

# Development of chlorotriazine polymer dehydrocondensing reagents (Poly-Trzs)

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**Abstract**—Polymer-type dehydrocondensing reagents comprising of a triazine dehydrocondensing reagent, itself in a polymerized form (Poly-Trz—MMs'), have been developed by exploiting the chemical properties of cyanuric chloride that readily binds to alcohol or amines. A chlorotriazine polymer bearing two alkoxy substituents at the 4- and 6- positions (Poly-O-Trz-Cl) was prepared by alternating copolymerization between cyanuric chloride and tetra(ethylene glycol). Similarly, polymers bearing both alkoxy and amino substituents (Poly-N-Trz-Cl) were synthesized from tetra(ethylene glycol) bis(4,6-dichlorotriazin-2-yl) ether **6** and tris(2-aminoethyl)amine **7** and/or ethylenediamine **8**. All the polymers were shown to be good reagents for dehydrocondensation of carboxylic acids and amines in the presence of NMM, compared to the corresponding monomeric dehydrocondensing reagent (DMT-MM). The advantages of the polymeric reagents are as follows: (1) both the reaction and isolation procedure of dehydrocondensation can be greatly simplified, (2) the dehydrocondensation can be conducted in protic solvents as well as in common organic solvents, (3) the reagents can be efficiently prepared at a low cost, and (4) these reagents are considered eco-friendly, generating a lower amount of waste compared to conventionally related reagents because of high loading of the dehydrocondensing activity (ca. 3 mequiv/g).

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## 1. Introduction

In general, solid-supported reagents have advantages. For example, the isolation and purification of desired products, as well as the recovery of the reagents, can be simply performed.<sup>1</sup> The use of solid-phase reagents has advantages over solid-phase synthesis, in that consumption of starting materials and formation of desired products can be simply monitored by chromatographic methods such as TLC. Furthermore, when a reagent itself is toxic or has an irritating odor, these properties can be buried by supporting it on a polymer. In association with the progress in the field of combinatorial chemistry, development and utilization of solid-supported reagents were actively pursued for the purpose of automating the synthetic process.

Because of both the research and industrial importance of amides and esters, development of useful dehydrocondensing reagents has received much attention. In spite of many reports on dehydrocondensing reagents, reports on developing solid-supported reagents of this type are limited. There

are many reports on polymer-supported acyl group-activating reagents consisting of a nitrophenol,<sup>2</sup> 1-hydroxybenzotriazole (HOBt),<sup>3</sup> *N*-hydroxysuccinimide (HOSu),<sup>4</sup> pyridine,<sup>5</sup> and so on.<sup>6</sup> For these polymer-supported reagents, however, monomeric reagents for acylation or dehydrocondensation, such as acid chlorides or 1,3-dicyclohexylcarbodiimide (DCC) is additionally required to introduce acyl groups into the polymers.

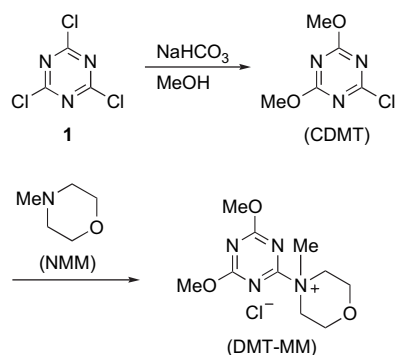
In contrast, solid-supported dehydrocondensing reagents are very useful because they do not require the use of such additional coupling reagents. However, most reagents of this type suffer disadvantages in practical use. For example, for the preparation of reported polymer reagents carrying 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), DCC, 1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium tetrafluoroborate 3-oxide (TBTU), or 1,3-dimethyl-2-imidazolidinone (DMC), chemical transformations of the insoluble polymer under heterogeneous conditions were required.<sup>7</sup> In contrast, a polymer-supported carbodiimide (P-EDC), in which 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) is connected via its dimethylamino group can be prepared with relative ease. However, the reaction introducing EDC to a polymer requires an excess amount of expensive EDC under forcing conditions.<sup>8</sup> It was reported that polymer-supported Mukaiyama reagents

**Keywords:** Dehydrocondensing reagent; Triazine; Polymer; Immobilized reagent.

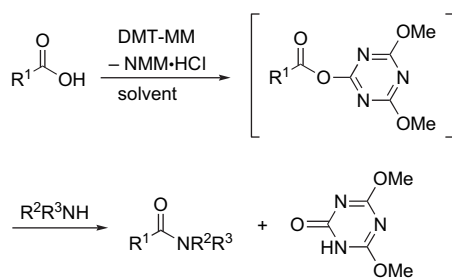
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could also be easily prepared by introducing 2-chloropyridine to either Wang resin or Merrifield's resin.<sup>9</sup> On the other hand, the weight proportion of the solid carrier relative to the amount of solid-supported reagent is generally high, which inevitably generates a large amount of waste, a serious problem common to solid-supported reagents. For instance, the molecular weight per unit reactivity of the aforementioned P-EDC and polymer-supported Mukaiyama reagents reaches about 1250 and 800, respectively. Therefore, practically useful solid-supported dehydrocondensing reagents that do not have these disadvantages have been sought.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium (DMT-MM), a triazine-type dehydrocondensing reagent developed at our and other laboratories, can be simply obtained by mixing 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) (Scheme 1).<sup>10,11</sup> We have originally found that DMT-MM with an high water solubility enables the efficient conduction of an amide-forming reaction in a protic solvent such as alcohols or water (Scheme 2).<sup>11,12</sup> The coproduced 4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one was shown to be recyclable.<sup>13</sup> Furthermore, cyanuric chloride **1**, used as a starting material for synthesizing DMT-MM, has the advantage of being inexpensive. In addition to its cost effectiveness, the use of this starting material allows chemical modifications to be made easily by selective substitution of its chloro substituents. Taking advantage of the chemical property of this triazine dehydrocondensing reagent, we have succeeded in solving the aforementioned problems associated with solid-supported condensing agents. We report herein the development of polymer dehydrocondensing reagents comprised of chlorotriazines, which have excellent cost effectiveness as well as good reactivity.<sup>14</sup>



Scheme 1.



Scheme 2.

