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UGI THREE-COMPONENT POLYMERIZATION TOWARD POLY(A-AMINO AMIDE)S

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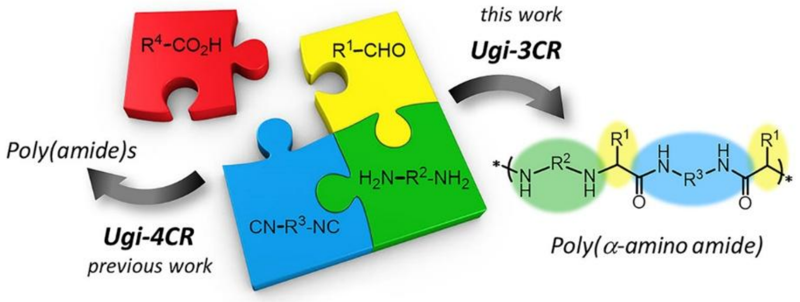
ABSTRACT

Due to their great modularity, ease of implementation, and atom economy, multicomponent reactions (MCRs) are becoming increasingly popular macromolecular engineering tools. In this context, MCRs suitable in polymer synthesis are eagerly searched for. This work demonstrates the potential of the Ugi-three component reaction (Ugi-3CR) for the design of polymers and, in particular, of poly(α-amino amide)s. A series of polymers containing amino and amido groups within their backbone were obtained through a one-pot process by reacting aliphatic or aromatic diamines, diisocyanides, and aldehydes. The impact of temperature, concentration, catalyst loading, and substrates on polymerization efficiency is discussed. A preliminary study on the thermal properties and the solution behavior of these poly(α-amino amide)s was carried out. An aliphatic-rich derivative notably showed some pH-responsiveness in water via protonation–deprotonation of its amino groups.



The demand for diversely substituted multifunctional polymers able to sustain cutting-edge applications is steadily increasing these days. In this context, the development of simple and efficient macromolecular engineering tools becomes essential, and the emergence of multicomponent reactions (MCR) in polymer science takes on its full meaning.[1–4] By definition, MCRs are highly efficient reactions involving more than two compounds that react and form one molecule containing essentially all atoms of the starting reagents.[5–7] Such a straightforward and atom economic approach is highly valuable when considering the design of structurally complex macromolecules. MCRs have notably been used for monomer synthesis[8–12] and polymer postmodification,[13–19] in one-pot processes combining MCRs and radical polymerization,[19–22] in strategies combining MCRs with click chemistry for the production of complex and functional macromolecular structures,[23,24] but also as polymerization tools in step-growth processes.[1–4] Only a few MCRs have been used in step-growth polymerization, which requires very high efficiency, including Biginelli,[25–29] Hantzsch,[29,30] Kabachnick-fields,[31] Radziszewski,[32–34] and the transition metal-catalyzed MCR[35–37], but the most popular ones consist in isocyanide-based MCRs,[38] namely, the Passerini[39–44] and the Ugi four-component (Ugi-4CR)[45–52] reactions.

The Ugi-4CR is based on the concomitant reaction of primary amine, aldehyde, isocyanide, and carboxylic acid. The mechanism relies on the formation of a nitrilium ion intermediate resulting from the addition of the isocyanide onto the iminium generated through amine-aldehyde condensation. This intermediate then undergoes a nucleophilic addition of the carboxylate, followed by an acyl migration leading to α-amido amides, with water as the sole byproduct (Figure 1a).[53] Since the pioneering work by Meier et al. on the synthesis of polyamides by Ugi-4CR polymerization (Figure 1b),[45] this MCR was exploited for the synthesis of several polymers bearing α-amido amide moieties in their repeating units,[45–52] including polypeptoids[48,49,54] and alternating poly(peptide-peptoid)s copolymers.[50–52,54] A variant of the Ugi4CR, that is, the Ugi five-component reaction (Ugi-5CR),[55] was also investigated in step-growth polymerization.[56] Typically, a carbonate, formed in situ by a reaction between an alcohol and carbon dioxide, plays the role of the nucleophile, leading to poly(urethane-amide)s (Figure 1a).[56]

