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Supported Catalytically-Active Supramolecular Hydrogels for Continuous Flow Chemistry

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Dedicated to Professor Jean-Marie Lehn on the occasion of his 80th birthday.

Abstract: Inspired from biology, one current goal in supramolecular chemistry is to control the emergence of new functionalities arising from self-assembly of molecules. In particular, some peptides can self-assemble and lead to exceptional catalytically-active fibrous networks able to underpin hydrogels. Unfortunately, the mechanical fragility of these materials is incompatible with process developments relaying this exciting field to academic curiosity. Here, we show that this drawback can be circumvented using enzyme-assisted self-assembly of peptides initiated at the walls of a supporting porous material. We apply this strategy to grow an esterase-like catalytically-active supramolecular hydrogel (CASH) in an open-cell polymer foam, filling the whole interior space of it. Our so-supported-CASH is highly efficient toward inactivated esters and shows kinetic resolution of racemates. This hybrid material is robust enough to be used in continuous flow reactors, reusable and stable over months.

One current goal in supramolecular chemistry is to control the emergence of new functionalities coming from self-assembled organizations built using a bottom up approach.[1,2] Recently, supramolecular hydrogels prepared from the self-assembly of low molecular weight hydrogelators (LMWH), mainly peptide derivatives, exhibiting catalytic properties were reported.[3,4] Based on the specific organization of peptide hydrogelators in nanofibers, the network displays enzyme like features. Unfortunately, their catalytic activity used to be evaluated on solely model substrates. For instance only very few works have been reported on supramolecular hydrogels displaying esterase activity on non-activated substrates. In addition, the use of CASH is not obvious: these reported hydrogels must be first vortexed to get a liquid solution of catalytic self-assembled fibers, complicating their separation from the product formed. Furthermore, when the process is based on the substrate solution diffusing into a CASH in order to let the chemical transformation taking place within the gel, the recovering of the product formed requires the entire destruction of the CASH to be isolated. Last but not least, all CASH are not mechanically robust, restricting their handling and use in a chemical reactor.[5]

To provide mechanical robustness to highly soft materials such as hydrogels, the use of polymer foams as internal skeleton that will rigidify the matter is an interesting approach.[6] In case of peptide-based hydrogels, a first technological issue that needs to be resolved is the spatial localization of the hydrogel growth from the surface of the polymer foam in order to link the hydrogel and the polymer material. This can be achieved by immobilizing a (bio)catalyst on a planar surface.[7,8,9,10] We use the surface immobilization of an enzyme able to transform non-self-assembling precursors present in solution into self-assembling building blocks.[11] The confinement of these building blocks at the material-water interface induces the growth of nanofibers anchored on the surface and underpinning the hydrogel.[12,13,14]

The development of a supported-CASH is based on the appropriate choice of the precursor which has to fulfill two essential conditions: (*i*) generate self-assembling derivatives in the presence of an adequate enzyme and (*ii*) to result in a supramolecular hydrogel exhibiting catalytic activity. Up to now, no such precursor of LMWH has been described. Among the catalytically-active supramolecular hydrogel examples reported in literature,[15] our attention focused on the following peptide sequence *Nap*-GFFYGHY (*Nap*=naphthalene) described by Yang et *al*.[16] This peptide is not soluble in water at room temperature but when a suspension of this peptide is heated close to 100°C and then cooled slowly, an esterase-like hydrogel is obtained, reactive towards the activated ester 4-nitrophenyl acetate (PNA). The most interesting aspect of this heptapeptide regarding to our goal lays in the presence of two tyrosine residues (Y) in positions 4 and 7: the phosphorylation of the two phenol groups was necessary to obtain a *bis*-phosphorylated heptapeptide Fmoc-GFF*p*YGH*p*Y (Fig. 1a) well soluble in water (ESI section 2).

When alkaline phosphatase (AP) is added to a 1% mol. solution of Fmoc-GFF*p*YGH*p*Y, a quasi-translucent hydrogel forms almost instantaneously (Fig. 1b) constituted of 97% of the twice dephosphorylated Fmoc-GFFYGHY (Fig. S1). This resulting peptide produced enzymatically *in situ* leads to an entanglement of several micrometers long fibers observable by transmission electron microscopy (TEM) (Fig. 1c). Magnification of these fibers suggests a ribbon shape of 27 nm in width, having a right-handed twist with roughly 300 nm pitch when two or more ribbons are associated together (Fig. 1d). The CD

