

Unexpected reversal of reactivity in organic functionalities when immobilized together in a metal-organic framework (MOF)

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A mixed-ligand metal-organic framework (MOF) material composed of both amine- and hydroxyl-bearing linkers, KSU-1, was reacted with a variety of isocyanates. The hydroxyl groups reacted to a greater extent than the amines, in conflict with the previously observed relative nucleophilicities of these functionalities in the same MOF. When immobilized individually in monofunctional MOFs, the amine-functionalized linker was more reactive than the hydroxyl linker, indicating that the reactivity reversal observed in KSU-1 is due to the groups' mutual confinement within the MOF.

As crystalline, multicomponent materials, metal-organic frameworks (MOFs) have properties that are a function of their metal clusters, organic linkers, and diverse topologies.^{1–3} From this combination of attributes, the confined space of MOF pores arises as an additional structural feature of interest, particularly with respect to catalysis.⁴ Confinement effects resulting from the size and shapes of the cavities,^{5–7} as well as the nature and proximity of functional groups within the pores^{8–12} have been postulated as influencing the activities and/or selectivities of substrates reacting within MOF pores. What has received less consideration, however, is the effect that this confinement has on the reactivities of the functional groups that decorate the frameworks themselves. Herein, we report how the presence of two different functional groups within a MOF material results in unexpected, and unique, changes in their relative reactivities.

Our group has previously worked with **KSU-1**,¹³ a pillared Zn-based MOF that is composed of the linkers, 2-aminobenzene-1,4-dicarboxylic acid (BDC-NH₂) and *meso*- α,β -di(4-pyridyl) glycol (DPG), which are functionalized with amine (–NH₂) and hydroxyl (–OH) groups respectively (Figure 1). The nucleophilic amine and hydroxyl groups are in well-defined locations throughout the framework and react independently with different acid anhydrides to yield uniformly bifunctionalized MOF materials. The independent functionalization with anhydrides is due to the greater nucleophilicity of the –NH₂ groups of the aniline linker compared to nucleophilicity the –OH groups of the glycol linker.¹⁴ To increase the range of products that we can obtain by uniform binary functionalization, we investigated the possibility of independent reactivity with isocyanates.^{15–17} Given the reported relative reactivities of different nucleophiles with isocyanates (Figure 1A),¹⁸ and the relative electrophilicities of differently-substituted isocyanates (Figure 1B),¹⁹ we speculated that it would be possible to achieve independent functionalization of **KSU-1** by judicious choice of isocyanate. Specifically, we supposed that

aliphatic isocyanates, which are the least electrophilic and therefore the least likely to react with the hydroxyl groups, could undergo addition at the –NH₂ groups of **KSU-1** exclusively, leaving the hydroxyls to react subsequently with a more electrophilic isocyanate (Figure 1C).

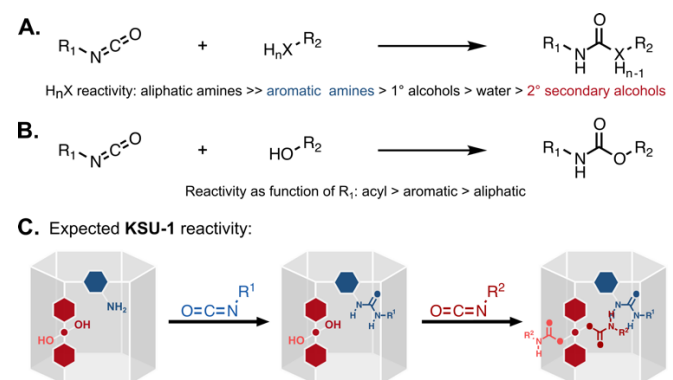


FIGURE 1. A: Order of nucleophile reactivity in their uncatalysed additions to isocyanates. B: Order of isocyanate reactivity depending on their substituents C: Expected order of reaction with isocyanates of functional groups in the independently functionalizable MOF **KSU-1**.