A few years ago, Ugi-type reactions involving only three components (Ugi-3CR), that is, amine/aldehyde/isocyanide, were also reported.[57–62] In these cases, water released during the imine formation plays the role of the nucleophile and traps the nitrilium key intermediate.[57–62] Such a reaction requires the presence of a catalyst and paves the way to α-amino amide [57–62] derivatives. Up to now, the Ugi-3CR has been disregarded in polymer chemistry, in spite of the increasing interest for macromolecules bearing α-amino amide motifs in their repeating unit. For example, poly(ε-lysine) is currently receiving much attention due to its wide application in pharmaceutical, food, medical, and biotechnology areas.[63] Recently, polymers bearing α-tertiary amino amide and phenol groups were produced via octylphosphonic acid (OPA)catalyzed MCR between diisocyanides and dibenzoxazines compounds.[64]

In this work, we explored for the first time the potential of the Ugi-3CR in polymer synthesis and prepared unique macromolecules containing α-amino amide moieties in their repeating units (Figure 1b). In particular, we focused on the reaction of diamine/diisocyanide/aldhehyde, which should lead to polymers with α-amino amide groups in their backbone. The step-growth polymerization conditions were optimized, and the nature of the building blocks was varied in order to evaluate the versatility of the approach and to modulate the structure of the polymers.

So far, best yields in Ugi-3CR (95%) were achieved by reacting aromatic aldehydes and amines with aliphatic isocyanides at 80°C in toluene using phenylphosphinic acid (PPA) as a catalyst.[60] Because we anticipated a poor solubility of the poly(α-amino amide)s prepared from aromatic monomers in this solvent, we first studied a model Ugi-3CR in DMF, a common solvent for aromatic polyamides. In practice, aniline (1 equiv), benzaldehyde (1 equiv), and PPA (0.1 equiv) were dissolved in DMF, followed by the addition of *t*BuNC (1 equiv) and heating at 80°C (Table S1). After 24h, the targeted α-amino amide was isolated by silica gel chromatography in 50% yield. The ^{1}H NMR analysis confirmed the product structure as indicated by characteristic signals of the methine group a in α position at 4.6ppm, the amine b at 4.5ppm, and the amide hydrogen c at 6.5ppm (Figure 2a). The structure of the model compound was further supported by ^{13}C NMR (Figure S1). In order to have a clear insight into the efficiency of the reaction, we evaluated the conversion of the reactants into the α-amino amide derivative by ^{1}H NMR of the crude mixture (Figure S2b−d). At 80°C, the formation of the α-amino amide reached 76% and 91% after 1 and 3 days, respectively (Table S1, entries 1 and 2). A similar trend was observed when carrying the reaction at 25°C (92% after 3 days, Table S1, entries 3 and 4). Overall, conversions superior to 90% were obtained in DMF, which was a strong incentive to test these conditions for the Ugi-3CR step-growth polymerization.

The first Ugi-3CR polymerizations were performed in DMF at 80°C using similar reactants compared to the model reaction, that is, para-phenylenediamine (1 equiv), freshly synthesized 1,6-diisocyanohexane (1 equiv), benzaldehyde (2.2 equiv), and 10mol % of PPA (Table 1, entry 1). In line with previous studies on Ugi-polymerization,[45,50] the monofunctional component was used in slight excess to guarantee its availability, even at high conversion. After 3 days under these conditions, the medium was homogeneous and the SEC analysis of the reaction mixture revealed the formation of very short polymer chains characterized by a M_n of 1400g/mol and a dispersity of 1.6 (Table 1, entry 1 and Figure S3a). The Ugi3CR polymerization was also carried out at lower temperatures, that is, 50 and 25°C (Table 1, entries 2−3 and Figure S3). As a result, polymers with higher molar mass were obtained, that is, 5900 and 6300g/mol at 50 and 25°C, respectively. These M_n values correspond to a DP of about 13. According to the Carother’s equation ($DP_n = 1/(1–p)$, where p designates conversion, a reaction efficiency of 92% is necessary to reach a DP of 13, which is perfectly in line with the conversion observed in our model reaction (Table S1, entry 4). The polymerization temperature was further decreased to 6°C but M_n no greater than 1700g/mol was observed after 3 days (Table 1, entry 4). Nonetheless, this value almost doubled when prolonging the polymerization time to 8 days at the same temperature (Table 1, entry 5). Overall, performing polymerizations at 6 or 80°C was clearly not optimal. In contrast, a polymer with M_n of 4300g/mol could be produced at intermediate temperature, that is, 50°C, even when shortening the polymerization time to 1 day (Table 1, entry 6). In order to optimize the Ugi-3CR polymerization, catalyst loading and concentration were varied. We notably doubled the concentration of the medium while keeping all other parameters constant but the molar mass dropped to 350g/mol (Table 1, entry 7). Moreover, higher catalyst loading did not further increase the molar masses. Polymers with quite similar M_n were obtained with 10, 20, or 50mol % of PPA (Table 1, entries 6, 8, and 9, respectively).

