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Entropic Effects on the Supramolecular Self-Assembly of Macromolecules

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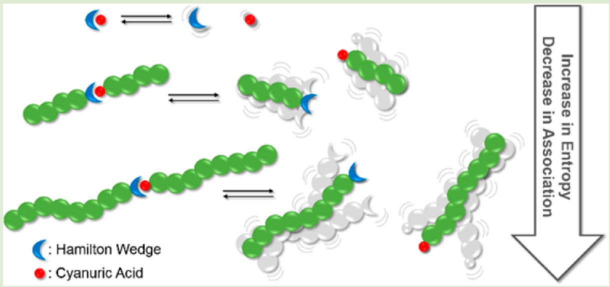
Supporting Information

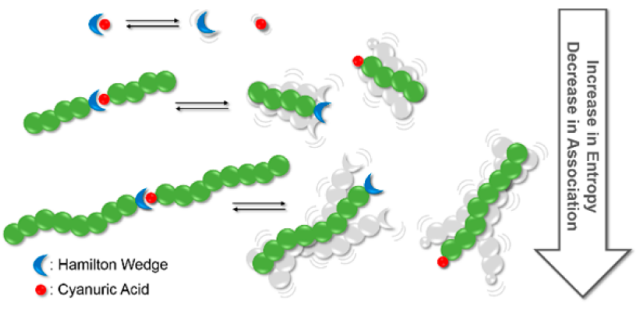
ABSTRACT: We report the transfer of entropic chain length effects into the realm of supramolecular chemistry and thereby demonstrate a macromolecular method to tune the reaction equilibria of hydrogen bonding motifs via the application of substituents of differing lengths and masses while not altering the actual recognition units to achieve a difference in the degree of association. The supramolecular adducts are characterized via temperature-dependent nuclear magnetic resonance (NMR) spectroscopy.



Supramolecular chemistry, for example, host−guest interactions, hydrogen bonding, or metal−ligand ligation with its reversible noncovalent character, allows for the formation of new materials with highly specific features, e.g., structural recognition, switchable or self-healing properties, self-assembly of block, star and ring polymers, bioactivity or the mimicking of enzymes and protein folding, and thus generated a large impact in recent scientific work.[1−18] Classically, the binding constants and thus the temperature-dependent equilibrium between adduct formation and decomposition of supramolecular—for example hydrogen bonding—motifs are tuned via the application of different recognition units, their preorganization, or the use of complementary and cooperativity effects and thereby via the identification of new and often complex chemical pathways to investigate, insert, or modify the appropriate ligation partners.[1,9,11,19−21] Recently, Barner−Kowollik and colleagues discovered a more universal approach for influencing the reaction equilibria of reversible covalent bonding systems such as for instance thermoreversible Diels−Alder (DA) cycloadditions via entropic molecular parameters while keeping the same basic reactive groups.[22,23] A chain length and mass effect could not only be predicted in quantum chemical calculations but also be reproduced in experiment. It could be demonstrated that longer and heavier chains connected to the DA adducts lead to higher degrees of debonding at one given temperature as the detachment of such building blocks leads to higher values of released entropy. In addition, the kinetics of polymer degradation have to be revisited, as we demonstrated that longer and heavier polymers synthesized via reversible addition−fragmentation chain transfer (RAFT) polymerization undergo faster thermal degradation than shorter ones.[24] As entropy-driven effects have been observed in noncovalently bound systems, for example in their self-aggregation behavior or the phase transition behavior of supramolecular diblocks, the latter also suggesting an—here mostly concentration driven—effect of chain length on association properties,[25−28] we herein transfer our findings on entropically driven dissociation from covalent to noncovalent systems (Scheme 1).

