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Consequences of Folding a Water-Soluble Polymer Around an Organocatalyst**

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Dedicated to Dr. Jef Vekemans on the occasion of his 65th birthday

Nature's ability to perform catalytic reactions in a fast and specific way has been a source of inspiration for chemists who seek to enhance catalytic efficiency. In addition to small-molecule catalysts, several artificial polymeric systems have been developed in recent years based on the current understanding of the action of enzymes.[1] Foldamers,[2] dendrimers,[3] and star polymers[4] are effective macromolecular catalysts in organic solvents, and high enantioselectivities are attained in a number of reactions. The ability of artificial metalloenzymes,[5] DNA-based catalysts,[6] amphiphilic block copolymers,[7] and micellar systems[8] to form hydrophobic domains in water in order to significantly increase the effectiveness of catalysts that are normally not compatible with water has been explored. In these systems, the importance of isolating the site of the catalytically active center is well recognized.

We recently introduced a novel concept that combines classic polymer chemistry and supramolecular chemistry to create polymers that fold 'on demand' into a single-chain polymeric nanoparticle (SCPN) that possesses a structured inner compartment.[9] The benzene-1,3,5-tricarboxamide (BTA) moiety was applied as the structuring unit in these SCPNs. BTAs self-assemble into helical stacks, which are stabilized by threefold intermolecular hydrogen bonding between consecutive discs.[10] The introduction of Ru-based complexes into the SCPNs allowed efficient transfer hydrogenations in water.[11] However, the necessity of the hydrophobic compartment, which is created by the self-assembly of the BTA units, to be conformationally adaptable for efficient catalysis was not proven. Inspired by Class I aldolase enzymes,[12] we explored the consequences of folding a water-soluble polymer around an organocatalytic unit based on L-proline (L-Pro), and discovered the importance of structuring conformationally adaptive elements within an SCPN to achieve efficient organocatalysis in water.

The effectiveness of many organocatalysts is often low in water because of a lack of hydrophobic shielding. For example, while L-Pro catalyzes a wide variety of C–C bond forming reactions, such as conjugated additions and aldol reactions,[13] its efficiency in water is typically poor,[14] and low yields/selectivities are obtained.[15] Herein, we show that hydrophobic, structured compartments, which isolate the L-Pro catalytic site from the bulk medium, are created through folding of the polymer (Figure 1). The compartments provide an appropriate environment for catalysis to occur, and they bring substrates into close proximity to each other, thus increasing the effective molarity.[16] The high local concentration of substrates and catalytic sites in the interior of the nanoparticles results in an unprecedentedly active catalyst, thus allowing us to use low catalyst loadings at low substrate concentrations.

By employing reversible addition–fragmentation chain-transfer (RAFT) polymerizations,[17] we synthesized water-soluble methacrylate random copolymer **P1a**, which contains 5% of L-Pro as catalytic units, 10% of chiral *S*-BTAs as structuring elements, and 85% of oligo(ethylene glycol) (OEG) units to ensure water-compatibility (Figure 1). The self-assembly of BTAs into helical stacks in combination with the hydrophobicity of the polymer backbone ensures the folding of the polymer in water.[11] **P1a** was fully characterized by ^{1}H NMR spectroscopy, size-exclusion chromatography (SEC, see Figures S1 and S4 in the Supporting Information), dynamic light scattering (DLS, Figure S5 and Table S1), and Maldi-TOF mass spectrometry (Figure S6). SEC shows a number-average molecular weight (M_n) of 28.5 kDa and a polydispersity index (PDI) of 1.56 (DMF, PEG standards), while the DLS data show that **P1a** forms SCPNs in water with a hydrodynamic radius of 6.3 nm.

