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COMMUNICATION

Towards multifunctional MOFs – transforming a side reaction into a post-synthetic protection/deprotection method

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K. M. Zwoliński,^a Piotr Nowak^a and M. J. Chmielewski^{a*}Received 00th January 2012,
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The contaminant commonly found in the important amino-substituted metal-organic framework UiO-66-NH₂ has been shown to arise from partial formylation during the synthesis in DMF. Mild conditions have now been developed for both post-synthetic deformylation and near-complete formylation, offering a new post-synthetic protection / deprotection method for the synthesis of multifunctional MOFs.

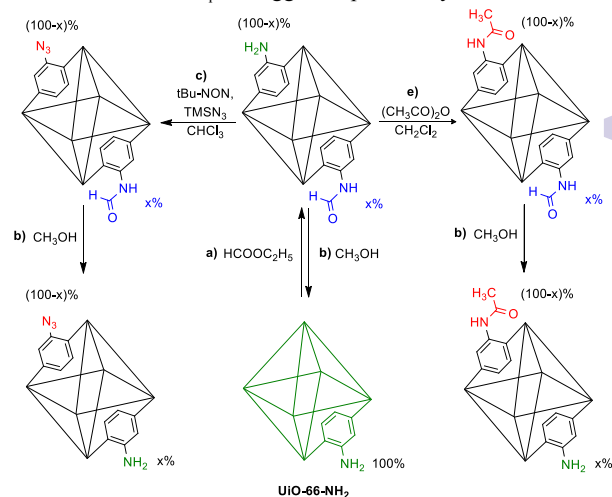
UiO-66-NH₂ is one of the most promising metal-organic frameworks (MOFs) for post-synthetic grafting owing to its high hydrolytic stability and the presence of easy-to-functionalise amino groups.¹ Several protocols for its synthesis have been published, most of them based on the reaction of inexpensive 2-amino-terephthalic acid (H₂BDC-NH₂, **1**) with ZrCl₄ in *N,N*-dimethylformamide (DMF) at elevated temperatures (80–120 °C).²

However, the materials thus obtained have been reported to contain substantial amounts (up to 30%) of an unidentified ligand³ and their reported BET surface areas vary greatly from 650 to 1630 m²/g.^{3,4} The material is therefore unsuitable for some applications and an improved synthetic method leading to well-defined, pure UiO-66-NH₂ is needed.

In this work, we show that the persistent impurity formed during the synthesis of UiO-66-NH₂ results from formylation of H₂BDC-NH₂ by DMF, describe mild methods to both remove and introduce formyl groups after the MOF's synthesis and demonstrate that the controlled formylation/deformylation is a promising protection/deprotection strategy for post-synthetic heterofunctionalisation⁵ of UiO-66-NH₂. To the best of our knowledge, this is the first report on post-synthetic protection-modification-deprotection (PMD) sequences in MOFs (Scheme 1).⁶ Preliminary mechanistic experiments indicate that our results are relevant also to other amino-substituted MOFs.

Initially, we synthesised UiO-66-NH₂ using three commonly used methods, the first one developed by Cohen and co-workers,⁷ the

second by Behrens and co-workers⁸ and the third by Hupp, Farla and co-workers.⁹ All samples, upon digestion in DMSO-d₆/HF_{aq}, were found to contain *ca.* 14–22% of the same impurity, as judged from ¹H NMR spectra. The impurity was isolated using analytical TLC (RP, C-18) and identified as 2-formamidoterephthalic acid (**2**) by ESI MS, NMR spectroscopy and independent synthesis (see ESI†). Such a by-product could only form during the synthesis of UiO-66-NH₂ in a transamidation reaction between the substrate **1** and the solvent, dimethylformamide, and not during the digestion of the MOF in DMSO-d₆/HF_{aq}, as suggested previously.¹⁰



Scheme 1. Post-synthetic modification of UiO-66-NH₂ via protection / azidation / deprotection (a/c/d) or protection / acylation / deprotection (a/e/f) sequences.

Our attempts to eliminate the impurity by lowering the reaction temperature or by using *N,N*-diethylformamide (DEF) instead of DMF proved unsuccessful. Moreover, survey kinetic experiments (Table 1) showed that formylation by DMF occurred under a

reaction conditions used thus far for the synthesis of UiO-66-NH₂ and is very likely to take place also during the synthesis of other amino-substituted MOFs. Although neither H₂BDC-NH₂ alone nor pure UiO-66-NH₂ are appreciably formylated by DMF at high temperature, the extent of formylation becomes significant in the presence of acids (Table 1). In general, the synthesis of MOFs involves either the deliberate addition of a Brønsted acid or its unavoidable generation as a result of hydrolysis of the metal salts necessarily present. Furthermore, various Lewis acids, and in particular zirconium complexes, are known to be excellent catalysts of transamidation reactions.¹¹ Thus, formylation by DMF is very likely to take place also during the synthesis of other amino-substituted MOFs. Indeed, undesired formylation has been reported during the synthesis of CAU-10-NH₂.¹²

Table 1. Formylation of H₂BDC-NH₂ and UiO-66-NH₂ in the presence of various acids. All samples were heated in DMF (2 ml) at 120 °C for 24 h. For more details see table S1 in the ESI.

