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

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Design, System, Application Statement

In efforts to synthesize materials that exhibit some of the salient features of enzyme active sites, our research group has been developing strategies for uniformly decorating the pores of metal-organic framework (MOF) materials with multiple functionalities. To that end we previously synthesized multi-reactive MOFs composed of two linkers, in well-defined locations with respect to each other, each bearing distinct reactive groups that can be addressed independently. In this work, we report how one such framework, bearing both amines and hydroxyls, exhibits surprising reactivity in its reaction with isocyanates. Specifically, we found that the presence of the amine functionality influences the reaction of the hydroxyls with unactivated isocyanates resulting in drastically increased conversions of the hydroxyl linkers (compared to when the hydroxyls are isolated alone in a MOF). The behavior of this system is reminiscent of how the physical properties of amino acid side chains are perturbed due to their mutual confinement with other functionalities in enzyme active sites, and portends the discovery of other emergent phenomena in similarly multifunctional MOF pores.

COMMUNICATION

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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 contflict with the previously observed relative nucleopholicities 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-NH_2) and *meso*-α,*β*-di(4-pyridyl) glycol (DPG), which are functionalized with amine (–NH_2) 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 –NH_2 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 –NH_2 groups of **KSU-1** exclusively, leaving the hydroxyls to react subsequently with a more electrophilic isocyanate (Figure 1C).

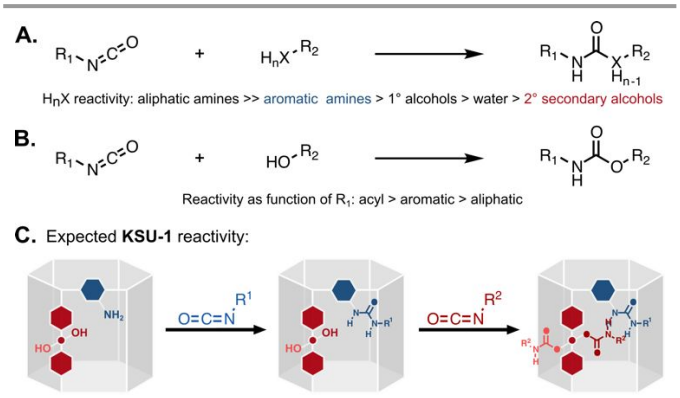

FIGURE 1. A: Order of nucleophile reactivity in their uncatalysed additions to isocyanates. B: Order of isocyanate reactivity depending on their substituents C: Expected order of reaction with isocyanates of functional groups in the independently functionalizable MOF **KSU-1**.

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Electronic Supplementary Information (ESI) available: Crystallographic data for this paper are contained in CCDC 2181792 (**KSU-1000**) and CCDC 2181793 (**KSU-3**). These data are provided by The Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Additional experimental details for MOF functionalization, ESI-MS spectra, representative ^{1}H-NMR of all MOF functionalizations, and PXRD and TGA of **KSU-1000** and **KSU-3** are available in a PDF. See DOI: 10.1039/x0xx00000x

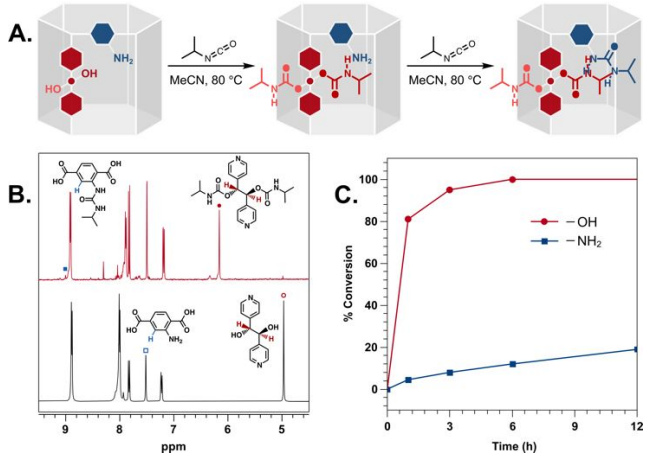

FIGURE 2. A: Observed order of reaction of the functional groups in **KSU-1** with *i*-PrNCO. B: ^{1}H-NMR spectra of **KSU-1** before (bottom), and after (top) incubation with *i*-PrNCO (MeCN, 3 h, 80 °C). Open symbols represent unreacted linkers; filled symbols represent the urea and carbamate products. C: Conversions of **KSU-1** –NH_2 and –OH over 12 h.

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 –NH_2 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 (^{1}H-NMR) spectroscopy of the MOF product digested in D_2SO_4/d_6-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-NH_2 (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 –NH_2 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).

Table 1. Comparison of reactivity of KSU-1 –NH_2 and –OH with different isocyanates.

Entry	Isocyanate	% conv. (stdev)	
		–NH_2	–OH
1	*i*-Propyl	7 (5)	97 (6)
2	Ethyl	10 (1)	68 (7)
3	*n*-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.

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 –NH_2 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).

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 –NH_2 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-NH_2 and 4,4'-dipyridyl (Figure 3A), and **KSU-3,** a version of **KSU-1** in which BDC-NH_2 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 resolvation, **KSU-3** does not.

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 –NH_2 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 (9Å vs 17Å). 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 $–NH_2$ groups in **KSU-1000**, the –OH groups in **KSU-3** reacted slower in all cases (Table 2), despite **KSU-3** having larger channels.

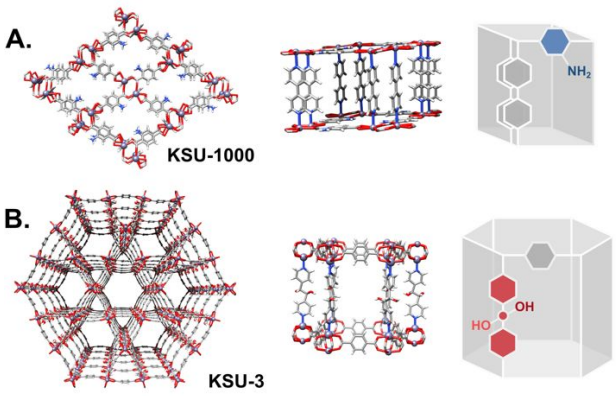

FIGURE 3. A: Isocyanate reaction of a MOF functionalized with $–NH_2$ only, **KSU-1000**. B: Isocyanate reaction of a MOF functionalized with –OH only, **KSU-3**.

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 $–NH_2$ 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 $–NH_2$ 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···$(H_2O)_n$···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.

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*-Propyl	4 (1): 64 (3)	10 (1)	3 (1)
2	Ethyl	8 (2): 38 (8)	13 (6)	6 (2)
3	*n*-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.

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-NH_2 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 $–NH_2$ 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 $–NH_2$ 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** $–NH_2$ 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 $–NH_2$ 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.

