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The Emergence of Anion−π Catalysis

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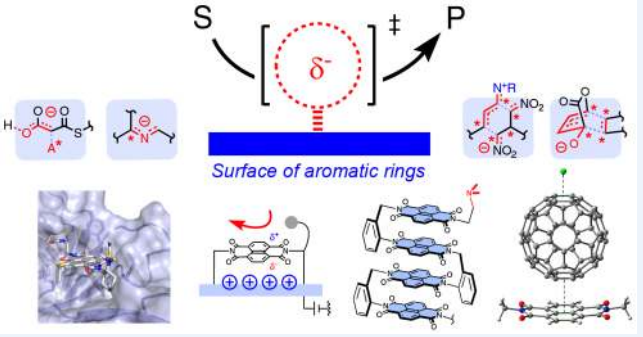
CONSPECTUS: The objective of this Account is to summarize the first five years of anion−π catalysis. The general idea of anion−π catalysis is to stabilize anionic transition states on aromatic surfaces. This is complementary to the stabilization of cationic transition states on aromatic surfaces, a mode of action that occurs in nature and is increasingly used in chemistry. Anion−π catalysis, however, rarely occurs in nature and has been unexplored in chemistry. Probably because the attraction of anions to π surfaces as such is counterintuitive, anion−π interactions in general are much younger than cation−π interactions and remain underrecognized until today. Anion−π catalysis has emerged from early findings that anion−π interactions can mediate the transport of anions across lipid bilayer membranes. With this evidence for stabilization in the ground state secured, there was no reason to believe that anion−π interactions could not also stabilize anionic transition states.



As an attractive reaction to develop anion−π catalysis, the addition of malonic acid half thioesters to enolate acceptors was selected. This choice was also made because without enzymes decarboxylation is preferred and anion−π interactions promised to catalyze selectively the disfavored but relevant enolate addition. Concerning anion−π catalysts, we started with naphthalene diimides (NDIs) because their intrinsic quadrupole moment is highly positive. The NDI scaffold was used to address questions such as the positioning of substrates on the catalytic π surface or the dependence of activity on the π acidity of this π surface. With the basics in place, the next milestone was the creation of anion−π enzymes, that is, enzymes that operate with an interaction rarely used in biology, at least on intrinsically π-acidic or highly polarizable aromatic amino-acid side chains. Electric-field-assisted anion−π catalysis addresses topics such as heterogeneous catalysis on electrodes and remote control of activity by voltage. On π-stacked foldamers, anion−$(π)_n$−π catalysis was discovered. Fullerenes emerged as the scaffold of choice to explore contributions from polarizability. On fullerenes, anionic transition states are stabilized by large macrodipoles that appear only in response to their presence.

With this growing collection of anion−π catalysts, several reactions beyond enolate addition have been explored so far. Initial efforts focused on asymmetric anion−π catalysis. Increasing enantioselectivity with increasing π acidity of the active π surface has been exemplified for enamine and iminium chemistry and for anion−π transaminase mimics. However, the delocalized nature of anion−π interactions calls for the stabilization of charge displacements over longer distances. The first step in this direction was the formation of cyclohexane rings with five stereogenic centers from achiral acyclic substrates on π-acidic surfaces. Moreover, the intrinsically disfavored *exo* transition state of anionic Diels−Alder reactions is stabilized selectively on π-acidic surfaces; *endo* products and otherwise preferred Michael addition products are completely suppressed. Taken together, we hope that these results on catalyst design and reaction scope will establish anion−π catalysis as a general principle in catalysis in the broadest sense.

1. INTRODUCTION

The term anion−π interaction refers to the binding of anions on aromatic surfaces.[1,2] This may appear counterintuitive because the electron clouds above and beneath aromatic surfaces inspire the attraction of cations rather than anions. The resulting cation−π interactions are indeed commonly accepted since the pioneering studies by Dennis Dougherty and others.[3] Cation−π interactions are ubiquitous in nature, known to stabilize cationic reactive intermediates in biosynthesis, with the cyclization of triterpenes into steroids as the most spectacular example.[3,4] They are also increasingly used in organocatalysis.[4]

To make aromatic surfaces attractive to anions rather than cations, one possibility is to invert the quadrupole moment perpendicular to the aromatic plane, that is, Q_{zz} (Figure 1).[1,2] The quadrupole moment of the π-basic benzene **1** is negative (Q_{zz} = −8.5 B, B = buckingham, equivalent to debye−angstrom).[1,2,5] Hexafluorobenzene **2** has a quadrupole moment of similar magnitude but opposite direction (Q_{zz} ≈ +9.5 B). Stronger quadrupole moments can be computed for trinitrobenzene **3** (Q_{zz} = +20 B). We have realized early on

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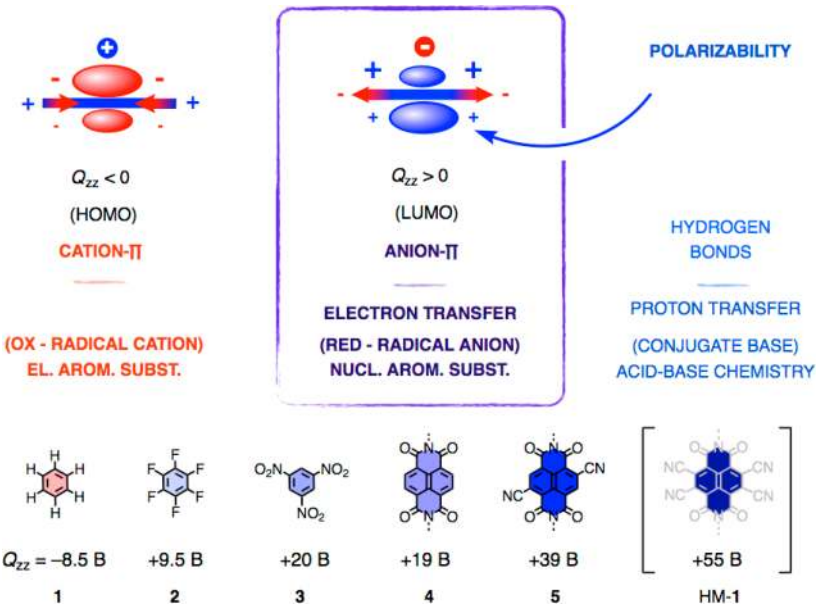

