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Synthesis of unsymmetrical sulfamides and polysulfamides *via* SuFEx click chemistry†

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As hydrogen-bond donors and acceptors, *N*,*N*′-disubstituted sulfamides have been used in a range of applications from medicinal chemistry to anion-binding catalysis. However, compared to ureas or thioureas, the utilization of this unique moiety remains marginal, in part because of a lack of general synthetic methods to access unsymmetrical sulfamides. Specifically, polysulfamides are a virtually unknown type of polymer despite their potential utility in non-covalent dynamic networks, an intense area of research in materials science. We report herein a practical and efficient process to prepare unsymmetrical sulfamides *via* Sulfur(VI)-Fluoride Exchange (SuFEx) click chemistry. This process was then applied to synthesize polysulfamides. Thermal analysis showed that this family of polymers possess high thermal stability and tunable glass transition temperatures. Finally, hydrolysis studies indicated that aromatic polysulfamides could be recycled back to their constituting monomers at the end of their life cycle.

Introduction

Condensation polymerization is at the core of many industrial processes producing high-commodity polymers, such as polyesters, polyamides, polycarbonates, and polyurethanes. The syntheses of these polymers largely rely on robust and high-yielding condensation reactions at activated carbonyl groups and have been optimized over decades of chemical research. The recent development of the Sulfur(VI)-Fluoride Exchange (SuFEx) click chemistry[1–3] has enabled the synthesis of unique classes of polymers wherein the conventional carbonyl group is replaced by the more esoteric –SO_2– linker. For example, polysulfates[4–7] and polysulfonates[8,9] have been accessed and their properties compared to the analogous polycarbonates and polyesters. Among the family of hexavalent sulfur moieties, sulfamides are especially intriguing. As an SO_2 analog of ureas, sulfamides can engage in hydrogen bonding as hydrogen-bond donors and acceptors,[10,11] a powerful feature for materials science and organic chemistry alike. For example, aliphatic *N*,*N*′-disubstituted sulfamides have been used as gelators to trigger the assembly of 3D networks and vesicles.[12–14] In a medicinal chemistry setting, sulfamides can be used as bioisosteres for amides, ureas, and carbamates, and have become more common in the medicinal chemist's arsenal.[15] For example, the broad-spectrum antibiotic doripenem contains a monosubstituted sulfamide pharmacophore.[16] Hydrogen-bonding organocatalysis could become a natural avenue of research for these compounds, but only a handful of useful transformations have been reported with sulfamides thus far.[17–21] A lack of attention towards this family of molecules stems from the challenging preparation of *unsymmetrical sulfamides*. Similarly, while polyureas are used as a commodity polymer (*e.g.*, spandex), only a few syntheses of polysulfamides have been reported, rendering their properties underexplored.[22] Early work in the 1960s demonstrated that condensation between aliphatic bis(amine) **1a** and sulfamide (**2a**) at high temperatures produced insoluble macromolecules that were not fully characterized (Fig. 1a).[23–25] More recently, Rudkevich and coworkers synthesized oligomer **3b** (M_n = 1.7 kg mol^{-1}) using 1,4-phenylenediamine (**1b**) in combination with SO_2, I_2, and pyridine or triethylamine (Fig. 1a).[22] The authors postulated the generation of a variety of hexavalent species including SO_2I_2.[26]

Considering the Carothers equation,[27] we hypothesized that in order to obtain polysulfamides with higher degrees of polymerization (DP), we should identify conditions that (1) afford control over the stoichiometry of AA/BB type monomers, and (2) avoid potential deleterious oxidative side-reactions that diminish the overall yield. We report herein the development of conditions based on SuFEx click chemistry for the high-yielding preparation of isolable sulfamoyl fluorides, unsymmetrical sulfamides, and polysulfamides (Fig. 1b).

