COMMUNICATION

Solvent-free mechanochemistry for the preparation of mixed-ligand cuboctahedral porous coordination cages

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Jahidul Hoq[a] and Eric D. Bloch*[a]

This study investigates post-synthetic ligand exchange in a series of copper(II) and chromium(II) cuboctahedral cages of the formula M_{24}(R-bdc)$_{24}$ through solvent-free mechanochemistry for the preparation of mixed-ligand cages. While ligand exchange does not proceed when the cages are insoluble or when they are dissolved in non-coordinating solvents, solvent-free mechanochemistry can be used to prepare a number of mixed-ligand cages featuring a variety of functional groups regardless of cage solubility. We further extend this strategy to intercage ligand exchange reactions where the solid-state reaction of cages proceeds in just ten minutes while corresponding solvent-based reactions require more than one week of reaction time. The results highlight mechanochemically-facilitated ligand exchange as exceptionally facile and efficient method for the production of mixed-ligand cuboctahedral cages.

Porous materials have undergone a transformative evolution over the last few decades, spurred by the advent of metal-organic frameworks (MOFs) and their corresponding molecular counterparts, porous coordination cages.[1,2,3] MOFs, with their structural versatility, enable precise tuning of pore size, shape, and properties at the atomic level through adjustable ligands and metal nodes.[4,5,6] In parallel, coordination cages have emerged as highly promising molecular analogs to MOFs, offering superior molecular-level tuning capabilities.[7,8,9] The distinctive benefit of coordination cages lies in their precise tunability and structurally tailored functionality, facilitating robust crystal structure design and customization of desired properties.[10,11,12,13] Porous cages with surface functionalization have even been used in the preparation of porous ionic liquids.[14] Judicious ligand functionalization plays a crucial role in achieving a robust molecular cage design, propelling advanced porous materials into new realms of research.

Paddlewheel-based porous coordination cages are among the most extensively investigated permanently porous cages as a result of their generally facile syntheses and compatibility with dicarboxylate-based ligands of various size, geometry, and surface functionalization.[15,16] Cuboctahedral paddlewheel cages are most prominently featured among these with structures reported for numerous functional groups and both early and late transition metals.[17,18,19,20] These isophthalic acid-based cuboctahedral cages generally consist of twelve bimetallic paddlewheel blocks connected by 24 bridging ligands with the installed functional groups sitting at the periphery of the cage. (**Fig. 1**).[21,22,23] Homoleptic cages based on a single type of organic linker can be used in the synthesis of new porous materials, such as alkoxide-functionalized cages for the preparation of mixed-metal (Cu^{2+}, Mo^{2+}) alloys of cuboctahedral cages.[24] Mixed-ligand cages, however, offer an added level of tunability as cage properties can be precisely adjusted based on the ratio of ligand functional groups on the cage surface. While such mixed ligand cages may be synthesized directly, post-synthetic ligand exchange is a valuable route when the direct synthesis of a mixed ligand product is not possible. However, there are a number of coordination cages that have been shown to be resistant to post-synthetic ligand exchange reactions. Recently, mechanochemistry has emerged as a promising technique for fine-tuning gas adsorption, stability, phase, and adsorption selectivity in metal-organic frameworks through solid-state mechanochemical ligand exchange. This technique, which may be neat or solvent assisted, has demonstrated its versatility and efficiency in modifying various MOFs, including UiO-66 and imidazole-based ZIF-8.[25,26]

In this context, we report mechanochemical ligand exchange for the synthesis of mixed-ligand porous coordination cages. Cu_{24}(R-bdc)$_{24}$ and Cr_{24}(R-bdc)$_{24}$ cages are shown to participate in cage-cage ligand exchange reactions in the solid state to afford mixed-ligand products. We further detail the use of mechanochemistry for the synthesis of mixed ligand cages, a subset of them bearing functional groups that often are difficult to incorporate into cages directly, including -OH, -CN, -H, and -CH_3 groups.

