

Modifying the Catalytic Activity of Lipopeptide Assemblies with Nucleobases

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Biohybrid catalysts that operate in aqueous media are intriguing for systems chemistry. In this paper, we investigate whether control over the self-assembly of biohybrid catalysts can tune their properties. As a model, we use the catalytic activity of functional hybrid molecules consisting of a catalytic H-DPro-Pro-Glu tripeptide, derivatized with fatty acid and nucleobase moieties. This combination of simple biological components merged the catalytic properties of the peptide with the self-assembly of the lipid, and the structural ordering of the

nucleobases. The biomolecule hybrids self-assemble in aqueous media into fibrillar assemblies and catalyze the reaction between butanal and nitrostyrene. The interactions between the nucleobases enhanced the order of the supramolecular structures and affected their catalytic activity and stereo-selectivity. The results point to the significant control and ordering that nucleobases can provide in the self-assembly of biologically inspired supramolecular catalysts.

Introduction

Systems chemistry represents a new approach in the chemical sciences and encompasses a holistic view of chemical systems, understood as sets of molecules interconnected through chemical transformation and/or self-assembly processes.^[1–3] The study of such dynamic chemical systems is expected to aid the resolution of questions regarding the origin of life.^[4] It should also facilitate the design of artificial systems and materials that emulate processes and features of living cells.^[5–7] To implement 'life-like' behaviors in synthetic chemical structures, one approach is to design and prepare hybrid molecules that merge different biological components,^[8–13] including lipid chains with

the capacity to induce self-assembly, or nucleobases with their inherent high specificity to control supramolecular processes that are relevant in Nature. Herein, such an approach was employed to interrogate whether supramolecular assembly can modify the catalytic activity of lipopeptide assemblies.

Catalysis plays a crucial role in living organisms.^[14] Complex networks of enzymatic transformations, for instance, allow biological systems to control cellular processes and achieve homeostasis. Thus, the introduction of catalytic functions is an important consideration for the design of synthetic mimics of biological systems.^[15–17] In this respect, prior studies combined catalysis with other 'life-like' features such as replication,^[18–20] dissipative self-assembly,^[21–25] or the formation of dynamic and responsive soft materials.^[26–28] Although there are examples of enhancement of activity of organocatalysts through formation of supramolecular assemblies,²⁹ there is little knowledge of how specific interactions within the assemblies affect their catalytic properties. As a consequence, tuning the activity and stereo-selectivity of supramolecular catalysts is far from trivial.^[30–32] Herein, we show that non-covalent interactions between

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202303395>

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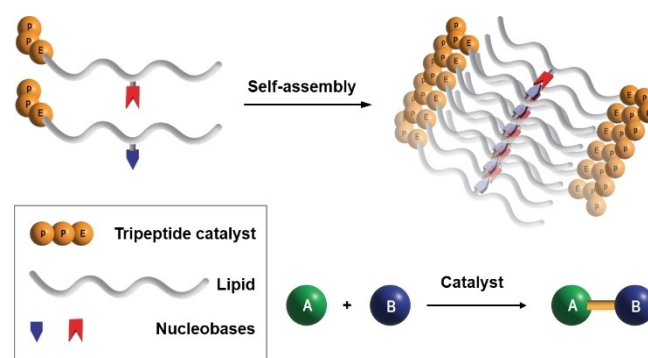


Figure 1. Cartoon representing the formation of catalytically active supramolecular assemblies by peptide-nucleolipid hybrids.

nucleobase units within catalytic multicomponent biohybrid assemblies allow for tuning of their catalytic activity (Figure 1).