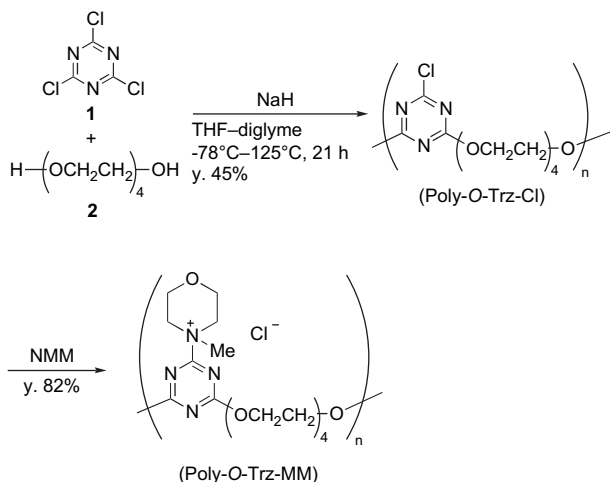
As an example of an immobilized reagent of triazine derivatives,<sup>15–17</sup> Taddei and Masala reported on a reagent in which cyanuric chloride is supported on the Wang resin, bearing amino functional groups.<sup>16a</sup> An improved polymer reagent, in which a cyanuric group is used as a spacer, has also been reported.<sup>16b</sup> Since the carrier resin used in these polymer-supported reagents contains 1.0 mequiv/g of amino group, the mean molecular weight per unit of the condensing reagent reached at least over 1000. Furthermore, a large excess (5 equiv) of cyanuric chloride had to be used to connect the triazino group to polymer. On the other hand, poly(ethylene glycol)-2,4-dichloro-1,3,5-triazine (PEG-DCT) was synthesized as a soluble nucleophilic scavenger by reacting poly(ethylene glycol) methyl ether (MeO-PEG-OH) with cyanuric chloride, but the generation of a large amount of waste was inevitable because MeO-PEG-OH has a large mean molecular weight, approximately 5000.<sup>17</sup> Although these polymers were synthesized utilizing the high reactivity of cyanuric chloride, the idea did not go beyond the conventional concept of supporting a reagent on an existing polymer; therefore, the disadvantage of the increase in molecular weight prevailed. We now show that a chlorotriazino group can be immobilized without great increase in molecular weight when cyanuric chloride **1** itself is converted to a polymer by efficiently exploiting the reactivity of all the chlorine atoms of **1**.<sup>18</sup>

## 2. Results and discussion

### 2.1. *O,O*-Type polymeric triazine reagent (Poly-*O*-Trz)

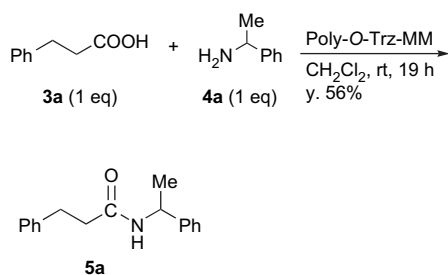
To retain the reactivity of DMT-MM, an *O,O*-type triazine structure bearing two oxygen substituents corresponding to 4,6-dimethoxy groups was considered favorable; thus we attempted to synthesize a straight-chain polymer by alternating copolymerization of cyanuric chloride **1** and tetra(ethylene glycol) **2**. First, we used sodium carbonate or *N,N*-diisopropylethylamine as a base, but were unable to obtain the desired polymer, perhaps, because the second chlorine atom of **1** was less reactive for the substitution by an alcoholic hydroxyl group.<sup>20</sup> Based on this reasoning, we replaced the base with sodium hydride to enhance the nucleophilicity of the hydroxyl group by converting it to the alkoxide; the reaction was performed in diglyme at 125 °C, giving precipitates. The polymer thus obtained was insoluble in any common solvents and could be simply purified by filtration followed by washing with water and THF. The theoretical structure of the polymer, based on mechanistic considerations of the reaction, is shown in Scheme 3 (Poly-*O*-Trz-Cl), and the yield of Poly-*O*-Trz-Cl was calculated as 45%, based on this structure. The linear chain of Poly-*O*-Trz-Cl might be partially branched because the third chloro group can undergo substitution with alkoxy group under these strong reaction conditions.<sup>21</sup> Poly-*O*-Trz-Cl was treated with an excess amount of NMM (3 equiv) to generate its active form (Poly-*O*-Trz-MM) in 82% yield.<sup>22,23</sup> The condensing reactivity of Poly-*O*-Trz-MM was determined by measuring the amount of free chloride ions released by the substitution reaction. As a result, the amount of chloride loaded on Poly-*O*-Trz-Cl was at least 3.07 mequiv/g, and the molecular weight per unit of the condensing activity was 326, indicating that our polymer was

high loading compared to conventional polymer-supported dehydrocondensing reagents.



Scheme 3. Synthesis of Poly-O-Trzs.

We examined dehydrocondensation between 3-phenylpropionic acid **3a** and *DL*-1-phenylethylamine **4a**, as model reactants. The reaction with Poly-O-Trz-MM (1.9 equiv based on the loading of chloride) in  $\text{CH}_2\text{Cl}_2$  for 19 h gave the amide **5a** in 56% yield in pure form after filtration followed by washing with water (Scheme 4). DMT-MM is known to readily decompose in less-polar organic solvents by dechloromethylation at the methylmorpholinio group.<sup>10a,b</sup> Thus, the methylmorpholinio group in a hydrophobic pocket of Poly-O-Trz-MM might partially undergo decomposition during isolation and on storage, which may be responsible for the observed moderate yield of **5a**. In order to avoid such decomposition, we employed in situ generation of Poly-O-Trz-MM from Poly-O-Trz-Cl and NMM. Thus, a solution of both the reactants (**3a** and **4a**) and NMM was added to Poly-O-Trz-Cl, and the suspension was stirred at room temperature. Results are summarized in Table 1.



Scheme 4.