[a] *Department of Chemistry, Indiana University, Bloomington, Indiana 47405, United States*

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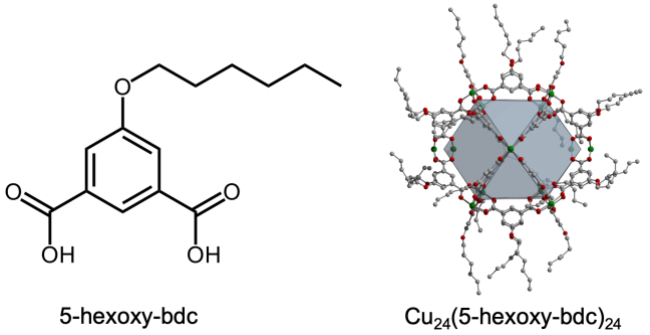

Fig. 1 The alkoxide-functionalized isophthalic acid ligand 5-hexoxy-bdc (bdc^{2-} = 1,3-benzenedicarboxylate) and the corresponding coordination cage based on the ligand, Cu_{24}(hexoxy-bdc)$_{24}$. Green, gray, and red spheres represent copper, carbon, and oxygen atoms, respectively. The blue polyhedron in the center of the cage is a guide to illustrate the open void inside the cage as well as the cuboctahedral structure.[24]

In order to assess the feasibility of post-synthetic ligand exchange via solvent-free mechanochemistry, we targeted $M_{24}L_{24}$ cuboctahedral cages. These are particularly interesting as they display some of the highest surface areas for permanently porous coordination cages,[27] have been synthesized for a wide variety of metal cations (Cr, Co, Ni, Cu, Mo, Ru, Rh, Pd/M), and are based on isophthalic acid.[28,29,30] This latter point is particularly useful as ligands of this type are easily functionalizeable at the 4, 5, or 6 positions and as a result, dozens of commercially available ligands are available. Many of these are further compatible with modification strategies either prior to or after cage synthesis.[31,32] In terms of functionalization of cuboctahedral cages based on these ligands, we have published reports of postsynthetic covalent modification.[33,34] To study the propensity of these cages to be amenable to post-synthetic mechanochemical ligand exchange, we targeted both copper and chromium-based cages as the Cu^{2+} versions participate in facile ligand exchange in solution while the Cr^{2+} versions are substitutionally inert.

For ease of characterization given its high solubility in various solvents, we sought to mechanochemically incorporate an 18-carbon alkoxide functionalized ligand into chromium or copper cages by exchanging it for a ligand that endows the cage with more limited solubility. To this end, the mechanochemical reaction of Cu_{24}(hexoxy-bdc)$_{24}$ with 24 equivalents of octadecoxy-bdc in the solid state in the absence of solvent proceeded via grinding in a mortar and pestle for 10 minutes. The resulting solid was washed with benzene to remove any unreacted octadecoxy-bdc and subsequently dried and digested for NMR analysis, which confirmed high incorporation of the ligand into the solid sample with a composition Cu_{24}(octadecoxy-bdc)$_{12}$(hexoxy-bdc)$_{12}$ (Fig. S5, ESI). Importantly, the moderate surface areas displayed by exchanged samples confirm the retention of a porous structure consistent with permanently porous cages (Fig. S51, ESI). To rule out solvent-mediated exchange during the benzene washing step, cage plus ligand samples were suspended in benzene and allowed to stir for 24 hours. NMR analysis of the isolated sample confirms no incorporation of octadecoxy-bdc into Cu_{24}(hexoxy-bdc)$_{24}$. This is not surprising given the likely necessity of a coordinating species for solvent assisted ligand exchange (SALE), a process that has been widely studied and utilized in MOFs.[35] The inverse exchange process was also tested where 24 equivalents of hexoxy-bdc was mechanochemically reacted with Cu_{24}(octadecoxy-bdc)$_{24}$ to afford Cu_{24}(octadecoxy-bdc)$_{12}$(hexoxy-bdc)$_{12}$ (Fig. S7, ESI) where unreacted hexoxy-bdc as well as exchanged octadecoxy-bdc, was removed from the ground solid through methanol wash (Fig. S8, ESI). Isolation of the Cu_{24}(octadecoxy-bdc)$_{12}$(hexoxy-bdc)$_{12}$ and subsequent mechanochemical exchange with 24 additional equivalents of hexoxy-bdc afforded Cu_{24}(octadecoxy-bdc)$_3$(hexoxy-bdc)$_{21}$ (Fig. S9, ESI).

