyl cation. The integrated extinction intensity was used to measure the output response in real time (0.1 Hz).

It was found that exposure of the DHI-functionalised fiber optic surface to aqueous solutions of the uranyl ion resulted in distinct spectral changes in aqueous solution (Figure 3). The detection limit was determined to be 10 ppb using the fiber-based spectrometer. The authors demonstrated that the uranyl complex was more labile when tethered to the fiber optic surface. As a consequence, the sensor system could be restored by subjecting the fiber to an aqueous basic wash. Potentially interfering cations were also tested. Of these, only Gd^{3+} gave rise to color changes similar to those produced by UO_2^{2+}; however, the response to Gd^{3+} could be readily discriminated from that produced by the uranyl complex by looking at the kinetic response of the sensors. Specifically, the response induced by UO_2^{2+} was fast, whereas that from Gd^{3+} proved slow. Using a tri-band detector, it was found that the optical response of the surface was solvent dependent. This adds uncertainty to the detection of analytes. Nevertheless, by correlating the response with a simultaneous refractive index sensor, high confidence levels could be achieved. Finally, success was achieved in initial field trials.

Another class of pyrrole-derived molecular receptor that has received significant attention for its ability to complex actinide species is a set of Schiff-base calixpyrrole analogues, first prepared independently by Sessler and co-workers[34] and by Love et al.[35] These so-called ‘Pacman’-type receptors combine the complexation and physiochemical properties of pyrrole with the synthetic versatility and simplicity of Schiff-base condensation procedures.[36] The flexible framework of the Pacman receptor is thought to underlie its ability to stabilize a number of bi- and multinuclear complexes.[37,38]

The basic synthesis of the parent Schiff-base calixpyrrole Pacman system is shown in Scheme 3. Briefly, methanolic solutions of *meso*-disubstituted diformyl pyrromethanes are reacted with *ortho*-phenylenediamine in the presence of *p*-toluenesulfonic acid (TsOH). The reaction is generally clean and the yields are high. Further, the procedure may be modified to include a variety of other diamines.[37]

Love and Arnold have utilized these materials with great effect to complex uranyl species. They observed that reacting **8** with the uranyl amide complex$[UO_2(THF)_2\{N\text{-}(SiMe_3)_2\}_2]$ in THF, resulted in the formation of a mono-uranyl complex (*trans*-$[UO_2(THF)(H_2\mathbf{8})]$) (cf.

Figure 4).[37a] Interestingly, a corresponding diuranyl complex was not observed, even when the reaction was conducted at elevated temperatures. The mono-uranyl complex was characterized by a single-crystal X-ray diffraction analysis. The resulting structure revealed that the N_4-donor compartment of the macrocycle expands to accommodate the *trans*-uranyl ion.

Love and Arnold postulated that the vacant N_4-donor compartment could support the formation of new uranyl cation-cation complexes. These types of cation–cation complexes are important species in neptunium and plutonium chemistry.[39] However, there are very few congeneric uranyl-based cation–cation complexes due to the inertness of the $[UO_2]^{2+}$ ion. It is thus noteworthy that Love and coworkers were able to show that reacting the mono-uranyl complex (*trans*-$[UO_2(THF)(H_2\mathbf{8})]$) with low-coordinate metal amide complexes of the general formula$[M\{N\text{-}(SiMe_3)_2\}_2]$ (M = Mn, Fe, and Co) in boiling THF results in the formation of brown cation–cation complexes $[UO_2(THF)(M)(THF)(\mathbf{8})]$ (Figure 5).[37a] As a general rule, these products were found to be neutral and stable. Specifically, they did not undergo exchange or redistribution reactions in the solvent systems tested.

In more recent studies, Love and Arnold have used Pacman receptors to explore the underlying chemistry of the uranyl diacation. In 2008, they demonstrated that once confined in the Pacman framework the uranyl dication simultaneous undergoes single-electron reduction with the result that selective covalent bond formation can be achieved.[40] In a separate report, this research team showed that sequential addition of a lithium metal base to the uranyl ion, while constrained in the Pacman receptor, resulted in lithium coordination to the U=O bonds, as well as single-electron reduction.[41] These advances demonstrate that under the appropriate conditions the uranyl oxo group will undergo radical reactions commonly associated with more classic metal oxo groups. Further, they may also provide models for highly radioactive plutonyl and neptunyl analogues found in nuclear waste. One may postulate that the integration of these versatile receptors into sensor materials could result in a novel approach to detection of radioactive species.

The work described in this section recounts recent progress made with two polypyrrolic systems, namely isoamethyrin and a Schiff-base calixpyrrole derivative, that have shown success in complexing and in some cases sensing actinide complexes. Efforts to convert these molecular systems into actual sensing devices are also summarized. While additional work is clearly needed, in due course this line of investigation could give rise to systems useful in reducing the threats associated with untoward environmental release of early actinide cations, such as, for example, from a nuclear power plant accident or so-called ‘dirty bombs’.

Pyrrole-Derived Receptors for Pertechnetate and Perrhenate

The design of molecular receptors capable of capturing and sensing anionic species of environmental and biological relevance has been an area that has attracted increasing interest during the last decade.[42] Anions are of ubiquitous importance in biology and are critical to a variety of physiological processes. Under other conditions, these same common anions, including chloride and phosphate, can be a source of concern (e.g., cystic fibrosis and hyperphosphatemia). Other anionic species, such as cyanide and aresenate, are directly toxic and play a less-than-salubrious role in the human body, while others, such as nitrate and phosphate (responsible for eutrophication), are a source of environmental concern. One anion with recognized “good” and “bad” character is the radioactive oxoanion, pertechnetate.[43] Pertechnetate (TcO_4^-) is the most stable form of the radioactive element technetium.[44] One isotope, Tc-99m,[45] is used in diagnostic imaging, whereas others isotopes with long half lives are produced as the result of the nuclear fuel cycle.

Pertechnetate is known for its ability to migrate readily within the superficial layers of the earth's crust, making it a particularly dangerous radioactive anion. This danger, in turn, is providing an incentive to develop systems that are capable of binding as well as detecting the pertechnetate anion in solution. Due to the restrictions associated with the study of pertechnetate, the perrhenate anion (ReO_4^-) is often used as a structural surrogate for the pertechnetate anion. However, this chemical analogy is not perfect. On the other hand, the perrhenate anion is of intrinsic interest since it (in the form of $^{186/188}Re$), like pertecnetate, is used in nuclear medicine.[46]

Only a few systems have been reported that display an ability to act as selective receptors for the pertechnetate and perrhenate anions.[47] This paucity may reflect the fact that in the case of most receptors, the enthalpic contributions to binding are relatively small.[48] Among the systems that have been recognized to bind these tetrahedral anions are urea-functionalized dendrimers,[49] amino-azacryptands,[50] tetra-substituted, lower rim functionalized calix[4] arenes,[51] and bimetallic cyclotriveratrylene hosts.[52] Expanded porphyrins and related pyrrolic macrocycles also show promise as receptors for the pertechnetate and perrhenate anions. Initial motivation to explore expanded porphyrins for the purpose of pertechnetate recognition came from an appreciation that certain protonated expanded porphyrins were capable of complexing other oxoanions, including sulfate and phosphate, as will be discussed further in the next section. It was also recognized that the large cavity of expanded porphyrins and their potential 'tunability' in terms of, for example, cavity size, shape, electronics, and number of hydrogen bond donor sites, could make them particular attractive as receptors for the TcO_4^- and ReO_4^- ions.

One class of expanded porphyrin capable of binding anions is the sapphyrins (e.g., **9**; Scheme 4). These compounds, which are among the oldest and best studied of the porphyrin analogues,[53] were found early on to act as receptors for the phosphate anion and some of its derivatives.[54] This led Sessler and co-workers to postulate that this polypyrrolic macrocycle could serve as a molecular receptor for pertechnetate. In 2004, the Sessler group reported that the mono-protonated form of sapphyrin (**9**) interacted with TcO_4^- as determined by UV/Vis spectrophotometric titrations.[55] Binding studies were carried out in 2.5% methanol and water (initial pH 7.0), and the solution contained no buffer so as to avoid competitive interactions between the host and anions present in the buffer. The binding profiles were consistent with a 1:1 binding mode and gave rise to a calculated K_a = 3900 $_M^{-1}$.

In a more recent study, Katayev et al. reported a bipyr-role-derived Schiff-base macrocycle (**10**) that contains six pyrrolic hydrogen-bond donor moieties.[56] This molecular receptor was specifically designed to incorporate a degree of flexibility, which was considered to be beneficial for the purpose of complexing tetrahedral species. In fact, it was found to bind the sulfate anion well. The authors thus sought to determine whether this system was capable of binding the perrhenate anion. Towards this end, a series of DFT charge-density calculations were carried out. On this basis it was predicted that receptor **10** would bind the perrhenate anion, although this binding ability would not necessarily extrapolate to the pertechnetate anion. In the event, this system was found to bind the perrhenate anion (in the form of is tetrabutylammonium salt (TBA)) in acetonitrile solution with a K_a =124 000 $_M^{-1}$, as determined by using standard UV/Vis spectroscopic titration procedures.

