Unorthodox Interactions at Work

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Abstract

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Reference


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Unorthodox Interactions at Work

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ABSTRACT. This perspective elaborates on the currently unfolding interest to integrate unorthodox non-covalent interactions into functional systems. Initial emphasis is on anion-π interactions at work, particularly in catalysis. Recent highlights are described in comparison to a coinciding renaissance of the more conventional, charge-inverted cation-π catalysis. Progress with these complementary aromatic systems is then compared to recent efforts to integrate halogen and chalcogen bonds, the unorthodox counterparts of hydrogen bonds, into functional systems. General focus is on catalysis, pertinent examples on self-assembly, transport, sensing and templation are covered as well.

1. INTRODUCTION

The use of unorthodox interactions to construct and operate functional systems attracts increasing attention. This is understandable because the discovery of conceptually innovative ways to create function promises to advance the chemical sciences in the most fundamental manner. The term “unorthodox” certainly depends on the circumstances. For example, cation-π interactions are very well recognized by now, but their explicit integration into the rational design of new catalysts remains remarkably rare and recent. In this perspective, we focus exclusively on experimental insights in support of the functional relevance of non-covalent unorthodox interactions. Initial emphasis is on anion-π interactions in comparison to cation-π interactions, their more conventional counterpart. Applying lessons from binding, transport, sensing as well as biosynthesis, their current integration into catalysis is motivated by the general idea to stabilize anionic and cationic transition states on π-acidic and π-basic aromatic surfaces, respectively. This unorthodox chemistry on aromatic surfaces is then connected to coinciding developments with halogen bonds, the unorthodox counterpart of hydrogen bonds, and with chalcogen bonds, the equally underexplored homolog of halogen bonds. Operating with σ holes rather than π holes, halogen and chalcogen bonds are of interest in functional systems because of their exceptional directionality, their strength and their overall low polarity. The objective of this perspective article is to bundle and compare these simultaneous recent developments toward unorthodox interactions that work, particularly in catalysis.

2. ANION-π INTERACTIONS AT WORK

The term “anion-π interaction” refers to the binding of anions on the π surface of aromatic systems, with distances around or pref-
The early 90’s.

ganocatalysis so far. Proof-of-principle has been available since
sis, particularly terpenoid cyclizations, it is surprising to realize
eudesmane-stabilizing residue confirmed the occurrence of cati-
creasing yield of aristolochene with decreasing
the intermediate eudesmane carbocation
formation of an allylic carbocation from nerol
lyst.

The original catalyst
Supralmolecular catalysts such as
Similares monoterpene cyclizations have been achieved with
Biosynthesis concerns the cyclization of farnesylpyrophosphate
Squaleneoxide into steroids.
lar is the stabilization of carbocation intermediates by a cluster of
catalyze key reactions in biosynthesis.

In a most recent highlight, the capsule 10$_6$ (H$_2$O)$_6$, formed by
self-assembly of resorcinarene 10, is introduced as cation-π cata-
lyst. The high Brønsted acidity within this capsule catalyzes the
formation of an allylic carbocation from nerol 11. Stabilized by
cation-π interactions within the capsule, this carbocation then
cyclizes first into α terpineol 12 and then into the bicyclic eucaly-
ptol 13. Without the capsule, these reactions do not occur selec-
tively, more complex product mixtures are usually observed.
The same capsule has been used before for cation-π catalysis of selec-
tive Wittig reactions and acetol hydrolysis.

Similar monoterpene cyclizations have been achieved with
supramolecular catalysts such as 14 (Figure 3). These tetrahedral,
highly anionic architectures are constructed by coordination of
catecholate ligands to gadolinium cations. Another reaction
catalyzed by the supramolecular capsule 14 is the solvolysis of

Figure 2. Cascade cyclizations with carbocation intermediates catalyzed by the recent cation-π catalysts 6-10, with indication of the dependence of stereoselectivity of the reaction on the quadrupole moment of the cation-π catalysts.

