

Primary Anion $-\pi$ Catalysis and Autocatalysis

Xiang Zhang,[#] Xiaoyu Hao,[#] Le Liu,^{#,†} Anh-Tuan Pham,[#] Javier López-Andarias,[#] Antonio Frontera,[‡]

[#]Department of Organic Chemistry, University of Geneva, Geneva CH 1211, Switzerland [‡]Department de Química, Universitat de les Illes Balears, Palma de Mallorca 07122, Spain

Supporting Information

ABSTRACT: Epoxide-opening ether cyclizations are shown to occur on π -acidic aromatic surfaces without the need of additional activating groups and with autocatalytic amplification. Increasing activity with the intrinsic π acidity of benzenes, naphthalenediimides (NDIs) and perylenediimides (PDIs) support that anion $-\pi$ interactions account for function. Rate enhancements maximize at 270 for an ion $-\pi$ catalysis on fullerenes and at 5100 M⁻¹ for autocatalysis. The occurrence of anion $-\pi$ autocatalysis is confirmed with increasing initial rates in the presence of additional product. Computational studies on autocatalysis reveal transition state and product forming a hydrogen-bonded noncovalent macrocycle, like holding their hands and dancing on the active π surface, with epoxide opening and nucleophile being activated by anion $-\pi$ interactions and hydrogen bonds to the product, respectively.

The idea of anion $-\pi$ catalysis is to stabilize anionic transition states on π -acidic aromatic surfaces. Since the beginning,¹ this has been realized for enolate, enamine and iminium chemistry, cascade cyclizations and concerted cycloadditions, also in the context of more advanced systems such as artificial enzymes, π -stacked foldamers, fullerene-centered triads, or electric-field-mediated catalysis.² All these results have been achieved with at least bifunctional systems, usually with the π -acidic surface for an ion- π interactions³ together with a Brønsted base to initiate the transformation by generating a negative charge on the substrate. Different from these initial studies, we here report functional systems that (i) operate with an ion $-\pi$ interactions as primary interactions and (ii) show autocatalysis.

Epoxide opening polyether cascade cyclizations are classics in chemistry and biology.⁴ They account, for example, for the biosynthesis of cyclic polyether natural products such as brevetoxin B 1, a THP oligomer,⁵ or monensin A 2, a THF oligomer (Figure 1).⁶ The selectivity of cyclization of epoxides as simple as 3 into THF and THP products 4 and 5, respectively, is described by the Baldwin rules.⁷ They predict that the 5-exo-tet or "spiro" transition state should be favored over the 6-endo-tet or "fused" transition state. Usually catalyzed by Brønsted acids, Baldwin and anti-Baldwin epoxide-opening ether cyclizations have attracted extensive attention during the last seven decades.⁴



Figure 1. Epoxide opening ether cyclization of 3 into THF and THP products 4 and 5 according to the Baldwin rules, with plausible mechanisms for primary anion- π catalysis (CS[‡]) and substrate activation by product (CPS, CPS[‡]) and substrate (CSS), and with examples for anti-Baldwin (1) and Baldwin (2) cascade cyclizations in biology.

In hexafluorobenzene 6, the cis-epoxide 3b was transformed into the THF product 4 within hours (Figures 2a, 3a red \blacklozenge ; Table 1, entry 4). In pentafluorobenzene 7, no reaction was observed. Traces of product appeared after 5 days in pentafluorobromobenzene 8 and pentafluoroiodobenzene 9 (entries 2, 3). Used as a catalyst in CD_2Cl_2 rather than as a

Received: November 1, 2018



Figure 2. Structure of catalyst candidates 6–19, with indication of contributions from (a) intrinsic (positive quadrupole moments) and (b) induced π acidity (polarizability). PDI 16 is a mixture of 1,6- and 1,7-dinitro isomers.