Receptors and Extractants for Sulfate Anions

As a general rule, hydrophobic anions are extracted into organic solvents with relative ease compared to more polar species. This effect, known as the Hofmeister bias,[57] reflects to a first approximation the hydration energies of the anions in question. Receptors that are

capable of overcoming the Hofmeister bias are expected to find application in a number of areas, including in the liquid–liquid extraction of highly charged species. One such highly charged species is the sulfate anion. Although not a hazardous species per se, an ability to manipulate and remove this anion could prove useful in terms of future remediation efforts involving highly radioactive and mixed hazardous waste.[58]

As a legacy of cold war era weapons production, highly radioactive and mixed hazardous waste are present at several National Laboratories in the U.S. Particularly large quantities, roughly 2×10^8 L corresponding to approximately 1.9×10^8 curies, are stored in underground storage tanks at the Hanford Site in Washington State.[59] It has been proposed that the waste could be disposed of through vitrification, which involves incorporation into transportable glass "logs", followed by deposition in a geological repository. However, this waste, which is rich in nitrate, contains a small amount of sulfate. This latter anion tends to interfere with the vitrification process due in part to its low solubility in borosilicate glass and has an adverse effect on long-term glass performance.[60] Thus, it would be ideal to remove sulfate from the nitrate-rich mixtures prior to the vitrification process. However, this presents a major problem in that removing sulfate from nitrate is extremely challenging. This problem is exacerbated under conditions of liquid–liquid extraction since it is necessary to overcome differences in hydration (ΔG_{hyd}= −300 vs. −1080 kJ mol^{-1} for NO_3^- and SO_4^{2-}, respectively), as per the Hofmeister bias.[57]

In 2002, the Sessler group reported the synthesis of cyclo[8]-pyrrole (**11**, [30]octaphyrin(0.0.0.0.0.0.0.0)). This *meso* substituent-free product was produced by the oxidative coupling of bipyrrole, using $FeCl_3$ as the oxidant (Scheme 5).[61,62] In contrast to what is seen in some expanded porphyrins, cyclo[8]pyrrole proved to contain an oligopyrrolic core that was essentially planar and flat, as inferred from a single X-ray crystal structure of the diprotonated form. This same analysis revealed that cyclo[8]pyrrole could incorporate one sulfate ion per macrocycle directly within the central cavity. The bound sulfate ion was seen to interact with all eight pyrrolic NH sites in the solid state through all four of its oxygen atoms.

The ease of synthesis and ability of cyclo[8]pyrrole to crystallize in its diprotonated form as the sulfate anion salt led Sessler and Moyer to explore the ability of this system to act as a sulfate extractant. The cyclo[8]pyrrole derivative **12** was originally developed in the context of preparing supramolecular liquid crystalline systems (vide infra).[63] It contains eight undecyl β-pyrrolic "side chains" and is soluble in hydrocarbon solvents. These solubility characteristics, coupled with the high rigidity and basicity of the cyclo[8]-pyrrole core present in **12** made this a potential candidate for overcoming the Hofmeister bias. In 2007, a study conducted by Sessler and Moyer showed that **12** could mediate sulfate exchange under interfacial conditions in the presence of a phase transfer catalyst (Figure 6).[64] Specifically, organic phases containing $[\mathbf{12}\cdot 2H]^{2+}\cdot(NO_3^-)_2$ (0.5 mM) and trioctyl-ammonium nitrate ($TOAH^+\cdot NO_3^-$; 0.1 mM) were obtained by repeatedly exposing solutions of $[\mathbf{12}\cdot 2H]^{2+}\cdot SO_4^-$ (0.5 mM) and TOA in toluene with aqueous 0.1 M HNO_3). Re-equilibration was rapidly detected when this organic phase was exposed to aqueous solutions of 0.02 mM Na_2SO_4 spiked with a $^{35}SO_4^{2-}$ tracer at μCimL^{-1} containing varying concentrations of $NaNO_3$ for 16 h. A conditional exchange constant, log(K'_{exch}) of roughly −1.1 was determined, while a D value (a measure of relative partitioning) of approximately 1000 was obtained at [$NaNO_3$] = 0.3 mM. These results led the authors to suggest that the more highly hydrated sulfate anion can be effectively extracted from a solution containing a higher concentration of the more hydrophobic anion, nitrate.

System **12** represents the first example of a supramolecular anion receptor that displays high sulfate-over-nitrate selectivity under conditions of solvent extraction. While the performance

parameters fall short of what would be needed for actual application, the results obtained with this system provide support for the notion that more optimized receptors could have a role to play in removing sulfate from radioactive waste prior to vitrification.

Chemosensors for Nitroaromatic Explosives

There is an almost self-evident need for fast and reliable detection methods for explosive compounds. Explosive detection is necessary for the protection of lives and property, and is also in high demand in forensic analysis and for a variety of security-related applications.[65] As detailed below, oligopyrroles have shown promise as receptors and chemosensors for nitroaromatic explosives. Trinitrotoluene (TNT) is perhaps the most familiar explosive in the nitroaromatic class. TNT is a powerful secondary explosive that is known for its convenient handling properties. In addition to concerns associated with its well-recognized role as an explosive, TNT presents an often-overlooked environmental hazard. In many instances, the soil and ground water of war zones and military facilities are contaminated with toxic levels of TNT and its degradation products.[66] TNT exposure has been associated with adverse affects that include skin irritation, abnormal liver function, male infertility, and it has also been regarded as a possible carcinogen.[67] The US Environmental Protection Agency (EPA) has set a limit of 2 ppb for TNT in drinking water.[68] On the other hand, TNT levels in ground water and soil samples taken from near un-detonated explosives can approach 500 ppb.[67] Not surprisingly therefore, considerable effort has thus been devoted to finding ways to detect TNT and related species. Below we highlight the use of oligopyrrolic species for the optical-based detection of nitroaromatic compounds, including TNT, as well as trinitrobenzene (TNB), and picric acid (i.e., trinitrophenol; TNP). The interested reader is referred to the primary literature for other approaches, many of which offer greater sensitivity, albeit at the cost of requiring far more sophisticated instrumentation.[69]

In 2007 Sessler and co-workers reported that exposing substituted cyclo[8]pyrrole derivatives such as, for example, **12**, **13**, and **14**, to electron-deficient acceptors, such as TNT, TNB, and TNP resulted in the formation of liquid crystalline (LC) phases, specifically hexagonal columnar (Col_h) mesophases.[63] Prior to this report only a few examples of mesophases formed from expanded porphyrins were known, and none had been studied in the context of nitroaromatic substrate recognition.[70] Initial preparation of LC samples was accomplished by dissolving stoichiometric amounts of the nitroaromatic electron acceptor and cyclo[8]pyrroles **12**–**14** in CH_2Cl_2 followed by solvent evaporation. The resulting products were analyzed with the use of an optical polarizing microscope, in combination with differential scanning calorimeter (DSC), and powder X-ray diffraction (PXRD). It was observed that mesophases were formed upon exposure of **13** to TNP and TNB, and that these mesophases displayed excellent stability. Further, it was found that exposing thin films of **13** and **14** (less than 1 μm thick) to vapors of TNT, volatilized by heating to 100 °C, resulted in the formation of mesophases. A polarizing optical microscope was used to confirm the induction of birefringence, as illustrated in Figure 7.

The authors also noted that exposure of **14** to TNT vapors had a dramatic effect on the UV/Vis absorption spectrum of **14**. The spectrum of **14** recorded as a thin film features a Soret band at 470 nm and an intense and red-shifted Q band at 1100–1200 nm. Upon subsequent exposure of the film to TNT vapor (as monitored by use of a polarizing microscope) reduced intensity was observed along with a change in the shape of the Q band. This effect was not observed when **14** was exposed to TNT in solution. The responsive nature and self-organization observed in cyclo[8]-pyrrole mesophases, as inferred from powder X-ray diffraction (PXRD) analyses, led the authors to suggest that this system is of potential

interest in the area of explosive sensing and could serve to complement other materials-based systems currently used for this purpose.[71]

In a separate set of studies, the Sessler and Becher groups developed a supramolecular system that proved efficient in the recognizing electron deficient species, namely nitroaromatic explosives. Specifically, tetrathiafulvalene (TTF), an organosulfur compound well known for its redox properties, was incorporated into the structural framework of calix[4]-pyrrole to give **15**.[72] The synthesis of this first generation system was readily accomplished by treating monopyrrolo-TTF, a precursor developed by the Becher group,[73] with an excess of TFA in a mixture of CH_2Cl_2 and Me_2CO (Scheme 6). System **15** was shown to produce a colorimetric response when exposed to TNB in organic media.

Direct evidence for the interaction between **15** and TNB, at least in the solid state, came from a single-crystal X-ray analysis (Figure 8). The resulting structure revealed two distinct tetra-TTF calix[4]pyrrole units (i.e., **15**), both of which contained two TNB guest molecules sandwiched between two sets of TTF “arms”. This arrangement, which exploits the favorable TTF–TTF separation present in the 1,3-alternate calix[4]pyrrole conformation, is fully consistent with the formation of a charge transfer (CT) complex and hence the colorimetric response seen in solution (noted above and discussed further below).

Further analyses of the binding interactions between **15** and TNB were made using UV/Vis spectroscopy. It was observed that addition of two equivalents of TNB to a CH_2Cl_2 solution of **15** resulted in a distinct colorimetric change from yellow to green that was easily detectable by the naked eye. The resulting UV/Vis spectrum displayed the presence of a distinct absorption band that was centered at $\lambda = 677$ nm ($\varepsilon = 477\ {}_{M}{}^{-1}\ cm^{-1}$). The authors postulated that these distinct optical transitions reflect the presence of CT interactions between the electron donor and acceptor species (i.e., **15** and TNB, respectively).