While investigations in the fields of enthalpy/entropy compensation already examined effects of differently sized short-chain substituents on supramolecular chemistry, they

Scheme 1. Schematic View of the Examined Chain Mass/Length Effect on Supramolecular Diblock Adducts Coupled via Hamilton Wedge (HW, Blue) and Cyanuric Acid (CA, Red) Functionalities



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treat the interaction of substituents with substrates and thereby expand the examined recognition units.[29] To have a closer look at the discussed problem, a set of experiments was designed comprising the temperature-dependent characterization of low molecular adducts of Hamilton wedge (HW) and cyanuric acid (CA) recognition units as well as four supramolecular diblock polymers featuring either poly(*n*-butyl acrylate) (P^{n}BuA) or poly(isobornyl acrylate) (P^{i}BoA) chains of different lengths connected via HW and CA motifs (Figure 1). While the effects in question are not exclusive for polymers, these model systems allow for the easy isolation and adjustment of the molecular properties under investigation and thus were chosen for the exemplary demonstration of the effects. Equimolar amounts of the small CA and HW functional molecules **1a** + **b** (Figure 1) were dissolved in an aprotic solvent, deuterated tetrachloroethane ($C_2D_2Cl_4$), and left for 6 h to achieve efficient equilibration.

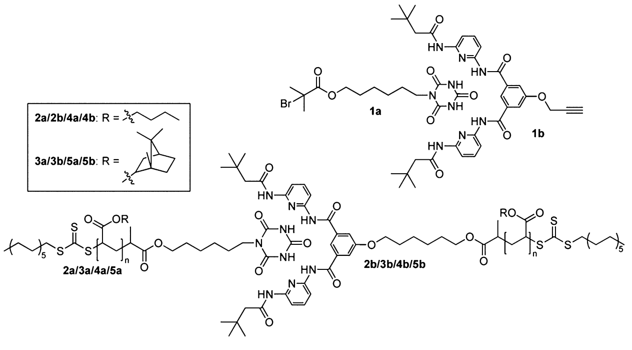

Figure 1. Applied (macro-) molecules of different functionality, chain length, and their corresponding average molecular mass: CA functional **1a** (378.22 g mol^{-1}), HW functional **1b** (598.69 g mol^{-1}), CA (**2a**) and HW (**2b**) functional P^{n}BuA$_{small}$ ($M_{n,avg.}$ = 3000 g mol^{-1}), P^{i}BoA$_{small}$ (**3a+b**, $M_{NMR,avg.}$ = 3300 g mol^{-1}), P^{n}BuA$_{medium}$ (**4a+b**, $M_{n,avg.}$ = 12700 g mol^{-1}), as well as P^{i}BoA$_{large}$ (**5a+b**, $M_{n,avg.}$ = 25000 g mol^{-1}).

The small molecules **1a+b** were chosen to resemble the motifs of the later employed polymeric building blocks. Consequently, available modified precursor compounds were used. The polymer blocks were synthesized via the widely used reversible addition−fragmentation chain transfer (RAFT) protocol with the help of CA- or HW-functional control agents to generate polymers with readily controllable chain lengths, low molecular weight dispersity, as well as high end-group fidelity due to the R-group approach.[30] These building blocks were characterized via ^{1}H NMR and SEC using appropriate Mark−Houwink−Kuhn−Sakurada- (MHKS, see Supporting Information, Table S1) parameters to confirm molecular weight and end-group fidelity (see Figure 2 for SEC chromatograms and Figure S3−10 in the Supporting Information for NMR spectra). For samples with a difference in the molecular weight determined via SEC and calculated via NMR, the values as determined via NMR (M_{NMR}) were applied. An aliphatic spacer length of six carbon atoms was chosen to circumvent competing intramolecular noncovalent interactions between the acrylate backbone and the hydrogen bonding motifs.[31]

Equimolar amounts of **2a+b**, **3a+b**, **4a+b**, as well as **5a+b** were dissolved in $C_2D_2Cl_4$ and equilibrated for 6 h. To exclude the effect of different end group concentrations and thus an unwanted shift of the reaction equilibrium, all samples were prepared with a concentration of 6 mmol L^{-1} per building block.[22] All materials were dried over sodium sulfate as well as *in vacuo* for 24 h and were stored in a desiccator over silica gel to avoid falsified measurements due to hydrogen bonding between water molecules and the supramolecular recognition units under investigation. Subsequently, high-temperature ^{1}H NMR characterization from 25 to 140 °C was conducted for each sample, and the temperature- as well as association-dependent chemical shift of the imide proton resonances of the cyanuric acid moieties was determined (see Figure 3 and Figures S11−14 in the Supporting Information).[32,33]