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spectrum is consistent with a β-sheet structure, in agreement with literature for similar assemblies of peptides.[17] IR spectra confirms that roughly 66% of peptides are associated in β-sheet structures.[18,19] Rheological study of this CASH hydrogel has provided 3,6 kPa and 0.3 kPa values at 0.3 Hz for G' and G'' respectively (Section 20 in SI). The hydrogelation process takes place in less than one minute. Below a strain value of 6% the supramolecular network behaves as a gel whereas above it becomes liquid-like. When the hydrogel is put in contact with a PNA solution (1 mM) as depicted in Fig. 1e (section 14 in ESI), the gel turns spontaneously to yellow due to *para*-nitrophenol production (Fig. S3). But this way to produce carboxylic acid derivatives is not practical: in addition to the mechanical fragility of such supramolecular hydrogel, the time to let the substrate penetrate within the CASH and the low reaction time to get a full conversion due to the substrate diffusion inside the hydrogel are long. More importantly, the isolation of the formed carboxylic acid derivatives requires the dissolution of the CASH followed by purification steps, sentencing this self-assembled catalytic material to a single run. Therefore this way to realize the catalytic reaction is time consuming, expensive and tedious, motivating our investigations toward supported-CASH developments.

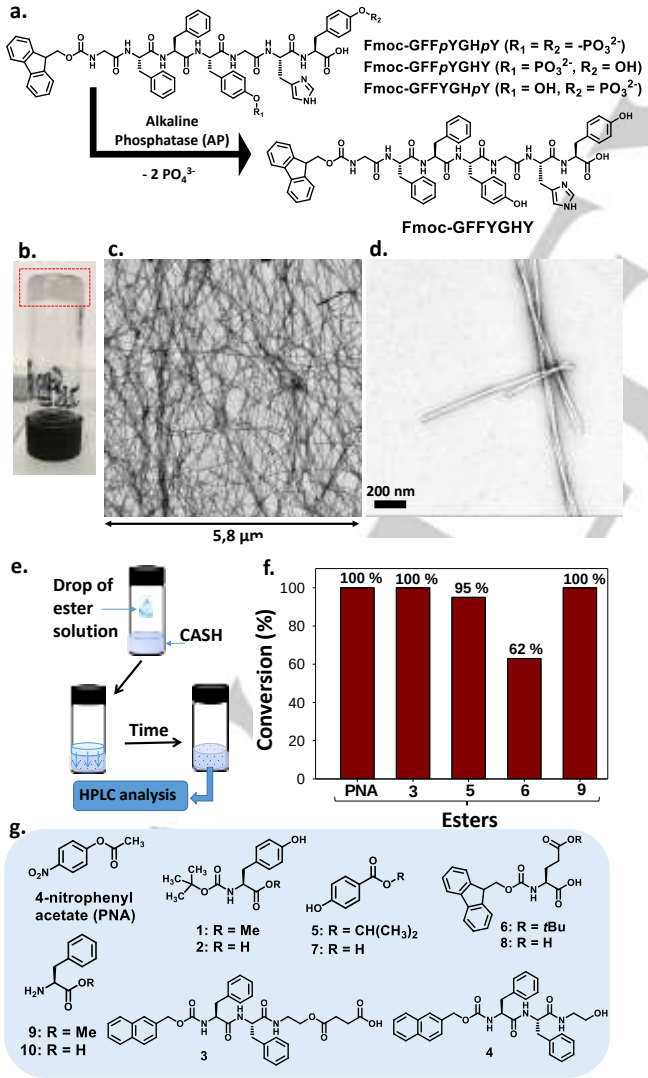

Figure 1. **a**) Enzymatic transformation of Fmoc-GFF*p*YGH*p*Y in Fmoc-GFFYGHY; **b**) Upside down vial containing the Fmoc-GFFYGHY hydrogel; **c**) TEM image of Fmoc-GFFYGHY self-assembly nanofibers; **d**) Magnification of TEM image; **e**) Schematic of the process based on the ester substrates diffusion within the CASH; **f**) Conversion of esters substrates PNA, **3**, **5**, **6** and **9**; **g**) Ester substrates and their corresponding carboxylic acids.

To build our supported-CASH we used as porous catalyst support, a commercial open cell melamine foam displaying diameter cells of roughly 200 µm (Fig. 2a). The foam was designed to get a suitable tubular shape and placed inside a metallic column as shown in Figure 2b (length: 15 cm; diameter: 4 mm). We deposited on the walls of the pores, a polyelectrolyte multilayer constituted of 2.5 PEI/PSS bilayers (PEI: poly(ethylene imine); PSS: poly(styrene sulfonate)) covered by an AP layer by dipping alternately in PEI, PSS and AP solutions (Fig. 2c). We then flowed a Fmoc-FF*p*YGH*p*Y solution through the functionalized column to form the supported-CASH (section 16 in ESI). Using *Cryo*-SEM (at low etching) of this coated foam shows that the supported-CASH is filling the whole space of the polymer foam (Fig. 2d).

