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Enantioselective adsorption of ibuprofen and lysine in metal–organic frameworks†

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This study reveals the efficient enantiomeric separation of bioactive molecules in the liquid phase. Chiral structure HMOF-1 separates racemic mixtures whereas heteroselectivity is observed for scalemic mixtures of ibuprofen using non-chiral MIL-47 and MIL-53. Lysine enantiomers are only separated by HMOF-1. These separations are controlled by the tight confinement of the molecules.

A chiral compound is a molecule that is non-superimposable with its mirror image; such a molecule and its mirror image are called enantiomers. Although the difference between enantiomers is subtle, metabolic biomolecules such as amino acids are produced in a specific chirality. This is a consequence of reactions taking place involving highly selective, chiral reaction sites in enzymes and other proteins. In contrast to the synthesis of biomolecules by organisms, laboratory techniques for the synthesis of chiral molecules generally lead to a 50/50 mixture of the enantiomers.

A large amount of pharmaceutical drugs currently in use are chiral compounds.[1] Ideally they should consist of the pure active chiral form that produces the desired biological effect (eutomer). If the other chiral form (distomer) is also administered, it may interact with different biological receptors and cause side effects often unrelated to the function of the active isomer, an effect known as chiral toxicology. These findings have motivated the pharmaceutical industry to increasingly seek either chiral switches with the ability to provide single enantiomers, or efficient methods to separate the isomers from the racemic mixtures, such as chiral chromatography,[2] in which the use of chiral Metal Organic Frameworks (MOFs) has been introduced as a stationary phase recently.[3–8] These structures can exhibit high enantioselectivity and high surface area and it is in this field that molecular simulations are acquiring high relevance.[9–11]

This work evaluates the enantioselective adsorption of three metal–organic frameworks (MOFs) looking into the conditions that enable the separation of enantiomeric mixtures. Ibuprofen and lysine are used in this study due to their commercial importance.

Ibuprofen has been used as an analgesic and anti-inflammatory agent over the last forty years. The racemate is in clinical use, though between the two enantiomers, *S*-ibuprofen is the active form both *in vivo* and *in vitro*. It was widely believed that the sole use of the active isomer does not possess any advantages since the inactive isomer is converted to the active form after absorption in the gastrointestinal tract. However, some studies have indicated that *S*-ibuprofen provides relief three times faster than its racemic mixture with fewer side effects. This implies that a reduction of dose and of metabolic load is possible if pure *S*-enantiomer is administered.[12] L-Lysine is an essential amino acid. The human body therefore relies on this amino acid from food or supplements. L-Lysine is important for proper growth, and it plays an essential role in the production of carnitine, a nutrient responsible for converting fatty acids into energy and helping to lower cholesterol. This amino acid also appears to help the body absorb calcium, and plays an important role in the formation of collagen, a substance important for bones and connective tissues including skin, tendon, and cartilage. Additionally, ibuprofen and lysine are often formulated together.

The high porosity and the wide range of chemical compositions and porous structures of metal–organic frameworks (MOFs) suggest possible applications for drug delivery[13,14] and in "chiral switching" to remove enantiomers. MIL-47[15] and MIL-53[16] are metal–organic frameworks that belong to the MIL series (Material Institut Lavoisier). The combination of 1,4-benzenedicarboxylate and metal centre generates orthorhombic unit cells with straight channels in one direction. As shown in Fig. 1, the unit cells in the open structure of MIL-53 (6.82 × 6.82 × 13.94 Å^3) are slightly smaller than in MIL-47 (6.82 × 16.73 × 13.04 Å^3). The metal centres in MIL-53 and MIL-47 are chromium and vanadium respectively. HMOF-1,[17] unlike the aforementioned structures,