Note that a precipitate appeared in the reaction mixture when the polymerization was carried out at 50°C or below. This precipitate was dissolved in DMF/LiBr upon heating prior SEC analysis (Figure S3b−d). Besides the signal corresponding to the polymer chains, very low molar mass products were detected on the SEC chromatograms. For the sake of clarity, this precipitate was isolated by centrifugation (13wt %) and the supernatant was dyalized against fresh DMF. Both samples were then submitted to SEC (Figure S4). These analyses demonstrated that the precipitate consists of low molar mass compounds, whereas the polymer chains P_1 are fully soluble in DMF. NMR and IR analyses of P_1 confirmed the expected structure of the poly(α-amino amide). The ^{1}H NMR spectrum carried out in DMSO-d_6 showed characteristic signals of the amine b at 5.4ppm, the methine hydrogen a in α position of the amide at 4.8ppm, and the amide hydrogen c at 8.2ppm (Figure 2b). Typical signals of the aliphatic hydrogens d−f, initially contained in the 1,6-diisocyanohexane, as well as aromatic hydrogens were also assigned on Figure 2b. ^{13}C NMR (Figure 2c), COSY, and HSQC analyses (Figure S5) provided additional evidence of the structure. As an illustration, the COSY spectrum showed cross peaks between hydrogen a in the α position of the amide and hydrogen b of the amine or between hydrogens c of the amido group and hydrogen d of the aliphatic chain. The presence of amides was also confirmed by infrared spectroscopy with specific peaks at 1650 cm^{-1} and at 1510 cm^{-1} corresponding, respectively, to C=O and N–H stretch for secondary amides (Figure S6a).P_1 was tentatively analyzed by MALDI-ToF but no signals corresponding to the polymer could be detected due to its low ability to be desorbed and/or ionized (Figure S7a). In contrast, the structure of the precipitate was elucidated by electrospray ionization (ESI) mass spectrometry (Figure 3). The latter consists of a cyclic unimer generated from one molecule of diamine, one molecule of diisocyanide, and two molecules of aldehyde. Indeed, peaks corresponding to the protonated, sodiated, and potassiated cyclic derivative were detected at *m/z* 457.2, 479.2, and 495.2, respectively (Figure 3a). The signal at *m/z* 913.5 was attributed to a protonated aggregate of two cyclic unimers rather than a twice larger cyclic molecule thanks to a collisioninduced dissociation (CID) experiment (Figure 3c). Indeed, this ion dissociated at low collisional energy (5 eV), consistent with noncovalent interactions, and gave rise to one main fragment at *m/z* 457.2, corresponding to the protonated cyclic unimer. IR as well as ^{1}H, ^{13}C, and 2D NMR analyses confirmed the nature of the cyclic unimer (Figures S8 and S9). Ultimately, the desired poly(α-amino amide)s could be collected free of this side product.

