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Biodynamers: Self-Organization-Driven Formation of Doubly Dynamic Proteoids

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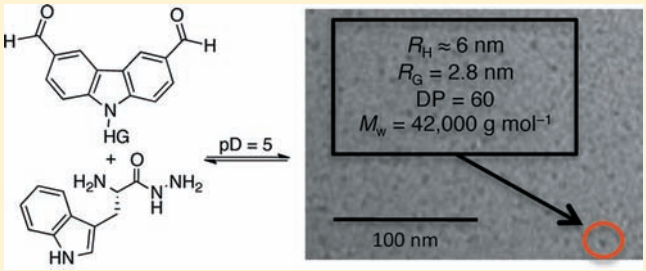
Supporting Information

ABSTRACT: Polypeptide-type dynamic biopolymers (biodynamers) have been generated by polycondensation via acylhydrazone and imine formation of amino-acid-derived components that polymerize driven by self-organization. They have been characterized as globular particles, reminiscent of folded proteins, by cryo-TEM, LS, DOSY NMR, and SANS studies. The reversible polymers obtained show remarkably low dispersity and feature double covalent dynamics allowing for fine-tuning of both exchange and incorporation processes through pH control. In the course of build-up, they perform a selection of the most suitable building block, as indicated by the preferential incorporation of the more hydrophobic amino-acid component with increased rate and higher molecular weight of the polymer formed. The system described displays nucleation-elongation behavior driven by hydrophobic effects and represents a model for the operation of adaptation processes in the evolution of complex matter.



INTRODUCTION

Dynamers, dynamic polymers, result from the application of constitutionally dynamic chemistry (CDC)[1] to polymer science.[2] They are characterized by the linkage of monomers by reversible connections, be they of supramolecular/non-covalent[1,2] or molecular/covalent[1−3] nature. If components of a biological type are used, dynamic analogues of natural macromolecules, or biodynamers, are generated that combine the benefits of constitutional dynamics with those of biologically significant residues.[4] As a result of their inherently dynamic nature, dynamers can undergo changes in their length, sequence, and constitution by monomer incorporation and exchange in response to external stimuli such as temperature or pH. The resulting materials may display novel properties and have great potential as stimulus-responsive or "smart" materials.[5] Given such promising perspectives, the development of dynamic analogues of the different biological macromolecules is highly desirable, as recently exemplified for dynamic analogues of polysaccharides[4a−c] and of nucleic acids.[4d]

Mimicking proteins is of particular interest given the prospect such systems should offer in terms of using the primary sequence to encode a well-defined three-dimensional structure. In addition to allowing for control of the structure of the biodynamers obtained, examination of such behavior deserves closer scrutiny in the light of postulates stating that protein folding has driven primary sequence development.[6] Investigating how supramolecular and medium effects, especially hydrophobic effects as in protein folding, can be exploited as driving force will be of fundamental importance, given that all reactions are to be carried out in an aqueous environment. Such factors also direct the formation of complex supramolecular assemblies of great interest in materials and biological sciences, in particular as biomaterials.[7−10]

Along these lines, we report here the design and synthesis of dynamic proteoidic polymers, their characterization by several physical methods as well as some of their mechanistic and dynamic features.[11]

RESULTS AND DISCUSSION

Design of Dynamic Proteoids. The formation of imine-type bonds[1−4] has been widely implemented in CDC as a reversible condensation reaction and is of broad applicability both in the fields of dynamers and biodynamers.[1−4] Depending on the type of amino and carbonyl groups used, the resulting dynamers have different stabilities and are formed more or less readily because of the different reactivities of different imine-type bonds, e.g., those of true imines and those of acylhydrazones.[12] Dynamic polymers generated from two different types of imine bonds offer particularly interesting prospects. Such polymers may be described as presenting double covalent dynamics in view of the occurrence of two different condensation reactions (constitutional dynamics); in

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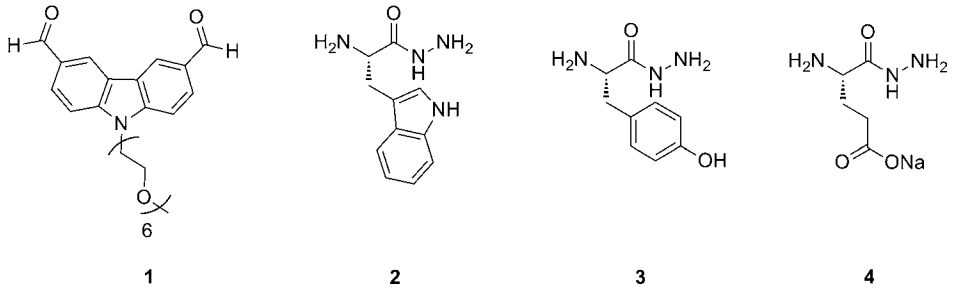

Figure 1. Structures of the dialdehyde **1** and of the amino-acid hydrazides **2**–**4** used in this study.