Figure 1. Graphical outline of the nature of anion–π interactions in comparison to cation–π interactions and hydrogen bonds, with representative π base (**1**) and π acids (**2**–**5**, HM = hypothetical molecule).

that naphthalenediimides (NDIs) **4** would be attractive to study anion–π interactions at work because their intrinsic quadrupole moment is in the same range (Q_{zz} = +19 B) and π acidity can be increased with substituents in the core.[5] Dicyano-NDIs **5** with Q_{zz} = +39 B are among the strongest π acids. Tetracyano-NDIs, HM-**1**, would afford Q_{zz} = +55 B but are presumably too deficient in electrons to exist (HM, hypothetical molecule).

Other aspects of anion–π interactions remain intensely discussed (Figure 1).[1,2] This includes the role of induced dipoles perpendicular to the aromatic plane from anion-induced polarization, in-plane dipoles from electron-withdrawing substituents, positive areas on molecular electrostatic potential (MEP) surfaces, also referred to as π holes, and dispersion forces. It is generally understood that anion–π interactions relate to the LUMO level, whereas cation–π interactions relate to the HOMO level. Although usually considered as electrostatic in nature, significant contributions from multicenter covalency have been computed as well.[6] Anion–π interactions that go too far can result in charge-transfer complexes and the formation of radical anions, just as overperforming cation–π interactions can result in the oxidation of the aromatic system. The relation between anion–π interactions and electron transfer can be considered as equivalent to hydrogen bonds and proton transfer. Alternatively, overperforming anion–π and cation–π interactions can proceed to nucleophilic and electrophilic aromatic substitution, respectively.

Presumably because they are counterintuitive and rare in nature (at least on intrinsically π-acidic or highly polarizable aromatic surfaces, with distances shorter than the sum of the van der Waals radii),[1,2,7,8] anion–π interactions are much younger than cation–π interactions. Preceded by casual observations,[9−11] they have been explicitly introduced with a series of computational studies in 2002.[12−14] We became interested in anion–π interactions in the context of anion transport across lipid bilayer membranes, with the first report appearing in 2006.[5] This was at a time when anion–π interactions were still highly controversial and far from being considered in the design of functional systems. However, with this evidence for the stabilization of anions in the ground state, there was no reason to believe that anion–π interactions could not stabilize anionic transition states as well. Initially, this was surprisingly difficult to realize. In 2013, we were finally ready to publish our first report on anion–π catalysis.[15] The first reaction accelerated on the π-acidic surface of NDIs was the Kemp elimination, a classical model reaction characterized by a single anionic transition state. In this study, we also adopted a benchmark test routinely used to probe cation–π interactions:[3,4] Increasing transition-state stabilization with decreasing LUMO energies (or increasing polarizability, *vide infra*) provides strong experimental support that anion–π interactions indeed account for the observed rate enhancements, that is, anion–π catalysis. Encouraged by these results with the Kemp elimination, we started looking for reactions with anionic transition states that are of central importance in chemistry and biology, the anionic counterparts of the carbocations stabilized by cation–π interactions in biosynthesis.[3,4] We settled on enolate chemistry.[16]

2. THE STRENGTH OF ANION–π INTERACTIONS

To quantify the strength of enolate–π interactions directly, we prepared a series of NDIs that are bridged with malonic acid dilactones (Figure 2).[17] In these macrocyclic systems, upfield shifts of the ^{1}H NMR signals show that the malonate α protons are indeed present above the π surface. With an NDI surface, the resonance of the malonate methylene protons shifted from 3.38 ppm for NDI-free malonate diethyl ester **6** to 1.60 ppm for macrodilactone **7** ($R^1 = R^2 = H$, $n = 1$).[18] Upon titration of a mixture of **7** and **6** with base, the upfield peak disappeared with much lower amount of base compared to the downfield peak. This directly observed high acidity of the malonate α protons on the NDI π surface in **7** confirmed that the conjugate base is stabilized by enolate–π interactions.

Deuterium exchange kinetics were measured to determine the pK_a of a series of macrodilactones including **7** and **8** because this well-established method is less interfering than base titrations.[17] Moreover, the conjugate base, which is the

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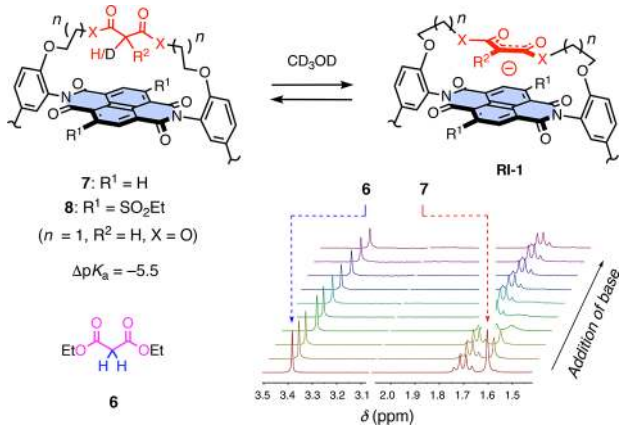

