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Polyhedral borane derivatives: Unique and versatile structural motifs*

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Abstract: Compounds with polyhedral borane moieties have demonstrated numerous unique properties for a variety of applications, including nanoelectronics, drug delivery vehicles, and live cell imaging. Polyhedral boranes are good pharmacophore analogs of carbocycles because polyhedral boranes are inherently insensitive to many undesirable enzymatic metabolic transformations typical for a majority of aromatic compounds. The defined shape, low molecular volume, and high 3D symmetry of the surface are useful for the application of the polyhedral borane scaffolds as universal and convenient spacers for the modular assembly approach with a controllable predisposition of peripheral groups.

Keywords: boranes; medicinal chemistry; nanostructures.

INTRODUCTION

Medicinal chemistry has been synonymous with organic chemistry for decades. Although nitrogen, oxygen, and halogens have found their rightful places in a variety of medicinal agents, the structural motifs of these entities are all carbon-based. Another carbon neighbor, boron, readily forms complex structural motifs; however, unlike hydrocarbons, boranes prefer to form polyhedral clusters rather than chain structures. Polyhedral borane clusters have demonstrated close relationships with traditional carbopolycyclic systems. This unprecedented analogy, along with their unique structural features and physicochemical properties, draw increasing attention to the use of polyhedral borane derivatives as versatile scaffolds for the creation of novel nanomaterials and medicinal agents [1–4].

Compounds that contain polyhedral borane moieties have demonstrated numerous unique properties for a variety of applications, including nanoelectronics, drug delivery vehicles, and live cell imaging. For example, carboranes have remarkable biological stability, are isosteric with aromatic and caged hydrocarbons, and demonstrate similar pharmacophoric features, such as the ability to bind to a biologically relevant lipophilic pocket of a druggable target. Boron neutron capture therapy (BNCT), which is based on the cytotoxic $^{10}B(n,\alpha)^{7}Li$ reaction, is another promising area in which polyhedral borane clusters are used. The dense clusters enable the design of boron carriers with high tumor-to-blood ratios suitable for the effective therapeutic application of BNCT agents. The high symmetry of polyhedral borane clusters, coupled with their rigid architecture and spherical 3D shape, makes these clusters useful scaffolds for diagnostic and therapeutic labeling and for theranostic applications. Nevertheless, an integrative approach to the practical implementation of these clusters requires the systematic exploration of the field in a multidisciplinary environment that would combine expertise in

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boron chemistry, medicinal chemistry, biology, toxicology, and medicine for the best synergetic effect. To address the growing interest in an application of polyhedral borane compounds, the International Institute of Nano and Molecular Medicine was founded in 2007. For more detailed information, please visit the Institute website [5].

BIOISOSTERISM AND PHARMACOPHORES

The unique physicochemical properties and the molecular dimensions of polyhedral borane compounds make these compounds close bioisosteric analogs of cyclic hydrocarbons [6–8]. In addition, polyhedral boranes are good pharmacophore analogs of carbocycles because polyhedral boranes are inherently insensitive to many undesirable enzymatic metabolic transformations typical of a majority of aromatic compounds. The defined shape, low molecular volume, and high 3D symmetry of the surface are useful for the application of the polyhedral borane scaffolds as universal and convenient spacers for the modular assembly approach with a controllable predisposition of peripheral groups. All of these features enable numerous opportunities for drug design with polyhedral borane species.

For example, *p*-carborane and permethyl-*p*-carborane have been used as hydrophobic globular groups in drug design (Fig. 1) [9].

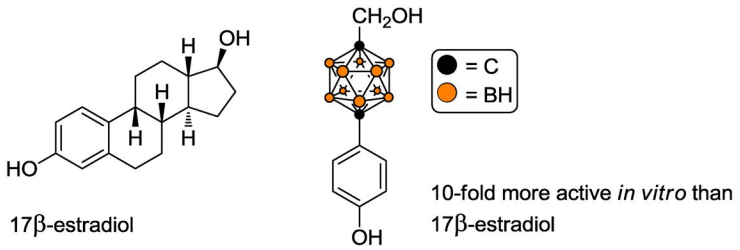

Fig. 1 17β-Estradiol and its *p*-carborane analog.

The absence of π–π stacking interactions allows these carboranes to overcome nonspecific activities and, as a result, eliminate the undesirable side effects associated with flat phenyl rings without deteriorating the specific activity. For example, the *o*-carborane analog of tamoxifen exhibits an activity similar to that of the parent tamoxifen in vitro (Fig. 2) [10].

