

Molecular Freaky Friday: Polarity reversal and resorcin[4]arenes as chloride receptors

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Intro: Resorcin[4]arenes, and other electron-rich macrocyclic molecules have long been studied for their utility as cation binders. In this issue of *Chem*, Szumna and co-workers show that through straightforward synthetic modifications, resorcin[4]arenes can be transformed into potent anion binders with record breaking dipole moments for a neutral molecule.

Body: The idea of umpolung, or polarity inversion, in chemistry has long been used to induce interesting reactivity. While quite powerful for the synthesis of unexpected or otherwise difficult

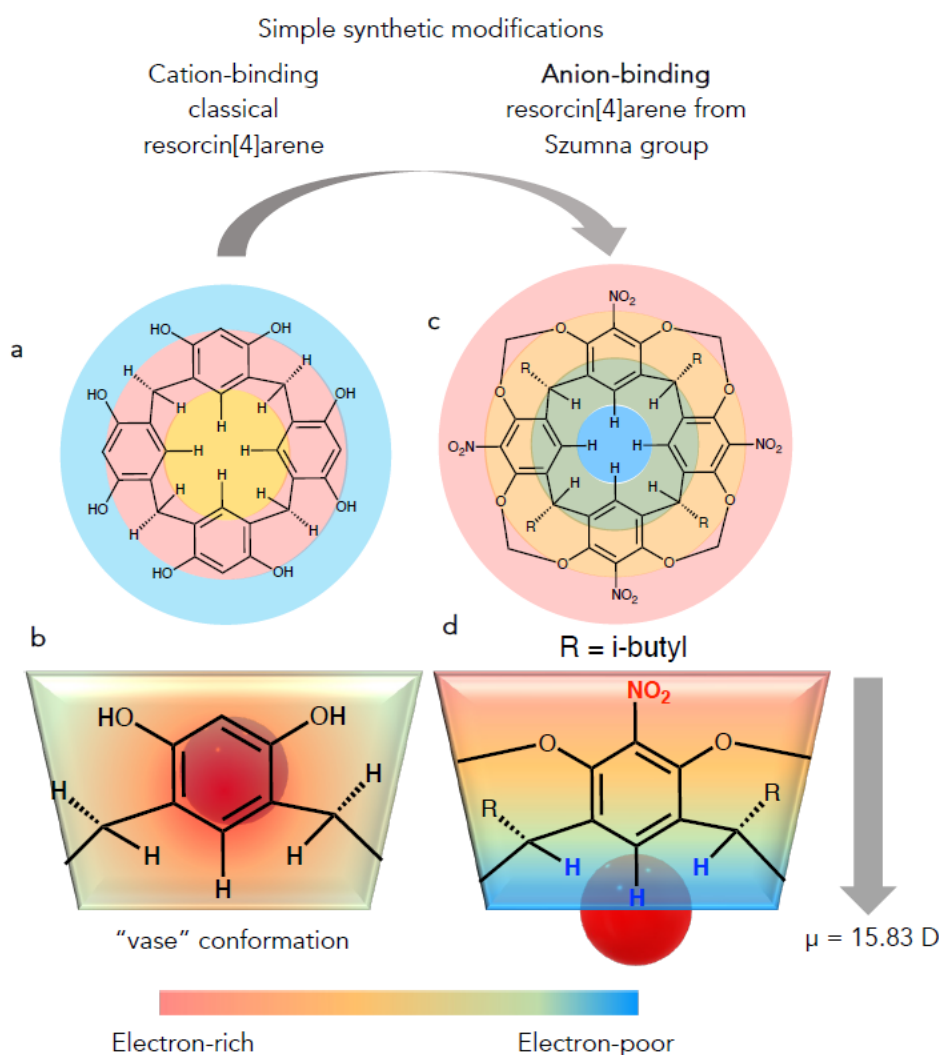


Figure 1. (a) Classical resorcin[4]arene structure; (b) electron density within classical resorcin[4]arene binding a cation in its electron-rich internal cavity while in the vase conformation; (c) Szumna group's modified resorcin[4]arene structure; and (d) electron density of Szumna's modified resorcin[4]arene binding an anion in its electron-poor lower rim through C-H...anion interactions.

to achieve targets, this idea is only beginning to appear in analyte sensing and host-guest chemistry applications of supramolecular chemistry. The structures explored by the Szumna group¹ not only challenge long held notions on the nature of the molecular properties of resorcin[4]arenes (Fig. 1a) and their historical inability to bind to electron-rich analytes, but they also advance previously relied upon design principles for anion-targeting host molecules more generally.

Resorcinarenes, like other macrocyclic aromatic hosts, are not typically considered as anion recognition scaffolds because their π -electron-rich cavities strongly bind cations, hydrophobic species, and other electron-deficient guests. Only recently have supramolecular chemists started to reconsider this paradigm. For instance, recent work from the Szumna² and Hooley³ groups has shown that this class of host molecules—including resorcin[4]arenes and related deep cavitands—that were previously overlooked for electron-rich guest binding, can be transformed into effective anion-binders with deliberate synthetic modifications. Both systems eschew the π -electron rich cation binding pocket and instead utilize the lower rim of these macrocycles to bind anions through hydrogen bonding and related coulombic interactions. These studies highlight that these aromatic scaffolds may have been overlooked historically as anion binding agents: paradoxically, the CH groups at the lower rim of these π -electron-rich hosts can serve as potent anion binding agents when suitably polarized.

