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# **Comparison of Lipoic and Asparagusic Acid for Surface-Initiated Disulfide-Exchange Polymerization**

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Although known since 1940s, disulfide-exchange polymerization does not enjoy much scientific attention.<sup>[1]</sup> This is surprising because the chemistry involved in this nearly forgotten process is mild, directional, reversible and very robust, “it really works.”<sup>[1]</sup> Protein folding stands out as an inspiring example from nature how the key advantages of disulfide-exchange chemistry can help to solve important problems. Contrary to poly(disulfide)s, disulfide-exchange chemistry is quite popular to analyze mixtures of dimers. Prominent examples include methods to determine the homogeneity of lipid bilayers,<sup>[2]</sup> protein-protein interactions,<sup>[3]</sup> and so on. Higher oligo(disulfide)s are of interest in the context of dynamic covalent chemistry.<sup>[4]</sup> Poly(disulfide)s are arguably best known from protein folding, the

vulcanization of rubber and, perhaps, from biodegradable gene transfection agents<sup>[5]</sup> or polymerized vesicles.<sup>[6]</sup> However, disulfide-exchange polymerization is really relevant only in the context of polymerized vesicles.<sup>[6]</sup> To our surprise, we have found recently that this underappreciated process is of great use to grow functional multicomponent architectures directly on solid surfaces (Fig. 1a).<sup>[7-9]</sup> Interested in the development of synthetic methods to tackle this fundamental challenge,<sup>[7-10]</sup> we noticed early on that many classical methods for surface-initiated polymerization can become problematic as soon as more demanding chemistry is involved. Looking for more robust alternatives, surface-initiated ring-opening disulfide-exchange polymerization turned out to work best. To build complex architectures, the new chemistry was used to develop self-organizing surface-initiated polymerization (SOSIP) as a general synthetic method.<sup>[7]</sup> In this approach, molecular recognition motifs are added to bring the propagators into perfect position to polymerize into highly ordered single-component architectures. The SOSIP strategy has been further expanded by templated self-sorting (TSS)<sup>[8]</sup> and templated stack exchange (TSE)<sup>[9]</sup> as complementary strategies to increase structural complexity.

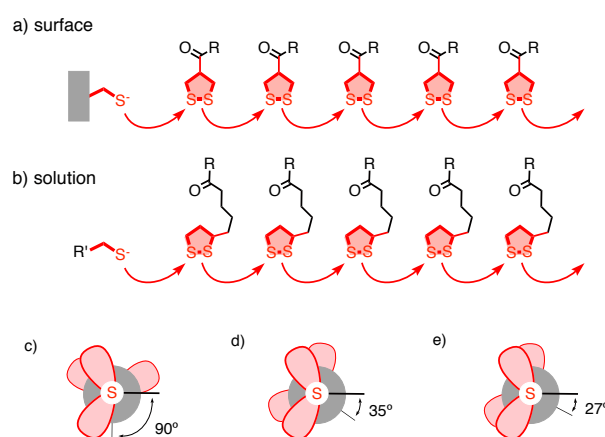


Figure 1. a) On surfaces, disulfide-exchange polymerization with propagators derived from asparagusic acid is ideal, whereas lipoic acid is not reactive enough. b) In solution, substrate-initiated disulfide-exchange polymerization with propagators derived from lipoic acid is ideal, whereas asparagusic acid is too reactive. These differences originate from different C-S-S-C dihedral angles in c) acyclic disulfides, d) lipoic acid and e) asparagusic acid.

