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Hydrogels of amphiphilic triblock copolymers with independently tunable pH and temperature-controlled exchange dynamics

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KEYWORDS amphiphilic block copolymer; exchange dynamics; pH-sensitive hydrogel; thermo-responsive hydrogel; poly(dimethyl acrylamide); rheology; poly(methoxyethyl acrylate); acrylic acid; charge distribution.

ABSTRACT

BAB amphiphilic triblock copolymers comprising a central A-block of polydimethyl acrylamide (PDMAc) and poly(2-methoxyethyl acrylate) (PMEA) B-blocks containing 5 mol% of acrylic acid (AA), $P(\text{MEA}_{0.95}\text{-co-AA}_{0.05})_{100}\text{-}b\text{-PDMAc}_{400}\text{-}b\text{-P}(\text{MEA}_{0.95}\text{-co-AA}_{0.05})_{100}$, were prepared by RAFT polymerization. The BAB triblocks form transient physical networks in aqueous solution, their rheological properties being primarily controlled by the exchange rate of the B-blocks, which act as physical crosslinks bridged by A-blocks. We showed that combining a thermo-sensitive PMEA block with a low fraction of pH-sensitive AA units resulted in a dual and independent control of the exchange dynamics of the B-blocks with T and pH. The MEA units give rise to thermo-thickening behavior (viscosity increases with T) that is opposite to conventional Arrhenius behavior, while the presence of only 5 mol% of AA units allows the exchange rate to be tuned over a wide range by varying pH. Overall, the rheological relaxation time could be tuned over 5 orders of magnitude with pH and/or T. The impact of the distribution of AA units within the B-blocks or of the presence of divalent Ca^{2+} salts on the exchange rate was also investigated, but no significant variation was observed.

Introduction

Amphiphilic block copolymers (ABCP) consist of covalently connected hydrophobic and hydrophilic blocks. Their hydrophobic blocks collapse in water to reduce unfavorable interactions, leading to the formation of nanoscale aggregates, which are stabilized by the hydrophilic blocks¹⁻⁴. These aggregates are often kinetically frozen in aqueous medium: they do not reach thermodynamic equilibrium because exchange of unimers (free polymer chains) between aggregates is usually slow.⁵ The characteristics of frozen aggregates strongly depend on the preparation pathway⁶⁻⁹, implying complex preparation procedures/pathways (use of organic co-solvents, heating, dialysis...) and/or reproducibility issues, whereas dynamic aggregates of ABCP that can rapidly exchange unimers can reach thermodynamic equilibrium, leading to self-assemblies that are pathway-independent and can reversibly adapt to changes in their environment¹⁰⁻¹³. Transient hydrogels formed by three-dimensional self-assembly of BAB triblock copolymers exhibit rheological properties which are primarily controlled by the exchange rate of the hydrophobic B-blocks.¹⁴⁻¹⁸ These highly hydrated polymeric networks find many applications, particularly in biomedicine (coatings, drug delivery, tissue engineering)^{2, 4, 16, 19}.

According to Halperin and Alexander²⁰, the hydrophobicity of the core-forming block has a major influence on the exchange dynamics. This hydrophobicity can be tuned by modifying the B-block length^{17, 21-24} or by changing the chemistry of the hydrophobic block itself^{25, 26}. One versatile strategy is to incorporate hydrophilic units into the hydrophobic blocks. This was illustrated by Bendejacq et al.²⁷ and Billon et al.²⁸ who demonstrated that frozen block copolymers containing hydrophobic polystyrene B-blocks became dynamic when acrylic acid (AA) units were incorporated through copolymerization within the B-blocks. Similarly, incorporation of AA^{10, 11, 28-31}, dimethylaminoethyl methacrylate (DMAEMA)^{32, 33} or tri(ethylene glycol) methacrylate

(TEGA)^{34, 35} hydrophilic units into ABCP containing hydrophobic poly(*n*-butyl (meth)acrylate) (P*n*BA or P*n*BMA) blocks transformed frozen assemblies into dynamic ones.

The presence of stimuli-responsive hydrophilic units may moreover impart stimuli-responsiveness to BAB triblock copolymers. The exchange dynamics of triblock copolymer gels containing AA^{10, 11, 30} or DMAEMA³³ units in the hydrophobic block vary over several orders of magnitude in response to changes in pH and/or ionic strength. Additionally, triblock copolymer networks containing thermo-responsive units in the B-blocks, such as TEGA^{34, 35} or neutral DMAEMA³³ exhibit unimer exchange rates that slow down when the temperature is increased, which is the opposite of conventional Arrhenius behavior. Independently combining both T- and pH-responsive exchange dynamics has scarcely been described in the literature, however. P(*n*BMA-*stat*-DMAEMA)-*b*-PDMAEMA-*b*-P(*n*BMA-*stat*-DMAEMA)³³ triblock copolymers correspond to a rare example that exhibits both pH and temperature responsiveness, but the two stimuli could not be applied independently. Instead, the temperature-responsiveness imparted by neutral DMAEMA units was lost when the DMAEMA units became ionized, leading to a conventional Arrhenius behavior. Hydrogels of P(DEGEEA_{140-co-AA7})-*b*-PEO-*b*-P(DEGEEA_{140-co-AA7}), studied by O'Lenick et al³⁶ displayed a reversible sol-gel transition that depended on both T and pH, suggesting that their exchange dynamics could be controlled by both parameters. However, the influence of the two stimuli on the exchange dynamics was not investigated in detail.

Inspired by these works, we synthesized BAB triblock copolymers with a central neutral hydrophilic poly(dimethyl acrylamide) (PDMAc) block connected to two moderately hydrophobic blocks of poly(2-methoxyethyl acrylate-*co*-acrylic acid) (P(MEA-*co*-AA)), see Figure 1a and b. PMEA-*b*-PDMAc-*b*-PMEA triblock copolymers were previously shown to exhibit thermo-thickening properties with an exchange rate that increases by more than 3 orders of magnitude

upon increasing the temperature from 10 to 30 °C.³² In the present study, we chose to incorporate a low fraction of AA (5 mol%) within the PMEAs B-blocks. This relatively small proportion of AA was chosen as pure PMEA_{100} blocks already exhibit quite rapid dynamics. Greater amounts of AA could indeed lead to exchange rates that are too fast to be determined experimentally with sufficient accuracy^{30, 37}.

