MOLECULAR FRAMEWORKS AS PLATFORMS FOR CHEMISTRY IN CONFINED SPACE

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Confinement in chemistry

The concept of chemistry in confined spaces has evolved from a scientific curiosity into a thriving research frontier. Confinement effects—now widely observed across chemistry—are inspired by how enzymes and cellular compartments use spatial restriction to precisely control reactivity, selectivity, and molecular transport. Due to its broad scope and versatility, confinement is poised to impact fields ranging from sustainable energy and circular chemistry to precision medicine and quantum information technology—there is hardly any area in chemistry untouched by confinement effects. Although its conceptual power has long been recognized, the field now stands at a critical juncture—ready to transition from descriptive understanding to quantitative analysis and, ultimately, predictive control.

Confinement effects are well-recognized at a phenomenological level, with a growing body of evidence showing how spatial restrictions at the nanometer scale and below drastically alter (physico)chemical behavior. Fundamentally, confinement can lead to altered thermodynamics (e.g. changes in phase transition temperatures or the dielectric constant in nanoconfinement [1]), kinetics (i.e. modified reaction dynamics [2]), or changes in transport behaviour (e.g. water in (sub)nanopores shows anomalously high flow rates, similar to aquaporines [3,4]).

Researchers already benefit from a diverse toolbox to study and harness confinement, both in terms of materials and methodological advances: Confinement can be realized across multiple length scales and material classes—ranging from micropores (zeolites) to mesoporous materials (e.g., silica, metal oxides) and highly tunable porous frameworks such as COFs and MOFs: multivariate reticular solids that span both the micro- and mesoporous regime [5,6].

In recent decades, a systematic understanding of confinement effects across different applications has begun to emerge. What is still missing, however, is a quantitative and broadly generalizable framework that would allow these effects to be harnessed in scalable settings—such as the industrial production of platform chemicals, precision medicine, or energy conversion and storage. The opportunities, however, are immense:

(i) **Catalysis (platform and fine chemical synthesis, medicine):** Confinement can enrich or accumulate reactive intermediates and products; transition states are modified due to enthalpic and entropic changes, as well as magnetic, electric, and dielectric effects within pores [7].

(ii) **Gas storage and selective separation (CO_2 capture, H_2 storage):** Confined environments can lead to selective and enhanced gas uptake, e.g. through changes in adsorption strength or oversolubility effects [8].

(iii) **Energy storage (supercapacitors, nanofiltration, desalination)**: Tailored pore systems and dielectric environments spanning from nanofluidic to Angstrofluidic scales can enhance mass transport properties and enable new forms of ion conductivity and charge screening, e.g. electrolytes in nanopores show altered ion solvation and enhanced capacitance [9].

Quantifying, scaling and controlling these effects for specific functions remains a key challenge—and the next big frontier. Just as catalysis once evolved from empirical recipes to mechanistic design, chemistry in confinement is now seeking the same transformation.

Our recent research contributions to chemistry in confined space

Our contribution to the study of confinement effects is intimately linked to the design and characterization of reticular porous materials including covalent organic frameworks (COFs), metal-organic frameworks (MOFs) and a new generation of hybrid frameworks—called MOCOFs—with tailored pore sizes, achieving angstrom-level precision [10]. These works form the basis for leveraging reticular solids as powerful platforms to explore and precisely control confinement effects in catalysis.

With their modular and crystalline structures, paired with "simple" 1D pore systems, COFs have allowed us to systematically tune pore size, polarity, and chemical functionality—making them ideal for studying how spatial confinement influences chemical and (photo)electrocatalytic reactivity in heterogenized single-site molecular catalysts [11]. By varying building blocks and linkage chemistries, we created frameworks with distinct pore-wall polarities and functional anchoring sites, enabling the selective immobilization of molecular catalysts [12-14]. This fine control has allowed us to design and probe confinement environments for specific catalytic transformations in thermal and photo(electro)catalysis [15-17].

For example, using click chemistry, we covalently attached a hydrogen evolution catalyst (cobaloxime) into COF pores, which resulted in markedly improved photocatalytic activity and stability compared to non-covalent analogues [18,19]. We attribute this to improved interfacial electron transfer and the suppression of catalyst deactivation pathways within the confined environment (Fig. 1). Together with the Buchmeiser and Laschat groups we demonstrated confined olefin metathesis and asymmetric catalysis, revealing how pore structure and functional group placement influence selectivity and product distribution [20,21].