Interestingly, the authors demonstrated that formation of the complex **15**·$(TNB)_2$ could be reversed by the addition of an appropriately chosen anion source, such as tetrabutylammonium chloride (TBACl). Specifically, it was found that addition of five equivalents of TBACl resulted in a colorimetric shift from green back to yellow. This easy-to-visualize change is thought to result from a “switching” from the 1,3-altenate conformation of calix[4]pyrrole to the corresponding cone conformation.[5a] Furthermore, the changes in question are accompanied by the disappearance of the CT absorption band centered at $\lambda = 677$ nm in the UV/Vis spectrum (Figure 9). It is believed that addition of the chloride ions to the solution of **15**·$(TNB)_2$ results in competition for the NH protons of **15**. Therefore, a competition between the 1,3-alternate and cone conformation is established. The relatively large association constant corresponding to the interaction between calix[4]pyrrole and chloride causes the equilibrium to shift in favor of the cone conformation upon exposure to the chloride ion. The shift in structural conformation disrupts the binding between **15** and TNB and leads to presence of free TNB in solution. The authors were able to regenerate the **15**·$(TNB)_2$ complex by extracting the TBACl salt into aqueous solution; this results in a return of the green color characteristic of the original charge-transfer complex (Figure 9d). The dynamic recognition capabilities of this molecular receptor, its ability to bind electron deficient guests, including the test nitroaromatic explosive TNB, and its colorimetric response to external stimuli make this a platform one of considerable interest as a “switchable” supramolecular sensor system. However, only modest binding affinities were observed for TNB and high solution concentrations were required to produce colorimetric responses that could be observed with the naked eye. Thus, it was recognized that yet-improved systems would be desirable.

In an effort to improve the response seen with **15**, Park, et al., synthesized the corresponding thieno- and benzo-annulated analogues (**16** and **17**, respectively).[74] These new receptors were found to display a positive allosteric response toward nitroaromatic explosive guests, including TNB, TNT, and TNP.

Cooperative reactions play important roles in many complex biological processes, including enzymatic processes[75] and the binding of oxygen to hemoglobin.[76] On the other hand, synthetic neutral substrate recognition systems that display this type of response are rare,[77] especially in the case of nitroaromatic explosive detection. In the case of **16** and **17**, the authors predicted that the structural modifications associated with annulation would serve to enlarge and rigidify the "TTF walls", thus creating receptors with better size and shape complementarity for electron-deficient substrates. This was expected to lead to higher overall binding affinities. It was also considered likely to give rise to an improved cooperative response since binding of a first electron deficient guest was expected to facilitate recognition of the second.

Initial evidence that these new tetra-TTF calix[4]pyrroles could complex nitroaromatic explosive guests came from a single-crystal X-ray diffraction analysis of the 1:2 complex of **17**·$(TNP)_2$. The resulting structure was found to bear analogy to that of first generation complex **15**·$(TNB)_2$ discussed above. In particular, each of the TNP guests was found sandwiched between two TTF arms.

The interactions between all three available TTF-calix[4]-pyrroles, namely **15**–**17** (see Scheme 6) and nitroaromatic guests were then investigated in greater detail by carrying out standard visible spectrophotometric titrations in $CHCl_3$ solution using the test substrates TNB, TNP, and TNT. Strong colorimetric changes were seen upon addition of these three explosives, especially in the case of the newer derivatives **16** and **17**. The associated changes in spectral intensity were monitored and found to be consistent with positive allosteric binding behavior. The cooperative nature of the underlying interactions was analyzed by using the Hill equation, Scatchard plots, and nonlinear regression of the two-site Adair equation. These results provided support for the notion that a 1:2 host–guest binding event takes place and that positive cooperative binding is seen to varying extents for all combinations of **15**, **16**, and **17** with TNB, TBP, and TNT, respectively. The calculated association constants showed that **16** binds to all three tests substrates (i.e., TNB, TNP, and TNT) with a higher affinity than receptor **17**. However, both receptors **16** and **17** proved more effective for the recognition and colorimetric sensing of nitroaromatic explosives than their non-annulated counterpart **15**. Effectively binding was seen for the new systems in polar media, such as H_2O, even in the presence of anions. These results led the authors to suggest that receptors such as **16** and **17** could have a role to play as simple colorimetric chemosensors for TNB, TNP, and TNT and might prove useful as complements to current nitroaromatic explosive sensing technologies, many of which require expensive instrumentation or trained operators to achieve optimal performance.

Conclusion

Oligopyrrolic macrocycles are a diverse class of molecular receptors that are capable of binding a wide variety of guest species. The examples presented in this Concept article are designed to highlight the potential utility such sensors may have in the sequestration, removal, and detection of hazardous materials. However, there is still a need to create better receptors, obtain more effective extractants, improve chemosensor detection levels, and develop field-ready devices. It is hoped that the present overview will inspire additional progress in pursuit of these challenging goals.

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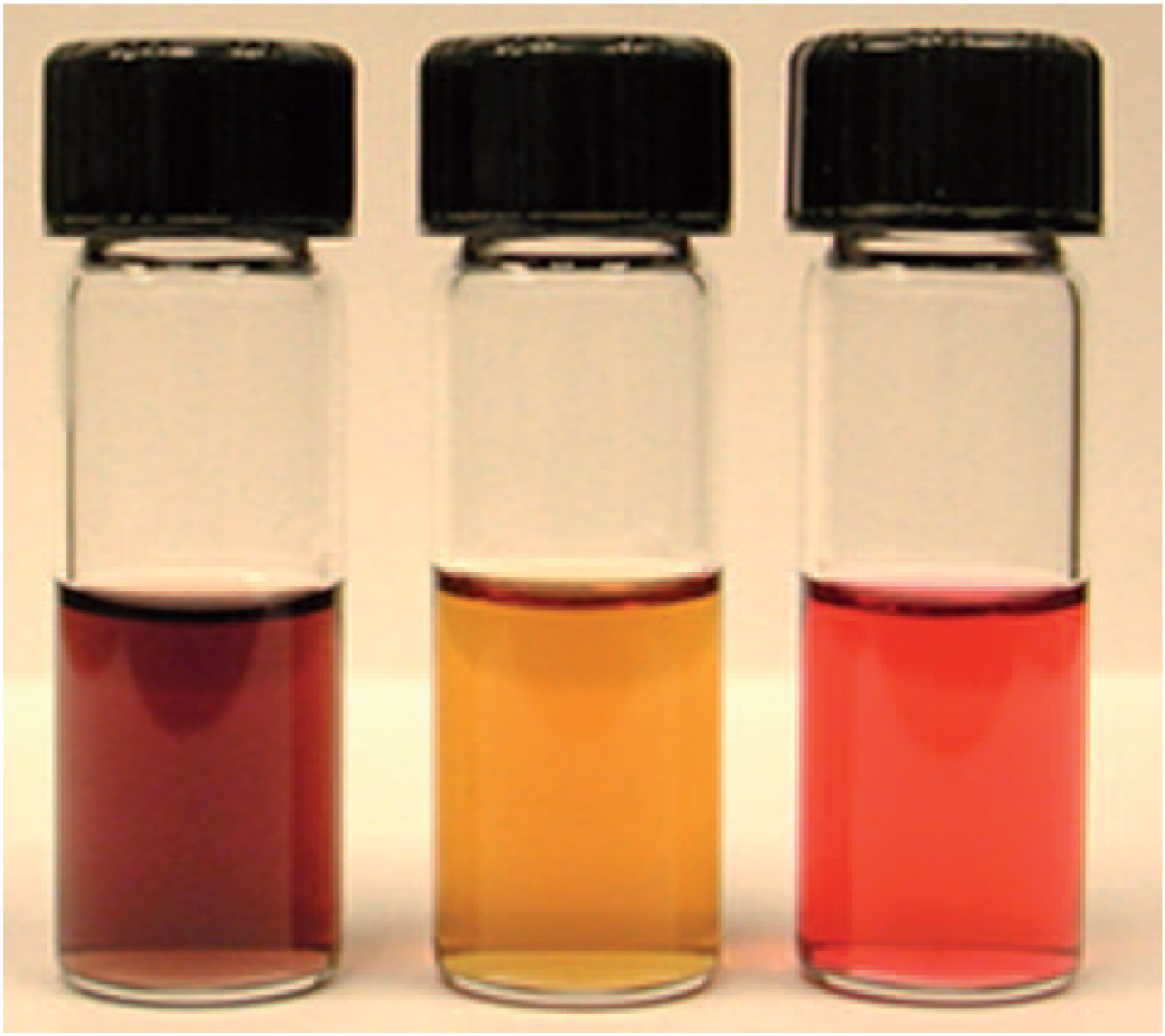


Figure 1.
Photograph showing the color changes seen upon the addition of uranyl acetate to solutions of isoamethyrin. Left: Acid salt of isoamethyrin; Middle: After addition of 10 equivalents of Et_3N. Right: UO_2^{2+} complex. Solutions of uranyl acetate and isoamethryin) were made up using a 3:4 (v/v) mixture of methanol and dichloromethane. This figure, which originally appeared in reference [24], is reproduced with permission.