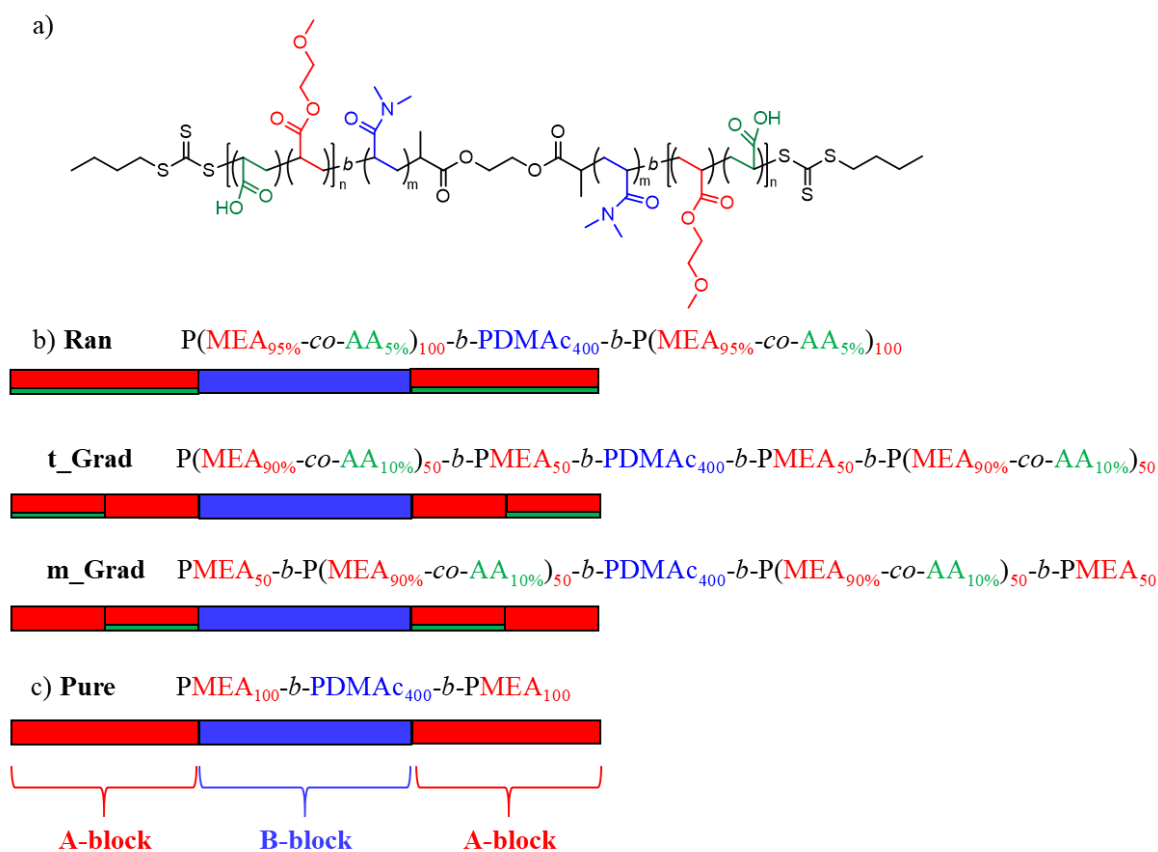


Figure 1. BAB triblock copolymers consisting of a PDMAc hydrophilic A-block and PMEAs-rich B-blocks. a) Chemical structure of **Ran**, containing 5 mol% of AA units randomly distributed within the B-blocks; b) Schematic representation of **Ran**, containing 5 mol% of AA units randomly distributed within the B-blocks, **t_Grad**, enriched in AA in the terminal part of the B-blocks, and

m_Grad, enriched in the medial part of the B-blocks; c) Schematic representation of **Pure**, containing no AA in the B-blocks, used as a reference.

The exchange rate of the B-blocks was probed using linear rheology. It has previously been shown that the relaxation time measured by dynamic oscillatory rheological measurements is primarily controlled by the exchange rate of the B-blocks between different hydrophobic cores of the transient physical network¹⁴⁻¹⁸. For BAB triblocks consisting of monodisperse hydrophobic B-blocks at intermediate concentrations well above the percolation concentration C_p , the relaxation time of the B-blocks measured for AB diblock copolymers by time-resolved small angle neutron scattering (TR-SANS) perfectly matches the rheological relaxation time.¹⁵ At lower concentrations, defects in the network such as super-bridges cause the rheological relaxation time to be smaller than the exchange time measured by TR-SANS on the corresponding diblocks, while at higher concentrations the exchange time may increase as the micellar coronas strongly overlap leading to a denser polymer network and slower diffusion.^{38, 39} Another limitation of rheology as a probe of the exchange time is that for B-blocks exhibiting dispersity in length, a distribution of relaxation times is measured (non-maxwellian behavior). The relaxation time measured at the crossover point where the elastic modulus (G') equals the viscous modulus (G'') is biased towards a lower value because of the shortest B-blocks which exchange more rapidly.¹⁴ Still, the same activation energy was measured by rheology independently of the polymer concentration and by TR-SANS on equivalent diblock copolymers, proving that in spite of these limitations, the primary mechanism controlling the rheological properties of BAB triblocks is indeed the rate of exchange of B-blocks^{14, 15} and that rheology can be used to probe the evolution of this rate as a function of different stimuli.

Statistical incorporation of only 5 mol% AA within the PMEA blocks (**Ran** in Figure 1) resulted in hydrogels whose rheological properties can be controlled independently by temperature and/or degree of ionization (α) of the AA units. Neither the distribution of AA units within the B-blocks (Figure 1b) nor the presence of monovalent or divalent salts had a significant impact on the exchange dynamics.

Material and Methods

Synthesis of triblock copolymers

Three $P(\text{MEA}_{0.95}\text{-co-AA}_{0.05})_{100}\text{-}b\text{-PDMAC}_{400}\text{-}b\text{-P}(\text{MEA}_{0.95}\text{-co-AA}_{0.05})_{100}$ triblock copolymers with distinct composition profiles were prepared by RAFT polymerization as described in section 1 of the Supporting Information. The spatial distribution of AA units in the B-blocks was varied, giving copolymers in which the AA was concentrated close to the central PDMAc block, far from the central block, or uniformly distributed throughout the $P(\text{MEA-co-AA})$ blocks (Figure 1). A $\text{PMEA}_{100}\text{-}b\text{-PDMAC}_{400}\text{-}b\text{-PMEA}_{100}$ triblock copolymer containing no AA units whose synthesis was reported in a previous work³⁷ was used as a reference.

Sample preparation for rheology and light scattering

Aqueous polymer samples were prepared by directly dispersing the polymer powder in deionized water (Millipore, 18 M Ω .cm) at room temperature. For samples containing AA, hydrogels were prepared by dissolving the polymer with the addition of NaOH (0.1 M) or HCl (0.1 M) to reach the desired degree of ionization (see calculations below). The samples were then stored at least 24 h in the fridge (~ 5 °C) to make sure that equilibrium was reached. For conditions leading to highly viscous solutions or hydrogels, the samples were placed in an ice bath (~ 0 °C)

or in a fridge ($\sim 5\text{ }^{\circ}\text{C}$) and regularly homogenized by manual shaking to accelerate the dissolution process. Homogeneous samples were obtained after one to three days and were stored in the fridge until use.

For samples with added Ca^{2+} or Na^{+} , aqueous solutions of CaCl_2 (0.1 and 1 M) or NaCl (1 M and 4 M) were added at $20\text{ }^{\circ}\text{C}$ to already prepared samples. Samples were cooled in an ice bath ($\sim 0\text{ }^{\circ}\text{C}$) and then stored for at least 24 h in the fridge ($\sim 5\text{ }^{\circ}\text{C}$) before measurements.

The degree of ionization (α) is defined as the ratio of the number of ionized AA units (n_{AA-} , mol) to the total number of AA units ($n_{AA_{tot}}$, mol) along the polymer chain.

$$\alpha = \frac{n_{AA-}}{n_{AA_{tot}}} \quad (1)$$

where $n_{AA_{tot}} = n_{AA/g_{pol}} \cdot m_{polymer}$

$m_{polymer}$ is the polymer mass within the sample (g), and $n_{AA/g_{pol}}$ the molar amount of AA units per gram of polymer (mol/g) (see Table S2).