The folding–unfolding behavior of BTA/L-Pro/OEG copolymer **P1a** in water was studied using temperature-dependent ultraviolet (UV) and circular dichroism (CD) spectroscopy. The transition from the unfolded state (high temperatures, no BTA aggregation) to the folded state (low temperature, aggregated BTAs) of polymer **P1a** in water is clearly evidenced in the UV spectrum by a shift of λ_{max} from 204 nm at 80 °C to 196 nm at 0 °C (Figure 2 A). The folding can be probed in more detail by CD spectroscopy, because of the chirality of the BTA moiety. At room temperature, **P1a** shows a negative Cotton effect at 223 nm, indicating helical aggregates with a preferred left-handed (*M*) helical sense,[10a,d]

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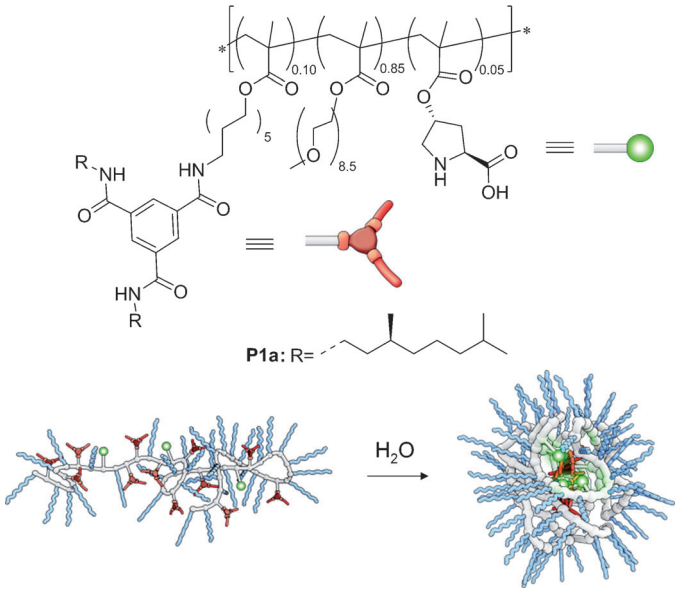


Figure 1. Chemical structure of L-proline-functionalized catalytic polymer **P1 a** (top) and schematic representation of the unfolded polymer and the formation of the compartmentalized catalytic structure in water (bottom).

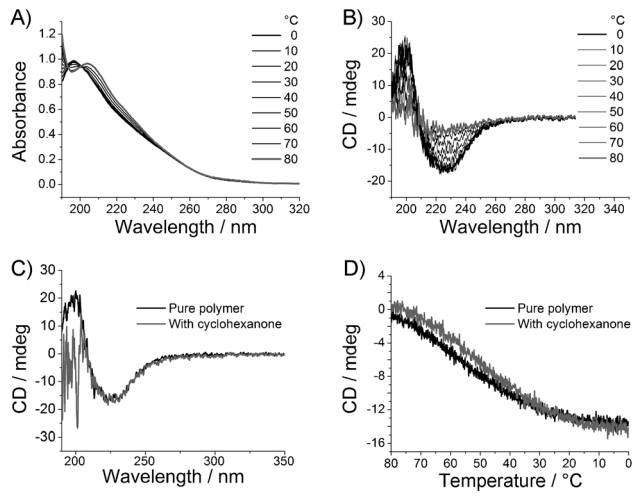
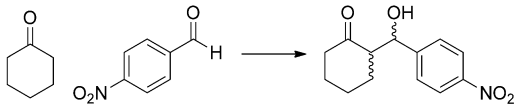


Figure 2. Spectroscopic characterization of polymer **P1 a** in water. A) UV and B) CD spectra at different temperatures; C) CD trace, and D) CD signal versus temperature monitored at $\lambda = 223$ nm, of polymer **P1 a** (black traces) and **P1 a** after addition of cyclohexanone (10 μL, working conditions, grey traces). $c_{BTA} = 50$ μM, optical-path length = 0.5 cm.

and an intensity and shape similar to BTA/OEG-based copolymers that lack the L-proline unit.[11] These observations suggest that L-Pro does not interfere with the stacking of BTA units within the polymer chain. As expected, the intensity of the CD effect varies with temperature. At 80 °C, the CD signal almost disappears, indicating the absence of stacked BTAs (Figure 2 B and D, black trace). Hysteresis was not observed in the folding and unfolding of this polymer (Figure S6). The full reversibility of this folding–unfolding process accounts for the dynamic nature of the hydrogen bonds that stabilize the helical stacks.[10] In addition, we investigated the stability of the folded conformation of **P1 a** in conditions that we apply during catalysis (see below). The addition of an excess of cyclohexanone (10 μL, 17 000 equiv) in water as co-solvent does not interfere with BTA stacking. In addition, the cooling curves before and after the addition cyclohexanone are almost superimposable (Figure 2 C and D, gray traces).