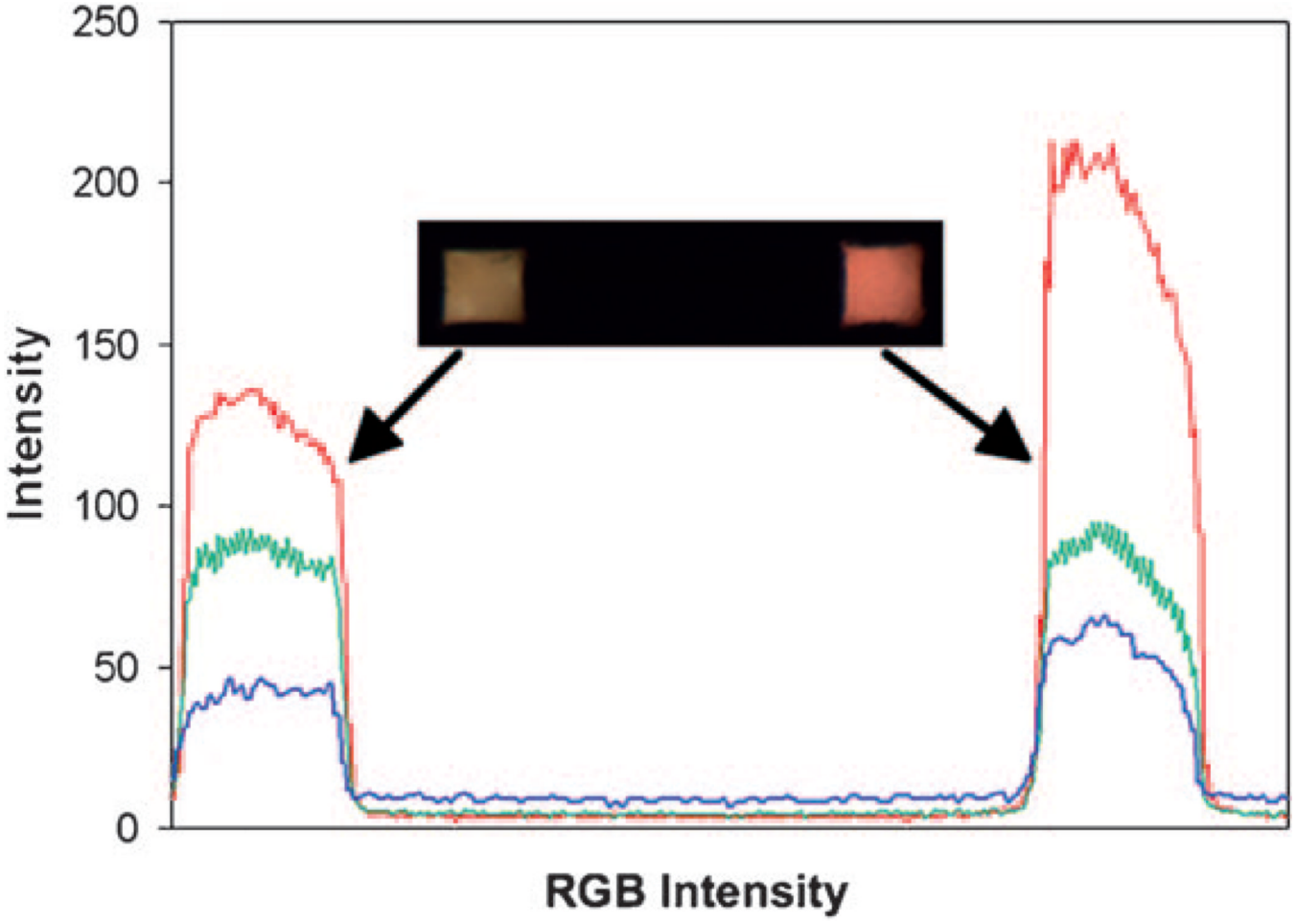


Figure 2.
A graph displaying intensity values of the red (red line), green (green line), and blue (blue line) channels for a TentaGel resin bead containing the free base of **6** (left side, 6.4% amine coverage), as well as a resin bead exposed to a 0.0024 M solution of uranyl acetate in methanol for nine days (right side). This figure, which originally appeared in reference [28], is reproduced with permission.

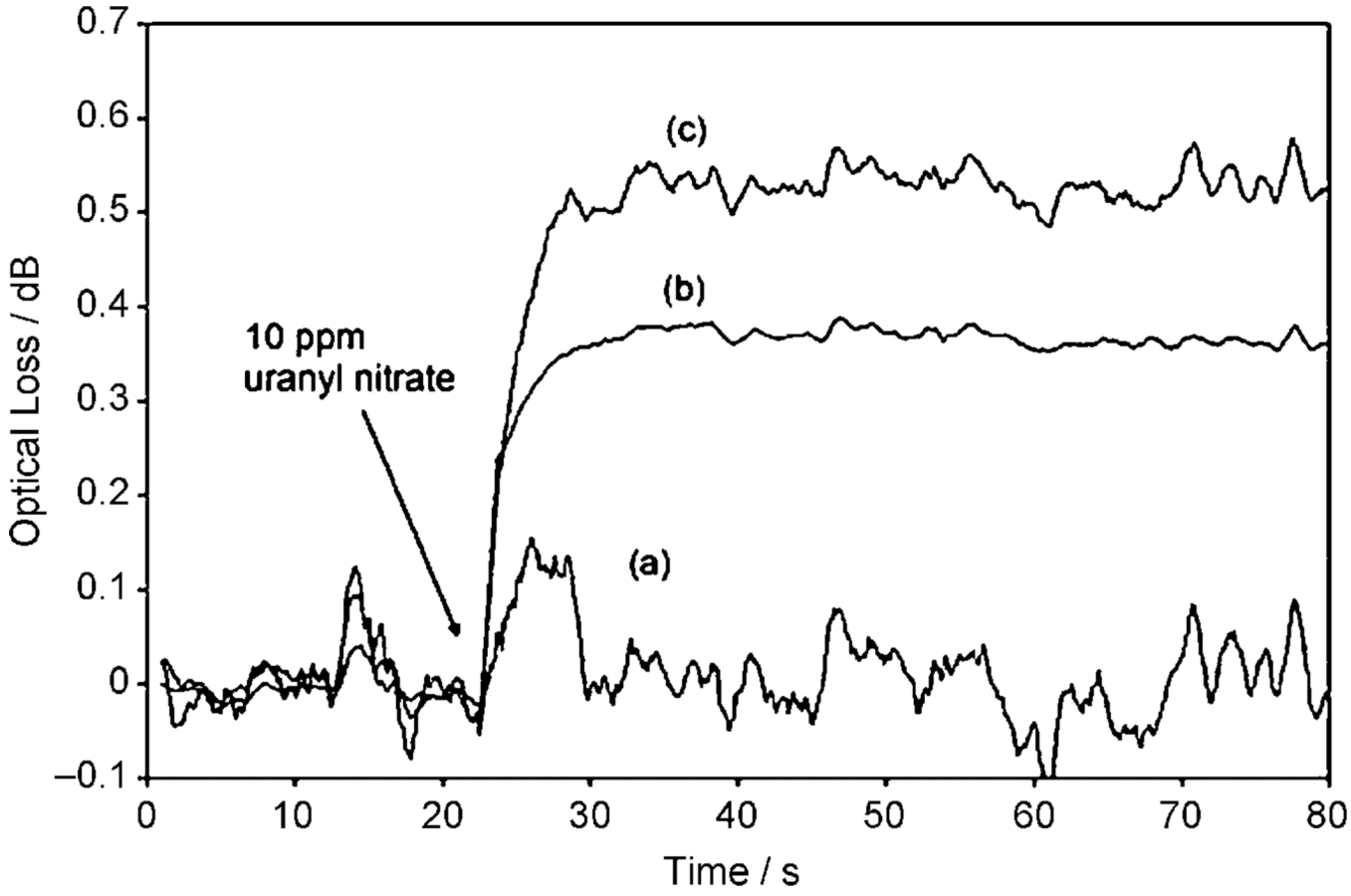


Figure 3.
Response in the red (a), green (b), and blue (c) channels seen when a DHI-functionalized fiber optic sensor was exposed to uranyl nitrate. This figure, which originally appeared in reference [32], is reproduced with permission.

