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Polyether Natural Product Inspired Cascade Cyclizations Autocatalyzed on π-Acidic Aromatic Surfaces

Miguel Paraja,[#] Xiaoyu Hao,[#] and Stefan Matile[a]*

Abstract: Anion-π catalysis, that is the stabilization of anionic transition states on aromatic π surfaces, provides a new approach to molecular transformation. Explored with several reactions during the first five years, the delocalized nature of anion-π interactions has always suggested that they should serve best in stabilizing long-distance charge displacements. Aiming therefore for an anionic cascade reaction that is as charismatic as the steroid cyclization is for conventional cation-π biocatalysis, we here report anion-π catalysis of epoxide-opening ether cyclizations of oligomers up to tetramers. Only on π-acidic aromatic surfaces with positive quadrupole moment, from hexafluorobenzene to naphthalenediimides, these natural product inspired polyether cascade cyclizations proceed with exceptionally high autocatalysis (rate enhancements $k_{auto}/k_{cat} > 10^4$ M^{-1}). This distinctive characteristic adds complexity to reaction mechanisms (Goldilocks-type substrate concentration dependence, entropy-centered substrate destabilization) and opens up intriguing perspectives for future developments.

In this report, the catalysis of the cascade cyclization of oligoepoxides[1–6] up to tetramers **1** and **2** into oligooxolanes **3** and **4** and isomers with anion-π interactions[7] is described (Figure 1a). In nature, the cyclization of terpenes into steroids is arguably the most spectacular expression of cation-π catalysis (Figure 1b).[8,9] In the enzyme, the carbocations moving along the emerging rings are stabilized on the π surface of a cluster of π-basic amino acids, as outlined in transition states **TS–1**.[8] Perhaps because it is counterintuitive and rare in nature, the complementary anion-π catalysis, that is the stabilization of anionic rather than cationic transition states on π-acidic rather than π-basic aromatic

surfaces, has been unknown until recently, that is 2013.[10] Since then, anion-π catalysis has been evolving rapidly with regard to the number of realized catalysts and reactions.[11,12] However, the delocalized nature of anion-π interactions[7] called for reactions that involve long-distance charge displacements, somehow the anionic versions of steroid cyclizations. Lessons from nature supported epoxide-opening polyether cascade cyclizations of polyketides as cascades of choice for this purpose.[1–6] Popular examples include oligooxolanes like the monensins on the one hand or brevetoxin-like ladder oligomers on the other (Figure 1b).[2] Inspired by the Cane-Celmer-Westley hypothesis[5] **TS-2** and Nakanishi hypothesis[6] for the biosynthesis of monensin- and brevetoxin-type architectures, respectively, cascade cyclizations that follow and violate the Baldwin rules[13] have attracted intense scientific attention (Figure 1b).[1,2] Compatibility with anion-π catalysis has been demonstrated recently with model monomers.[14] On aromatic surfaces, epoxide-opening monoether cyclizations occurred with primary anion-π interactions, i.e., without the need of additional activating groups. These model studies encouraged the move from monomer cyclizations toward the oligomer cascades reported in the following.

With a positive quadrupole moment Q_{zz} = +9.5 B compared to Q_{zz} = –8.5 B for benzene, hexafluorobenzene (HFB) **5** is not the strongest but arguably the most popular π acid.[7,11] Dissolved in HFB at room temperature, 250 mM tetraepoxide **1** – prepared by multistep synthesis as a mixture of all-*trans* stereoisomers (Scheme S3) – was fully converted within 20 days. With 750 mM tetraepoxide **1**, the cascade cyclization took one month. Epoxide opening was clearly detectable by ^{1}H NMR kinetics and found to be stepwise and directional, proceeding from ring *1* to ring *4* (Figures 2a, S5). Comparison of the complex NMR spectra of the main product with shorter oligomers (Figures 2b, c, S1-S4) supported the formation of a mixture of stereoisomers of oxolane tetramers **3**, that is the existence of an anion-π catalyzed Baldwin-selective cascade cyclization as outlined **TS-3** (Figure 1a). The conversion times of these shorter oligomers **6**–**8** (synthesis: Schemes S1, S2) into oxolanes **9**–**11** decreased with oligomer length, from 7 days for trimer **8** to 2 days for dimer **7** to hours for monomer

6 (Figures 3a, S1, S2, S4). More detailed studies were thus performed with the shortest possible dimer **7**. ^{1}H NMR kinetics in HFB **5** confirmed that the cascade cyclizations are directional, presumably stepwise and in clude significant contributions from anion-π templated autocatalysis (Figure 4a). Kinetics analysis of substrate conversion afforded a formal autocatalytic rate enhancement k_{auto}/k_{cat} = 180 M^{-1}. *p*-Bromo benzoylation provided access to chiral HPLC analysis, which for *trans* dimer **7** revealed the expected four stereoisomers and their conversion on aromatic surfaces without any preference (Figures S12-S14).