We incubated **KSU-1** in an acetonitrile solution of isopropyl isocyanate (*i*-PrNCO) at 80 °C for 3 h, intending to halt the reaction after only the –NH₂ groups had reacted. Instead, surprisingly, we found that the hydroxyls had reacted nearly to completion while only a small amount of the amines had been converted (Figure 2A). This result was observed by proton nuclear magnetic resonance (¹H-NMR) spectroscopy of the MOF product digested in D₂SO₄/d₆-DMSO (Figure 2B). The spectrum showed the near complete disappearance of the peak corresponding to the α -protons of the DPG hydroxyls (4.98 ppm), along with the appearance of a peak corresponding to the same protons in the DPG dicarbamate product (6.15 ppm). Meanwhile, the peak corresponding to the aromatic proton *ortho* to the urea of reacted BDC-NH₂ (9.00 ppm) was barely visible. High-resolution mass spectrometry (HRMS) of the product digested in 1,4-diazabicyclo[2.2.2]octane (DABCO) confirmed the product of the reaction to be DPG isopropyl dicarbamate (Figure S1). Interestingly, when we monitored the reaction over time, we saw that it occurred almost exclusively at –OH before proceeding at the –NH₂ groups (Figure 2C). Additionally, while the reaction slowed at room temperature, it still followed the same order of reactivity, with the hydroxyls reacting to a greater extent than the amines (Table S2; Entry 1).

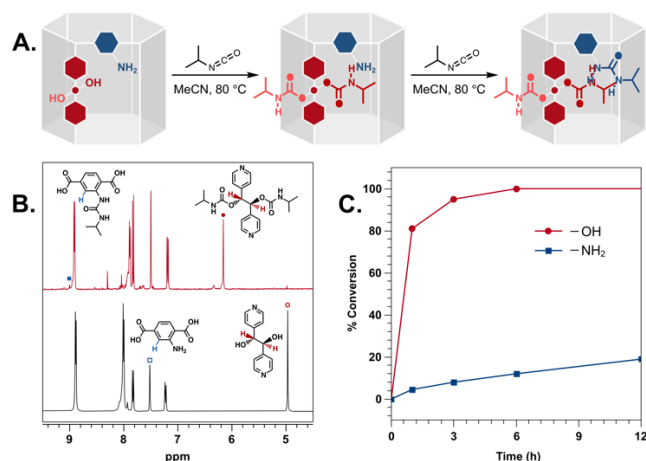


FIGURE 2. A: Observed order of reaction of the functional groups in **KSU-1** with *i*-PrNCO. B: ¹H-NMR spectra of **KSU-1** before (bottom), and after (top) incubation with *i*-PrNCO (MeCN, 3 h, 80 °C). Open symbols represent unreacted linkers; filled symbols represent the urea and carbamate products. C: Conversions of **KSU-1** -NH₂ and -OH over 12 h.

We speculated that this reversal in expected reactivity of the functional groups in **KSU-1** could be due to the protonation of the amine groups, which would slow down their addition to isocyanates. However, when we added “Proton Sponge” (1,8-bis(dimethylamino)naphthalene), a bulky organic base that cannot catalyse the reaction,²⁰ we observed no change in the order of reactivity (Table S2; Entry 2). We then considered the possibility of a steric effect due to the proximity of the -NH₂ groups to the metal corners, in contrast to the more accessible -OH groups. However, when we conducted the reaction with less bulky isocyanates (ethyl, propyl, and allyl), we observed similar behaviour (Table 1; Entries 2-4). Next, we investigated the behaviour of more reactive isocyanates.²¹ With phenyl isocyanate, we observed that the amines reacted to a more significant extent, though still less than the hydroxyls (Table 1; Entry 5). Interestingly, with the 4-iodophenyl and 3-pyridyl isocyanates, the behaviour was as we would normally expect, with the amine conversion advancing further than that of the hydroxyls (Table 1; Entries 6-7).

Table 1. Comparison of reactivity of **KSU-1** -NH₂ and -OH with different isocyanates.

Entry	Isocyanate	% conv. (stdev)	
		-NH ₂	-OH
1	<i>i</i> -Propyl	7 (5)	97 (6)
2	Ethyl	10 (1)	68 (7)
3	<i>n</i> -Propyl	12 (3)	81 (6)
4	Allyl	18 (1)	82 (3)
5	Phenyl	60 (4)	92 (3)
6	4-Iodophenyl	89 (1)	72 (4)
7	3-pyridyl	80 (12)	20 (4)