We sought to expand this method and test its broad applicability by targeting an expanded set of ligands for mechanochemical exchange. In this approach, Cu_{24}(octadecoxy-bdc)$_{24}$ was ground with either 4 or 8 equivalents of 5-R-bdc (R = H, OH, CH_3, or CN) for 10 minutes and washed with benzene to remove exchanged octadecoxy-bdc or unreacted or minimally exchanged Cu_{24}(octadecoxy-bdc)$_{24}$. Unreacted 5-R-bdc ligands have low solubility in benzene so subsequent extended methanol washing procedure was employed to remove them from the product phase. Analysis of the solid isolated from the benzene wash reveals little to no copper-based materials, as evidenced by the color of the filtrate, consistent with the insolubility of ligand-exchanged cages. ^{1}H NMR analysis of the solids recovered from the benzene solution (Fig. S16, 17, 18, ESI) as well as after digestion of the benzene-insoluble product (Fig. S19, 20, 21. 22, ESI) confirms significant ligand exchange (**Fig. 2**) upon separation of unreacted R-bdc ligands (negligible quantity in NMR analysis) from ground solid through methanol wash. If ligand exchange is complete, we would expect, on average, Cu_{24}(R-bdc)$_{3.5}$(octadecoxy-bdc)$_{20.5}$ or Cu_{24}(R-bdc)$_6$(octadecoxy-bdc)$_{18}$ depending on if 4 or 8 equivalents of ligand were added. Analysis of solid samples obtained via this route confirms presence of the targeted functional groups and with the expected composition: Cu_{24}(octadecoxy-bdc)$_{18}$(H-bdc)$_6$, Cu_{24}(octadecoxy-bdc)$_{20}$(OH-bdc)$_4$, Cu_{24}(octadecoxy-bdc)$_{18}$(CH_3-bdc)$_6$, and Cu_{24}(octadecoxy-bdc)$_{18}$(CN-bdc)$_6$. Similar reactions employing 24 equivalents of functionalized ligands afforded Cu_{24}(R-bdc)$_{12}$(octadecoxy-bdc)$_{12}$ for R = H, OH, CH_3, and CN (Fig. S23, ESI).

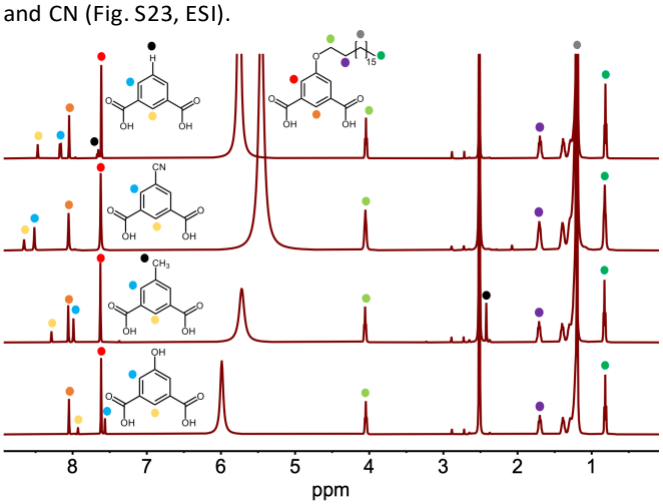

Fig. 2 ^{1}H NMR spectra of digested cages after the mechanochemical reaction of Cu_{24}(octadecoxy-bdc)$_{24}$ with the indicated ligands.

Given the limited solubility of many isophthalic acid ligands in methanol, extended washing protocols were necessary to ensure the complete removal of unreacted ligands from product phases. In order to devise a strategy to address this, we pursued ligand exchange chemistry between two cages in

the solid state. Here, for example, the reaction of $M_{24}(L)_{24}$ with $M_{24}(L')_{24}$ would be expected to afford two equivalents of $M_{24}(L)_{12}(L')_{12}$ without the production of non-cage ligand. Such cage-cage ligand exchange has been observed for copper cages in solution while the other members of these families remain unreactive to solution-state cage-cage ligand exchange.[33] Non-mechanochemical ligand exchange was first surveyed by stirring mixtures of cages in a non-coordinating solvent where only one of the two cages is soluble. In this approach, changes in solubility can be used to qualitatively follow ligand exchange.