Table 1. Attempts to produce **5a** in various solvents by a combination of Poly-O-Trz-Cl and NMM (in situ generation of Poly-O-Trz-MM)

Run	Solvent	Poly-O-Trz-Cl (equiv)	Time (h)	Yield <sup>a</sup> of <b>5a</b> (%)
1	$\text{CH}_2\text{Cl}_2$	1.1	22	52
2	$\text{CH}_2\text{Cl}_2$	2.0	3	84
3	$\text{CH}_2\text{Cl}_2$	2.0	21	90
4	$\text{CH}_2\text{Cl}_2$	3.0	21	90
5	THF	2.0	3	64
6	MeOH	3.0	21	89
7	$\text{H}_2\text{O}$	3.0	21	76
8	AcOEt	3.0	21	87
9	$\text{CH}_3\text{CN}$	2.0	21	55
10	MeOH	2.0	21	87

<sup>a</sup> Isolated yield.

When an excess of Poly-O-Trz-Cl (2 equiv) was used in  $\text{CH}_2\text{Cl}_2$ , the reaction proceeded and gave the desired product in good yield (Runs 1 and 2). The reaction seemed to be almost complete at room temperature within 3 h; the yield of the amide was not greatly improved by prolongation of the reaction time (Runs 2 and 3). It is noteworthy that water or methanol as well as commonly used neutral organic solvents could be used. The swelling of the polymer was insufficient in THF or acetonitrile, which may explain the decreased yield of the amide in these solvents.

The dehydrocondensation of various carboxylic acids with amines was examined under the conditions using 2 equiv of Poly-O-Trz-Cl with NMM in  $\text{CH}_2\text{Cl}_2$  (Table 2). The reaction was also found to proceed with  $\alpha,\beta$ -unsaturated carboxylic acid **3c** or aromatic carboxylic acid **3d** at room temperature to give moderate to good yield within 3–4 h. With regard to amines, the reaction proceeded not only with primary amines, but also with bulky secondary amines such as **4c** (Run 5).

## 2.2. *N,O*-Type polymeric triazine reagent (Poly-N-Trzs)<sup>14a</sup>

Although Poly-O-Trz-MM bearing two oxygen atoms in its triazine rings showed good reactivity comparable to that of DMT-MM, there were disadvantages in the reaction for preparation of Poly-O-Trz-Cl; strong basic conditions and a long heating time were required because the polymer was not readily precipitated on polymerization. To solve the problem, we planned to synthesize a cross-linked polymer under milder conditions (at a lower temperature within a shorter reaction period) by using an amino group with higher nucleophilicity compared to that of a hydroxyl group. Since the electron-donating property toward the triazine ring is higher for nitrogen than for oxygen, it was anticipated that dehydrocondensing reactivity might differ between an

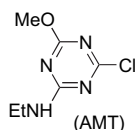
Table 2. Attempts to produce **5a** in various solvents by a combination of Poly-O-Trz-Cl and NMM (in situ generation of Poly-O-Trz-MM)<sup>a</sup>

Run	Carboxylic acids	Amines	Amides	Yield <sup>b</sup> (%)
1	<b>3a</b>	$\text{Ph}(\text{CH}_2)_2\text{NH}_2$ ( <b>4b</b> )	$\text{Ph}(\text{CH}_2)_2\text{CONH}(\text{CH}_2)_2\text{Ph}$ ( <b>5b</b> )	80
2	<i>p</i> -MeO- $\text{C}_6\text{H}_4\text{CH}_2\text{COOH}$ ( <b>3b</b> )	<b>4b</b>	<i>p</i> -MeO- $\text{C}_6\text{H}_4\text{CH}_2\text{CONH}(\text{CH}_2)_2\text{Ph}$ ( <b>5c</b> )	71
3	$\text{PhCH}=\text{CHCOOH}$ ( <b>3c</b> )	<b>4b</b>	$\text{PhCH}=\text{CHCONH}(\text{CH}_2)_2\text{Ph}$ ( <b>5d</b> )	63
4	$\text{PhCOOH}$ ( <b>3d</b> )	<b>4b</b>	$\text{PhCONH}(\text{CH}_2)_2\text{Ph}$ ( <b>5e</b> )	76
5	<b>3a</b>	$\text{PhCH}_2\text{NHMe}$ ( <b>4c</b> )	$\text{Ph}(\text{CH}_2)_2\text{CONMeCH}_2\text{Ph}$ ( <b>5f</b> )	71

<sup>a</sup> The reaction was performed with Poly-O-Trz-Cl (2.1 equiv) and NMM (2.1 equiv) at rt for 3–4 h.

<sup>b</sup> Isolated yield.

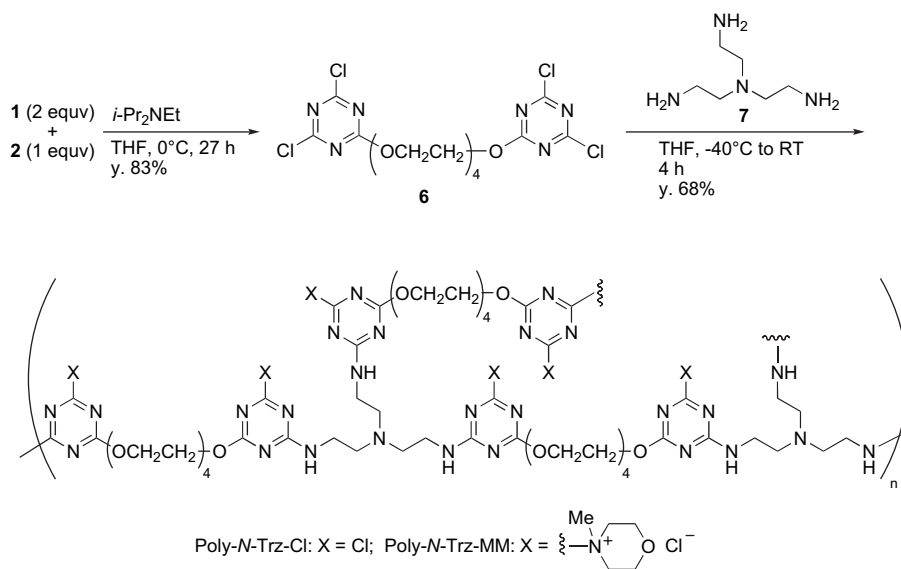
*N,O*-type cross-linked polymer and an *O,O*-type polymer. Thus, in a preliminary experiment, we synthesized 2-chloro-6-ethylamino-4-methoxy-1,3,5-triazine (AMT), an *N,O*-type monomer bearing both methoxy and ethylamino groups, as a model compound, and examined its reactivity. The reactivity of AMT seemed somewhat lower than that of CDMT; when a mixture of **3a** and **4a** was allowed to react with AMT (1.2 equiv) in the presence of NMM (1.8 equiv) at room temperature for 24 h, the desired amide **5a** was obtained in 62% yield in CH<sub>2</sub>Cl<sub>2</sub>. The reaction yield was improved to 95% within 3 h by increasing the amount of AMT (2 equiv) and NMM (3 equiv).



