THE CRYSTALLINE SPONGE METHOD: ABSOLUTE STRUCTURE DETERMINATION OF OILS, LIQUIDS, AND TRACE SAMPLES

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BACKGROUND

Structure determination is one of the cornerstones of organic chemistry. The development of infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance (NMR) spectroscopy revolutionized the speed with which information pertaining to structure and composition of new organic molecules is obtained.[1] While not as straightforward as the previous methods, single-crystal X-ray diffraction (SCD) remains the most conclusive method to date for full structure determination, providing structural information on the atomic level.[2] However, the inherent limitation of X-ray crystallography is the requirement for a single high quality crystal, often an impossible challenge for liquid samples. Thus, methods to determine absolute structure for such samples are highly sought after.

STRUCTURE DETERMINATION

In 2013, Fujita and coworkers reported a new SCD method that avoids direct crystallization of an organic sample.[2] Instead, a porous metal-organic framework (a crystalline sponge) composed of zinc iodide nodes and trispyridyl triazine ligands is used to absorb the target molecule. The result is uniform orientation of the target within the framework (Figure 1) which is then observable by SCD.[2] This method has been applied to different molecular scaffolds containing a variety of functional groups, all generally under 400 Da (Figure 2).[2-5] When chiral molecules are included in the MOF, a change in space group is observed (achiral to chiral) allowing for determination of absolute stereochemistry using heavy atom anomalous scattering from the zinc and iodine atoms present in the framework.[2] A significant application of this method is the analysis of trace amounts of sample (nanogram and microgram quantities), and has far-reaching implications for the characterization of complex mixtures. The Fujita group showed in their original report (and further work in 2016), that the method can be directly coupled with HPLC analysis of natural product mixtures where analytes are only present in microgram quantities.[2,4]

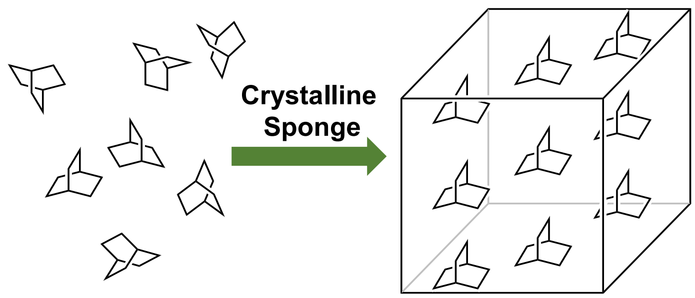

Figure 1. Schematic of crystalline sponge method.

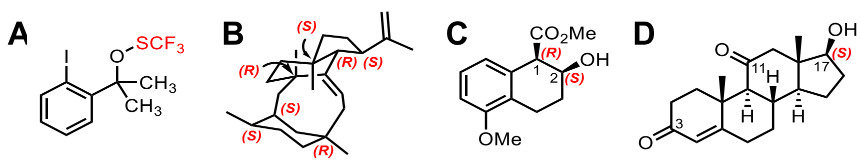

Figure 2. Selected examples of small molecules use for absolute structures determination by the crystalline sponge method. A) trifluoromethylthiol transfer reagent, B) astellifadine, C) tetralone derivative, D) adrenosterone derivative.

MECHANISTIC INSIGHTS

In addition to structural information, SCD can also provide important mechanistic information. Recently, the crystalline sponge method, combined with time-dependent X-ray diffraction, allowed observation of transient intermediates of a palladium-mediated aromatic bromination (Figure 3).[6] Introduction of a planar organopalladium species results in an intercalated crystalline sponge in which the Pd center adopts a square planar geometry within the pores. Subsequent addition of NBS to the crystalline sponge and X-ray diffraction at 90 K showed retention of square planar geometry throughout the reaction, evidenced by the electron density maps in Figure 3.[6] This analysis indicates procession through a Pd(0)/Pd(II) mechanism rather than Pd(II)/Pd(IV) in the crystalline environment. Further uses of this method to observe reactions and hard-isolate intermediates are also appearing in the literature.[7]

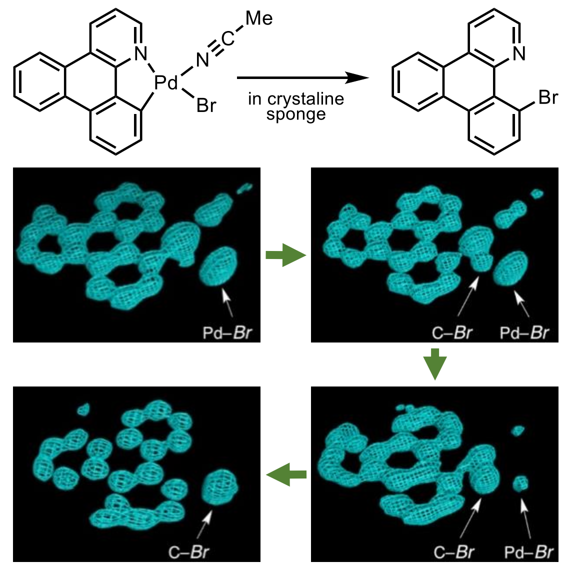

Figure 3. Time-dependent X-ray diffraction of palladium-mediated aromatic bromination.

FUTURE DIRECTIONS

The crystalline sponge method has the potential to revolutionize small molecule structure determination. However, size constraints and certain functional group incompatibilities (particularly aliphatic amines) are the current limitations for everyday use. Design of new crystalline sponge networks to meet these needs will comprise the immediate future development of this method. Already underway, the last step to worldwide use will be commercialization of the method and off-the-shelf availability of the crystalline sponges.[8]

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