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Dynablocks: Structural Modulation of Responsive Combinatorial Self-Assemblies at Mesoscale

Rémi Nguyen,[†] Eric Buhler,[‡] and Nicolas Giuseppone*[,†]

[†]SAMS Research Group, icFRC, Université de Strasbourg (UdS), and Institut Charles Sadron (ICS) CNRS-UPR 22, 23 rue du Loess BP 84047, 67034 Strasbourg Cedex 2, France, and [‡]Matière et Systèmes Complexes (MSC) Laboratory, Université Paris Diderot−Paris VII, UMR 7057, Bâtiment Condorcet, 75205 Paris Cedex 13, France

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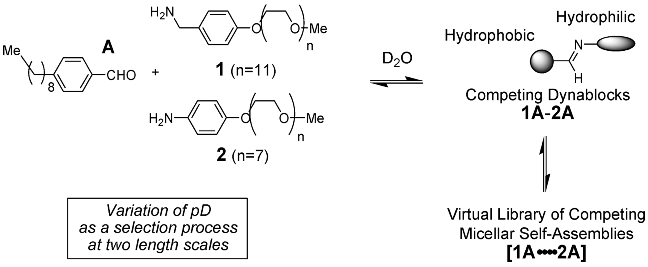
Dynamic combinatorial chemistry (DCC) rests on the construction of libraries of discrete constituents which are produced by reversible (supra)molecular associations among sets of building blocks.[1] The thermodynamic control of the products distribution confers to dynamic combinatorial libraries (DCLs) receptiveness to a number of internal or external parameters that modify their constitution/energy landscapes. These triggering parameters are divided between (i) the template-type processes and (ii) the other chemical or physical stimuli which are able to drive the reorganization within the DCLs. In the first group (i), three main categories could be defined as the casting, molding,[2] and duplicating modes, which respectively screen for hosts,[3] guests,[4,5] and replicators.[6,7] In the second group (ii), pH,[8] metal ions concentration,[9] temperature,[10] and electric fields[11] are some demonstrated examples of possible intensive parameters which are able to modulate the expression of the competing constituents. These triggers are particularly attractive to modify the structures and functions of (macro)molecular objects in order to access a new class of responsive materials.[12] To date, DCC has been mainly limited to relatively small (supra)molecules and dynamers;[9,10,13] its implementation toward the design of large self-assemblies, capable of producing nanostructures at mesoscale,[14] was very scarcely discussed.[15,16] However, such an approach would lead to the development of a new class responsive nanosystems.

Recently, we introduced the concept of amphiphilic dynamic block copolymers (dynablocks) in which hydrophobic and hydrophilic blocks can reversibly combine with a high kinetic lability.[16] We have highlighted that when several dynablocks compete between a set of constituents, the differential stabilities of the supramolecular structures at mesoscale confer to these systems the propensity to induce in turn recombination processes at the molecular level. Here we extend the chemistry of dynablocks by showing the possibility to reversibly trigger the shapes and sizes of micellar nano-objects by an external effector. Indeed, we show the possibility to tune the associations of dynablocks at the molecular level by using pH modulations, which results in structuring variations at mesoscale.

With such an aim in view, we used a set of building blocks that are (i) hydrophobic aromatic aldehyde **A**; (ii) benzylamine derivative **1** (pK_a = 9.5), having a hydrophilic PEG chain of 11 units; and (iii) aniline derivative **2** (pK_a = 4.5), having a shorter PEG chain length of 7 units (Scheme 1). The individual condensations of these blocks lead to amphiphilic imines **1A** and **2A** which then respectively self-assemble in water to produce micelles. We then quantified by ^{1}H NMR spectroscopy the selection operating, upon pD modulation,[8] on the imine formation when **A**, **1**, and **2** were mixed with a 1:2:1 ratio in deuterated water and with $[\mathbf{A}]_i$ = 50 mM (black and white data in Figure 1).

Scheme 1. Set of Constituents Reversibly Competing at the Molecular Level for the Reversible Covalent Condensation of Imine Dynablocks 1A−2A and Produced from Hydrophobic Aldehyde A, Benzylic Hydrophilic Amine 1, and Hydrophilic Aniline 2[a]



[a] The length ratio between the amphiphilic blocks of each dynablock in water, as well as the **1A/2A** concentration ratio, mainly determines the subsequent structuring of the large micellar self-assemblies at the supramolecular level. At this scale, the system can be described as a virtual library of nano-objects continuously capable of reorganization—in space and time—within the bounded group of composition [**1A**····**2A**].

The behavior revealed by the concentration plot as a function of pD is in agreement with the expected evolution of the system as determined by the pK_a values of **1** and **2**. With pD values higher than pK_a**2** and lower than pK_a**1** ([4.5−9.5]), the formation of **2A** is favored because **1**H$^+$ is trapped by protonation.