Rheology

Rheological measurements were carried out using a Discovery HR-3 rheometer (TA Instruments) equipped with cone–plate geometries (angle ($^{\circ}$)/ diameter (mm)/ truncation (μm) = 1/20/28 or 2/40/59); chosen depending on the sample viscosity. Temperature was controlled by a Peltier system.

Samples were loaded onto the rheometer at 10 or $20\text{ }^{\circ}\text{C}$ and homogenized by pre-shearing at 3 rad/s for about 30 s . The free sample surface was covered with silicone oil to prevent water evaporation during the measurements. At steady state, oscillatory frequency-sweep shear measurements were done in the linear response domain between 0.01 and 10 Hz at temperatures ranging from 5 to $60\text{ }^{\circ}\text{C}$ (for instance, for $C = 100\text{ g/L}$ the applied strain goes from $\varepsilon = 5\%$ to 39

% for $\alpha = 0$). All viscosities measured at $C \geq 80$ g/L were determined by oscillatory shear measurements in the linear domain. Additionally, shear flow measurements were conducted at lower concentrations to estimate C_p . These experiments were conducted at shear rates in the linear domain.

The elastic modulus, G_e was taken as the value of G' at $f = 100 \cdot f_r$ (f_r = crossover frequency where $G' = G''$). The formation of master curves by frequency-temperature superposition enabled us to obtain values of G_e when they could not be determined directly within the measured frequency range. G_e was compared to $G_{e_{ideal}}$ which corresponds to the elastic modulus of an ideal network where all BAB chains are elastically active (equation 2).

$$G_{e_{ideal}} = v_{ideal} \cdot k_B \cdot T = \frac{C \cdot N_A}{M_n} \cdot k_B \cdot T \quad (2)$$

in which v_{ideal} is the total number concentration of triblock copolymer chains (number of molecules. m^{-3}), k_B ($\sim 1.38 \cdot 10^{-23}$ J/K) is Boltzmann's constant, N_A ($\sim 6.02 \cdot 10^{23}$ mol $^{-1}$) is Avogadro's number, C is the polymer concentration in g/L and M_n is the number average molecular weight of the polymer in g/mol.

Determination of the temperature range for the rheological measurements

Temperature sweeps revealed a peculiar reorganization phenomenon above a critical transition temperature, T_c , which alters the behavior of the network and has been discussed in detail in a previous work for BAB triblocks consisting of pure PMEAA blocks³⁷. Above T_c , the rheological properties of the polymers were not always reproducible and the T-sensitivity was not fully reversible. For these reasons, the rheological properties of the triblocks were studied only below T_c . For the copolymers comprising AA units in the B-blocks, T_c was observed to vary with α ($T_c \sim 35$ °C, 45 °C and 55 °C respectively for $\alpha = 0, 0.2$ and 0.5). Below T_c and for $C > 60$ g/L, the

reversibility of the hydrogel properties was checked after α modification and T modification (Figures in S13 and S14). Moreover, it was checked that the hydrogels were characterized at steady state (Figures S11, S12).

Light scattering

Light scattering measurements were obtained using ALV-CGS3 and ALV-CGS8 systems operating with a vertically polarized He-Ne laser with a wavelength $\lambda = 633$ nm (ALV-GmbH, Germany) coupled with an ALV-5004 and ALV-5003 multi tau correlator system (ALV-GmbH, Germany) respectively. Samples were placed in a thermostated decalin bath that is quasi isorefractive with glass in order to reduce reflections at the surface of the light scattering cells.

The measurements were done over a wide range of scattering wave vectors $q = 6.8 \cdot 10^4 - 2.5 \cdot 10^5$ cm^{-1} defined as $q = \frac{4\pi n}{\lambda} \sin\left(\frac{\theta}{2}\right)$ (with $n = 1.33$ the refractive index of the solvent that is water in the present investigation, and $\theta = 30^\circ - 150^\circ$ the angle of observation). Polymer solutions were studied by light scattering in a concentration range $C = 3 - 10$ g/L. The temperature was controlled between 10 and 50°C by a thermostated bath within $\pm 0.2^\circ C$.

Dynamic Light Scattering (DLS). The Siegert equation $g_2(t) = 1 + \beta g_1^2(t)$, where β is the spatial coherence factor, was used to determine the electric field autocorrelation function, $g_1(t)$, from the measured normalized autocorrelation function of the scattered light intensity, $g_2(t)$. The relaxation time (τ) distributions, $A(\tau)$, were extracted from $g_1(t)$ using the REPES^{40, 41} routine (equation 3).

$$g_1(t) = \int A(\tau) \exp\left(-\frac{t}{\tau}\right) d\tau \quad (3)$$

In the concentration range investigated, a single relaxation mode was observed. The cooperative diffusion coefficient, D , was determined from the average relaxation rate : $D = \frac{\langle \tau^{-1} \rangle}{q^2}$ and is linked to the z-average hydrodynamic radius R_h of the solute using the Stokes-Einstein equation (equation 4).

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

With $k = 1.38 \cdot 10^{-23}$ J/K Boltzmann's constant, η the solvent (water) viscosity which depends on temperature, T .

Static Light Scattering (SLS). The Rayleigh ratio, R_θ , was calculated according to equation 3.

$$R_\theta = \frac{I_{\text{solution}}(\theta) - I_{\text{solvent}}(\theta)}{I_{\text{toluene}}(\theta)} \left(\frac{n_{\text{solvent}}}{n_{\text{toluene}}} \right)^2 R_{\text{toluene}} \quad (5)$$

where I_{solution} , I_{solvent} and I_{toluene} are the average intensities scattered respectively by the solution, the solvent, and the reference (toluene). The Rayleigh ratio of the reference is $R_{\text{toluene}} = 1.35 \cdot 10^{-5}$ cm^{-1} , and the refractive indexes of the reference and the solvent (water) are respectively $n_{\text{toluene}} = 1.496$ and $n_{\text{solvent}} = 1.333$.

The apparent molar mass (M_{app}) of the solute at concentration C was calculated from the Rayleigh ratio of the solution according to equation 6.

$$R_\theta = KCM_{\text{app}}S(q) \quad (6)$$

where $S(q)$ is the structure factor and K a constant defined in equation 7.

$$K = \frac{4\pi^2 n_{\text{solvent}}^2}{\lambda^4 N_A} \left(\frac{\partial n}{\partial c} \right)^2 \quad (7)$$

where $\partial n / \partial c$ is the specific refractive index increment of the solute and N_A is Avogadro's number.

A refractive index increment $\partial n / \partial c = 0.15$ mL/g was measured with a differential refractometer

(Oprilab rEX – Wyatt Technology Corporation) at $\lambda = 633$ nm for one of the triblock copolymers with solutions at a concentration between 1 and 5 g/L.

In dilute solutions ($C = 3 - 10$ g/L), a single population of scatterers was observed by DLS for all conditions investigated. M_{app} exhibited no significant angular dependency for $C = 5 - 10$ g/L, implying that $S(q) \sim 1$ and that the radius of gyration R_g of the scatterers was too small to be determined accurately ($R_g < 20$ nm). Moreover, M_{app} (resp. $R_{h,app}$) did not vary strongly with C in the concentration range investigated, implying that it is close to the true weight average molecular weight, M_w , of the scatterers (resp. true hydrodynamic radius, R_h) with an uncertainty of about 10%. The aggregation number, N_{agg} , corresponding to the number of B-blocks within the self-assembled structures, was determined as $N_{agg} = \frac{2 \cdot M_w}{M_{w,triblock}}$ taking into account that each triblock copolymer possesses two B-blocks, see Figure S8.