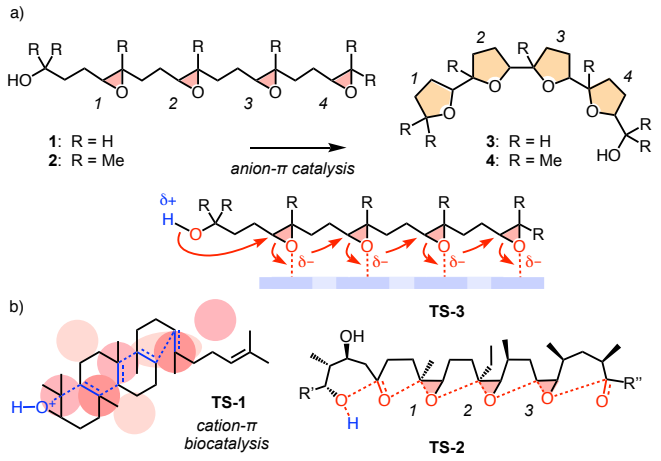

Figure 1. Anion-π catalysis of epoxide-opening polyether cascade cyclization of tetraepoxides **1** and **2** into mostly tetraoxolanes **3** and **4**, with putative transition state **TS-3** (π-acidic surfaces in blue) compared to **TS-1** leading to steroids (with position of π-basic residues in the enzyme indicated in red) and **TS-2** leading to monensins (Cane-Celmer-Westley hypothesis; **2**: Mixture of *cis*/*trans* isomers).

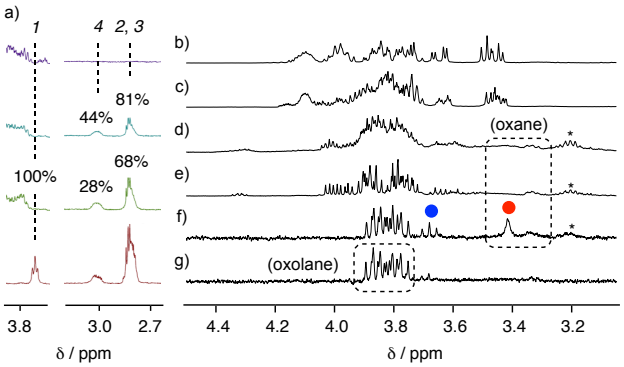

Figure 2. a) Diagnostic regions of ^{1}H NMR spectra of **1** (750 mM) after 0, 13, 21 and 34 d in HFB **5** (bottom to top), with distinct signals and conversions of epoxides *1-4*. b-g) Diagnostic region of ^{1}H NMR spectra of representative product mixtures with mostly b) **10** (from **7** in **5**), c) **3** (from **1** in **5**), d) **4** (from **2** with **12** in CD_2Cl_2), e) **18** (from **15** with **12**), f) **17** (from **14** with **12**; peaks marked with blue and red circles are assigned to the correspondingly colored protons of **20**, Figure 3) and g) **17** (from **14** with AcOH). *Peaks from catalyst **12**.

However, with the π-acidic HFB **5** used as a catalyst in CH_2Cl_2 rather than as a solvent, dimer **7** did not react (Figure 4f□). The same was true for naphthalenediimide[15] (NDI) **12**, a much more powerful anion-π catalyst due to more positive quadrupole moment, lower LUMO energy and higher polarizability[11,14] (Figures 3b, 4d, 4f■). To increase reactivity, a series of permethylated[16] oligomers **13**–**15**, **2** was prepared by multistep synthesis (Figures 3a, 1a; Schemes S4-S6). Besides more specific contributions (below), permethylation could be expected to produce more basic *tert*-alcoholate nucleophiles and stronger alcoholate-π interactions to compensate for poorer leaving groups, and stabilize partial positive charges building up on the central carbon in transition (Figures 3c, d). The Baldwin rules predicted that a formal 5-*exo*-*tet* cascade cyclization into oligomers **16**–**18**, **4** should be preferred. Contrary to **7**, the pentamethylated *cis* dimer **14** was readily converted by NDI **12**. With 5 mol% NDI **12** in CD_2Cl_2, the conversion of 1 M tetraepoxide **2** into mostly tetraoxolane **4** was completed in 12 days. The conversion of substrate **14** in the presence of 20 mol% NDI catalysts