In order to further characterize the supported-CASH, and because the use of the multilayer renders the buildup process independent of the substrate, we investigated it on flat surfaces where more characterization techniques are available. We modified the surfaces with an enzymatically-active multilayer similar to that deposited on the foam walls. The buildup of the multilayer was first monitored by quartz crystal microbalance with dissipation (QCM-D) and leads to a 19 nm thick $(PEI/PSS)_2$/PEI/AP film (section 5 in ESI). When this so-modified substrate was brought in contact with Fmoc-GFF*p*YGH*p*Y solution, a huge decrease of all QCM frequencies was observed, characteristic of a highly hydrated mass deposition. Then this decrease continues more slowly over 13 hours without levelling off, suggesting a continuing gelation process over this time (Fig. S4).[13,14] AFM, SEM, HPLC composition analysis and fluorescence emission intensity measurements confirm the nanofibrous architecture of the hydrogel made up the hydrogelator Fmoc-GFFYGHY with Fmoc groups stacking the resulting assembly (Fig. S5-7).[13,17] *Cryo*-SEM analysis was realized on CASH grown up from a silica wafer. The sample was cut in the z-section in order to measure the thickness of the formed hydrogel when the substrate was 12 hours in contact with the Fmoc-GFF*p*YGH*p*Y solution. The CASH thickness is roughly 31 µm, a regular value all along the sample (Fig. 2e). Strikingly, we noticed a perpendicular orientation of the fibers starting from the surface as already observed:[20] a fibrous architecture different from what is observed when the hydrogel is formed in the bulk. Some of the fibers are collapsed to each other but thinner fibers are also present (Fig. 2f). As observed by TEM, these nanofibers seem to have a chiral twisted ribbon shape (Fig. 2g). A complete ester hydrolysis was observed in few minutes when this silica wafer-supported hydrogel layer was dipped into PNA solution (Section 14 and Fig. S8 in ESI).

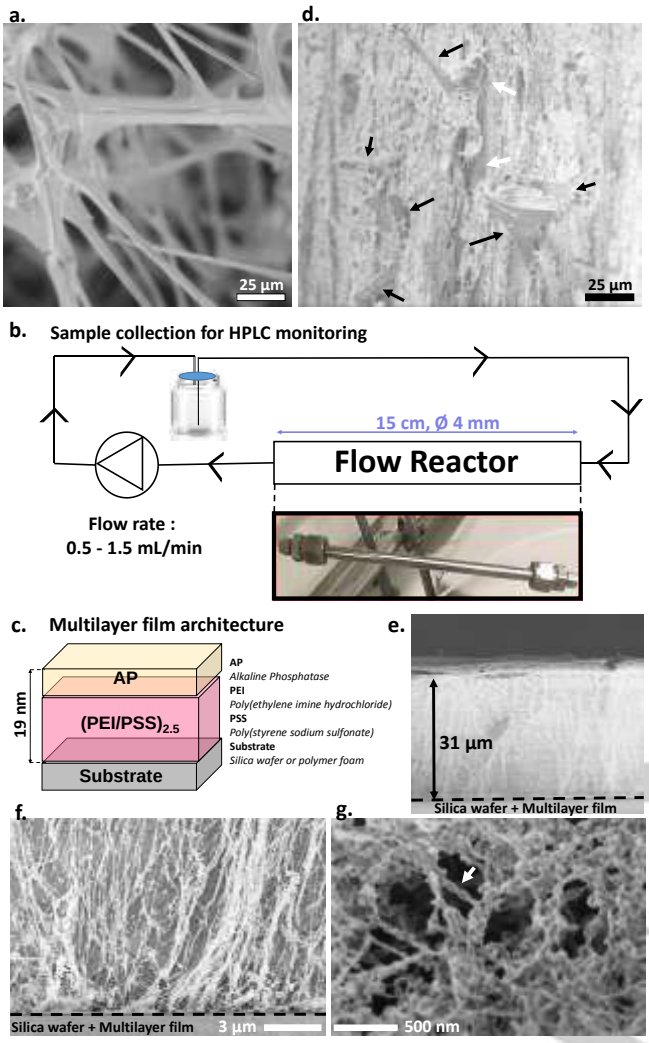

Figure 2. **a**) Melamine open cell foam observed by SEM; **b**) Continuous flow reactor; **c**) Multilayer film architecture; **d**) Z-section view of CASH supported on melamine open cell foam observed by *cryo*-SEM. Black arrows indicate the backbone of the polymer foam. White arrows show the fibrous network located everywhere within the interior space of the hydrogel-filled foam; **e**) *Cryo*-SEM image of the CASH formed on a silica wafer; **f**) magnification of the interface substrate/CASH and **g**) magnification of helical shape nanofibers (white arrow) .