Results and Discussion

Design and synthesis of the hybrid catalysts

To study the effect of assembly morphology on the catalytic performance of biohybrid self-assembled catalysts, we designed compounds containing three components: a catalytic site, a nucleobase, and a lipid. As a catalyst, we chose the lipidated peptide H-DPro-Pro-Glu-NHC₁₂H₂₅ (**1**), which is a highly active and stereoselective organocatalyst for conjugate addition reactions between aldehydes and nitroolefins in water.^[33–37] This amphiphilic peptide forms a foam in water, and the reaction occurs in the hydrophobic microenvironments.^[36,37] The second key component of the hybrid system is the lipophilic oleic acid residue, envisioned to direct the self-assembly process of the lipopeptide conjugate. The third key component is a nucleobase for directing the self-assembly process. We chose adenine and thymine as bases that form complementary base pairs. The lipidated peptide and the nucleobase were linked through a spacer composed of an aliphatic chain (10 carbon atoms) and an amino acid, either glycine (**2a**), alanine (**2b**), or β -aminoalanine (**3a** and **3b**; Figure 2; for details on the synthesis see the SI). For lipopeptides **2a** and **2b**, the main driving force of self-assembly was expected to be their amphiphilic nature and, thus, the hydrophobic effect. Additionally, H-bonding interactions between the amino acid units in the linker could also contribute to the self-assembly process. Alanine was introduced in **2b** and glycine in **2a** to study the effect of a chiral linker on the organization of the nanostructures. The β -aminoalanine residue in compounds **3a** and **3b** allowed derivatization with both an oleic acid chain and a carboxymethyl-derivative of a nucleobase (either thymine for **3a** or adenine for **3b**).

With the biohybrids in hand, we studied their self-assembly and catalytic properties using lipidated peptide **1** as reference.

Spectroscopic studies

The self-assembly of the conjugates was studied at concentrations between 10–600 μ M in 50 mM potassium phosphate buffer (KPi) at pH 8 (protocol for sample preparation in the SI). To assess self-assembly, we first performed turbidimetric studies using UV-Vis spectroscopy and measured the absorbance at 400 nm. The molecularly dissolved compounds do not absorb at this wavelength, but once a critical aggregation concentration (cac) is reached, assembly formation results in the scattering of light. The features of lipopeptides **2a** and **2b**, which lack a nucleobase, were similar, with no increase in absorbance up to a concentration of 200 μ M (Figures S1B and S1C), and low light scattering over the entire concentration range. On the contrary, solutions of compounds **3a** and **3b** were turbid throughout the entire concentration range (Figures S1D and S1E, respectively). Turbidity increased linearly with

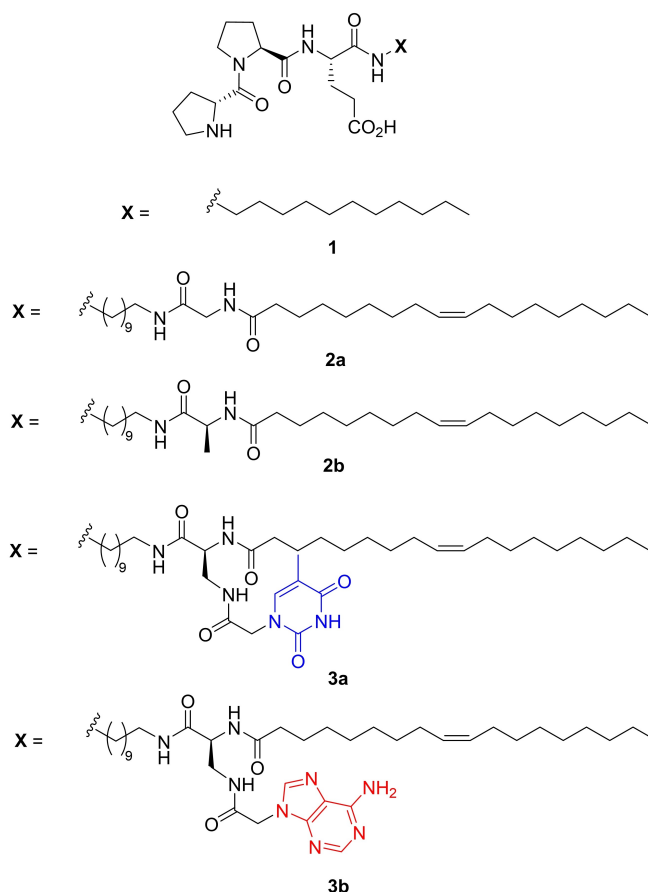


Figure 2. Structures of the studied catalytic lipopeptide (**2a** and **2b**) and peptide-nucleolipid (**3a** and **3b**) conjugates and reference compound **1**.