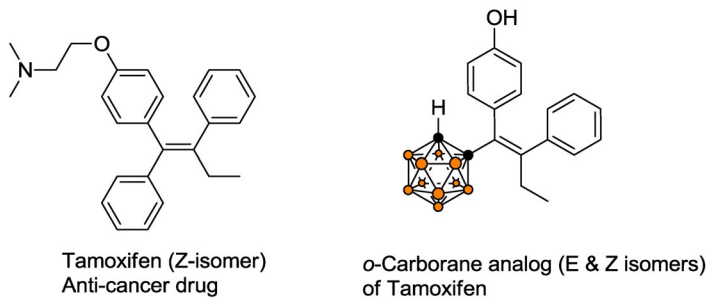

Fig. 2 Tamoxifen and its *o*-carborane analog.

Recently, we have demonstrated a successful application of carborane pharmacophores as transthyretin (TTR) inhibitors. TTR is a 55 kDa homotetrameric protein found in blood plasma that is bound together by thyroxine (T4) (Fig. 3). TTR is produced in the liver and transmits T4 in the spinal

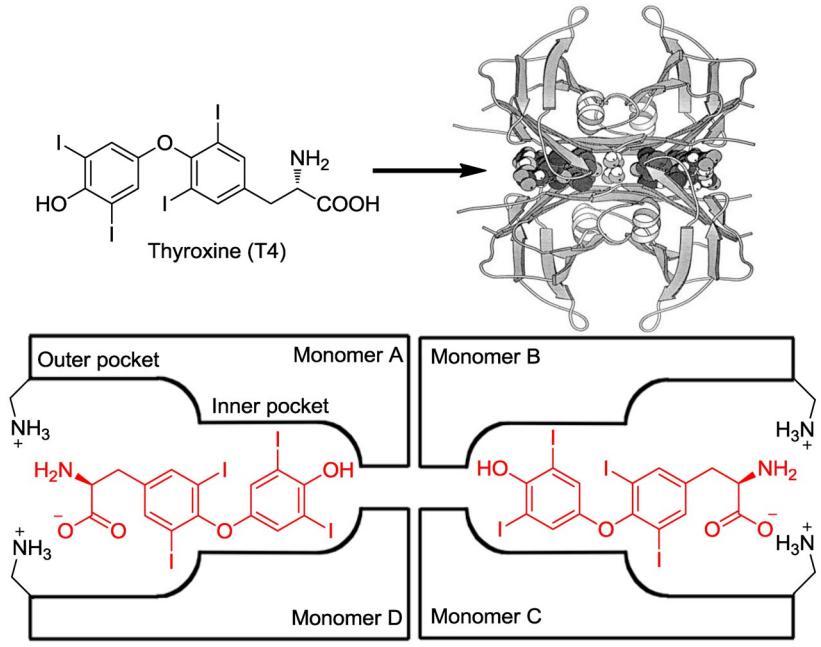

Fig. 3 TTR structure with its natural substrate.

fluids and serum. In some circumstances, the release of T4 causes the tetrameric form of TTR to disintegrate into its monomeric components, which aggregate to form amyloid fibrils. The process of TTR amyloidogenesis appears to cause three different amyloid diseases: senile systemic amyloidosis (SSA), familial amyloid polyneuropathy (FAP), and familial amyloid cardiomyopathy (FAC) [11,12]. Current treatment employs gene therapy involving liver transplantation to replace variant TTR in the blood with the wild-type (WT) protein. TTR contains two identical funnel-shaped hydrophobic binding sites where T4 binds. T4 binding has been shown to inhibit protein dissociation and subsequent aggregation [12].

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as flufenamic acid, diclofenac, flurbiprofen, and diflunisal have been explored as stabilizers of TTR [13]. These NSAIDs are also cyclooxygenase (COX)-1 and COX-2 inhibitors and exhibit side effects associated with these roles (Fig. 4). The development of a stabilizer with high TTR affinity in the blood that does not inhibit COX-1 and COX-2 remains a desirable goal in the treatment of TTR amyloidoses (Fig. 5).