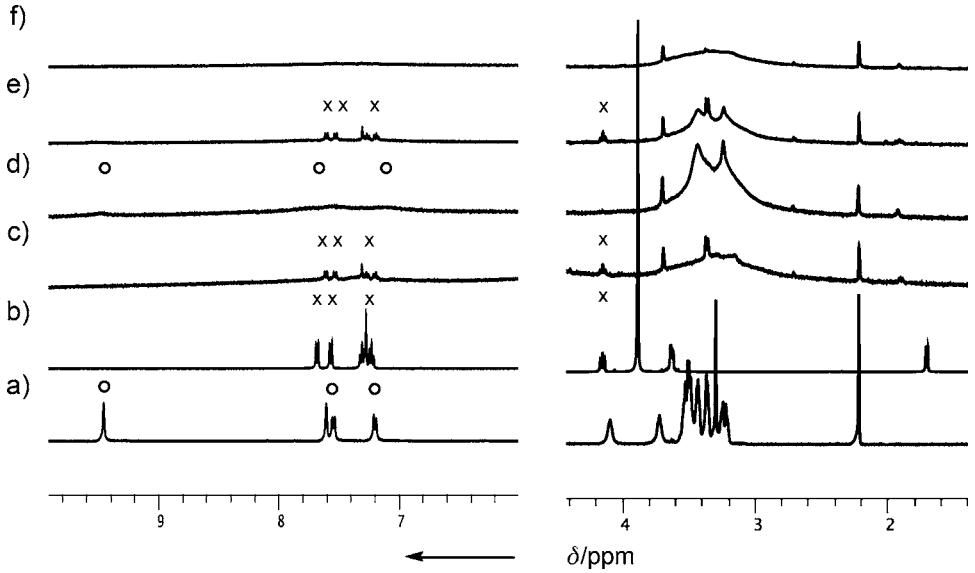

Figure 2. Polymerization under conditions of imbalanced stoichiometry (cf. Scheme 5SI). Parts of the ^{1}H NMR spectrum in D_2O (0.1 M d_3-acetate buffer, pD 5, 400 MHz, 298 K) of a solution of (a) dialdehyde **1**, (b) monomer **2**, (c) solution of **2** (2 equiv., 10.0 mm) and **1** (1 equiv., 5.0 mM) at pD 5 after 21 h, (d) solution of **2** (2 equiv., 6.7 mM) and **1** (3 equiv., 10.0 mM) after 4 h, (e and f) solutions of **2** and **1** (3 equiv. each, 7.5 mM) at pD 5 at different time points: (e) after 10 min, (f) after 52 h. Selected signals arising from **1** and **2** are marked with circles and crosses, respectively.

addition, they display a third dynamic behavior through structure-formation processes (conformational dynamics).[13] The condensation of water-soluble dialdehydes and amino-acid derivatives featuring two types of amino functional groups, namely amines and hydrazides (derived from the carboxylic acid function), leads to a doubly dynamic proteoidic system, based on two reversible reactions that might be amenable to stepwise build-up or be fine-tuned (e.g., by adjusting the pH) to control the stability of the biodynamers. Imine bonds display low formation efficiency in an aqueous environment, but by carefully designing the monomers this feature can be exploited in polymerization reactions because of the high reversibility it confers on the resulting polymeric materials compared to the regular poly(acylhydrazones) themselves.

