



Application Note SC-XRD 517

The D8 QUEST ECO for Crystal Sponge Investigations

- Bachelor Student Training Leads to New Polymorph

Introduction

In 2013, Fujita *et al.* published the protocol of the structure determination of compounds, which for various reasons are difficult to crystallize.[1] This new method is referred to as “crystalline sponge method” and uses a single crystal of an ingeniously designed metal organic framework (MOF—the “sponge”) that can incorporate the guest molecules of interest (the “analyte”). Because the analyte is trapped in a periodic arrangement, X-ray diffraction allows for the determination of the analyte’s molecular structure.

The method also allows the investigation of oily compounds, works with analyte amounts down to the nanogram range, and provides the opportunity to investigate other traditionally inaccessible candidates like reactive intermediates.[3, 4] It is well-known that chemical reactions with compounds in a crystalline state often lead to the loss of crystallinity.[5] In most cases, whenever a molecule in a crystal changes its shape or size, the lattice gets destroyed, leading to an amorphous product.

However, if the supporting framework does not participate in the reaction, it is possible for molecular transformations to occur whilst preserving crystallinity. With this method it is even possible to observe reactive species using single crystal X-ray diffraction as demonstrated by Vinogradova *et al.* with a hypervalent iodine reagent[6], Ikemoto *et al.* for a palladium-catalyzed bromination[7], and Fujita *et al.* for ozonolysis intermediates.[15]

To date, the majority of crystalline sponge research has been performed by the Fujita group, which has published further experimental details in order to enable other scientists to reproduce and extend the crystalline sponge method.[9-12] In general, the crystalline sponge research—despite the huge interest it caused—is still in a relatively early stage.[13] Although it is known that the ZnI_2 nodes function as H-bond acceptors and the pyridinic ortho-H-atoms function as H-bond donors, it is not currently possible to predict if a molecule can be studied by this method.[10,14]

As part of a three-month (bachelor) student training, we set out to reproduce literature results published by Fujita *et al.* and compare the quality of the acquired data to reported values. In this work we focus on two analyte compounds: 4-nitrobenzaldehyde and 2,6-diisopropylaniline.

Experimental

The synthesis of the $[(ZnI_2)_3(tpt)_2] \cdot (\text{cyclohexane})$ ($tpt = \text{tris}(4\text{-pyridyl})\text{-}1,3,5\text{-triazene}$) crystalline sponge was carried out according to the literature.[9, 10]

The guest uptake procedure

Cyclohexane (5 mL) was added to the individual $[(ZnI_2)_3(tpt)_2] \cdot (\text{cyclohexane})$ crystals in a small amount of mother liquid in a Petri dish. Two crystals (*cf.* visual guidance in [9]) were carefully selected under a microscope and each one was transferred to a small vial with 45 μL of solvent. The target compounds (analyte) were diluted in dichloromethane in a 1:1 volume ratio and 5 μL of guest solution was added to each vial. The septa of the vials were pierced with a needle of 0.5 mm diameter, after which they were placed into an oven at 50 $^\circ\text{C}$ for 48 hours with the needle still in. The crystals might change color during absorption, depending on the guest that is used. In this case, 2,6-diisopropylaniline induced a color change from clear to red and 4-nitrobenzaldehyde did not.

After two days, the “loaded” crystalline sponge crystals were transferred to a drop of mineral oil on a microscope slide for final inspection under an optical microscope. The best candidate was then picked up with a single-crystal sample holder and quickly transferred to the goniometer head of the diffractometer. The sample was flash-cooled to 150 K in a cold nitrogen stream using a low-temperature device and was kept at this temperature during the data acquisition.

Discussion

The X-ray data were collected to a resolution of 0.84 \AA on a D8 QUEST ECO diffractometer equipped with a TRIUMPH monochromator and a PHOTON detector, using $\text{Mo K}\alpha$ radiation ($\lambda = 0.71073 \text{\AA}$). The data collection and evaluation were carried out with the APEX3 software suite, which comes with the D8 QUEST ECO.

The unit cell of the sponge crystal was determined using the pre-experiment frames of a fast scan (180 degree phi scan with short exposure time). Based on the unit cell and crystal orientation, the data collection strategy was optimized to achieve data completeness as quickly as possible with a multiplicity of at least three. After the data collection finished, the frames were integrated, and intensities were scaled and corrected for absorption with SAINT and SADABS from within APEX3. The structures were solved using intrinsic phasing (XT), the powerful default method of APEX3's ‘Solve Structure’ plug-in. The least-squares refinement against R^2 of all reflections was performed with XL. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were set to idealized positions and refined with a riding model.