Figure 3. The retention of configuration during the nucleophilic substitution from (S)-15 to (S)-16 is thought to originate the stereoselective stabilization of reactive intermediate TS2 by cation-π interactions within the supramolecular catalyst 14.

enantiopure substrate (S)-15 with up to 74% retention of configu-
ration. This is remarkable because conventional catalysts afford
product (R)-16 with up to 84% inversion of configuration as ex-
pected for an S$_{N}2$ reaction. The unexpected stereoselectivity of
the supramolecular catalyst 14 has been rationalized by the stabil-
ization of the increasing positive charge on the benzylic carbon in
TS2 by cation-π interactions with the π-basic naphthalenes of the

The MacMillan catalyst 17$^{34}$ has been suspected early on to
operate with cation-π interactions (Figure 4). This intriguing
hypothesis could recently be validated with a systematic study
using the Friedel-Crafts alkylation of methylpyrrole 18 as model
reaction. In this process, enone 19 first reacts with the catalyst to

Figure 4. The stereoselectivity of the Friedel-Crafts alkylation decreases with increasing π acidity of cation-π catalysts 17 and 21-23. TS4 highlights the difference between cation-π interactions with π bases that do (solid arrow) and do not (dashed arrow) continue with an electrophilic aromatic substitution.

2
form an iminium intermediate. This covalent intermediate then reacts with the methylpyrrole 18 as outlined in TS3 and TS4. Subsequent aldehyde reduction affords product 20. To assess the possible stabilization of the iminium intermediate by cation-π interactions, catalysts 21-23 were prepared. With increasingly negative quadrupole moment of the π base in the catalyst, the stereoselectivity of the reaction increased. This stereoselective Friedel-Crafts alkylation also provides a great illustration of the notion developed in the introduction that “too strong” cation-π interactions can result in electrophilic aromatic substitution: Whereas the π bases in the catalysts just interact, the more π-basic substrate 18 reacts (compare TS4, dashed vs solid arrow).

2.2. Anion-π Catalysis. The first report on anion-π catalysis appeared in 2013.7 Extensively used for conceptual innovation in catalysis, the Kemp elimination was selected as simplest possible model reaction to elaborate on the concept (Figure 5). The key to success was the covalent positioning of a weak carboxylate base on the π-acidic surface of either a naphthalenediamide (NDI, m = 0) or a perylenediamide (PDI, m = 1).5,36 In the resulting bifunctional catalysts such as 24, anion-π interactions could turn on during deprotonation of substrate 25 to stabilize the single anionic transition state TS5 as soon as the negative charge is injected into the substrate. Proton transfer to the obtained phenolate then causes the release of the repulsive product 26 and restores the carboxylate in the catalyst. Fortunately, the kinetics observed for the Kemp elimination showed Michaelis-Menten behavior. This was important to extract absolute values for ground- and transition-state stabilization by anion-π interactions. Best results were obtained with NDI catalysts such as 24 with cyano or sulfoxide acceptors in the core and concise Leonard turns (n = 1) to place the carboxylate on the π-acidic surface. Transition-state recognition calculated to $K_{TS} = 4.9 \mu M$ (1) or $\Delta G_{TS} = -28.3$ kJ mol$^{-1}$, ground-state recognition to $K_M = 56.5$ mM or $\Delta G_{TS} = -7.1$ kJ mol$^{-1}$. Most importantly, transition-state stabilization increased with increasing π acidity of the aromatic surface.

To explore anion-π catalysis with more significant reactions, the addition of malonic acid half thioesters (MAHTs) 27 to enolate acceptors such as nitroolefins 28 was selected (Figure 6).6 This enolate chemistry represents one of the most important anionic reactive intermediates in chemistry and biology. With the Claisen condensation between acetyl-CoA and malonyl-CoA, MHT addition marks the beginning of all biosynthesis and is then repeated most impressively in polyketide synthesis. Interestingly, in solution without enzymes, the addition of MAHTs 27 to enolate acceptors such as 28 is not favored. Decarboxylation products such as 29 are obtained as main products instead of the desired addition products 30. The selectivity between the two competing reactions is possibly controlled on the level of MHT tautomers.