Results and discussion

Synthesis of the triblock copolymers

The main objective of this work was to incorporate a small fraction of pH-responsive AA units in the PMEA lateral blocks of BAB triblock copolymers in order to prepare hydrogels exhibiting independent pH- and T- sensitive exchange dynamics. Therefore, a BAB triblock copolymer with a long, hydrophilic and neutral PDMAc middle block surrounded by two hydrophobic PMEA-based B-blocks containing 5 mol% of statistically distributed AA units was synthesized using RAFT-mediated polymerization according to our previously reported procedure³⁷ (**Ran** in Figure 1a and b and Scheme S2 in SI).

In order to study the impact of the position of the pH-sensitive units within the PMEA block, two additional triblock copolymers containing the same average AA content in the B-blocks (5

mol%), but with a gradient-like distribution of the AA units were also synthesized (Figure 1b and Schemes S3 and S4 in SI). Several recent publications have reported that the composition profile can have a significant effect on the properties of ABCP self-assemblies,^{13, 42, 43} but the impact of this parameter on the exchange dynamics has not yet been investigated. For **m_Grad** and **t_Grad**, the B-blocks consisted of two segments mimicking a gradient composition profile: a pure PMEA₅₀ segment and a random P(MEA_{90%-co-AA_{10%})₅₀ segment containing 10 mol% of AA units. Depending on the order of these two segments, polymers were prepared with the AA-containing segment either in a medial position, i.e. next to the PDMAc central block (**m_Grad**), or in a terminal position at the chain ends (**t_Grad**).}

All polymers were obtained in two or three successive polymerization steps. The first polymerization step consisted in the synthesis of the long PDMAc macroRAFT agent with a DP_n close to 400 (PDMAc₄₀₀-TTC) using CTA-1 (Scheme S1). After purification, the PDMAc macroRAFT agent was chain extended to form the targeted BAB copolymers. **Ran** and **t_Grad** were obtained in one pot, whereas **m_Grad** was synthesized in two separate polymerization steps (Schemes S2, S3 and S4 in SI). The [monomers]₀/[CTA]₀ ratio and the composition of the monomer feed were adapted for each step so that the desired degree of polymerization was reached at approximately 30 % conversion. The degree of polymerization of the copolymers was always close to the target and well-defined structures with dispersities ≤ 1.2 were obtained (Table S2 in SI). A PMEA-*b*-PDMAc-*b*-PMEA triblock copolymer containing no AA units (**Pure**) whose synthesis has previously been reported³⁷ was used as a reference.

Investigation of the T- and α -dependent self-assembly of Ran by light scattering

The self-assembly of **Ran** was first studied in the dilute regime by static and dynamic light scattering to verify that self-assembly occurred and to probe the effect of T and α on the self-assembly. All studies were conducted at 5 g/L, at which concentration interactions between the self-assembled particles could be neglected (see Figure S8). Figures 2 and 3 confirm that **Ran** forms self-assembled particles in the whole studied range of α (0-0.9) and T (10-50 °C), and that the self-assembly depends on both parameters: the aggregation number decreases with increasing α (Figure 2) and increases with increasing T (Figure 3). Both behaviors are fully reversible and were respectively attributed to the ionization of the AA units, which become more hydrophilic and charged resulting in electrostatic repulsion limiting aggregation, and the inherent thermosensitivity of the PMEAs-rich block, which becomes more hydrophobic as the temperature increases.³⁷

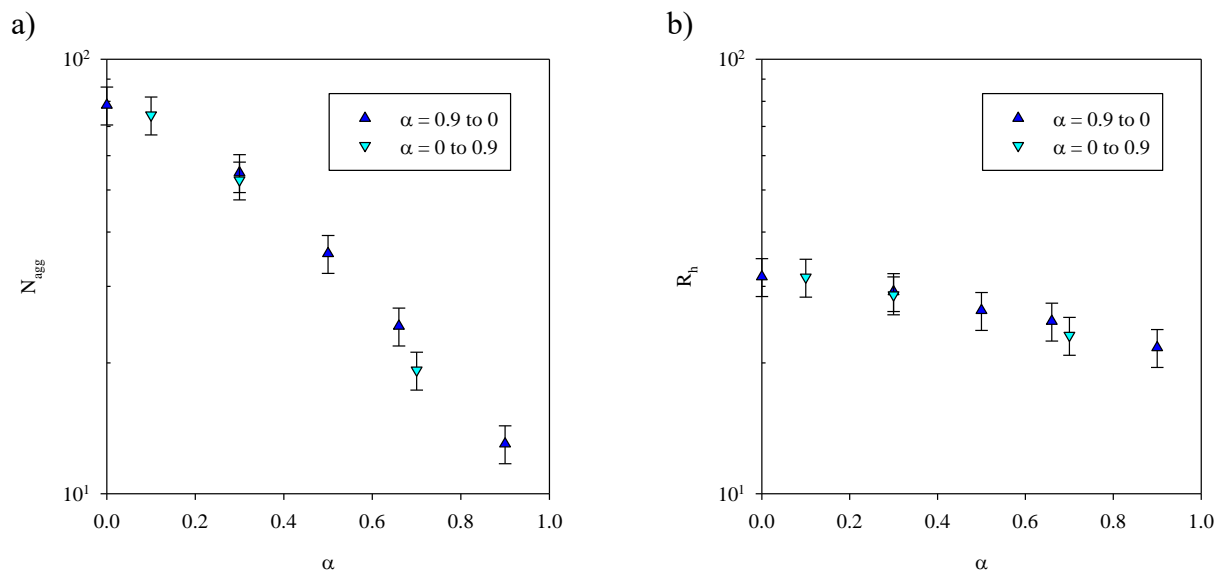


Figure 2. Evolution of a) the aggregation number and b) the hydrodynamic radius of **Ran** as a function of the degree of ionization (α) for $C = 5$ g/L with $[\text{Na}^+] = 0.1$ M at 20 °C.