Figure 2. Macrodilactones made to measure enolate−π interactions in reactive intermediate **RI-1** by deuterium exchange kinetics. The ^{1}H NMR spectra show changes in the diagnostic regions of a mixture of **6** and **7** in response to the addition of base. Adapted with permission from ref 18. Copyright 2014 Springer Nature.

enolate anion of interest, is characterized as a reactive intermediate **RI-1**, thus revealing not only thermodynamic but also kinetic information. The results with extreme π acidities were instructive. At one extreme, NDIs with Q_{zz} < 10 B failed to lower the pK_a of the malonate α protons on their surface (e.g., R^1 = OR, NHR, Figure 2). It should thus not surprise when studies with hexafluorobenzene and related π acids reach the conclusion that anion−π interactions are not very significant; cation−π interactions with benzene are not stronger.[1,2] At the other extreme, with maximized π acidity in NDI **8** with two sulfone acceptors in the core, the acidity of the malonate α protons on the π surface increased by ΔpK_a = −5.5 compared to NDI-free **6**. This increase in Brønsted acidity corresponds to the difference between an alcohol and a phenol or between a phenol and a carboxylic acid or the deprotonation of arginines in neutral water, often considered as impossible in biology.[19]

3. ENOLATE CHEMISTRY

Among the many reactions with anionic transition states, enolate chemistry was selected to elaborate on anion−π catalysis because of its importance in chemistry and biology. At the very beginning of most biosyntheses and repeated many times to grow polyketide oligomers, the addition of malonic acid half thioester (MAHT) **9** to enolate acceptors such as **10** is arguably among the most charismatic expressions of enolate chemistry (Figure 3A). Without enzymes, however, the formation of enolate addition products such as **11** is usually disfavored. Decarboxylation affords **12** as the main product instead.[16]

To invert this selectivity and catalyze the formation of the disfavored but relevant addition product exclusively, we thought that the key is the discrimination between the tautomers of malonate half thioesters (MHTs), that is, the conjugate base of MAHT **9**, the first reactive intermediate in both processes (Figure 3D).[16] We assumed that "enol" tautomers as in transition state **TS-1** would undergo addition rather than decarboxylation. In contrast, "keto" tautomers as in **TS-2** would rather decarboxylate than react with an enolate acceptor. The difference between the two tautomers is that enol tautomers with sp^2 α carbons are planar, and the negative charge is delocalized over both carbonyls, whereas keto

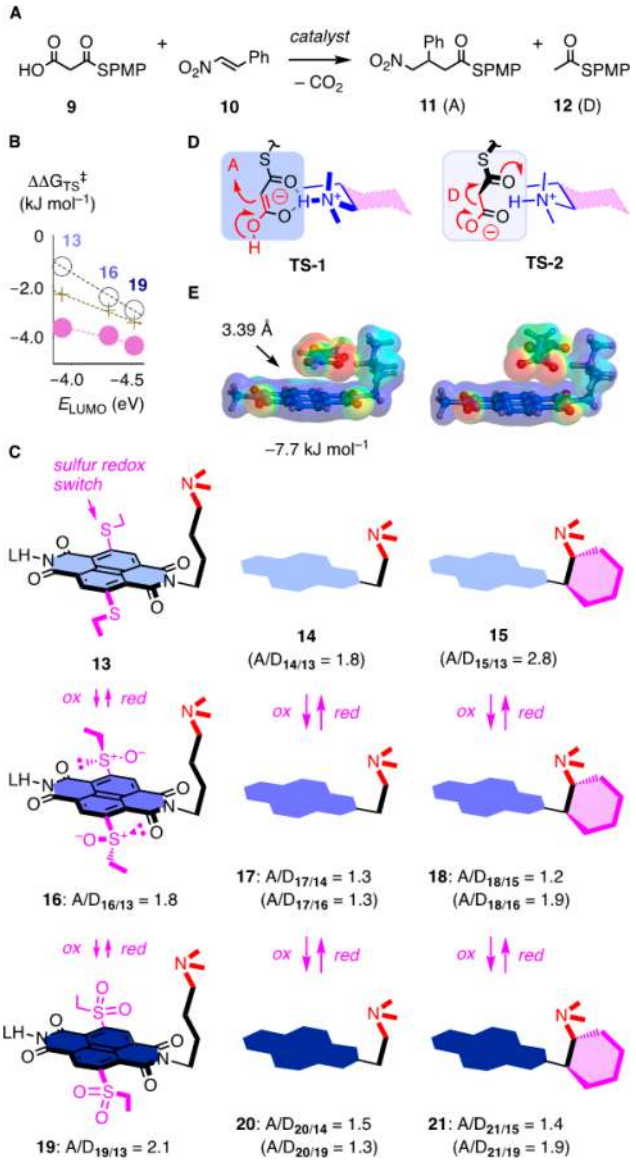

Figure 3. (A) With base catalysis, malonic acid half thioesters **9** either add to enolate acceptors **10** to give **11** or decarboxylate to give **12** (PMP = *p*-methoxyphenyl). (B) Dependence of the differential transition-state stabilization $\Delta\Delta G^{\ddagger}_{TS}$ for addition minus decarboxylation on the LUMO level of NDIs with (C) sulfides (**13**−**15**), sulfoxides (**16**−**18**) and sulfones in the core (**19**−**21**) and loose (**13**, **16**, **19**; ○), flexible (**14**, **17**, **20**; +), and fixed turns (**15**, **18**, **21**; ●); LH = leucylhexyl. (D) Discrimination of enol tautomers in transition state **TS-1**, promoting addition, and keto tautomers in **TS-2**, supporting decarboxylation, with (E) energy-minimized model structures. Panel B adapted with permission from ref 21. Copyright 2016 Wiley-VCH.

tautomers with tetrahedral sp^3 α carbons are bent, and the negative charge is localized on the carboxylate. We thought that π-acidic aromatic surfaces would be just perfect to feel this subtle difference. Recent computational studies from the Frontera group confirmed that these initial speculations were correct.[20] In NDI catalysts (*vide infra*), the enol tautomer resides coplanar 3.39 Å above the π surface (Figure 3E). The bent keto tautomer yields edge-to-face carboxylate−π interactions, with an interaction energy that is +7.7 kJ mol^{-1} weaker compared to the enol tautomer.

