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Ion and Molecular Recognition Using Aryl–Ethyne Scaffolding

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Abstract

The aryl–ethyne linkage has been extensively employed in the construction of hosts for a variety of guests. Uses range from ion detection (e.g., of metal cations in the environment or industrial waste and of anions prevalent in nature), to molecular mimics for biological systems, and to applications targeting future safety issues (such as CO₂ capture and indicators for the manufacture of chemical weapons). This Focus Review examines the utilization of the aryl–ethyne linkage in engineering host molecules for a variety of different guests, and how the alkyne unit plays an integral part as both a rigid scaffolding section in host geometry design as well as a linker to allow conjugative communication between discrete π -electron systems.

Keywords

aryl-ethyne; fluorescent probes; host–guest systems; sensors; supramolecular chemistry

1. Introduction

The use of defined, preorganized scaffolds for host–guest chemistry originates in the discovery of cyclodextrins, and the recognition of their rich intermolecular interactions in the earlier half of the 20th century.^[1] Quickly thereafter, the field of inclusion chemistry exploded with the advent of crown ethers, cryptands, and cavitands, which defined the discipline of supramolecular chemistry.^[2] Since their inception, synthetic molecular hosts have utilized a variety of linkers to elaborate their binding cavities. Oftentimes, structural rigidity must be considered as a design principle in host construction. For example, a large segment of macrocyclic receptors use the rigidity inherent in aryl–aryl linkages to create the appropriate geometries for suitable guest inclusion.^[3] Alternatively, inclusion of an alkyne linkage between aryl groups has been utilized within synthetic molecular hosts, both for its ability to directly connect two units by an essentially inflexible spacer, and for the electronic conjugation it enables between the two aryl units.^[4]

Alkynes are installed synthetically via a variety of well-proven techniques. Classically, the alkyne functionality can be formed through dehydrohalogenation reactions or via nucleophilic attack of an acetylide anion. There are also a number of routes to access the alkyne unit from carbonyls, via the Corey–Fuchs reaction, the Colvin rearrangement, or the

Seyferth–Gilbert homologation.^[5] These methods all suffer from harsh reaction conditions, typically requiring a strong base and thus precluding the use of more functionally diverse starting materials. Some work has been done to extend the scope of these reactions to gentler conditions, such as the modified Bestmann–Ohira homologation, though this route is still limited to the formation of terminal alkynes.^[6] For the preparation of aryl–ethynyl linkages, however, few reactions can match the robustness and versatility of the Sonogashira cross-coupling reaction.^[7–9] A large variety of aryl–ethynyl scaffolds are now easily accessible because of the gentle conditions, high yields, and wide functional group tolerance of this reaction.

As the supramolecular chemistry field has grown and the need for new receptors has increased, the alkyne linkage has emerged as a useful rigid unit for construction of receptors with designed cavities. In addition, this motif allows spatial separation of the binding site and a spectroscopic handle, yet still confers the electronic effects of the binding event. In this way, the binding event and the spectroscopic changes can act independently, with the alkyne acting as a wire to convey the electronic perturbations of the binding event to the spectroscopic site.

In this Focus Review, we explore recent advances in the use of aryl–ethynyl receptors in the host–guest chemistry of analyte sensing. The major families of analytes are covered, from cationic metal species to anionic or neutral species prevalent in biological systems. As well, we will cover host use in the development of sensor molecules for a variety of applications, such as detection of chemical weapons. This is not intended to be a comprehensive review, but rather a survey of recent literature exemplifying the utility and versatility of the aryl–ethynyl unit as a structural and/or sensing motif in the construction of molecular receptors. This review focuses mostly on the use of small-molecule synthetic hosts. Except for a few specific examples, the vast, well-studied area of arylene–ethynylene polymers in such sensing applications will not be covered as it has already garnered multiple reviews.^[10]

2. Sensing Strategies

Numerous strategies for the detection of analytes have been employed in recent years. The classic observable changes utilized are either colorimetric or fluorometric, although sensors based upon a gelation response^[11] or other physical state changes have also been developed.^[12, 13] Chiroptical changes measured by circular dichroism (CD) enhancement is emerging as a new method for analyte detection.^[14] Fluorescence remains the most commonly utilized spectroscopic change because of the enhanced sensitivity compared to colorimetric changes.^[15] Fluorescence also lends itself well to sensing within biological microenvironments, such as those inside cells, as native fluorescence of cells can be filtered out by selecting a fluorophore possessing non-competitive emission or excitation.^[16, 17] As well, the variety of fluorescence mechanisms aids in the design of sensor molecules.