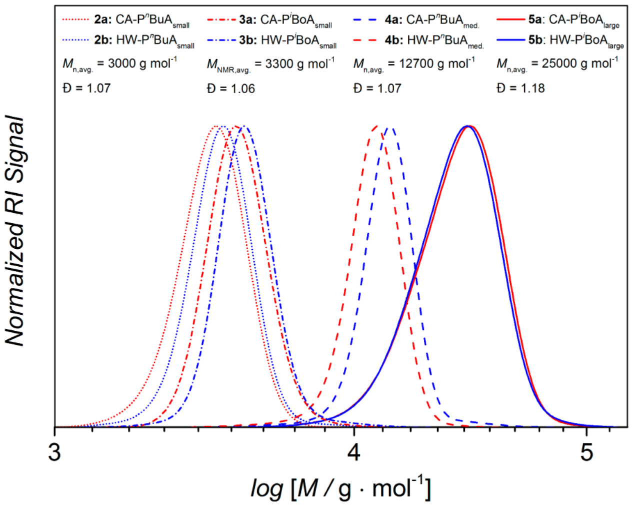

Figure 2. SEC chromatograms of the employed CA- and HW-functional polymer building blocks.

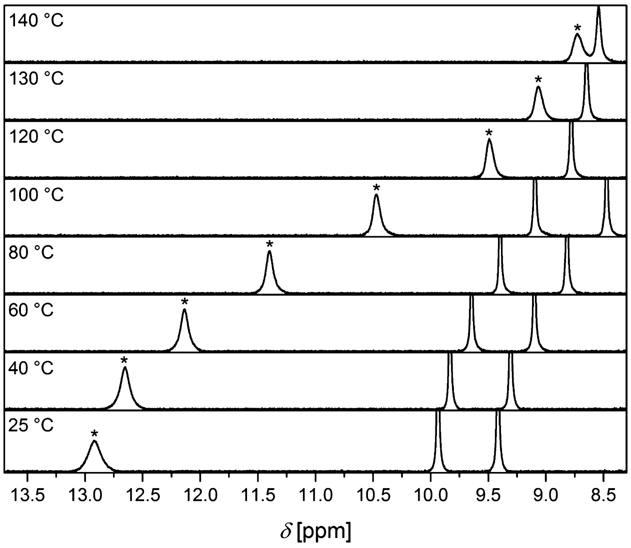

Figure 3. Exemplary temperature-dependent ^{1}H NMR spectra of **1a+b** in $C_2D_2Cl_4$ with the association-dependent shift of the CA imide proton resonance (*).

Tetramethylsilane (TMS, δ = 0 ppm) was used as an internal standard to allow for a consistent evaluation of the NMR spectra. To ensure that the applied polyacrylate backbones are not altering the hydrogen bonding properties, additional HT NMR measurements using equimolar amounts of **1a+b** and a readily available nonfunctional P^{i}BoA as well as a nonfunctional P^{n}BuA were conducted, yielding no significant differences (see

Supporting Information, Figures S15 and 16). The determined chemical shift values of the CA imide proton resonances with chain substituents of differing lengths are plotted vs the temperature in Figure 4.

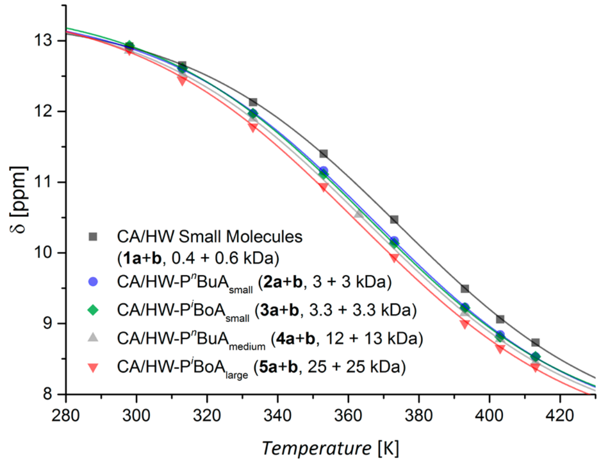

Figure 4. Temperature-dependent chemical shift values of the CA imide proton resonance for CA and HW functional building block pairings of different lengths and masses.

