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VIP Anion–π Interactions Very Important Paper

DOI: 10.1002/ange.201305356

Catalysis with Anion–π Interactions**

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The expansion of the number of intermolecular interactions available to create molecular functional systems is of paramount importance. Quite recently, we have identified synthetic transport systems as attractive tools to elaborate on interactions that are otherwise difficult to detect.[1–4] Realized examples include anion–π interactions,[1,2] halogen bonds,[2,3] and anion–macrodipole interactions.[4] Intriguing results with transport promised attractive applications to catalysis, because evidence for anion binding in the ground state implied that anionic transition states could be similarly stabilized. Anion–π interactions[5–14] were particularly interesting for this purpose because wonderful examples exist for catalysis with complementary cation–π interactions,[15] reaching from carbocation stabilization in terpenoid and steroid cyclization to surprisingly rare and recent use in organocatalysis.[16] Anion–π interactions, however, have essentially[5–7] not been used in catalysis.[5–14] This is understandable, because experimental evidence for their functional relevance appeared only recently,[1] and discussions concerning their nature and significance continue.[5–14] The poor development of the field presumably originates from the limited occurrence, availability, and diversity of the required π-acids, that is aromatic rings with strong enough electron-withdrawing substituents to invert their usually negative quadrupole moments into positive ones.

The Kemp elimination is an established tool to develop conceptually innovative catalysts.[17–20] Useless with regard to applications in organocatalysis, this reaction has served well to elaborate on theoretically designed enzymes, catalytic antibodies, promiscuous proteins, synthetic polymers, macrocyclic model systems, vesicles, micelles, and non-specific medium effects.[17–20] The key step is the deprotonation of a carbon in the benzisoxazole substrate **S** by a general base (Figure 1). The reaction then proceeds with a single anionic transition state to afford the nitrophenolate either as intermediate or product, depending on conditions. There is general agreement that catalysis in its most general sense occurs by transition-state stabilization.[21] The anionic nature of the transition state thus qualified the Kemp elimination as a valid tool to identify contributions from anion–π interactions to catalysis. Herein, we report that π-acidic naphthalenediimides (NDIs)[1] with a covalently attached carboxylate base can catalyze the Kemp elimination and, most importantly, that the stabilization of the anionic transition state of this transformation increases with increasing π-acidity of the new catalysts.

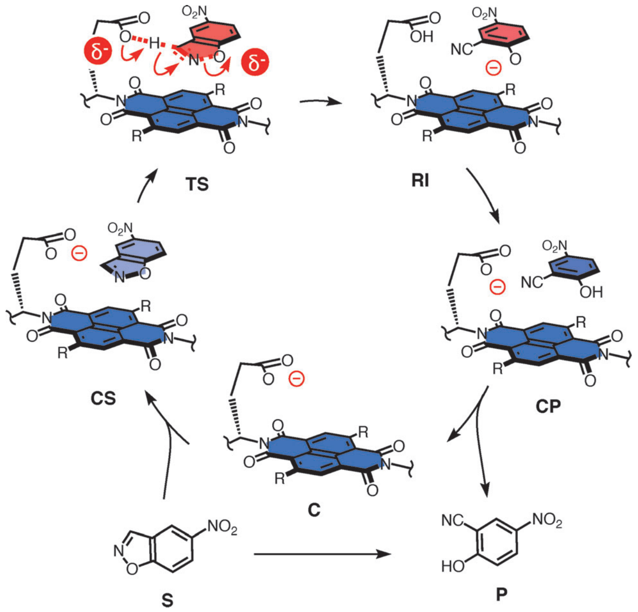

Figure 1. Catalysis of the Kemp elimination with anion–π interactions. A carboxylate is placed as general base near the π-acidic surface of catalyst **C** to 1) couple deprotonation with the onset of anion–π interactions for transition-state (**TS**) stabilization, and 2) protonate the phenolate in the reactive intermediate (**RI**) to avoid product inhibition. blue = electron deficient, red = electron rich, **S** = substrate, **P** = product, **CS** = catalyst–substrate complex, **CP** = catalyst–product complex.

The key to "anion–π catalysis" was to take the π-acidic surface of an NDI (variable and strong), and to attach a carboxylate base on one side and a solubilizing tail on the other side (Figure 2). With this design, π-stacking between substrate and catalyst should hold throughout the transformation. The onset of anion–π interactions between the compound in transformation and the catalyst **C** (Figure 1), however, should coincide exactly with the key step, that is the injection of a negative charge from the proximal carboxylate into the substrate. The translocation of this negative charge over five atoms (from the carboxylate oxygen to the

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[**] We thank the NMR and MS platforms for services, the University of Geneva, the European Research Council (ERC Advanced Investigator), the National Centre of Competence in Research (NCCR) Chemical Biology and the Swiss NSF for financial support, and the Swiss National Supercomputing Center (CSCS) in Lugano-Cornaredo for CPU time. E.O. acknowledges a Sciex Fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305356.