The more common and more widely understood mechanisms are photo-induced electron transfer (PET), intramolecular charge transfer (ICT), metal-ligand charge transfer (MLCT), twisted intramolecular charge transfer (TICT),^[18] electronic energy transfer (EET), fluorescence resonance energy transfer (FRET), and excimer/excimer formation. Some of

the more recently developed fluorescent mechanisms are aggregation-induced emission (AIE)^[19] and excited-state intramolecular proton transfer (ESIPT). All of these methods have been utilized for detection of analytes, with particular attention paid to AIE and ESIPT in recent years.^[20, 21]

The aryl-ethynyl scaffold can readily participate in many of these mechanisms toward sensing strategies, as it provides a rigid structural unit for the formation of an appropriate binding cavity, allows for conjugative communication between aryl units for appropriate fluorescent responses, and has fewer degrees of freedom than an alkyl chain, disfavoring non-radiative decay. While free rotation around an alkyne-arene C-C single bond can lead to detrimental non-radiative decay, this conformational flexibility provides a useful handle for sensing purposes utilizing AIE or TICT (Figure 1), where inclusion of an appropriate guest can restrict rotation and yield a spectroscopic response through either twisted relaxation of the excited state, or aggregation of the now-hindered fluorophore to initiate an AIE process.^[22]

Classically, sensor molecules were built utilizing principles outlined in de Silva's seminal review of fluorescent recognition events.^[15] For a PET-based response (Figure 2), the common method of sensor design utilizes an electron-rich donor site (D) as the recognition element tethered to a fluorophore (F). Until the binding event occurs, PET from the donor to the fluorophore quenches fluorescence; however, upon coordination of a cationic or suitably electron-poor guest (G), electron donation ceases and fluorescence turns on. This technique has been utilized since the early 1970s to build sensor molecules, and can be related conceptually to the original complexone sensors first described in the 1950s.^[23]

For many fluorescent sensing mechanisms, the aryl-ethynyl functionality confers the three concepts of the so-called 'magic triangle' of sensor design: rigidification, to confer a large quantum yield; preorganization, to build a binding site already tailored to the intended guest; and electronic decoupling, where the binding subunit and fluorophore are spatially separated enough to inhibit direct interaction of the guest.^[24] To control the signaling response of the host molecule, modification of electron-withdrawing/donating groups attached to a fluorophore significantly affects the spectroscopic changes of the binding event. For example, in our studies, changing the appended groups alters the electron density within an anion sensor and thus the nature of the fluorescent response from different anionic guests (see below).^[25, 26]

Conformational changes upon a binding event can also play a large role in spectroscopic sensing responses. Alkyne linkers provide an axle about which the host molecule can rotate, affording differing conformations upon inclusion of diverse guests. Within our group we have found that an aryl-ethynyl scaffold can adopt varying conformations in the solid state or in solution when influenced by a guest (see below).^[27-29] These conformational changes have a direct effect on the conjugation throughout the system, giving rise to differences in the emission spectra.

3. Charged Species

3.1. Cations

Sensing and quantification of metal cations in solution and complex media is needed due to their environmental prevalence and human health relevance (both beneficial and detrimental). In humans the three most common metal cations are Fe, Zn, and Cu.^[30] Since disruption of homeostasis by these metal ions is causative in many diseases, a more complete understanding of their roles in the body would be beneficial to the medical field.^[30, 31] In addition, the detection of heavy metal cations such as Cd, Hg, Cr, and Pb is an integral research area due to their presence in waste streams and their detrimental effects on living organisms. Molecules selective for these metal ions are thus essential for both environmental and biological sciences. To this end, many sensors based upon aryl-ethynyl scaffolding have been developed to detect metal ions in recent years, with some key examples outlined below. While there are many mechanisms to sense metal cations based upon the variety of interactions with the host molecule, that subject is not broached here as a number of comprehensive reviews are available in the literature.^[30–37]

A tris-phenanthrolyl oligomer connected via ethynyl linkers was used to selectively sense Cr^{III} over other metal cations.^[38] Upon full occupation of the three phenanthroline units, the emission spectrum was shifted by 100 nm, allowing quantification across a range of concentrations. An OFF–ON assay to determine the concentration of Cr^{III} in solution was realized through the Cu^{II} complex with quenched fluorescence; in the presence of Cr^{III} the emission was restored. In addition, a ratiometric assay of Cr^{II} and Cr^{III} was possible through the use of monomeric **1** (Figure 3).

Similar utilization of an acetylene unit as a conjugative linker was realized by Tung, who employed a D-A dyad connected via an alkyne bridge to detect Pb^{II} in solution (**2**, Figure 3).^[39] The 4-pyridyl unit coordinated to Pb^{II} ions and changed the nature of the D-A interaction to give a measurable UV/Vis spectral response, with a binding constant of $\log(K_a)=3.76$ in acetonitrile. Interaction between Pb^{II} and the donor tetrathiafulvalene (TTF) led to no spectroscopic change, as demonstrated with a phenyl analogue.

TTFs are widely used as donors in sensing scaffolds. In one example, a crown-ether-fused π -expanded tetrathiafulvalene (**3**, exTTF) attached to ethynyl anthracenes experienced PET quenching of the anthracene fluorophores (Figure 4),^[40] similar to classical complexone-type sensors.^[41] Upon binding a cation, the donor ability decreases and disables PET to yield an OFF–ON fluorescent sensor for cations. Receptor **3** displayed a selective spectroscopic response for large, soft cations such as Ba²⁺, with a $\log(K_a)$ of 4.11 in THF.

Alkynes define the binding pocket with naphthalene walls in cation sensor **4** (Figure 5), allowing selective fluorometric detection of Fe^{III} ions over a variety of other metal cations.^[42] The alkyne linker provided facile synthetic access to the target sensor molecules (through Sonogashira methodologies) and rigidified the binding site.