On the basis of these findings an *N,O*-type polymer (Poly-*N*-Trz), in which nitrogen and oxygen functionalities of different reactivities are selectively introduced into the triazino group was synthesized (Scheme 5). Initially, **1** (2 equiv) was allowed to react with **2** (1 equiv) in THF at 0 °C for 27 h, giving an *O,O'*-bis(dichlorotriazino) compound **6**<sup>14a</sup>

in 83% yield. A copolymerization was conducted by reacting **6** with the cross-linking reagent **7**, bearing three primary amino groups, at -40 °C to room temperature, giving Poly-*N*-Trz-Cl in 68% yield. The polymerization was completed within 4 h under milder conditions compared to the polymerization for producing Poly-*O*-Trz-Cl. The amount of reactive chlorotriazinyl group loaded on Poly-*N*-Trz-Cl was 2.91 mequiv/g.<sup>25</sup>

The dehydrocondensation of **3a** and **4a** was performed using Poly-*N*-Trz-MM generated in situ from Poly-*N*-Trz-Cl and NMM in CH<sub>2</sub>Cl<sub>2</sub>, in a manner similar to that of Poly-*O*-Trz-Cl (Table 3). Although the reaction was slower, than that when AMT or Poly-*O*-Trz-Cl was used, **5a** was obtained in a good yield (82%) after being treated at room temperature for 19 h (Run 1). The amides produced could be simply obtained in an almost pure form by filtering the reaction mixture, followed by washing the filtrate with water. When the reaction mixture was treated with an anion-exchange resin (Amberlite IRA-400) for 30 min, the desired product could be more simply obtained in good purity by concentrating the filtrate without washing with water (Runs 3, 6–8).  $\alpha,\beta$ -Unsaturated carboxylic acid **3c** as well as aliphatic carboxylic acids **3a** and **3b** were also found to condense with primary amines **4a** and **4b**, or bulky secondary amine **4d**, giving the corresponding amides in good



Scheme 5. Synthesis of Poly-*N*-Trzs.

Table 3. Condensation of carboxylic acids with amines in CH<sub>2</sub>Cl<sub>2</sub> (in situ generation of Poly-*N*-Trz-MM)

Run	Carboxylic acid	Amine	Poly- <i>N</i> -Trz-Cl (equiv)	NMM (equiv)	Time (h)	Product	Yield (%)
1	<b>3a</b>	<b>4a</b>	3.0	3.0	19	<b>5a</b>	82
2	<b>3a</b>	<b>4b</b>	3.0	3.0	19	<b>5b</b>	97
3 <sup>a</sup>	<b>3a</b>	<b>4b</b>	2.0	2.0	20	<b>5b</b>	85
4	<b>3b</b>	<b>4b</b>	3.0	3.0	19	<b>5c</b>	Quant
5	<b>3c</b>	<b>4b</b>	3.0	3.0	19	<b>5d</b>	97
6 <sup>a</sup>	<b>3a</b>	Et <sub>2</sub> NH ( <b>4d</b> )	2.5	2.5	20	Ph(CH <sub>2</sub> ) <sub>2</sub> CONEt <sub>2</sub> ( <b>5g</b> )	83
7 <sup>a</sup>	Z-Gly-OH ( <b>3e</b> )	H-Phe-OMe ( <b>4e</b> )	2.5	4.0	20	Z-Gly-Phe-OMe ( <b>5h</b> )	81
8	Boc-Leu-OH ( <b>3f</b> )	<b>4e</b>	2.5	4.0	20	Boc-Leu-Phe-OMe ( <b>5i</b> )	92 <sup>b</sup>
9 <sup>a</sup>	<b>3a</b>	HO(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ( <b>4f</b> )	2.5	2.5	20	Ph(CH <sub>2</sub> ) <sub>2</sub> CONH(CH <sub>2</sub> ) <sub>2</sub> OH ( <b>5j</b> )	87

<sup>a</sup> The reaction mixture was treated with Amberlite IRA-400 OH and then filtered.

<sup>b</sup> No detectable amount of the epimer was observed by HPLC.



**Table 4.** Yield and loading of lower degrees of cross-linked Poly-*N*-Trzs-Cl

Cross-linking (%)	Molar ratio 6:7:8	Yield (%)	Loading (mequiv/g)	MW <sub>av</sub>
50	5:2:2	63	3.76	266
25	9:2:6	70	3.30	303
10	21:2:18	64	2.85	351

yields under the same conditions. When polar compounds are used for the reaction of non-immobilized monomeric reagents such as DMT-MM and EDC, the isolation procedures may be troublesome. Condensation of amino acid derivatives **3e**, **3f**, and **4e**, or hydroxyethylamine **4f**, could be readily performed, and the desired products were isolated by the simple procedures of filtration and concentration (Runs 7–9). Notably, a selective reaction occurred at the nitrogen atom, producing the corresponding amide in the case of the reaction of **4f** (Run 9).