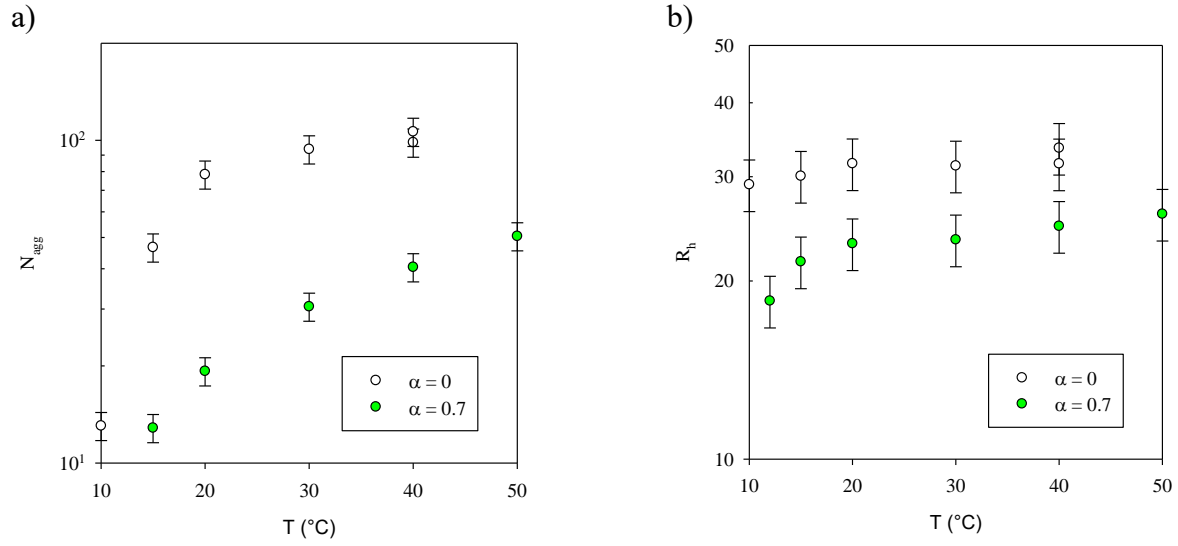


Figure 3. Evolution of a) the aggregation number and b) the hydrodynamic radius of **Ran** as a function of temperature for C = 5 g/L, [Na⁺] = 0.1 M and $\alpha = 0$ (O) or $\alpha = 0.7$ (●).

Effect of pH, temperature, ionic strength and composition profile on the exchange dynamics and resulting rheological properties

Typical behavior of Ran

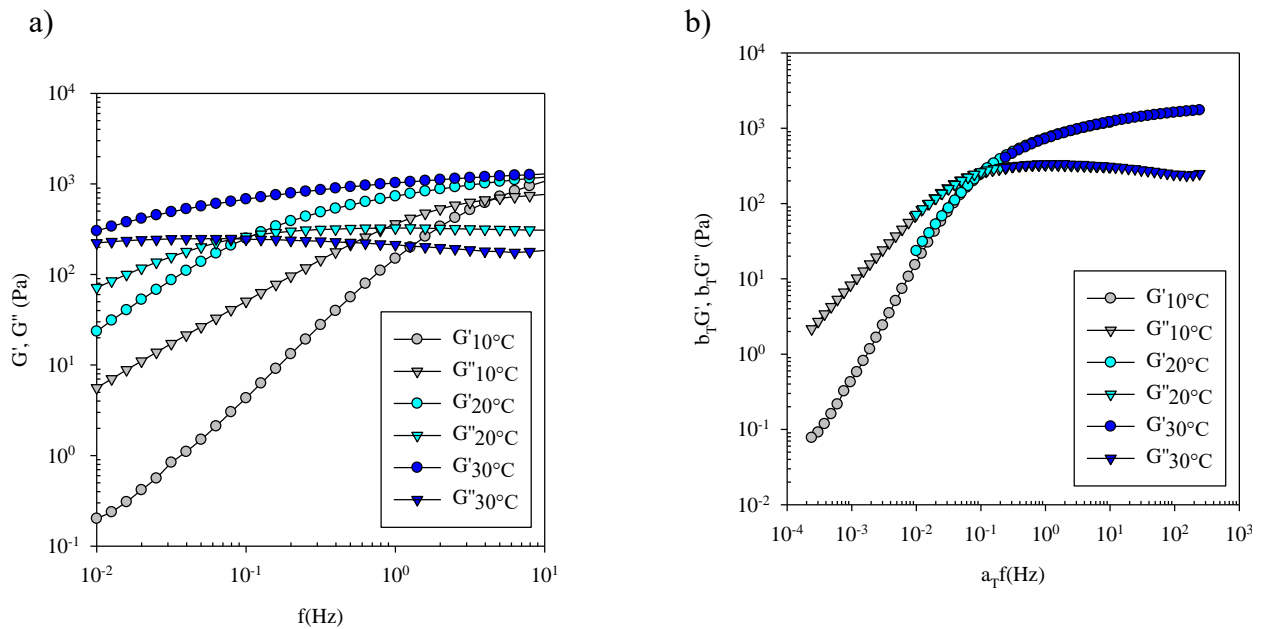


Figure 4. a) Frequency dependence of the storage (●) G' and loss (▼) G'' moduli at different T ($^{\circ}\text{C}$): $10\text{ }^{\circ}\text{C}$ (●, ▼); $20\text{ }^{\circ}\text{C}$ (●, ▼); $30\text{ }^{\circ}\text{C}$ (●, ▼); for the **Ran** triblock copolymer at $C = 80\text{ g/L}$ in water with b) corresponding temperature-master curves at $T_{\text{ref}} = 20\text{ }^{\circ}\text{C}$. The horizontal and vertical shift factors are represented by a_T and b_T , respectively. Lines are guides to the eye.

Figure 4a) shows the evolution of the elastic (G') and loss (G'') moduli of **Ran** as a function of frequency at $T = 20\text{ }^{\circ}\text{C}$, $C = 80\text{ g/L}$ and $\alpha = 0$. The polymer dispersion behaves as a liquid at low frequencies ($G' < G''$) and as a solid at high frequencies ($G' > G''$). The cross-over frequency (f_c) where $G' = G''$ may be used to define a characteristic relaxation time of the network $\tau = \frac{1}{2\pi f_c}$. This is the typical behavior expected for a 3D-spanning transient physical network, formed by BAB triblock copolymer chains assembling into B-rich hydrophobic cores bridged by A-blocks (Figure 4a), for which the relaxation is primarily caused by the exchange of the B-blocks between different hydrophobic cores¹⁴⁻¹⁸.

Close to the percolation concentration (C_p), the network contains defects (loops, superbridges, etc.), so that the rheological relaxation time is usually much smaller than the actual exchange time of the B-blocks¹⁵⁻¹⁷. The number of defects should decrease with increasing polymer concentration, so that for $C > C_p$ the relaxation time increases with polymer concentration, until a constant value is reached that is representative of the exchange time of the B-blocks. Experiments were therefore conducted at different polymer concentrations to determine the evolution of τ with concentration and C_p . At $C < 60\text{ g/L}$, a continuous evolution of the moduli with time was observed for $T > 20\text{ }^{\circ}\text{C}$ (Figures S9 and S10), implying that the hydrogels were progressively reinforcing so that the properties at steady state could not be investigated. This prevented accurate determination

of C_p , which was nevertheless estimated to be around 40 g/L (Figure S7) since at lower concentrations the signature of a network ($G' > G''$ at high frequencies) was no longer observed.

At $C \geq 60$ g/L, the rheological properties reached steady state within a few seconds. In terms of reproducibility, about a decade of variation of the rheological relaxation time was observed for independently prepared samples measured under identical conditions, while a variation of about a factor of two was observed for repeated measurements on the same sample (Figures S13 to S16).

At $C \geq 60$ g/L, the relaxation of the transient network was characterized by a broad distribution of relaxation times (Figure 4). This behavior differs from that of telechelic poly(ethylene oxide) chains (A-block) functionalized at both ends by well-defined monodisperse short alkyl chains^{15, 17} (B “blocks”) which exhibit maxwellian behavior with a single relaxation time. A distribution of relaxation times was previously observed for other BAB triblock copolymers and can be explained by the dispersity in length of the B-blocks^{10, 16, 44, 45}, even when the molar mass dispersity was as low as 1.06¹⁴. Moreover, here the B-blocks are copolymers and therefore also exhibit a dispersity in composition which may further contribute to a dispersity in relaxation time. The elastic modulus of the network (G_e) was defined to be the value of G' at $f = 100 \cdot f_c$, i.e. when most bridging chains did not relax. Master curves formed by frequency-temperature superposition (Figure 4b) enabled us to obtain values of G_e when they could not be determined directly within the measured frequency range. At $C = 80$ g/L, G_e was close to the elastic modulus of an ideal network with no defects ($G_{e_{ideal}}$). It indicates that nearly all BAB chains were elastically active in the network (equation 2). Therefore, the relaxation time determined at $C = 80$ -100 g/L was considered to be a fair estimate of the exchange time of the B-blocks.