Evaluation of the catalytic activity of this supported-CASH in a flow reactor was first done using PNA as substrate at 1 mM with 1.5 mL/min as flow rate: 98% of hydrolysis is obtained in 2.8 minutes. This duration corresponds to the cumulate residence time of the substrate spent when passing through the supported CASH column in a closed loop system. It can be noticed that the flow for this kind of reactor where it flows through a porous material, follows a plug flow.[21] HPLC analysis confirms also that no constituting peptide hydrogel, *i.e.* Fmoc-GFFYGHY, was released from the column, suggesting the preservation of its integrity during the catalytic process. Five successive runs have been realized in identical conditions without loss of catalytic efficiency highlighting the effective recycling of the supported-CASH. Remarkably, this catalytic reactor can be stored (4°C) at least for one month and reused again without losing activity (Fig. S9). Because the catalytic property results from the peptide self-assembly, this repeatability highlights the robustness of the nanofibrous network in flow conditions. Moreover, we have also shown that the value of the applied flow rate which was varied over two orders of magnitude, does not affect the conversion for a fixed residence time of the substrate. This is one more proof that the self-assembled architecture is not affected by the flow in our conditions (Figure S10). We also verified that the catalytic activity remains independent of the location along the tubular reactor (Fig. S11), showing that the catalytic hydrogel formed along the porous support is homogeneously distributed all over the tubular foam. Using concentrations of PNA lower than 2.20 mM leads to a full ester hydrolysis and thus 2.20 mM of *para*nitrophenol is generated. But when higher concentration of PNA is used, such as 2.78, 8.20, 10, 22 and 44 mM only 141 ±7 µmoles of PNA is transformed in *para*nitrophenol corresponding to 99, 52, 49, 24 and 17 % conversion respectively, as shown in Fig. 3a. This result suggests that PNA poisons the catalytic self-assembly when high concentration of this substrate is used. Actually, *para*nitrophenyl esters are well-known to be powerful acyl agents toward imidazole groups.[22] By using a non acylating substrate such as the methyl ester **1**, a complete hydrolysis is observed whatever its concentration: 1.0, 2.2, 8.2, 22.0 to 44.0 mM (Fig. 3c). Because one PNA can acylate only one imidazole group, it is possible to calculate the number of histidine residues involved in the catalytic pocket: thus we have determined that one of eleven peptides is involved in the catalytic self-assembly (Section 17 in ESI). But the acylation of imidazole is a reversible reaction and washing the column with adequate amount of water restores entirely its initial catalytic activity (Fig. S12).[23]

Molecular dynamics show the spatial organization of 16 Fmoc-GFFYGHY (Figures 3b, S13 and section 19 in ESI) calculated from an initial random distribution state of all peptides in a cubic simulation box (edge: 5.2 nm). After equilibration the system was let to evolve during 50 µs. Fmoc groups are stacked together through π-π interactions with distances going roughly from 3.97 to 5.10 angstroms (Fig. S13). Interestingly, two pairs of histidine residues linked together through hydrogen bonding appear in Figure 3b. The organization of two histidine residues allows cooperative actions leading to amplified catalytic properties. The histidine residue is directly involved in the esterase activity of the assembly where the pKa of the imidazole group plays a crucial role in the catalytic efficiency. The pKa of imidazole group in histidine residue is 6.8. But it is known that the environment can impact this value.[24] The pKa of imidazole of peptide Fmoc-GFFYGHY in the self-assembled state was determined and is 5.4 ± 0.5 (SI section 21). This indicates an increase in basicity of the imidazole groups due to the environment created by the self-assembly. The diameter of this simulated fiber-like structure is lower than the one measured on the fibers observed by TEM (Fig. 1d). It can be expected that lateral interactions between fiber-like structures may results in nanofibrils organization.