Results and discussion

While several methods producing sulfamides have been reported, they generally suffer from narrow substrate scope and variable yields.[28–37] Moreover, the iterative addition of two

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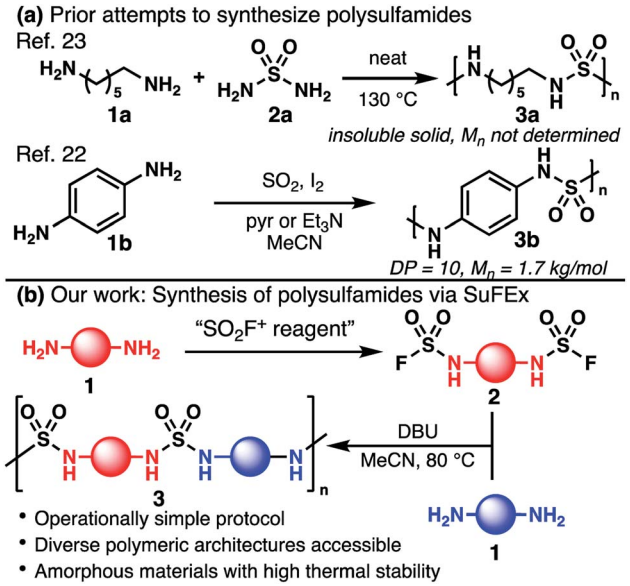


Fig. 1 (a) Early efforts toward polysulfamides led to oligomers or insoluble solids. (b) Synthesis of fully characterizable polysulfamides *via* SuFEx click chemistry.

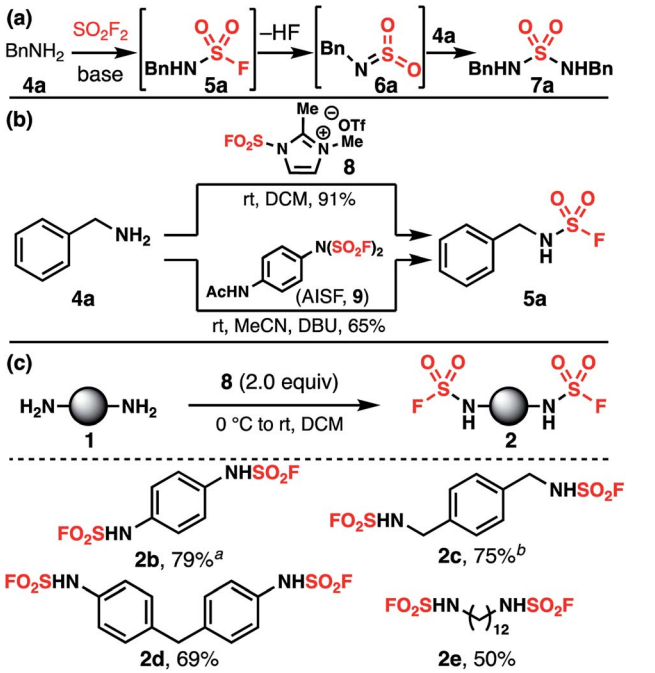
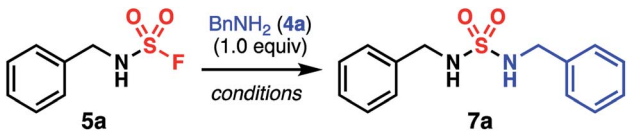


Fig. 2 (a) Undesired formation of symmetrical sulfamide **7a** from **4a** using SO_2F_2. (b) Sulfamoylation of primary amines with reagents **8** or **9**. (c) Synthesis of bis(sulfamoyl fluoride) monomers **2** from primary bis(amine)s **1**. Deviations from standard conditions: [a]1.8 equiv. of **8**; [b]MeCN as solvent.