Cruciform-shaped molecules have been extensively employed as sensors for metal cations as well as for neutral molecules. Bunz et al. found that a series of structures such as **5** and **6**

(Figure 6)^[43] when utilized in a differential sensing array could discriminate between a variety of metal cations and amines via both colorimetric and fluorometric responses and solvatochromic behaviors.^[44–46] Variants with non-conjugated amine substituents selectively interacted with Zn cations over other metals, while those with conjugated coordinating groups had differing responses.^[47] These structurally simple systems provide superior HOMO–LUMO separation along the X and Y axes, yielding distinctive solvatochromic and analyte-sensitive spectroscopic changes.

Another class of cruciform sensors based on 1,2,4,5-tetrakis-(arylethynyl)benzenes is exemplified by the work of Haley et al.,^[48] where the molecules were found to have selective responses to a variety of metal ions. This class of aryl–ethynyl cruciforms has seen extensive exploration in the literature from fundamental structure–property studies as substructures of larger dehydrobenzannulene derivatives,^[49, 50] as well as by the group of Baxter in their work on strained- and oligo-cruciform aryl–alkynyl systems.^[51, 52]

3.2. Anions

3.2.1. Anion Sensing Mechanisms—In recent years, anion recognition has begun to compete with cation sensing in the literature as a major research thrust. Cation sensor development was spurred in the mid-1960s by the advent of crown ethers and continues to be quite thoroughly explored.^[31, 53] Anion recognition has been slower to progress because of the difficulties of sensing anions over other analytes, with numerous books and reviews citing poorly-defined solvation geometries, low basicity, and high hydration energies among the limitations in coordinating anionic species.^[54–58] A wide variety of mechanisms have been employed to produce a sensing response for an anion over competing analytes.^[59]

Fluorophore collisional quenching is the most easily accessed mechanism for anion sensing, with a variety of neutral and cationic fluorophores having been developed based on this mechanism. Fluorescent polymers are able to maximize the resulting fluorogenic response by providing multiple binding sites. Bringing the anion closer to the fluorophore, as in guanidinium probe **7a**, can also increase the quenching effect (Figure 7).^[60] The increased proximity produced a four-fold increase in response compared to a similar ammonium probe (**7b**).

The second method for designing fluorogenic sensors relies on the ability of the aryl–ethynyl unit to relay electrons in a PET sensor. Unlike the turn-on response commonly encountered with cations, anions typically produce a turn-off fluorescence response when the mechanism is PET-based. This mechanism has been used extensively to produce sensors for the common water contaminant fluoride.^[61] In the BODIPY probe **8** (Figure 8), the terminal boronyl sites are able to selectively coordinate F[−] in the presence of competing anions. The additional electron density of -BMes₂F[−] is transferred through the ethynyl linker and quenches the BODIPY dye upon excitation.^[62]

PET anion sensors also utilize protons as messengers to detect anions, especially more basic anions such as F[−]. A solution of hemi-cruciform **9** (Figure 9) exhibits a large bathochromic shift and quenching upon addition of excess of TBA⁺F[−], which is likely due to deprotonation of the benzimidazole core.^[63] A similar response to acids, bases, and anions

was observed with cruciform **10**.^[64] Gratifyingly, a combination of PET and solvatochromism allowed the absolute identification of numerous amines, boronic acids, and anions.^[65] As with all cruciform structures, their interesting fluorescent behavior is attributed to the excellent orbital separation of the HOMO and LUMO, which facilitates energy transfer during fluorescence and is easily perturbed by analytes.

Altering the angle or freedom of rotation about the alkyne can also cause a change in fluorescence upon anion binding.^[22] The first examples of such a system were bis-ureas **11** and **12** with mono- or dialkyne linker (Figure 10).^[66] A low barrier to rotation provides easy access to the desired *syn* binding conformation from the stable unbound *anti* conformer. In addition, enforced planarity by anion binding causes the energy for non-emissive internal conversion to increase, and the result is a 'turn-on' fluorescent response to Cl^- . The effect of induced planarity is reinforced by titrating in AcO^- , which binds 1:2 to a solution of $\mathbf{12} \cdot \text{Cl}^-$, and observing a decreased quantum yield as the AcO^- displaces Cl^- . Whereas both PET and collisional quenching mechanisms result in 'turn-off' fluorescent responses, the alkyne rotor mechanism is able to generate a turn-on response, which is much easier to detect, and warrants further investigation.

Insight into the turn-on response can be found in the parallel field of molecular switches. The lowest energy conformation of molecular rotors **13** and **14** is 'closed' in the unbound state with two intramolecular hydrogen bonds (Figure 11).^[67] The alkyne can be switched to a second 'closed' state by introducing Cl^- , and the rotor now forms a stable complex with two intermolecular and one intramolecular hydrogen bond. A new Na^+ complex has been observed by cryogenic ion vibrational predissociation spectroscopy that is analogous to the rotational transition state between the two 'closed' states.^[68] The 'open' state can also be considered similar to the unbound state of an alkyne anion host that lacks preorganization.