Figure 3. (a–c) Reaction kinetics of (a) 3a (green ▲), 3b (red ♦), and 3c (purple ▼, all 840 mM) in 6 (neat), of (b) 3b (240 mM) in 6 (red ♦) and 3b (840 mM) in CD₂Cl₂ with AcOH (100 mol %, +), and of (c) 3b (840 mM) in CD₂Cl₂ with 6 (red ▲), 11 (pink △), 12 (brown ∇), 13 (teal \bigcirc) or 14 (blue ●, 20 mol %). (d) Dependence of k_{cat}/k_{non} (red \bigcirc) and k_{ac}/k_{non} (blue \blacksquare) on LUMO energies of NDIs (red ● blue \blacksquare) and PDIs (red \bigcirc blue \square). (e) Kinetics of 3b in the presence of 4b (blue ●, 0; light-blue \bigcirc , 10; blue ∇ , 50; light-blue \square , 66; teal \blacksquare , 174 mol %) and with (blue \bigcirc 0 light-blue \square teal \blacksquare) or without (blue ∇) 11. (f–i) Dependence of the conversion of 3b on the initial concentration of (f) product 4b (with 11, 10 mol %), (g) substrate 3b (with 6 as solvent), (h) catalyst 11, and (i) inhibitor TBANO₃ (with 11).

solvent, hexafluorobenzene **6** was inactive (Figure 3c red \blacktriangle , entry 7; deactivation occurred already in the presence of small percentages of CD₂Cl₂, Figure S5C). With π -acidic benzene derivatives at 20 mol %, only the dinitrobenzoate **10** produced traces of **4b** in the same period of time (entry 8).

NDIs have served well in anion $-\pi$ catalysis because of their high intrinsic π acidity, as indicated by their strongly positive quadrupole moments (Figure 2a).^{1,2} At 20 mol % in CD₂Cl₂, NDI 11 produced 78% of THF product 4b (Figure 3c pink \triangle ; entry 9). This NDI 11 and all other catalyst candidates were synthesized by following or adapting previously reported procedures;⁸ all details on multistep synthesis of substrates 3 and catalyst candidates 11–19 can be found in the SI (Schemes S1–S3). Variation of the solubilizing imide side chains in 12 reduced activity (Figure 3c brown \bigtriangledown ; entry 10). Replacement of ethyl sulfones in NDI 11 gave highly active catalysts 13 and particularly 14, presumably due to interactions with the π -basic and π -acidic "wings"⁸ around the central NDI

Table 1. Anion– π Catalysis and Autocatalysis ^{<i>a</i>}							
	C ^b	s ^c	c (M) ^d	Solvent	${k_{ m cat}}/{k_{ m non}}e$	${k_{ m ac}}/{k_{ m non}}$	$\eta \ (\%)^{g} \ (M^{-1})$
1	_	3b	0	CD_2Cl_2	1	-	-
2	8	3b	≈6.8	(neat)	14	643	4
3	9	3b	≈6.3	(neat)	17	571	5
4	6	3b	≈7.3	(neat)	3736	60964	100
5	6	3a	≈7.3	(neat)	2058	81248	100
6	6	3c	≈7.3	(neat)	529	25770	84 ^h
7	6	3b	0.17	CD_2Cl_2	-	-	-
8	10	3b	0.17	CD_2Cl_2	4	-	1
9	11	3b	0.17	CD_2Cl_2	256	1764	78 ⁱ
10	12	3b	0.17	CD_2Cl_2	63	1232	27
11	13	3b	0.17	CD_2Cl_2	220	1514	69
12	14	3b	0.17	CD_2Cl_2	229	5100	100
13	15	3b	0.17	CD_2Cl_2	17	370	4
14	16	3b	0.085	CD_2Cl_2	113	2139	67 ^j
15	17	3b	0.17	CD_2Cl_2	10	462	4
16	18	3b	0.085	CD_2Cl_2	15	687	5
17	19	3b	0.17	CD_2Cl_2	-	_	_
18	18	3b	0.085	7	270	1045	64
19	15	3b	0.17	7	30	-	6
20	17	3b	0.17	7	7	1102	4 ¹