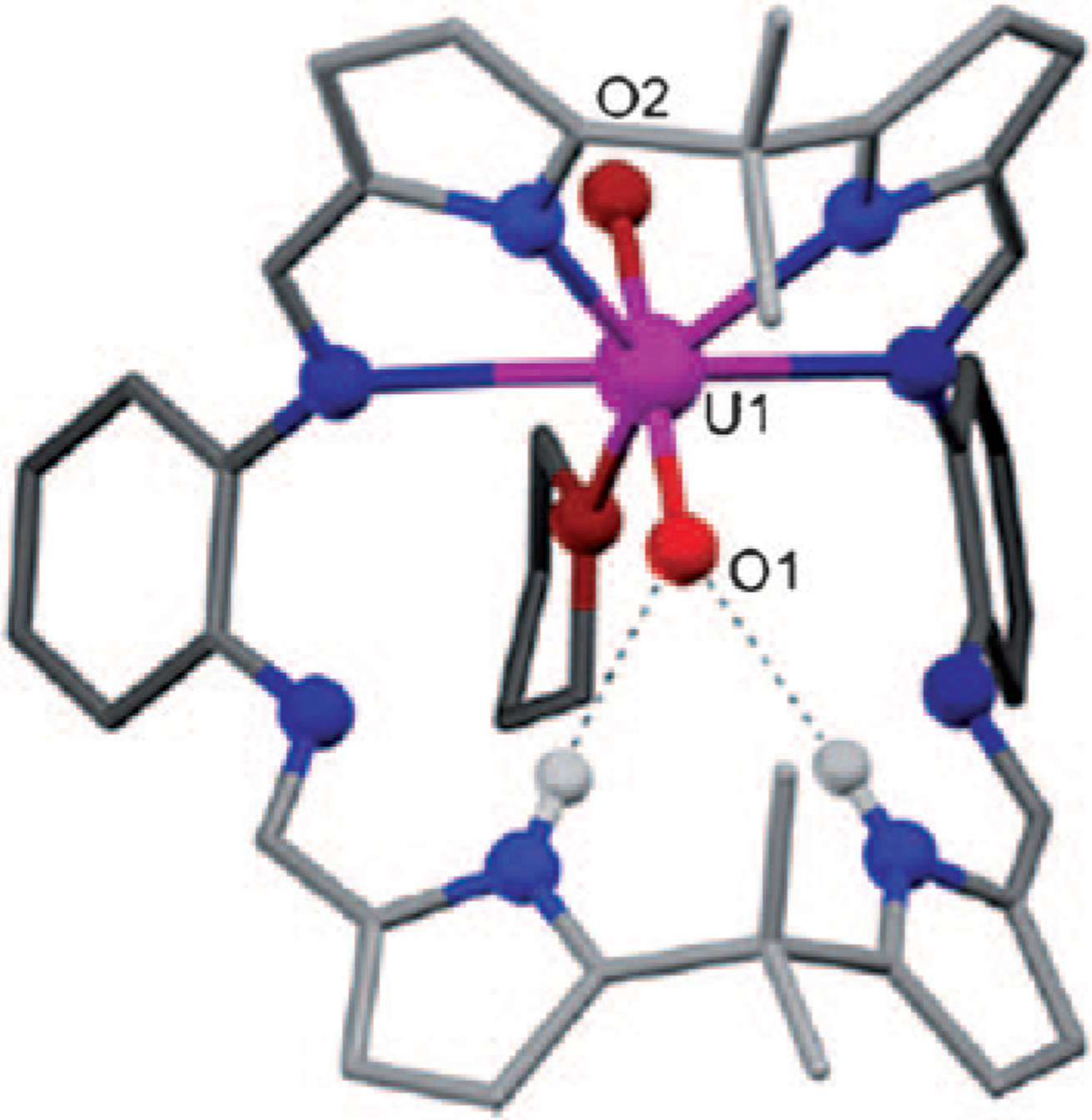


Figure 4.
Single-crystal X-ray structure of the uranyl complex, *trans*-[UO_2(THF)(H_2**8**)]. This figure, which originally appeared in reference [37a], is reproduced with permission.

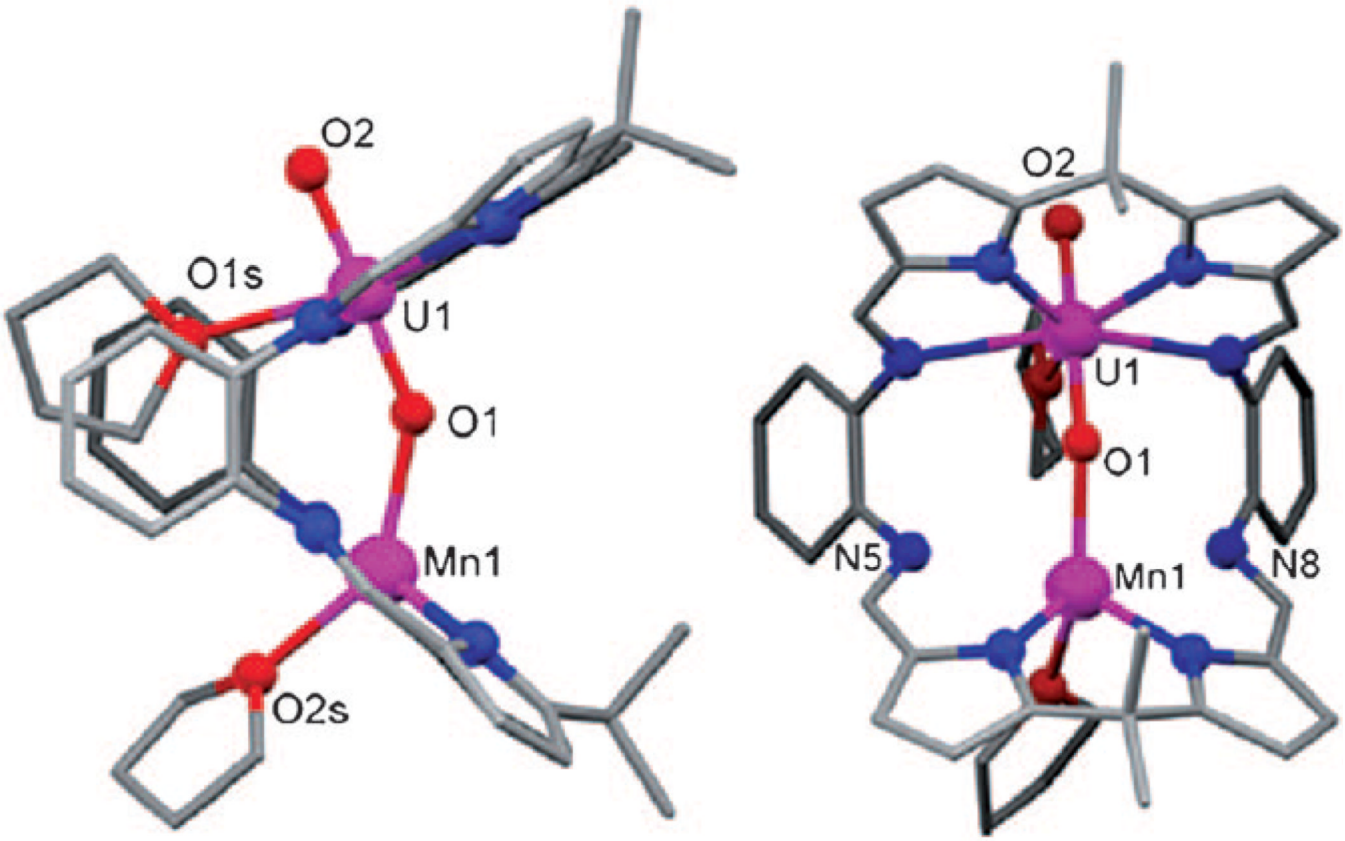


Figure 5.
Side and face-on views of the single X-ray crystal structure of the uranyl cation–cation complex UO_2(THF)Mn(THF) (**8**). This figure, which originally appeared in reference [37a], is reproduced with permission.

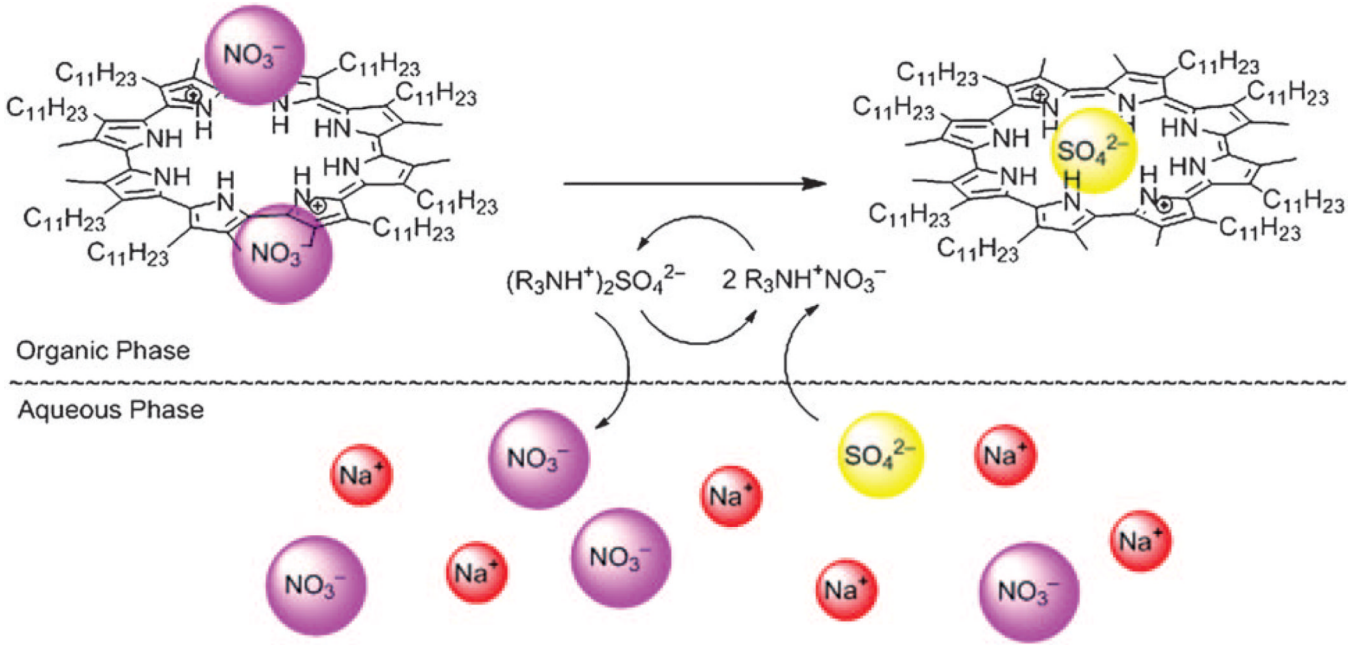


Figure 6.
Schematic showing anion exchange and subsequent phase transfer of sulfate as induced by **12**. This figure, which originally appeared in reference [64a], is reproduced with permission.