different amines to an electrophilic sulfur(VI) reagent is often complicated by either the high instability of the intermediate or, on the contrary, insufficient reactivity of this species. SuFEx is attractive due to its mildness, efficiency, atom-economy, and stability of the fluoride-containing intermediate. For example, Sharpless disclosed an efficient synthesis of an unsymmetrical tetraalkylated sulfamide using SO_2F_2 and two secondary amines. Importantly, the sulfamoyl fluoride intermediate could be isolated and purified.[38] However, these conditions are known to be unsuitable for primary amines.[1,39,40] Indeed, treating benzylamine (**4a**) with SO_2F_2 (commercial or *ex situ* generated)[41] led to the formation of undesired symmetrical sulfamide **7a** as the major product, likely through the generation of azasulfene **6a** (Fig. 2a, S1 and S2†).[42] We instead turned our attention to SO_2F_2 alternatives. Sulfamides have been synthesized using thionyl tetrafluoride (SOF_4), but this gas is not commercially available and its preparation is hazardous.[43] Dong and Sharpless demonstrated that imidazolium derivative **8**, a shelf-stable crystalline solid analog of SO_2F_2, allows for the preparation of monosubstituted sulfamoyl fluoride in high yield (Fig. 2b).[44] We were pleased to find that this reagent afforded a variety of bis(sulfamoyl fluoride) monomers (**2b–e**) when used in combination with simple primary bis(amine)s in DCM (Fig. 2c). Notably, no precautions were taken to remove water and oxygen from the reaction, and both alkyl and aryl monomers can be synthesized in good yields. These monomers are shelf-stable for several days, but should be stored at 0 °C for extended periods of time to prevent slow decomposition. While decomposition is rapid in basic media, these monomers, apart from **2b**, exhibit high tolerance to acidic conditions and can be purified through column chromatography. Yet, most impurities can be removed through aqueous workup, which is a testament to the practicality of the sulfamoylation protocol. Finally, it was found that [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF, **9**),[45] another crystalline solid analog of SO_2F_2, can also be used to functionalize primary alkyl amines (Fig. 2b). Yields were found to be lower and these conditions are not applicable to aromatic amines, but SO_2F_2 is not required for the preparation of AISF—by contrast to that of **8**—which can be advantageous for laboratories not equipped with this reagent.

With sulfamoyl fluoride monomers in hand, we focused on the optimization of the second step of the SuFEx coupling. Treatment of **5a** with benzylamine (**4a**) in MeCN afforded dibenzylsulfamide (**7a**) in 70% yield after 2 h at 80 °C (Table 1, entry 1). Addition of a catalytic amount of DBU increased the yield to 78%, while with a stoichiometric amount of DBU, the yield improved to 97% (entries 2 and 3). Using a less basic aromatic amine as the coupling partner resulted in lower yield in the absence of additional base (Tables S1 and S2†). With our goal of developing a robust and universal protocol independent of the innate basicity of the amine partner, the amount of added base was kept to at least one equivalent, which also allows for trapping the resulting fluoride as a base-H^+–F^- salt. Triethylamine and potassium carbonate were found to afford similar yields to DBU (entries 4 and 5). Pyridine (entry 6) did not provide a noticeable improvement as compared to entry 1 but was found to perform best for aryl sulfamoyl fluorides (Fig. 3). A variety of solvents were screened as well (Table S1†). Interestingly, a nonpolar aromatic solvent such as PhMe delivered **7a** in a similar yield as with MeCN, while DMF showed a decrease in yield (entries 7 and 8). Finally, quantitative yield could be achieved by running the reaction in MeCN at 50 °C for 4 h (entry 9).[46] Again, all reactions

Table 1 Optimization of the sulfamide synthesis



Entry[a]	Solvent	Temp. (°C)	Base (equiv.)	Time (h)	Yield[b] (%)
1	MeCN	80	—	2	70
2	MeCN	80	DBU (0.1)	2	78
3	MeCN	80	DBU (1.0)	2	97
4	MeCN	80	Et_3N (1.0)	2	95
5	MeCN	80	K_2CO_3 (1.0)	2	94
6	MeCN	80	Pyr. (1.0)	2	71
7	PhMe	80	DBU (1.0)	2	89
8	DMF	80	DBU (1.0)	2	77
9	MeCN	50	DBU (1.0)	4	99

[a] Reactions were run on 0.1 mmol scale. [b] NMR yields using an internal standard.