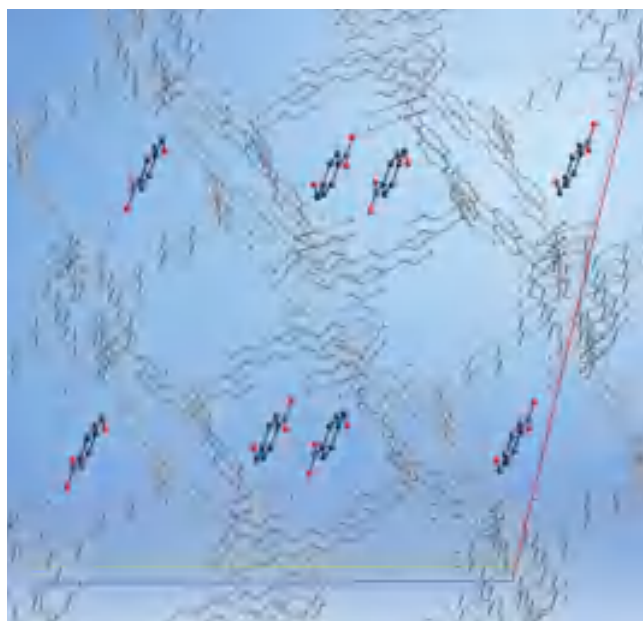


Figure 1: Unit cell of the sponge loaded with 4-nitrobenzaldehyde along **b**.

Crystal formation

The yield of suitable sponge crystals is hard to quantify and varies from batch to batch. By qualitatively comparing the morphology of the crystals from multiple syntheses, some crucial steps could be identified. The crude sponge crystals are prone to degradation during the nitrobenzene-to-cyclohexane solvent exchange. The crystallization vials need to be agitated daily to prevent crystal clumping, which leads to a loss in crystallinity within three days.

Different types of zinc halide salts can be used to create the crude sponge. However, zinc iodide gave by far the best crystals compared to zinc bromide and chloride, which yielded a high amount of needle-like one-dimensional crystals. These are not well-suited for this X-ray diffraction experiment. The zinc iodide corners also increase the anomalous differences, facilitating determination of absolute configuration. An alternative chloroform-based approach to synthesize the crystalline sponge[8] also led to a large number of needle- and plate-like crystals.

During our tests, the zinc iodide cyclohexane sponge proved to be the easiest to synthesize and crystallize.

Guest soak

The guest uptake procedure was the most difficult to reproduce. Even applying the detailed procedures from the literature, each analyte was absorbed at a different rate into the framework, thus making it difficult to produce a universal protocol. It is also challenging to perform the absorption non-destructively because the cyclohexane-containing crystals deteriorate quickly when they are removed from the mother liquid. Moreover, the crystals are different sizes, and size impacts the speed of the overall process. Consequently, the absorption might be complete in one crystal while still underway in another. Yet, this can only be determined after the refinement of the analyte's occupancy at the end of the crystal structure analysis. The two literature-reported structures for 2,6-diisopropylaniline and 4-nitrobenzaldehyde both contain more than one analyte molecule with a 'site occupation factor' (s.o.f.) lower than 1.

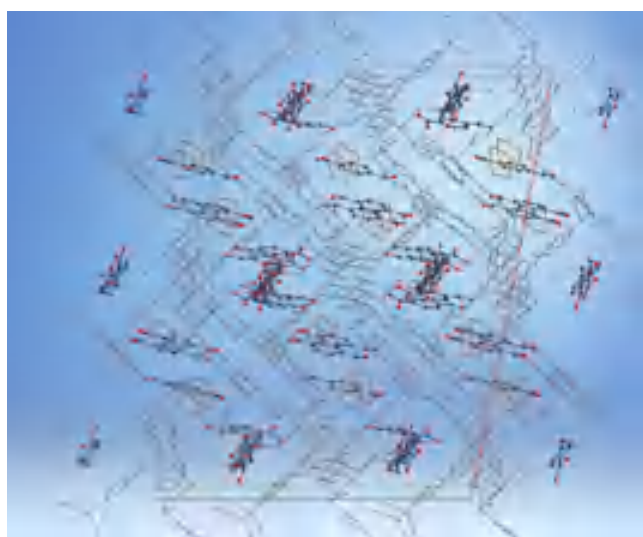


Figure 2: Unit cell of the sponge loaded with 4-nitrobenzaldehyde along **b** as published by Fujita.[10].

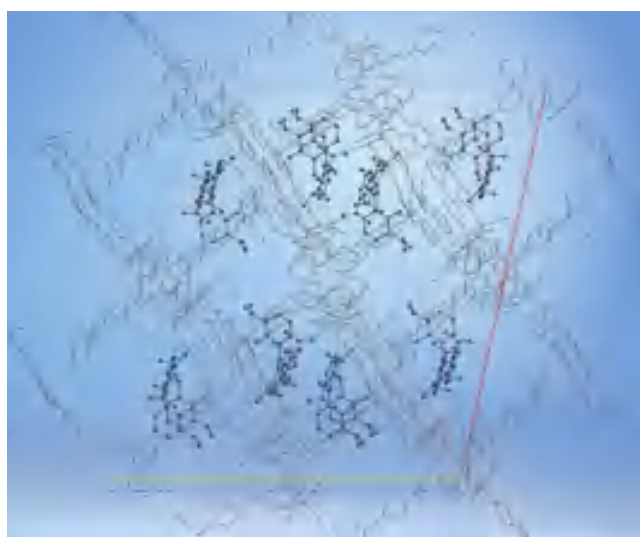


Figure 3: Unit cell of the sponge loaded with 2,6-diisopropylaniline along **b**.