Impressed by the excellent properties on surfaces, we decided to explore the same process in solution.<sup>[11]</sup> The idea was to grow cell-penetrating poly(disulfide)s directly on thiol-containing substrates for covalent delivery and depolymerize the transporters right after cellular uptake to eliminate toxicity and release the unmodified substrates. To elaborate on this idea, several propagators composed of strained disulfides and guanidinium cations were prepared and tested. Propagators derived from lipoic acid, a natural product involved in acyl group transfer and antioxidative protection,<sup>[6][12-15]</sup> turned out to be ideal for ring-opening disulfide-exchange polymerization in neutral water (Fig. 1b), whereas propagators derived from asparagusic acid were too reactive for controlled substrate-initiated polymerization.<sup>[11]</sup> In clear contrast, propagators derived from asparagusic acid, the natural product whose metabolites we can smell in urine after the consumption of asparagus,<sup>[14][15]</sup> gave excellent results with surface-initiated polymerization (Fig. 1a).<sup>[7-9]</sup>

The reactivity of cyclic disulfides is determined by their ring tension.<sup>[13][14]</sup> Tension-free alkyl disulfides in six-membered rings exist preferably in cyclic form. This property accounts, for example, for the reductive power of DTT. Alkyl disulfides in five-membered rings, however, are strained. Their reactivity is mostly determined by the C-S-S-C torsion angle and the length of the S-S bond.<sup>[14]</sup> In open chain disulfides, the dihedral angle is  $\sim 90^\circ$  and the S-S bond length is 2.02 Å (Fig. 1c). In lipoic acid, the C-S-S-C torsion angle is  $35^\circ$  and the S-S bond length is 2.05 Å (Fig. 1d). In asparagusic acid, the C-S-S-C torsion angle is  $27^\circ$  and the S-S bond length is 2.10 Å (Fig. 1e). These reduced torsion angles increase the reactivity of the strained disulfides because of unfavorable interactions between the sulfur lone pairs. The result that propagators derived from lipoic acid are perfect but propagators derived from asparagusic acid are too reactive for substrate-initiated disulfide-exchange polymerization in solution<sup>[11]</sup> was thus in excellent agreement with expectations from theory.<sup>[1][6][12-14]</sup> This finding suggested that the impression that propagators derived from asparagusic acid are best for surface-initiated polymerization<sup>[7-9]</sup> would deserve a closer look. In the following, the required direct comparison of self-organizing surface-initiated polymerization with propagators derived from lipoic and asparagusic acid is reported.

To compare lipoic and asparagusic acid in surface-initiated polymerization, we selected compound **1** as a starting point. This is an optimized propagator for SOSIP-TSE of functional multicomponent architectures (Fig. 2).<sup>[9]</sup> It is built around a central aromatic unit, here a naphthalenediimide (NDI). This aromatic core is expected to contribute to the self-organization of SOSIP by  $\pi$ - $\pi$  interactions, and to afford charge-transporting  $\pi$ -stacks in the final poly(disulfide) architecture **1P**. The peptide-like domain around the NDI in **1** is placed to enhance the self-organization of the SOSIP and to surround the final  $\pi$ -stack in **1P** with a hydrogen-bonding network. The strained disulfides from asparagusic acid at two termini of **1** account for the disulfide exchange polymerization into the ladderphane<sup>[16]</sup> architecture **1P** as discussed in the introduction. The benzaldehyde hydrazones at the other two termini template for post-SOSIP TSE.

The ladderphane architecture **1P** shown in Figure 2 is an idealized structure. In reality, there will be defects. However, these defects are expected to be minimized by self-organization of the polymerization process. Experimental evidence for self-repair of artificially added defects exists. Decreasing self-repair with increasing polymerization temperature confirms that molecular recognition accounts for self-repair.<sup>[8a]</sup> Control experiments have shown that two strained disulfides per propagator are essential for SOSIP.<sup>[7a]</sup> Propagators with one disulfide only polymerize at much higher concentrations and give much shorter polymers. More favorable detachment of the growing poly(disulfide)s from the surface by intramolecular macrocyclization presumably accounts for the poor results obtained with monovalent propagators.<sup>[7a]</sup> Both increasing self-repair with decreasing temperature and poor polymerization with monovalent propagators confirm the importance of self-organization for SOSIP and support the formation of ladderphane architectures **1P** without too many defects. Phase-contrast AFM images show low-defect architectures with long-range organization down to the molecular level.<sup>[7a]</sup>