The hydrophobic effect is a major driving force for protein folding. In order to explore this behavior and to obtain biodynamers that would display main-chain dynamics and be susceptible of nucleation- elongation (N-E) behavior, we chose as monomers, on the one hand the well-characterized, amphiphilic dialdehyde **1**,[3a,14] consisting of a hydrophobic tricyclic aromatic core and a hydrophilic hexaglyme chain, and on the other hand, the hydrazides of two amino acids bearing aromatic side chains, namely tryptophan hydrazide (**2**) and tyrosine hydrazide (**3**) (Figure 1). Glutamic acid monohydrazide (**4**) was included in this study to evaluate the possible importance of solubility issues (Figure 1 and Scheme S1). Dynamers incorporating the dialdehyde **1** have been used to investigate the interplay between primary and secondary structure of amphiphilic dynamers and are known to fold in a hydrophobically driven manner with component selection.[3a,14] The aromatic amino-acid derivatives were chosen to study the effect of their different hydrophobicities and sizes on their complementarity with the hydrophobic core of the dialdehyde. In maximizing the hydrophobic effect, the resulting biodynamers would be expected to adopt a well-defined structure in which the aromatic moieties benefit from hydrophobic $\pi-\pi$ stacking interactions within the folded structure, while the hydrophilic hexaglyme chains are solvent-exposed and extend into the aqueous environment.

Generation of Dynamic Proteoids: Synthesis and Mechanism. In order to verify that the present bifunctional monomers **2**–**4** were amenable to the generation of doubly dynamic polymers, the difference in reactivity of the amine and acylhydrazide functional groups was first investigated. Reacting an aromatic monoaldehyde with either an aliphatic monoamine or with representative amino-acid monohydrazides, clearly demonstrated that careful control of the pH of the aqueous reaction medium leads to highly selective reactivity of one of the two amine functional groups. At pD 5, acylhydrazone formation proceeded readily and went to completion whereas the amine did not afford the corresponding imine. At pD 10, acylhydrazone formation still proceeded and partial imine

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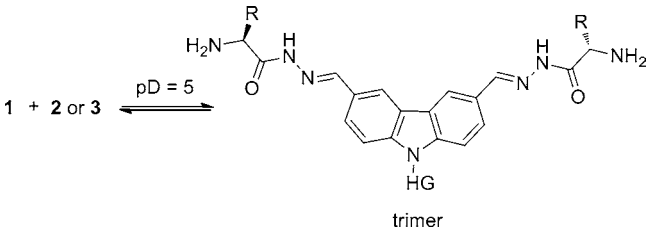
formation took place, although the latter did not go to completion (see Figures S1−S3 and Schemes S2−S4).

With this information in hand, we envisaged testing whether our building blocks would lend themselves to a stepwise build-up of the polymer chain. Reacting one equivalent of the dialdehyde **1** with two equivalents of the hydrophobic amino-acid hydrazides **2** or **3** at pD 5 afforded a polymeric material **5** that resisted the incorporation of excess monomer components (Figures 2 and S4 and Schemes S5 and S6). The expected bis-acylhydrazone "trimer" was not observed, despite the fact that imine formation was found not to go to completion in the model systems under the same conditions (Scheme 1). This

Scheme 1. Envisaged Buildup of the Trimeric Species Using One Equivalent of Dialdehyde 1 and Two Equivalents of Monomers 2 or 3 (5.0 and 10.0 mM, Respectively in d_3-Acetate Buffer at pD 5)