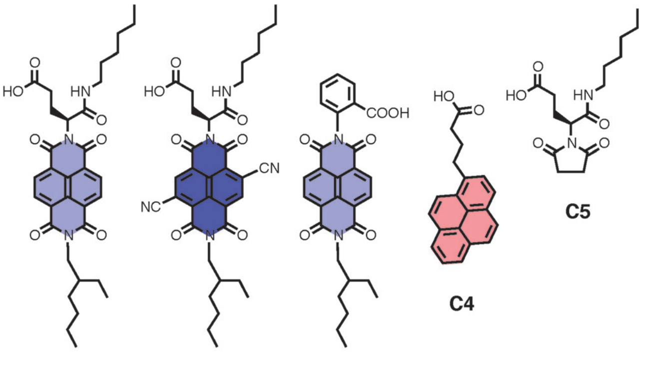

Figure 2. Structure of the operational catalysts **C1** and **C2** together with control molecules **C3**–**C5**.

benzisoxazole oxygen) on the π-acidic surface is a powerful expression of operational anion–π interactions in the transition state. Stabilization by anion–π interactions should continue with the similarly anionic phenolate in the reactive intermediate **RI** and vanish only with the neutral phenol in **CP**. Acidified by intramolecular anion–π interactions with the NDI surface, the carboxylic acid in catalyst **C** should be strong enough to protonate the weakly basic nitrophenolate in **RI**,[12,20] less acidic ammonium cations, pyridinium cations, thiols, or phenols would fail to do so.

To elaborate on possible contributions of anion–π interactions to catalysis, the collection of candidates and controls **C1**–**C5** was considered (Figure 2). Based on established procedures, their synthesis was very straightforward. Details can be found in the Supporting Information. NDIs **C1**–**C3** were selected to explore anion–π catalysis because their π-acidity is very high.[1] Unsubstituted NDIs with peripheral phenyl substituents already have a quadrupole moment ($Q_{zz}=+19$ B) that is in the range of π-acids such as the explosive trinitrotoluene (TNT). Analogous NDIs with two cyano groups in the core, as in catalyst **C2** ($Q_{zz}=+39$ B), are probably the strongest organic π-acids known today.[1] This increase in Q_{zz} naturally coincides with a decreasing LUMO energy of −4.31 eV for unsubstituted NDIs such as **C1** to −4.78 eV for dicyano NDIs such as **C2**.

Pyrenebutyrate **C4** ($Q_{zz}=-14$ B) was selected as a π-basic control. It is almost as π-basic as the native NDI **C1** is π-acidic, and operational cation–π interactions on the π-basic surface have been suspected in the context of cell-penetrating peptides.[22] This was an important choice because theoretically designed enzymes, catalytic antibodies, and synthetic model systems all contain π-basic groups in their active site.[17–20] Extensive computational studies have suggested that these π-bases could serve to stabilize the transition state.[17–20] This conclusion is surprising because, from π-bases, one would expect ground-state stabilization of catalyst–substrate or catalyst–product complexes, whereas interactions in the anionic transition state should be repulsive with π-bases and attractive with π-acids (Figure 1). Control **C3** features a fully contracted and rigidified bridge between NDI and carboxylate, control **C5** contains all structural motifs of **C1** and **C2** except for the π-acidic naphthalenes.

Kemp elimination in the presence of the catalysts was continuously followed by ^{1}H NMR spectroscopy. In a typical experiment, substrate **S** and catalysts **C** were dissolved in CD_3OD at different concentrations and ratios. The reaction was initiated by partial deprotonation of **C** with 0.5 equivalents of tetrabutylammonium hydroxide (TBAOH). Initial velocities of product formation were measured first as a function of catalyst concentration (Figure 3a). Product formation in the presence of the π-acidic NDI **C1** was clearly faster than in the presence of controls **C3** and **C4. C3** is thus too rigid to attain the optimum geometry in the substrate–catalyst complex, and transition-state stabilization with the π-basic **C4** is as ineffective as expected. Turnovers were followed for up to 13 substrates per catalyst **C1**, more should be possible without any problems.