After establishing the polymer folding, we assessed the catalytic activity of **P1 a** in a model aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone (Table 1). Reactions were carried out in water with an aldehyde concentration of 50 mM and a variable amount of cyclohexanone (Table 1, entries 1–3). With an aldehyde/ketone ratio of 1:10, the highest conversion was reached after 24 hours (74 %, Table 1, entry 2); an increase of the aldehyde/ketone ratio to 1:50 resulted in a small decrease in conversion (Table 1, entry 3). The diastereomeric excess (*de*) slightly decreased upon increasing the aldehyde/ketone ratio (Table 1, entries 1 and 2), while the enantiomeric excess (*ee*) remained constant. In all cases, the aldol product was obtained quantitatively after 120 hours with high diastereoselectivity and moderate enantioselectivity (Table 1, entries 4–6). When the loading of the catalyst was decreased by 50 %, the system still exhibited good conversion and selectivity after 120 hours (Table 1, entry 7).

Table 1: Aldol reaction catalyzed by L-proline containing polymer **P1 a**.[a]



Entry	Load.[b] [mol %]	Ratio a/k[c]	*t* [h]	Conv.[d,e] [%]	de_{anti}[e] [%]	ee_{anti}[f] [%]
1	1.6	1:5	24	30	94	70
2	1.6	1:10	24	74	90	71
3	1.6	1:50	24	52	90	n.d.
4	1.6	1:5	120	99	92	73
5	1.6	1:10	120	99	91	72
6	1.6	1:50	120	98	91	70
7	0.8	1:5	120	88	91	74

[a] Reactions were carried out in water (0.5 mL) at room temperature using *p*-nitrobenzaldehyde (1 equiv, 0.025 mmol), cyclohexanone (5, 10 or 50 equiv), and catalytic polymer **P1 a**. [b] Loading of catalytic polymer. [c] Ratio of *p*-nitrobenzaldehyde (a) to cyclohexanone (k). [d] Conversion of aldehyde into aldol product. [e] Determined by ^{1}H NMR spectroscopy. [f] Measured by HPLC on a chiral stationary phase (Chiralpak-IA) in hexane/THF = 75:25, 1 mL min^{-1}.

It is noteworthy that catalysis is efficient in this random copolymer system, which comprises many different microenvironments around the catalytic units. In fact, we expected that differences in the polymer sequence, length or composition, can have a significant effect on the catalytic activity. Thus, we prepared a variety of water-soluble copolymers, **P1 b–e**, **P2**, and **P3**, which contained different numbers of L-proline as catalytic units per chain (see Table 2, and Schemes S3 and S4 in the Supporting Information).

Table 2: Characteristics of the RAFT polymers as determined by SEC, and ^{1}H NMR and CD spectroscopy.

Catalyst	L-Pro [%]	BTA [%]	M_n[a] [kDa]	PDI[a] (−)	M_n[b] [kDa]	BTA[c]	L-Pro[c]	CD[d] [mdeg]
P1a	5	10	28.5	1.56	58.3	12.2	6.1	−15
P1b	5	10	37.1	2.19	135.2	19.2	9.6	−13
P1c	5	10	38.5	2.19	140.9	20	10	−18
P1d	5	10	27.6	1.48	56.5	11.8	5.9	0
P1e	5	10	27.5	1.56	56.5	11.8	5.9	−14
P2	10	10	44.5	1.58	95.1	19.7	19.7	−16
P3	2	10	40.7	1.28	110.0	20	4.2	−21
PC1	2	0	34.9	1.28	95.0	0	4.3	n.a.
PC2	5	0	21.9	1.30	62.6	0	6.9	n.a.