^aMeasured with 840 mM 3 and 170 mM catalyst in CD₂Cl₂ (unless stated otherwise: neat, entries 1–6; 85 mM, entries 14, 16, 18), at 20 °C. ^bCatalysts, see Figure 2. ^cSubstrates, see Figure 1. ^dCatalyst concentration. Values in entries 2–6 were calculated assuming the density of 3 as 1. ^eEnhancement of initial rate relative to $v_{ini} = 3.57 \times 10^{-8}$ M s⁻¹ for 3b. $k_{non} = 4.25 \times 10^{-9}$ s⁻¹, calculated from high-temperatures measurements using $k = Ae^{-E_z/(RT)}$, $E_a = 28.4$ kcal mol⁻¹. ^JEnhancement of maximal rate relative to $v_{ini} = 3.57 \times 10^{-8}$ M s⁻¹ for 3b, k_{ac} from autocatalysis curve fit. ^gConversion into 4 after 5 days. ^h40% 4c, 44% 5c. ⁱFull conversion in 8 days. ^jFull conversion in 10 days. ^lConversion after 7 days.

surface (Figure 3c teal \bigcirc blue \bigcirc ; entries 11, 12). Poor activity of NDI **15** with sulfide donors and inactivity of control **19** supported that contributions from hydrogen bonding with the amides in the imide substituent are not of primary importance (entries 13, 17).

PDIs have received little attention in anion- π catalysis, although they can reach exceptionally positive Q_{zz} (Figure 2a).⁹ PDI 16 with two nitro acceptors in the core was almost as active as the best NDI 14, although only 10 mol % catalyst could be used because of poor solubility (entry 14). Removal of one nitro acceptor in 17 decreased activity (entry 15). Overall increasing catalytic activity with increasing intrinsic π acidity (i.e., LUMO energies, positive Q_{zz}) identified for various benzenes (6 \gg 8 \sim 9 > 7), NDIs and PDIs (Figure

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3d) provided strong experimental support for operational anion– π catalysis.

Fullerenes have been introduced to an ion- π catalysis because their high polarizability is ideal to explore induced π acidity (i.e., induced macrodipoles that appear only in the presence of an anion or anionic transition state, Figure 2b), without complications from intrinsic π acidity (Figure 2a).¹⁰ The solubility of pristine C₆₀ was insufficient to study catalysis. With better soluble Bingel products, measurements were possible at 10 mol % in CD_2Cl_2 . The activity of fullerenes 18 (entry 16) was like less performing benzenes, NDIs and PDIs (entries 8, 13, 15). In pentafluorobenzene 7, however, fullerenes 18 showed much higher initial velocities (k_{cat}/k_{non}) = 270; entry 18). Pentafluorobenzene 7 alone as a solvent was inactive and failed to activate comparable NDIs and PDIs (entries 19, 20). Pentafluorobenzene 7 was thus likely to activate fullerenes 18 by increasing solubility and, perhaps, extending polarizability with remote donor-acceptor complexes (Figure 2b).¹⁰

Slow at room temperature, epoxide-opening ether cyclization of 3b in CD₂Cl₂ without catalyst was measured at higher temperature to extrapolate a $k_{non} = 4.25 \times 10^{-9} \text{ s}^{-1}$ (entry 1). At room temperature in hexafluorobenzene 6, the initial rate enhancement with 3b was $k_{cat}/k_{non} = 3.7 \times 10^3$ (entry 4). The dependence of product formation on time was sigmoidal (Figure 3a,b, red \blacklozenge). Similar behavior was observed with most anion- π catalysts (Figure 3c), but not with a simple acid catalyst, AcOH (Figure 3b+). Using NDI 11 as an example, the occurrence of autocatalysis¹¹ was supported by the increasing initial rate of the substrate conversion with increasing concentration of product 4b from the beginning $(EC_{50} = 530 \text{ mM}, \text{ Figure 3e,f})$. Controls confirmed that without anion- π catalysts, product 4b alone does not accelerate the reaction (Figure 3e blue ∇). Applying the analysis of autocatalytic reactions,¹¹ we obtained maximal $k_{\rm ac}$ / $k_{\rm non} = 6.1 \times 10^4 \text{ M}^{-1}$ (entry 4). Anion $-\pi$ autocatalysis was inhibited by nitrate due to the interruption of anion- π interactions between transition state and NDI surface (IC_{50} = 470 mM, Figure 3i). The dependence of initial rate on the substrate concentration followed a second-order power law, implying cooperative substrate activation (Figure 3g). The dependence on the concentration of catalyst 11 was linear, indicating that the catalysts function as monomers (Figure 3h. For 6, highly superlinear dependence on catalyst concentration supported that more than one π surface is needed to accommodate substrate and product in close proximity (Figure S5C); at very high substrate concentrations, decreasing concentrations of the solvent catalyst resulted in decreasing activities for the same reason (Figure S5D)). Controls in the dark confirmed independence from light.