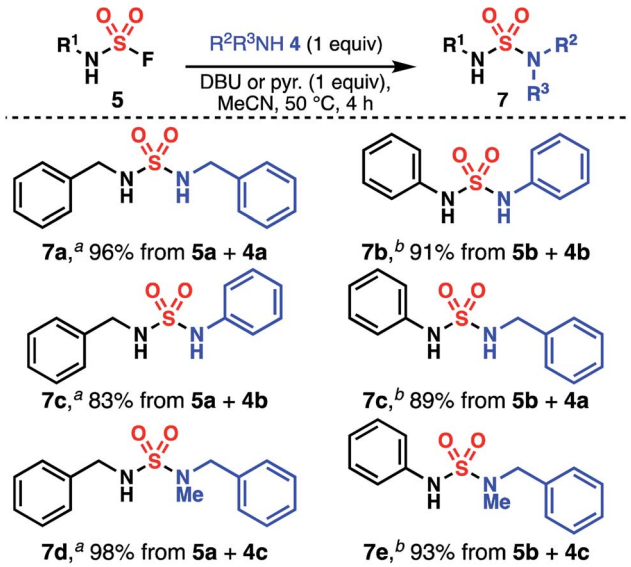


Fig. 3 Synthesis of a variety of sulfamides *via* SuFEx with isolated yields (0.5–0.6 mmol scale). [a]DBU; [b]pyridine.

were performed without removal of water or oxygen, which renders the overall SuFEx process operationally very simple. The optimized conditions were then used to synthesize a variety of sulfamides (Fig. 3). Monosubstituted alkyl sulfamoyl fluoride **5a** was coupled with benzylamine (**4a**) and aniline (**4b**) in high yields (products **7a** and **7c**) using DBU. Monosubstituted aryl sulfamoyl fluoride **5b** afforded similar yields with the same coupling partners (products **7b** and **7c**) using pyridine instead. Secondary amines such as *N*-benzylmethylamine (**4c**) can also be used in the second step to deliver trisubstituted sulfamides **7d** and **7e**. The lack of reactivity of dialkylated sulfamoyl fluoride such as **S4** (Fig. S3†), as well as ^{19}F NMR analysis of a solution of **5a** and base (Fig. S4†), strongly suggest the generation of azasulfene intermediates in this process.[42]

These reaction conditions were then applied to the synthesis of polysulfamides using bis(sulfamoyl fluoride) monomers **2** and commercially available bis(amine)s **1** (Fig. 4). Although premature precipitation of the growing polymers in MeCN was observed initially, this was overcome by increasing the temperature of the reaction to 80 °C and adding an excess of DBU (5 equiv.). A broad array of polymers was obtained with diverse architectures and M_n's between 3 and 9 kg mol^{-1}. Notably, polymer **3b** showed a DP of 39 (M_n = 6.7 kg mol^{-1}) using this protocol, which compares favorably to the prior synthesis of **3b** (DP = 10, M_n = 1.7 kg mol^{-1}, Fig. 1a).[22] Attempts to directly polymerize bis(amine) monomer **1b** with SO_2F_2 failed. Additionally, aryl and alkyl sulfamides can be incorporated in the polymer backbone with similar ease. All synthesized polymers were soluble in DMSO and most in DMAc or DMF, which allowed for full characterization using NMR and size-exclusion chromatography (SEC) (ESI†). Thermal properties of this family of polymers were explored *via* thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). All polymers exhibited high thermal stability with decomposition temperatures ranging from 198 °C for **3b** to 265 °C for **3n**. Although polymers **3b–3n** all contain hydrogen-bond donors and acceptors in their repeating units, an impressive range of glass-transition temperatures were measured. T_g's as low as 46 °C and 49 °C were determined for **3j** and **3l** with aliphatic segments in the backbone, while T_g's above 170 °C were observed for **3f**, **3k**, and **3n**, all three polymers characterized by stiffer aromatic and cyclic repeating motifs. Copolymers **3o** and **3p** were synthesized using bis(sulfamoyl fluoride) **2c** and bis(-amine)s **1b** and **1g** in different ratios. The T_g's of **3o** and **3p**, 62 °C and 88 °C respectively, are in between that of homopolymers **3j** (46 °C) and **3f** (170 °C). Interestingly, the T_g of the copolymers differs from the value predicted using the Fox equation (Table S6†).[47] These discrepancies are likely the result of intermolecular interactions such as hydrogen bonding. Overall, T_g increases with an increasing amount of monomer **1b**, which highlights the facile tunability of T_g as a function of the molecular structure of the monomers. Strikingly, DSC analysis revealed an absence of crystallization and melting temperatures for all these materials. This thermal response contrasts with the melting temperatures measured in low-molecular-weight sulfamide films[13] and the high-crystallinity observed with these small molecules.[10–14] Powder X-ray diffraction performed on polysulfamides **3b–3n** provided a more precise depiction of their structural order (ESI†). Polysulfamides exhibited varying degrees of crystallinity, from amorphous for **3i**, **3k**, **3m**, and **3n** to semicrystalline for **3c**, **3e**, **3f**, **3j**, and **3l**. This behavior is reminiscent of work by Aida and coworkers,[48] which demonstrated that low M_n polythioureas may be amorphous due to a zig-zag arrangement of the hydrogen-bond network. As a result, these polythioureas can be processed into materials mechanically robust and self-healable. Polyureas, on the other hand, are generally characterized by a linear array of hydrogen-bond networks,[49,50] rendering them semicrystalline and brittle. IR spectroscopy was used to probe the hydrogen-bond interactions in **3b–3n** in the solid state. Strong $\tilde{\nu}_{NH}$ peaks at approximately 3290 cm^{-1} were found in

