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Primary Anion-π Catalysis of Epoxide-Opening Ether Cyclizations into Rings of Different Sizes: Access to New Reactivities

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Abstract: The concept of anion-π catalysis focuses on the stabilization of anionic transition states on aromatic π surfaces. Recently we demonstrated the occurrence of epoxide-opening ether cyclizations on aromatic π surfaces. Although the reaction proceeded through unconventional mechanisms, the obtained products are the same as with conventional Brønsted acid catalysis, and in agreement with the Baldwin selectivity rules. Different mechanisms, however, should ultimately lead to new products, a promise anion-π catalysis has been reluctant to live up to. Here, we report non-trivial reactions that work with anion-π catalysis but not with Brønsted acids under comparable conditions. Namely, we show that the anion-π templated autocatalysis and epoxide opening with alcoholate-π interactions can provide access to extreme ring chemistry. For smaller rings, anion-π catalysis affords anti-Baldwin oxolanes, 2-oxabicyclo[3.3.0]octanes and the expansion of Baldwin oxetanes via methyl migration. For larger rings, anion-π templated autocatalysis is thought to alleviate the entropic penalty of folding to enable disfavored anti-Baldwin cyclizations into oxepanes and oxocanes.

The Nakanishi hypothesis of the cascade cyclization of polyketide precursors into brevetoxin B (**1**) ranks among the most adventurous expressions of epoxide-opening polyether cascade cyclizations (Figure 1a).[1] The Baldwin rules predict *exo-tet* over *endo-tet* preference almost independent of the involved ring sizes.[2] To obtain the ladder-shaped oligomer **1**, the Baldwin rules are thus formally[2] violated in every step. Because of their importance in chemistry and biology, epoxide-opening ether and polyether cyclizations have become classics in organic chemistry. They have been explored

extensively with regard to Baldwin selectivity, different ring sizes, substituents and oligomers (Figure 1).[3–9]

Epoxide-opening ether cyclizations have been identified less than two years ago as attractive reactions for anion-π catalysis.[10] This concept[11] focuses on anion-π interactions[12] to stabilize anionic transition states on aromatic π surfaces (often supported by contributions from lonepair-π,[13] ionpair-π,[14] π-π,[15] anion-macrodipole[16] and other related interactions).[11] Counterintuitive and essentially unknown in chemistry and biology, anion-π catalysis has been introduced explicitly only seven years ago[15] and validated since then for a growing collection of catalysts and reactions.[11,17] Epoxide-opening ether cyclizations were identified as unique in this context because they i) occur with primary anion-π interactions (i.e., without the need of additional activators, even in hexafluorobenzene (HFB)[10–12] **6**) and ii) show autocatalytic behavior (Figure 1b).[10] However, despite this new and intriguing reaction mechanism, the products obtained were identical with those resulting from conventional Brønsted acid catalysis.[10] Anion-π catalysis, offering a new interaction to catalysis, has in general afforded new mechanisms and altered selectivities but has failed so far to yield new products.[11] This is contrary to the general expectation that the integration of unorthodox interactions into catalysis should ultimately provide access to new products.[18] Here, we show that epoxide-opening ether cyclization of substrates **2**–**5** on π-acidic aromatic surfaces provides access to extreme ring sizes that are beyond reach for Brønsted acids under comparable conditions.

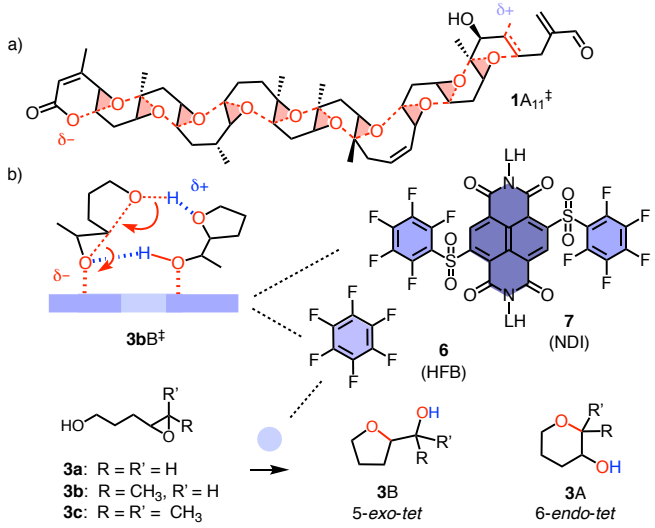

Figure 1. a) Hypothetical transition state (‡) of an all-anti-Baldwin (A_{11}) cascade cyclization leading to brevetoxin B (**1**). b) Computed[10] transition state of the autocatalytic cyclization of **3b** on π-acidic surfaces (blue), with structure of substrates **3a**–**3c**, Baldwin products **3**B, anti-Baldwin products **3**A, and anion-π catalysts **6** and **7**.