To compare the usefulness of propagators derived from lipoic and asparagusic acid for SOSIP, we decided to prepare propagator **2** and explore SOSIP into the corresponding ladderphane architecture **2P**. In propagator **2**, the structure of the established propagator **1** is preserved except for the substitution of

the two natural products at the termini. Possible alternatives with only one lipoic acid were not considered because SOSIP with the corresponding monovalent propagators with asparagusic acid failed.<sup>[7a]</sup> For practical reasons, we decided to use racemic lipoic acid first and explore enantiopure material only in the case of promising results. Diastereoselectivity is not expected because of the long distance between the chiral centers in lipoic acids and lysines.

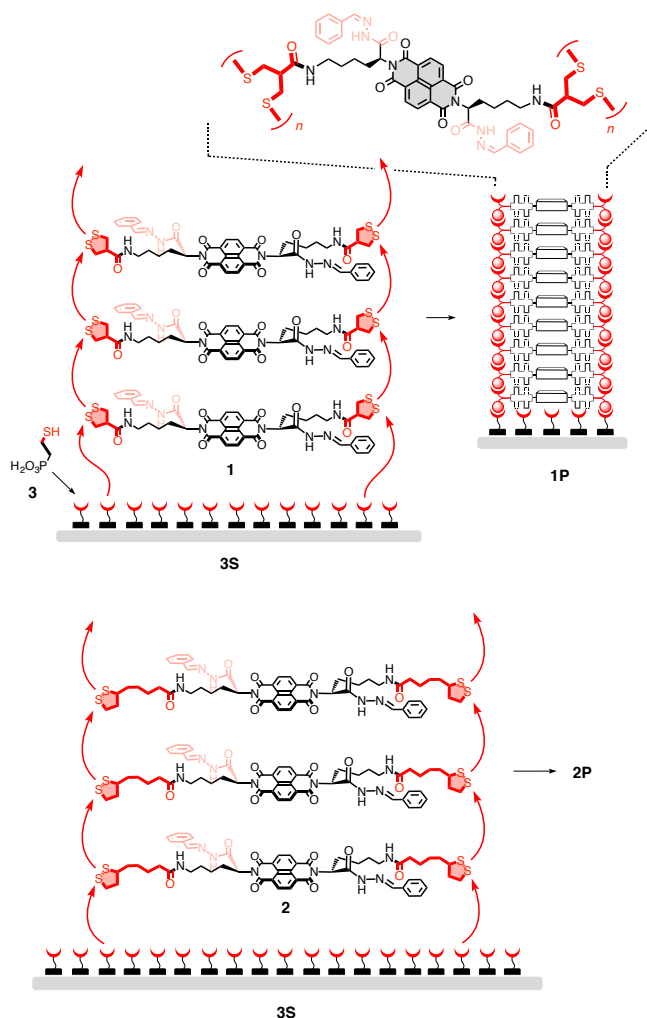


Figure 2. Structure of the new propagator **2** compared to propagator **1** that is routinely used for SOSIP of poly(disulfide) **1P** on either self-organizing or non-organizing monolayers **3S** prepared with initiator **3**.