Master curves could be obtained by frequency/temperature superposition (Figure 4b), implying a similar relaxation mechanism (exchange of B-blocks) independently of temperature in this range.

Influence of temperature at $\alpha = 0$

Ran was first studied at $\alpha = 0$, i.e. with fully protonated AA units. Figure 5a reveals that the relaxation time increased with increasing temperature, implying a decrease in the exchange rate of the B-blocks at higher T. Figure 5 shows the evolutions of τ , $G_e/G_{e_{ideal}}$ and η , as a function of temperature for **Ran** ($C = 100$ g/L, $\alpha = 0$). τ increased by more than 4 orders of magnitude upon heating from 7 °C to 30 °C (Figure 5a), whereas $G_e/G_{e_{ideal}}$ varies only by a factor 2 (Figure 5b). This behavior is opposite to the conventional Arrhenius behavior of non-thermoresponsive polymers¹⁰. No activation energy could therefore be determined (Figure S17). Similar behavior has previously been reported for amphiphilic triblock copolymers with PMEA homopolymer B-blocks³⁷ and was confirmed here with the **Pure** triblock containing no AA units, presented as a reference in Figure 5. The strong increase of τ with increasing temperature explains the corresponding increase in viscosity (Figure 5c).

Both the relaxation times and the temperature dependence of τ are nearly identical for **Pure** and **Ran** at $\alpha = 0$ as shown in Figure 5. Therefore, as long as they remain uncharged, the few AA units in the B-blocks of **Ran** do not have a significant effect on the exchange rate of these blocks.

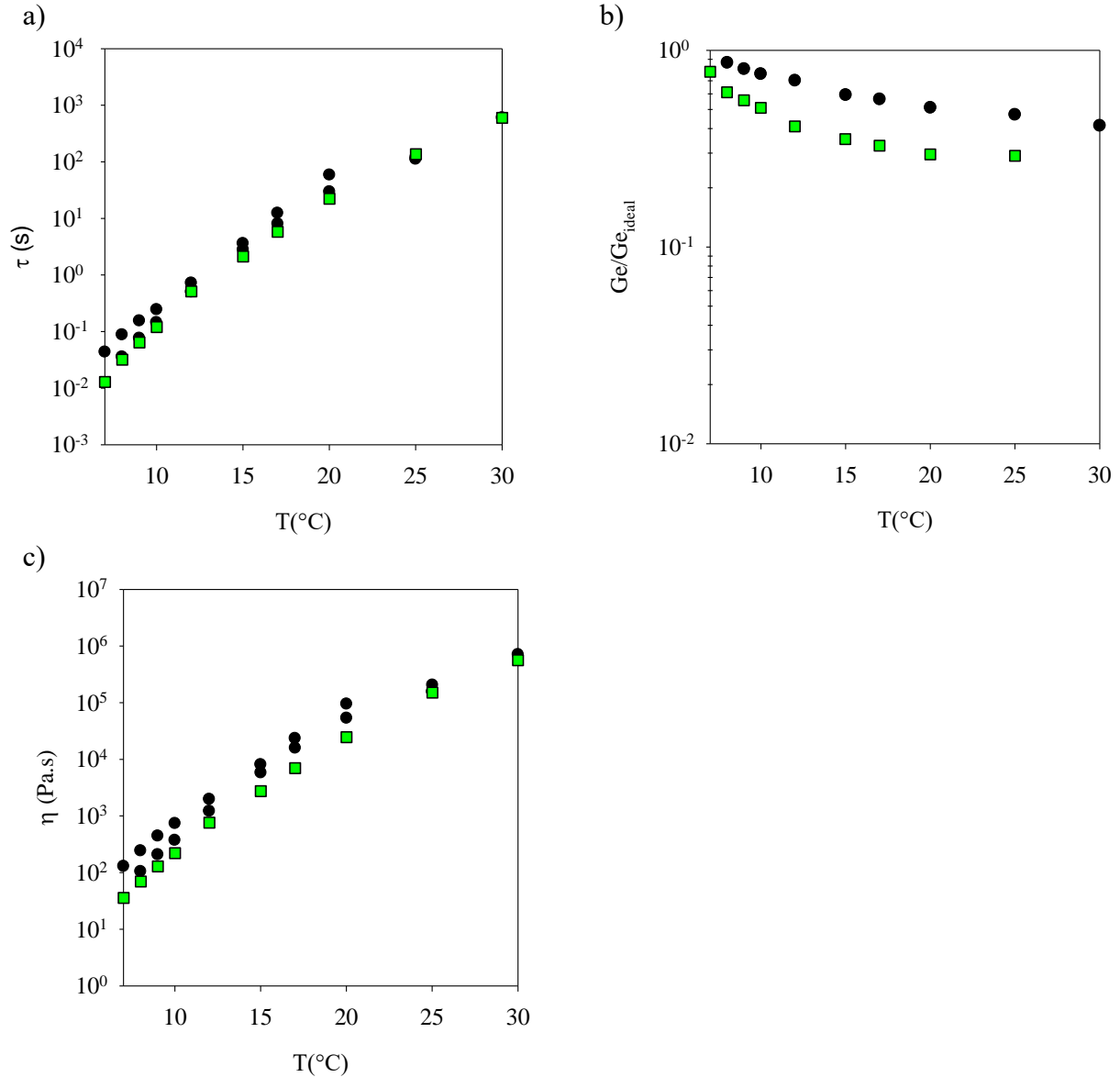


Figure 5. a) τ (s), b) $G_e/G_{e_{ideal}}$ and c) η (Pa.s) as function of temperature (°C) at C = 100 g/L without added salt for **Ran** (●) with $\alpha = 0$ and **Pure** (■). Note that the error in τ for repeated measurements of a single sample was estimated to be about a factor two, whereas measurements of independently prepared samples can vary over about one decade.