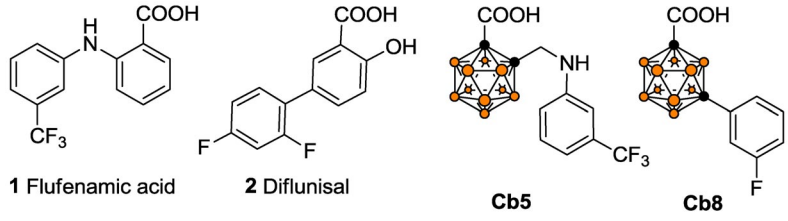

Fig. 4 The NSAID-family TTR aggregation inhibitors and their carborane-based analogs.

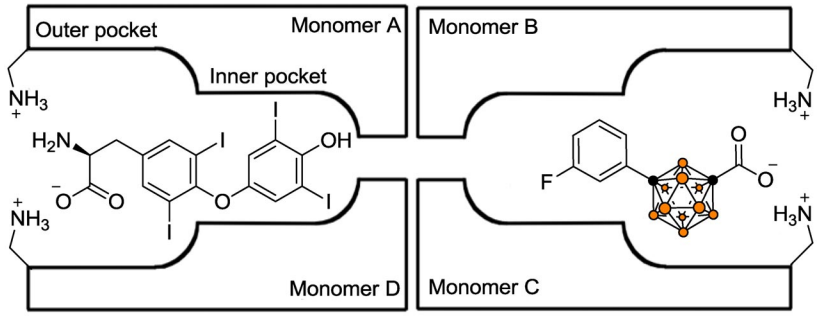

Fig. 5 The binding of T4 and carborane-based drugs to the TTR homotetramer.

The replacement of a phenyl ring in the NSAID-family TTR aggregation inhibitors with the carborane motif leads to the following advantageous outcomes (Table 1) [14]:

- Similar to NSAIDs, the high specificity of carborane-based inhibitors to TTR without COX inhibition is due to the lack of π–π stacking.
- The metabolic stability of the carborane analogs makes these analogs more attractive pharmacophores for long-term therapy because they cannot be oxidized to a quinone structure.

Table 1 Inhibition of TTR fibril formation by NSAIDs and their carborane-based analogs.

	1	**Cb5**	**2**	**Cb8**
1X concentration	3.6 μm	3.6 μm	3.6 μm	3.6 μm
% Fibriol formation	26	22	37	15
2X concentration	7.2 μm	7.2 μm	7.2 μm	7.2 μm
% Fibriol formation	3.4	2.4	5.2	7

A time course assay for the inhibition of fibril formation (Fig. 6) demonstrates that flufenamic acid and the carborane derivatives have comparable activities. A colorimetric COX activity assay [15] indicates that there is no noticeable level of COX inhibition for **Cb8** (Fig. 7). These experimental data clearly demonstrate the high potential of the carborane pharmacophore for the treatment of TTR amyloidoses.

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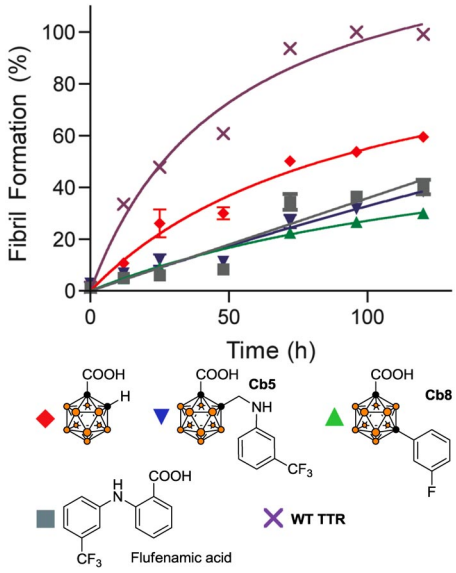

Fig. 6 Comparative assay of flufenamic acid and the carborane derivatives investigating the inhibition of fibril formation.