All substrates used in this study were readily accessible by adapting[4] routine synthetic procedures (Schemes S1-S23, Figures S3-S50). Anion-π catalyst **7** was prepared following previously reported procedures.[19] It consists of a central naphthalenediimide (NDI)[20] plane and two pentafluorophenyl "wings." The much higher activity of NDIs like **7** compared to HFB coincides with more positive quadrupole moments, lower LUMO energies, and higher polarizability.[11] Catalytic activities of 5 mol% NDI **7** in CD_2Cl_2 were compared to solvent catalysis in HFB **6** and to 100 mol%, i.e., 20-times more concentrated AcOH as meaningful conventional Brønsted acid control (The most adequate control for non-covalent anion-π catalysis in HFB would be non-covalent hydrogen-bonding catalysis). Anion-π catalyzed cyclization of 4,5-epoxy alcohols **3a**–**3c** followed the Baldwin (B) rules to afford *5-exo-tet* oxolane products **3**B with the exception of oxirane **3c**, which gave almost equal amounts of anti-Baldwin (A) oxane **3c**A already with AcOH (Figure 1b).[10]

Epoxide-opening ether cyclization into larger rings is more demanding because the entropy penalty increases with every rotatable bond added between epoxide and nucleophile (Figure 2c, red arrow to S‡). Anion-π templated autocatalysis promised to reduce this problem because in the computed transition state **3a**B‡, substrate and product form two hydrogen bonds to activate nucleophile and electrophile, respectively (Figure 1b). The formation of this non-covalent macrocycle already in the catalyst-product-substrate complex (CPS, Figure 2a) should shift the entropy-centered destabilization from the transition state CPS‡ (Figure 2b) to the ground state CPS and thus alleviate the entropy penalty of the cyclization into larger rings (Figure 2c). With such contributions originating from ground-state destabilization rather than transition-state stabilization,[21] anion-π catalysis of epoxide-opening ether cyclization would be independent of ring size.

Cyclizations into larger rings were launched with 5,6-epoxy alcohols **4a**–**4c**, the single-carbon homologs of the originals **3a**–**3c** (Figure 2e). In the presence of 5 mol% NDI **7** in CD_2Cl_2 at 40 ºC, conversion of 1.0 M **4a** into the Baldwin oxane **4a**B[5] was very slow (Table 1, entry 1; Figures 2e, S2, S51, S52). Similarly poor reactivity was found in HFB **6**. Introduction of one terminal methyl in oxirane **4b** (*cis*/*trans* 4:1) and two in **4c** accelerated conversion with the strongly π-acidic catalyst **7** but neither in the weakly π-acidic solvent **6** nor with AcOH controls (entries 2, 3, Figures S1, S2). Increasing conversion with NDI **7** compared to HFB **6** coincided with increasing formation of the expanded anti-Baldwin oxepane **4c**A (entries 2, 3; Figures S53–S68). This trend, and dominant Baldwin selectivity also with AcOH controls, supported that epoxide opening with alcoholate-π interactions could cause a shift of reactivity from formal S_N2 toward S_N1 type behavior.