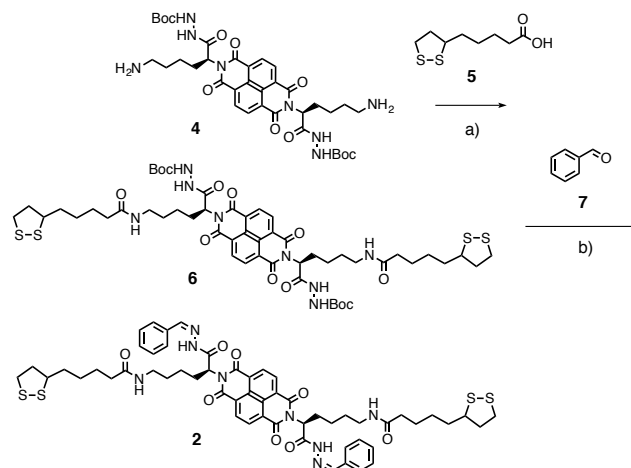
The distance between the two strained disulfides in propagator **2** is longer than that in propagator **1**. This implied that SOSIP with the two propagators should be compared on a non-organizing initiator. In classical SOSIP, topologically matching initiators are used to maximize the self-organization of the process. These initiators are essential for TSS<sup>[8b]</sup> as well as for functional aspects.<sup>[9c]</sup> However, as pointed out early on, topologically matching initiators are not essential for SOSIP itself.<sup>[7a]</sup> A thiol-rich surface without particular organization is sufficient to initiate SOSIP, and the first propagator that is covalently bound to the surface self-organizes the reaction with the next incoming propagator. The simplest possible initiator for SOSIP on ITO (indium tin oxide) is compound **3** with a phosphonate to bind to the surface and a thiol to initiate the process. The formation of monolayer **3S** has been reported, SOSIP of photosystems very similar to **1P** as well.<sup>[7a]</sup>

The new propagator **2** was very easily synthesized from the previously reported diamine **4** (Scheme 1).<sup>[9a][17]</sup> Reaction with racemic lipoic acid **5** gave diamide **6**. The hydrazide in **6** was then deprotected with acid and reacted in situ with benzaldehyde **7**.

Initiator **3** was deposited on ITO as described.<sup>[7a][17]</sup> In brief, ITO plates were cleaned for 15 minutes in boiling RCA solution (H<sub>2</sub>O/NH<sub>4</sub>OH/H<sub>2</sub>O<sub>2</sub> 5:1:1), washed, dried and incubated for 98 h in a 10 mM solution of **3** in DMSO. Full coverage was confirmed by cyclic voltammetry, showing complete suppression of the redox wave of ferricyanide in solution. Then the monolayer **3S** was annealed in the oven (1 h, 120 °C).

SOSIP on monolayer **3S** was first tested for propagator **1** derived from asparagusic acid under established conditions. Namely, monolayer **3S** was incubated together with a blank ITO plate in solution of **1** in CHCl<sub>3</sub>/MeOH 1:1 containing 100 mM DIPEA to deprotonate the thiols on the surface. The growth of polydisulfide **1P** was measured following the NDI absorption at 385 nm. After 24 h,<sup>[7a]</sup> increasing absorption with increasing concentration of propagator **1** was observed (Fig. 3a). Around  $c_{\text{SOSIP}} \sim 5 \text{ mM}$  **1**, poly(disulfide)s **1P** were formed exclusively on monolayer **3S**, the blank control electrode showed no

NDI absorption. At higher concentration, polymerization occurred also in solution, at lower concentration, polymerization did not occur at all.



Scheme 1. Synthesis of propagator **2**. a) CDI, DMF/DCM, rt, 2 h, 44%. b) **7**, TFA, DCM, thioanisole, rt, 1 h, 77%.

Under identical conditions, SOSIP with the new propagator **2** derived from lipoic acid did not occur, even at concentrations up to 352 mM (Table 1, entry 1 vs 2). Screening of other solvent mixtures that have previously enabled SOSIP with propagators derived from asparagusic acid did not enable SOSIP with the propagator **2** either (Table 1, entries 3-5). To possibly encourage SOSIP with lipoic acid, we considered the long alkyl chains from lipoic acid should increase the hydrophobicity of propagator **2**. Strengthened hydrophobic interactions in more polar solvents could thus provide access to SOSIP with derivatives of lipoic acid. However, addition of water to the original  $\text{CHCl}_3/\text{MeOH}$  1:1 did not solve the problem, also because of emerging solubility problems (Table 1, entries 6 and 7). Surface-initiated polymerization was finally realized by increasing the MeOH content to  $\text{CHCl}_3/\text{MeOH}$  4:10 (Table 1, entry 8).