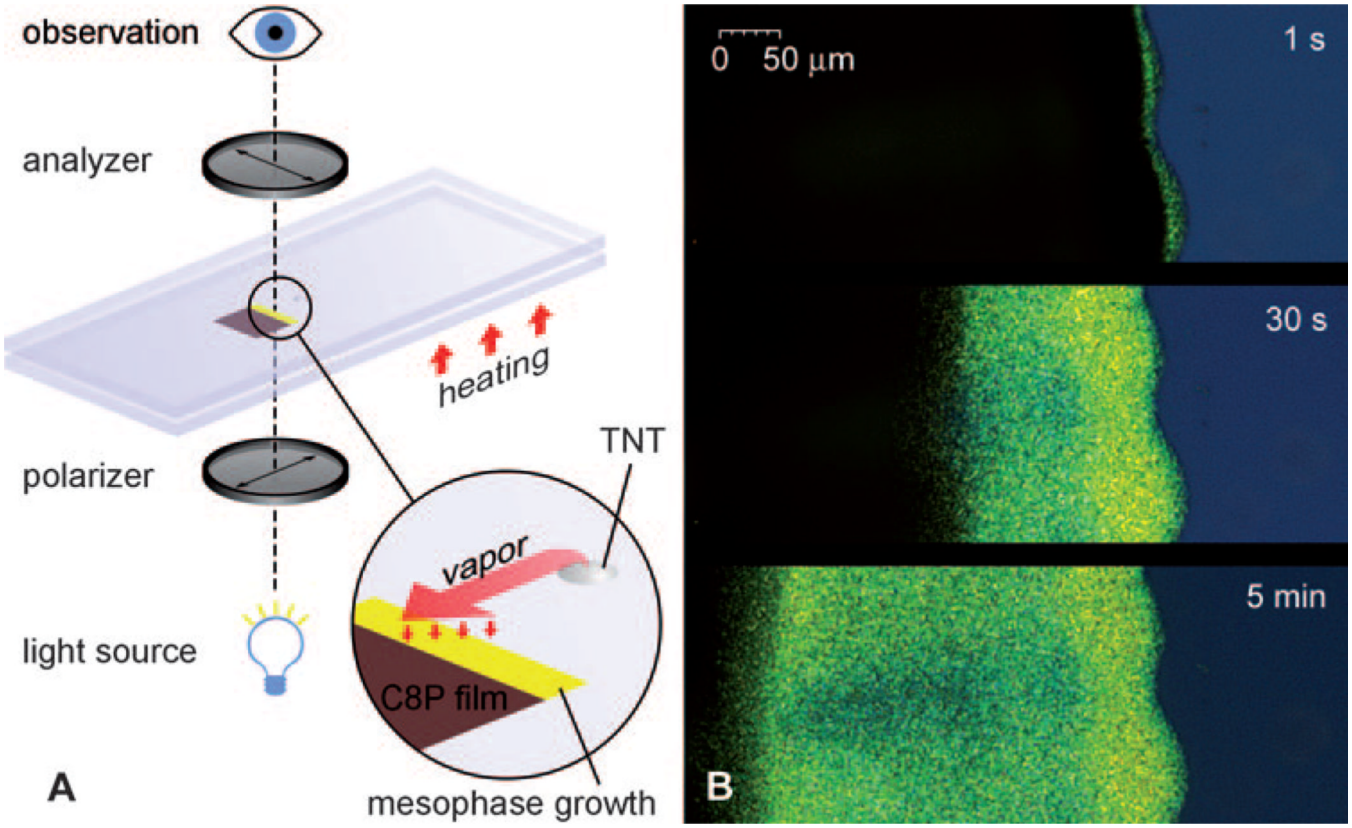


Figure 7.
Visual evidence put forward to support the proposition that mesophases, are formed upon exposure of thin films of cyclo[8]pyrrole **14** to vapors of TNT. A) Experimental design for optical studies (not to scale and with microscope optics omitted for clarity). B) Optical changes observed when **14** at 100 °C is exposed to TNT vapor. Left side: isotropic film, dark brown; middle: mesophase, bright yellow to green; right: background, dark blue. The photographs shown were taken 1 s, 30 s, and 5 min after an aliquot of TNT (0.1 µg) was placed on the microscope slide, approximately 1 mm from the right hand edge of the **14** film. This figure, which originally appeared in reference [63], is reproduced with permission.

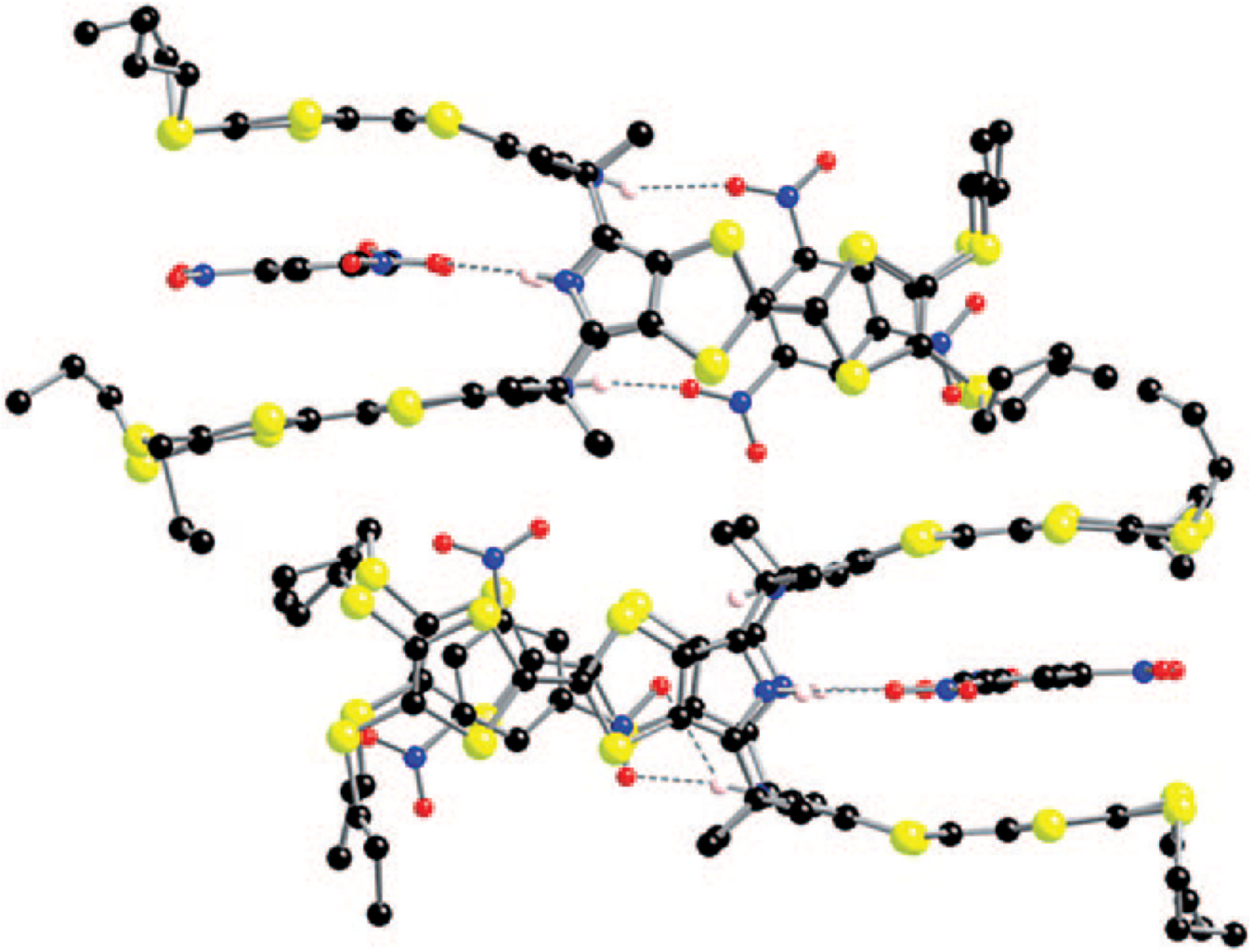


Figure 8.
Single-crystal X-ray structure of **15** and TNB. The view illustrates the H-bonding interactions (dashed lines) between the host and guests in the supramolecular complex **15**·$(TNB)_2$. This figure, which originally appeared in reference [72], is reproduced with permission.