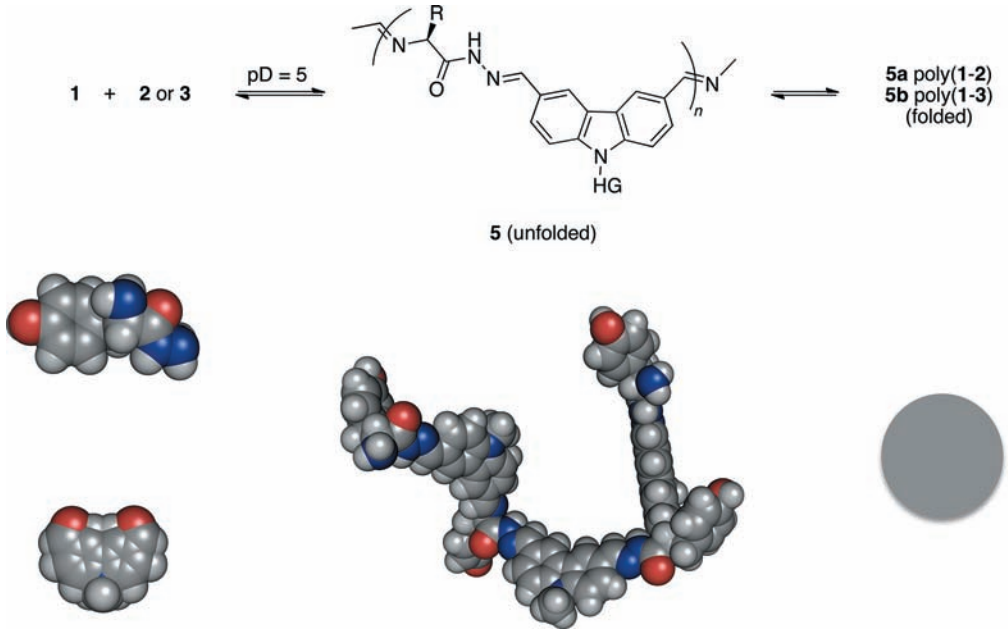


behavior may be taken to indicate that stabilization by folding of the chain constitutes the driving force, leading to complete consumption of the dialdehyde **1** and is consistent with previous studies, in which folding was shown to enhance the stabilities of dynamers through favorable hydrophobic and $\pi-\pi$ -stacking effects, leading to the observed N-E behavior.[3a,g,14,15] Addition of a monomer to the end of an existing chain is energetically more favorable than the creation of a new dimer because of the resulting favorable interactions between the newly introduced building block and the units of the chain. In the polymers studied, this behavior was best exemplified in conditions of imbalanced stoichiometry,[15b] which did not afford the expected distribution of oligomers arising from entropic control, but rather true polymers. Thus, the structural organization of the folded polymer chain drives imine formation to completion.

Remarkably, two equivalents of the hydrophilic amino-acid hydrazide monomer **4** and one equivalent of dialdehyde **1** afforded a mixture of oligomers and monomers, whereas addition of another two equivalents of dialdehyde **1** led again to N-E behavior (Figure S5 and Scheme S7). Thus, the nature of the amino-acid side chain has a direct influence on the mechanism of polymerization, presumably due to different degrees of stabilization depending on the supramolecular interactions involved.

Encouraged by the formation of polymers even in conditions of imbalanced stoichiometry, the preparation of the bio-dynamers poly(**1**−**2**), **5a**, and poly(**1**−**3**), **5b** (Scheme 2), was undertaken by polycondensation of a dilute solution of dialdehyde **1** and amino-acid hydrazides **2** or **3** in d_3-acetate buffer under mildly acidic conditions (5 mM, pD 5, see Figures 2 and S4 and Schemes S8−S9). The polymer is arbitrarily depicted to be ordered with a particular sequence. The imine and acylhydrazone bonds could equally well be linked the other way around. In addition, a given polymer chain might also feature mixed sequences. The polymerization reaction, monitored by ^{1}H-NMR spectroscopy, was very fast and went to completion. The extreme line broadening observed is characteristic of polymeric materials and appeared more rapidly

Scheme 2. Generation of the Globular Biodynamers of Type 5 Used in This Study[a]



[a]The reversible polycondensation of the monomers **1** and **2** or **3** affords a dynamic copolymer, which adopts a folded structure minimizing the contact of the hydrophobic surface area with water, whilst the hydrophilic hexaglyme chains may extend into the aqueous environment. HG = $(CH_2CH_2O)_6CH_3$. The polymer is arbitrarily depicted to be ordered with a particular sequence. The imine and acylhydrazone bonds could equally well be linked the other way around. In addition, a given polymer chain might also feature mixed sequences. The monomers **1** and **3** and an unfolded heptamer are shown as spacefilling models (HG groups omitted for clarity).

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Table 1. Physicochemical Characterization of the Globular Polymers Poly(1−2) and Poly(1−3) as Determined by SANS, cryo-TEM, DLS, and DOSY Experiments[a]

sample	M_w [g mol^{-1}]	R_g [nm][b]	R_h [nm][c]	R_h [nm][d]	R_h [nm][e]	DP
poly(**1**−**2**)	42 000	2.8 ± 0.3	5.0 ± 0.5	6.4 ± 0.6	6.0 ± 0.5	60
poly(**1**−**3**)	16 000	3.1 ± 0.3	5.0 ± 0.5	6.8 ± 0.7	5.0 ± 0.5	23

[a] M_w = weight-averaged molecular weight; R_g = radius of gyration; R_h = hydrodynamic radius; DP = degree of polymerization. [b] Obtained from SANS experiments. [c] Obtained from DOSY-NMR experiments. [d] Obtained from cryo-TEM experiments. [e] Obtained from DLS measurements.