The tautomer in TS6 can decarboxylate (solid arrows) before addition (dashed arrows), whereas the tautomers in TS7 or TS8 have to react before decarboxylation. To sense the subtle difference between these anionic tautomers - charge-delocalized planar forms against charge-localized non-planar form -, π-acidic surfaces appeared well-suited. Anion-π tweezers 31 or 32 with a central tertiary amine as base catalyst were already sufficient to overcome the preference for decarboxylation product 29. Increasing π acidity in anion-π tweezers 33 and 34 caused an inversion of selectivity. A disfavored/favored relative yield changing from $\eta^\text{d/f} = 0.6$ for controls to $\eta^\text{d/f} = 1.9$ for tweezers 34 supported that anion-π interactions can selectively accelerate the disfavored yet relevant reaction. Reaction kinetics indicated that the origin of this inversion of selectivity is twofold: With increasing π acidity, i.e., lower $E_{\text{LUMO}}$ of the catalyst, the favored decarboxylation decelerates ($\Delta E^\text{i} > 0$), whereas the intrinsically disfavored enolate addition accelerates ($\Delta E^\text{a} < 0$, Figure 4, right). Most recent results on this system include the introduction of rigidified Leonard turns between π-surface and amine base (providing access to $\eta^\text{d/f} = 4.3$), the interfacing with more complex systems (providing access to enantioselectivity), covalent macrocldiatons to systematically characterize enolate-π interactions (increasing acidity by up to $\Delta pK_a = 5.5$), and the application to more demanding cascade processes.37

Asymmetric anion-π catalysis was realized first with enamine chemistry (Figure 7). In catalysts 33-35, a proline is placed at some distance at one side of the π-acidic surface, and a glutamate in close proximity at the other side. Enamine formation then prepares for the addition of aldehyde 38 to nitroolefin 28 (TS9). Subsequent proton transfer from the proximal acid to the nitronate intermediate shifts the rate-limiting step from TS10 to C-C bond formation in TS9. This design assures that the reaction occurs on the π-acidic surface (esterification inactivated the trifunctional catalysts). With increasing π acidity from 35 to 37, both rate and stereoselectivity of the reaction increased, independent of the configuration on the proline side (Figure 7, right side; the glutamate was kept constant). Results with catalysts 36 were more complex because of the additional stereogenic centers of the

![Figure 5](image5.png)

**Figure 5.** Transition-state stabilization of the Kemp elimination increases with increasing π acidity of anion-π catalysts (R = H, CN (24), SET, SOEt, m = 0, n = 1).

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![Figure 6](image6.png)

**Figure 6.** Anion-π catalysts 31-34 for the selective acceleration of the intrinsically disfavored (d) but biological most relevant addition of malonates 27 to enolate acceptors such as 28.
Figure 7. In asymmetric anion-π catalysis with trifunctional systems 35-37, rates and enantioselectivity of enamine addition to nitroolefins increase with the π acidity of the catalysts.

sulfoxides at the edge of the π surface. However, with perfectly matched, fully rigidified architectures, catalysts 36 with chiral π surfaces afforded product 39 with highest rate, enantioselectivity and diastereoselectivity.

Contributions of anion-π interactions to anion-binding catalysis have been suggested recently.  Chloride elimination from substrate 40 (TS11) followed by addition of the resulting carbocation to silyl enol ether 41 gives ester 42 (Figure 8). This transformation has been introduced as model reaction to probe for anion-binding catalysis. In catalyst 43, anion binding is accomplished by an electron-deficient pyridinium cation. Anion-π interactions with the pentafluorobenzyl substituent have been confirmed to occur in solid and solution. However, catalytic activity of pentafluorobenzyl catalyst 43 did not differ much from other withdrawing substituents such as cyanomethyl.

Figure 8. Anion-binding catalysis with possible contributions from anion-π interactions.

In nature, anion-π catalysis is almost absent because π-acidic aromatics exist neither in proteins nor in nucleic acids. However, intriguing exceptions from this rule have been identified recently.

With regard to both anion-π and cation-π catalysis, the role the counterion deserves special attention. Ion pairs near aromatic systems are ubiquitous in nature and have been explored theoretically and experimentally in several elegant model systems. However, the aromatic systems involved are usually too small and too π-basic to bind both ions on their surface. Usually, the anion is left on the side. Most recently, ion pair-π interactions have been introduced to accommodate both, the anion and the cation, on polarized push-pull π surfaces. Significant contributions to the spectral tuning of push-pull chromophores and the activation of cell-penetrating peptides have been identified. Applications to catalysis have so far not been reported.