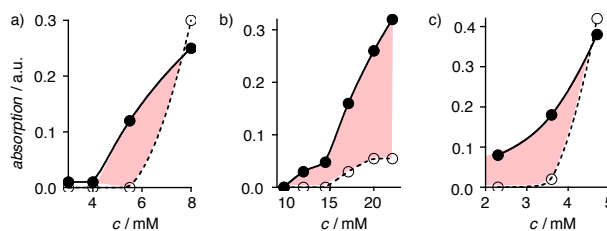


Figure 3. Absorption of ITO electrodes at 385 nm with (●) and without (○) initiator **3** after incubation with (a) propagator **1** in CHCl<sub>3</sub>/MeOH 1:1, (b) propagator **2** in CHCl<sub>3</sub>/MeOH 4:10, and (c) propagator **1** in CHCl<sub>3</sub>/MeOH 4:10 for 24 h. Demonstrating surface-initiated polymerization,  $c_{\text{SOSIP}}$  is the propagator concentration sufficient for SOSIP (●) but low enough to avoid random polymerization in solution (○), here (a) ~5 mM, (b) ~18 mM and (c) ~3.5 mM.

This systematic study confirmed the validity of two important lessons. Firstly, SOSIP is highly dependent on conditions. Secondly, and most importantly, operational conditions for SOSIP can be deduced with rational arguments. With the present system, SOSIP with the less reactive lipoic acid could be achieved by strengthening the hydrophobic interactions between the bridging alkyl chains in a more polar environment. In an earlier example, the addition of octanol was the key to disrupt destructive interactions between long peripheral alkyl chains attached to the propagators.<sup>[8a]</sup>

Under optimized conditions in CHCl<sub>3</sub>/MeOH 4:10, the dose response curve for SOSIP with propagator **2** was recorded (Fig. 3b). A  $c_{\text{SOSIP}}$  ~18 mM was found, with polymerization taking place almost exclusively on monolayer **3S**. Only little deposition of polymers was also observed on the blank electrode up to 22 mM propagator **2**. Under conditions optimized for SOSIP with propagator **2**, propagator **1** gave also positive results. Consistent with the higher reactivity of asparagusic acid, a  $c_{\text{SOSIP}}$  ~3.5 mM was found for **1** in CHCl<sub>3</sub>/MeOH 4:10 (Fig. 3c) compared to  $c_{\text{SOSIP}}$  ~18 mM for **2** (Fig. 3b, Table 1). Clearly below the  $c_{\text{SOSIP}}$  ~5 mM in CHCl<sub>3</sub>/MeOH 1:1, this result showed that the reactivity of **1** also increases in hydrophilic solvents (Fig. 3a vs 3c). However, the influence of solvent polarity is less

dramatic than for the more hydrophobic, less reactive propagator **2**, which polymerized only in CHCl<sub>3</sub>/MeOH 4:10 and not in CHCl<sub>3</sub>/MeOH 1:1.

