Scientists investigate fast reaction dynamics in synthetic molecules immobilized in porous protein cages

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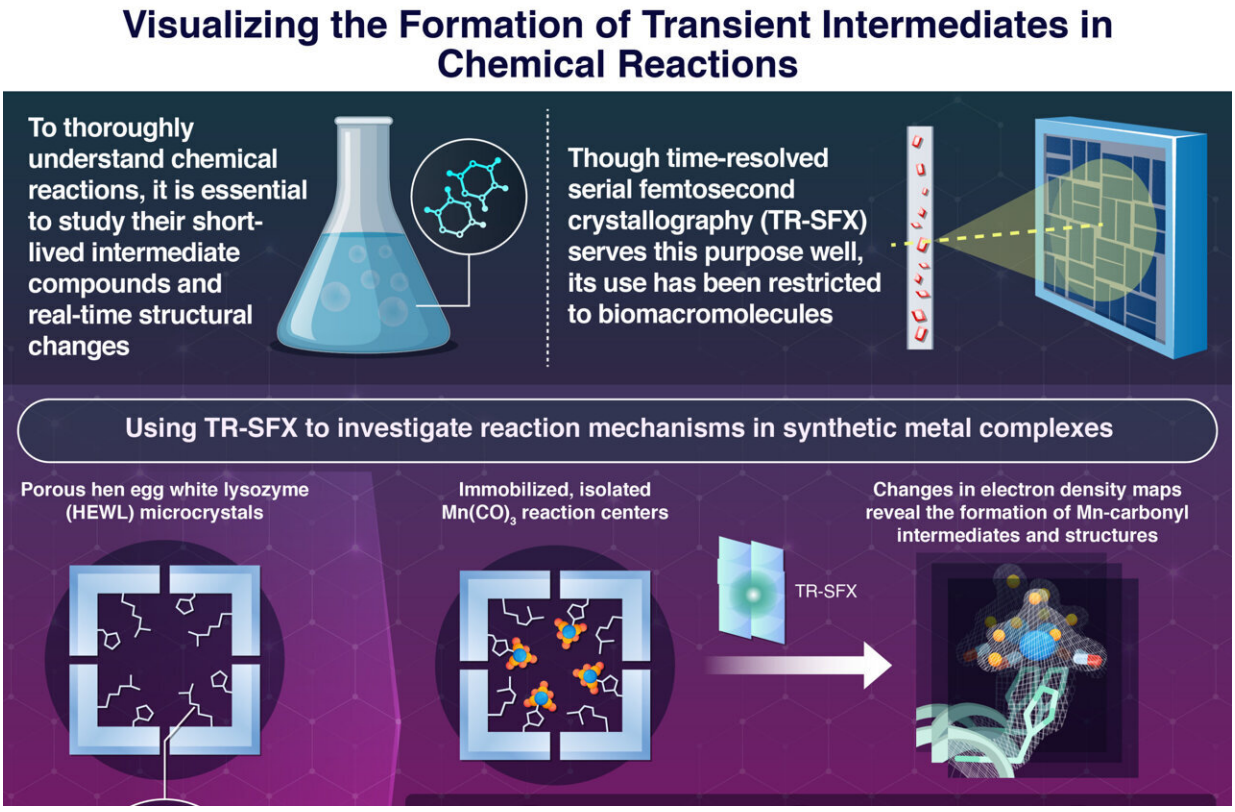

This technique will facilitate the design of synthetic bio-inspired catalysts and enzymatic systems with precise chemical reaction mechanisms. Credit: Tokyo Institute of Technology

Immobilizing small synthetic molecules inside protein crystals proves to be a promising avenue for studying intermediate compounds formed during chemical reactions, report scientists from Tokyo Tech. By integrating this method with time-resolved serial femtosecond crystallography, they successfully visualized reaction dynamics and rapid structural changes occurring within reaction centers immobilized inside protein crystals. Their study was published in *Nature Communications*.

This innovative strategy holds significant potential for the intelligent design of drugs, catalysts, and functional materials.

Most complex chemical reactions, whether synthetic or biological, do not involve a direct transformation of reactants into products. Instead, they often proceed through the formation of short-lived intermediate compounds that undergo further reactions until the final products are obtained.

Understanding these stepwise processes in detail is crucial for advancements in fields such as energy generation, catalysis, and medicine. However, visualizing short-lived intermediates in chemical reactions is quite challenging, especially if one needs to capture structural changes in a molecule at the atomic level.

One cutting-edge method to achieve this is time-resolved serial femtosecond crystallography (TR-SFX). This technique involves shooting extremely fast electron laser pulses at crystallized molecular structures and capturing the ensuing diffraction patterns.

These molecular structures are in various stages of a chemical reaction, allowing the reaction dynamics to be recorded. Despite its astonishing capabilities, the use of TR-SFX thus far has been mostly limited to biomacromolecules.

To extend the applications of this powerful technique and showcase its potential for other types of molecules, a research team from Japan, led by Professor Takafumi Ueno, decided to use it to analyze reactions in synthetic compounds. Using an innovative approach, they successfully captured the dynamics of carbon monoxide (CO) release from $Mn(CO)_3$.

One significant limitation that the researchers had to overcome is the fact that TR-SFX works best with microcrystals, such as those formed by biomacromolecules. Additionally, although small molecules can form crystals suitable for TR-SFX, these crystals are generally tightly packed, leaving little room for reactions to occur.

To address these issues, the team developed an innovative strategy based around hen egg-white lysozyme (HEWL). This naturally occurring protein not only crystallizes into a nanoporous structure suitable for TR-SFX, but also contains His15 terminals that bind strongly to metals. The researchers took advantage of these properties to immobilize a light-sensitive $Mn(CO)_3$-containing compound inside HEWL crystals.

This setup provided a suitable environment for studying CO release reactions, which were triggered by shooting light pulses at the crystals at carefully controlled time intervals relative to the TR-SFX electron laser pulses.

Overall, this protocol proved highly promising for investigating the target reaction by analyzing changes in electron density maps obtained via TR-SFX.

"After CO release, Mn centers typically undergo dimerization, aerial oxidation or precipitation in solution, which complicates mechanistic investigations. In our work, by isolating the Mn reaction centers in a restricted protein environment, we enabled a detailed experimental analysis of the intermediates generated during the progression of the

reaction," explains Ueno.

Worth noting, the experimental results were in excellent agreement with quantum mechanical calculations, validating the proposed strategy. "We have established that, by using protein crystals as a matrix, the reactions of synthetic metal complex can be studied, including the determination of any intermediate structures," concludes Ueno.

"This advancement holds the potential to facilitate the design of artificial metalloenzymes with precise mechanisms, empowering the design, control, and development of innovative reactions."

The method developed in this work provides an avenue for the smart design of new drugs, catalysts, and enzymatic systems involving non-biological components.

More information: Basudev Maity et al, Real-time observation of a metal complex-driven reaction intermediate using a porous protein crystal and serial femtosecond crystallography, *Nature Communications* (2024). DOI: 10.1038/s41467-024-49814-9

Provided by Tokyo Institute of Technology

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