in the formation of poly(**1**−**2**) than poly(**1**−**3**), possibly indicating that the former, the more hydrophobic, had a stronger driving force for polymerization (Figure S6 and S7). Further characterization by several methods including mass spectrometry (cf. Supporting Information), dynamic light scattering (DLS), small-angle neutron scattering (SANS), diffusion-ordered spectroscopy (DOSY) NMR,[16] and cryo-transmission-electron microscopy (cryo-TEM) confirmed this initial observation and provided additional information on the shape and size of the polymers obtained.

Structural Characterization of the Dynamic Proteoids. In contrast to previous studies using the same dialdehyde **1** that gave rise to rod-like nanostructures in solution,[3a,14] the current system yielded globular, spherical objects, very much reminiscent of folded protein assemblies. Their physicochemical and structural features are summarized in Table 1. The globular nature of the objects obtained is also in line with observations on classical, protein-like copolymers known to afford spherical objects, if both hydrophobic and hydrophilic monomers are used.[17] Fitting the data obtained from SANS and DLS experiments provided information on the structure, shape and dimensions of the globules.

Figure 3 displays the scattering pattern obtained for poly(**1**−**2**) and poly(**1**−**3**) using SANS. Each scattering profile exhibits:

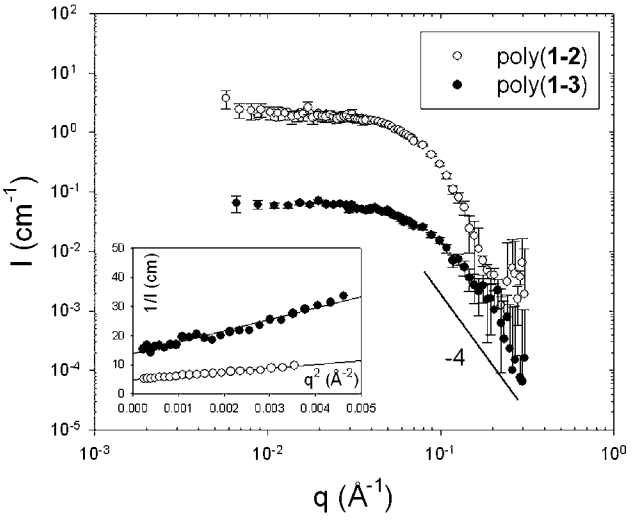

Figure 3. SANS scattered intensity as a function of q for biodynamers poly(**1**−**2**) and poly(**1**−**3**) at pD 5 and with a monomer concentration of 5.0 mM. For clarity, the spectra have been shifted by one log unit along the y-axis with respect to each other. The linear correlation between $1/I(q)$ and q^2 in the intermediate q range is represented in the inset.

(i) a well-defined Guinier regime associated with the mass and size of the scattered objects at low q; and (ii) a regime at high q in which the q dependence of the scattered intensity can be described by a power law with an exponent close to −4 and characteristic of dense objects with a sharp interface.[18] This sequence is the signature of dense nano-objects. The data at low q can be fitted by the following Guinier expression, giving the radius of gyration, R_g, of the dynamic proteoids

$$\frac{1}{I(q)} = \frac{1}{I(0)}\left(1 + \frac{q^2 R_g{}^2}{3}\right) \quad (1)$$

From the best linear fits (see inset of Figure 3) to the data, one obtains for poly(**1**−**2**) and poly(**1**−**3**) R_g = 2.8 and 3.1 nm, respectively. Neglecting the excluded volume interactions, the extrapolation to zero-q of the scattered intensity, $I(q^2 = 0)$, provides a direct measure of the weight-average molecular weight of the polymers, M_w

$$M_w = \frac{I(q^2 = 0)N_A}{(\Delta\rho)^2 \phi v} \quad (2)$$

where $(\Delta\rho)^2$ is the contrast per unit volume between the polymer and the solvent, which was determined from the known chemical composition, N_A is the Avogadro number, ϕ is the volume fraction of monomers, and v is the specific volume of monomers (cf. Supporting Information).