Above a pD value of 9.5, **1** becomes more nucleophilic than **2** and dominates the competition. It is also observed that, in the pD range of 6.3−12, the system always keeps a high degree of condensation with only a minor amount of free aldehyde. Moreover, the system displays full reversibility as it was proved by making three cycles between the two pD extrema. This global variation of the selection process at the molecular level over six pD units was more than sufficient to lead dramatic changes of the mixed supramolecular structures [**1A**····**2A**] at mesoscale. This was demonstrated by the quantitative determinations in sizes and shapes of the micellar self-assemblies using small-angle neutron scattering (SANS) experiments (see Figure 2). SANS indeed represents an appealing method of major benefit for the study of the present self-assemblies in solution because it provides all the structural information at different length scales.[17]

In the available range of scattered wave-vector, q, the scattered intensity is proportional to the form factor, $P(q)$, of the assemblies (see Supporting Information). Each scattering curve exhibits the same overall behavior, characterized by the following sequence: (i) a Guinier regime in the low-q range, associated with the finite size of the supramolecular self-assemblies; (ii) one intermediate regime, in which the q-dependence of the scattered intensity can be described by a power law with an exponent close to -1; (iii) another Guinier regime at higher q, corresponding to the cross section of the assemblies; and (iv) a last q^{-1}-regime in the high-q range. The data obtained at low-q can be fitted by a Guinier expression giving

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*Corresponding author. E-mail: giuseppone@unistra.fr. Telephone: +33(0)3 88 41 41 66. Fax: +33(0)3 88 41 40.

the radius of gyration, R_G: $1/I(q) = 1/I(0) \times (1 + q^2R_G^2/3)$; a typical plot of $1/I(q)$ vs q^2 is given in the Supporting Information. Neglecting the virial effects and the contribution of the free hydrophilic blocks,[18] the extrapolation to zero-q of the scattered intensity, $I(0)$, provides a measurement of the weight-average molecular weight of the assemblies, M_w (Table 1).

In the intermediate q^{-1}-regime, which is much more extended at pD = 12, the scattering curves can be fitted satisfactorily by a rigid rod model: $I(q) \sim P(q) = \pi/qL$, where L is the length of the rod. The second Guinier regime at higher q can be fitted by a Guinier expression for the form factor of the cross section:[17] $V_{chain}P(q) = \pi S/q \exp(-q^2r_c^2/2)$, where r_c is the radius of gyration of the cross section. By fitting the two above equations to the experimental data (see Figure S1), we were able to determine the mass per unit length of the rodlike supramolecular assemblies, M_L, the section, S, and the radius of gyration, r_c, of the cross section. For example, we obtained $M_W = 3.1 \times 10^5$ g/mol, $R_G = 115$ Å, $M_L = 840$ g/mol/Å, $S = 2015$ Å^2, and $r_c = 25$ Å at pD = 12 and $M_W = 2.62 \times 10^6$ g/mol, $R_G = 272$ Å, $M_L = 2259$ g/mol/Å, $S = 1880$ Å^2, and $r_c = 27$ Å at pD = 6.3. The values for the intermediate pD are collected in Table 1. At very large q values, the second q^{-1} dependence is characteristic of rodlike particles. The fit shown in the Supporting Information gives a constant linear mass density $M_L = 15.3 \pm 2$ g/mol/Å, which is in excellent agreement with the linear mass density of a single unimer polymer chain showing their rodlike behavior inside the micelles. While cylindrical for the whole pD range, the length, the mass, the aggregation number, and the structural parameters are highly dependent on the pD; i.e. on the micellar composition. For instance, the red data plotted in Figure 1 show that the mass of the dynamic self-assembly continuously varies by nearly a factor of 10 between the two pD extrema, and follows the general dynablocks' composition. Moreover, for the micelles mostly constituted by **2A**, the linear mass density of the cylinders is increased, because of the more important associated π–stacking effect. The radius of gyration of the cylindrical section, which is dominated by the signal of the dense hydrophobic core, is constant with the micellar composition and equal to 26 ± 1 Å, whereas the section is increased at high pD, the corona of the cylinders being larger with PEG_{11} hydrophilic blocks.