12, was formally[17] autocatalytic (Figure 4c●, k_{auto}/k_{cat} = 3.0 x 10^4 M^{-1}). Compared to **7** with HFB as a solvent catalysts, autocatalysis for **14** with 20 mol% of the more powerful anion-π catalysts **12** was more than 160 times more pronounced. In sharp contrast, the conversion of **14** with AcOH was clearly not autocatalytic, independent of catalyst concentration, and clearly much slower (Figures 4cX, 4e). Extrapolation of the model for primary anion-π autocatalysis computed on the monomer level[14] afforded hypothetical transition states like **TS-4** (Figure 3c). **TS-4** consists of an oxolane product next to the processed epoxide oligomer on the π-acidic surface. This oxolane product activates the nucleophile and the intramolecular epoxide leaving group with one hydrogen bond each. The resulting non-covalent macrocyclization should shift the entropy losses from ether cyclization from transition to ground state and thus further contribute to catalysis by entropic substrate destabilization, that is preorganization.[18] The decisive anion-π interaction then stabilizes the alcoholate leaving group obtained from the rate-limiting epoxide opening. Absent in the many studies on the topic,[1–3] this templation of autocatalysis[17] of epoxide-opening polyether cyclizations is a so far unique characteristic of anion-π catalysis.

With catalyst **12** at constant concentration, the dependence on the concentration of substrate **14** showed first saturation behavior, followed by a strong decrease (Figures 4d●, S8). Saturation behavior could support the existence of substrate binding sites, whereas post-saturation substrate inhibition could indicate interference with product binding, i.e., anion-π templated autocatalysis. These "Goldilocks" profiles[19] for dependence on substrate concentration were significant and general. For HFB solvent catalysis, it accounted for an inversion of reactivity, with **7** being faster at low and **14** being faster at high concentration (Figures 4b, □, ○, S6, S7). This inversion could be understood with decreasing substrate recognition from **7** to **14**, presumably also reducing post-saturation interference with anion-π templated autocatalysis. Decreasing ground-state and increasing transition-state recognition from **7** to **14** (tertiary vs secondary alcoholate-π interactions, **TS-4**), both

reducing activation energy,[18] were consistent with the much higher reactivity of permethylated oligomers up to tetramer **2** with NDI **12** (Figure 3d, f, ● vs ■).

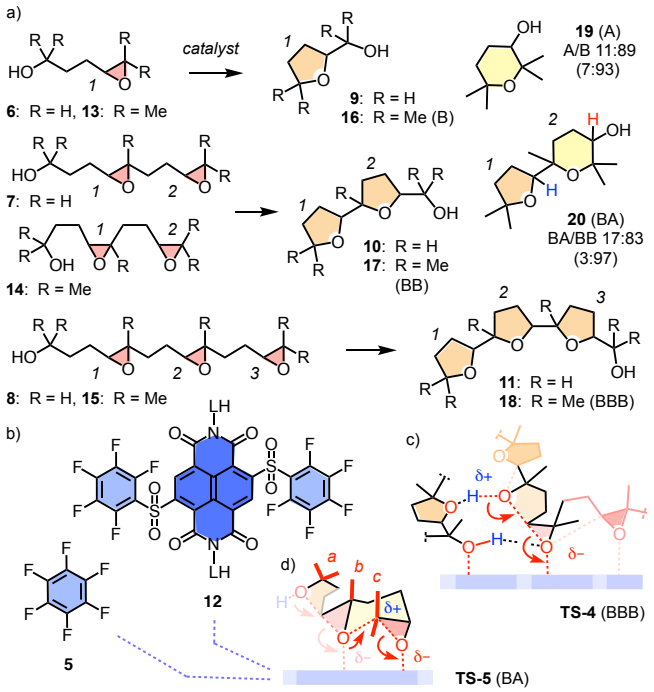

Figure 3. a) Oligomer series explored with b) selected anion-π catalysts; A/B selectivity ratios are for **12** compared to AcOH in parenthesis (tetramers **1**, **2**: Figure 1; LH = Leu-hexyl). c) Transition-state hypothesis for primary anion-π autocatalysis of epoxide-opening polyether cascade cyclizations following the Baldwin rules (BBB). d) Transition-state hypothesis for anti-Baldwin (A) cyclization into **20**; *a-c*: Directing methyl activators.

Like substrate dependence, the dependence on the concentration of catalyst **12** at constant substrate **14** naturally varied strongly with reaction time (Figure 4c●). The linear dependence found around maximal autocatalysis after 19 h mostly reflected the shortening of the lag period (Figure 4f●; Figure S9), whereas after 6 h, before the onset of autocatalysis, increasing catalyst concentrations gave the expected superlinear increase in activity for the same reason (Figure S9).