The slow reaction using a combination of Poly-*N*-Trz-Cl/NMM was due to not only electron-donating amino substituents at the triazine ring (as observed in AMT), but also as a consequence of the highly cross-linked structure of the polymer in which access of the reactants to the reaction center may be hindered. Thus, we attempted to prepare polymers with low degrees of cross-linking, in which the tris-primary amine **7** was partially substituted with ethylenediamine **8**. Three types of Poly-*N*-Trz-Cl with different degrees of cross-linking (50%, 25%, and 10%) were prepared,<sup>14b</sup> and all of these were found to be high loading (Table 4).<sup>26</sup> The polymer with 10% cross-linking was found

**Table 5.** Effect of the degree of cross-linking on the synthesis of **5b**

Cross-linking (%)	Time (h)	Yield of <b>5b</b> (%)
100	10	71
100	20	81
50	20	88
25	10	73
25	20	88

**Table 6.** Condensation of carboxylic acids with amines by in situ generation of Poly-*N*-Trz-MM with different degrees of cross-linking<sup>a</sup>

Run	Product	Solvent	Yield (%)	
			Cross-linking	
			50%	25%
1	Ph(CH <sub>2</sub> ) <sub>2</sub> CONHCHMePh ( <b>5a</b> )	CH <sub>2</sub> Cl <sub>2</sub>	85	62
2	Ph(CH <sub>2</sub> ) <sub>2</sub> CONH(CH <sub>2</sub> ) <sub>2</sub> Ph ( <b>5b</b> )	CH <sub>2</sub> Cl <sub>2</sub>	88	87
3 <sup>b</sup>	<b>5b</b>	MeOH	85	nc <sup>f</sup>
4 <sup>b</sup>	<b>5b</b>	H <sub>2</sub> O	46	45
5	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CONH(CH <sub>2</sub> ) <sub>2</sub> Ph ( <b>5c</b> )	CH <sub>2</sub> Cl <sub>2</sub>	92	93
6	PhCH=CHCONH(CH <sub>2</sub> ) <sub>2</sub> Ph ( <b>5d</b> )	CH <sub>2</sub> Cl <sub>2</sub>	79	73
7	PhCONH(CH <sub>2</sub> ) <sub>2</sub> Ph ( <b>5e</b> )	CH <sub>2</sub> Cl <sub>2</sub>	80	71
8	Ph(CH <sub>2</sub> ) <sub>2</sub> CONEt <sub>2</sub> ( <b>5g</b> )	CH <sub>2</sub> Cl <sub>2</sub>	91	93
9 <sup>c,d</sup>	Z-Gly-Phe-OMe ( <b>5h</b> )	CH <sub>2</sub> Cl <sub>2</sub>	87	88
10 <sup>d</sup>	Boc-Leu-Phe-OMe ( <b>5i</b> )	CH <sub>2</sub> Cl <sub>2</sub>	85 <sup>e</sup>	nc <sup>f</sup>
11 <sup>c</sup>	Ph(CH <sub>2</sub> ) <sub>2</sub> CONH(CH <sub>2</sub> ) <sub>2</sub> OH ( <b>5j</b> )	CH <sub>2</sub> Cl <sub>2</sub>	77	77
12 <sup>b</sup>	<b>5j</b>	MeOH	83	76

<sup>a</sup> Reactions were performed with **3** (1.0 equiv), **4** (1.5 equiv), Poly-*N*-Trz-Cl (2.5 equiv), and NMM (2.5 equiv) at rt for 20 h.

<sup>b</sup> Reactions were performed with **3** (1.5 equiv) and **4** (1.0 equiv).

<sup>c</sup> The reaction mixture was treated with Amberlite IRA-400 OH.

<sup>d</sup> Four equivalents of NMM were used.

<sup>e</sup> A trace amount of the epimer (0.2%) was detected by HPLC.

<sup>f</sup> Reaction was not conducted.

unsuitable for practical use because it is very sticky. Thus, the polymers with 50% (Poly-*N*-Trz<sub>50</sub>-Cl) and 25% (Poly-*N*-Trz<sub>25</sub>-Cl) cross-linking were examined for dehydrocondensation to give **5b** (Table 5). Both of them were found to give amides in good yields in CH<sub>2</sub>Cl<sub>2</sub>, and a slight improvement in reaction yield was observed compared with, Poly-*N*-Trz-Cl with 100% cross-linking (Poly-*N*-Trz<sub>100</sub>-Cl). The results may indicate that Poly-*N*-Trz<sub>100</sub>-Cl has a sufficient space, which is attributable to the long chain of tetra(ethylene glycol) connecting two triazinyl groups, allowing reactants to approach to the triazinyl group inside the polymer network. The dehydrocondensation of various compounds was found to proceed in good yields by using Poly-*N*-Trz<sub>50</sub>-Cl and Poly-*N*-Trz<sub>25</sub>-Cl (Table 6). Amides can be prepared in MeOH in good yields and, in water, in moderate yields.

### 3. Conclusion

In conclusion, by exploiting the reactivity of chlorotriazines, we succeeded in developing new practical polymeric condensing reagents. The polymers developed here have an important, distinguishing characteristic, they are produced by copolymerization of a monomeric condensing reagent. The polymer can be synthesized in a homogeneous medium, therefore, the polymerization proceeds with high efficiency and only a stoichiometric amount of the chlorotriazine derivatives is needed. Because no carrier is used, the amount of waste can be greatly reduced. Furthermore, cyanuric chloride and ethylene glycols used as starting materials are inexpensive, affording excellent cost effectiveness. Condensation can be performed by a very simple procedure, mixing a carboxylic acid and an amine together with the polymer. In particular, there is a great advantage in Poly-*N*-Trzs, because protic solvents such as eco-friendly water or alcohols can be used. Unfortunately, however, an attempt in regenerating the Poly-*O*-Trz-Cl, after it had been used for condensation, according to our procedure for regeneration of CDMT using POCl<sub>3</sub>/Et<sub>2</sub>NPh was unsuccessful.<sup>13</sup> We are currently seeking a suitable method for recycling the polymers. It is expected that more highly functionalized polymeric dehydrocondensing reagents can be synthesized by extending the concept developed here, because it is possible to introduce various types of hydroxyl or amino functionality in the side chain of the triazinyl group.

## 4. Experimental section

### 4.1. General methods

<sup>1</sup>H NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported as  $\delta$  values relative to tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet FT-IR AVATER 360 spectrometer. Mass spectra were measured on a Micromass Zq2000 spectrometer (ESI-MS), and a JEOL The MStation JMS-700 (EI-MS). Differential scanning calorimetric (DSC) study was performed with Shimadzu DSC-50 with thermal analyzer (TA-50WS); a polymer (4–5 mg) was loaded into aluminum sample pan, sealed, and heated at a rate of 10 °C/min in the temperature range of –20 °C to 150 °C under a nitrogen flow of 20 mL/min.

All solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Preparative thin-layer chromatography (TLC) was performed on Merck precoated silica gel plates.