concentration, as expected based on previously studied nucleolipid systems.^[11] For equimolar mixtures of **3a/3b**, the absorbance at 400 nm increased up to a concentration of 200 μ M and approached a plateau at higher concentrations (Figure S1F). Similar results were obtained by fluorescence spectroscopy, for which 1,6-diphenyl-1,3,5-hexatriene (DPH) (2.5 μ M) was used as a probe to monitor assembly formation. Upon excitation with light of 355 nm, DPH emits at 428 nm when inserted in the hydrophobic pocket of organic aggregates but not when in solution. Interestingly, for lipopeptides **2a**, **2b**, peptide-nucleolipids **3a**, **3b**, as well as for the **3a/3b** equimolar mixture, a linear increase in fluorescence intensity occurred with the gradual increase in the concentration of each amphiphile (Figure S2). Thus, the UV-Vis and fluorescence experiments indicate the formation of aggregates by all compounds.

For insight into the molecular organization of the supramolecular assemblies we performed circular dichroism (CD) experiments. The experiments were carried out in KPi buffer (pH 8) at 1 mM concentration for compounds **1**, **2a** and **2b**, and at 200 μ M for compounds **3a**, **3b** and the **3a/3b** mixture due to their lower cac. The CD spectra of compounds **1**, **2a**, and **2b** exhibit only a signal below 240 nm, while the nucleobase provides the spectra of **3a** and **3b** with clearly

distinguishable Cotton effects between 240–310 nm (Figure 3A). While the thymine derivative **3a** (Figure 3A, blue) exhibited in this spectral region a positive-to-negative Cotton effect from 304 to 240 nm (with maxima at 287 and 257 nm), the adenine derivative **3b** showed a hypsochromically shifted (~17 nm) positive Cotton effect with a maximum at 264 nm (Figure 3A, red). These differences indicate a different ordering within the assembly of the thymine- and adenine-based peptide-nucleolipid systems. The spectrum of the **3a/3b** equimolar mixture (Figure 3A, purple) displayed maxima between those found in the spectra of the individual components. This spectrum is substantially different from the sum of the individual spectra of **3a** and **3b** (dashed purple line), which indicates the formation of mixed assemblies by the two peptide-nucleolipids.

In the low-wavelength region (< 240 nm), the CD spectra of lipopeptides **1**, **2a**, and **2b** differ significantly from those of the peptide-nucleolipids **3a** and **3b**. The spectra of the former display a negative Cotton effect with maxima at 207, 211, and 214 nm, respectively, while the spectra of the latter show a positive Cotton effect below 230 nm. These differences point to a different organization of the tripeptide in the supramolecular assemblies of **3a** and **3b** compared to **1**, **2a**, and **2b**, suggesting that the nucleobases influence the self-assembly process.

To further explore the influence of the nucleobase component on the self-assembly of **3a**, **3b**, and **3a/3b**, and to explore whether base complementarity is important for the aggregation process, we added 2-aminopurine (2-AP) and 5-bromouracil (5-BU), the complementary nucleobase analogs,^[38,39] to the self-assemblies of **3a** and **3b** (Figure 3B–D). Upon addition of the complementary base, the Cotton effect at the low-wavelength

region changed to the opposite sign when **2-AP** was added to the solution of **3a** (Figure 3B), and when **5-BU** was added to the solution of **3b** (Figure 3C) or the **3a/3b** mixture (Figure 3D). Remarkably, the spectra did not change at wavelengths greater than 240 nm. These results support the presence of a non-covalent interaction between the nucleobase and the peptide in the supramolecular assemblies formed by compounds of type **3**. This interaction is disrupted in the presence of a complementary nucleobase.

To probe the interaction between H-DPro-Pro-Glu-NH₂ and nucleobases, we used ¹H NMR spectroscopy. Upon addition of thymine to a solution of H-pPE-NH₂, notable downfield shifts of the signals corresponding to the H_α and H_β protons of the N-terminal proline were observed (Figure S3). In addition, shifts of the signals corresponding to the H_α and H_γ protons of the glutamic acid, albeit less significant, were also noted. These observations suggest that thymine interacts with the peptide. Titration experiments allowed for the determination of a binding affinity of $K_a = 74 \text{ M}^{-1}$ (Figures S4–S6). Upon addition of adenine to a solution of H-pPE-NH₂, none of the signals shifted (Figure S3), suggesting that this nucleobase does not interact with the tripeptide.