No.	Ligand/MOF	Additives	% _{NHCHO}
1		- blank experiment	6%
2	H ₂ BDC-NH ₂	50 μl HCOOH (1.33 mmol)	27%
3	(20 mg, 0.11 mmol)	5 μl HCOOH (0.133 mmol)	8%
4		14 μl 36% HCl (0.44 mmol) ^a	3%
5		147 μl 36% HCl (4.60 mmol) ^b	12%
6	UiO-66-NH ₂	- blank experiment	2%
7	(32 mg, 0.018 mmol, containing 0.11 mmol of H ₂ BDC-NH ₂)	50 μl (1.33 mmol) HCOOH	32%
8		14 μl 36% HCl (0.44 mmol) ^a	5%
9		147 μl 36% HCl (4.60 mmol) ^b	26%

a) 4 equivalents with respect to H₂BDC-NH₂ - the amount of HCl that corresponds to complete hydrolysis of the amount of ZrCl₄ added in the synthesis of UiO-66-NH₂
 b) the amount of HCl added to the synthesis of UiO-66-NH₂ according to Farha, Hupp and co-workers [ref. 7]

In view of these results, we turned our attention to post-synthetic methods for deprotection of HCONH- groups. Heating of partially formylated UiO-66-NH₂ in a DMF/H₂O mixture for 24 h resulted in only partial deprotection - from 23 to 11%. However, heating at reflux in both MeOH/H₂O and MeOH led to slow but clean and complete regeneration of NH₂ groups. Of these two, we choose boiling in MeOH as the mildest deprotection method for further investigations. Thus, for example, as-synthesized UiO-66-NH₂ containing ca. 15% of HCONH- groups could be purified by Soxhlet extraction with boiling methanol for 24 h. The resulting material contained no traces of HCONH- residues and was ca. 98% pure by ¹H NMR. Since Soxhlet extraction with MeOH has been sometimes used to activate UiO-66-NH₂ after synthesis, it is probable that some previously synthesised samples contained only small amounts of the formylated ligand.

Complete deprotection of highly formylated samples (*vide infra*) took many days of refluxing in MeOH, but could also be achieved in a much shorter time by heating at temperatures exceeding the boiling point of MeOH under autogenous pressure. For instance, UiO-66-NH₂ containing 50% of HCONH-groups was completely deprotected in 48 h at 80 °C in a sealed high-pressure vial.

Our mild method for the removal of formyl groups opens the door to a new protection/deprotection strategy for post-synthetic grafting of UiO-66-NH₂ with two or more different functional groups. To this end, we first sought a method for high-yielding formylation of UiO-66-NH₂. Among several methods described in the literature for homogeneous formylation of amino groups,¹³ the most promising seemed to be heating with ethyl formate, a molecule small enough to easily penetrate MOF pores and highly volatile (b.p. 54 °C), so that it can be easily removed from MOFs after the synthesis. Indeed,

refluxing UiO-66-NH₂ in HCOOEt protected up to 75% of the NH₂ groups after 7 days at 54 °C, or in just 24 h at 100 °C in a sealed vial. Increasing the temperature to 120 °C provided material containing 80% and 87% of NHCHO groups after 24 and 92 h, respectively, but the final product was contaminated by ca. 2-4% of a new by-product (possibly N-alkylated BDC).¹⁴ The amount of this by-product further increased with temperatures above 120 °C. Interestingly, fully protected UiO-66-NHCHO material is also difficult to obtain *de novo* - all our attempts to synthesise UiO-66-NHCHO from pure H₂BDC-NHCHO gave materials with less than 80% of formamido groups. Partial deformylation of the ligand during the synthesis of MOF can be ascribed to hydrolysis¹⁵ or transamidation with dimethylamine (from the decomposition of DMF).

All post-synthetically protected UiO-66-NH₂/NHCHO materials maintained the high porosity and crystallinity of the parent framework as confirmed by their nitrogen adsorption isotherms (Fig. 1) and unchanged PXRD patterns (Fig. 2). Notably, the BET surface area of the materials decreased only slightly with the extent of protection, at least as far as 50 % formylation, owing to the very small size of the formyl protecting group.

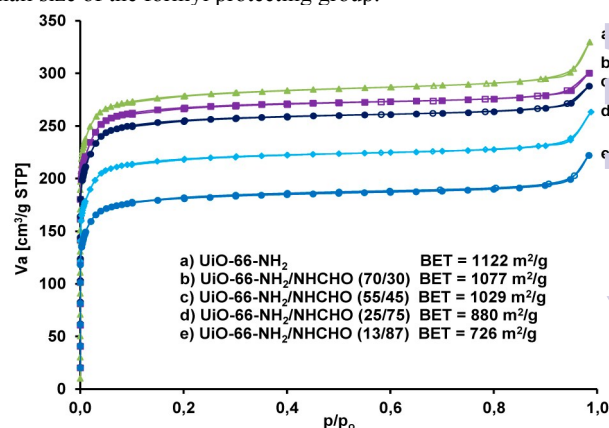


Figure 1. N₂ adsorption (solid symbols) and desorption (open symbols) isotherms of UiO-66-NH₂/NHCHO materials. All isotherms measured at 77 K.