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As characteristics of anion−π catalysts, the ratio of the yield of addition (A) product **11** and the decarboxylation (D) product **12** is reported. This A/D value of a given catalyst depends on conditions, particularly, the solvent. To compare results obtained under different conditions, we use relative $A/D_{x/r}$ values in the following to calibrate A/D_x of catalyst *x* against an A/D_r of a reference catalyst.

4. ANION−π CATALYSIS ON NDIs

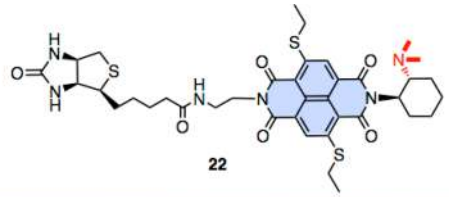
To benefit from anion−π interactions as soon as the negative charge is injected into the MAHT substrate **9**, a tertiary amine base had to be positioned next to the π acidic surface.[21] A rather loose *n*-butyl turn as in NDI **13** will not enforce close contacts between anionic intermediates or transition states and the π surface (Figure 3C). To tighten contacts, flexible Leonard turns as in NDI **14** and conformationally constrained, that is, fixed, Leonard turns as in NDI **15** have been introduced (Figure 3C,D). In their simplest form, Leonard turns refer to a chain of three tetrahedral atoms that fold into half of a cyclohexane-type chair conformation.[22] This folded conformation forces the substituent attached to one end of the turn to sit on the aromatic surface attached to the other end of the turn, as outlined in **TS-1** and **TS-2** (Figure 3D,E). In THF at room temperature, the NDI-amine dyad **13** with a loose turn catalyzed the reaction with a preference for addition over decarboxylation (A/D = 1.1), opposite to that of the NDI-free control (A/D = 0.7). This preference increased with flexible Leonard turns (**14**, A/D = 2.0) and further with the fixed variants (**15**, A/D = 3.1, that is, $A/D_{15/13}$ = 2.8, Figure 3C).

To increase π acidity with minimal global structural changes, we have introduced a sulfur redox switch.[23] Two sulfide donors in the NDI core such as **13**−**15** decreased the π acidity of unsubstituted NDIs slightly (ΔE_{LUMO} = +0.09 eV).[24] Their oxidation affords more π-acidic sulfoxide (**16**−**18**; ΔE_{LUMO} = −0.30 eV) and sulfone containing catalysts (**19**−**21**; ΔE_{LUMO} = −0.51 eV). Application of the sulfur redox switch resulted in increased activity for all catalysts, thus providing experimental support for operational anion−π catalysis (Figure 3C).[21] Compared to a series of anion−π catalysts with loose turns ($A/D_{16/13}$ = 1.8, $A/D_{19/13}$ = 2.1), the response of the better Leonard turn containing series was weaker ($A/D_{18/15}$ = 1.2, $A/D_{21/15}$ = 1.4). The differential in transition-state stabilization for addition against decarboxylation obtained by kinetic analysis gave the same trends: Excellent activity even at low π acidity with tightly positioned base (Figure 3B(●)) and better response to increasing π acidity with loosely positioned base (Figure 3B(○)). Thus, for significant function, maximal π acidity is essential to attract loosely placed substrates to the π surface, whereas weaker anion−π interactions require tight positioning on the π surface to be operational.[21]

5. ANION−π ENZYMES

All canonical aromatic amino-acid residues in enzymes are π basic (W, −13.6 B; F, −8.2 B; Y, −8.5 B; H, −5.9 B); the same is true for nucleobases with one less significant exception (A, −9.0 B; G, −9.2 B; C, −6.6 B; U, +2.0 B).[7] Interactions of anions with π-basic residues in proteins, including enzymes, are dominated by C−H···anion interactions at the side of the aromatic plane.[7,8] Nonassisted anion−π interactions do not occur on small π-basic surfaces, as they are repulsive. To approach these repulsive π surfaces closely (<3.5 Å) and produce significant anion−π interactions, with distances shorter than the sum of the van der Waals radii, cooperative support from cation−π and π−π interactions is needed. Several elegant architectures that realize such cooperative multicomponent interactions have been observed in nature.[7]

These observations called for the construction of artificial enzymes that function by an interaction that is essentially absent in biological enzymes (at least in this form, based on strongly positive quadrupole moments Q_{zz}). To create such an anion−π enzyme, the popular biotin−streptavidin recognition was used.[25] With conjugate **22**, composed of a catalyst **15** and a biotin, the mutant library from the Ward group was screened (Figure 4). The best results were obtained with the S112Y