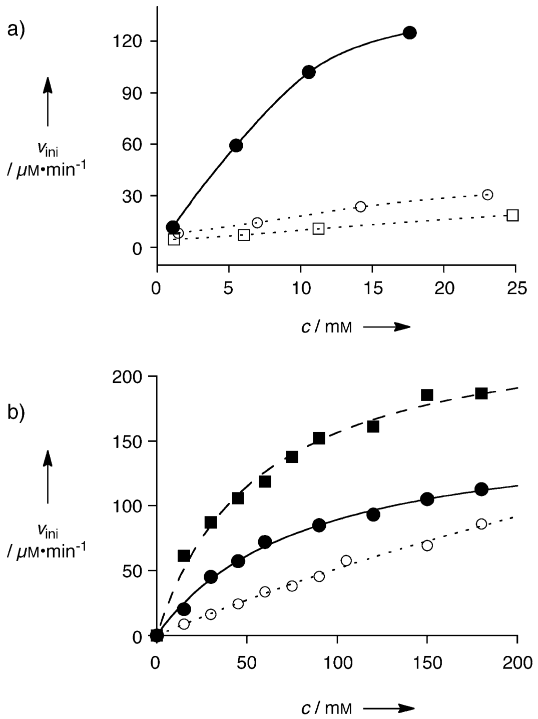

Figure 3. a) Initial velocity of product formation as a function of the concentration of **C1** (●), **C3** (□) and **C4** (○); **S** (13 mM), TBAOH (0.5 equiv), CD_3OD, room temperature. b) Initial velocity of product formation as a function of the concentration of substrate **S** in the presence of 8.3 mM **C1** (●), **C2** (■) and **C5** (○); TBAOH (5.0 mM), $CD_3OD/CDCl_3$ 1:1, room temperature; with linear (○) or Michaelis–Menten (●, ■) curve fit.

The dependence on the substrate concentration at constant catalyst concentration in 1:1 $CD_3OD/CDCl_3$ revealed saturation behavior for the π-acidic catalyst **C1**, but not for the close control **C5** (Figure 3b, ● vs. ○). This finding was important; it demonstrated the formation of catalyst–substrate complex **CS1**, whereas **CS5** is too weak to be detected under the same conditions. A K_M of 82.5 ± 7.9 mM was determined by Michaelis–Menten analysis, which translated into a ground-state stabilization of $\Delta\Delta G_{GS}=6.2\pm0.2$ kJ mol^{-1} for **CS1** (Figures 1 and 4).

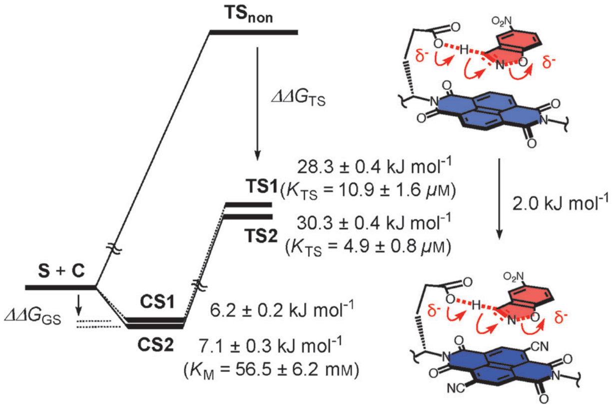

Figure 4. Energy diagram for the Kemp elimination catalyzed with anion–π interactions. Ground-state stabilization ΔΔG_{GS} (K_M) and transition-state stabilization ΔΔG_{TS} (K_{TS}) for **C1** and **C2** obtained from Michaelis–Menten analysis (compare with Figure 3 b).

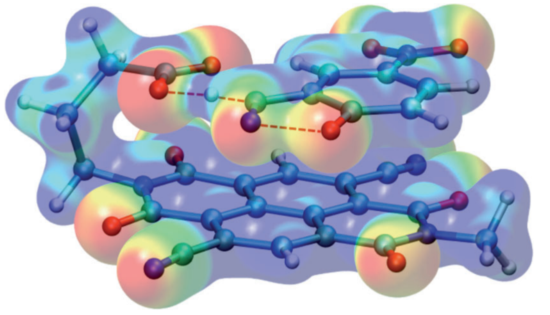

Figure 5. Molecular model of the transition state. Optimized geometry (M06L/6-311G**) for **TS2** is shown in the same orientation as in Figures 1 and 4. Electrostatic potential surface (blue = positive, red = negative; −262.6/+170.1 kJ mol^{-1}) computed at the MP2/6-311G**//M06 L/6-311G** level highlights the electron-transfer pathway on the π-acidic surface of the NDI (the branched alkyl substituent is replaced by a methyl group).