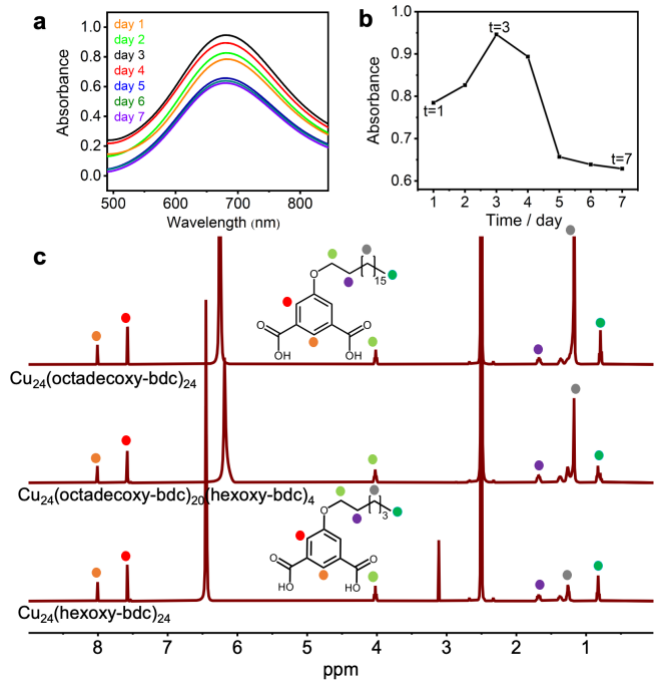

Fig. 3 Solvent-assisted ligand exchange between Cu_{24}(octadecoxy-bdc)$_{24}$ and Cu_{24}(hexoxy-bdc)$_{24}$ in benzene. UV-vis spectra for the benzene-soluble portion (**a**) shows an initial increase in absorbance followed by a substantial decrease (**b**) over the course of 7 days which corresponds to partial exchange to afford a larger quantity of soluble cage followed by further exchange producing insoluble cages. ^{1}H NMR spectra for the starting cages (**c**) and soluble product isolated at the end of the reaction indicating a composition of Cu_{24}(octadecoxy-bdc)$_{20}$(hexoxy-bdc)$_4$.

In this experiment, Cu_{24}(octadecoxy-bdc)$_{24}$ was dissolved in benzene and stirred with one equivalent of insoluble Cu_{24}(hexoxy-bdc)$_{24}$ for one week. UV-vis spectroscopy was used to monitor the concentration of dissolved cages throughout this process (**Fig. 3a, 3b**). After one day, we observed a slight increase in the concentration of dissolved cages as evidenced by an increase in absorbance from 0.78 to 0.83. As Cu_{24}(hexoxy-bdc)$_{24}$ is completely insoluble in benzene, this suggests ligand exchange between the two cages to afford a mixed ligand sample with the composition Cu_{24}(octadecoxy-bdc)$_{22.6}$(hexoxy-bdc)$_{1.4}$. After an additional 24 hours of stirring, the solution concentration again increased with a corresponding absorbance of 0.95. This corresponds to a ~22 % increase in soluble cage. Based on the increase in absorbance, NMR digestions, and the composition of the solid samples, the dissolved cages have (on average) composition of Cu_{24}(octadecoxy-bdc)$_{20}$(hexoxy-bdc)$_4$ (Fig. S24, S25, ESI). Additional stirring results in a decrease in dissolved cage as further incorporation of hexoxy-bdc ligand renders the cages insoluble in benzene. After one week, the remaining dissolved cages have composition Cu_{24}(octadecoxy-bdc)$_{20}$(hexoxy-bdc)$_4$ (Fig. S26, ESI) while the solid sample has a composition of Cu_{24}(octadecoxy-bdc)$_4$(hexoxy-bdc)$_{20}$ (Fig. S27, ESI). Although this approach did afford mixed ligand cages, it is limited and impractical as the exchange process is sluggish in benzene.