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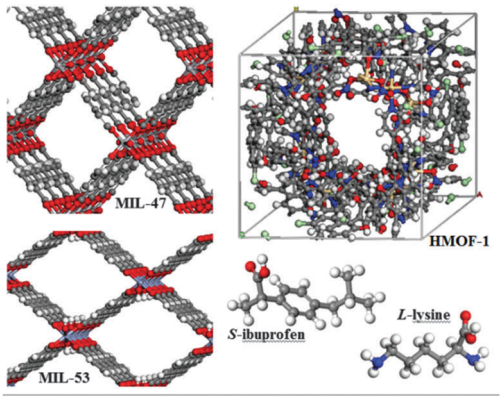

Fig. 1 Front view of the unidirectional channels in MIL-47, MIL-53 and HMOF-1. Molecular representation of *S*-ibuprofen and L-lysine.

is a chiral MOF. It is formed by cadmium atoms as metal centres and an axially chiral ligand (*R*)-6,6′-dichloro-2,2′-dihydroxy-1,1′-binaphthyl-4,4′-bipyridine, which connects the metal centres generating unit cells with dimensions 20.305 × 20.305 × 49.641 Å^3 and helicoidal pores (Fig. 1). The models for the structures are rigid and based on UFF[18] and Dreiding[19] force fields (Tables S1–S3 in the ESI†).

The mechanisms of enantioselective adsorption in MOFs and other porous materials such as zeolites have been recently elucidated at the atomic level for chiral hydrocarbons and other molecules, showing that an enantiomeric excess (ee) of over 50% can be achieved.[9–11,20–25] However, to the best of our knowledge, enantioselective separation of more complex molecules in liquid phase has not yet been studied.

The molecule of ibuprofen contains a chiral centre in the α-carbon of the propionate moiety. Lysine also contains a chiral centre on the alpha-carbon and its properties will be determined by two amino and a carboxyl group (Fig. 1). Both enantiomers of these molecules have been modelled using flexible full-atom models based on CVFF force fields[26,27] (Tables S4 and S5 in the ESI†).

The selective adsorption of the isomers of ibuprofen and lysine was computed in the liquid phase. A liquid phase in the context of this work refers to aqueous ibuprofen or lysine solutions. The adsorption isotherms of a liquid feed with a solute/solvent mole fraction comprised between 0.2 and 1% were computed using Grand-Canonical Monte Carlo simulations. Liquid phase fugacities are computed from the saturated vapour pressures of the components and the liquid phase activity coefficients. The latter are calculated from the experimental vapour–liquid equilibrium data. The adsorption isotherm obtained for the solutions of *S*-ibuprofen and L-lysine in any of the three MOFs show that at saturation pressure water does not enter the structure (Fig. S4 and S5 in the ESI†). Similar results were obtained for *R*-ibuprofen and D-lysine in calculations that were similarly conducted at 300 K.

A recent work of Bernini *et al.* reported the adsorption mechanism of ibuprofen in MIL-53. In this structure, adsorbate–adsorbent interactions are stronger than adsorbate–adsorbate interactions. Therefore, the adsorption pattern consists of a small loading at low fugacity followed by a sudden increase to reach saturation.[28] This pattern is in agreement with our simulations of aqueous

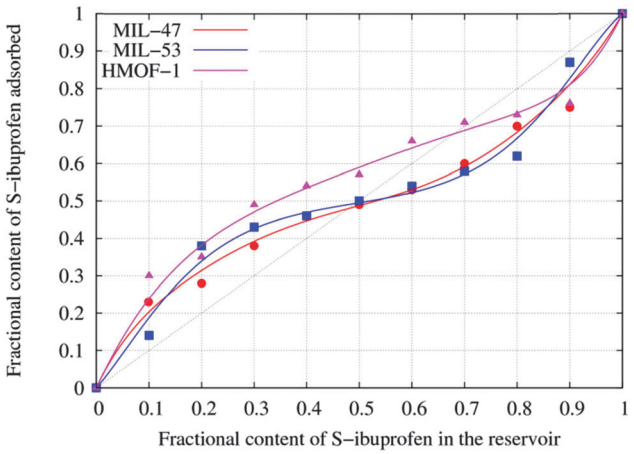

Fig. 2 Adsorbed fractional content of *S*-ibuprofen as a function of the *S*-fraction in an *R*/*S* mixture in the reservoir for MIL-47 (red), MIL-53 (blue) and HMOF-1 (pink). The straight line would indicate that the adsorbed composition is identical to that in the reservoir.