Table 1. Conditions tested for surface-initiated polymerization.<sup>[a]</sup>

| Entry | Propagator | Solvent                                | <i>c</i><br>(mM) <sup>[b]</sup> | <i>c</i> <sub>SOSIP</sub><br>(mM) <sup>[d]</sup> |
|-------|------------|----------------------------------------|---------------------------------|--------------------------------------------------|
| 1     | <b>1</b>   | CHCl <sub>3</sub> /MeOH 1:1            | 3 – 9                           | 5 <sup>[e]</sup>                                 |
| 2     | <b>2</b>   | CHCl <sub>3</sub> /MeOH 1:1            | 27, 238, 352                    | -                                                |
| 3     | <b>2</b>   | CHCl <sub>3</sub> /MeOH 1:1, 10% TFE   | 175, 330                        | -                                                |
| 4     | <b>2</b>   | CHCl <sub>3</sub> /octanol 1:1         | 42                              | -                                                |
| 5     | <b>2</b>   | CHCl <sub>3</sub> /MeOH/octanol 10:1:1 | 76                              | -                                                |
| 6     | <b>2</b>   | CHCl <sub>3</sub> /MeOH 1:1, 5% water  | 42                              | -                                                |
| 7     | <b>2</b>   | CHCl <sub>3</sub> /MeOH 1:1, 15% water | 17                              | -                                                |
| 8     | <b>2</b>   | CHCl <sub>3</sub> /MeOH 4:10           |                                 | 18 <sup>[f]</sup>                                |
| 9     | <b>1</b>   | CHCl <sub>3</sub> /MeOH 4:10           |                                 | 3.5 <sup>[e]</sup>                               |

[a] Variable solvent mixture, variable propagator concentration, 100 mM DIPEA, rt, 25 °C, 12 h. [b] Propagator concentration. [c] SOSIP concentration, that is the optimal concentration for polymerization taking place on surface only and not in solution, compare text; - indicates failure to observe SOSIP. [e] Compare Fig. 3a; ordered architectures are obtained, see Figs. 4 and 5. [f] Compare Fig. 3b; disordered architectures are obtained, see Figs. 4 and 5.

The absorption spectrum of photosystem **2P** obtained from lipoic acid showed strong background contributions, increasing with decreasing wavelength (Fig. 4, solid). This background noise was not obtained with photosystem **1P** from asparagusic acid and is commonly absent in SOSIP architectures (Fig. 4, dashed). Most likely originating from scattering, it suggested that SOSIP with lipoic acid, although achievable under optimized conditions, produces less organized architectures.

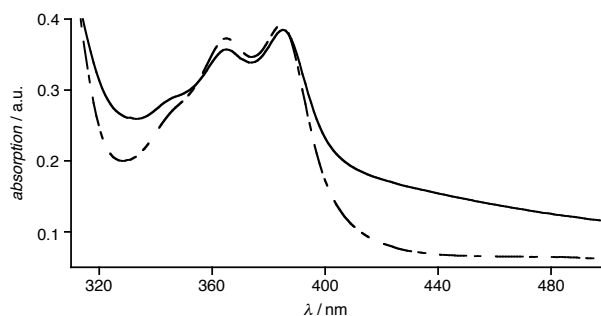


Figure 4. Absorption spectra of SOSIP architectures **1P** obtained by incubation with 4 mM propagator **1** in CHCl<sub>3</sub>/MeOH 4:10 (dashed) and SOSIP architectures **2P** obtained by incubation with 18 mM propagator **2** in CHCl<sub>3</sub>/MeOH 4:10 (solid).

The validity of this conclusion was confirmed by atomic force microscopy (AFM). Height images of photosystem **1P** obtained from asparagusic acid revealed the smooth surface that is characteristic of SOSIP architectures (Fig. 5a). A surface roughness of  $R_a = 2.37$  nm was measured. The phase-contrast images of photosystem **1P** showed the quite remarkable organization of SOSIP architectures, homogenous over long distances with little irregularities and with finestructures resolved down toward the molecular level (Fig. 5c).

The AFM images of photosystem **2P** obtained from lipioic acid were totally different. Height images revealed a highly irregular surface (Fig. 5b). The surface roughness was with  $R_a = 8.84$  nm more than three times that of the positive control **1P**. The phase-contrast images showed a striking loss in finestructure (Fig. 5d). The use of racemic lipioic acid could possibly contribute to these disordered surface architectures. However, results from in-depth studies with propagators from asparagusic acid suggested that operational SOSIP would prevent the polymerization of mismatched stereoisomers by self-sorting and repair eventual errors.<sup>[8]</sup> Considering the reluctance of propagator **2** to polymerize (Table 1, entries 2-8), the disordered systems obtained with lipioic acid were thus most likely the result of

dysfunctional SOSIP rather than stereochemical mismatch. Studies with enantiopure lipoic acid to explore the validity of this interpretation appeared redundant in view of the clear uselessness of racemic lipoic acid for SOSIP.