Evidence of the strong influence of α and of the independent pH and T-response

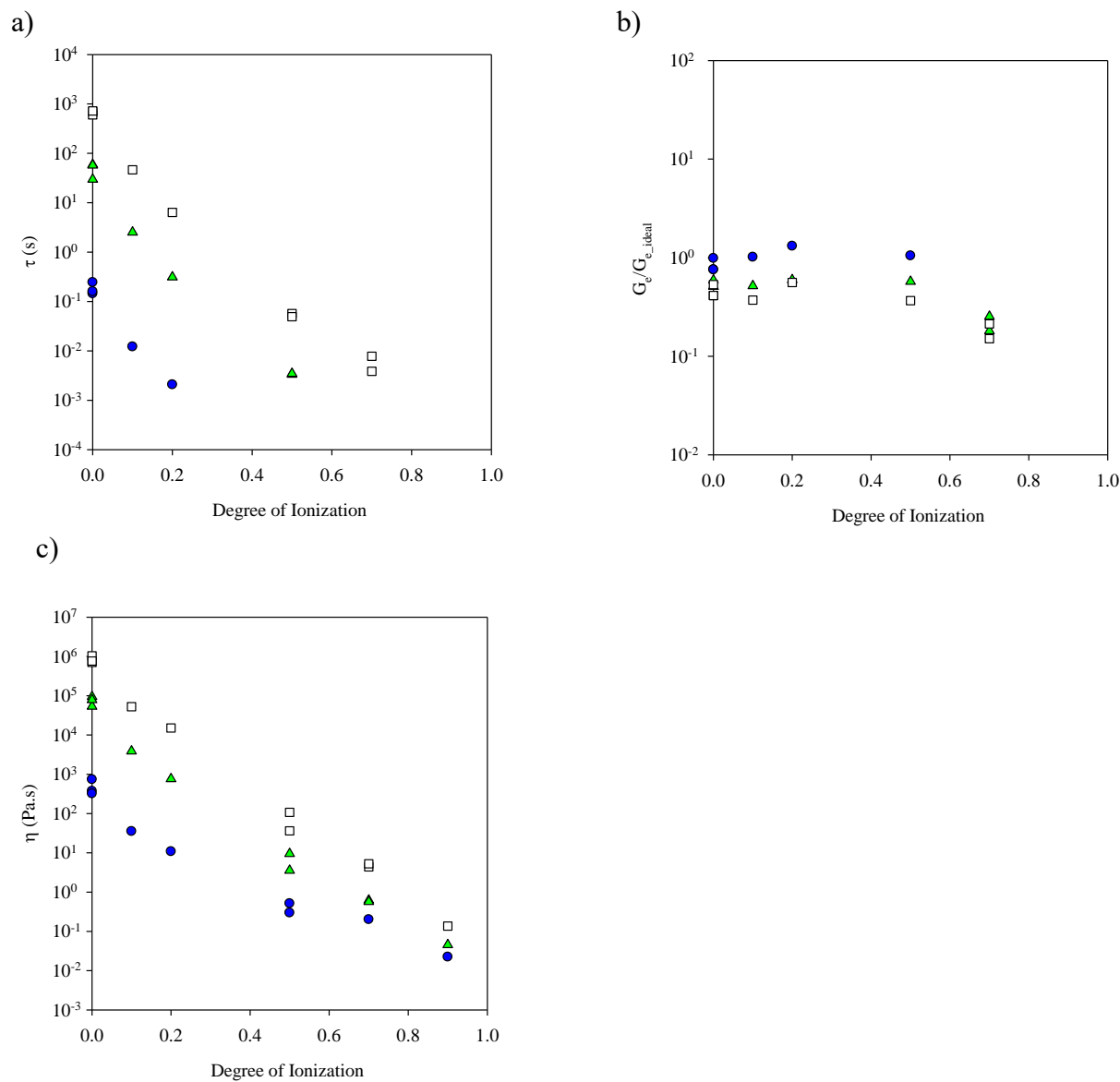


Figure 6. a) τ (s), b) $G_e/G_{e_{ideal}}$ and c) η (Pa.s) as function of the degree of ionization at $C = 100$ g/L without added salt for $T = 10$ °C (●), 20 °C (▲) and 30 °C (□) for the **Ran** triblock copolymer.

Figure 6 shows the evolution of τ , $G_e/G_{e_{ideal}}$ and η for the **Ran** triblock copolymer at 100 g/L as a function of α and for different temperatures. At 30 °C, a decrease of more than 4 decades in the

relaxation time is observed upon increasing α (Figure 6a), while $G_e/G_{e_{ideal}}$ does not vary much up to $\alpha = 0.5$. The decrease in $G_e/G_{e_{ideal}}$ at $\alpha = 0.7$ indicates that fewer chains are involved in the transient network.

The strong increase of the exchange rate of the B blocks with increasing α , which explains the sharp decrease in η (Figure 6c), is attributed to an increase in the hydrophilic character of the B-blocks due to the presence of charged units as reported for other amphiphilic block copolymers^{10, 11, 30, 33}. The behavior of **Ran** is however particularly noteworthy given the very small number of charges within the B-blocks: at $\alpha = 0.5$, each B-block contains only 2.5 charged AA units on average ($DP_n = 100$, 5 mol% AA), corresponding to one charged unit every 40 units in the B blocks on average, and still the relaxation time decreases by 4 decades compared to $\alpha = 0$.

Measurement of τ and G_e at $\alpha \geq 0.5$ becomes difficult at $T \leq 20$ °C as the exchange of B-blocks becomes very fast. As a result, measurements of G' are less precise and it is difficult to obtain a master curve (Figure 6a). In this case, the evolution of the viscosity (Figure 6c) was used as a qualitative estimate of the variation of τ . A key result illustrated by Figure 6a and 6c is that the impact of α is maintained at all temperatures.

Additionally, Figure 6c suggests that the effect of T is maintained with the same amplitude up to $\alpha = 0.5$. For $\alpha \geq 0.7$ the viscosity is much less sensitive to changes in temperature, suggesting a reduced effect of the temperature on the exchange dynamics. The decreased effect of T on η at $\alpha \geq 0.7$ may indicate that the B-blocks become so hydrophilic that their intrinsic thermosensitivity shifts to higher temperature and/or is blurred. Similar evolutions can be observed at 80 g/L (Figure S18).

While the incorporation of a few protonated AA units had no significant effect, the presence of a few charged pH-sensitive AA units in the thermoresponsive PMEAA block results in a strong

reduction of the exchange time, and thereby produces an independent dual-responsiveness of the exchange dynamics. This allows the rheological properties of the resulting transient hydrogels to be controlled independently by varying T and/or α .

Increasing the degree of ionization creates charges within the B-blocks and induces faster exchange dynamics. We therefore wondered whether the addition of salt would screen repulsive interactions between the ionized AA units, giving a similar effect as decreasing α . The effect on τ of adding 0.1 M of monovalent (Na^+) or bivalent (Ca^{2+}) salt to the **Ran** hydrogel was investigated at $C = 80$ g/L, 20 °C and $\alpha = 0.5$. The addition of 0.1 M of NaCl, which is usually enough to induce charge screening¹¹, had a negligible effect on hydrogel properties and the exchange dynamics (Figure S19). Screening electrostatic interactions by addition of salt therefore cannot be used to control τ . This might be due to the fact that there is little interaction between the charges in the hydrophobic PMEA environment. The effect of α on τ is therefore probably due to the increased hydrophilic character of the ionized AA units compared to neutral ones. Addition of 0 to 0.02 M of Ca^{2+} had no impact on hydrogel properties (corresponding to up to 2 equivalents of Ca^{2+} compared to the number of charged AA units – Figure S19). This is surprising as Ca^{2+} is a divalent ion which would have been expected to bind to two acrylate units⁴²⁻⁴⁵, causing physical cross-linking of the B-blocks within the core and thereby decreasing their exchange rate. Moreover, the PAA/ Ca^{2+} interaction is entropically favored as shown by isothermal titration calorimetry (ITC)⁴⁶ with the liberation of ten water molecules per bound Ca^{2+} ⁴⁷⁻⁴⁹. The PAA (charged)/ Ca^{2+} interaction does not seem to be strong enough in these conditions to have an impact on the exchange dynamics.