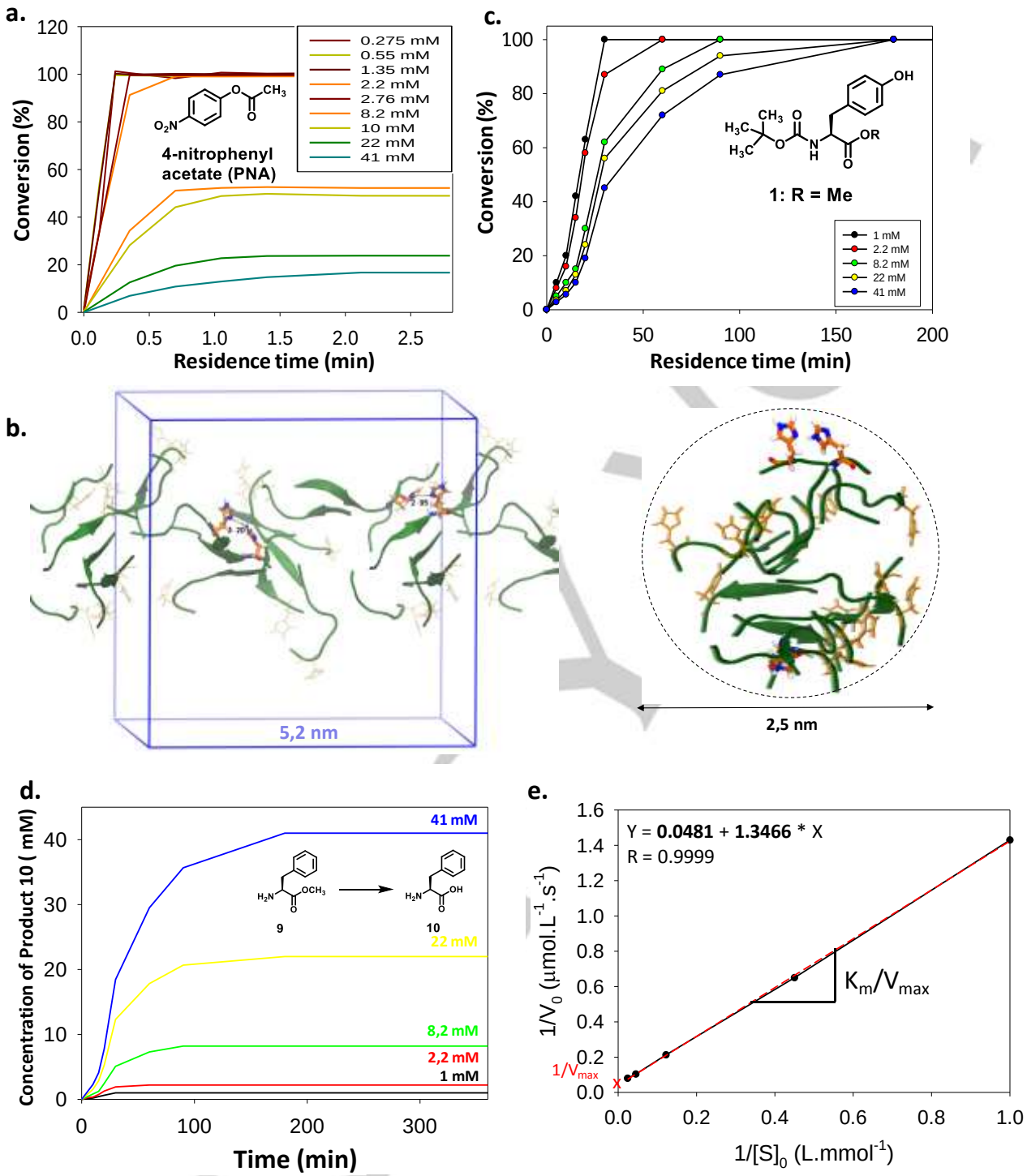

Figure 3. **a**) PNA conversion over time; **b**) (*left*) Molecular dynamics of 16 peptides Fmoc-GFFYGHY showing a fiber-like spatial arrangement (blue square represents the unit cubic simulation box to which 3D periodic boundary conditions have been applied. Fmoc groups are not represented for sake of clarity). (*right*) The fiber diameter is 2,5 nm. Two pairs of histidine residues linked together through hydrogel bonding are bolded and colored in orange (others histidine are colored in light yellow); **c**) Hydrolysis conversion of ester **1** over time; **d**) Production of the acid **10** over time from ester **9**; **e**) Determination of V_{max} and K_m according to the Lineweaver and Burk model (linear regression in dashed red).