ibuprofen solution. The presence of water enhances the ibuprofen uptake slightly at the lowest values of fugacity, but does not affect saturation (Fig. S4 in the ESI†). Above 10^{-10} and 10^{-3} Pa ibuprofen and lysine systems, respectively, were in the saturation regime, with 16 ibuprofen or 30 lysine molecules per simulation cell. The simulation cells are 27.28 × 27.28 × 27.88 Å^3 (MIL-47), 27.28 × 33.46 × 26.08 Å^3 (MIL-53), and 20.305 × 20.305 × 49.641 Å^3 (HMOF-1). Then it is possible to study chiral mixtures in which the *S* (ibuprofen) or the L (lysine) fraction is varied between 0.1 and 0.9 in the external reservoir in such a way that the enantiomers can vary while the total number of molecules remains constant (Fig. 2 and 3). To perform these simulations efficiently we use Monte Carlo moves that have been previously developed for dense systems[23] and that are needed to obtain highly converged values.

Fig. 2 shows the fraction of adsorbed *S*-ibuprofen as a function of the enantiomeric ratio in the external reservoir in

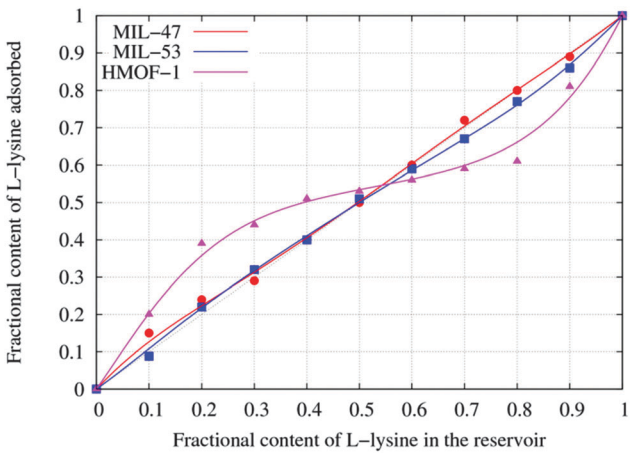

Fig. 3 Adsorbed fractional content of L-lysine as a function of the L-fraction in a D/L mixture in the reservoir for MIL-47 (red), MIL-53 (blue) and HMOF-1 (pink). The straight line would indicate that the adsorbed composition is identical to that in the reservoir.

HMOF-1, MIL-53 and MIL-47. For the three structures we found a significant deviation of the curve from a straight line, which is the behaviour one would expect if no preferential adsorption of one isomer over another takes place. As expected, the graph obtained for the last two MOFs were checked to be symmetric and passing through the (0.5, 0.5) point. In other words, these structures which are non-chiral are unable to induce an enantiomeric excess when starting from a racemic mixture. However, they deplete scalemic mixtures and the form of the curve indicates heteroselective adsorption. The main enantiomeric form in the reservoir is less readily adsorbed, *i.e.* the adsorbent levels the enantiomeric ratio towards that of racemic mixtures and enriches the reservoir. Except at low fractions of *S*-ibuprofen, deviations from the straight line are larger for MIL-53 than for MIL-47, probably due to the narrower pores of the former structure. HMOF-1 is also heteroselective and, more importantly, this structure is able to separate the racemic mixture. At low and medium fractions of *S*-ibuprofen this enantiomer is enhanced by the heteroselective packing effect in the MOF structure that provides an R-type chiral environment. At high fractions of *S*-ibuprofen there is a competition between the heteroselective behaviour in the system and the chiral effect induced by the chirality of the MOF, and thus the selectivity is reduced.