2.3. Self-Assembly with Anion-π Interactions. Pioneering studies on anion-π interactions at work have appeared recently also with regard to self-assembly. Anion-π interactions with the neutral tetraoxacalix[2]arene[2]triazine 44 have been studied in much detail (Figure 9). As with many other architectures, nitrate-π (or in catalysis, nitronate-π) interactions were found to be particularly favorable. Very recently, the formation of supramolecular amphiphiles has been explored with the macrocyclic π acid 44 and hydrophobic anions such as sodium dodecylsulfate (SDS, 45), laurate, and so on. In water, the obtained supramolecular amphiphiles were found to self-assemble into vesicles. Control experiments revealed that macrocycles with donating amines in place of the chloro substituents in 44 form neither micelles nor vesicles. Moreover, the addition of competing anions such as NO₃⁻, Cl⁻ and Br⁻ caused the disassembly of the vesicles and release of their content. Vesicle disassembly was also observed upon protonation of the anions in the supramolecular amphiphiles. These results have been interpreted as experimental support for contributions of anion-π interactions to self-assembly.

Another indication for contributions of anion-π interactions to self-assembly has been observed with NDI trimers 46. These chiral macrocycles offer a π-acidic cavity for the inclusion of anions. The inclusion of I⁻ initiated the self-assembly of NDI trimers 46 into chiral helices. The structure of these supramolecular anion-π helices has been resolved by X-ray crystallography.

Figure 9. Self-assembly of macrocycles 44 and 46 into vesicles and helices in the presence of anions 45 and I⁻, respectively.

3. HALOGEN BONDS AT WORK

Similar to the relation between anion-π and cation-π interactions, halogen bonds are often described as the underrecognized counterpart of hydrogen bonds. They originate from the so-called σ hole, an electron-poor area that appears on “top” of electron-deficient halogen atoms, exactly opposite to the covalent bond to the withdrawing substituent. This localized σ hole makes halogen bonds highly directional, characterized by a bond angle of 180° at the halogen atom. Such a strict, linear directionality contrasts sharply to the almost “directionless” π holes, i.e. the much larger cluster of multiple shallow local minima on π-acidic surfaces that accounts for anion-π interactions. These complementary characteristics of σ and π holes determine their respective advantages in functional systems. Compared to hydrogen-bond donors, halogen-bond donors are not only of comparable in strength and better in directionality, they are also more
more demanding examples for halogen bond catalysis exist. The topic has been explored extensively for anion-binding catalysis, many examples for halogen bond catalysis include dienes 52 / 58 and dienophiles 53 / 57, respectively, and the more complex alkylation of 60.

3.1. Catalysis with Halogen Bonds. Several pioneering examples for halogen bond catalysis in exist. The topic has been launched in 2008 with the hydrogen-transfer reduction of quinolone derivatives including 47 to secondary amines 48 (Figure 10).12 Originally, simple fluorinated alkyliodides 49 were used to activate acceptor 47 with a Hantzsch ester 50 (TS12). Later on, more powerful, divalent, cationic halogen-bond donors such as 51 were introduced to catalyze the same reaction as well as the general transfer hydrogenation of imines.13

Carbon-carbon bond formation with halogen bonds was achieved with a Diels-Alder reaction between cyclopentadiene 52 and enone 53 to give the bicyclic ketone 54 (Figure 11).14 Halogen bonds from the divalent and cationic donors 55 to the carbonyl lone pairs were expected to activate dienophile 53. This and several similar, more advanced (bis)halobenzimidazolium catalysts have been explored extensively for anion-binding catalysis of the model reaction between 1-chloroisocroman 40 and silyl enol ether 41 (Figure 8).15 Halogen-bond catalysis of a similar Diels-Alder reaction has been accomplished with catalyst 56 (Figure 11).16 In this version, imine 57 is activated by halogen bonds to react with the Danishevsky diene 58 and afford heterocycle 59 after the elimination of methanol.