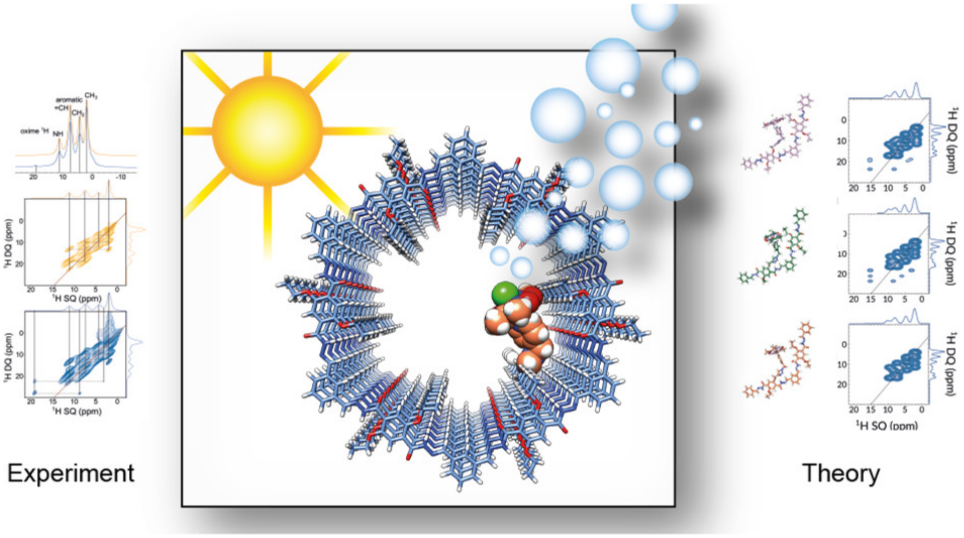

Fig. 1. Rational design of covalently tethered COF-cobaloxime hybrids for enhanced photocatalytic hydrogen eovlution. Figure taken from ref [19].

We are currently extending the use of COFs as confining matrices to electrocatalytic CO_2 reduction and urea synthesis, where small-pore COFs create confined environments that stabilize and enrich key intermediates (for example, promoting enhanced C–C coupling toward C_{2+} products) and help control complex product distributions. Moreover, electrified COF pores offer a unique handle for tuning the electrochemical double layer as well as the dielectric properties and solvent dynamics near the electrode. Together with the Tschulik group, we recently demonstrated a correlation between COF pore size and hydrogen-bonding strength, local pH, and CO enrichment—highlighting the pivotal role of COF pores in steering product selectivity while suppressing the parasitic HER.

However, a major limitation of using COFs as confining matrices lies in their susceptibility to real-structure effects—an outcome of what we term the *COF trilemma*, which captures the inherent challenge of balancing crystallinity, stability and functionality in COFs [22]. Defects and disorder—such as stacking faults or local pore corrugations, which are common in COFs—underscore the need to better understand their real (in addition to their average) structures in order to unravel and harness confinement effects in these soft materials. By combining space-averaging and local structural probes including pair distribution function analysis (PDF), 3D ΔPDF and pulsed-field gradient (PFG) NMR spectroscopy, we have been able to pinpoint real-structure effects and their impact on the effective pore size [23,24] and transport limitations in COFs [25,26]. To mitigate the latter, we have introduced hierarchical mesoporosity into COFs, which enables bulk-like diffusivities that are crucial for minimizing diffusion limitations during electrocatalytic CO_2 reduction [27].

Outlook to future developments of research on chemistry in confined space

As the field matures, I envisage two research directions as particularly promising:
(1) To move from isolated case-by-case studies to more concerted efforts at quantifying, predicting and exploiting confinement effects for desired functions, most notably in catalysis. These efforts must encompass the entire value chain—from materials design, physico-chemical understanding, and theoretical modelling of confinement effects to reaction engineering—tightly integrated through an iterative feedback loop.
(2) To seek smarter, more complex, and more dynamic confinement. The next era will likely be defined by new paradigms that (i) embrace complexity, (ii) adaptability, and (iii) computational intelligence:

(i) Embracing Complexity and Aperiodicity

One of the profound questions facing the materials community is: Why does nature often avoid perfect order? The answer lies in information content. Purely periodic systems–and hence also porous confinement matrices–are limited in function: each pore repeats identically. But biological systems succeed because they combine order with purposeful—sometimes superimposed—disorder.

The challenge (for synthetic chemistry) therefore is to design materials where single-sized, periodic pores are imprinted with symmetry-breaking, programmed function, needed e.g. for directional processes such as cascade chemical reactions. This transition demands a new design philosophy: Moving beyond ordered confinement to multi-functional, complex confinement, i.e. from uniform geometric confinement to custom-made pores imparted with pore-specific functions.

(ii) Dynamic Confinement and Responsive Architectures

A promising direction is the development of dynamic or adaptive confinement systems, where pores can open, close, expand, or contract in response to stimuli. This is already seen e.g. in dynamic, breathing MOFs, which respond to guest molecules or temperature changes [28]. Dynamic confinement links directly with themes in living chemistry, where adaptability, feedback, and evolution are key.

(iii) AI-Powered Design of Confinement Systems

Artificial intelligence (AI) offers a radical new way to understand, predict, and design confinement systems, which the community can harness to not just study, but predict and use confinement effects in scalable settings. AI is thus expected to be key in scaling up complexity while maintaining control, enabling the programmable, intelligent design of confined chemical environments.

The future of chemistry in confined space is not just smaller, but smarter. By embracing complexity, dynamic behavior, and computational design, researchers are poised to unlock confinement as a true design principle—not just a phenomenon to observe, but a tool to control.

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