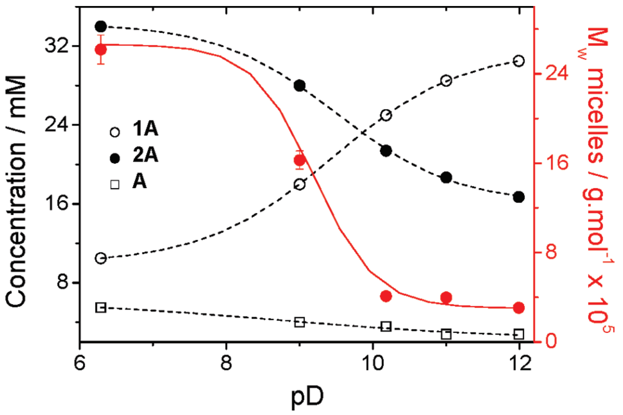

Figure 1. Black and white data: Concentration plot of **A**, **1A**, and **2A**, as a function of pD, and determined by ^{1}H NMR spectroscopy in D_2O at thermodynamic equilibrium (T = 293 K). $[\mathbf{A}]_i$ = 50 mM; $[\mathbf{1}]_i$ = 100 mM; $[\mathbf{2}]_i$ = 50 mM. Red data: Molecular weight of the micellar self-assemblies produced in the DCL, as a function of pD, in the same conditions of concentration and at T = 293 K (these data were measured with a maximum standard deviation of 10% from neutron scattering experiments, see Figure 2). The lines connecting the experimental results are drawn to guide the eye.

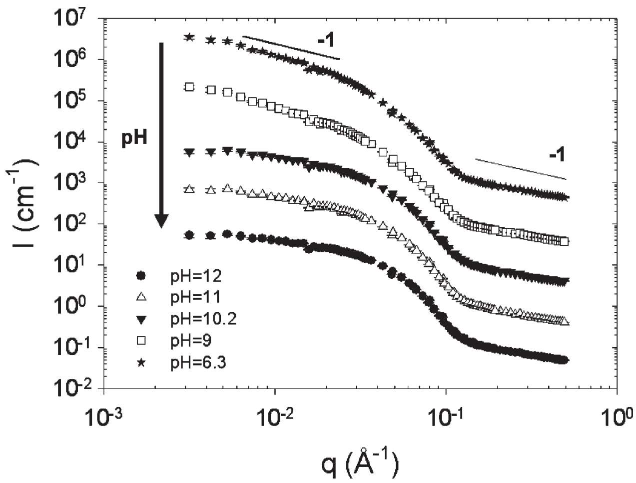

Figure 2. Neutron scattering data showing, as a function of pD and at thermodynamic equilibrium, the structuring of the micellar self-assemblies made of competing dynablocks **1A** and **2A** in D_2O, at T = 293 K. For clarity, the curves are shifted with respect to each other by one log unit.

In conclusion, we have demonstrated that it is possible to use the fundamental rules of DCC in order to enrich the toolbox for the design and the control of large responsive nanostructures based on microphase separation. Because of the high number of monomeric components constituting the objects at mesoscale, the variation of the concentration ratio between only two dynablocks is sufficient—while not necessarily limited to—for the production of a huge number of virtual nanostructures within the bounded group of their possible composition [**1A**· · · **2A**]. In other words, the pH modulation results in a signal transduction involving a binary treatment at the molecular level and a subsequent analogical response at the supramolecular level. The possibility to digitally regulate the analogical structuring of nano-objects as well as their associated physical properties, over the control of their various molecular combinations in libraries, is of interest for the development of a new class of responsive systems and "smart" materials. Thus, we assume that the general approach of DCC involving dynablocks will enable the convenient construction of number of responsive/adaptive nanostructured systems because, by just using an initial pool of few basic components and simple rules of interactions, it allows modular access—in space and time—to a rich collection of dynamic self-assemblies at mesoscale.

Table 1. Effect of the pD for the Competition Experiment Described in Scheme 1, at T = 293 K, on the Zero-q Scattered Intensity, the Weight-Average Molecular Weight (M_W), the Weight-Average Aggregation Number of Diblocks 1A and 2A Associated Inside the Micelles (N), the Radius of Gyration (R_G), the Linear Mass Density (M_L), the Radius of Gyration of the Section (r_c), and the Section (S) of the Supramolecular Assemblies

pD	$I(q^2 = 0)$ (cm^{-1})	M_W (kg/mol)	N	R_G (Å)	M_L (g/mol/Å)	r_c (Å)	S (Å^2)
11.99	57.23 ± 3	307 ± 30	407	115 ± 10	840 ± 80	25 ± 2	2015 ± 200
11	73.78 ± 4	399 ± 40	536	140 ± 10	847 ± 80	26 ± 2	1959 ± 190
10.18	73.8 ± 4	410 ± 40	559	130 ± 10	870 ± 80	26.7 ± 2	1826 ± 180
9	280.83 ± 15	1628 ± 160	2309	309 ± 25	1268 ± 100	27 ± 2	1777 ± 180
6.28	425.9 ± 20	2617 ± 200	3868	272 ± 25	2259 ± 200	27 ± 2	1880 ± 180

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Supporting Information Available: Text discussing the small angle neutron scattering studies and figures showing the SANS spectra and the variation of $1/I(q)$ with q^2 in the low-q range. This material is available free of charge via the Internet at http://pubs.acs.org.

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