**Title:** Pnictogen-Bonding Catalysis and Transport Combined: Polyether Transporters Made In Situ

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**Abstract:** The combination of catalysis and transport across lipid bilayer membranes promises directional access to a solvent-free and structured nanospace that could accelerate, modulate, and, at best, enable new chemical reactions. To elaborate on these expectations, anion transport and catalysis with pnictogen and tetrel bonds are combined with polyether cascade cyclizations into bioinspired cation transporters. Characterized separately, synergistic anion and cation transporters of very high activity are identified. Combined for catalysis in membranes, cascade cyclizations are found to occur with a formal rate enhancement beyond one million compared to bulk solution and product formation is detected in situ as an increase in transport activity. With this operational system in place, intriguing perspectives open up to exploit all aspects of this unique nanospace for important chemical transformations.

**Keywords:** Ion transport, catalysis, pnictogen bonds, polyethers, cascade cyclizations

**Reactions** that occur in lipid bilayer membranes continue to fascinate us, from early oscillating oxidations,1 self-replicating vesicles,2 templated polymerizations,3−5 photoredox processes,6−9 and catalytic pores10 to more recent dynamic covalent chemistry,11,12 molecular rockets,13−15 multistep cascades,16−18 and signal transduction systems.19−21 The direct combination of reactions with transmembrane transport has received less attention. The most developed systems operate with existing biological protein architectures19 thus avoiding synthetic efforts and direct participation of the membrane in the process. However, the coupling of catalysis and transport appears promising for several reasons in addition to the obvious unique detectability. Most importantly, lipid bilayer membranes offer a solvent-free environment that should strengthen noncovalent interactions. This removal of the often undesired contributions of solvents to catalysis is reminiscent of transformations in the gas phase or in silico. The volume provided for these solvent-free reactions is small and structured: A confined nanospace that appears ideal to maximize effective concentrations and control selectivity. Moreover, the combination of catalysis with transport adds directionality along a polarity gradient, promising remote control over diffusion20−23 along changing environments to maximize transition-state stabilization, minimize product inhibition, vary selectivity, and so on. Compartmentalization further invites multistep processes6−10,14,15 and various forms of detection.10,19 Taken together, these intriguing characteristics promise access to rate enhancements, new selectivity, and, at best, new reactivity. To thus explore the possible combination of catalysis and ion transport within lipid bilayer membranes, we decided to couple two topics of current concern, that is, transport and catalysis with chalcogen, pnictogen, and tetrel bonds and the biomimetic epoxide-opening cascade cyclizations into polyether cation transporters (graphical abstract).

Anion transport24−37 with pnictogen bonds38−44 has been realized recently31−33 as logical continuation of the earlier studies with chalcogen34,35 and halogen36,37 bonds. These unorthodox interactions all originate from σ holes and, related to σ* antibonding orbitals, extend linearly from all covalent bonds made by the element (Figure 1a, see refs 44 and 38 for electrostatic potential surfaces).45−56 Their strength increases with withdrawing substituents and polarizability of the element, that increases top−down and right−left in the periodic table.31

Fluorophenyl derivatives 1−12 were considered to act as both anion transporters and catalysts. They were prepared following reported procedures (Scheme S1).31,44 Ion transport was measured in EYPC LUVs with the classical HPTS assay.57,58 In this assay, EYPC LUVs (egg yolk phosphatidylcholine large unilamellar vesicles) are prepared with entrapped HPTS, a pH-sensitive fluorophore. Then the
transporter is added, followed by a base pulse (or vice versa). The dissipation of the resulting pH gradient is then followed by ratiometric changes in HPTS fluorescence, reporting on OH⁻/anion and H⁺/cation antiport and on OH⁻/M⁺ and H⁺/X⁻ symport. At the end of the experiment, an excess of channel forming peptide gramicidin D is added to determine maximal fluorescence intensity for calibration. Results are summarized in dose–response curves (DRCs) and reported as EC50, the effective transporter concentration needed to reach 50% activity.