One of the difficulties of binding anions using C-H hydrogen bonding lies in the need to have a highly polarized C-H bond, allowing for a partially positive hydrogen atom to interact with the electron-rich anion. As a result, classical hydrogen bonds typically utilize acidic O-H or N-H motifs, posing problems for recognizing reactive anions, binding anions under basic conditions, or preventing chemical exchange at the hydrogen bonding site. To combat this, Szumna and co-workers highlight the importance of C-H hydrogen bonding for selective and strong anion recognition. The C-H hydrogen bond has a long, tumultuous history, with early elegant investigations establishing the existence of C-H hydrogen bonds⁴ undertaken as early as the 1960s by Dr. D. June Sutor, a crystallographer who began by looking at C-H...O contact distances and angles in a series of crystal structures. Unfortunately, the field was not initially receptive to these early studies, resulting in years of debate, controversy, and resistance to accepting the C-H hydrogen bond, now widely accepted as an important member of the hydrogen bond family with wide ranging relevance to structural biology. Fortunately, despite the bumpy road, Dr. Sutor's work was vindicated in an influential review by Desiraju, who wrote: "It is a privilege to dedicate this Account to the memory of D. June Sutor (1929–1990), from whose early work on C-H...O hydrogen bonding much has followed."⁵

Sixty-two years after the initial publication of Dr. Sutor's results, it is now accepted that C-H hydrogen bonds are an important motif within biology and, perhaps unsurprisingly, finding utility within the field of biological anion recognition and supramolecular chemistry. Szumna and coworkers offer a beautiful example of this interaction motif, which enables the transport of anions, engenders an extremely strong dipole moment, and provides for potent anion binding using solely C-H hydrogen bonds. This builds on earlier work in the field of supramolecular chemistry showing the C-H hydrogen bond is effective for binding mildly basic and reactive anionic species, like hydrosulfide. HS⁻ is the conjugate base of the biological gasotransmitter H₂S and serves as a weak base and reactive nucleophile. Recent work from Pluth and co-workers⁶ has shown that weakly acidic and stable C-H hydrogen bond donors can enable reversible and

selective binding of hydrosulfide within a macrocyclic host. Similarly, the state-of-the-art in C-H hydrogen bond potency belongs to the class of macrocyclic and cage receptors from the Flood group, which includes a tripodal cryptand that binds chloride with attomolar binding affinities⁷.

Two key features stand out in the resorcin[4]arenes of Szumna and coworkers from these earlier studies: 1) the clever use of physical organic chemistry to inform design principles in tuning the lower rim of macrocycle as a potent anion binder, and 2) the potentially record breaking calculated dipole moment that results from the most extreme of these designs (Fig. 1c). The highly polar nature of the Szumna macrocycle is particularly interesting because of the presence of the resorcinarene methyleneoxy groups *meta* to the aryl-C-H hydrogen bond, the site of highest (most positive) electrostatic potential in the molecule. The nitro group *para* to each of these C-H hydrogen bond donors provides a strong electron-withdrawing presence through resonance and induction. What is surprising—and seems to have been largely overlooked in resorcinarenes generally—is how much the methyleneoxy groups *meta* to these CH groups also influence the lower rim polarity. Classical courses and textbooks in physical organic chemistry teach the dichotomy of methoxy (and alkoxy, amino, etc.) substituents, which are most often considered as π -electron donating through resonance, particularly in the *para* position according to classical Hammett parameters. Therefore, they are perhaps not the go-to functional group for polarizing hydrogen bonds for anion recognition through electron withdrawal. However, -OMe groups can also be σ -electron withdrawing through induction due to the strongly electronegative oxygen atom. By using both the inductive electron-withdrawing nature of the *meta* alkoxy substituent coupled to the strong resonance and inductive withdrawal of the nitro group, the Szumna lab's macrocycle boasts a calculated dipole moment of 15.83 D, rivaling the 12.7 D reported for a hexacyanosubstituted benzene molecule, which at the time of publication was considered to have the highest known dipole moment for a neutral small molecule⁸. This surprising discovery injects new life into resorcinarenes as potent anion binding agents when the lower rim is suitably polarized. Furthermore, control experiments in this paper investigating the interplay between methoxy- and nitro-substituted model compounds show the combination of these substituents within the resorcinarene amplify the effect, suggesting there is still more to learn on the sometimes perplexing methoxy substituent and its Hammett parameters⁹.

Nearly six decades after the initial discovery of C-H hydrogen bonds by June Sutor, these interactions are finding a home in the field of anion recognition and transport. In their report, Szumna and coworkers have communicated their work on an unexpected resorcin[4]arene-based chloride binder that not only shows strong binding of the anion in its lower-rim through C-H...Cl⁻ binding, but also shows promise as a selective chloride membrane transporter in biological media. Aside from the exciting emerging applications of these molecules, they remind us that venerable macrocyclic systems can receive new life through clever physical organic and synthetic chemistry designs when investigated under a new light.

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- (9) In Discussions with Prof. Eric V. Anslyn, we have both remarked anecdotally that while methoxy substituents often fit ideally within standard LFER plots, they are also perplexingly the substituent most likely to be an outlier in otherwise well-fit Hammett plots. This might suggest that additional scrutiny of the methoxy substituent and its Hammett parameters is warranted.