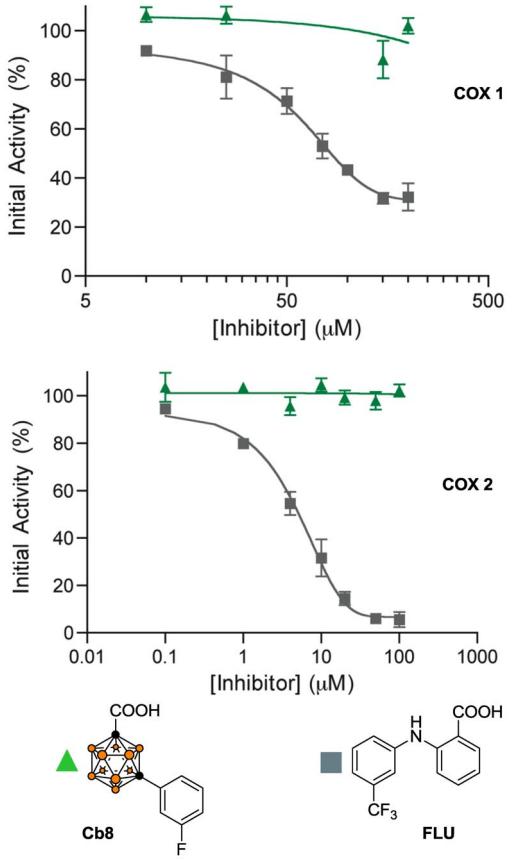

Fig. 7 Comparative COX inhibition assay of flufenamic acid and its carborane derivative.

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CLOSOMERS: NEW STRUCTURAL MOTIFS IN MOLECULAR ARCHITECTURE

The extensive substitution of a *closo*-polyhedral borane or carborane surface by precisely defined moieties forms structures known as "closomers", which are monodisperse molecular nanoparticles. Closomers may have several types of substituents, such as branched (dendritic) or linear (oligomeric) chains (Fig. 8). A polyhedral borane scaffold such as icosahedral $[closo\text{-}B_{12}H_{12}]^{2-}$ is compatible with many chemical-modification reactions that result in structures carrying peripheral chains that have a wide variety of functional groups. Closomeric structures provide camouflaged, multifunctional modules of controlled size, shape, charge, hydrophobicity, etc. designed to accomplish specific functions important in biomedicine and materials science [16,17].

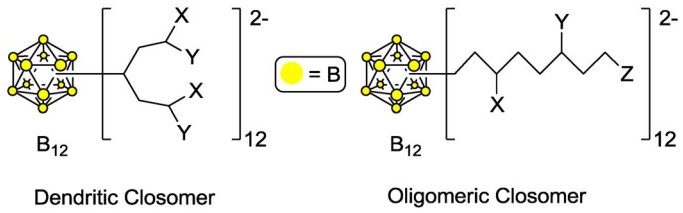

Fig. 8 Dendritic and oligomeric closomers.

The closomers can be synthesized in high yield from readily available starting materials, such as $[closo\text{-}B_{12}H_{12}]^{2-}$, via the perhydroxylation of icosahedral borane and carborane derivatives with an excess of hydrogen peroxide (Fig. 9). The reaction produces stable hydrophilic species with easily derivatizable OH peripheral groups [18,19].

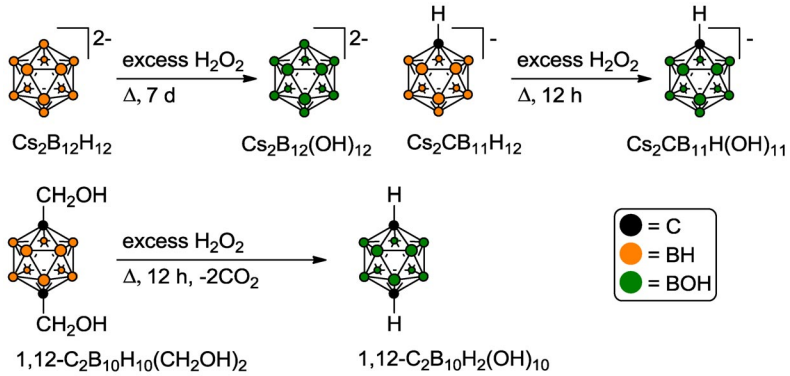

Fig. 9 Chemical routes to closomers.

Although hydrogen peroxide has been proven to be a superior and inexpensive reagent for closomer synthesis, its potentially hazardous nature prompted us to investigate alternative approaches to the $[closo\text{-}B_{12}(OH)_{12}]^{2-}$ synthesis. For example, under the Periana catalytic hydroxylation reaction conditions [20], the *closo*-dodecaborane was successfully converted into the corresponding dodecahydroxy-*closo*-dodecaborane (Fig. 10) by the use of fuming sulfuric acid [21].

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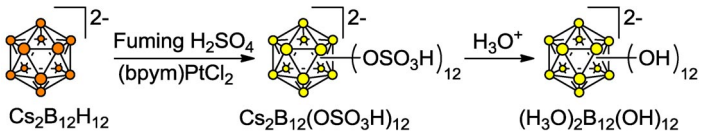

Fig. 10 Catalytic hydroxylation of $[closo\text{-}B_{12}H_{12}]^{2-}$.