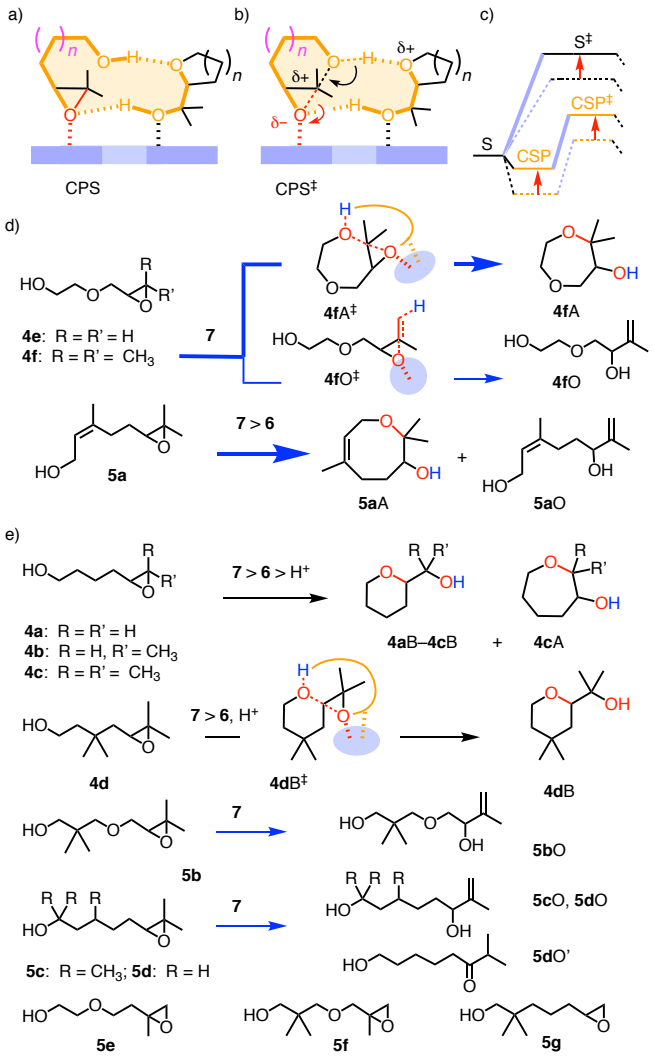

Figure 2. Notional structures of a) ground-state (CPS) and b) transition-state complexes (CPS‡) of autocatalytic anti-Baldwin cyclization on π surfaces (S, substrate; P, product; C, catalyst). c) Hypothetical energy diagram indicating how the macrocyclic nature of CPS and CPS‡ (a-c, gold) could shift the entropy penalty (red arrows) of forming large (solid) rather than small rings (dashed) from CPS‡ to CPS and thus account for catalysis by ground-state destabilization (blue lines). d) Anion-π specific key transformations and e) supportive material for cyclizations into large rings and other (O) products catalyzed by NDI **7**, HFB **6** or AcOH (H^+), with selected notional transition states. Blue arrows: Observed only with anion-π catalysis, compare Table 1 (entries 8–13, Figure 2e).

The insertion of a *gem*-dimethyl group in **4d** to preorganize cyclization[6,22] caused rate enhancements compared to **4a** without changing selectivity for **4d**B (entry 4). Replacement of the

gem-dimethyl motif by an oxygen to inactivate the *endo* carbon relative to the *exo* carbon removed all reactivity for **4e** (entry 5, Figure 2d).[7] Considering efficient conversion with increasing anti-Baldwin selectivity of **4c** with anion-π catalyst **7** (entry 3), the *exo* carbon in **4e** was equipped with two methyl groups. Conversion of the resulting **4f** with NDI **7** afforded the formal anti-Baldwin 1,4-dioxepane **4f**A, together with allyl alcohol **4f**O and traces of **4f**B (entry 6; Figures S75–S84). The cyclization into the large ring **4f**A was unique for strong anion-π catalysts, it occurred neither in HFB **6** nor with AcOH.

Table 1. Epoxide-opening ether cyclizations into expanded and contracted rings.[a]