The polymeric particles have a radius of gyration of ca. 3 nm and molecular weights of 42 000 and 16 000 g mol^{-1}, corresponding to 60 and 23 monomeric units for poly(**1**−**2**) and poly(**1**−**3**), respectively. The difference in molecular weight is in line with the difference in rates of polymerization (see above) and may be attributed to the difference in hydrophobicity. The more hydrophobic amino-acid hydrazide **2** (cLogP = −0.50) leads to longer, more tightly packed polymer chains benefiting from larger contact areas and stronger hydrophobic effects than the somewhat less hydrophobic monomer **3** (cLogP = −1.16).[19] Such factors were found to operate in the selection process displayed by dynamers incorporating dialdehyde **1**.[3a,14]

The time autocorrelation function of the scattered field, $g^{(1)}(q,t)$, is monomodal as shown by the examples given in Figure 4 and can be described by a simple exponential relaxation.

The angular dependence shows that this relaxation is diffusive with a characteristic time inversely proportioned to q^2. In the case of a diffusive process, $g^{(1)}(q,t)$ is given by

$$g^{(1)}(q, t) = \exp(-Dq^2 t) \quad (3)$$

where D is the diffusion coefficient. The hydrodynamic radius, R_h, of the diffusive particles in dilute solutions is given by

$$R_h = \frac{kT}{6\pi\eta_s D} \quad (4)$$

where η_s is the viscosity of the solvent and k the Boltzmann constant. One obtains for poly(**1**−**2**) and poly(**1**−**3**), R_h = 6.0 and 5.0 nm, respectively (see Table 1). The normalized

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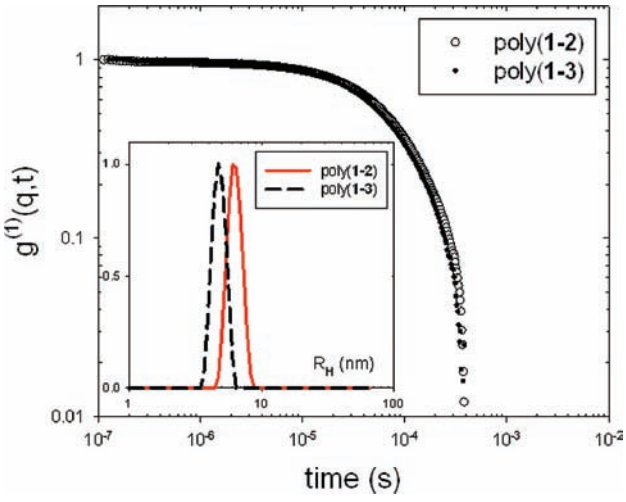

Figure 4. Scattered electric field autocorrelation function, $g^{(1)}(q,t)$, at θ = 90°, for 5.0 mM poly(**1**−**2**) and poly(**1**−**3**) solutions at pD 5. The normalized distribution of the scattered intensity as a function of the size, obtained with the Contin method, is shown in the inset.

distribution of the scattered intensity as a function of the size, obtained using the Contin procedure and presented in the inset of Figure 4, is very narrow, showing that the particles exhibit a low dispersity.[20] The polydispersity index (PDI), k_2/k_1^2, was obtained using the classical cumulant analysis,[21] where k_1 and k_2 represent the first and the second cumulant, respectively (see eq 7 in the Supporting Information). For poly(**1**−**2**) and poly(**1**−**3**) we found a PDI of ∼0.03, a value characteristic of systems with a very low dispersity and usually obtained for proteins.[18] Also, important indications on the topology of the biodynamers (structure and degree of compactness) can be provided by the ratio R_g/R_h. Neglecting virial effects, the value of the ratio R_g/R_h is lower than 1 (∼0.6 that can be calculated from SANS, DLS, cryoTEM, and DOSY data) and close to 0.775, a value calculated for homogeneous hard spheres and thus showing the formation of dense, globular structures (as already shown by the q^{-4} dependence of the SANS scattered intensity observed in the high q range). In addition, DLS experiments show no time evolution of the systems. Thus, biodynamers poly(**1**−**2**) and poly(**1**−**3**) are well dispersed and stable in solution and show no tendency to aggregate with time. The concentration and temperature dependence as well as the influence of the solvent were studied by DLS (Figures S8−S10).

The DLS data showed the biodynamers to feature remarkably low dispersity. Thus, designing dynamers to polymerize with a N-E mechanism overcomes the main challenge faced by reversible polymers, namely high dispersity. In other words, the structural organization of the polymers ensures low dispersity of the population. This feature also has implications for the generation of tailored nanostructures for (bio)nanotechnology.