[a] Determined by SEC in DMF with LiBr (10 mM), 1 mL min^{-1}, PEG standards. Measured before cleavage of *t*Boc group. [b] Based on conversion determined by ^{1}H NMR spectroscopy. [c] Average number of units per polymer chain. [d] CD intensity at 223 nm and 20 °C at $c_{BTA} = 50$ μM in H_2O, optical-path length = 0.5 mm. n.a = not applicable. DMF = *N*,*N*-dimethylformamide, PEG = poly(ethylene glycol).

All polymers contained 10% of BTA units to promote the folding into SCPNs. Polymers **P1b** and **P1c** contain the same loading of L-Pro and *S*-BTA per chain (5 and 10%, respectively) as **P1a**, but differ in length and polydispersity. To evaluate the influence of a preferred helicity, **P1d**, which bears achiral BTAs that form equal amounts of *P* and *M* helical aggregates, was synthesized. In addition, the effect of a higher content of apolar domains in the polymer chain was evaluated with polymer **P1e**, which contains an additional amount of hydrophobic propargyl groups (5%). On the other hand, polymers **P2** and **P3**, which contain 10 and 2% of L-Pro, respectively, were used to investigate the effect of the local concentration of catalytic units per polymer chain. As a control, polymers **PC1** and **PC2**, which contain 2 and 5% of L-Pro, respectively, and 10% of *n*-dodecyl chains as a BTA surrogate (Table 2, Scheme S5), were prepared in order to assess the consequence of a dynamically folded compartment for efficient catalysis.

The new series of (L-Pro/BTA/OEG)-based copolymers was fully characterized using ^{1}H NMR spectroscopy, SEC, and DLS (Table 2 and Table S1). It is worth mentioning that the proline methacrylate has a negative influence on the control of the polymerization, and consequently the PDI. DLS showed similar hydrodynamic radii for all the polymers, even under working conditions (Table S1). UV and CD spectroscopy gave spectra similar to that discussed for **P1a**: BTAs are aggregated at room temperature and negative Cotton effects for **P1b**, **P1c**, **P1e**, **P2**, and **P3** indicate a preferred *M*-helicity. Moreover, the intensity of the CD signal at 223 nm (room temperature, $c_{BTA} = 50$ μM in water) is approximately the same for the polymers **P1a–c**, **P1e**, **P2**, and **P3**. The magnitudes of the CD effect correspond well with those of similar BTA/OEG-based copolymers that lack L-proline, even in the case of **P2**, which contains twice as much L-Pro per chain.[11] The CD cooling curves were measured for all these polymers and showed the same type of behavior (Figures S9–S15 in the Supporting Information).

The catalytic activity of all the aforementioned polymers in the model aldol reaction was assessed by comparing the conversions after 24 hours. All reactions were carried out in water at room temperature and with an aldehyde concentration of 50 mM. The overall concentration of L-Pro sites was identical in all cases (Table 3). In general, there are notable differences between polymers that appear rather similar. Polymers **P1b** ($M_{n,GPC} = 37.1$ kDa) and **P1c** ($M_{n,GPC} = 38.5$ kDa) showed significantly higher conversions after 24 hours (Table 3, entries 3–6) compared to **P1a** ($M_{n,GPC} = 28.5$ kDa, Table 3, entries 1 and 2). Interestingly, the catalytic reaction that was performed with these polymers, was not diastereoselective anymore, and the enantioselectivity was significantly reduced. In addition, polymers **P1d** and **P1e**, which have similar molecular weights as **P1a** (**P1d**: $M_{n,GPC} = 27.6$ kDa, **P1e**: $M_{n,GPC} = 27.5$ kDa), showed similar conversions after 24 hours. **P1d** resulted in a moderated diastereoselectivity (67%, Table 3, entries 7 and 8) compared to that obtained with **P1a** (94%, Table 3, entry 1). When **P1e** was employed (Table 3, entries 9–10), a slight increase in diastereoselectivity (72%) was observed compared to **P1d**, whereas the enantioselectivity (67%) remained the same. The results of the catalysis with **P1d**, which bears achiral BTAs, can be rationalized as follows: either the chirality of the pocket does not affect the stability of the transition state of the condensation reaction, or the catalytic sites are too remote from the helical stack to be affected. Because these polymers have a random sequence of monomers in the chain, the proximity of the chiral apolar domains to the catalytic sites is not ensured. Therefore, the effect on the selectivity is almost negligible.