		7[b]				**6**[b]			H^+[b]
	S[c]	*t* / h[d]	n_t / %[e]	A/B/O[f]	auto[g]	*t* / h[d]	n_t / %[e]	A/B/O[f]	n_t / %[h]
1	**4a**	280	79	0:100:0		140	89	0:100:0	89
2	**4b**	210	81	0:100:0	+	170	59	0:100:0	66
3	**4c**	140	100	24:76:0	+	170	48	11:89:0	53[i]
4[j]	**4d**	160	100	0:100:0	+	210	81	0:100:0	100
5	**4e**	>200	0	-					0
6	**4f**	230	100	52:9:39		160	0	-	0
7	**5a**	160	100	59:0:41	+	160	100	40:0:60	0
8	**5b**	400	100	0:0:100		>200	0	-	0
9	**5c**	120	100	0:0:100		>200	0		0
10	**5d**	260	100	*mxt*		>200	0	-	0
11	**5e**	120	100	*mxt*		>200	0	-	0
12	**5f**	>200	0	-					0
13	**5g**	>200	0	-					0
14	**2a**	40	100	100:0:0	+	310	81	100:0:0	100
15	**2b**	270	75	100:0:0	+	>200	0	-	0
16	**2c**	90	100	0:92:8	+			-	
17	**2c**	160	100	0:0:100		160	0		45[k]
18	**2d**	310	50	0:100:0	+				
19	**2d**	570	100	*mxt*		160	0		25[k]
20	**2e**	>200	0	-					0
21	**2f**	>200	0	-					0
22	**2g**	40	100	*mxt*		>200	0	-	0
23	**2h**	>200	0	-					0
24	**2i**	>200	0	-					0
25	**2j**	140	100	*mxt*		160	0		0

[a] Conditions: 1.0 M S with i) 5 mol% **7** in CD_2Cl_2, ii) **6** as a solvent, or iii) 1.0 equivalent AcOH (H^+) in CD_2Cl_2, 40 °C; followed by ^{1}H NMR spectroscopy. [b] Catalysts, see Figure 1. [c] Substrates, see Figures 2, 3. [d] Reaction time. [e] Conversion at given reaction time. [f] Product distribution: A = anti-Baldwin, B = Baldwin, O = other product; NMR spectra: Figures S51–S119; *mxt*: Product mixtures. [g] Autocatalytic behavior noted. [h] Conversion by 1 equivalent AcOH (H^+) after at least 200 h. [i] A/B = 11:89 after 200 h. [i] Reaction run at rt. [k] A/B/O = 0:100:0 after 300 h.

In brevetoxin B, the hypothetical anti-Baldwin cyclization into an oxacane is preorganized by a *cis* alkene (Figure 1a).[1,3] 6,7-Epoxy alcohol **5a** with a *cis* alkene in position 2 was obtained by epoxidation of the monoterpene nerol (Scheme S6). Reacted under standard conditions with **7**, **5a** afforded oxocane **5a**A (entry 7, Figures 2d, S85–S89). Oxocane **5a**A was also observed as important side product in HFB **6** but not with AcOH. Cyclization of 6,7-epoxy alcohols **5b**–**5g** without *cis* alkene did not occur (entries 8–13, Figure 2e).

Access to large rings, from **4f**A to **5a**A, was consistent with the working hypothesis of anion-π templated entropy-centered ground-state destabilization (Figure 2a), anti-Baldwin selectivity with contributions from S_N1-type behavior. The latter was consistent with allyl alcohol **5a**O as side product (entry 7, Figure 2d) and **5b**O and **5c**O as only products obtained with **7** (entry 8, 9, Figure 2e). Poor conversion of other epoxides **5d**–**5g** confirmed decreasing reactivity with larger rings (entries 10–13). Pinacol rearrangement into ketone **5d**O' besides the allyl alcohol **5d**O is often considered as evidence for trapped carbocation intermediates (Figures 2e, S93–S95).

Moving form large to small rings, preorganization with *gem*-dimethyls[22] in 3,4-epoxy alcohol **2a** provided clean access to **2a**A with all catalysts, although anion-π catalyst **7** performed clearly better than the rest (entry 14, Figures 3b, S97–S101). The templated[8] anti-Baldwin cyclization of **2b** into *trans*-fused 2-oxabicyclo[3.3.0]octane **2b**A occurred only with **7**, neither in HFB **6** nor with AcOH (entry 15). In **2c**, a reversal from 5-*endo*-*tet* to 4-*exo*-*tet* Baldwin selectivity was possible with **7** (entry 16, Figures 3a, S107–S111). With time, oxetane **2c**B expanded into oxolane **2c**O (entry 17, Figures S112–S116). The substitution pattern of **2c**O suggested that alcoholate-π interactions catalyze oxetane opening **2c**O‡ followed by methyl migration **2c**O‡' to the tertiary carbocation and ring closure **2c**O‡'' (Figure 3a). This interpretation was supported by epoxide **2d** with a *gem*-isopropyl alcohol nucleophile. Formation of **2d**B was as with **2c**C (entry 18, Figure S117). The following ring expansion, however, resulted in a complex mixture (entry 19), thus supporting the importance of methyl migration and tertiary carbocations for the cascade transformation of **2c** into **2c**O (entry 17).