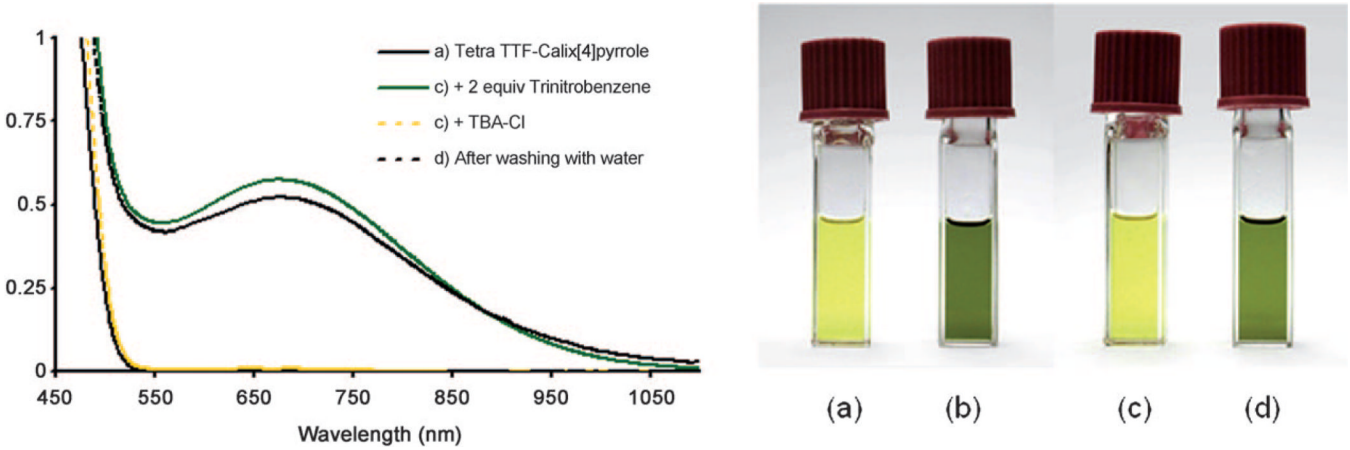
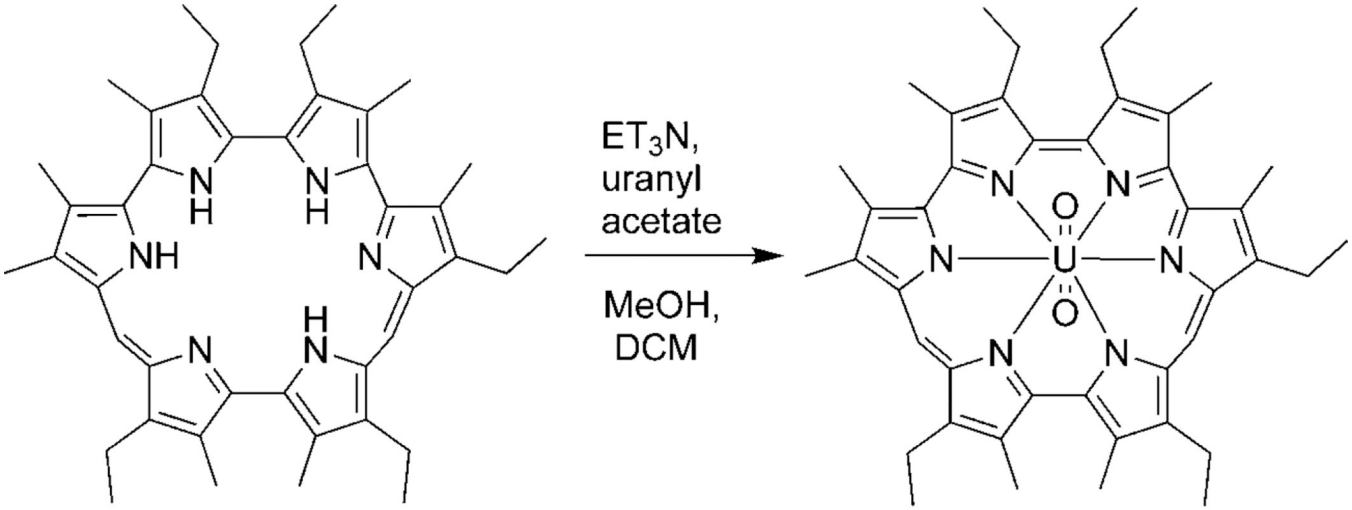
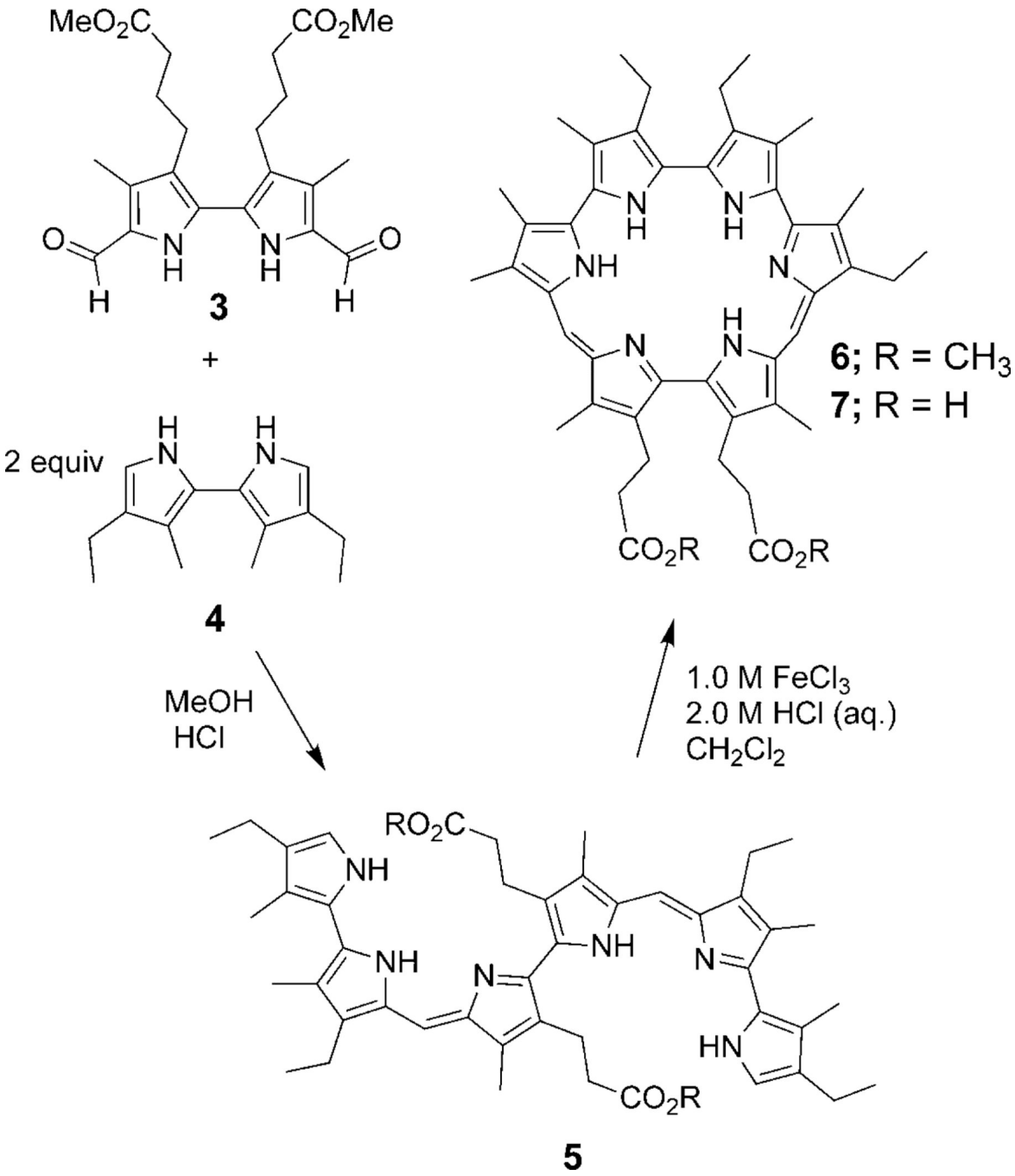


Figure 9.

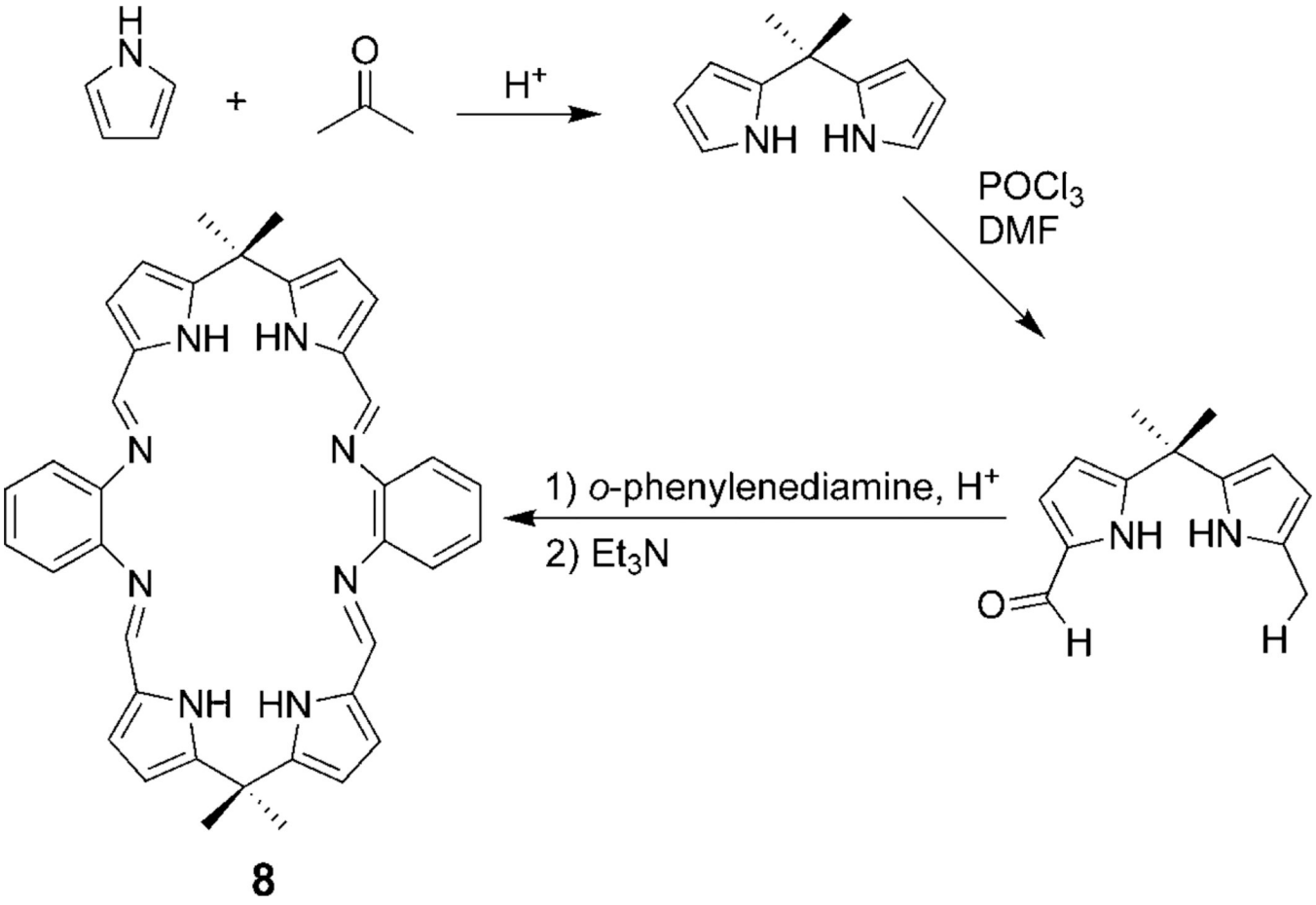
UV/Vis absorption spectra (CH_2Cl_2) of a) **15** (1.0 mM), b) **15** with two equivalents of TNB, c) **15** with two equivalents of TNB and five equivalents of TBACl, and d) solution after washing with H_2O. This figure is modified from one, which originally appeared in reference [72].