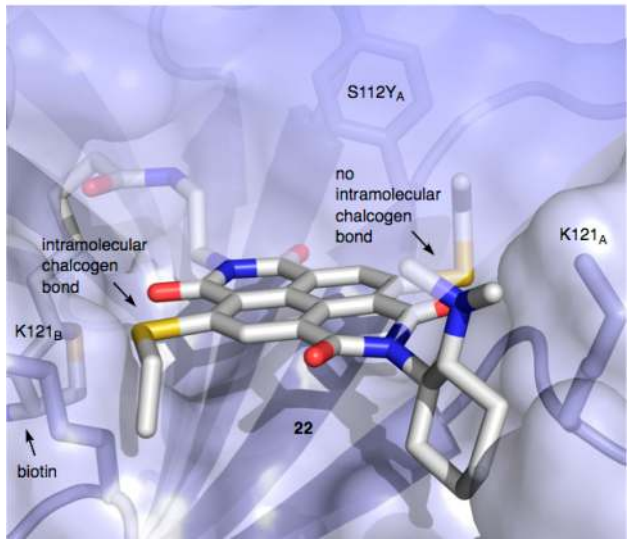


Figure 4. Model of anion−π enzymes, showing the NDI−biotin conjugate **22** bound to the streptavidin mutant S112Y (A and B refer to different monomers of the streptavidin tetramer). Adapted with permission from ref 25. Copyright 2016 American Chemical Society.

mutant, which catalyzed the addition of MAHT **9** to enolate acceptor **10** with 95% ee and without detectable decarboxylation. Without the chiral protein environment, anion−π catalysis of the same reaction with NDI **15** was not stereoselective. The contribution of anion−π interactions to catalysis was demonstrated by inhibition with nitrate. Also noteworthy among much information collected from mutant library screening was the increase in stereoselectivity with rate, that is, increasing transition-state recognition.

Docking simulations suggested how anion−π enzymes might work. In Figure 4, the biotin of conjugate **22** is seen on the left side at the bottom deep inside the streptavidin β barrel. The NDI of conjugate **22** resides in a pocket on the surface of the streptavidin tetramer. The essential S112Y mutant twists one $-CH_2S-$ out of coplanarity with the π plane, thus breaking an intramolecular chalcogen bond[1] to an imide oxygen to asymmetrize the π surface. The two essential K121 residues from two different streptavidin monomers are likely to sufficiently reduce the basicity of the proximal amine base

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from **22** to remain at least partially deprotonated under experimental conditions. Such pK_a modulation by proximal charges is very common in enzymology.[19]

6. ELECTRIC-FIELD-ASSISTED ANION–π CATALYSIS

Electric-field-assisted catalysis is a general topic of current interest because of its promise in remotely controlling molecular transformations, from chemo-, regio-, and stereoselectivities to multistep organic synthesis, in programmable devices.[26] Anion–π catalysis appeared particularly suited for this form of remote control. Electric fields could polarize the π surface, induce an oriented macrodipole perpendicular to the aromatic plane, and thus increase π acidity. Alternatively, electric fields could simply lower LUMO energies, with the same consequences.

To anchor itself on indium tin oxide (ITO) surfaces, anion–π catalyst **15** was equipped with two diphosphonate feet (Figure 5).[27] Extensive studies on artificial photosystems[28]

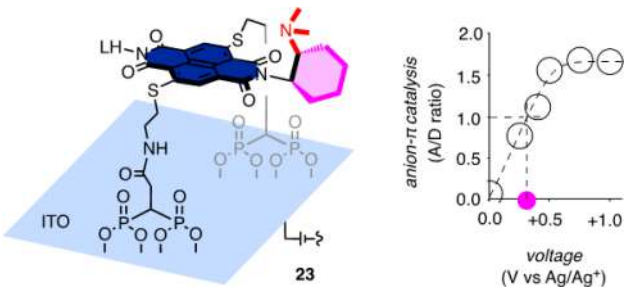

Figure 5. Electric-field-assisted anion–π catalysis on monolayers of NDI-diphosphonates **23** on ITO electrodes, with a dependence of A/D selectivity on the applied voltage.

have taught us that their binding would position the NDI plane in parallel orientation on the conductive solid surface. The monolayers obtained with catalyst **23** covered the ITO surface without detectable leaks.

Heterogeneous catalysis with **23** on ITO electrodes made the addition of MAHT **9** to acceptor **10** very unfavorable at 0 V against Ag/Ag^+ (A/D $\ll$ 1, Figure 5). With applied voltage, enolate addition became increasingly competitive. The nearly linear A/D ratio to voltage dependence was characterized by an inversion potential (A/D = 1) of 330 mV and saturation at A/D = 1.8. Kinetic analysis showed that this voltage dependence originates from a more than 100-fold rate enhancement of enolate addition, that is an increase in selective transition-state recognition by -14.8 kJ mol^{-1} at $V \geq 0.5$ V. These results agree with the expected increase in anion–π interactions by applied electric fields.

7. ANION–$(\pi)_n$–π CATALYSIS

Theoretical studies have predicted early on that anion binding to one face of the surface of a hexafluorobenzene **2** would increase if a second hexafluorobenzene would be stacked to the other face.[7,20] To explore the existence of such anion–$(\pi)_n$–π interactions and their significance in catalysis, we synthesized foldamers **24**–**26** with up to four face-to-face stacked NDIs (Figure 6).[20] Spectroscopic data revealed that the foldamers exist as single conformers independent of solvent and temperature, resisting thermal denaturation also in toluene at 100 °C.