According to the HPTS assay, the most active anion transporters were σ-hole donors 1–4 equipped with 3,4,5-trifluorophenyl (FP345) substituents (Figure 1a). Anion transport with tetrel bonds as in stannane 1 is novel in this series, and activities were with EC50 = 2.3 ± 0.4 nM, very high (Figure S6). Tris(3,4,5-trifluorophenyl)stibine (Sb(F345)3) 2 was similarly active, while bismuthane 3 was less powerful because, presumably, of the more dominant metallic character. The still high activity of tellane 4 followed polarizability trends. An only micromolar EC50 of germanane 5 was consistent with the previously described44 inaccessibility of the σ holes on the too small element.

The FP2₂₋₄ series 6–911 was overall less active compared to 1–5 because intramolecular pnictogen bonding of the ortho fluorenes weakens anion binding (Figure 1a,b).44 The ortho hydrogens in FP345 1–5, in contrast, are repelled by the σ holes and can further assist anion binding in the catalyst–anion (CX) complex 13. While FP2₂₋₄ 9 and 10 were unstable, FP2₄₋₆ analogues 11 and 12 confirmed that ortho fluorenes indeed weaken anion transport significantly. FP2₄₋₆ 11 and 12 and all other compounds were stable in buffer (Figures S2–S5). This included the best pnictogen-bonding catalyst 2 and marked a clear contrast to ligand-exchanging, water-incompatible general Lewis acid catalysts.

To facilitate comparison, some EC50’s are also reported in mol% lipid. Today’s record among small molecule transporters is arguably EC50 = 6.1 × 10⁻³ mol% for the tridentate HX binding natural product prodigiosin 14, closely followed by a multidentate oligo-urea macrocycle.30 A 1000 times weaker EC50 = 0.01 mol% has been recently reported for bidentate halogen-bonding transporters as current best in the context of σ-hole transporters.15 The EC50 = 1.8 × 10⁻³ and 2.1 × 10⁻³ mol% of the monodentate and neutral 1 and 2, only about 30 times weaker than cation 14, thus confirmed the power of anion transport with the hydrophobic, strong and directional tetrel and pnictogen bonds.

Polyether cascade cyclizations were selected as reactions of choice for this study. Polyothers are among the most popular cation transporters.59–63 Examples reach from tetrahydrofuran (THF) oligomers such as the natural product monensin A 15 and early artificial ion channels59 to most popular crown ethers60–64 and acyclic motifs (Figure 2).54,65 In nature, polyether transporters are synthesized by epoxide-opening cascade cyclizations.66–74 These charismatic processes have been studied extensively,66–71 recently also with anion–π catalysis.72–74 To further expand the integration of unorthodox interactions, pnictogen-bonding catalysis has been introduced as noncovalent counterpart of Lewis acid catalysis.44 Polyether cascade cyclizations have served well to demonstrate that the two are not the same, just like noncovalent hydrogen bonding and covalent Bronsted acid catalysis have their distinct advantages.44

Oligo-epoxides 16 and 17 cyclize selectively into 18 and 19, respectively (Figure 2).72 The four compounds and their analogues were synthesized following reported procedures (Figure S14).72 The transport activity of THF oligomers increased with length as expected, from less active monomers and dimers (EC50 = 1.1 ± 0.4 nM) up to tetramer 19 (Figure 2). Compared to 19, monensin A 15 was more active without but less active with the proton carrier FCCP, indicating that 19 is a better sodium transporter and a weaker proton transporter.57,58 A previously unexplored family, the oligo-epoxides 16 and 17 were identified as weak ion transporters. Multiply methylated analogues were more active (EC50 = 8.9 ± 0.7 μM for tetramers, Figure S19) but less attractive for catalysis studies because of violations of the Baldwin rules44 and relatively high background reaction in water.