AIE is another promising mechanism for designing turn-on fluorescent sensors. The close packing of fluorophores into aggregates blocks non-emissive conformers, similar to the alkyne rotors. The Allen group's synthesis of a series of fluorescent lipid mimics incorporating both an anion coordination site and the zwitterionic phosphocholine group (**15**, Figure 12) is an example of AIE in sensors.^[69] The complimentary urea and phosphate groups form head-to-tail dimers in non-coordinating solvents. Fluorescence studies revealed that weakly basic anions (Cl^- or NO_3^-) do not disrupt the dimers, but that more basic anions (H_2PO_4^- or HCO_3^-) cause dissociation and quenching. This offers the possibility of using an anion to template the assembly of non-emissive aryl-ethynyls into emissive dimers or oligomers for a turn-on response.

3.2.2. Selectivity—Considerable effort has gone into the design of reporting mechanisms for anion sensing. The next necessary step is to provide these sensors with not just strong anion binding but selectivity as well. To accomplish this, a variety of methods have been used to develop catalogues of discriminating hosts by altering the selectivity within a single structural family. The most direct method is to alter the size or shape of a rigid binding pocket. For example, the constrictive binding pocket in bisindolocarbazole macrocycle **16** forces N_3^- to bind upright, or perpendicular to the plane of the host (Figure 13).^[70] The N_3^-

can rotate 90° to bind parallel to the plane of the host simply by expanding the pocket to 1,3-diyne **17**.

Selectivity through bottom-up design can nonetheless be time-consuming. As a result, several groups have developed methods for quickly modifying existing hosts to equip a trusted scaffold with new selectivity, for instance, molecular self-assembly, post-synthetic modification, and photoswitching. A particularly ambitious method for quickly building a library of hosts is through the anion-templated assembly of coordination complexes. Two $[M_2L_4]^{4+}$ monomers, with $M=Pd^{2+}$ and $L=18$ (Figure 14), assemble around a single BF_4^- into an interlocked structure, $[M_2L_4]_2^{8+}$, with two additional binding pockets.^[71] The interlocked structure encapsulates BF_4^- , as observed in ^{19}F NMR and ESI-MS data. The $[M_2L_4]_2^{8+}$ complex also exhibited strong allosteric Cl^- binding, where the first equivalent of Cl^- caused a collapse of the outer cavities and facilitated the binding of a second Cl^- .

A single step modification of **18** led to more sterically bulky ligands **19–21** (Figure 14), which formed stable $[M_2L_4]^{4+}$ complexes with BF_4^- templates. Adding Cl^- drove formation of a $[M_2L_4]_2^{8+}$ interlocked cage with Cl^- trapped inside the smaller central cavity.^[72] The smaller central cavity leaves more space in the outer cavities, and the weakly bound BF_4^- undergoes ion exchange with ReO_4^- , to give the final structure $[Pd_2L_4]_2[Cl][ReO_4]_2^{5+}$. Photoswitchable ligand **22** forms a stable $[M_2L_4]^{4+}$ cage upon addition of Pd^{2+} .^[73] This structure is intriguing because it reversibly switches between open and closed conformations upon irradiation with UV (open $\rightarrow$ closed) or visible light (closed $\rightarrow$ open). The open cage has a 47-fold higher affinity for $B_{12}F_{12}^{2-}$ than the closed cage, likely due to increased rigidity preventing Pd^{2+} to $B_{12}F_{12}^{2-}$ close contacts. The ability to control anion binding or selectivity through light stimulus is an exciting opportunity for controlling anion concentration or removing harmful anions with a reusable ligand.

Not surprisingly, the complex host–guest interactions that are important for efficient anion coordination can also be used to quickly change anion selectivity. In systems large enough to bind multiple guests, such as ditopic receptors, the first guest can be used to tune selectivity. The 1,3-diyne macrocyclic host **23** (Figure 15) is capable of exhibiting two binding modes.^[74] First, two independent binding sites coordinate anions inside through hydrogen bonds with one cation external and a second found between the anions. Enclosing a cation inside the binding pocket leads Cl^- to be favored over linear anions and a large cooperativity factor for binding Cl^- . Interestingly, host **13** also assembles into a pseudorotaxane by hydrogen bonding with 3,5-pyridinecarboxamide-*N*-oxide.^[75] The smaller binding pocket still provides six hydrogen bond donors and is selective for linear anions, cyanate or azide. In this case, three distinct binding modes have been demonstrated with a single rigid host molecule.

Rigid host molecules provide the greatest degree of control over the size and shape of the anion binding pocket. While they can be tuned through synthetic modification and secondary guest–guest interactions, sometimes the best method is to provide the host with a certain degree of flexibility to choose its own best guest. Bis-indolocarbazole host **24** (Figure 16) binds SO_4^{2-} ($K_a=25\,000\,M^{-1}$) with a 2500-fold selectivity over other anions in 10% (v/v) MeOH/acetone. Conformationally free hosts can exhibit weaker anion binding

than their rigid counterparts; however, this can be overcome by using noncovalent interactions to favor a preorganized binding pocket. Internal hydrogen bonds organize **24** into a pocket too large for halides, but one that embraces SO_4^{2-} comfortably through eight hydrogen bonds.^[76]