Fig. 3 shows the fraction of adsorbed L-lysine as a function of the enantiomeric fraction in the reservoir for the three MOFs. No separation is observed at any mole fraction in the non-chiral structures MIL-47 and MIL-53. It appears that this molecule is less commensurable with the pores of these structures than ibuprofen. In HMOF-1, however, a heteroselective effect is present, although the intrinsic chirality of this MOF only favours a slight preference. Unlike the ibuprofen case, this structure is unable to separate racemic mixtures.

The ee obtained for ibuprofen and lysine in HMOF-1 is 18% and 4%, respectively. For the non-chiral MOFs we use an adapted enantiomeric excess (ee*),[29] which graphically corresponds to the maximum vertical displacement from the diagonal of the *S*-curves plotted in Fig. 2 and 3. The ee* values obtained for ibuprofen in MIL-47 and MIL-53 are 12% and 19%, and for lysine 3% (MIL-47) and 2% (MIL-53). These data highlight the importance of guest–guest interactions in these systems, occurring at saturation values, when molecules pack and create an additional chiral environment in the case of non-chiral MOFs, or enhancing this environment in homochiral MOFs.[25] The packing effect found for these systems is not specific to MOFs. It can also be found in other systems, since the effect is not directly related to enantioselectivity but to many other factors such as channel shape, pore size, steric fit, and interaction with the framework.[5,7–9,25,29]

To get a deep understanding of this behaviour we provide insights into the microscopic assembly in the systems. We evaluated the hydrogen bonding (HB) between guest molecules using a specific criterion for HB definition.[30] The results and details of the calculations are given in Table S6 in the ESI.† Overall, the molecular association between guest molecules is an important factor. Despite data dispersion, there is clear evidence of preferential hydrogen-bond formation between *R* and *S* molecules of ibuprofen in MIL-47, which leads to heteroselectivity. In MIL-53, however, heteroselectivity is promoted by preferential hydrogen-bond formation of the minority enantiomers of the same type. In HMOF-1, it would appear that the reason for the selectivity behaviour in Fig. 2 is a combination of *R*–*S* H-bonds being favoured at high concentrations of *S*-ibuprofen and a preferential same-type minor enantiomer association. Regarding lysine in HMOF-1, both factors at work in ibuprofen also apply to promote heteroselectivity, although in lysine the number of guest–guest bonds formed is generally lower than in ibuprofen. Likewise, we computed the average minimum intermolecular distances between oxygen atoms of the carboxyl group and the distances of these atoms to the metal centres of the host structures (Tables S7 and S8 in the ESI†). These values provide information on the strength of the interaction of the molecules, and host–guest forces, and show that the double bonded oxygen in the carboxylic group (C═O) of both ibuprofen and lysine is more likely to form H-bonds than the single bonded oxygen in the carboxylic group (C–O–H). This is in agreement with the radial distribution functions obtained by Bernini *et al.* for ibuprofen in MIL-53.[28]

This work shows that molecular simulation allows predicting molecular adsorption and enantioselectivity in porous materials, providing important information about the interactions established, the confinement of molecules and the chiral environment inside the porous structures. The MOF structures studied are able to separate mixtures of lysine enantiomers and mixtures of ibuprofen enantiomers. HMOF-1, which has a chiral structure, separates racemic mixtures of ibuprofen and surprisingly, the non-chiral structures of MIL-47 and MIL-53 are able to separate scalemic mixtures of ibuprofen. We have correlated this with the microscopical behaviour. Confinement of the bulky ibuprofen in the narrow pores of MIL-47 and MIL-53 favours the formation of hydrogen bonds between *R* and *S* enantiomers. This finding opens new prospects for the development of porous materials and new interpretations regarding the molecular mechanisms involved in chiral separations. It shows that it is difficult to make predictions *a priori* without a very detailed molecular knowledge of the system, and that neither a chiral MOF necessarily implies the ability to separate small isomers nor is a non-chiral MOF necessarily unselective towards some mixtures of enantiomers.

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