Table 3: Aldol reaction catalyzed by L-proline-containing polymer **P1a**.[a]

Entry	Polymer	Load.[b] [mol%]	Ratio a/k[c]	Conv.[d,e] [%]	de_{anti}[e] [%]	ee_{anti}[f] [%]
1	**P1a**	1.6	1:5	30	94	70
2	**P1a**	1.6	1:10	74	92	71
3[g,i]	**P1a**	1.6	1:5	0	–	–
4	**P1b**	1.0	1:5	87	0	46(0)[h]
5	**P1b**	1.0	1:10	95	33	45(2)[h]
6	**P1c**	1.0	1:5	85	0	25(−29)[h]
7	**P1c**	1.0	1:10	99	0	41(−11)[h]
8	**P1d**	1.6	1:5	41	67	66
9	**P1d**	1.6	1:10	86	67	68
10	**P1e**	1.6	1:5	54	72	67
11	**P1e**	1.6	1:10	81	72	70
12	**P2**	0.5	1:5	96	33	55(6)[h]
13	**P2**	0.5	1:10	99	50	54(2)[h]
14[i]	**P3**	2.4	1:10	96	72	63
15[i]	**PC1**	2.3	1:10	0	–	–
16[i]	**PC2**	1.4	1:10	0	–	–

[a] Reactions were carried out in water (0.5 mL) for 24 h at room temperature, using *p*-nitrobenzaldehyde (1 equiv, 0.025 mmol), cyclohexanone (5 or 10 equiv), and the catalytic polymer. In all the cases, the overall concentration of L-proline in the reaction is the same (10 mol%). [b] Loading of catalytic polymer. [c] Ratio of *p*-nitrobenzaldehyde (a) to cyclohexanone (k). [d] Conversion of aldehyde into aldol product. [e] Determined by ^{1}H NMR spectroscopy. [f] Measured by HPLC on a chiral stationary phase (Chiralpak-IA) in hexane/THF = 75:25, 1 mL min^{-1}, $\lambda = 269$ nm. [g] Reaction conducted in $CHCl_3$ (0.5 mL). [h] The *ee* value measured for the *syn* diasteromer is given in brackets. [i] Conversion measured after 120 h.

The local concentration of catalytic L-Pro units per polymer chain has a significant effect on the activity of the

catalysts. **P2** and **P3** showed an increase and decrease, respectively, in activity compared to **P1a**. In fact, the activity of polymer **P2** is unprecedentedly high for a synthetic polymer under these aqueous conditions.[15e–h] The aldol reactions proceed very efficiently, even at substrate concentrations lower than 5 mM (see below) and loadings of the catalytic polymer as low as 0.05 mol% (Table S3, entries 11–20). The selectivity of polymer **P3** is similar to that of **P1e**, whereas **P2** showed lower diastereo- and enantioselectivity (Table 3, entries 11–13).