0.2 M in acetonitrile, 3 h, 80 °C.

These results suggested that the extent to which one functionality reacted preferentially over the other depended on the electrophilicity of the isocyanates, i.e., less electrophilic isocyanates reacted preferentially with the

hydroxyls, and more reactive isocyanates with the amines. When we reacted **KSU-1** with *i*-PrNCO in the presence of triethylamine, an amine that catalyses the reaction by activating the isocyanate,²² the conversion of the **KSU-1** amines did increase, but it was still lower than that of the hydroxyls (Table S2; Entry 3). With the least reactive isocyanates reacting preferentially with the hydroxyls in **KSU-1**, we hypothesized that, for less activated isocyanates, the -NH₂ groups help to promote the reaction at the hydroxyls, with the hydroxyls unable to return the favour. To test this theory, we attempted to compare the reactivities of the linkers in solution, but found comparisons difficult to make as DPG, and its dimethylated salt, were both insoluble in all applicable solvents. To address this challenge, we synthesized MOFs in which the amines and hydroxyls are present alone: **KSU-1000**, composed of BDC-NH₂ and 4,4'-dipyridyl (Figure 3A), and **KSU-3**, a version of **KSU-1** in which BDC-NH₂ has been replaced with benzene dicarboxylate (BDC; Figure 3B). It should be noted that, as with **KSU-1**, neither of the new MOFs are permanently microporous, both experiencing pore collapse and loss of crystallinity with evacuation (Figures S17-18). While **KSU-1000** recovers crystallinity after resolution, **KSU-3** does not.

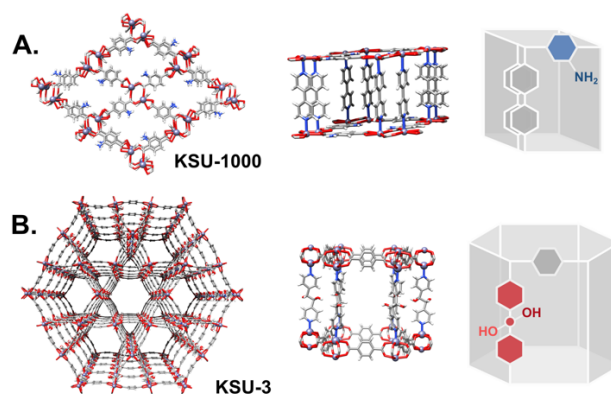


FIGURE 3. A: Isocyanate reaction of a MOF functionalized with -NH₂ only, **KSU-1000**. B: Isocyanate reaction of a MOF functionalized with -OH only, **KSU-3**.

To compare functional group reactivities in **KSU-1**, **KSU-1000**, and **KSU-3**, we incubated the MOFs with various isocyanates under previous reaction conditions except we quantified the conversions before most of the reactions had reached completion. At 1 h, **KSU-1** exhibited similar reactivity as before, with aliphatic isocyanates reacting preferentially with the hydroxyls, and more reactive isocyanates reacting preferentially with the amines (Table 2). In **KSU-1000**, the -NH₂ groups reacted according to the expected literature trend:²³ aliphatic isocyanates gave lower conversions than their aromatic counterparts, and isocyanates with activating groups had the highest conversions (Table 2).¹⁹ Additionally, the conversions were uniformly higher than those of the amines in **KSU-1** despite **KSU-1000** having smaller channels (9 Å vs 17 Å). For **KSU-3**, the -OH groups were converted to a significantly lower extent than they were in **KSU-1** for all isocyanates (Table 2). Additionally, when compared to the reactivity of the -NH₂ groups in **KSU-1000**, the -OH groups in **KSU-3** reacted

slower in all cases (Table 2), despite **KSU-3** having larger channels.

Table 2. The reactivity of different isocyanates with **KSU-1**, **KSU-1000**, and **KSU-3**.

Entry	Isocyanate	%conv. (stdev)		
		KSU-1 –NH ₂ :–OH	KSU-1000	KSU-3
1	<i>i</i> -Propyl	4 (1): 64 (3)	10 (1)	3 (1)
2	Ethyl	8 (2): 38 (8)	13 (6)	6 (2)
3	<i>n</i> -Propyl	5 (2): 52 (6)	12 (4)	2 (1)
4	Allyl	10(2):41 (2)	16 (7)	5 (1)
5	Phenyl	36(1):75 (8)	80 (1)	8 (2)
6	4-Iodophenyl	70(3):54 (2)	100 (0)	31 (1)
7	3-Pyridyl	78(1):21 (2)	100 (0)	66 (9)