A more challenging example for halogen bonds in catalysis is the coupling of alcohols 60 with organosilanes 61 to afford alkene 62 in the presence of molecular iodine.17 Catalyst 63 has been proposed to activate the iodide leaving group on the iodosilane intermediate by halogen bonding, which in turn is thought to cause the elimination of the hydroxide from substrate 60 (TS13, Figure 11). Contrary to the five years younger anion-π catalysis, several other examples exist already for halogen-bond catalysis. They include early Ritter-type reactions,45 elegant semi-pinacol rearrangements,46 and the ring-opening polymerization of L-lactide into poly(L-lactide).47

Asymmetric halogen-bond catalysis remains challenging. As far as biological systems are concerned, halogen bonds have been explored in the oxyanion hole of ketosteroid isomerase. However, the results were disappointing, either because the donors used were too weak or the bond angle incorrect, i.e., < 180°.48

Figure 10. Initial studies on catalysis with halogen bonds focused on hydrogenation of 47. The σ holes on iodine atoms are indicated blue on red.

Figure 11. Recent examples for catalysis with halogen bonds include Diels-Alder reactions between dienes 52 / 58 and dienophiles 53 / 57, respectively, and the more complex alkylation of 60.

3.2. Halogen Bonds in Templated Transformations. Templation by halogen bonds has been the key for the synthesis of poly(diododiacytelene)s 64 (Figure 12).19 This conjugated polymer is of interest because it contains only carbons and iodines and promises access to new ordered forms of carbon by removal of the iodine. Poly(diacytelene)s in general are accessible by topochemical polymerization of butadiynes in ordered materials, often solids. For the synthesis of poly(diododiacytelene)s 64, co-crystals 65 composed of diiodobutadiyne 66 and self-organizing halogen-bond donors such as bis(pyridyl)oxalimide 67 were grown. Whereas the common initiation of topochemical polymerization with light was ineffective, the crystals were found to gradually change color under pressure. Brownish color at 3 GPa indicated incomplete polymerization. At 6 GPa and more, the crystals turned dark blue. The possibility to remove templates such as 67 and isolate and study pure poly(diododiacytelenes) 64 seems to exist. This example is of particular interest because polymer 64 with all its promising structure, properties and perspectives could not be obtained without templation from halogen bonds.

Other examples for transformations templated by halogen bonds include the synthesis of several rotaxanes and catenanes with interesting structures and functions, mostly anion binding.40 An excellent example of this series is the synthesis of rotaxane 68 from acyclic substrate 69 by ring-closing olefin metathesis in the presence of anions (Figure 11).19

4. CHALCOGEN BONDS AT WORK

Like halogen bonds, chalcogen bonds originate from σ holes,24,49 Directed by the σ holes opposite to the covalent bond, halogen bonds are linear. The σ holes of electron-deficient, bivalent sulfur atoms are also opposite to each covalent bond. As a result, they appear on the side of the sulfur atom, just next to the other
covalent bond (Figure 13). The resulting small bond angle has perhaps discouraged the use of intermolecular chalcogen bonds in the design of functional systems. Intramolecular non-covalent sulfur interactions, however, find broad use for conformational control. Examples reach from drug design in medicinal chemistry to the materials sciences. Most common are 1,4, 1,5 and 1,6 O−S and N=S interactions with sulfur atoms in aromatic heterocycles, particularly thiazoles and thiophenes, serving as chalcogen-bond donors.

4.1. Catalysis with Chalcogen Bonds. Asymmetric acyl transfer is one of the few examples for chalcogen bonds in catalysis. The bicyclic isothiourea 70 was shown to resolve racemic secondary benzyl alcohols 71 by stereoselective acylation, yielding ester 72 and leaving enantioenriched substrate 73 behind (Figure 13). As with standard catalysts such as DMAP or DBU, anhydrides like Ac₂O first acylate the catalyst 70. In the acylated intermediate in TS14, an intramolecular 1,5 S=O bond from the endocyclic donor is decisive to orient the carbonyl for stereoselective addition. The approach of benzylalcohol 71 is controlled by π-π interactions with the aromatic rings in the catalyst and steric repulsion from the phenyl substituent. Amidine analogs and the removal of the aromatic group both decrease stereoselectivity significantly. Intramolecular 1,5 chalcogen bonds were further considered to account for stereoselectivity of β-lactonizations and Michael additions.