Interestingly, we discovered that this CASH is also highly effective to hydrolyze a wide panel of inactivated esters, which is rarely reported, when the substrate has diffused within the catalytic hydrogel (Fig. 1g). Tertiary ester such as **6** requires more time to be fully hydrolyzed (Fig. S14) and complex structures such as **3** can self-assemble when its ester moiety is chemically cleaved[25] giving thus rise to a second self-assembled architecture growing within the CASH (Fig. S15).[26] This substrate versatility is crucial with regard to developments for

chemical synthetic tools. Using a flow reactor, the hydrolysis reaction is fast (Fig. S16). For instance, the inactivated methyl ester **9** (1 mM) is entirely hydrolyzed into **10** in less than 40 minutes (25°C, 1.5 mL/min). Increasing the concentration of **9** extends the necessary residence time but without inhibition effect, as expected for this non-acylating substrate (Fig. 3c). A linear dependence of $1/V_0$ with 1/[S] where V_0 represents the reaction rate at the initial time and [S] the substrate **9** concentration (Fig. 3d and Section 18 in ESI) was observed showing the Michaelis Menten behavior of our enzyme-like supported-CASH (Fig. S17). We determined the following values of K_m = 28 mM, V_{max} = 20,8 µmol.s^{-1} and k_{cat} = 3.0 x 10^3 s^{-1}. This last k_{cat} value is at least ten times higher than those reported for others CASH determined on activated *para*-nitrophenol ester derivatives.[27,28]

In the literature, few CASH described enantioselective processes[29,30] and the kinetic resolution of inactivated esters using CASH is still an unsuccessful challenge.[15,27,31] We observed a strong discrimination from the supported-CASH between the *L* and *D* amino-acid *tertio*butyl esters **6**: indeed, after 30 minutes of residence time, we observed that almost 45% of the natural enantiomer *L*-**6** was hydrolyzed whereas the *D*-**6** was not yet affected (Fig. 4a). By decreasing the flow rate to 0.5 mL/min, it was possible to obtain more than 90% conversion of the *L*-**6** into its corresponding acid derivative *L*-**8** (Fig. 4b). After loading the flow reactor with 200 mg of racemic *rac*-**6** and using a flow rate of 0.5 mL/min, we stopped the reaction after 30 minutes of running. The reaction medium was slightly basified and extracted with dichloromethane yielding to 95% of a white solid being the chemically pure acid *L*-**8** with 99% of enantiomeric excess (ee) from the aqueous phase (Fig 4b,c). The non-hydrolyzed ester *D*-**6** was isolated with a chemical yield of 96% and 92% ee from the organic layer. Enantio-enriched *L*-**6** (40% ee) lead quasi-quantitative isolation of both enantiopure *L*-**8** and the ester *D*-**6** (Fig. S18). Racemic amino-acid *tertio*-butyl esters such as the lysine and tyrosine were also tested: in both cases we observed a faster kinetic hydrolysis of the *L* enantiomer (Fig. 4d-e) highlighting the ability of the catalytic pocket to react faster with the natural amino-acids. Finally, other kind of racemic esters can be envisioned such as the oxirane of 4-methoxycinnamic methyl ester were the (*R*,*R*) enantiomer is hydrolyzed faster than the (*S*,*S*) one (Fig. S19): this compound is a key intermediate in the industrial preparation of the Diltiazem, a drug used to treat high blood pressure, angina and certain heart arrhythmias.

Continuous flow chemistry appears particularly well adapted for CASH applications since the flow through the catalytic hydrogel compensates the low diffusion rate of substrates under static conditions (decreasing thus the reaction time) and provides also an easy separation way between products and the catalytic phase. These features were not obvious because supramolecular hydrogels are physical gels resulting from the self-assembly of small molecules and thus a gradual delamination of the CASH through the shear stress induced by the flow is a scenario that was not possible to rule out at first sight.