Decreasing rates with increasingly substituted epoxides from **3a** to **3c** (Figure 3a) supported a concerted mechanism with the displacement of partial negative charges along the molecule to the intramolecular alcoholate leaving group and the complementary partial positive charges accumulating on hydrogens but not on carbons, as outlined in CS[‡] and CPS[‡] (Figure 1). In CPS[‡] computed for catalyst **11**', S[‡] and P are connected with two H bonds and form a noncovalent macrocycle on the π surface (Figure 4, B3LYP/6-31+G^{*}, CH₂Cl₂ continuum). Both S[‡] and P contact the π surface with one oxygen. The shorter O- π distance with S[‡] (2.57 Å) compared to P (2.79 Å) was consistent with a more advanced transition from lone pair (lp)- π interactions to anion- π



Figure 4. Structure of transition state CPS[‡] for catalyst 11' (Me imides), product 4b and substrate 3b (hydrogens and NDI substituents mostly omitted, distances in Å), and computed energy diagram (energies in kcal mol⁻¹, noninteracting compounds included in energy estimations listed only for initial S).

interactions to attract and stabilize electron density on the alcoholate leaving group (Figure 4). The location of the hydrogen between the two oxygens on the π surface confirmed that in the transition state, the negative charge accumulating on this emerging alcoholate oxygen is stabilized by anion $-\pi$ interactions rather than neutralized by proton transfer. Removal of this H bond shortened the $O-\pi$ distance from S^{\ddagger} (2.57 \rightarrow 2.36 Å) and the H bond from the nucleophile (1.87 \rightarrow 1.64 Å), indicating the release of some tension in the supramolecular macrocycle "dancing" on the π surface (Figure S23). As a result, the loss of a H bond is nearly compensated by stronger anion $-\pi$ interactions to activate the leaving group and stronger H bonds to activate the nucleophile.

In the computed energy diagram, rate enhancements $E_a(CPS) \sim E_a(CSS) < E_a(CS) < E_a(CS)$ were consistent with both anion- π catalysis and autocatalysis (Figures 4, S18–S23). Ternary complexes with either an additional product (autocatalysis) or an additional substrate gave similar activation energies but differed on the level of ground-state (CPS > CSS) and transition-state recognition (CPS[‡] > CSS[‡]), i.e., catalytic efficiency and proficiency.^{12,13}

The Baldwin products were obtained exclusively except for the dimethylated substrate **3c** (Figure 1). Product ratios inverted from PDI **16** (THP/THF (**5c**/**4c**) = 0.7) over NDI **11** without selectivity (THP/THF = 1.0) to NDI **14**, the most active anion- π catalyst (THP/THF = 1.2). These first indications of anti-Baldwin behavior encourage further investigation, together with studies on asymmetric catalysis, ring expansion and contraction as well as cascade cyclizations into higher oligomers (Figure 1). Preliminary results are available up to trimers.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11788.

Detailed experimental procedures (PDF)

AUTHOR INFORMATION

Corresponding Author

*stefan.matile@unige.ch ORCID © Antonio Frontera: 0000-0001-7840-2139 Stefan Matile: 0000-0002-8537-8349

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Present Address

[†]Department of Chemistry, University of Zurich, Zurich CH 8057, Switzerland

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank NMR and MS platforms for services, and the University of Geneva, the Swiss National Centre of Competence in Research (NCCR) Chemical Biology, the NCCR Molecular Systems Engineering and the Swiss NSF for financial support. A.F. thanks the MINECO/AEI (project CTQ2017-85821-R, FEDER funds) of Spain for financial support. J.L.-A. is a Curie Fellow.

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