Effect of the composition profile

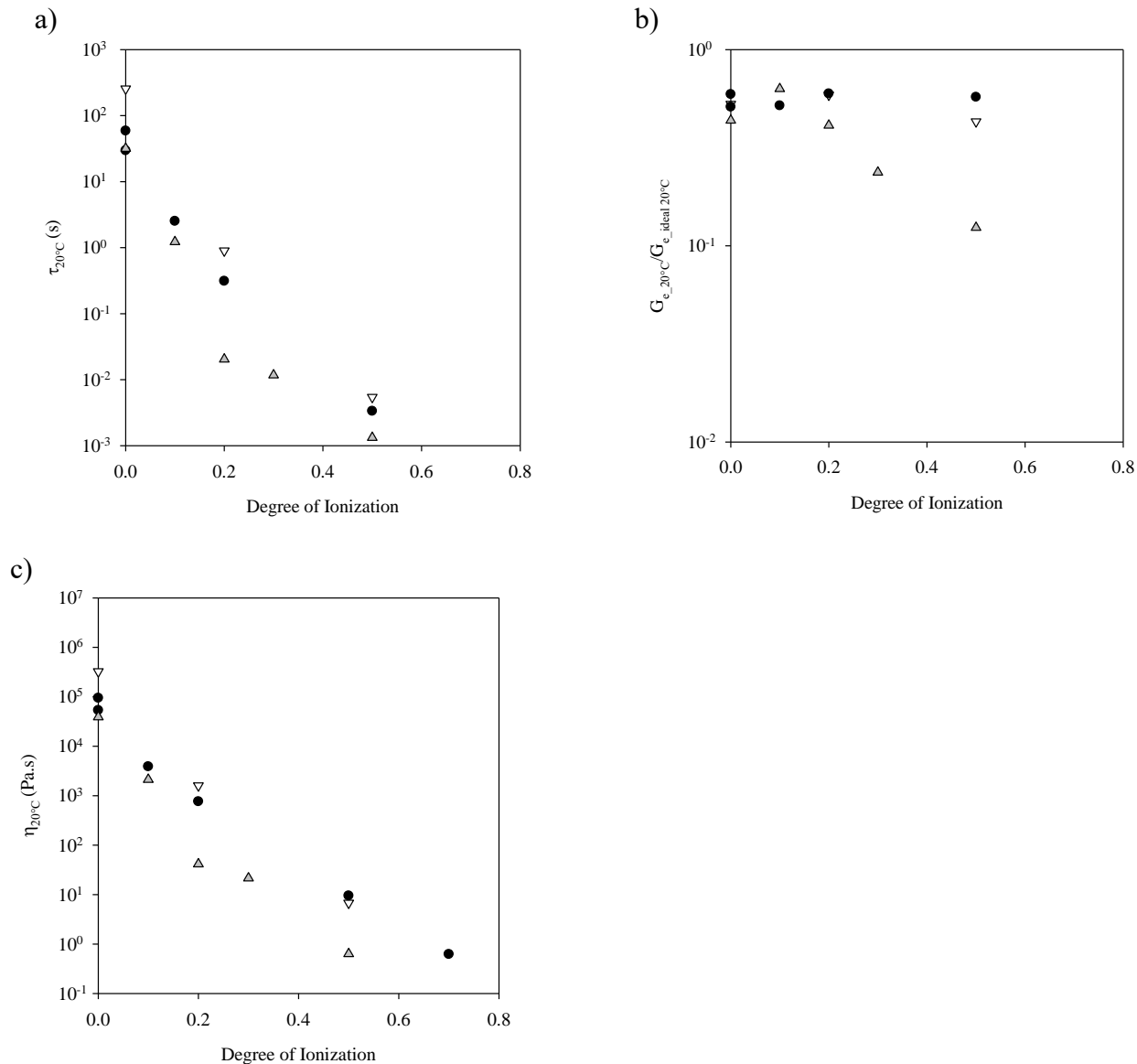


Figure 7. a) τ (s), b) $G_e/G_{e_{ideal}}$ and c) η (Pa.s) as function of the degree of ionization at $C = 100$ g/L without added salt for $T = 20^\circ\text{C}$ for **Ran** (●), **m_Grad** (▽) and **t_Grad** (▲).

The behavior of **Ran** was compared to that of the two gradient copolymers **m_Grad** and **t_Grad** consisting of B-blocks containing the same molar fraction of AA units (5 mol%) but exhibiting different composition profiles (Figure 1). Figure 7 shows the evolution of τ , $G_e/G_{e_{ideal}}$ and η as a

function of α for **Ran**, **m_Grad** and **t_Grad** in aqueous solution at 100 g/L and 20 °C. The sensitivity of the three triblock copolymers towards α and T is quite similar, as shown in more detail in Figures S20 to 23. A difference of about a decade in the relaxation time observed between **t_Grad** and the two other polymers at $\alpha = 0.2$ suggests a possible effect of the distribution of AA units. However, the difference remains small compared to the variability between independently prepared samples (1 decade) and is much smaller than the effects of T and α .

It remains possible that greater fractions of AA units in the B-blocks might lead to significant differences in rheological behavior when the composition profile is varied. However, a different polymer would be required for such a study. Due to the weak hydrophobicity of PMEA, the exchange rate with homopolymeric PMEA blocks (**Pure**) is already fairly rapid and becomes almost too fast to be measured with only 5 mol% of partially ionized AA units. Further increase in the amount of AA within the PMEA blocks would certainly lead to immeasurably fast exchange rates with little hope to quantify the impact of the composition profile.

Conclusion

The impact of the addition of 5 mol% of AA within the B-blocks of self-assembling amphiphilic BAB triblock copolymers on their exchange dynamic was investigated by rheology. It was shown that combining thermoresponsive PMEA B-blocks with pH-sensitive AA units resulted in transient hydrogels whose exchange dynamics could be tuned independently by changing the temperature and the degree of ionization of the AA units. The impact of the AA units on the exchange dynamics was negligible as long as the AA units remained uncharged. However, a dramatically faster exchange rate of the B-blocks was measured on increasing α from 0 to 0.5, with an increase of 4 orders of magnitude at all temperatures even though at $\alpha = 0.5$ each B-block contains on average

only 2.5 charged AA units (corresponding to one charged unit every 40 monomer units). This effect was unaltered by the presence of 0.1 M NaCl and was therefore due not to repulsive electrostatic interactions, but to the increased hydrophilic character of the B-block in the presence of charges. Heating led to a slowdown of the exchange dynamics for degrees of ionization up to 0.5, which is opposite to conventional Arrhenius behavior and is attributed to the thermosensitivity of the PMEA blocks. Incorporation of AA within the PMEA blocks of PMEA-*b*-PDMAc-*b*-PMEA triblock copolymers therefore resulted in hydrogels whose rheological properties can be controlled independently by the degree of ionization of the AA units and/or by the temperature. By contrast, varying the composition profile of the B-blocks or adding Ca²⁺ to physically cross-link the hydrophobic cores has a small or negligible effect on the rheological properties.

ASSOCIATED CONTENT

Supporting Information.

This material is available free of charge via the Internet at <http://pubs.acs.org>.

1. Synthesis of the triblock copolymers; 2. Additional technical information; 3. Additional information on the effect of pH, temperature, ionic strength and composition profile on the exchange dynamics and resulting rheological properties.

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