The optimized polymerization conditions were then applied to various aromatic and aliphatic compounds in order to synthesize a series of poly(α-amino amide)s with tunable structures (Table 2). Instead of the *para*-phenylenediamine, the ortho- and the *meta*-phenylenediamine were reacted with benzaldehyde and 1,6-diisocyanohexane in DMF at 50°C in the presence of 10mol % of PPA (Table 2, entries 3 and 4). When using the *ortho*-phenylenediamine, only oligomers P_3 ($M_n \sim$ 900g/mol) were produced most probably as a result of steric hindrance induced by the proximity of the amine functions on the aromatic ring. However, a polymer P_4 characterized by a M_n of 7100g/mol and a dispersity of 1.7 was obtained with the *meta*-phenylenediamine, which is almost twice higher in M_n compared to P_1 and P_2 obtained from the *para* derivative. Contrary to the reactions performed with the *para*-phenylenediamine, we did not observe the precipitation of low molar mass cyclic compound when using *meta*-phenylenediamine, even at 50°C. The structure of P_4 was fully characterized by ^{1}H NMR (Figure 4a), HSQC (Figure S11a), solid-state NMR (SSNMR) (Figure S12), and IR (Figure S6b). Attempts to analyze P_4, and all poly(α-amino amide)s produced in this study, by MALDI-TOF failed as a result of its low ability to be desorbed and ionized (Figure S7). Signals typical of P_4 were identified on the ^{1}H NMR spectrum in DMF-d_7 (Figure 4a), including aromatic protons between 5.5 and 7.8ppm, methylene protons **e** and **f** ranging from 0.5 and 1.5ppm, and hydrogens **d** showing two peaks, at 3.0 and 3.5pm, as a result of the different possible configurations of the amide function. We also distinguished a low intensity signal at 8.3ppm assigned to the amide hydrogen **c** and a peak corresponding to the methine hydrogen **a** around 5ppm. The latter assignments were confirmed by HSQC (Figure S11a). The presence of amide was further evidenced by a characteristic signal at 172ppm in solid-state ^{13}C NMR (Figure S12) assigned to the ipso carbon of the amido group and by ATR analysis showing peaks at 1660 and 1510cm^{-1} typical of the C = O and NH stretching, respectively (Figure S6b).

An aliphatic aldehyde, that is, isobutyraldehyde, was also reacted with the *meta*-phenylenediamine and 1,6-diisocyanohexane under the same experimental conditions (Table 2, entry 5). Nevertheless, we only collected oligomers P_5 ($M_n \sim$ 1200g/mol), suggesting a lower efficiency of the Ugi-3CR with aliphatic aldehyde, in line with the observations made by List et al.[60] The structure of the diisocyanide was also varied. An aromatic isocyanide, namely, 1,4-phenylenediisocyanide, was first reacted with *meta*-phenylenediamine (1 equiv) and benzaldehyde (2.2 equiv) for 72h, leading to P_6 with a M_n of 7300g/mol (Table 2, entry 6). When the reaction time was shortened to 24h, the M_n of this polymer only slightly decreased (M_n = 6400g/mol, $Đ$ = 2.76). Moreover, similar molar mass (M_n = 6700g/mol, $Đ$

= 3.00) was observed when using a stoichiometric amount of aldehyde, amine, and isocyanide functions. The structure of the poly(α-amino amide) P_6 was proved by ^{1}H NMR, HSQC, and IR (Figures 4b, S11b, and S6c, respectively). The *meta*-phenylenediamine and 1,4-phenylendiisocyanide were also reacted with an aliphatic aldehyde, that is, isobutyraldehyde (Table 2, entry 7). The resulting polymer P_7 exhibited a lower M_n (3000g/mol, DP = 8) compared to P_6 (M_n = 6400g/mol, DP = 14), suggesting a lower efficiency of the Ugi-3CR for aliphatic compounds. To overcome this issue, we repeated the same reaction with 20mol % of PPA (Table 2, entry 8) and obtained P_8 with a much higher M_n, that is, 12600g/mol. ^{1}H NMR, HSQC, and IR analyses of P_8 are provided in Figures 4c, S11c, and S6d, respectively. Finally, phenylenediamine was substituted for hexamethylenediamine in order to further increase the aliphatic content in the polymer structure (Table 2, entries 9 and 10). This Ugi-3CR polymerization was tested with two catalyst loadings, that is, 10mol % and 20mol % (Table 2, entries 9 and 10). Expectedly, better results were obtained with 20mol % of catalyst leading to P_{10} with a molar mass of 2900g/mol compared to P_9 (1700g/mol) produced in the presence of 10mol % of PPA. Again, a confirmation of the polymer structure was obtained by NMR, HSQC, and IR (Figure 4d, S11d, and S6e, respectively). These results illustrate the versatility of the Ugi-3CR polymerization.