The planarization of conjugated polymers 64 composed of carbons and iodines and to anion-binding rotaxane 68 (blue circles: halogen-bond donors, red circles: anions) requires templation by halogen bonds (RCM: Ring-closing metathesis).

4.2. Sensing with Chalcogen Bonds. The planarization of conductive polymers with intramolecular chalcogen bonds is extensively used in the materials sciences. Because of its use in organic solar cells, PEDOT might be the most popular example. Planarizing 1,5 O=O interactions are also expected to contribute to the properties of NDIs with sulfides in the core, including anion-π catalysts 31 and 35 (Figures 6, 7). For sensing applications, the control of the planarity of polythiophenes has been maximized with a combination of attraction to and repulsion from “chalcogenic” π holes (Figure 14). In solution, “chalcogen-hole repulsion” between the endocyclic sulfur and the methyl substituents in polythiophene 76 dominates. Twisted out of conjugation, this deplanarization results in yellow colored polymers. Planarization is supported by the complementary chalcogen bond between the sulfur donors and the alkoxy substituents. Fully planarized, polymers 77 have bright red color. This change in color upon planarization was of interest for sensing applications. To non-specifically bind to DNA, the alkoxy substituents were equipped with imidazolium cations. In the presence of both single- and double-stranded DNA, the yellow sensors 76 turned red, presumably due to planarization into the conformer 77.

The concept of planarizable push-pull probes has been introduced to create mechanosensitive membrane probes. For high mechanosensitivity and long fluorescent lifetime, two thiophenes each were bridged with a “sulfide” for the donor and a “sulfone” for the acceptor in push-pull mechanophore 78. The highly fluorescent dithienothiophene S,S-dioxide was further supported by an aldehyde acceptor. Deplanarization of the push-pull mechanophore was achieved by “chalcogen-hole repulsion” between endocyclic donors and exocyclic methyls. A negative charge was attached for delivery and oriented partitioning into lipid bilayer membranes. Consistent with planarization into high-energy conformer 79 in confined space, the excitation maximum shifted up to 80 nm to the red in response to increasing order in the membrane, from liquid-disordered (L₀) to liquid-ordered (Lₐ) and solid-ordered phase (Sₒ). Unchanged emission maxima confirmed that chalcogenic ground-state twisting of push-pull mechanophores provides conceptually new probes that are unrelated with TICT rotors or solvatochromic dyes. In mixed membranes of giant unilamellar vesicles, the different domains could be imaged with the same probe, more disordered ones with twisted probes 78.
excited at shorter wavelength, and more ordered ones with planarized probes 79, excited at longer wavelength.

Figure 14. Sensing with chalcogen-hole attraction and repulsion. Examples include DNA sensing with twisted polythiophenes 76 and planarizable push-pull probes 78 as mechanosensitive membrane probes. The σ holes on endocyclic sulfur atoms are indicated blue on red, chalcogen-bond acceptors in red, chalcogen-hole repulsion in blue.

5. CONCLUDING REMARKS

The objective of this perspective article was to elaborate, in a comparative manner, on the recently emerging interest to integrate unorthodox interactions into functional systems. Emphasis was on ongoing progress toward catalytic systems that operate with π-hole and σ-hole interactions, i.e., anion-π interactions, halogen bonds and chalcogen bonds. The charge-inverted cation-π catalysis was added to this list because, although important in biology, it remains almost as underexplored in chemistry as the complementary anion-π catalysis. Most functional systems operating with unorthodox non-covalent interactions that have been realized so far focus on conceptual innovation rather than practical use. These priorities are fully appropriate, even essential at this stage. However, the rapid growth of asymmetric ion-pairing catalysis has nicely illustrated how already the clever use of orthodox interactions can rapidly change a field to a quite remarkable extent. Considering these attractive perspectives, the next milestones will concern processes that are important but cannot be realized without unorthodox interactions. This general objective is true not only for catalysis but also for other functions mentioned throughout the text, including self-assembly, templation, sensing, transport, and so on. As elaborated in this perspective, pioneering examples this direction, i.e., toward unorthodox interactions that achieve the otherwise unachievable, already exist. They encourage high expectations.

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