Imaging by cryo-TEM provided a direct visualization of the spherical particles (Figure 5). The small size in combination with the substantial molecular weights of the polymers are related to very tightly packed globules that have maximized favorable hydrophobic effects in the process of N-E polymerization along with concomitant maximization of hydrophilic interactions of the hexaglyme tails. The fact that the aromatic region of the NMR spectra is extremely broadened gives further evidence for this well-packed, rigid structure.

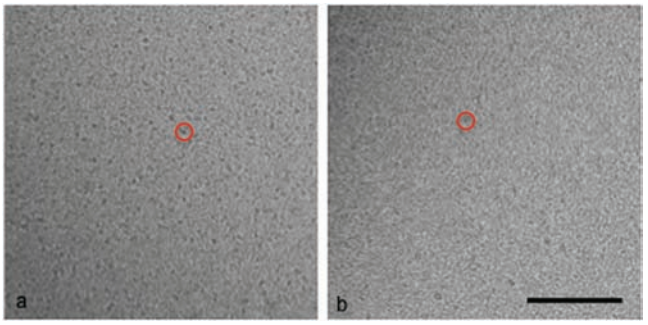

Figure 5. Cryo-TEM images demonstrating the globular morphology of (a) poly(**1**−**2**) and (b) poly(**1**−**3**) prepared by mixing the corresponding monomers (5.0 mM each in d_3-acetate buffer) and allowing reaction at pD 5 for two weeks. Exemplary globules are circled. No stain was used and image acquisition was achieved at a 2 μm defocus. Scale bar = 100 nm.

DOSY-NMR experiments confirmed the size of the globular particles and provided further evidence for the low dispersity of the biodynamers (Figures 6 and S11). Poly(**1**−**2**) displays a diffusion coefficient of 40 μm^2 s^{-1} that corresponds to R_h = 5.0−5.5 nm, using the Stokes−Einstein equation. Moreover, a difference in mobility is observed for the polymer: The aromatic moieties are very rigid and give very broad signals by ^{1}H NMR. Consequently, the signal-to-noise ratio of this spectral region is very low and the calculation of the DOSY spectrum was only done on the aliphatic region of the spectrum.

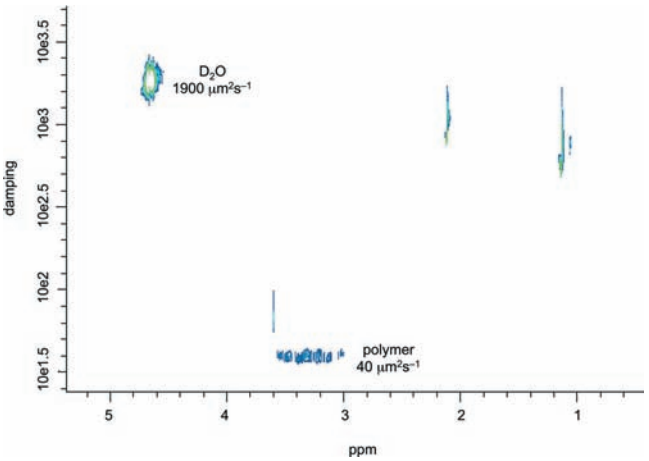

Figure 6. DOSY-NMR spectrum of poly(**1**−**2**) (5.0 mM each in d_3-acetate buffer).

Dynamic and Selectivity Features. The dynamic character of the biodynamers was demonstrated by adding an equimolar amount of the amino-acid hydrazide **2** to the polymer poly(**1**−**3**) and monitoring its incorporation into the polymeric chain by ^{1}H-NMR spectroscopy in acidic conditions (Figure 7). While the aromatic region remained rather broad, the signal of the α-carbon atom was clearly visible, enabling its assignment and integration. Monomer **2** was preferentially substituted for monomer **3**, leading to a 1:3 distribution of both monomers in solution.