Microscopy studies

Transmission electron microscopy (TEM) revealed that all lipopeptides (**2a**, **2b**) and peptide-nucleolipids (**3a**, **3b**, **3a/3b**) form tubular assemblies with average diameters around 9 nm, whereas lipidated peptide **1** forms spherical objects, likely micelles (Figure 3E,F, Figures S7–S12).³⁶ These TEM images were

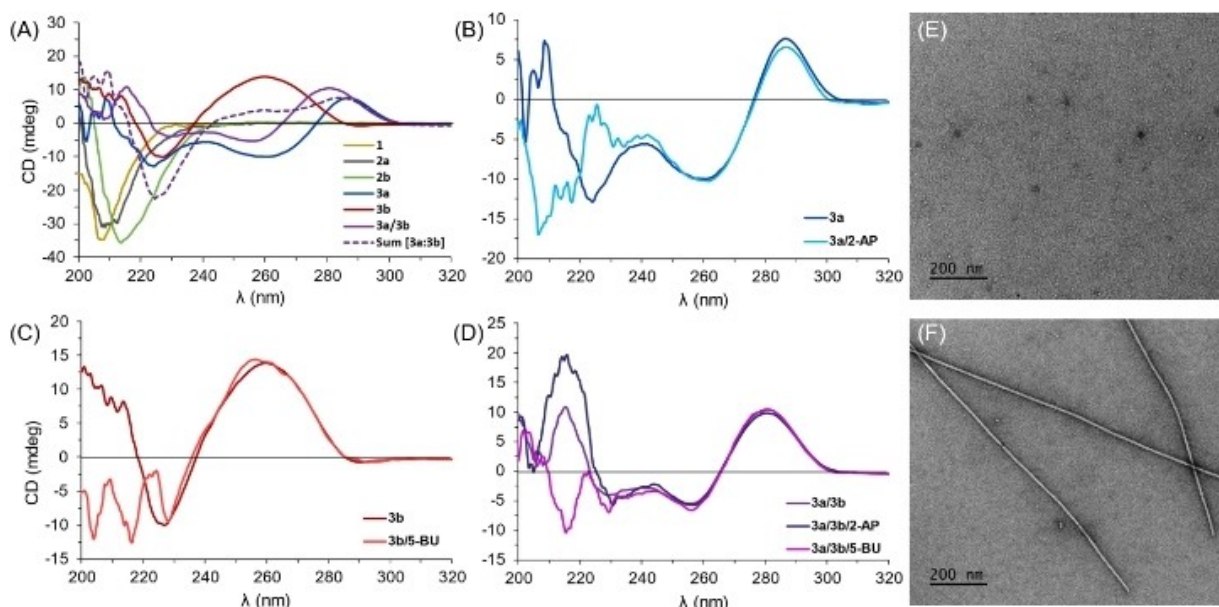


Figure 3. (A) Circular dichroism (CD) spectra of the studied lipopeptides, in 50 mM KPi buffer at pH 8, with concentrations of 1 mM for **1**, **2a** and **2b** or 200 μM for **3a**, **3b** and **3a/3b**, and the sum of the spectra from **3a** and **3b** (purple dashed line). (B–D) Comparison of the CD spectra of the nucleolipopeptides **3a** (B), **3b** (C) and the **3a/3b** mixture (D), with those upon addition of the corresponding complementary nucleobase analogue **2-AP** or **5-BU** (each compound at 200 μM). (E,F) Representative TEM images of the spherical aggregates formed by reference compound **1** (E) and the tubular assemblies resulting from the **3a/3b** mixture.

recorded from samples prepared from solutions above the cac (e.g., at 300 μ M) on carbon-coated copper grids that were previously hydrophilized by glow discharge. These results confirm that the self-assembly is predominantly driven by the oleic acid and nucleobase components.