Because stannane 1 is a weaker catalyst,44 anion transporter 2 and cation transporters 17 and 19 were selected to combine transport and catalysis (Figure 3). However, the outstanding transport activity of 2 prevented access to the high concentrations of substrate and catalyst needed to observe sufficiently fast initial rates for direct detection (Figure 3b).
The replacement of the chloride anions in the buffer by sulfates, which are more difficult to dehydrate and transport, solved this problem: The EC$_{50}$ of 2 increased almost 1000 times to EC$_{50}$ = 14 ± 3 μM (Figures 3c and 1).

Original HPTS kinetics under these conditions for 2 at the most sensitive 50% activity (green), 19 at minimal detectable activity (red), and both transporting together (ruby) revealed that their activities were overadditive (Figure 3d). Similar overadditivity was found for 2 and 17 (Figure S23). Cooperativity rather than anticooperativity demonstrated that the transport–ion complexes 20, 21, and 13 are more stable than catalyst–substrate (CS) complex 22 and CP 23 (Figure 3a). Such less stable CS and CP are beneficial to avoid antibactericidal and product inhibition.

In the presence of 20 μM 2, the differences in transport activity between 17 and 19 were well preserved (Figure 3e, Hill coefficients n > 1 especially for 19 suggested that PM 21 might be a 2:1 complex, Tables S3 and S4). To stabilize the system and access higher concentrations for faster conversion, the lipid concentration was increased. With four times more vesicles and 100 μM 2, the transport activities of 17 (EC$_{50}$ = 200 ± 75 μM) and 19 (EC$_{50}$ = 48 ± 7 μM) decreased correspondingly, while the range for in situ detection of their conversion increased from 5–30 μM to 40–200 μM substrate (Figure 3ef, red areas).

Under these optimized conditions, 2 was nearly inactive (Figure 3g). The difference between 17 and 19 in the presence of 2 remained significant, promising detectability of the cyclization (Figure 3g, red area). The substrate, catalyst, and vesicles were thus mixed together under these conditions and stirred for given times before transport activity measurements. Activities increased with reaction time (Figure 3hi). With 100 μM substrate and catalyst at 20 °C, full conversion was reached in 1 h (Figures 3g,h, ruby). Controls with either catalyst or substrate alone did not generate similar activity (Figure 3i). Repetition at different substrate and constant catalyst concentrations gave the expected changes in initial velocity (Figure 3j).

Cyclization of 2.0 M monoepoxide with 100 mol% stibine 2 in CD$_2$Cl$_2$ takes 48 h at 40 °C. When reacted at 1.0 M concentrations for 4 days, tetra-epoxide 17 was fully converted into 19 (Figure S25). Comparison of 1.0 M substrate converted in 96 h at 40 °C with 100 μM substrate converted in 1 h at 20 °C, also considering the van’t Hoff equation, implied a rate enhancement beyond 6 orders of magnitude. Based on the lipid concentrations used, the high local concentration in membranes can only account for about 10$^3$-fold increases in rate. The found rate enhancement was thus significant, possibly reflecting a shift from more stepwise to more concerted cascade cyclizations.

In summary, we introduce an operational system that combines catalysis and transport in lipid bilayer membranes, with synergistic anion and cation transporters realizing pnictogen-bonding catalysis under conditions that do not work in bulk solution. With the methods in place, these results provide a solid basis to exploit the many aspects of lipid bilayer membranes as a unique, directionally accessible, solvent-free, and structured nanospace for translocation-coupled molecular transformation.

### ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.1c00345.
Detailed experimental procedures, materials and methods, compound synthesis and characterization, original fluorescence kinetics traces, dose-response curves, Hill analyses, data summarizing tables (PDF)

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Q. Laurent for assistance with synthesis, the NMR and MS platforms for services, and the University of Geneva, the National Centre for Competence in Research (NCCR) Molecular Systems Engineering, the NCCR Chemical Biology, and the Swiss NSF for financial support.

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