Non-rigid hosts can also be tuned for a desired anion by changing the size and shape of the binding pocket. We have developed a research program that utilizes a modular approach to synthesize highly conjugated arylethynyl receptors for anion recognition. Unlike many fluorescent anion sensors, these sensors contain an inherently fluorescent backbone that features an arylethynyl core as opposed to a pendant fluorophore unit. We have previously described a series of both bis(-sulfonamido)- and bis(urea)ethynylpyridines that exhibit positive fluorescent responses to anions with the right combination of electron-donating and/or electron-withdrawing substituents on the pendant phenyl rings.^[4, 25–29, 77] The bis-ureas (e.g., **25–28**, Figure 17) exhibit a rich solvent-based conformational dependence, showing in the solid state that “S”-, “U”- and “W”-type conformations are all possible depending on solvent guests (for instance, “S” shown in **28**, “U” shown in **25–27**).^[27]

More recently we discovered a NO_3^- selective probe, realized by modification of bis-urea scaffold to add an additional binding site that forms an idealized pocket for trigonal planar anions (e.g., **29–30**).^[78] The desired selectivity of **29** for NO_3^- over halides was supported by ^1H NMR titrations in 10% DMSO/ CDCl_3 . The X-ray crystal structure favors an uncommon explanation for selectivity, namely an anion- π type interaction between NO_3^- and the alkyne attached to the central arene, where the anion rests offset from the center of a tripodal binding pocket (Figure 17 colored inset). Whereas the anion- π interaction is engendered by electron-poor receptor **29**, it is not observed in non-fluorinated receptor **30**, which also loses NO_3^- selectivity over the halogens. ^1H NMR spectroscopy titrations reveal a large shift in the central arene protons of **30** upon complexation to Cl^- , suggesting a $\text{C}-\text{H}\cdots\text{X}^-$ hydrogen bonding interaction (as depicted in Figure 17) that is not observed in the presence of NO_3^- .

The formation of a $\text{C}-\text{H}\cdots\text{halide}$ hydrogen bond is not unique to the tripodal ligand. Two-armed host **27** (Figure 17) also forms strong $\text{C}-\text{H}\cdots\text{X}^-$ hydrogen bonds, both in solution and in the solid state.^[89] X-ray crystal structure determination of the **27**· Cl^- complex showed a short and highly linear $\text{C}-\text{H}\cdots\text{Cl}^-$ contact. The hydrogen bonding interaction was also evident in solution by a large downfield shift of the core proton upon addition of anions. The additional hydrogen bond resulted in a 10-fold increase of the association constant over the free-base parent pyridine host **25**.

Another example of $\text{C}-\text{H}\cdots\text{X}^-$ binding in one of our bis-urea hosts surprisingly led to an anion controlled, three-way molecular switch. Bipy-based ligand **28** (Figure 17) was designed as a selective probe for the complexation of H_2PO_4^- over halides and other oxoanions.^[29, 80] Including hydrogen bond acceptors and donors in the binding pocket improved the selectivity by matching the two-donor, two-acceptor architecture of H_2PO_4^- and allowed the host to bind this ideal guest in a “U” conformation. Titrations and X-ray crystal structures revealed an alternative “S” binding mode for the halides, wherein a urea arm rotates about the alkyne linkage to form a $\text{C}-\text{H}\cdots\text{X}^-$ hydrogen bond at the 3-position of

the bipy subunit. The two distinct binding modes can be accessed sequentially, making the bipy ligand a three-way switchable probe.

An extreme case of a conformationally flexible anion host not only requires internal organization but also relies on two or more host molecules to assemble around a guest. A family of bis-diketodipyrrole receptors (Figure 18) was synthesized to study anion-templated assemblies;^[81] diyne **31** formed a [2+2] double helix as a major species under controlled conditions ($1 \times 10^{-3} \text{ M}$ [7], low $[\text{Cl}^-]$, -50°C). Appending additional arenes stabilized the dimeric complex and facilitated observation in solution at room temperature. A *cis*-Pt linked ligand was also of a suitable geometry to form [2+2] complexes with Cl^- under specific conditions.

Despite the numerous hurdles set up by anions to hinder efforts in designing potent and selective hosts, complex coordination events that were previously only possible with metals have been achieved. The ability of aryl-ethynyl hosts to act as building blocks or foldamers is not restricted to anions as templates. Methods for using the aryl-ethynyl for chiral sensing and even more complex architectures have also been achieved.

4. Emerging Areas

4.1. Chirality

Chirality sensing is the basis of many biological processes and an emerging field for synthetic receptor design. Novel aryl-ethynyl sensors have been synthesized which report the absolute chirality of analytes. Sensors have also been developed that use circular dichroism spectroscopy as a mechanism for selective reporting of non-chiral analytes. Polymeric receptors in the burgeoning field of chiral detection have intriguing prospects for the assembly of supramolecular architectures to mimic natural structures such as proteins and enzymes. Though a detailed discussion on the use of polymeric receptors is beyond this review, a few notable examples will be highlighted in the context of chirality sensing.

Fluorescent aryl-ethynyl polymers have been modified for chiral detection by incorporating chiral binding sites. The Zhu group used a binaphthalene derivative with axial chirality, in conjunction with a Schiff base binding site, to give sensor **32**, which has selectivity for (*D*)-phenylalaninol (Figure 19).^[82]

Another interesting area of research for aryl-ethynyl oligomers and polymers is reproducing the double-stranded helix of DNA with synthetic precursors, which can then be used as induced chiral reporters. In solution and in the solid state, *m*-terphenyl polymers and oligomers such as **33** were found to form an achiral mixture of double helices through carboxylate salt bridges (Figure 20).^[83] The addition of chiral secondary amines induced the dimers to refold into chiral double helices, held together via a salt bridge. The handedness is dependent on the chirality of the amine and could be measured both in solution by CD and in the solid state by AFM. Further studies elucidated a large “sergeant and soldiers” effect, as well as a “majority rules” effect on the chirality.