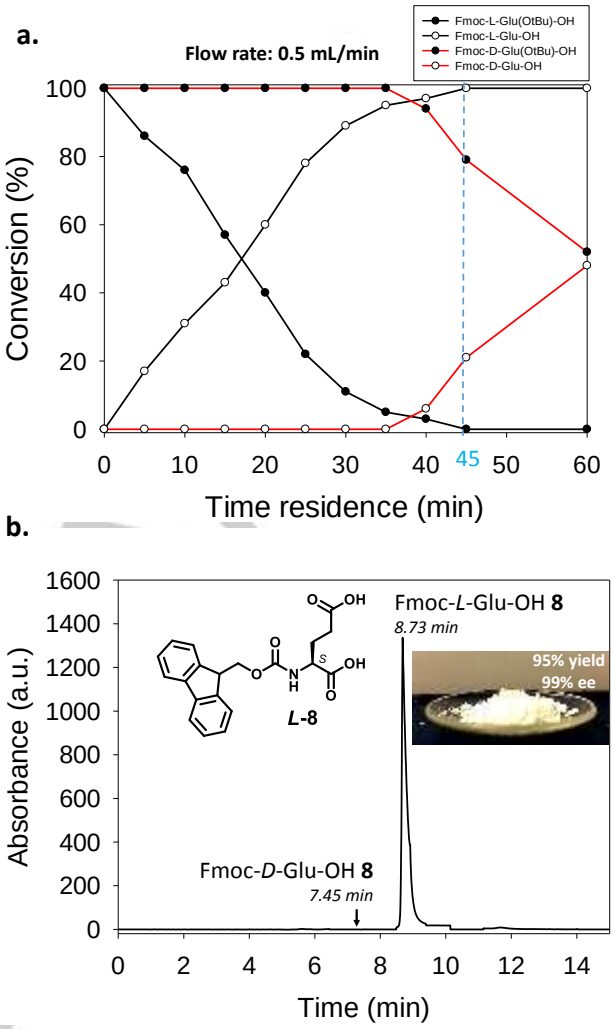

Figure 4. a) Proportion of *L*-**6**, *D*-**6** and their corresponding hydrolyzed derivatives *L*-**8** and *D*-**8** over time using 0.5 ml/min as flow rate; **b**) (left) ee determination of isolated *L*-**8** by chiral HPLC and (right) quantitative mass of chemically and enantiomerically pure *L*-**8** using supported CASH in a continuous flow process.

Yet supported-CASH proved to be stable with respect to flow and over time and the catalytic process could be repeated several times without any catalytic loss. Our designed supported-CASH gives rise to an efficient esterase-like hydrogel active towards activated esters but also towards a large panel of inactivated substrates such as methyl, primary, secondary and tertiary ester classes, a feature never reported which increases its interest for the chemist's community. Last but not least, our supported CASH shows also kinetic resolution capacity allowing to isolate quantitative amount of enantiopure carboxylic acids from racemic or enantio-enriched inactivated esters. The precise tuning of molecular assembly directing the emergence of functional nanostructures through a bottom up approach and leading to highly functional material is a new concept recently introduced by Ariga.[32,33]In our work, we have shown that the spatial control of peptide self-assembly from the surface of porous polymer materials leads to the growth of nanofibrous

networks. From this nanoorganization arise catalytic properties allowing to design a functional material for applications in flow chemistry. We thus highlight that supported-CASH can be a powerful tool for the design of new nanoarchitectonic systems and can find an echo in various communities of chemists going from synthetic chemistry to material science and chemical engineering.[34]

Experimental Section

All additional figures and experimental protocols are given in the electronic supporting information.

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Keywords: enzyme-assisted self-assembly • gels • organocatalysis • supported catalysis • kinetic resolution