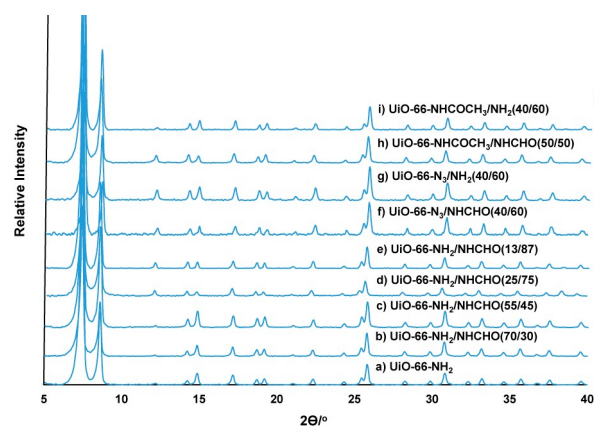


Figure 2. PXRD patterns of the UiO-66-NH₂ derived materials.

Having established mild protection and deprotection protocols for UiO-66-NH₂, we investigated their application for heterofunctionalisation of the material. As the first model reaction we choose acylation with acetic anhydride. We reasoned that selective deprotection of HCONH- in the presence of very similar CH₃CONH- groups would be a stringent test for our approach. A sample containing 50% of formyl groups was thus treated with an

excess of acetic anhydride in CH_2Cl_2 .¹⁶ The conversion of residual amino groups to acetamido was quantitative. Subsequent heating in MeOH at 80°C for 4 days removed all the formyl groups together with a small fraction of the acetyl groups, leading to UiO-66-NH₂ 41% acetylated.

Going further, we have found that our protection/deprotection method also enables conversion of a desired fraction of NH₂ groups into N₃ residues, potentially useful for the click reaction. Thus, treatment of partially protected samples with *tert*-butyl nitrite and TMSN₃ in CHCl_3 ¹⁷ converted all the free amino groups into azides in a two-step, one-pot diazotisation/Sandmeyer reaction. Deprotection of formylated NH₂ groups in MeOH at 80°C for 24 h smoothly gave material with a desired proportion of N₃ and NH₂ residues.

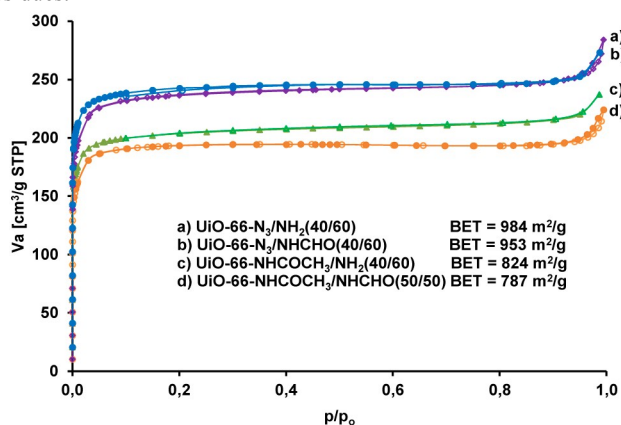


Figure 3. N₂ adsorption (solid symbols) and desorption (open symbols) isotherms at 77K for new post-synthetically modified UiO-66-NH₂ materials.

As before, all the post-synthetically modified UiO-66-NH₂ materials maintained crystallinity and porosity over three or four post-synthetic steps respectively (Fig. 2 and 3). For all four bifunctional materials type I isotherms were obtained with BET surface areas ranging from 787 to 984m²/g.

Conclusions

The established protocols for the synthesis of an important MOF, UiO-66-NH₂, give materials with significant fractions of formylated amino groups, due to the side reaction with DMF solvent. The side reaction is difficult to avoid under the acidic conditions typical for the synthesis of many MOFs, so it is likely to impair also the synthesis of other amino-containing MOFs. What we have found, however, is that simply heating the crude products in MeOH leads to deformylation. Further, UiO-66-NH₂ can be post-synthetically formylated and deformylated in a controlled manner under mild conditions, providing a basis for selective protection/deprotection in subsequent functionalization of the MOF. Owing to its very small size the formyl group seem to be particularly well suited to protect functional groups in MOFs. This procedure has been shown to be compatible with acylation and diazotization followed by conversion to azide, leading to the first two post-synthetic protection/modification/protection sequences known for MOFs. We are working towards extension of the method to other hydrolytically stable MOFs.

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^a Krzysztof Zwoliński, Piotr Nowak and Michał J. Chmielewski; Faculty of Chemistry, Biological and Chemical Research Centre, University of Warsaw, Żwirki i Wigury 101, 02-089 Warszawa

Electronic Supplementary Information (ESI) available: synthetic details and characterisation data: NMR, ESI-MS and FTIR-ATR spectra, PXRD, TGA, N₂ adsorption isotherms. See DOI: 10.1039/c000000x/

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