The transition-state stabilization by anion–π catalyst **C1** was estimated from Michaelis–Menten analysis.[21] A rate enhancement of $k_{cat}/k_{non} = 7606$, a catalytic efficiency of $k_{cat}/K_M = 6.5\times10^{-3}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ and a catalytic proficiency of $(k_{cat}/K_M)/k_{non} = 9.2\times10^{4}\,\mathrm{M}^{-1}$ were obtained en route to a transition-state stabilization $K_{TS} = 10.9 \pm 1.6$ μM, which translated into $\Delta\Delta G_{TS} = 28.3 \pm 0.4$ kJ mol^{-1} for **TS1** (Figure 4).

To further elaborate on the relevance of anion–π interactions for catalysis with **C1**, we decided to synthesize catalyst **C2** with maximized π-acidity. As with **C1**, the catalysis of the Kemp elimination with **C2** showed saturation behavior (Figure 3 b, ■). According to Michaelis–Menten analysis, ground-state stabilization increased by 0.9 kJ mol^{-1} to $\Delta\Delta G_{GS} = 7.1 \pm 0.3$ kJ mol^{-1}. With increasing π-acidity of the catalyst, transition-state stabilization increased more than twice as much (2.0 kJ mol^{-1}; Figure 4). This is a very reasonable value.[5–14] The $\Delta\Delta G_{TS} = 30.3 \pm 0.4$ kJ mol^{-1} corresponds to a transition-state recognition by the most π-acidic catalyst **C2** with an apparent dissociation constant of $K_{TS} = 4.9 \pm 0.8$ μM. The catalytic proficiency more than doubled from $(k_{cat}/K_M)/k_{non} = 9.2\times10^{4}\,\mathrm{M}^{-1}$ for **C1** to $(k_{cat}/K_M)/k_{non} = 2.0\times10^{5}\,\mathrm{M}^{-1}$ for **C2**.

Molecular models of the anionic transition state **TS2** were computed using the M06-2X/6-311G**//M06L/6-311G** level of theory.[23,24] In all convincing structures, the electron flow from the carboxylate to the benzisoxazole oxygen occurs on the π-acidic surface (Figure 5). In agreement with operational anion–π interactions, the distance between the electron-transfer cascade and the π-acidic surface decreases from 3.347 Å in **CS2** to 3.290 Å in **TS2** and finally to 3.247 Å in **RI2**. Structure analysis suggests that **TS2** is an early transition state with C···H and O···H distances of 1.223 and 1.430 Å, respectively. The carboxylate base of the catalyst is found on top of the electron-deficient area of the pyridinedione heterocycle. One oxygen atom is on the way to accept the proton from the isoxazole ring of the substrate, the other forms an O···H-C interaction with the phenyl ring of the substrate. The formation of the carbanion in the isoxazole ring, the critical step of this reaction,[17–20] is stabilized on top of one aromatic ring of the naphthalene. A detailed computational analysis of the quite complex situation is ongoing and will be reported in due course.

This study provides experimental evidence for contributions of anion–π interactions to catalysis. The presence of a π-acidic surface in the catalyst is shown to stabilize the anionic transition state of the selected reaction. Most importantly, increasing π-acidity of the catalyst increases the stabilization of the anionic transition state. This finding demonstrates that anion–π interactions contribute to catalysis, the exact mode of anion binding is irrelevant for the validity of this conclusion. Naturally delocalized and enhanced by π–π interactions, these interactions are necessarily beyond the strict definition of pure anion–π interactions. They encourage continuation of the thoughts formulated concerning nitrate recognition[1,13] by possible contributions from π–π interactions and complement evolution in the perception of cation–π interactions, particularly when applied to catalysis.[15,16]

In conclusion, the herein reported experimental evidence for contributions of anion–π interactions to catalysis enriches our understanding of organocatalysis and will lead to conceptually innovative design strategies to stabilize anionic transition states. Ongoing studies with modified, sulfur-containing NDI catalysts[14] confirm the general validity of increasing transition-state stabilization with increasing π-acidity with regard to the Kemp elimination. Preliminary results further indicate that anion–π interactions will become applicable to the stabilization of the anionic tetrahedral intermediates of addition and substitution reactions on carbonyl groups. Enolate chemistry is particularly appealing for anion–π catalysis, also because their importance in polyketide biosynthesis is nicely complementary to carbocation chemistry in terpenoid and steroid biosynthesis. However, in sharp contrast to the cation–π interactions contributing to the latter, catalysis with anion–π interactions is new and clearly moves beyond the grand principles operating in nature.[6]

Received: June 21, 2013

Keywords: kinetics · molecular recognition · noncovalent interactions · organocatalysis · transition states

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