## 4.2. Preparation of Poly-*O*-Trz-Cl

To a suspension of sodium hydride (5.47 g, 228 mmol) in THF (40 mL) was added tetra(ethylene glycol) (**2**, 23.2 g, 119 mmol) at 0 °C under nitrogen atmosphere and stirred for 1 h at 0 °C and for 1 h at room temperature. The reaction mixture was cooled to –78 °C, and cyanuric chloride (**1**, 20.0 g, 109 mmol) dissolved in THF (70 mL) was added dropwise. The resulting mixture was stirred successively at –78 °C, –40 °C, 0 °C, and at room temperature in each for 1 h. After addition of diglyme (35 mL), the mixture was stirred at 50 °C for 1 h and then heated to 125 °C, during which THF was distilled off. After heating for 16 h at 125 °C, the resulting mixture was cooled to 0 °C, and solid material was collected by suction, followed by successive washing with THF, water, and THF, and drying in vacuo to give 14.8 g of (45% yield) Poly-*O*-Trz-Cl. IR (KBr): 1628, 1490, 1141, 1112, 1058, 858, 813, 1646, 1557 cm<sup>-1</sup>.

## 4.3. Determination of the activity of Poly-*O*-Trz-Cl by titration of chloride

To a suspension of Poly-*O*-Trz-Cl (62.0 mg) in distilled water (10 mL) was added NMM (0.61 mmol, 61.6 mg) at room temperature. After being stirred for 1 h at room temperature, sodium nitrate (1.01 mmol, 86.2 mg) was added, and stirred for 2 h. The resulting suspension was diluted with distilled water, and titrated with silver nitrate (0.01 mol/L). The amount of chloride collected was 0.190 mmol, which indicated the unit activity to be 3.07 mequiv/g (0.190 mmol/62.0 mg).

## 4.4. Preparation of Poly-*O*-Trz-MM

NMM (399 mg, 3.94 mmol) was added to a suspension of Poly-*O*-Trz-Cl (402 mg, 1.23 mmol) in THF (10 mL) at room temperature. After being stirred for 20 min, the reaction mixture was filtered to collect solid material, which was washed with THF, followed by Et<sub>2</sub>O, and then dried in vacuo to give Poly-*O*-Trz-MM (432.5 mg). IR (KBr): 1302, 1333 cm<sup>-1</sup>; the signals at 1058, 858, and 813 cm<sup>-1</sup> observed in Poly-*O*-Trz-Cl, which can be assigned for C–Cl stretching of chlorotriazine, disappeared in the polymer product.

**4.4.1. Synthesis of *N*-(1-phenylethyl)-3-phenylpropanamide (**5a**) with Poly-*O*-Trz-MM.** A mixture of 3-phenylpropionic acid (**3a**, 0.150 mmol, 22.5 mg) and DL-1-phenethylamine (**4a**, 0.150 mmol, 18.1 mg) was added to Poly-*O*-Trz-MM (0.285 mmol) at room temperature, and the mixture was stirred for 19 h at room temperature followed by filtration. Solid material was washed successively with CH<sub>2</sub>Cl<sub>2</sub>–acetone (1:1), and the organic phases were combined and concentrated. The residue was dissolved in Et<sub>2</sub>O, and the resulting solution was washed successively with water, NaHCO<sub>3</sub>, water, HCl (1 mol/L), water, and brine. The solution was dried over MgSO<sub>4</sub> and concentrated to give a 21.4 mg of **5a**<sup>17</sup> (56%). Colorless crystals; mp 50–51 °C;

IR (KBr): 3260, 1646, 1557 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.40 (d, *J*=6.9 Hz, 3H), 2.46–2.50 (m, 2H), 2.97 (t, *J*=7.5 Hz, 2H), 5.10 (qd, *J*=6.9, 7.2 Hz, 1H), 5.51 (br s, 1H), 7.16–7.32 (m, 10H); HRMS (EI) *m/z* calcd for C<sub>17</sub>H<sub>19</sub>NO (M<sup>+</sup>) 253.1467, found 253.1457.

**4.4.2. *N*-Phenethyl-3-phenylpropanamide (**5b**).**<sup>10b</sup> Colorless crystals; mp 94.5–95.5 °C; IR (KBr): 3299, 1635, 1544 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.42 (t, *J*=7.7 Hz, 2H), 2.74 (t, *J*=6.9 Hz, 2H), 2.94 (t, *J*=7.7 Hz, 2H), 3.48 (td, *J*=6.9, 6.0 Hz, 2H), 5.31 (br s, 1H), 7.07–7.10 (m, 5H); HRMS (EI) *m/z* calcd for C<sub>17</sub>H<sub>19</sub>NO (M<sup>+</sup>) 253.1467, found 253.1476.

**4.4.3. 2-(4-Methoxyphenyl)-*N*-phenethylacetamide (**5c**).**<sup>10b</sup> Colorless crystals; mp 98–98.5 °C; IR (KBr): 3286, 1643, 1544, 1241, 1037 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.71 (t, *J*=6.8 Hz, 2H), 3.45 (td, *J*=6.8, 6.1 Hz, 2H), 3.46 (s, 2H), 5.39 (br s, 1H), 6.82–6.87 (m, 2H), 7.02–7.10 (m, 4H), 7.18–7.26 (m, 3H); HRMS (EI) *m/z* calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>2</sub> (M<sup>+</sup>) 269.1416, found 269.1425.

**4.4.4. *N*-Phenethylcinnamamide (**5d**).**<sup>10b</sup> Colorless needles; mp 126–127 °C; IR (KBr): 3299, 1650, 1614, 1544 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.89 (t, *J*=6.9 Hz, 2H), 3.66 (td, *J*=6.9, 6.0 Hz, 2H), 5.73 (br s, 1H), 7.21–7.37 (m, 8H), 7.45–7.50 (m, 2H), 7.62 (d, *J*=15.6 Hz, 1H); HRMS (EI) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>NO (M<sup>+</sup>) 251.1310, found 251.1319.

**4.4.5. *N*-Phenethylbenzamide (**5e**).**<sup>10b</sup> Colorless crystals; mp 113–114 °C; IR (KBr): 3345, 1639, 1542 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.93 (t, *J*=6.9 Hz, 2H), 3.71 (td, *J*=6.9, 5.9 Hz, 2H), 6.24 (br s, 1H), 7.21–7.27 (m, 3H), 7.29–7.35 (m, 2H), 7.36–7.42 (m, 2H), 7.44–7.50 (m, 1H), 7.67–7.71 (m, 2H); HRMS (EI) *m/z* calcd for C<sub>15</sub>H<sub>15</sub>NO (M<sup>+</sup>) 225.1154, found 225.1161.