Finally, a preliminary study of the thermal and solution properties of these poly(α-amino amide)s was conducted. All poly(α-amino amide)s showed a decomposition onset temperature (T_{DO}) comprised between 289 and 327°C (Figure S13). Expectedly, P_{10}, having the lowest amount of aromatic groups in its repeating unit, was the least stable (T_{DO} = 289°C), whereas P_6 and P_8, containing two aromatic groups per repeating units in their backbone, were the most thermally stable and showed a broad degradation profile. In general, these poly(α-amino amide)s appear less thermally stable than classical aromatic and semiaromatic polyamides, for example, poly(*m*-phenylene isophtalamide)[65] and poly(hexamethylene isophtalamide),[66] that are stable at least up to 400°C. It is thus reasonable to assume that the amino groups accelerate the thermal decomposition of the poly(α-amino amide)s. Nevertheless, the latter possess a rather large temperature window for processing. The thermal transitions of the polymers were then analyzed by DSC (Figure S14). No glass transition temperature (T_g) was detected below 250°C, except for P_{10} and P_1 showing a T_g at 78 and 117°C, respectively. The rather low T_g recorded for these two polymers probably results from their higher flexibility due to the lower aromatic content in their backbone. The same trend was observed for classical polyamides. For example, the T_g of semiaromatic polyamidelike poly(hexamethylene isophtalamide) (T_g = 124°C)[67] is lower compared to their corresponding aromatic polyamide, such as poly(m-phenylene isophtalamide) (T_g = 285°C).[68] Regarding their solubility, all polymers were soluble in DMF, sometimes after heating. Interestingly, the aliphatic-rich poly(α-amino amide) P_{10} is also soluble in methanol and exhibits a pH responsive behavior in water (Figure S15). Insoluble when placed in water at pH7 at 5mg/mL, P_{10} becomes fully soluble at pH1 upon addition of HCl as a result of the protonation of the amino group. A gradual return to pH6 by addition of NaOH, triggered the precipitation of the polymer which increased the turbidity of the solution. The transition was observed around pH5.5. Note that the other polymers containing more aromatic groups in their structure, especially in their backbone, remained insoluble in water, even at low pH. This preliminary experiment emphasizes the potential of such an aliphatic-rich poly(α-amino amide)s as novel pH-responsive sequence.

In conclusion, we investigated for the very first time the Ugithree component reaction in polymer synthesis. This straightforward and highly atom economic strategy paved the way to unprecedented poly(α-amino amide)s. After a preliminary study of a model reaction, the experimental Ugi-3CR polymerization conditions were optimized, and most of the polymers exhibited a molar mass comprised between 3000 and 12600g/mol. These values could be improved in the future in parallel with progress in the optimization and mechanistic understanding of the catalytic Ugi-3CR reaction. As an illustration of the versatility of the Ugi-3CR polymerization, various aromatic and aliphatic components were used as starting materials leading to a series of poly(α-amino amide)s. In this work, diamines, diisocyanides, and aldehydes were combined in order to incorporate the amino and amido groups within the polymer backbone. Nevertheless, dialdehydes could also be associated with diamines or diisocyanides in the presence of the third monofunctional component giving access to macromolecules with lateral amino and amido groups. While further investigation is necessary to establish their full potential, we carried out preliminary studies of the thermal and solution properties of these poly(α-amino amide)s. The aliphatic-rich derivative notably showed some pH-responsiveness in water via protonation−deprotonation of its amine functions. Overall, the present study represents a significant step forward in the design of poly(α-amino amide)s and adds a new string to the bow of the increasingly popular macromolecular engineering based on multicomponent reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.9b00182. Detailed experimental procedures, GPC, infrared, and NMR spectra of the polymers (PDF)

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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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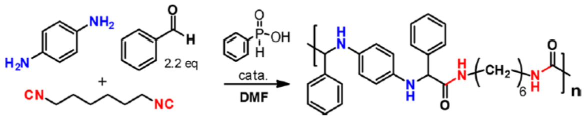
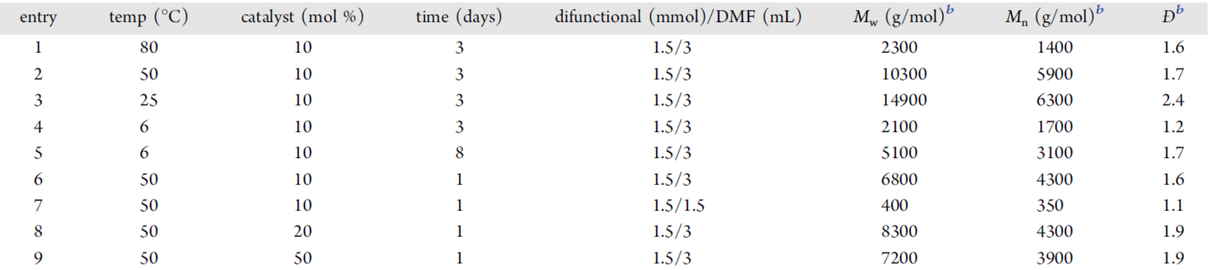
Table