Remarkably, only those polymers that contain the structuring element showed catalytic activity. **PC1** and **PC2**, which lack the BTA units, do not show any activity in water, not even after long reaction times, thus signifying that the presence of a structured, conformationally adaptable pocket is a requirement to achieve efficient catalysis. To further evaluate the importance of compartmentalization, we carried out the reaction with polymer **P1a** in chloroform, a solvent in which BTAs do not aggregate (Table 3, entry 3, and Figure S16).[18] At the low substrate concentration applied here, the polymer did not exhibit any catalytic activity, and no conversion was observed, even after long reaction times. This result is consistent with our hypothesis that a high effective molarity is crucial for this system to be active, and this is only achieved in the folded state and in the presence of structured hydrophobic compartments. Furthermore, control experiments that were performed with unsupported L-proline,[19] BTA/OEG-based copolymer that lacks the L-proline unit, and a mixture of unsupported L-proline and BTA/OEG-based copolymer[20] (Table S2) did not yield any aldol product under similar conditions. As in natural enzymatic systems, the catalytic activity of this polymeric system is only expressed in the folded state. However, in contrast to enzymes, this system consists of randomly distributed catalytic sites and structuring units.

In order to show the usefulness of this catalytic system, we also tested its recyclability with polymer **P1e**. For that, the aldol reaction was carried out under the conditions previously described. After 48 hours, the products were filtered off, fresh substrates were added to the aqueous layer, which contained the catalyst, and the reaction was continued for an additional 48 hours. After three consecutive cycles, the conversion was higher than 90% and the diastereo- and enantioselectivities remained unchanged (see Table S5 in the Supporting Information). Degradation of L-proline was not observed in any of the cases.[21] Thus, the catalyst can be easily recovered from the aqueous phase after separation of the aldol products by filtration and reused without additional purification.

We were intrigued by the general mechanism by which these compartmentalized polymers catalyze the aldol reaction, and whether it fits a Michaelis–Menten model. Thus, the kinetic profile of the reaction between cyclohexanone and *p*-nitrobenzaldehyde was measured at different substrate (aldehyde) concentrations in order to assess for enzyme-like behavior. The kinetics experiments were carried out with **P2**, because this polymer showed the highest activity. **P2** showed full conversion at an aldehyde concentration of 5 mM and 0.5 mol% loading of catalytic polymer after 96 h (Table S3, entry 20 in the Supporting Information) Preliminary kinetic experiments were carried out at substrate concentrations ranging from 10 mM to 2 mM to asses for Michaelis–Menten behavior. The system showed saturation at a substrate concentration of around 5 mM. Above this value, the rate of the reaction was constant (Figure S19). The catalytic polymer **P2** showed an apparent Michaelis–Menten constant ($K_{M,app}$) of 5.36 mM and an apparent catalytic constant ($k_{cat,app}$) of 0.053 s^{-1} (see the Supporting Information for experimental details).[22] The efficiency ($K_{cat,app}/K_{M,app}$) of this system is comparable to those of some aldolase mutants[12] and much higher than those of computationally designed systems,[23] although wild-type Class I aldolase enzymes are still superior.[12]

In conclusion, we introduced folded, catalytically active polymers that behave comparable to an enzyme, as their catalytic activity is only expressed in their folded conformation. The necessity for a structured and conformationally adaptive environment around the catalytic center is shown by a large number of reference experiments. Moreover, with the model substrates selected here, recyclability becomes a very simple process. The consequences of the enzyme-like behavior of these catalytically active single-chain polymeric nanoparticles allowed us to obtain an exceedingly active catalyst. Indeed, low catalyst loadings and substrate concentrations can be used to achieve very efficient catalysis. However, the system needs subtle optimization of the folded microstructure around the catalytic site in order to control other features, such as (stereo-)selectivity. With this contribution we are opening the way for a new family of efficient and selective enzyme-like catalysts. The effective shielding of the active site makes these catalysts highly promising for multi-step cascade reactions in water.[24]

Experimental Section

General procedure for aldol reaction in water: Catalytic polymer was dissolved in deionized water (0.5 mL). Aldehyde (1 equiv, 0.025 mmol) and ketone (5 equiv, 0.125 mmol or 10 equiv, 0.25 mmol) were added to the solution and the mixture was stirred at room temperature. Aldol products were extracted with diethyl ether (3 × 1 mL) and dried under air. The crude products were analyzed by ^{1}H NMR spectroscopy ($CDCl_3$) and HPLC on a chiral stationary phase (Chiralpak IA) without further purification.

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