0.2 M in acetonitrile, 1 h, 80 °C.

Analysing our results in totality, we see that when the MOFs are monofunctional, the nucleophiles follow the normally expected reactivity, with the amines reacting faster than the hydroxyls. When the functional groups are in the pores together, the reaction at the hydroxyls is accelerated at the expense of the amine reaction. However, it is only with less activated electrophiles that the –OH groups react before the –NH₂ groups. This suggests that when both reactions are slow, rather than reacting themselves, the amines somehow promote the reaction at the hydroxyls. Given the large distance between the –OH and –NH₂ groups in the framework (6 Å), it is unlikely that the promotion of the hydroxyl reaction involves amine catalysis via a direct amine...isocyanate...hydroxyl interaction. Another possibility is that the amines interact with the isocyanates via water-mediated H-bonds, activating the isocyanates through amine... (H₂O)_n...isocyanate...hydroxyl chains.^{24,25} The elevated temperature at which the reaction is conducted makes the formation of such chains with adventitious water unlikely,²⁶ however we do not discount the possibility.

Finally, to gain more insight into the reactivity of **KSU-1**, we investigated the reactions of the three MOF materials with *i*-PrNCO in different solvents. Du Bois and Matzger reported that the reactivities a BDC-NH₂ based MOF with different isocyanates is affected by solvent choice, with the solvent influence also depending on the identity of the isocyanate.²¹ Comparing the *i*-PrNCO reactions in acetonitrile, chloroform, and toluene, we found that the reactions of the –NH₂ groups in **KSU-1000** and the –OH groups in **KSU-3** were both slowest in acetonitrile and fastest in chloroform (Table 3). For **KSU-1**, the hydroxyls were still more reactive than the amines in all three solvents, but the extent of –NH₂ conversion increased significantly in toluene and chloroform (Table 3; Entries 2-3). These results support the observation that the reversal in reactivity in the bifunctional MOF is more marked under conditions where the reactions are slowest for the isolated functionalities.

Table 3. Comparison of the reactivity of **KSU-1** –NH₂ and –OH in different solvents.

Entry	Solvent	% conv. (stdev)			
		KSU-1000	KSU-3	KSU-1	
		–NH ₂	–OH	–NH ₂	–OH
1	MeCN	13 (3)	19 (3)	7 (5)	97 (6)
2	Toluene	16 (3)	32 (8)	39 (6)	85 (5)
3	CHCl ₃	27 (8)	42 (1)	60 (8)	78 (9)

0.2 M *i*-PrNCO, 3 h, 80 °C.

Based on the results we have obtained, we conclude that the reaction of the –OH groups with isocyanates is promoted, in preference to reaction at the –NH₂ groups, by confinement of the functional groups together in the MOF pores. We also note that the effect is greatest when the reaction would have been slowest for both functionalities. While the origin of this reversal in expected reactivity is yet to be determined, it does offer a tantalizing preview of the confinement effects that can be realized in the pores of multifunctional MOFs. It also lends credence to the parallel that is often drawn between MOFs and enzymes, as there are several examples of the perturbation of the properties of chemical functionalities as a result of mutual confinement with other functional groups in enzyme cavities.^{27–29} Thus, this result has exciting implications for MOF applications, such as catalysis and sensing, that will rely on the action of multiple functional groups within confined spaces.

P. Matseketsa: Investigation (lead); writing – review and editing (supporting). D. Mafukidze: Investigation (supporting). L. Pothupitiya: Investigation (supporting); writing – review and editing (supporting). U.P. Otuonye: Investigation (supporting). Y.C. Mutlu: Investigation (supporting). B. Averkiev: Investigation (supporting). T. Gadzikwa: Conceptualization (lead); writing – original draft (lead); writing – review and editing (lead).

