

# Molecular basis of activity changes in acid catalysis within nanoconfined water

The behaviour of nanoconfined water can be very different from that of the bulk and is challenging to understand at a molecular level. Now, molecular simulations and kinetic experiments provide insight into the increased activity of hydronium ions in water nanoconfined within zeolite pores.

## This is a summary of:

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## The question

Chemical processes are being developed to produce commodity chemicals – traditionally oil-derived – from renewable lignocellulosic biomass<sup>1</sup>. Lignin can now be efficiently depolymerized into a mixture of oxygenated aromatics, which can then be dealkylated to obtain simpler, more valuable products. The dealkylation is typically conducted in hot-pressurized water and is acid catalysed or, in other words, facilitated by the presence of hydronium ions (H<sub>3</sub>O<sup>+</sup>). These ions can be freely dissolved in the water, if coming from a mineral acid such as HCl, or confined in the micropores of an acidic zeolite, which have diameters of molecular dimensions. The reactivity of hydronium ions in water changes considerably within confined environments<sup>2,3</sup>; however, a clear molecular-level picture of the chemical differences between water in bulk and within zeolites has been missing.

## The observation

A better understanding of how hydronium ions behave in bulk versus nanoconfined water is essential for the development of efficient biorefinery processes. However, this goal requires a link to be made between the macroscale properties and the behaviour of single molecules at the nanoscale. To this end, we combined advanced molecular simulations with numerous kinetic experiments and studied a key reaction of the lignin conversion process – the *O*-demethylation of guaiacol – both with a homogeneous (HCl) and a heterogeneous (H-beta zeolite) catalyst. First-principles molecular dynamics simulations under operando conditions were used to simulate the reactive environment as close as possible to the complex experimental conditions<sup>4</sup>, including solvent molecules and the catalyst at high temperatures and pressures.

Experimental kinetic measurements showed that guaiacol *O*-demethylation proceeds much faster in the nanoconfined zeolite pores than in bulk water. To explain this observation, we used molecular simulations to investigate the reaction mechanism (Fig. 1). It has been assumed that the reaction proceeds via a protonated oxonium ion intermediate. However, under operando conditions, our simulations indicated that the preferred mechanism, with either the homogeneous or heterogeneous catalyst, is a one-step bimolecular nucleophilic substitution reaction. This finding is corroborated by the experimental observation of a strong inverse solvent kinetic isotope effect.

To explore what makes the zeolite such a good catalyst, we conducted additional

simulations of hypothetical reactive systems in which we changed the number of water molecules in the zeolite or its framework topology to modulate the confinement effects. Two main conclusions can be drawn from these simulations. First, the hydronium ions in zeolites are undercoordinated, which increases their reactivity and decreases the enthalpic requirements for the reaction. Second, and complementary, the water distribution and the channel architecture in the zeolite have a key role in bringing together the reactants and the hydronium ions, modulating the reaction kinetics by changing the entropy requirement of the reaction.

## Future directions

Although the higher activity of hydronium ions in confined environments is insufficient to completely characterize the reaction kinetics, this finding opens the door to the rational design of more effective catalysts for bimolecular reactions. For example, theory predicts that the loading of water in the zeolite has a major effect on the reaction kinetics and could be tweaked by the insertion of hydrophilic sites to achieve the desired catalytic properties.

This study provides fundamental insight into the chemistry of hydronium ions in confined environments, but the complexity of the problem has only been scratched. Indeed, water can lead to more severe modifications of the zeolite framework, creating additional species such as framework-associated and extra-framework aluminium<sup>5</sup>. The influence of these sites on the overall reactivity is probably non-negligible, and thus it is crucial to investigate their roles within the confined environment.

An extensive investigation of additional sites and reactive environments was unfeasible when the simulations were performed, as they are based on expensive quantum-mechanical calculations. However, molecular simulations are being revolutionized by the advent of machine learning interatomic potentials, which can reduce simulation times by multiple orders of magnitude. With accurate interatomic potentials, full in silico screening of different active sites and, potentially, the automated discovery of reactive paths is within reach. This advance would enable simulations to become predictive and, in our opinion, is the natural future of computational catalysis.

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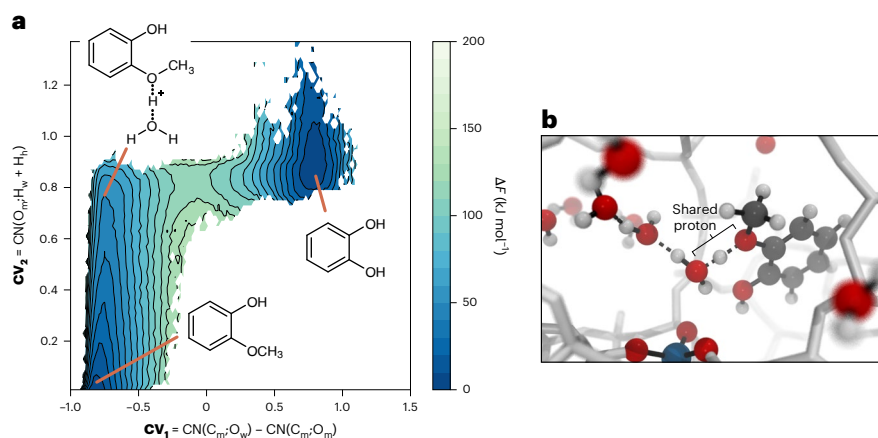
## FROM THE EDITOR

“The balanced combination of experiments and simulations in this paper reveals important details on the mechanism of biomass-related hydrolysis within a confined space — a riddle in the field — and points

to an unusual type of mechanism for the demethylation of guaiacol. Hopefully, such mechanistic insight will facilitate the design of effective biorefinery schemes.”

**Editorial Team, *Nature Catalysis*.**

## FIGURE



**Fig. 1 | Guaiacol *O*-demethylation proceeds through an unusual one-step mechanism, without the formation of an intermediate oxonium ion. a**, Free energy surface ( $\Delta F$ ) of the guaiacol *O*-demethylation reaction to catechol and methanol in the H-beta zeolite. The surface is obtained from first-principles enhanced sampling molecular dynamics simulations, in which the system is biased along two collective variables (CVs) made of different coordination numbers (CNs). **b**, Snapshot extracted from the molecular dynamics simulations, showing proton transfer from the hydronium ion to guaiacol at the onset of the bimolecular nucleophilic substitution reaction within the zeolite (H is shown in white, O in red and C in dark grey). © 2025, Bocus, M. et al.

## BEHIND THE PAPER

This research is part of a collaborative project with the overarching goal of converting wood chips into high added-value chemicals. The dealkylation of lignin-derived molecules, an essential part of the lignin-to-chemicals process, was therefore being assiduously investigated by the experimental groups of Bert F. Sels and Bert U.W. Maes. In the cooperative spirit, we began a complementary study of the reaction in silico. For modellers, the key challenge of research at the theory–experiment interface is bridging the gap between the behaviour of

$\sim 10^2$  atoms in models and the observations made in the lab by looking at  $10^{23}$  of them. Within V.V.S.’s group, modelling methods are being developed to follow in time complex chemical transformations under operating conditions. Owing to limitations in computing power, brute-force simulations of a full catalyst particle with a mole of water molecules are beyond reach. Therefore, a fascinating aspect of computational chemistry is to design simplified systems that can approximate the experimental complexity. **M.B. & V.V.S.**

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