An oligomeric double-helix was prepared by ring-closing metathesis of salt-bridged *m*-terphenyl monomeric derivatives of **33** appended with alkenes.^[84] The dimeric helix

produced a large CD response with little solvent dependence, compared to a model dimer that displayed a small CD signal. The addition of TFA or Zn^{2+} caused a near complete loss of the observed chirality in the helix due to disruption of the salt bridges. In addition, Zn^{2+} produced a turn-on fluorescence response. The chirality could be returned by addition of sequestering agents for the initial stimuli, addition of DIPEA for acid or [2.2.1] cryptand for Zn^{2+} .

The design strategy of combining a fluorescent molecule with a probe group has also been used for modular, fluorescent chirality sensors. A phenothiazine fluorophore linked with both a chiral amine and boronic acid binding sites furnished **34** (Figure 21).^[85] The resulting aryl-ethynyl sensor provided enantioselective determination of a variety of sugars and organic acids.

The Wolf group has developed a chirality sensing scaffold by appending aryl-amines or aldehydes to a central aryl-ethynyl rod, giving sensors with the general scaffold of **35–36** (Figure 21).^[86–88] The functionalized aryl-ethynyl rotors form imines upon reaction with amine or aldehyde analytes. Chiral diamines or dialdehydes lock the probe in a single chiral conformer, which leads to a large Cotton effect, and quantitative determination of *ee* is possible. Further studies with mono-substituted chiral analytes revealed similar large Cotton effects and linear calibration curves for *ee* determination via CD analysis.

The ethynyl-indolocarbazole anion sensors of Jeong have also been reengineered to act as both a chiral reporter for achiral analytes and a enantiomer-selective sensor for chiral analytes (Figure 22).^[89] The addition of chiral methylene groups to a known indolocarbazole anion probe produced foldamer **37** with a strong helicity preference measured by CD in non-polar solvents. The chiral response of this probe is affected by both the solvent polarity and the presence of anions in solution. For instance, changing the solvent from toluene to CH_2Cl_2 or CHCl_3 resulted in a decrease of the CD signal by half; further increasing the polarity to DMSO or CH_3CN caused a near complete loss of the chirality. Notably, the switchable chirality could also be used to detect anions by noting the CD signal inversion in the presence of Cl^- , Br^- , or AcO^- .

The absolute configuration and *ee* of amino acids can also be determined using indolocarbazole foldamers.^[90, 91] Bis(ethynyl- indolocarbazole)s with appended aryl-aldehydes such as **38** form chiral helices in the presence of *N*-Boc protected amino acids; these helices can subsequently be locked in place by imine formation with ethylene-1,2-diamine. The resulting chiral macrocycles produce a large CD response, and calibration with mixtures of isomers permits rapid determination of *ee* for a given sample. Analysis of X-ray crystal structures and computational models revealed that this stereoselectivity is likely due to steric interactions between amino acid side chains and the bis-alkyne. The development of novel chirality sensors brings supramolecular chemistry closer to its roots in biology and biomolecules.

4.2. Biological Species

One of the primary purposes for synthesizing anion-selective fluorescent probes is to provide biologists and biochemists with better tools for studying anion-regulated cellular

processes. A corollary to this purpose is the synthesis of small molecule- based anion transporters or anion channel mimics. These mimics are useful for studying the mechanisms of cellular anion transport and as possible treatments for anion transport protein deficiencies. The Jeong group was successfully able to design a synthetic chloride channel to mimic the *S. typhimurium* protein.^[92] The combination of four hydrogen-bond donors in an anion-binding pocket with judicious side-chain selection produced a potent anion binder and anion transporter. The presence of both a greasy side-chain and activated alcohols was necessary for efficient anion transport.

Ion transport across cell membranes has also been achieved by designing synthetic molecules to form porous channels.^[93] Oligomers with alternating regions of hydrophilic and hydrophobic chains interpenetrate the lipid bilayer and form supramolecular assemblies. The timescale of the ion transport, measured by time-dependent conductance, indicates a pore formation mechanism, not flip-flopping. Transport rates with various alkali metals allowed for rough determination of the pore size as 0.53 nm.

The work of Moore et al. has gone a long way in proving the viability of designing artificial protein mimics from aryl-ethynyl scaffolds.^[94] Oligomers of phenylacetylene form a helical structure with a well-defined hydrophobic cavity that is able to bind guests in water. Replacement of a single phenyl with a pyridine in the chain provides a reactive site for guest modification either by protonation or methylation reactions. Aryl-ethynyl foldamers have also been used to selectively bind saccharides.^[95–97] A pyridineacetylene foldamer offers multiple hydrogen bond acceptors and provides good shape complementarity. Covalent linkage of the foldamer with a coherent saccharide allows for the synthesis of stable, chiral aryl-ethynyl foldamers (Figure 23). This method of covalent linkage also allows for the possibility of a displacement assay for other guests.