Table 1. *Ugi-3 CR Polymerization Involving p-Phenylenediamine, Benzaldehyde, and 1,6-Diisocyanohexane*[a]



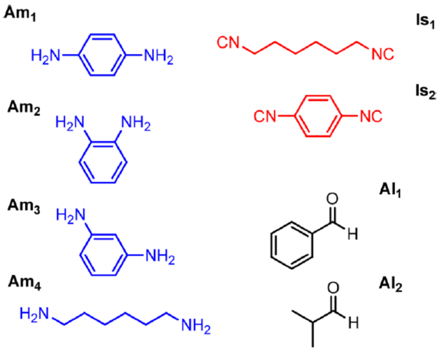


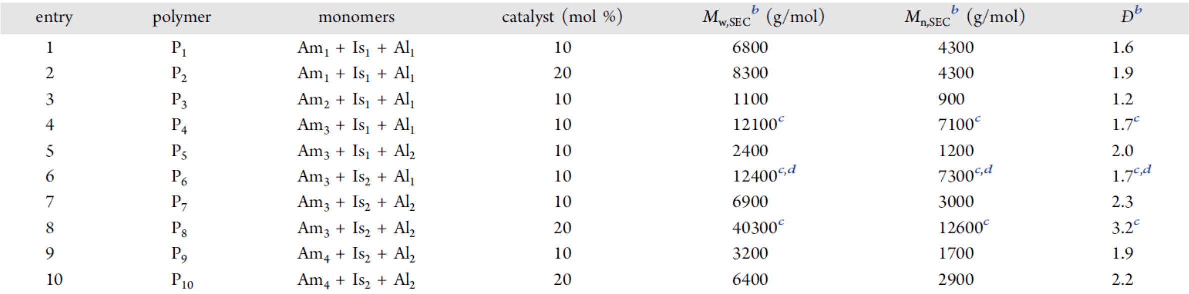
entry	temp (°C)	catalyst (mol %)	time (days)	difunctional (mmol)/DMF (mL)	M_{w} (g/mol)[b]	M_{n} (g/mol)[b]	Đ[b]
1	80	10	3	1.5/3	2300	1400	1.6
2	50	10	3	1.5/3	10300	5900	1.7
3	25	10	3	1.5/3	14900	6300	2.4
4	6	10	3	1.5/3	2100	1700	1.2
5	6	10	8	1.5/3	5100	3100	1.7
6	50	10	1	1.5/3	6800	4300	1.6
7	50	10	1	1.5/1.5	400	350	1.1
8	50	20	1	1.5/3	8300	4300	1.9
9	50	50	1	1.5/3	7200	3900	1.9

[a] *Reaction conditions: PPA, p-phenylenediamine (1.5mmol), benzaldehyde (3.3mmol), and 1,6 diisocyanohexane (1.5mmol) in DMF.*

[b] *Determined by SEC in DMF.*

Table 2. *Synthesis of a Series of Poly(α-amino amide)s by Ugi-3CR*





entry	polymer	monomers	catalyst (mol %)	$M_{\mathrm{w,SEC}}$[b] (g/mol)	$M_{\mathrm{n,SEC}}$[b] (g/mol)	Đ[b]
1	P_1	$Am_1 + Is_1 + Al_1$	10	6800	4300	1.6
2	P_2	$Am_1 + Is_1 + Al_1$	20	8300	4300	1.9
3	P_3	$Am_2 + Is_1 + Al_1$	10	1100	900	1.2
4	P_4	$Am_3 + Is_1 + Al_1$	10	12100[c]	7100[c]	1.7[c]
5	P_5	$Am_3 + Is_1 + Al_2$	10	2400	1200	2.0
6	P_6	$Am_3 + Is_2 + Al_1$	10	12400[c,d]	7300[c,d]	1.7[c,d]
7	P_7	$Am_3 + Is_2 + Al_2$	10	6900	3000	2.3
8	P_8	$Am_3 + Is_2 + Al_2$	20	40300[c]	12600[c]	3.2[c]
9	P_9	$Am_4 + Is_2 + Al_2$	10	3200	1700	1.9
10	P_{10}	$Am_4 + Is_2 + Al_2$	20	6400	2900	2.2