Taken together, absorption spectra and AFM images demonstrate that surface-initiated disulfide-exchange polymerization with derivatives from lipoic acid does not yield the highly ordered architectures expected from SOSIP. These disordered systems, together with the difficulties to encourage surface-initiated polymerization to occur, demonstrate convincingly that SOSIP, and synthetic methods developed based on this process, i.e., TSS and TSE, work with derivatives from the more reactive asparagusic acid but not with derivatives from the less reactive lipoic acid.

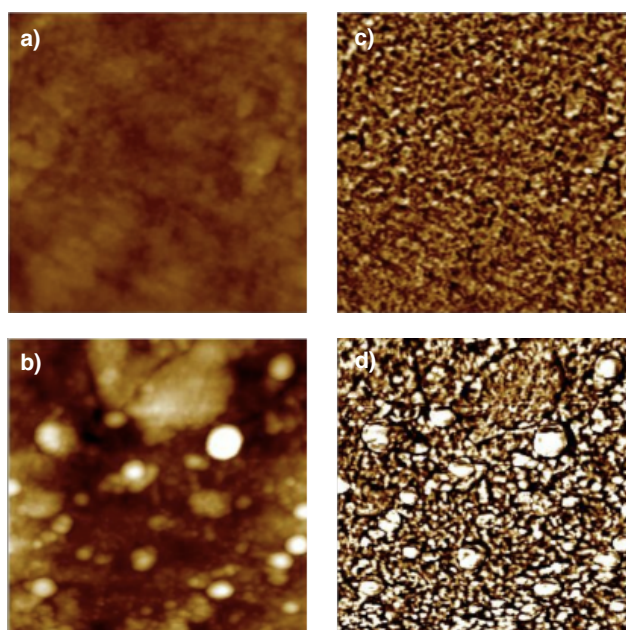


Figure 5. AFM height (a, b) and phase-contrast images (c, d) of SOSIP architectures **1P** obtained with propagator **1** derived from asparagusic acid (a, c) and **2P** obtained with propagator **2** derived from lipoic acid (b, d). Length: 1  $\mu\text{m}$ , height: 0-100 nm, phase: 50°.

In summary, this study nicely illustrates that organic chemistry on surfaces and in solution is not the same. Reactivities often differ much more than one would expect. Many processes that work perfectly well in solution cause problems on surfaces. Attentive analysis of the literature supports this impression. For example, ring-opening olefin metathesis polymerization, one of the most powerful synthetic method in solution, has a surprisingly poor record on surfaces.<sup>[18]</sup> Reminiscent of protein folding in nature, disulfide-exchange polymerization is currently emerging as a powerful process that really works on surfaces to reliably grow multicomponent architectures.<sup>[7-9]</sup> Most propagators used for disulfide-exchange polymerization are derived from either asparagusic or lipoic acid. In a comparative study, we here show that propagators made from asparagusic acid are ideal for surface-initiated polymerization, whereas lipoic acid is not reactive enough. We also show that surface-initiated polymerization with lipoic acid can be enforced in more hydrophilic media. However, the obtained surface architectures compare poorly to the perfect systems obtained with asparagusic acid. Remarkably, these complementary characteristics originate from a very small difference in disulfide torsion angle, i.e., 8°. A disulfide torsion angle of 27° as in asparagusic acid is ideal for disulfide-exchange polymerization on surfaces, whereas the 35° of lipoic acid are needed to achieve the same in solution.<sup>[11]</sup>

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