Further modification of the perhydroxydodecaborane $[closo\text{-}B_{12}(OH)_{12}]^{2-}$ can be achieved via standard organic reactions to yield the corresponding ether and ester closomers (Fig. 11) [16,17,19,22,23]. Excessively functionalized closomers have ideal spherical symmetry and monodispersity, which make them perfect and unique monomolecular organic nanoparticles (Fig. 12) [17].

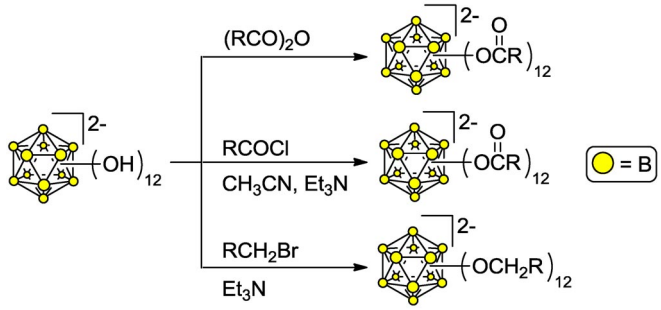

Fig. 11 Synthesis of functionalized closomers.

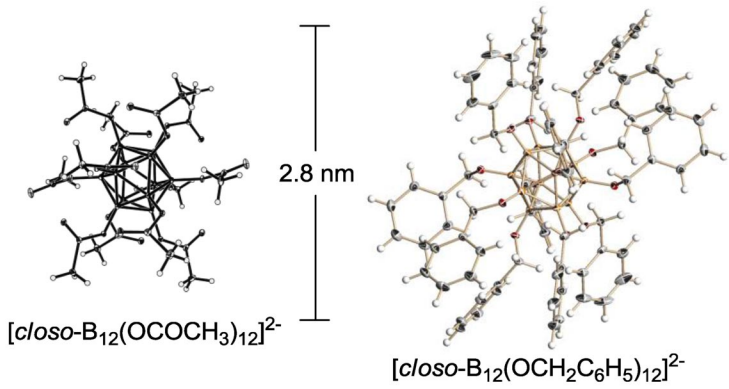

Fig. 12 Representative crystal structures of the closomer ester and closomer ether.

Organic ether and ester closomer derivatives are nontoxic, water-soluble, and hydrolytically stable (pH 3–12) compounds with a rigid spherical 3D shape. The simple preparation and tractable chemistry of the polyfunctional scaffolds are valuable aspects for the design of multivalent molecular assemblies for biomedical applications, e.g., the delivery of diagnostic and theranostic agents. Recently, we demonstrated a two-step modification of dodecahydroxy-*closo*-dodecaborane with a variety of terminal groups, including pharmacophore or fluorescent imaging displays [24]. Thus, $[closo\text{-}B_{12}(OH)_{12}]^{2-}$ reacts with arylchloroformates to form the corresponding dodecaaryl carbonates. These B_{12}-carbonate closomers are susceptible to nucleophilic substitution, and, upon reaction with amines, they form the

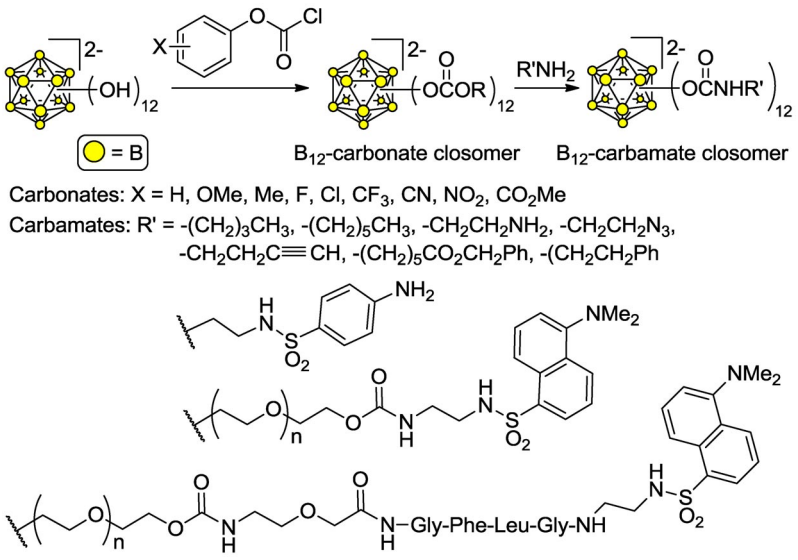

Fig. 13 Closomer carbonates and carbamates.

corresponding B_{12}-carbamate closomers (Fig. 13). The lability of the phenolate moiety increases with the presence of electron-withdrawing groups in the aryl ring.