[a] *Conditions: diamine (1.5mmol), diisocyanide (1.5mmol), aldehyde (3.3mmol), PPA (10 or 20mol %), DMF, 50°C, 24h. Analyses performed after dialysis against DMF except for P_3 and P_5 having low M_n.*

[b] *SEC in DMF/LiBr with PS calibration.*

[c] *Polymers treated with trichloroacetyl isocyanate before SEC to avoid aggregation (Figure S10).*

[d] *72h reaction.*

Figures

***Figure 1**. (a) General mechanisms of Ugi three-, four-, and five-component reactions. (b) Examples of polymers produced via Ugitype polymerizations.*

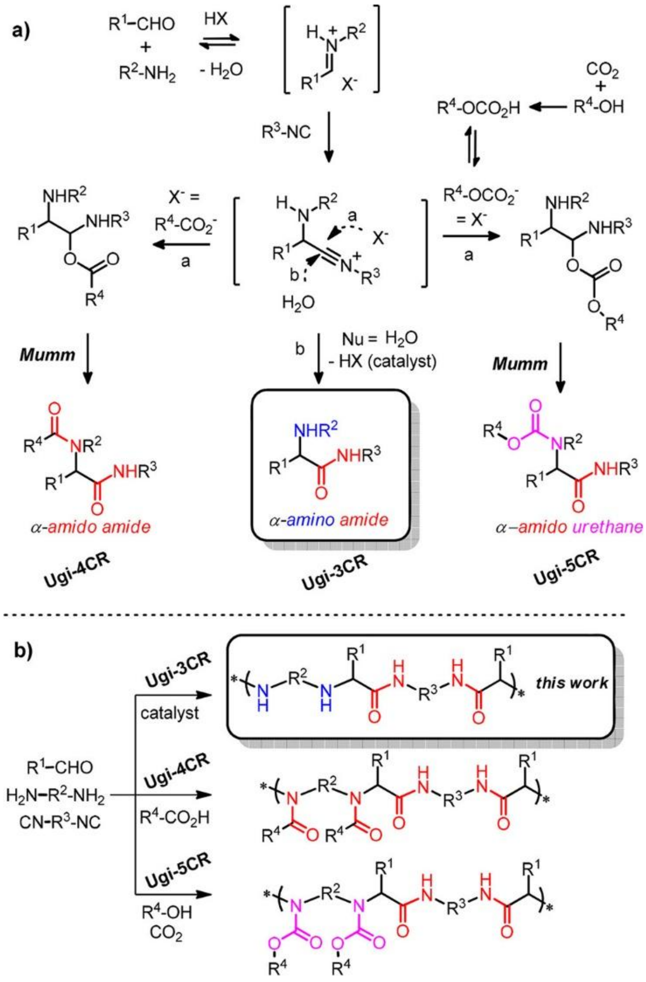


Figure 2. *^{1}H NMR analysis of the model α-amino amide (a), as well as ^{1}H NMR (b) and ^{13}C NMR (c) spectra of polymer P_1, in deuterated dimethyl sulfoxide after purification by dialysis (cut off 1kD) against DMF, followed by precipitation in Et_2O.*