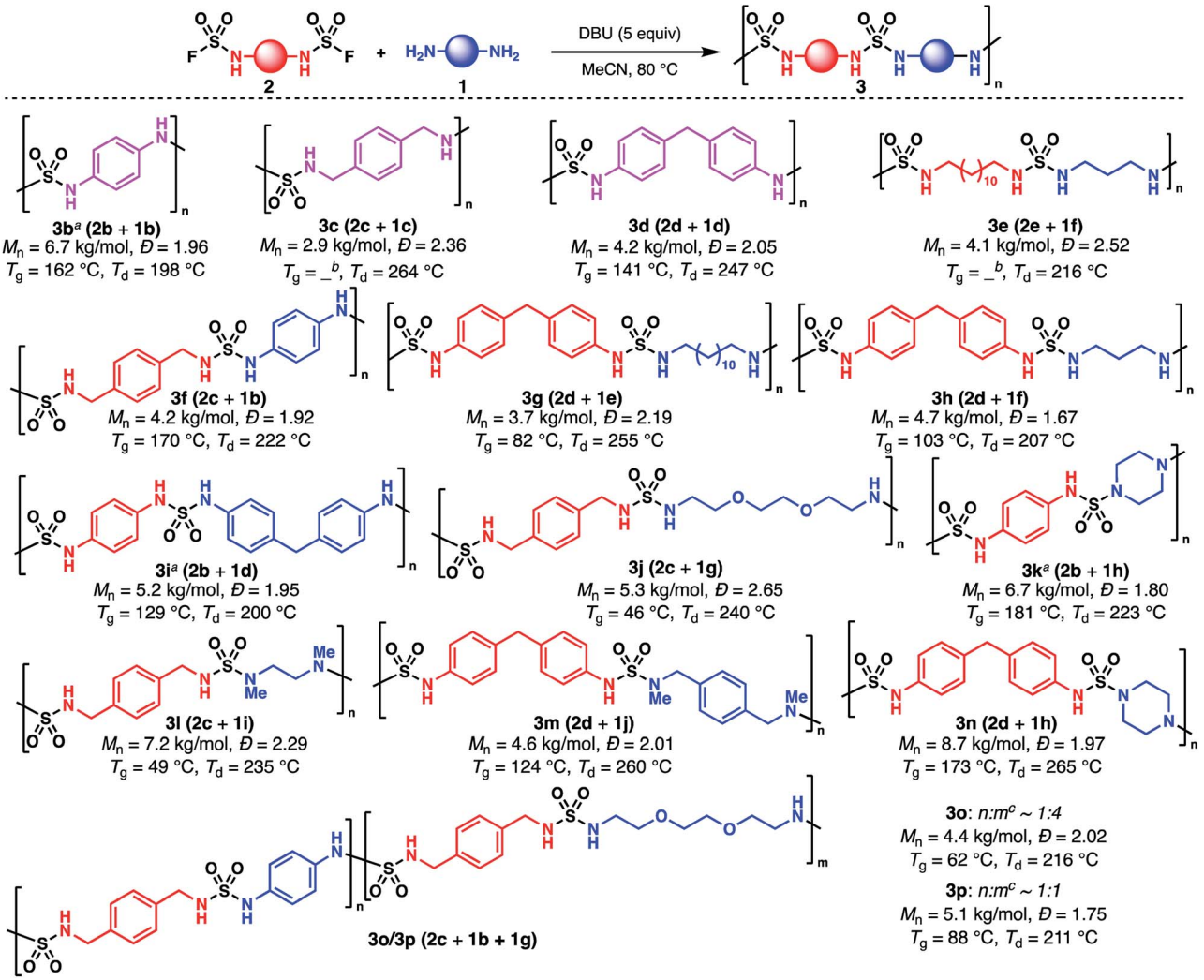
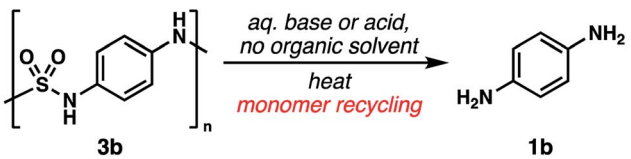