For deeper insight into the structural differences between the assemblies formed by the different compounds, scanning electron microscopy (SEM) analyses were performed after depositing a drop of a 200 μ M solution of each conjugate (in kPi buffer, pH 8) on a 10 nm gold-coated sample holder (Figure 4). Similar to the TEM analyses, spherical and amorphous structures were observed in the sample containing peptide **1** (Figure 4A and S13). Compounds **2a** (Figure 4B and S14) and **2b** (Figure 4C and S15) formed very long fibrillar structures akin to the nanotubes observed by TEM, which are intertwined with each other. In the case of **3a** (Figure 4D and S16) and **3b** (Figure 4E and S17), a qualitatively greater number of intertwined 1D assemblies with similar diameters was observed. Finally, in the case of the **3a/3b** mixture (Figure 4F and S18), large bundles of significantly wider fibers, which were not observed in the previous samples, were found, implying that the complementarity of nucleobases allows the formation of higher-ordered assemblies. Related 1D nanostructures were also observed in the SEM images of samples containing mixtures of **3a** or **3b** with **2-AP** or **5-BU**, respectively (Figures S19 and S20), but none of them gave rise to the degree of order achieved with the equimolar mixture of **3a** and **3b**.

Catalysis studies

To test the catalytic properties of the supramolecular assemblies formed by the peptide-nucleolipid conjugates, we used the conjugate addition between butanal and nitrostyrene as a

model reaction. The supramolecular assemblies provide a hydrophobic microenvironment allowing for substrate solubility. The reaction was carried out at pH 8 in kPi buffer (50 mM), at a 50 mM concentration of the nitroolefin, two equivalents of butanal, and 3 mol% of the catalyst. Of note, these reaction conditions are optimal for the self-assembly of the peptide-nucleolipid conjugates but not for catalysis.^[36,37] In fact, the reactivity and stereoselectivity of lipidated peptide **1** are significantly lower at pH 8 compared to pH 7.4 (pH 7.4: >95% conv., 91% ee; pH 8: 84% conv., 85% ee). Furthermore, the basic conditions cause product epimerization, which reduces the diastereoselectivity (pH 7.4: 18:1 d.r., pH 8: 7:1 d.r.).

A conversion to the product of ~80% with a diastereoselectivity of 5:1 was observed in the reactions catalyzed by compounds **2a** and **2b** after 20 h (Table 1, entries 2 and 3). Similar results were obtained with reference compound **1** (entry 1). The presence of nucleobases in the peptide-nucleolipid conjugates (**3a** or **3b**) diminished the enantioselectivity of the reaction (Table 1, entries 4 and 5), and in the case of the thymine-functionalized compound (**3a**) also the conversion (64%). A similarly low conversion was observed when catalyst **1** was used in the presence of an equimolar amount of thymine (Table 1, entry 6). This finding suggests that an interaction between thymine and the tripeptide, observed by the CD and NMR spectroscopic studies, diminishes the catalytic activity of the peptide. Both the conversion ($\geq 95\%$) and the d.r. (10:1) of the conjugate addition product increased when an equimolecular mixture of **3a** and **3b** was used as catalyst (at two different catalytic loadings; entries 7 and 8). Similar results were obtained in the reactions catalyzed by **3a** and **3b** in the presence of the complementary nucleobase analogues **2-AP** and **5-BU** (Table 1, entries 9 and 10). Furthermore, a reaction catalyzed by **1** in the presence of both thymine and adenine (entry 11) yielded the product with similar conversion and stereoselectivity as the