The azide-alkyne 1,3-dipolar cycloaddition reaction has gained wide use as an efficient "click reaction" for the bioconjugation and synthesis of molecular probes [25]. We have found this reaction to be a very efficient route for the 12-fold functionalization of closomers (Fig. 14) [26].

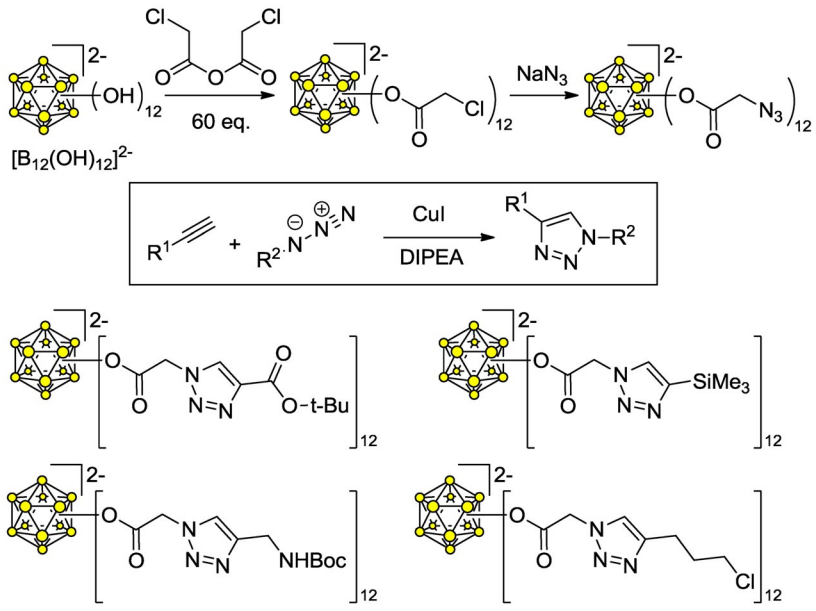

Fig. 14 Closomer 12-fold "click reaction".

Closomer ethers exhibit unique electrochemical properties. Due to strong back-bonding from the ether oxygen to the polyhedral borane cage, the ethers can exist in three discrete oxidation states: as 26-electron dianions, as 25-electron ion radicals, and as 24-electron neutral species (Fig. 15) [17,27]. The transitions between these states are reversible, and the redox potentials strongly depend on the structural features of the alkoxy groups [27]. The relationships between the structure of the ether residue and the corresponding closomer redox potentials are summarized in Table 2.

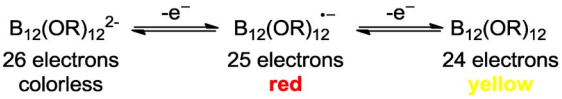

Fig. 15 Three discrete oxidation states of ether closomers.

Table 2 Redox potentials of various closomer ethers.

Closomer substituent	$E_{1/2}$(-2/-1) (V vs. SHE)	$E_{1/2}$(-1/0) (V vs. SHE)
1-Hexyl	–0.73	–0.21
3-Methyl-1-butyl	–0.72	–0.23
1-Pentyl	–0.71	–0.18
1-Butyl	–0.71	–0.18
Ethyl	–0.63	–0.06
1-Buten-4-yl	–0.45	–0.01
Methyl	–0.33	0.14
Allyl	–0.29	0.20
p-Methylbenzyl	–0.45	0.09
p-Methoxybenzyl	–0.42	0.15
benzyl	–0.29	0.22
p-Fluorobenzyl	–0.21	0.37
p-Chlorobenzyl	–0.11	0.47
p-Bromobenzyl	–0.08	0.48
m-Fluorobenzyl	–0.07	0.48
m-Bromobenzyl	–0.06	0.49

The differences in the electronic structures of the closomer ether species result in differences in their physical properties, e.g., a colorless dianion, an intensely red ion-radical, and a yellow or orange neutral ether (Fig. 15). The remarkably tunable pseudometallic properties of these nanomolecular ions empower the closomers with an additional unique aspect for potential applications in nanoscience, such as molecular electronics, electrocatalysis, drug delivery systems, information storage, radionuclide carriers, fluorophores, and electrochromic materials.

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