This preferential incorporation of monomer **2** in the polymeric chain is presumably due to the more hydrophobic character and the better size match between the carbazole

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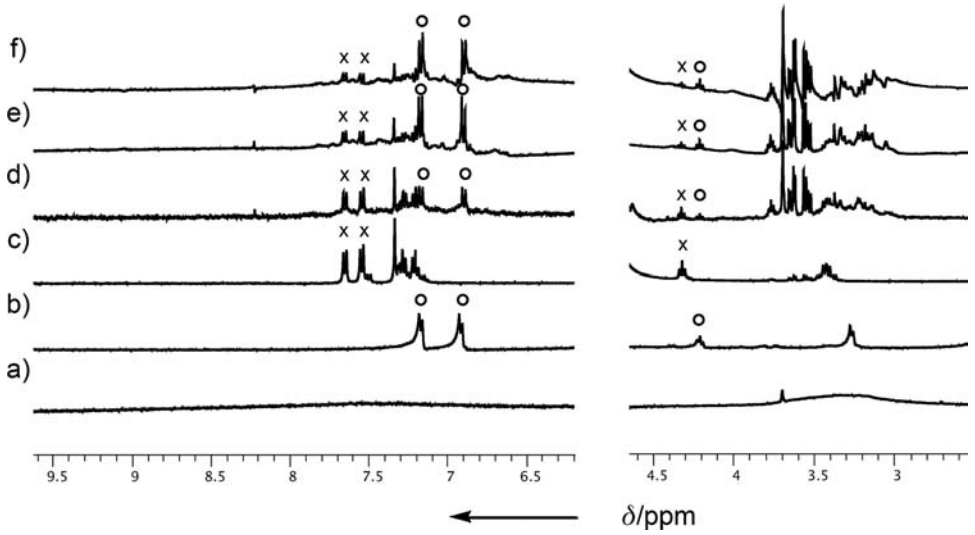

Figure 7. Polymer exchange of the polymer poly(**1**−**3**) after addition of monomer **2** (1 equiv., 5.0 mM). (a) Polymer poly(**1**−**3**); (b) monomer **3**; (c) monomer **2**; (d−f) solution of poly(**1**−**3**) and monomer **2** (5.0 mM) after adjustment to pD 2 at 25 °C after different times: (d) 1h15; (e) 2h30; and (f) 24 h. Selected signals arising from **2** and **3** are marked with crosses and circles, respectively.

moiety of dialdehyde **1** and the indole side chain of monomer **2**. This structural preference was corroborated by the finding that addition of an equimolar amount of **3** to polymer (**1**-**2**) led to nearly no extrusion of monomer **2** (less than 10%) (Figure S12). The preferential incorporation of **2** over **3** in the dynaproteoid chain is in line with the relative rates of formation and molecular weights mentioned above, as well as with the selection of the component featuring the largest hydrophobic core observed for dynamers derived from **1**.[3a,14] The fact that no monomer exchange was observed in neutral conditions indicates that the biodynamers can be considered constitutionally static under these conditions. This behavior enables the control of both polymerization and exchange processes by adjusting the pH value.

■ CONCLUSIONS

We have described herein the first proteoidic biodynamers, displaying polymerization driven by the self-organization/folding of the polymeric material formed, highly reminiscent of the hydrophobic effect acting as a driving force for protein folding. They may be considered as hybrid dynamic materials, combining components of nonbiological and biological types, thus also offering a wide palette of structural and functional diversity. The observed N-E behavior affords proteoidic polymers that feature remarkably low dispersity and double covalent dynamics through the use of two different types of imine bonds, allowing for the fine-tuning of both assembly and disassembly/exchange reactions. Selection of the most suitable building block from a pool of monomers as well as optimization of the properties of the biodynamers can be envisaged. Their selection/self-sorting and reversibility behavior also confers in principle variability in structural ordering, a feature of interest in view of the possibility that well-ordered structures might not be required for the function of proteins.[22] Such dynamic biomaterials should lend themselves to numerous applications in both biology and medicine. Furthermore, in line with previously reported results for dynamers derived from component **1**,[3a,14] as well as for the self-organization of supramolecular, doubly dynamic hydrogels,[1,23] we would like to stress the role played, in the generation of the present dynamic proteoids, by structure-forming N-E processes, driven by physicochemical medium/environmental factors (such as hydrophobic effects here), with selection of the components leading to the best organized, thermodynamically favored entity. Such behavior is also of significance for the (prebiotic) chemical evolution toward increasingly organized, complex molecular matter.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H NMR spectra of the test, polymerization, and exchange reactions; polymerization reaction profiles, investigation of the temperature, concentration and solvent dependence of the polymerization reaction, the DOSY-NMR spectrum of poly(**1**−**3**) and the reaction schemes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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