Water-soluble aryl-ethynyl probes have also been applied as selective binders and stabilizers for G-quadruplex DNA structures. A series of triazole (**39**) and trisamide (**40**) functionalized aryl-ethynyl-pyridines were studied for the effects of structural modifications on G-quadruplex stabilization and sequence selectivity (Figure 24).^[98] The trisamide was found to be the most potent ligand at stabilizing a range of G-quadruplex sequences with a 2-fold increase in T_m over the parent bisamide ligand. Addition of a triazole to the bisamide by click chemistry improved the T_m , albeit less than the trisamide. Surface plasmon resonance (SPR) was used to elucidate the kinetics and equilibrium binding constants, K_d , for each ligand. The triazole ligand was found to have good selectivity for one G-quadruplex sequence over others; however, the trisamide was found to have lower sequence selectivity, and both ligands displayed non-specific or multiple binding at high [L].

4.3. Chemical Warfare Agents

Another targeted application where aryl-ethynyls have proven their utility is the sensing of chemical warfare agents and high-energy organic compounds. Recent events have reemphasized these compounds as an important area for sensor development. The principles of aryl-ethynyl sensor design pioneered with simple metals and halides, and including structure design, π -conjugation, π -stacking, and metal coordination have been invaluable when applied to more dangerous compounds.

Stang et al. and Mukherjee et al. have developed a series of cages utilizing alkyne linkers and various metal centers whose native fluorescence is quenched in the presence of nitro-aromatics.^[99, 100] The quenching response of cages such as **41–43** (Figure 25) was selective for nitrated aromatics typical to explosives manufacture over other electron-poor aromatic molecules. A similar quenching response was found in a series of alkyne-linked dendrimers, based upon a silole core. These fully conjugated dendrimers exhibited a fluorescence emission which was selectively quenched in the presence of nitrated aromatics.^[101]

In addition to sensing mechanisms utilizing the quenching abilities of nitrated aromatics, Wild et al. developed a series of alkyne-linked terpyridine Zn complexes such as **44** (Figure 26).^[102] These complexes responded selectively to organophosphate model compounds that are representative of the G-series of nerve agents. These sensor compounds were loaded on a solid support to create a test strip for nerve agents in the gaseous phase.

4.4. Gas Storage

In addition to their use in sensing nitrated aromatics, macrocyclic cage structures assembled from aryl–ethynyl linkages have been used for the selective storage and subsequent release of gases such as CO₂ over other atmospheric gases. The Zhang group has developed a family of organic molecular cages assembled with aryl–ethynyl linkages (Figure 27). These cages demonstrate selective adsorption of CO₂ in the presence of N₂, which shows promise in carbon capture applications; the ability to filter out and separate CO₂ in the presence of N₂ carrier gas is a potent method for the reduction of carbon emissions from industrial processes.^[103] By assembly through dynamic covalent chemistry, formation of the cages **45** and **46** proceeded with exceedingly good yields. Comparison of alkyne-based **46** against previously developed anthracene-based cage **45** showed over a twofold increase in CO₂ selectivity versus N₂ in the solid phase (138/1 for **46** vs. 62/1 for **45**).^[104, 105] Crosslinking **46** via Sonogashira cross-coupling with *p*-diethynylbenzene formed an all-organic framework which demonstrated lower CO₂ selectivity (63/1) over N₂, but higher absorption of CO₂ by weight than all other cages studied (8.01 cm³/g vs. 5.58–3.32 cm³/g).

5.0 Conclusion

In summary, a variety of methods for incorporating aryl–ethynyl groups into recognition scaffolds, and their unique roles as both rigid structural units and conjugative linkers have been summarized. The methods covered utilize the unique characteristics of the ethynyl group to provide selectivity and responsiveness to designed sensors. The simplest usage relies only on acetylenes as rigid, conjugated linkers for reporter and recognition units. However, the complexity of possible aryl–ethynyl-based systems is limited only by the designer's imagination. This has been demonstrated by such a variety of uses as multianalyte responsiveness from a single probe and analyte-responsive mimics of large biomolecules, proteins, and DNA, in addition to the classical guests such as the inorganic anions and cations.

The future directions of aryl–ethynyl compounds in sensing and recognition purposes shows a strong potential for artificial protein mimics, where the alkyne-linked foldamers can construct a chiral structure with a hydrophobic central cavity for stereoselective

supramolecular catalysis. When appended with water-solubilizing groups, this can yield a powerful methodology for water-based supramolecular chemistry. As the field of supramolecular chemistry grows, the aryl–ethynyl linkage is showing itself to be a privileged scaffold for the construction of both molecular machines and supramolecular architectures.

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Biographies

Michael M. Haley studied cyclopropene and cycloproparene chemistry with Prof. Ed Billups at Rice University where he earned both his BA (1987) and PhD degrees (1991). In 1991 he received an NSF Postdoctoral Fellowship to work with Prof. Peter Vollhardt on [N]phenylene chemistry at the University of California, Berkeley. In 1993 he joined the faculty at the University of Oregon where he is currently the Richard M. and Patricia H. Noyes Professor in the Department of Chemistry & Biochemistry. His current research focuses on the chemistry of electron-accepting indenofluorenes, molecules based on phenyl-acetylene scaffolding and other novel carbon-rich/pi-electron-rich systems.