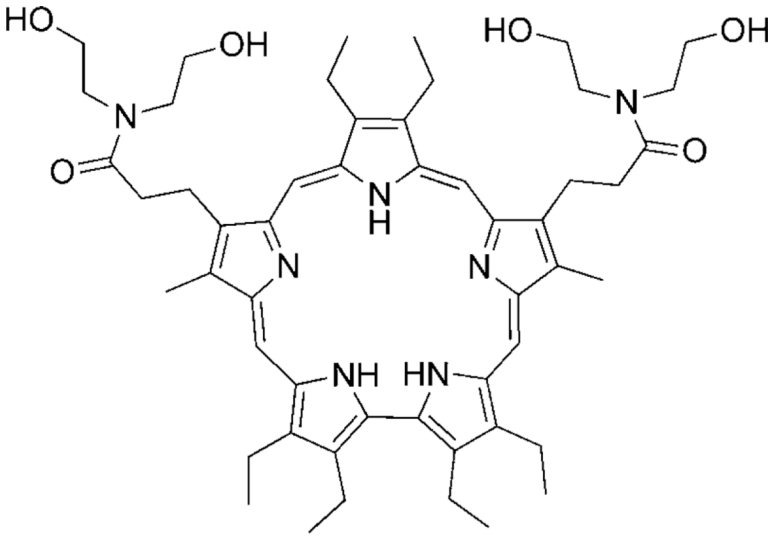
Scheme 1.
Formation of a uranyl complex using isoamethyrin.[23] The reaction is carried out in the presence of air and involves an oxidation of the macrocycle to produce a formally aromatic species with a 22 π-electron periphery.



Scheme 2.
Synthesis of the carboxyl-functionalized isoamethyrin **7**.[28]



Scheme 3.
Synthesis of “Pacman” Schiff-base calixpyrrole derivatives.



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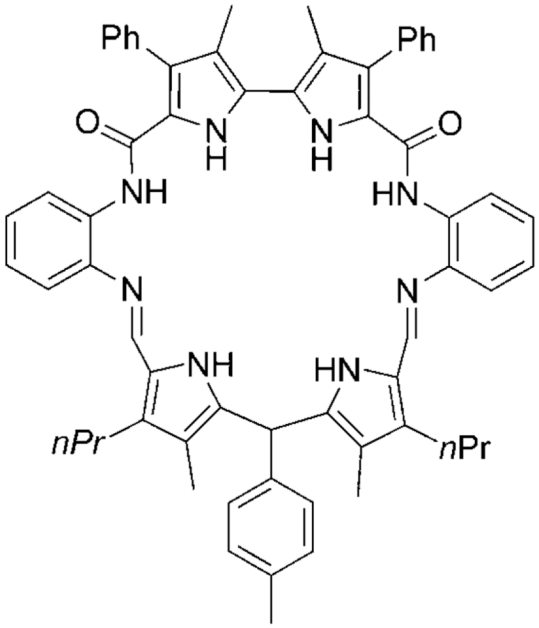
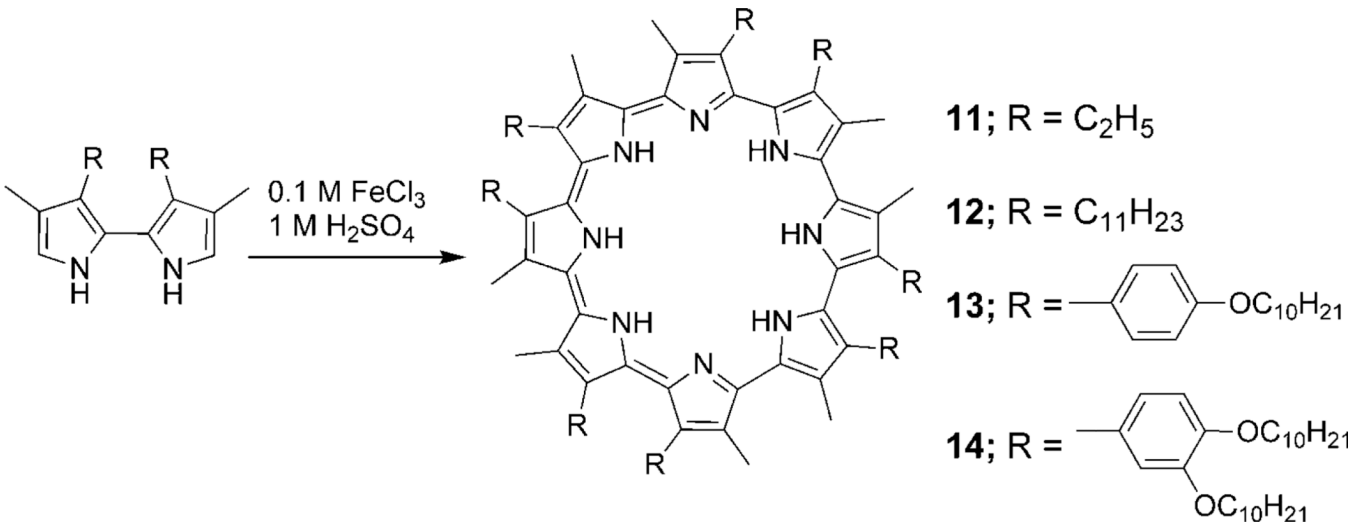
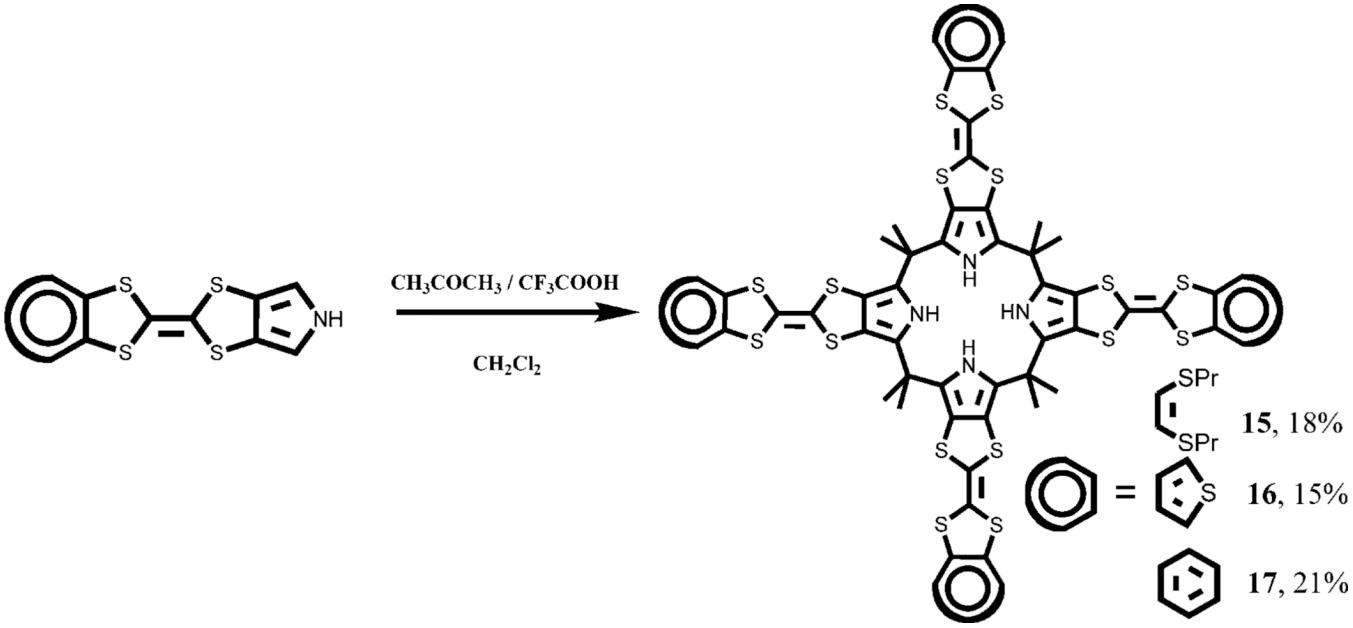


10

Scheme 4.
Chemical structures of sapphyrin (**9**) and Schiff-base macrocycle (**10**).



Scheme 5.
Oxidative coupling of bipyrrolic fragments to form cyclo[8]pyrroles (**11** and **14**).



Scheme 6.
Synthesis of tetra-TTF calix[4]pyrrole derivatives **15**, **16**, and **17**.