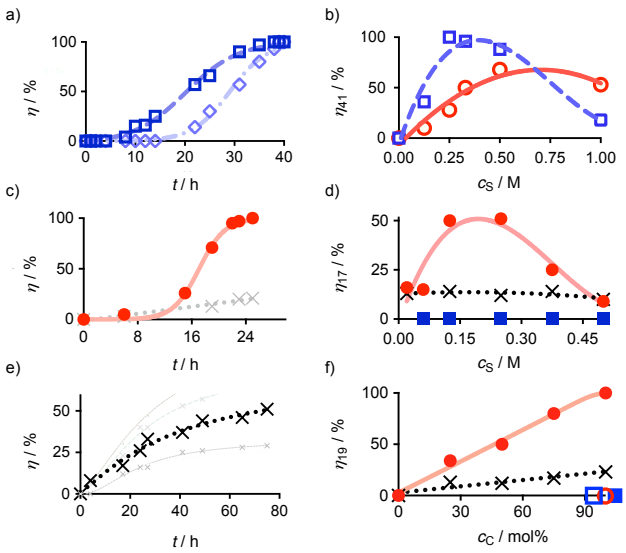

Figure 4. a) Conversion □ of epoxide *1* (□) and *2* (◇) of substrate **7** (250 mM) with time *t* in HFB at room temperature (compare Figure 2a). b) Substrate conversion $\square_{41}$ after 41 h in HFB as a function of the concentration of substrates **7** (□) and **14** (○). c) Conversion of **14** in CD_2Cl_2 with 20 mol% **12** (●) and 25 mol% AcOH (X). d) Substrate conversion after 17 h as a function of the concentration of substrates **7** (■) and **14** (●, X) at constant concentration of catalyst **12** (●, ■, 50 mM) and AcOH (X, 250 mM) in CD_2Cl_2. e) Conversion of **14** with 75 mol% AcOH (grey: 25, 100, 130 mol%). f) Conversion after 19 h for substrates **7** (■, □) and **14** (●, ○, X) at constant concentration (250 mM) with increasing concentration of catalyst **12** (●, ■), **5** (○, □) and AcOH (X) in CD_2Cl_2 (**14**: Mixture of *cis*/*trans* isomers used for kinetics only).

The methyl activators[16] in oligomers up to tetramer **2** provided not only compatibility with anion-π catalysis but also access to the first violations of the Baldwin (B) rules. The 11% anti-Baldwin (A) oxane **19** obtained with NDI **12** was not significantly higher than the 7% with AcOH controls (Figure 3a). More important were the 17% BA dimer **20** obtained from **14** with NDI **12** (Figures 2f, 3a, S74-S78). They originated from anion-π catalysis, while the AcOH control, much slower, gave only Baldwin dimer **17**[3] (Figure 2g). Considering that epoxide opening by alcoholate-π interactions accounts mostly for anion-π catalysis, the formation of anti-Baldwin ring *2* implied a different

interaction of **14** with the π surface leading to a different orientation of the incoming nucleophile with respect to the epoxide to add up in a chair-like transition state, and contributions from *gem*-dimethyls *c* to stabilize the partial positive charge on the central carbon (**TS-5**, Figure 3d). Although impossible to specify from increasingly complex NMR spectra with longer oligomers, access to AB dimer **20** implied that anion-π catalysis will provide also access to permethylated anti-Baldwin isomers besides the BBB trimer **18** and BBBB tetramer **4** as main products (Figures 1a, 2, 3a).

With this study, the dream of an anionic version of the cation-π catalyzed steroid cyclization for anion-π catalysis becomes reality: Epoxide-opening polyether cyclizations are realized on π-acidic surfaces up to tetramers (Figure 1), and examples are provided for exclusive access with primary anion-π autocatalysis (Figure 4c-f). Besides obvious continuation toward stereo-pure substrates for simpler NMR spectra and asymmetric catalysis,[11] longer monensin- and also brevetoxin-like oligomers,[20,21] ring contractions and expansions,[21] and so on, we find it important to fully explore the unique autocatalysis of cascade cyclizations on π-acidic surfaces. More precisely, products added at the beginning of the reaction have already been shown on the monomer level to shorten the lag time and thus confirm the existence of autocatalysis,[14] The optimization of such co-catalysts will likely result in optimized cascade oligomerizations, not only with regard to BA chemoselectivity but particularly with regard to asymmetric anion-π catalysis. Tantalizing also are the perspectives of cascade cyclization control in more complex systems, particularly voltage-gated anion-π catalysis on electrodes,[11] and of ion binding and transport not only with monensin-like products[1,4] but also with the unexplored oligoepoxide substrates, anion-π catalysts,[22] and both together.[23]

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Keywords: Anion-π catalysis • epoxide-opening polyether cyclizations • cascade reactions • autocatalysis • substrate destabilization • naphthalenediimides •

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[21] A first series on monomers of different ring size has afforded examples for products that are obtained only with anion-π catalysis and not with Brønsted acid controls under comparable conditions, including access to large anti-Baldwin oxepanes and oxocane and to small Baldwin oxetanes and their rearrangement into oxolanes (M. Paraja, S. Matile, *Angew. Chem. Int. Ed.*, in press, DOI: 10.1002/anie.202000579, *Angew. Chem.*, 10.1002/ange.202000579).

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