**4.4.6. *N*-Benzyl-*N*-methyl-3-phenylpropanamide (**5f**).**<sup>11</sup> Colorless oil; IR (neat): 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) for a major conformational isomer δ: 2.64–2.71 (m, 2H), 2.84 (s, 3H), 2.97–3.06 (m, 2H), 4.59 (s, 2H), 7.15–7.35 (m, 10H); for a minor conformational isomer δ: 2.64–2.71 (m, 2H), 2.84 (s, 3H), 2.97–3.06 (m, 2H), 4.45 (s, 2H), 7.06–7.10 (m, 2H), 7.15–7.35 (m, 8H); HRMS (EI) *m/z* calcd for C<sub>17</sub>H<sub>19</sub>NO (M<sup>+</sup>) 253.1467, found 253.1461.

**4.4.7. *N,N*-Diethyl-3-phenylpropanamide (**5g**).**<sup>11</sup> Colorless oil; IR (neat): 1641 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.10 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H), 2.59 (t, *J*=7.9 Hz, 2H), 2.99 (t, *J*=7.9 Hz, 2H), 3.22 (q, *J*=7.1 Hz, 2H), 3.38 (q, *J*=7.1 Hz, 2H), 7.17–7.31 (m, 5H); HRMS (EI) *m/z* calcd for C<sub>13</sub>H<sub>19</sub>NO (M<sup>+</sup>) 205.1467, found 205.1460.

**4.4.8. *Z*-Gly-Phe-OMe (**5h**).**<sup>27</sup> Colorless oil; IR (neat): 1731, 1673, 1531 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 2.86–3.01 (m, 2H), 3.56 (s, 3H), 3.51–3.64 (m, 2H), 4.42–4.48 (m, 1H), 4.99 (s, 2H), 7.16–7.38 (m, 11H), 8.28 (d, *J*=8.0 Hz, 1H); HRMS (FAB) *m/z* calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> [(M+1)<sup>+</sup>] 371.1607, found 371.1619.

**4.4.9. Boc-Leu-Phe-OMe (**5i**).**<sup>11</sup> Colorless crystals; mp 83.5–84 °C; IR (KBr): 3342, 3307, 1743, 1666, 1523 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.91 (d, *J*=6.2 Hz, 3H),

0.92 (d,  $J=6.4$  Hz, 3H), 1.24–1.31 (m, 1H), 1.44 (s, 9H), 1.57–1.69 (m, 2H), 3.09 (dd,  $J=5.9$ , 13.7 Hz, 1H), 3.14 (dd,  $J=5.8$ , 13.7 Hz, 1H), 3.71 (s, 3H), 4.07 (br s, 1H), 4.77 (br s, 1H), 4.84 (td,  $J=5.9$ , 7.8 Hz, 1H), 6.44 (br d,  $J=7.5$  Hz, 1H), 7.08–7.13 (m, 2H), 7.21–7.31 (m, 3H); MS (EI)  $m/z$ : 392 ( $M^+$ ).

#### 4.4.10. *N*-(2-Hydroxyethyl)-3-phenylpropanamide (**5j**).<sup>11</sup>

Colorless needles; mp 72.5–73.5 °C (AcOEt/hexane); IR (KBr): 3293, 1646, 1556  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.36 (br s, 1H), 2.50 (t,  $J=7.6$  Hz, 2H), 2.98 (t,  $J=7.6$  Hz, 2H), 3.33–3.39 (m, 2H), 3.63 (d,  $J=5.0$  Hz, 2H), 5.58 (br s, 1H), 5.72 (dd,  $J=17.6$ , 0.9 Hz, 1H), 7.18–7.24 (m, 3H), 7.27–7.32 (m, 2H). Anal. Calcd for  $\text{C}_{11}\text{H}_{15}\text{NO}_2$ : C, 68.37; H, 7.82. Found: C, 68.19; H, 7.82.

#### 4.5. General procedure for the synthesis of amides with Poly-*O*-Trz-Cl

A mixture of **3a** (0.194 mmol, 29.1 mg), **4a** (0.194 mmol, 23.5 mg), and NMM (0.41 mmol, 41.7 mg) was added to Poly-*O*-Trz-Cl (0.41 mmol) at room temperature, and the mixture was stirred for 21 h at the same temperature. The reaction mixture was filtered, and solid material was washed with  $\text{CH}_2\text{Cl}_2$ -acetone (1:1) and MeOH. The filtrate was combined with the organic phases, and concentrated. The residue was dissolved in  $\text{Et}_2\text{O}$ , and the resulting solution was washed successively with water,  $\text{NaHCO}_3$ , water, HCl (1 mol/L), water, and brine. The solution was dried over  $\text{MgSO}_4$  and concentrated to give a crude product, which was purified on preparative TLC (hexane-AcOEt=1:1) to give 44.2 mg of **5a** (90%).

#### 4.6. Synthesis of 2-chloro-6-ethylamino-4-methoxy-1,3,5-triazine (AMT)

To a solution of 2-methoxy-4,6-dichloro-1,3,5-triazine (5.00 g, 27.8 mmol) in dry THF (200 mL) was added dropwise *N,N*-diisopropylethylamine (10.8 g, 83.3 mmol), followed by ethylamine hydrochloride (2.27 g, 27.8 mmol). After being stirred for 48 h, the solvent was removed in vacuo, and the resulting crude product was dissolved in AcOEt, followed by washing with 0.1 M HCl and water. The organic phase was dried over  $\text{MgSO}_4$ , and concentrated in vacuo. Silica gel column chromatography (hexane-AcOEt=7:3) yielded AMT (4.24 g, 81%): colorless crystals; mp 89–91 °C, IR (KBr): 3268, 1637, 1570, 1299, 802  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) [a mixture of conformational isomers (ca. 1:2)]  $\delta$ : 1.24 (t,  $J=7.2$  Hz, 3H), 3.45–3.54 (m, 2H), 3.94 (s,  $\text{OCH}_3$  of the minor isomer), 4.00 (s,  $\text{OCH}_3$  of the major isomer), 5.61 (br s, CONH of the minor isomer), 5.83 (br s, CONH of the major isomer);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) the major conformational isomer:  $\delta$ : 14.9, 36.5, 55.6, 167.2, 170.5, 171.7; the minor conformational isomer:  $\delta$ : 15.1, 36.6, 55.5, 167.3, 171.0, 171.8. Anal. Calcd for  $\text{C}_6\text{H}_9\text{ClN}_4\text{O}$ : C, 38.21; H, 4.81; Cl, 18.80; N, 29.70. Found: C, 38.11; H, 4.64; Cl, 18.76; N, 29.96.