Fig. 4 Synthesized polysulfamides *via* SuFEx chemistry. M_n's and $Đ$'s were determined by SEC (DMAc + 5% LiCl) using poly(methyl methacrylate) standards. T_d = 5% weight loss temperature. [a]Pyridine was used instead of DBU. [b]No clear T_g was observed by DSC. [c]Determined by ^{1}H NMR.

both **3c** and *N*,*N*′-dibenzylsulfamide (**7a**) (Fig. S6†) and are consistent with N–H bonds engaged in hydrogen-bonding based on prior studies.[12–14] By contrast, the IR spectrum of **3b** displayed much broader $\tilde{\nu}_{NH}$ peaks, suggesting that the structure of the backbone strongly affects the hydrogen bonding ability of the repeating sulfamide groups. In-depth characterization of the hydrogen-bonding architecture in various polysulfamides will therefore be necessary to shed light on their specific thermal and mechanical properties.

The synthesized polysulfamides showcased high thermal stability, a desirable feature for many applications. However, the global accumulation of plastic waste has created a dire environmental crisis that must be addressed by the development of recyclable polymers. Knowing the hydrolytic stability of polyureas,[51] the depolymerization of the synthesized polysulfamides was investigated. While alkyl polysulfamide **3l** displayed remarkable stability in acidic or basic media at elevated temperatures (ESI†), aryl polysulfamide **3b** could be hydrolyzed in a variety of aqueous conditions.[52,53] **3b** was typically suspended in an aqueous solution and heated for 40 h. The resulting aqueous solution was then extracted at pH ~ 14 with EtOAc and the amount of bis(amine) monomer **1b** was quantified (Table 2). After treatment with a basic solution containing

Table 2 Hydrolysis of aryl polysulfamides



Entry[a]	Aq. base/acid	Temp. (°C)	Monomer recovery[b] (%)
1	NaOH (4 M)	80	32
2	NaOH (4 M)	125	42
3	NH_4OH (18 M)	80	53
4	HCl (4 M)	80	63[c]
5	HCl (4 M)	125	74

[a] Hydrolysis reactions were conducted for 40 h. [b] Based on isolated **1b**. [c] Some polymer remained in suspension.

NaOH or NH_4OH for 40 h at 80 °C or 125 °C, up to 53% of pure **1b** was isolated, while in HCl at 125 °C for the same amount of time, the recovery was improved to 74%. This initial study will serve as a blueprint to investigate the recyclability potential of aromatic polysulfamides.

Conclusions

In summary, we have developed an efficient, practical, and general synthesis of sulfamides and polysulfamides based on SuFEx click chemistry. We anticipate that this robust and mild method will impact the fields of medicinal chemistry and hydrogen-bond catalysis, areas in which sulfamides have demonstrated exciting promise. This process was adapted to produce and evaluate polysulfamides, a virtually unknown class of polymers. Characterization of these polymers revealed a high thermal stability as well as modular T_g's depending on the monomer structure. IR spectroscopy and power X-ray diffraction revealed that hydrogen-bonding interactions and the degree of crystallinity are strongly influenced by the structure of the polymer backbone. Finally, aromatic polysulfamide **3b** was depolymerized upon heating in basic or acidic aqueous solution, which suggests that these materials could be efficiently recycled after use.

Conflicts of interest

There are no conflicts to declare.

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