Steady-state and transient absorption, excimer emission, and cyclic voltammetry all supported that electronic communication within the π-stacked foldamers exists and increases with the length of the stacks. The increase per monomer added obeyed the sublinear power laws of diminishing returns of oligomer chemistry. However, the selectivity of MAHT addition to enolate acceptor **10** increased linearly with the length of the stacks to reach a record A/D = 10.5 for anion–$(\pi)_3$–π catalysis on tetramer **26**. As a result, the dependence of catalytic activity on electron sharing with increasing stack length was superlinear (Figure 6). This violation of the sublinear power laws of oligomer chemistry revealed a synergistic amplification of catalytic activity by remote control over the entire stack. Computational data supported all observations, including increased MHT tautomer discrimination with stack length (compare Figure 3E). These results demonstrate the existence and functional relevance of anion–$(\pi)_n$–π interactions. Their discovery and use for anion–$(\pi)_n$–π catalysis are significant also because they reveal perspectives that are unique for anion–π interactions: Cation–$(\pi)_n$–π interactions on π-stacked foldamers are inconceivable because the repulsive π-basic aromatics do not stack.

8. ANION–π CATALYSIS ON FULLERENES

The origin of anion–π interactions can be divided into intrinsic and induced components. Intrinsic π acidity covers all aspects that are inherent to the π system also in the absence of anions or anionic transition states on the surface (low LUMOs,

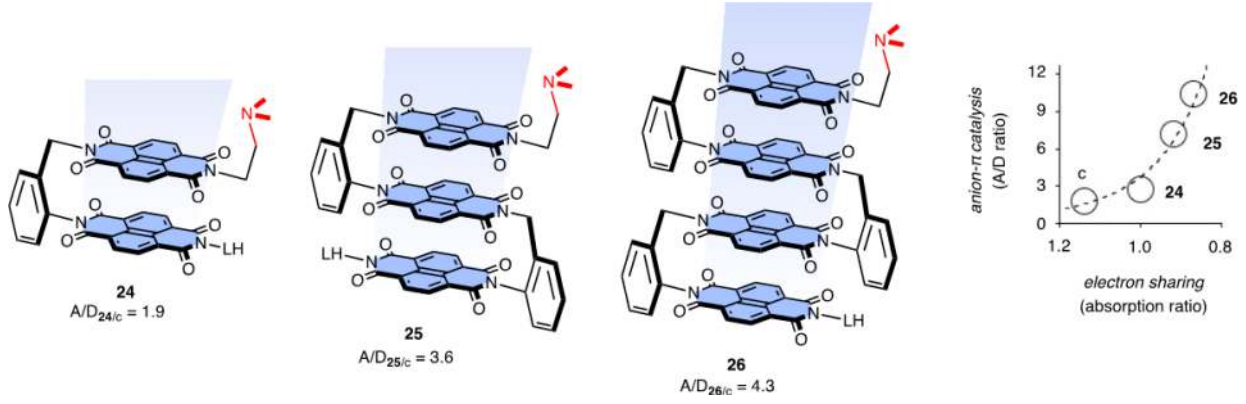

Figure 6. Anion–$(\pi)_n$–π catalysis on π-stacked foldamers, with the dependence of A/D selectivity on electron sharing for π stacks of increasing length; c = monomeric control.

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positive Q_{zz}, positive π holes, and so on, Figure 1). Induced π acidity concerns changes of the π system in response to the binding of anions or anionic transition states on their surface. Most important among them is the oriented macrodipole anions induce in polarizable π systems to support their own binding (Figure 7).

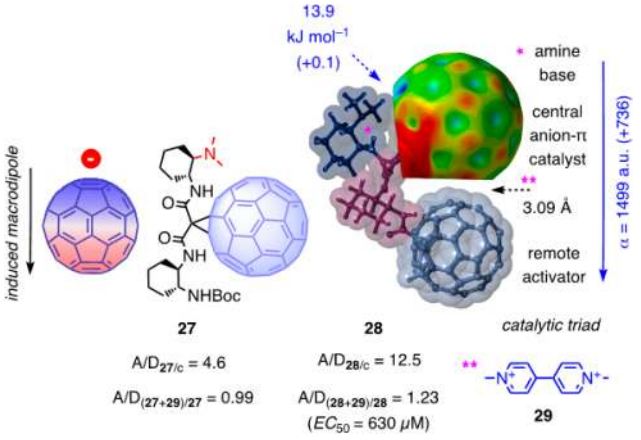

Figure 7. Anion−π catalysis on fullerenes: Exceptional polarizability should create large induced macrodipoles in response to contact with anions and anionic transition states, that is, high induced π acidity (left). The $A/D_{x/c}$ values of catalyst **27** and fullerene-centered catalytic triad **28** with remote covalent (peripheral fullerene) and noncovalent polarizability enhancers (MV intercalator **29**) support these expectations. Adapted with permission from ref 31. Copyright 2018 Wiley-VCH.

Fullerenes offer the purest π system to explore the importance of polarizability for anion−π catalysis in solution without complications from substituents, positive quadrupole moments and in-plane dipoles (Figure 7).[29] The perspective of polarizability-induced anion−π catalysis on fullerenes was attractive because both catalysis and anion−π interactions on this most popular carbon allotrope have received very little attention so far.[30]

Compared to the corresponding control catalyst without fullerene, the selectivity of MAHT addition to enolate acceptor **10** by the catalytic dyad **27** increased by $A/D_{27/c} = 4.6$ (Figure 7).[30,31] This activity is comparable to that of the longest π stacks **26** (Figure 6). In the catalytic triad **28**, a remote fullerene is added on the side opposite to the active site with the amine base.[31] The presence of this remote fullerene pushed anion−π catalysis to $A/D_{28/c} = 12.5$. Polarizability, α, experienced a similarly dramatic boost from the remote fullerene in triad **28**, whereas the intrinsic π acidity was almost unchanged (+0.1 kJ mol^{-1}, Figure 7).