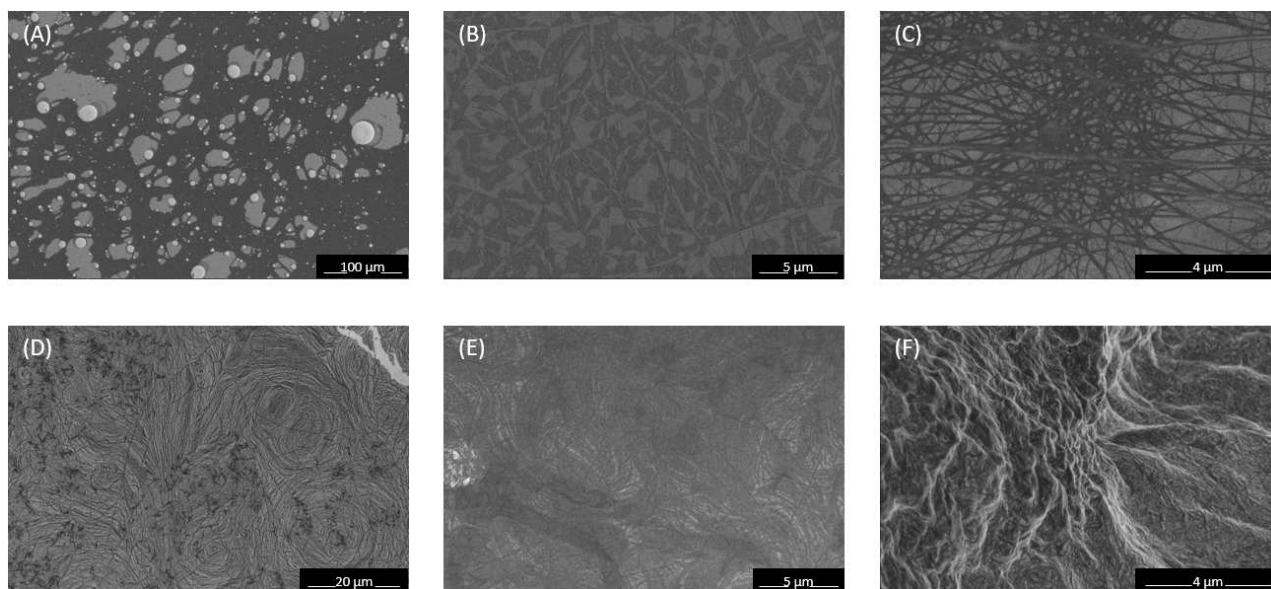
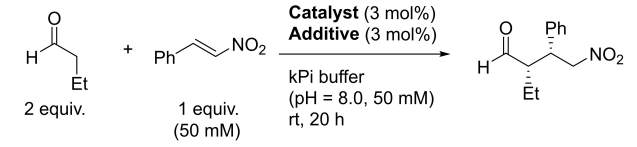


Figure 4. Representative SEM images of the spherical structures formed by the reference peptide **1** (A) and the fibrillar structures formed by **2a** (B), **2b** (C), **3a** (D), **3b** (E), and **3a/3b** (F).

Table 1. Catalysis with nucleo-lipopeptide assemblies.

					
Entry	Catalyst	Additive	Conv. (%) ^[a]	d.r. ^[a]	ee (%) ^[b]
1	1	—	84	7:1	85
2	2a	—	82	5:1	82
3	2b	—	78	5:1	84
4	3a	—	64	5:1	78
5	3b	—	91	5:1	76
6	1	T	68	6:1	84
7	3a/3b	—	95	10:1	77
8 ^[c]	3a/3b	—	> 95	10:1	77
9	3a	2-AP	91	7:1	77
10	3b	5-BU	93	10:1	79
11	1	T + A	85	8:1	86
12	—	2-AP	0	—	—
13	—	5-BU	0	—	—

[a] Conversion and d.r. were determined by ¹H NMR spectroscopic analysis of the crude mixture. The reactions were run in triplicate and variations of 1–3% in conversion were observed. The average conversion values are reported. [b] The ee was determined by chiral stationary phase HPLC. [c] 3 mol% of each building block was used.

experiment without nucleobase additives (entry 1). These results show that the formation of complementary hydrogen bonds between adenine/2-aminopurine and thymine prevents the tripeptide-thymine interaction and restores the catalytic performance of the peptide.

Conclusions

In this work, we prepared peptide-nucleolipid conjugates and investigated their self-assembly and catalytic properties. We showed that the conjugates self-assemble in aqueous buffers into fibers and that the complementary interactions between nucleobases induce a higher degree of order in the formed assemblies. Owing to the presence of a catalytically active H-D-Pro-Pro-Glu tripeptide fragment, the peptide-nucleolipid conjugates catalyze the stereoselective addition of butanal to nitrostyrene in aqueous buffers. The self-assembly provides a hydrophobic microenvironment and thus solubilizes the reaction substrates. Thymine diminished the catalytic activity of the conjugates, most likely due to interaction with the tripeptide. Adding a complementary nucleobase to thymine restored the catalytic activity of the lipopeptide-nucleobase hybrids.