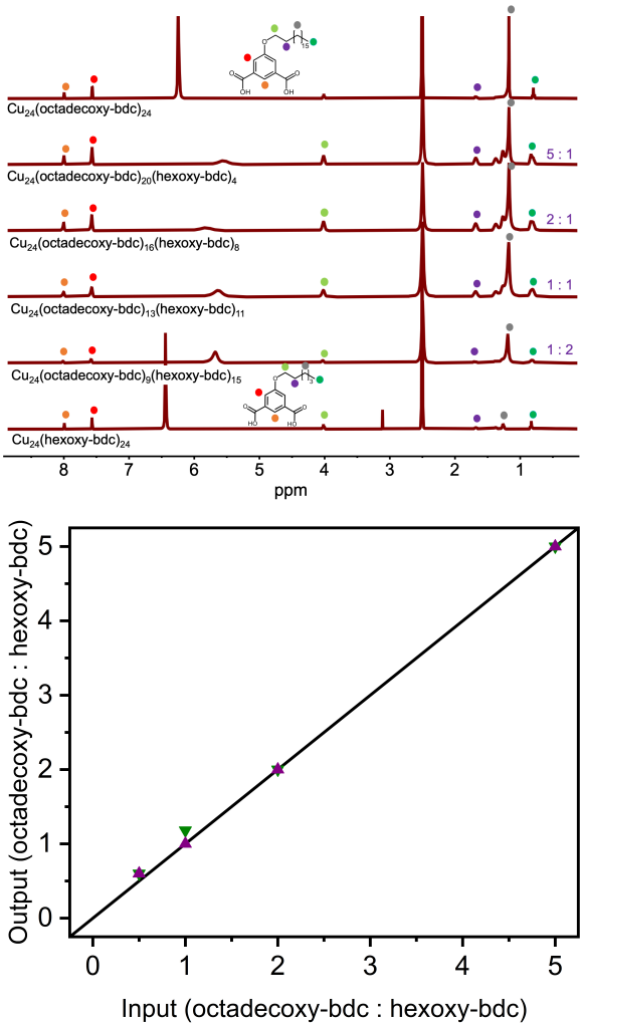

Fig. 4 Mechanochemical reaction of Cu_{24}(octadecoxy-bdc)$_{24}$ (green triangles) and Cu_{24}(hexoxy-bdc)$_{24}$ in the indicated ratios affords mixed ligand product of the given composition (top) as determined by ^{1}H NMR. A graphical representation of the ratio of ligands in the starting mixture and product phase shows ligand exchange takes place at the expected statistical ratio (purple = chromium; green = copper)

It was expected that mechanochemical mixing of two cages would facilitate ligand exchange in a manner analogous to the post-synthetic ligand exchange reactions. We prepared activated samples of Cu_{24}(octadecoxy-bdc)$_{24}$ and Cu_{24}(hexoxy-bdc)$_{24}$, mixed them in 1:2, 1:1, 2:1, and 5:1 ratios, and ground them in a mortar and pestle for 10 minutes. The ground solid was then quickly washed in benzene to remove soluble fraction from the insoluble cage. The benzene was removed from the filtrate and evaporated while the solid was dried under vacuum. Both phases were then digested for NMR analysis. The benzene soluble phases, as expected, were nearly completely comprised of octadecoxy-bdc based cages with an average composition of Cu_{24}(octadecoxy-bdc)$_{24}$ for the samples

with excess octadecoxy cage (Fig. S28, 29, 30, 31, ESI). Analysis of the isolated insoluble phase revealed significant ligand exchange with product of the formula Cu_{24}(octadecoxy-bdc)$_n$(hexoxy-bdc)$_{24-n}$ (n = 9, 13, 16, 20 for 1:2, 1:1, 2:1, 5:1) (**Fig. 4 top**) (Fig. S32, 33, 34, 35, ESI). To assess the broad compatibility of this approach for paddlewheel cages, similar experiments were performed for $Cr_{24}(L_{24})$ cages (L = hexoxy-bdc; octadecoxy-bdc). In contrast to solution-based chemistry where these cages do not participate in ligand exchange,[33] mechanochemical grinding of cage mixtures facilitates ligand exchange. Again mixing combinations of 1:2, 1:1, 2:1, and 5:1 octadecoxy-bdc and hexoxy-bdc afforded mixed ligand products where the benzene soluble portion was typically Cr_{24}(octadecoxy-bdc)$_{24}$ (Fig. S38, 39, 40, 41, ESI) and the insoluble phase had the formula Cr_{24}(octadecoxy-bdc)$_n$(hexoxy-bdc)$_{24-n}$ where n = 9, 12, 16, 20 for the 1:2, 1:1, 2:1, and 5:1 mixtures, respectively (**Fig. 4 bottom**) (Fig. S42, 43, 44, 45, ESI).

In conclusion, this study introduces a novel approach to mixed-ligand functionalization of porous cuboctahedral cages through mechanochemical ligand exchange. The extent of ligand exchange was confirmed by ^{1}H NMR analysis of product phases and shows that rapid exchange, at near statistical levels, is facilitated in the matter of minutes where corresponding solvent assisted ligand exchange with a non-coordinating solvent is incredibly sluggish. The detailed procedures and outcomes presented in this paper provide valuable insights into the application of mechanochemistry for ligand exchange in porous coordination cages. These findings offer a practical and efficient method for achieving mixed ligand functionalization, opening new avenues for controlled design and customization of porous materials.

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Conflicts of interest

There are no conflicts to declare.

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