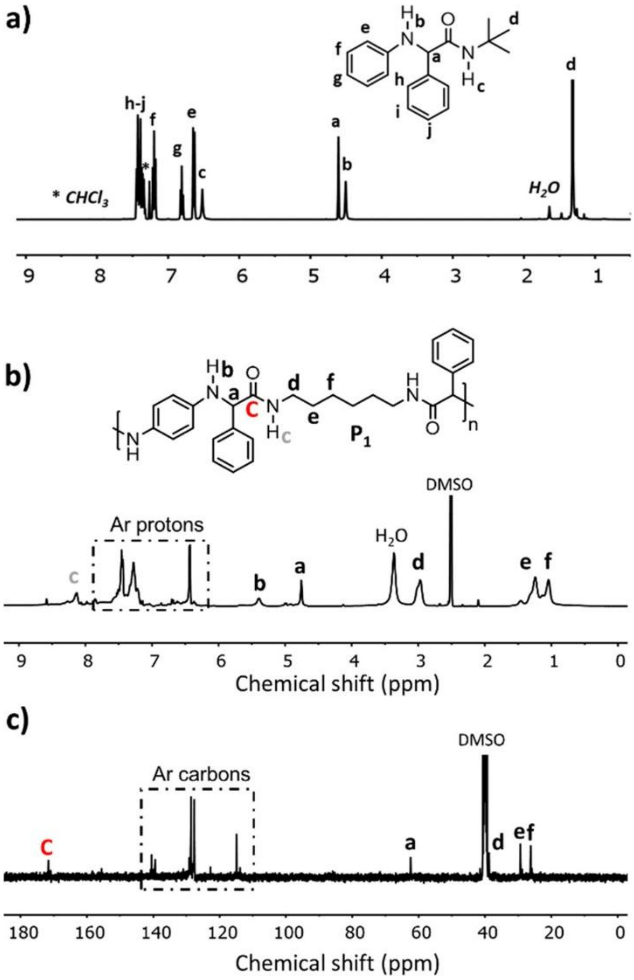


Figure 3. *(a) ESI/MS spectrum of the cyclic unimer, (b) isotopic distribution for the sodiated cyclic unimer, and (c) collision-induced dissociation (CID) analysis carried out at low collisional energy (5eV) on the m/z 913.5 ions.*

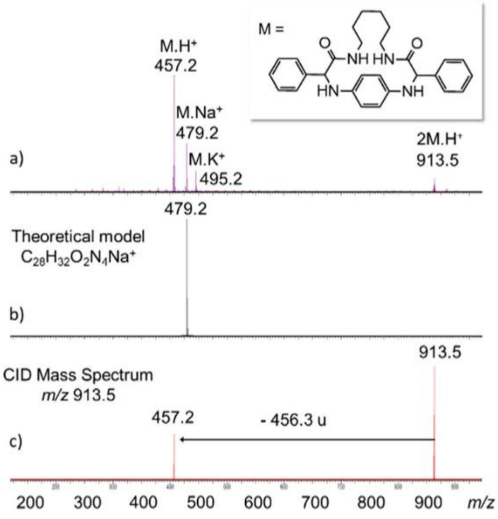
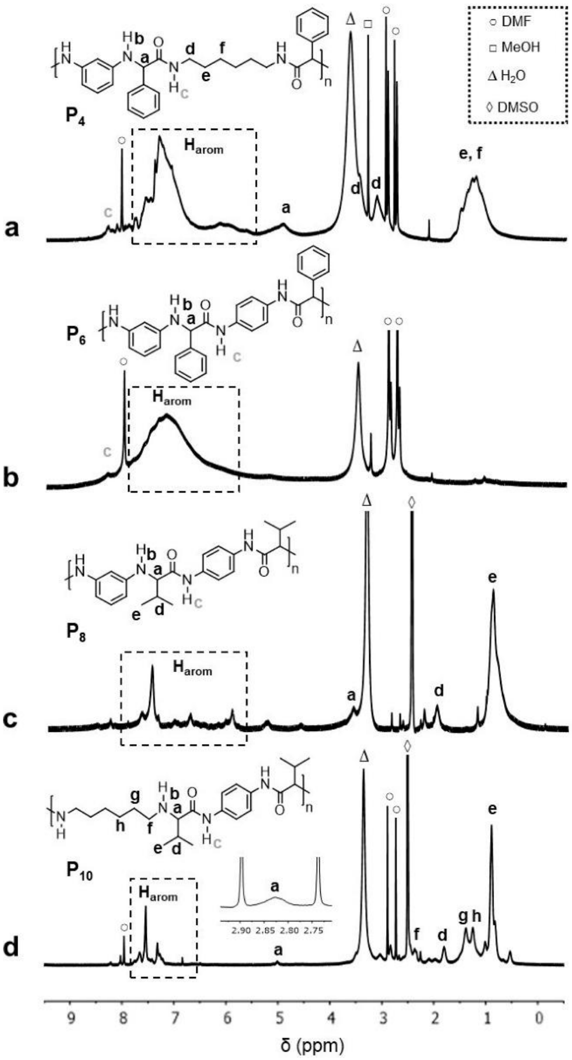


Figure 4. *^{1}H NMR spectra of polymer (a) P_4, (b) P_6, (c) P_8, and (d) P_{10} in DMF-d_7 or DMSO-d_6 after purification by dialysis (cut off 1kD) against DMF, followed by precipitation in Et_2O.*



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