In the presence of methyl viologen (MV) **29**, even higher selectivity was obtained for triad **28** but not for dyad **27**. This difference indicated that MV intercalates between the two fullerenes in triad **28** (Figure 7**). Such intercalation increases both the intrinsic and induced π acidities by attracting electron density from the central fullerene and by further increasing polarizability, respectively. Replacement of the remote fullerene in triad **28** with an NDI did increase intrinsic π acidity by attracting electron density from the fullerene, but neither polarizability nor anion−π catalysis changed much compared to control dyad **27**. High-performance anion−π catalysis on fullerene−fullerene−amine triad **28** thus suggests that the functional relevance of induced π acidity exceeds that of intrinsic π acidity by far. This conclusion might call for a shift of attention from small π surfaces with high quadrupole moments to π surfaces as large and π stacks as thick and long as possible, including higher carbon allotropes.

9. ASYMMETRIC ANION−π CATALYSIS

The reaction of aldehydes **30** with a proline derivative is known to produce an enamine intermediate that can add to acceptors **10** to ultimately yield products **31** with two stereogenic centers.[32] With peptide catalysts, it was shown that a carboxylic acid placed at the right distance from the proline accelerates this reaction, presumably by protonation of the nitronate intermediate resulting from enamine addition. Considering these observations, we thought that the insertion of a π-acidic surface between a proline and a carboxylic acid would be perfect to stabilize the anionic transition states around the nitronate intermediate with anion−π interactions as outlined in **TS-3** (Figure 8).

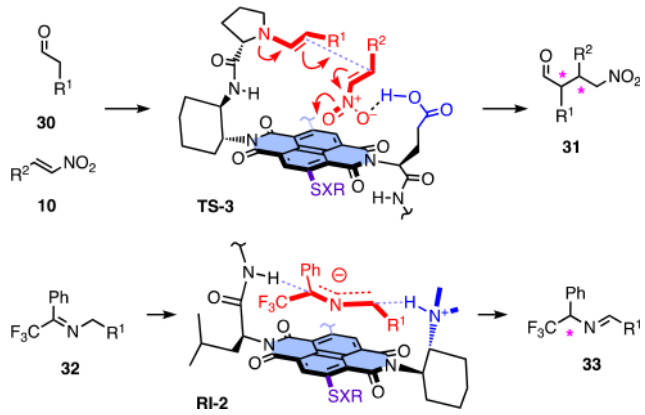

Figure 8. Enamine chemistry and anion−π transaminase mimics.

In the presence of both proline and carboxylic acid at opposite sides of the NDI surface, enantioselectivity and rate of the enamine addition increased with increasing π acidity of the NDI (**TS-3**, X = −, O, O_2). This observation provided the essential evidence that anion−π interactions contribute not only to catalysis but also to stereoselectivity. The chiral sulfoxides at the edge of the π surface influenced the stereoselectivity significantly, with results reaching from the worst to the best.

Anion−π transaminase mimics were conceivable considering that the base-catalyzed imine isomerization from the achiral substrate **32** to the chiral product **33** involves an intriguing 2-aza-allyl anion.[33] The stabilization of the anionic transition states around this reactive intermediate **RI-2** by anion−π interactions was achieved on NDI surfaces with a Leonard-turned amine base on one side to place the substrate directly on the NDI surface, a hydrogen-bond donating amide on the other side, and the standard sulfur switch in the NDI core to vary π acidity without global structural changes. Another recent example for asymmetric anion−π catalysis focused on the creation of nonadjacent stereocenters in 4-chloro-2,4-dicyano-2-phenylbutanoates.[34]

10. CASCADES AND CYCLOADDITIONS

Delocalized over large aromatic surfaces, anion−π interactions appear particularly suited to stabilize charge displacements over long distances in coupled or concerted cascades of anionic

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reactive intermediates and transition states. From this point of view, the holy grail of anion−π catalysis is the anionic counterpart of the cyclization of terpenes into steroids.[3,4] Starting from acyclic and achiral substrates **34** and **35**, the synthesis of a cyclohexane ring with five stereogenic centers on a π-acidic surface is a first step in this direction (Figure 9).[35]

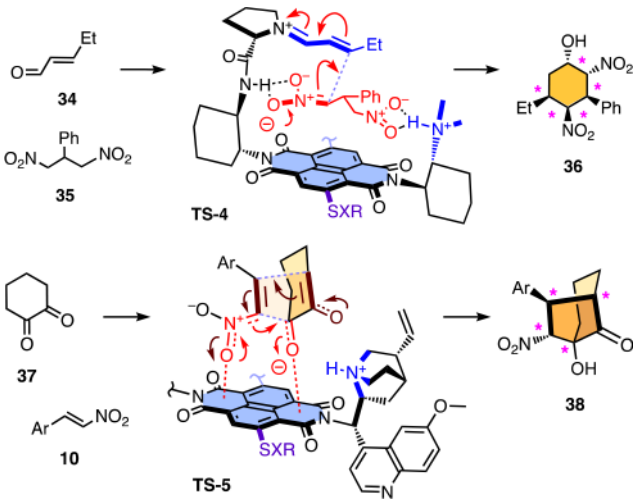

Figure 9. Anion−π catalysis of cascade cyclizations.

This cascade process also integrates iminium chemistry into the repertoire of anion−π catalysis. Iminium chemistry may sound counterintuitive because cations call for stabilization by cation−π rather than anion−π interactions. In the trifunctional anion−π catalyst, the proline is thus placed far from the repulsive π surface to yield a cationic iminium intermediate without close contacts. On the other side, an amine is positioned nearby to intercalate an anionic nitronate intermediate between the attractive π surface and the iminium for conjugate addition as outlined in **TS-4**. Hydrolysis of the resulting enamine and intramolecular Henry reaction with a second nitronate and the released aldehyde then affords cyclohexane **36**. Under conditions optimized for anion−π catalysis, results exceeded the performance of conventional Jørgenson−Hayashi catalysts concerning yield (91% vs 81%), diastereoselectivity (65:14:21 vs 60:21:19), and enantioselectivity (70% ee vs −46% ee).