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 V. V. Butova, M. A. Soldatov, A. A. Guda, K. A. Lomachenko and C. Lamberti, *Russ. Chem. Rev.*, 2016, **85**, 280.
- 2 T. C. Nicholas, E. V. Alexandrov, V. A. Blatov, A. P. Shevchenko, D. M. Proserpio, A. L. Goodwin and V. L. Deringer, *Chem. Mater.*, 2021, **33**, 8289–8300.
- 3 A. Ejsmont, J. Andreo, A. Lanza, A. Galarda, L. Macreadie, S. Wuttke, S. Canossa, E. Ploetz and J. Goscianska, *Coord. Chem. Rev.*, 2021, **430**, 213655.
- 4 K. Hemmer, M. Cokoja and R. A. Fischer, *ChemCatChem*, 2021, **13**, 1683–1691.
- 5 T. Uemura, R. Kitaura, Y. Ohta, M. Nagaoka and S. Kitagawa, *Angew. Chem.*, 2006, **118**, 4218–4222.
- 6 M. Zheng, Y. Liu, C. Wang, S. Liu and W. Lin, *Chem. Sci.*, 2012, **3**, 2623–2627.
- 7 S. Nießing and C. Janiak, *Mol. Catal.*, 2019, **467**, 70–77.
- 8 D. J. Xiao, J. Oktawiec, P. J. Milner and J. R. Long, *J. Am. Chem. Soc.*, 2016, **138**, 14371–14379.
- 9 L. Liu, T.-Y. Zhou and S. G. Telfer, *J. Am. Chem. Soc.*, 2017, **139**, 13936–13943.
- 10 T.-Y. Zhou, B. Auer, S. J. Lee and S. G. Telfer, *J. Am. Chem. Soc.*, 2019, **141**, 1577–1582.
- 11 Y. Quan, Y. Song, W. Shi, Z. Xu, J. S. Chen, X. Jiang, C. Wang and W. Lin, *J. Am. Chem. Soc.*, 2020, **142**, 8602–8607.
- 12 W. Yan, S. Li, T. Yang, Y. Xia, X. Zhang, C. Wang, Z. Yan, F. Deng, Q. Zhou and H. Deng, *J. Am. Chem. Soc.*, 2020, **142**, 16182–16187.
- 13 K. P. Samarakoon, C. S. Satterfield, M. C. McCoy, D. A. Pivaral-Urbina, T. Islamoglu, V. W. Day and T. Gadzikwa, *Inorg. Chem.*, 2019, **58**, 8906–8909.
- 14 H. Mayr and A. R. Ofial, *J. Phys. Org. Chem.*, 2008, **21**, 584–595.
- 15 E. Dugan, Z. Wang, M. Okamura, A. Medina and S. M. Cohen, *Chem. Commun.*, 2008, 3366–3368.
- 16 C. Volkringer and S. M. Cohen, *Angew. Chem.*, 2010, **122**, 4748–4752.
- 17 N. Tannert, Y. Sun, E. Hastürk, S. Nießing and C. Janiak, *Z. Für Anorg. Allg. Chem.*, 2021, **647**, 1124–1130.
- 18 E. Sharmin and F. Zafar, *Polyurethane: An Introduction*, IntechOpen, 2012.
- 19 R. G. Arnold, J. A. Nelson and J. J. Verbanc, *Chem. Rev.*, 1957, **57**, 47–76.
- 20 R. W. Alder, P. S. Bowman, W. R. S. Steele and D. R. Winterman, *Chem. Commun. Lond.*, 1968, 723–724.
- 21 D. R. Du Bois and A. J. Matzger, *J. Am. Chem. Soc.*, 2021, **143**, 671–674.
- 22 J. Burkus, *J. Org. Chem.*, 1961, **26**, 779–782.
- 23 E. Delebecq, J.-P. Pascault, B. Boutevin and F. Ganachaud, *Chem. Rev.*, 2013, **113**, 80–118.
- 24 G. Li, B. Wang, B. Chen and D. E. Resasco, *J. Catal.*, 2019, **377**, 245–254.
- 25 G. Li, B. Wang and D. E. Resasco, *ACS Catal.*, 2020, **10**, 1294–1309.
- 26 A. J. Mora, E. E. Avila, G. E. Delgado, A. N. Fitch and M. Brunelli, *Acta Crystallogr. B*, 2005, **61**, 96–102.
- 27 T. K. Harris and G. J. Turner, *IUBMB Life*, 2002, **53**, 85–98.
- 28 F. Hofer, J. Kraml, U. Kahler, A. S. Kamenik and K. R. Liedl, *J. Chem. Inf. Model.*, 2020, **60**, 3030–3042.
- 29 K. Mazmanian, K. Sargsyan and C. Lim, *J. Am. Chem. Soc.*, 2020, **142**, 9861–9871.