[1] J.-M. Lehn, *Angew. Chem.* **2015**, *127*, 3326-3340; *Angew. Chem., Int. Ed.* **2015**, *54*, 3276-3289.
[2] G. M. Whitesides, B. Grzybowski, *Science* **2002**, *295*, 2418-2421.
[3] M. O. Guler, S. I. Stupp, *J. Am. Chem. Soc.* **2007**, *129*, 12082-12083.
[4] F. Rodriguez-Llansola, B. Escuder, J.-F. Miravet, *J. Am. Chem. Soc.* **2009**, *131*, 11478-11484.
[5] R. G. Weiss, *J. Am. Chem. Soc.* **2014**, *136*, 7519-7530.
[6] N. Teramoto, O. Shigehiro, Y. Ogawa, Y. Maruyama, T. Shimasaki, M. Shibata, *Polymer J.* **2014**, *46*, 592-597.
[7] A. G. L. Olive, N. H. Abdullah, I. Ziemecka, E. Mendes, R. Eelkema, J. H. van Esch, *Angew. Chem.* **2014**, *126*, 4216-4220; *Angew. Chem., Int. Ed.* **2014**, *53*, 4132-4136.
[8] X. Du, J. Zhou, J. Shi, B. Xu, *Chem. Rev.* **2015**, *115*, 13165-13307.
[9] C. Vigier-Carrière, F. Boulmedais, P. Schaaf, L. Jierry, *Angew. Chem.* **2018**, *130*, 1462-1471; *Angew. Chem., Int. Ed.* **2018**, *57*, 1448-1456.
[10] B. Yang, D. J. Adams, M. Marlow, M. Zelzer, *Langmuir* **2018**, *34*, 15109-15125.
[11] Z. Yang, H. Gu, D. Fu, P. Gao, J. K. Lam, B. Xu, *Adv. Mater.* **2004**, *16*, 1440-1444.
[12] R. J. Williams, A. M. Smith, R. Collins, N. Hodson, A. K. Das, R. V. Ulijn, *Nat. Nanotech.* **2009**, *4*, 19-24.
[13] C. Vigier-Carrière, T. Garnier, D. Wagner, P. Lavalle, M. Rabineau, J. Hemmerlé, B. Senger, P. Schaaf, F. Boulmedais, L. Jierry, *Angew. Chem.* **2015**, *127*, 10336-10339; *Angew. Chem., Int. Ed.* **2015**, *54*, 10198-10201.
[14] J. Rodon Fores, M. L. M. Mendez, X. Mao, D. Wagner, M. Schmutz, M. Rabineau, P. Lavalle, P. Schaaf, F. Boulmedais, L. Jierry, *Angew. Chem.* **2017**, *129*, 16200-16204; *Angew. Chem., Int. Ed.* **2017**, *56*, 15984-15988.
[15] O. Zozulia, M. A. Dolan, I. V. Korendovych, *Chem. Soc. Rev.* **2018**, *47*, 3621- 3639.
[16] C. Yang, H. Wang, D. Li, L. Wang, *Chin. J. Chem.* **2013**, *31*, 494-500.
[17] A. M. Smith, R. J., Williams, C. Tang, P. Coppo, R. F. Collins, M. L. Turner, A. Saiani, R. V. Ulijn, *Adv. Mater.* **2008**, *20*, 37-41.
[18] N. Yamada, K. Ariga, M. Naito, K. Matsubara, E. Koyama, *J. Am. Chem. Soc.* **1998**, *120*, 12192-12199
[19] S. Fleming, P. W. J. M. Frederix, I. R. Sasselli, N. T. Hunt, R. V. Ulijn, T. Tuttle, *Langmuir* **2013**, *29*, 9510-9515.
[20] M. Reches, E. Gazit, *Nat. Nanotech.* **2006**, *1*, 195-200.
[21] H. Scott Fogler, *Elements of Chemical Reaction Engineering*, (3rd Ed.) **1999**, Prentice Hall, Upper Saddle River, USA.
[22] M. L. Bender, B. W. Turnquest, *J. Am. Chem. Soc.* **1957**, *79*, 1652-1655.
[23] Y. S. Moroz, T. T. Dunston, O. V. Makhlynets, O. V. Moroz, Y. Wu, J. H. Yoon, A. B. Olsen, J. M. McLaughlin, K. L. Mack, P. M. Gosavi, N. A. J. van Nuland, I. V. Korendovych, *J. Am. Chem. Soc.* **2015**, *137*, 14905-14911.
[24] K. Ariga, T. Nakanishi, J. P. Hill, M. Shirai, M. Okuno, T. Abe, *J. Am. Chem. Soc.* **2005**, *127,* 12074-12080.
[25] J. Li, Y. Kuang, J. Shi, J. Zhou, J. E. Medina, R. Zhou, D. Yuan, C. Yang, H. Wang, Z. Yang, J. Liu, D. M. Dinulescu, B. Xu, *Angew. Chem.* **2015**, *127*, 13505-13509; *Angew. Chem., Int. Ed.* **2015**, *54*, 13307-13311.
[26] N. Singh, C. Maity, K. Zhang, C. A. Angulo-Pachon, J. H. van Esch, R. Eelkema, B. Escuder, *Chem. Eur. J.* **2017**, *23*, 2018-2021.
[27] N. Singh, M. P. Conte, R. V. Ulijn, J. F. Miravet, B. Escuder, *Chem. Commun.* **2015**, *51*, 13213-13216.
[28] K. L. Duncan, R. V. Ulijn, *Biocatalysis* **2015**, *1*, 67-81.
[29] F. Rodriguez-Llansola, J. F. Miravet, B. Escuder, *Chem. Commun.* **2009**, 7303-7305.
[30] N. Singh, K. Zhang, C. A. Angulo-Pachon, E. Mendes, J. H. van Esch, B. Escuder, *Chem. Sci.* **2016**, *7*, 5568-5572.
[31] A. Som, S. Matile, *Eur. J. Org. Chem.* **2002**, 3874–3883.
[32] M. Aono, K. Ariga, *Adv. Mater.* **2016**, *28*, 989-992.
[33] M. Komiyama, K. Yoshimoto, M. Sisido, K. Ariga, *Bull. Chem. Soc. Jpn.* **2017**, *90,* 967-1004.
[34] L. Zhao, Q. Zou, X. Yan, *Bull. Chem. Soc. Jpn.* **2019**, *92*, 70-79.

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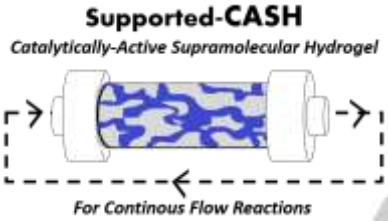

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Page No. – Page No.

Supported Catalytically-Active Supramolecular Hydrogels for Continuous Flow Chemistry

Layout 2:

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Page No. – Page No.