The logical next step was anion−π catalysis of a cascade cyclization of diketone **37** with **10** into bicyclic products, that is, bicyclo[3.2.1]octan-8-ones **38**.[36] Asymmetric stabilization of **TS-5**, realized also with cinchona alkaloid fusion catalysts and anion−π enzymes, culminated in unprecedented diastereospecificity (dr > 20:1).

Moving on from cascade cyclizations to concerted cycloadditions, we targeted the Diels−Alder reaction next.[37] In the base-catalyzed version, anionic dienes can be obtained from hydroxypyrones **39** and oxa- and thiazolones (Figure 10). Cycloaddition to cyclic and acyclic dienophiles such as maleimides **40** or fumarates affords cyclic products such as **41** with four new stereogenic centers. Bifunctional anion−π catalysts with tertiary amines next to the π surface appeared ideal for the selective stabilization of the open, surface-accessible *exo* transition state **TS-6** by similarly delocalized anion−π interactions. The secondary orbital interactions in **TS-7** that account for *endo* selectivity appeared incompatible with the stabilization on π-acidic aromatic surfaces. Increasing

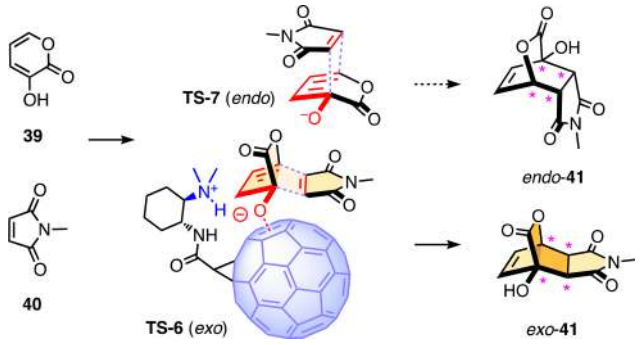

Figure 10. Anion−π catalysis of cycloadditions.

exo selectivity was observed with all catalysts and reactions tested, including examples for full inversion from *endo* to *exo* selectivity on π-acidic surfaces. As for other reactions, rates and chemo-, diastereo-, and enantioselectivities increased with π acidity, and inhibition with nitrate provided corroborative support for operational anion−π catalysis. Anion−π catalysis of Diels−Alder reactions worked not only on NDI surfaces with high intrinsic π acidity[37] but also on fullerene surfaces with high induced π acidity.[30]

One of the long-term objectives of anion−π catalysis is to address otherwise elusive reactivities. Anionic Diels−Alder reactions allowed for a first glimpse in this direction.[37] Catalyzed by 10 mol% TEA, the reaction of thiazolone **42** with maleimide **43** affords the Michael adduct **44** as the main product (Figure 11A, blue). The Diels−Alder product **45** is

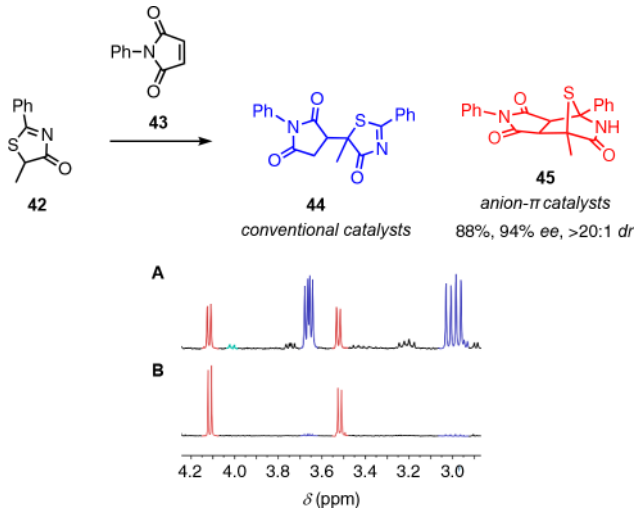

Figure 11. ^{1}H NMR spectra of the product mixtures of the reaction of **42** and **43** catalyzed by (A) TEA and (B) anion−π catalysts, with diagnostic signals for Michael product **44** in blue and *exo*-Diels−Alder product **45** in red. Adapted with permission from ref 37. Copyright 2017 Wiley-VCH.

obtained as a side product in 17% yield (Figure 11A, red). The ^{1}H NMR spectrum of the crude product mixture obtained with 10 mol% anion−π catalyst **15** (Figure 3, SPh instead of SEt) is shown in Figure 11B: Concerted cycloaddition affords the *exo* Diels−Alder product in 88% yield and 94% ee, with hardly detectable *endo* and Michael addition products.

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11. SUMMARY AND CONCLUSIONS

In general, anion−π catalysis functions by stabilizing anionic transition states on π-acidic aromatic surfaces. This is a new concept in catalysis. Since the first explicit study published in 2013,[15] steady progress has been made over the first five years concerning both catalyst design and reaction scope. Anion−π interactions are slowly being considered in catalyst design,[38,39] and more hidden occurrences of unrecognized or underdeveloped anion−π catalysis are likely to emerge,[40−43] particularly considering the importance of polarizability. The tremendous impact of recent progress made with more conventional ion pairing[44] and cation−π interactions[4] supports an optimistic outlook concerning the unorthodox anion−π catalysis. After all, it appears only reasonable to expect that a fundamentally new concept to realize molecular transformations will ultimately provide access to new reactivities and new products with properties that are otherwise beyond reach.

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