Other substrates for cyclization into small rings were not converted (**2e**[9]–**2j**, entries 20–25). Autocatalytic behavior, assumed also for entropy-centered ground-state destabilization (Figure 2a-c), was noticed for most reactions catalyzed by anion-π catalyst **7** but never with conventional AcOH catalysis (Table 1, Figure S2). Anion-π autocatalysis was however not further investigated because it has already been explored in detail for cyclization into standard oxetanes, in experiment and theory.[10]

In summary, anion-π catalysis of epoxide-opening ether cyclizations into rings of different size, from oxetanes to oxocanes, provides the access to new reactivities that has been expected since the beginning from catalysis with new interactions. The *trans*-fused 2-oxabicyclo[3.3.0]octane **2b**A, the rearrangement of the small oxetane **2c**B into oxolane **2c**O, and the large dioxepanes **4f**A and oxocane **5a**A all are obtained only with anion-π catalysis and not with Brønsted acid controls under comparable conditions. Contributions from S_N1-type behavior from epoxide opening by alcoholate-π interactions possibly account for access to small rings and general anti-Baldwin selectivity. Access to large rings is explained with a working hypothesis focusing on an entropy-centered ground-state destabilization derived from anion-π autocatalysis (Figure 2a-c). Both entropy-centered ground-state destabilization and contributions from S_N1-type behavior could be of use as predictive principles in future developments, particularly to control access to and chemo- and stereoselectivity of larger rings and oligomers. Contrary to Brønsted acid catalysis, for instance, reactivities of the electrophile carbons increase with the number of alkyl substituents (**4a**–**c**, Figure S2) and do not vanish with larger rings (**4f**A, **5a**A, Figure 2d), and cyclization selectivities shift toward more substituted carbons. The emergence of new reactivities with anion-π catalysis in general supports the principal expectation that the integration of unorthodox interactions into functional systems will provide access to new properties that may ultimately solve problems that are otherwise beyond reach.[18]

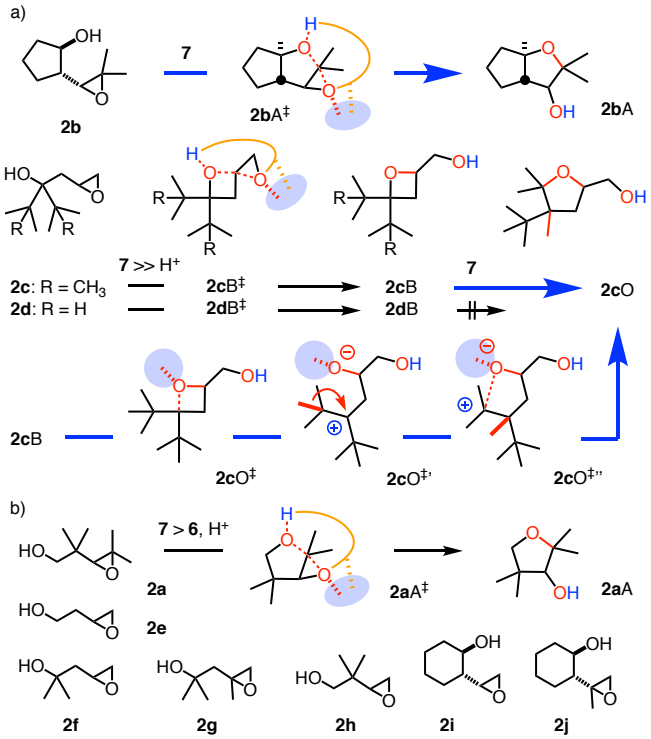

Figure 3. a) Anion-π specific key transformations and b) supportive material for for cyclizations into small rings and other products catalyzed by NDI **7**, HFB **6** or AcOH (H^+), compare Table 1 and Figure 2.

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Keywords: Anion-π catalysis • cyclizations • templation • preorganization • autocatalysis • cascade reactions • polyether natural product

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