The results of this work are relevant in the context of systems chemistry, where different approaches are used to mimic how catalysis takes place in living organisms, not only to understand how chemical evolution could have optimized catalytic molecules but also to design synthetic soft systems

and materials with tuned catalytic properties. In this respect, creating biohybrid non-covalent assemblies, where each biomolecular component plays a specific role in both the self-organization process and the catalytic activity, is key to studying the factors that allow for the optimization of these functions. Future studies will focus on extending the reaction scope of nucleobase-containing peptide assemblies and on evaluating other functions that could emerge from such biohybrid systems.

Experimental Section

General route for the synthesis of the hybrid catalysts. The synthesis of the four conjugates (**2a**, **2b**, **3a** and **3b**) was carried out from two different building blocks: one consisting of the catalytic tripeptide modified through an amide bond with 1,10-decadiamine as linker (compound **4** in Scheme S1), and the other one bearing the lipid part (building blocks **5**, **6**, **7** and **8**). To connect the two building blocks, **4** and **5–8**, via an amide bond, the latter was first activated with EDC and HOBt in presence of DIPEA and DMF as solvent, and then reacted at rt with the tripeptide derivative **4** for 48 h. In all cases, the product was obtained as a white solid in good yields after removal of the protecting groups with TFA and TIS in DCM. The detailed procedures and full characterization of intermediate and final products are described in the SI.

General protocol for the catalytic reactions. The peptide-nucleolipid catalyst (0.65 μmol) was dispersed in kPi buffer (0.4 mL). The mixture was sonicated for 10 seconds. Subsequently, butanal (3.6 μL, 40 μmol) and nitrostyrene (3 mg, 20 μmol) were added. The mixture was stirred vigorously (700 rpm) for 20 h at room temperature. The reaction mixture was then extracted with CDCl₃ (0.6 mL) and the organic extract was directly analysed by ¹H NMR to determine the conversion and the d.r., and by chiral stationary phase HPLC to determine the e.e.

Further details of the materials and methods employed for these experiments and the supramolecular studies carried out by UV-Vis and fluorescence spectroscopy, or by TEM and SEM microscopies, are provided in the SI.

Acknowledgements

This research was funded by the Spanish *Agencia Estatal de Investigación* (AEI, project PID2020-119306GB-I00) the European Union (AdLE, HW, CLASSY project, Grant Agreement N° 862081) and the Swiss National Science Foundation (HW, grant 200020_188729/1). We also acknowledge the service from the MiNa Laboratory at IMN, and funding from CM (project S2018/NMT-4291 TEC2SPACE), MINECO (project CSIC13-4E-1794) and EU (FEDER, FSE).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: assemblies · catalysis · lipopeptides · nucleobases · supramolecular

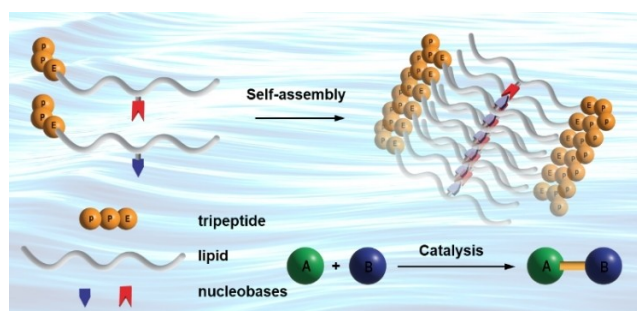
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Manuscript received: October 16, 2023

Accepted manuscript online: October 25, 2023

Version of record online: ■■■, ■■■

RESEARCH ARTICLE



Biomolecular conjugates consisting of a catalytic tripeptide, a fatty acid and nucleobase moieties form defined fibrillar assemblies in aqueous media and catalyze the reaction of butanal with nitrostyrene. The interaction between complementary nucleobases enhanced the order in the

supramolecular assemblies and influenced the catalytic properties of the peptide-nucleolipids, indicating that nucleobases can be valuable for control over the self-assembly and catalytic properties of biologically inspired supramolecular catalysts.

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Modifying the Catalytic Activity of Lipopeptide Assemblies with Nucleobases