Table 1. Crystallographic data overview

	4-NO ₂ -PhCHO		2,6- <i>i</i> Pr-PhNH ₂	
	D8 QUEST ECO	Fujita[10]	D8 QUEST ECO	Fujita [10]
wavelength	0.7107 Å	1.5418 Å	0.7107 Å	1.5418 Å
unit cell	<i>a</i> [Å]	35.755(3)	32.5791(8)	36.943(5)
	<i>b</i> [Å]	14.8090(14)	15.2458(3)	14.706(2)
	<i>c</i> [Å]	31.284(3)	29.0346(9)	30.802(4)
	β[°]	102.872(5)	98.398(2)	102.788(7)
	<i>V</i> [Å ³]	16149(3)	14266.7(6)	16320(5)
GOF		1.09	1.09	1.15
<i>R</i>1		0.071	0.067	0.058
<i>wR</i>2		0.254	0.206	0.195
Number of reflections		82973	38259	131951
multiplicity		5.8	2.6	9.2
completeness		99.7%	99.9%	99.5%

Molecular structure

The modelling of the sponge metal-organic framework was easily accomplished for both test cases, although the 4-nitrobenzaldehyde structure (Figure 1) differs substantially from the published work (Figure 2), *vide infra*. The literature-known guests 4-nitrobenzaldehyde and 2,6-diisopropylaniline were also clearly identified. One 2,6-diisopropylaniline molecule could even be refined entirely without restraints (Figure 3). Both models exhibit residual electron density in the pores that is difficult to assign. As shown in the literature, there is a high chance that the analytes share positions with solvents. This often makes it difficult to refine a model without using a large number of restraints.[10] However, the excellent data quality we achieved with the D8 QUEST ECO allowed us—without any prior experience in this field—to easily determine the analytes within the examined sponge crystals.

As shown in Table 1, all structures refined to a comparable level of quality. Interestingly, we found a modification of the sponge soaked with 4-nitrobenzaldehyde analyte different to the one reported in [10]. These crystals exhibited a larger unit cell with a volume of 16 149 Å³. Fujita's system showed a volume of 14 267 Å³. The new system is 13 percent greater volume. The flexibility of the zinc iodide corners allows the sponge to adjust its size to accompany more analyte molecules, the nitrogen-zinc-nitrogen angle, measures 103.18° in this structure, versus 97.61° in the literature reported structure. This new structure is not yet published (CSD database checked in Jan. 2018). Our new modification shows similar lattice parameters as the 2,6-diisopropylaniline soak in literature and in this work.

Summary

Within the limits typical for host-guest chemistry, we successfully applied the crystalline sponge method on 4-nitrobenzaldehyde and 2,6-diisopropylaniline. Using Molybdenum radiation did lead to a significantly higher number of reflections. The QUEST ECO with PHOTON detector proved to be an excellent, cost-efficient tool for these challenging crystal structure determinations.

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Tris(4-pyridyl)-1,3,5-triazene (69.3 mg, 0.222 mmol, 2 eq) was dissolved in a nitrobenzene (44 mL) / methanol (11 mL) mixture using an ultrasonic bath to aid dissolution. ZnI₂ (0.332 mmol, 3 eq) was dissolved in methanol (11 mL). Ten test tubes (160×15 mm) were placed in a rack and each was filled with 5 mL of tris(4-pyridyl)-1,3,5-triazene solution. Using a pipette, 1 mL of zinc halide solution was layered on top of the tris(4-pyridyl)-1,3,5-triazene solution. It is important that two layers are formed to induce reproducible crystallization, and as such the zinc halide solution should be layered carefully along the wall of the test tube. Each test tube was capped using a septum and the rack was placed in a fume hood for one week during which crystals formed on the walls and bottom of the test tube. After a week, the test tubes were inspected to identify good crystals, which were taken off the test tube walls using a plastic spatula. It was observed that better crystals usually formed further away from the layer interface. The crystals on the bottom of the test tube were taken up in a small amount of mother liquor using a pipette, then placed into another test tube. Approximately 10 mL of cyclohexane was added. The test tube was swirled and the solvent level was reduced as much as possible using a pipette. This process was repeated until no nitrobenzene layer could be observed at the bottom of the test tubes. All tubes were capped with septa and placed into an oven at 50 °C for a week. Each morning during incubation, the supernatant was replaced with fresh cyclohexane. It is important that the solid is swirled around to prevent clumping of the crystals, which leads to a loss of crystallinity. This procedure yielded about 50 [(ZnI₂)₃(tp)₂](cyclohexane) crystals after a week.