A typical experimental error of on average ±0.01 ppm can be assumed based on repeated measurements of the specimen. Comparing the CA imide resonance values of the different samples, a clear effect of the differently sized substituents can be observed, as the chemical shift values decrease successively with increasing molecular weight of the associated blocks, indicating an increasing degree of dissociation. While also other factors such as for example a difference in the temperature-dependent solubility or polarity may play a role in the association behavior of supramolecular diblock polymers, this outcome is in complete agreement with entropic chain length and mass effects which result in higher debonding or dissociation values for heavier and longer specimens, mainly due to higher translational and rotational entropy values of the released blocks, and presumably lies in the same dimension as entropic effects on reversibly bound covalent diblock polymers.[23] To quantify these results and exclude effects due to differences in the self-aggregation behavior, in a next step the dissociation constants K_{diss} for the different self-assembled diblock molecules were established via NMR titration methods at a concentration of 2 mmol L^{-1} (see Supporting Information, NMR Titration).[34] An intermediate temperature of 100 °C was chosen, not only as the proposed entropic effects and the differences in the observed chemical shift values are well pronounced in this temperature range but also to circumvent problems with intermediate exchange rates or resonance overlaps which could prevent a distinctive data evaluation. The resulting K_{diss} values vs average molecular building block weights can be seen in Figure 5.

The specificity of the effect of molecular weight in supramolecular bonding systems, especially at elevated temperatures, is clearly visible, as the dissociation constants are approximately doubled from small to large associates before the effect levels off, thus emphasizing the importance of the careful selection of possible assembly pairings along with their physical properties, which can thus also be employed as a method to influence binding constants and hence association strengths.

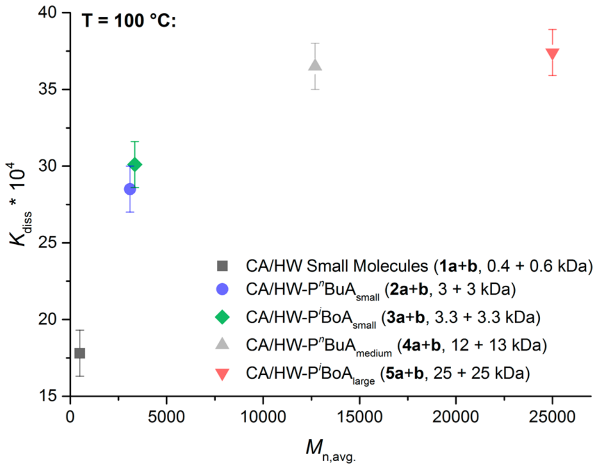

Figure 5. Dissociation constant values K_{diss} at 100 °C of differently sized CA and HW functional building block pairings, associated via hydrogen bonding.

The relatively low association forces of hydrogen bonds compared to binding constants of covalent bonds[23] may lead to a faster leveling off of the entropic effects, but nonetheless, we propose an analogue occurrence of entropic effects of chain length and mass in supramolecular systems.

In summary, we show that the association equilibria of supramolecular systems such as those driven by H-bonding can be tuned not only via the application of different motifs but also via differently sized substituents. We propose a connection of the physical properties of the associated molecules with entropic effects due to disparities in the translational, vibrational, and rotational entropy of the released building blocks during dissociation, which thereby lead to differences in the temperature-dependent degree of association. These effects can not only be utilized to further tune the desired bonding parameters of ligation sites but also have to be considered when transferring small molecular chemistry to larger systems such as, for example, polymers or proteins.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All experimental data concerning the synthesis of H-bonding molecules, RAFT agents, and polymers as well as their complementary characterization via NMR spectroscopy, ESI-MS, and SEC and a table of the dissociation constant values. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00335.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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