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Blakely W. Tresca is a PhD student in the Department of Chemistry and Biochemistry at the University of Oregon. In 2010, he received his BS in Biochemistry from Trinity University. His undergraduate research was studying antiaromaticity under Prof. Nancy Mills. He is currently a joint member of Profs. Darren Johnson's and Michael Haley's research groups, where he is studying the synthesis of aryl-ethynyl anion receptors and investigating the nature of weak hydrogen bonds.

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Figure 1.

Two common fluorescence mechanisms used in sensing: AIE, where hindrance of internal rotation via aggregation reduces non-radiative relaxation, and TICT, where interaction of a suitable guest causes the TICT state to no longer inhibit fluorescence.

Figure 2. Illustration of PET mechanism for sensing. Coordination of a guest (G) diminishes the electron-donation of the chelating group/electron donor (D), thus stopping quenching and enabling native fluorescence of the fluorophore (F).

Figure 3.

Two examples of metal coordination by nitrogen lone pairs in conjugated fluorophores: an alkyne-substituted phenanthroline monomer (**1**) for fluorescent detection of Cr^{II} and a donor-acceptor (D-A) fluorophore with a 4-pyridyl receptor (**2**).

Figure 4.

Structure of a crown-ether functionalized π -expanded fluorophore for the detection of large, soft metal cations. Inclusion of a cation within the crown-ether pincer limits PET between the exTTF donor and anthracene fluorophore, recovering the anthracene fluorescence of **3**.

Figure 5. Pincer-like molecule **4** with conjugated aromatic walls selectively senses Fe^{III} via an ON–OFF quenching response.

Figure 6. Cruciform molecules **5** and **6** with donor and acceptor groups or differing coordination groups.

Figure 7. Examples of collisional quenching in anion receptor design. Guanidinium- appended fluorophore **7a** provides hydrogen bonding and ion pairing in close proximity to the fluorophore for a high fluorescent response versus ammonium probe **7b**.

Figure 8. Addition of fluoride to aryl-ethynyl BODIPY fluorophore **8** quenches the fluorescence via a PET mechanism.

Figure 9. Cruciform architectures **9** and **10** used for the identification of whole structural families by differential analysis.

Figure 10.

The ability of aryl-ethynyl receptors to provide a desirable turnon response to anions was discovered using bis-ureas **11** and **12**. Cl^- binds 1:1 and turns on fluorescence, while AcO^- binds 1:2 and turns off fluorescence.

Figure 11.

Cryogenic ion vibrational predissociation experiments reveal three distinct states of aryl-ethynyl molecular switches **13** and **14**.

Figure 12. Phospholipid mimic **15** forms head-to-tail dimers that are emissive through an AIE mechanism.

Figure 13.

Ethynyl-linked bisindolyl host **16** binds N_3^- in an upright fashion, perpendicular to the host plane. Extended diethynyl-linked bisindolyl host **17** is able to accommodate linear N_3^- inside the binding pocket, parallel to the host plane.

Figure 14.

A variety of acetylene-linked pyridine ligands employed for constructing $[M^2L_4]^{2+}$ and $[M^2L_4]_2^{4+}$ cages for anion recognition.

Figure 15.

A tricyclic calix[4]pyrrole macrocyclic host (top) and the X-ray crystal structure of tricyclic host **23** (bottom) reveals the supramolecular assembly of a [1:2:2] ditopic receptor with TBA⁺Cl⁻. Hydrogen atoms have been omitted.

Figure 16.

Urea-appended indolocarbazole **24** forms an internal hydrogen-bond supported helix, which binds SO₄²⁻ selectively over other common anions.

Figure 17.

A family of aryl-ethynyl-urea receptors **25**–**30** for selective anion recognition; the inset shows the anion- π interaction between nitrate anion and the electron-deficient core arene and one alkyne group of receptor **29**.

Figure 18. Dipyrrole-diketone anion receptor **31** designed to have two anion binding pockets (top); X-ray crystal structure of **31** complexed with Cl^- (bottom). TBA^+ and hydrogen atoms have been omitted.

Figure 19.
Aryl-ethynyl polymer **32** with an integrated chiral receptor unit.

Figure 20.

Foldamer **33** acts as a chiral reporter in the presence of chiral amines, generating helices of a single handedness due to the amine's chirality.

Figure 21.

Examples of probes for determining chirality. **34**, a fluorescent sensor with chiral binding sites, shows chirally-selective recognition of chiral analytes. An achiral rotor within **35** and **36** can be induced to chiral conformations via imine formation.

Figure 22.

Foldamers **37** and **38** have been engineered to act as hosts for chiral guests using the aryl-ethynyl scaffolding.

Figure 23.

Aryl-ethynyl foldamers form complimentary binding pockets to provide guest selectivity, in conjunction with specific binding motifs.

Figure 24. Side-chain engineering provides both water solubility and G-quadruplex selectivity for bisethynylanilinopyridines.

Figure 25.

A family of macrocyclic hosts based on Pt (top) and X-ray crystal structure of another macrocyclic host based on Ru (bottom) for the detection of nitrated aromatics.

Figure 26.
Zn complex (top) utilized in the detection of common nerve agents (bottom).

Figure 27. Large molecular cages **45** and **46** demonstrate selective adsorption of CO₂ over other atmospheric gases.