#### 4.7. Synthesis of 1,11-bis(4,6-dichloro-1,3,5-triazin-2-ylxy)-3,6,9-trioxaundecane (**6**)<sup>14a</sup>

To a solution of **1** (17.0 g, 92.2 mmol) in dry THF (50 mL) was added a solution of **2** (8.95 g, 46.1 mmol) and *N,N*-

diisopropylethylamine (11.9 g, 92.2 mmol) in THF (6 mL) at 0 °C under nitrogen atmosphere. After being stirred for 27 h at 0 °C, the reaction mixture was filtered to remove insoluble material, and the filtrate was concentrated. The residue was dissolved in AcOEt and washed with water. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (hexane-AcOEt=8:2) to give 18.8 g of **6** (83%) as a colorless oil; IR (neat): 1541, 1508, 1252, 1054, 804  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.64–3.70 (m, 8H), 3.86–3.88 (m, 4H), 4.65–4.67 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 68.8, 69.8, 71.0, 71.2, 171.4, 172.8. Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{Cl}_4\text{N}_6\text{O}_5$ : C, 34.31; H, 3.29; N, 17.15; Cl, 28.93. Found: C, 34.12; H, 3.39; N, 16.96; Cl, 28.72.

#### 4.8. Preparation of Poly-*N*-Trz-Cl

To a solution of **6** (3.07 g, 6.26 mmol) in THF (4 mL) were added dropwise a solution of tris(2-aminoethyl)amine (**7**, 0.61 g, 4.18 mmol) and *N,N*-diisopropylethylamine (3.24 g, 25.1 mmol) in THF (2 mL) at –40 °C, and stirred for 1.5 h at the same temperature. The reaction mixture was allowed to warm to 0 °C and was stirred for 1.5 h, followed by stirring at room temperature for 1.5 h. The resulting solid material was collected by suction, and washed successively with dry THF, 2-PrOH, water, THF, and  $\text{Et}_2\text{O}$ , and dried in vacuo to give 2.18 g of Poly-*N*-Trz-Cl (68%); IR (KBr): 3284, 1517, 1336, 1289, 1125, 1057, 807  $\text{cm}^{-1}$ .

#### 4.9. Determination of the activity of Poly-*N*-Trz-Cl by titration of chloride

To a suspension of Poly-*N*-Trz-Cl (26.4 mg) in distilled water (10 mL) was added sodium nitrate (0.50 mmol, 43.6 mg). After being stirred for 10 min at room temperature, the mixture was filtered, and the solid was washed three times with distilled water 5 mL each. The resulting solid was treated with NMM (0.31 mmol, 31.2 mg) to determine the dehydrocondensing activity according to the method for Poly-*O*-Trz-Cl. The amount of chloride collected was 0.0769 mmol, which indicated the unit activity to be 2.91 mequiv/g (0.0769 mmol/26.4 mg).

#### 4.10. General procedure for the synthesis of amides with Poly-*N*-Trz-Cl

A mixture of **3a** (0.155 mmol, 23.3 mg), **4a** (0.155 mmol, 18.8 mg), and NMM (0.47 mmol, 47.1 mg) was added to Poly-*N*-Trz-Cl (0.47 mmol) at room temperature, and the mixture was stirred for 19 h at room temperature followed by filtering. The solid was washed with  $\text{CH}_2\text{Cl}_2$ -acetone (1:1), and the organic phases were combined and concentrated. The residue was dissolved in  $\text{Et}_2\text{O}$ , and the resulting solution was washed successively with water,  $\text{NaHCO}_3$ , water, 1 mol/L HCl, water, and brine. The solution was dried and concentrated to give 32.2 mg of **5a** (82%). Alternatively, for **5g–5i**, the reaction mixture was poured into a suspension of IRA-400 (OH type) in MeOH, and stirred for 30 min. The resulting mixture was filtered and concentrated to give **5**.

#### 4.11. General procedure for preparing lower cross-linked polymer (Poly-*N*-Trz<sub>50</sub>-Cl)

A solution of **7** (0.48 g, 3.26 mmol), ethylenediamine (**8**, 0.20 g, 3.26 mmol), and *N,N*-diisopropylethylamine

(2.11 g, 16.3 mmol) in THF (10 mL) was added dropwise to a solution of **6** (4.00 g, 8.16 mmol) in THF (4 mL) at  $-40^{\circ}\text{C}$ , and stirred for 1.0 h at the same temperature. The reaction mixture was allowed to warm to  $0^{\circ}\text{C}$  and stirred for 1.5 h, followed by stirring for 1.5 h at room temperature. The resulting solid material was collected by suction, and washed successively with dry THF, 2-PrOH, water, THF, and  $\text{Et}_2\text{O}$ , and dried in vacuo to give 2.56 g of Poly-*N*-Trz<sub>50</sub>-Cl (68%); IR (KBr): 3280, 1568, 1336, 1058, 807  $\text{cm}^{-1}$ .

DSC phase transition temperature (onset temperature): Poly-*N*-Trz<sub>50</sub>-Cl:  $74.6^{\circ}\text{C}$  (4.69 mg); Poly-*N*-Trz<sub>25</sub>-Cl:  $71.6^{\circ}\text{C}$  (4.98 mg); scan rate  $10^{\circ}\text{C}/\text{min}$ .

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### References and notes

- (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. C.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195; (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679; (c) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3694–4000; (d) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275–3300.
- (a) Fridkin, M.; Patchornik, A.; Katchalski, E. *J. Am. Chem. Soc.* **1966**, *88*, 3164–3165; (b) Kalir, R.; Fridkin, M.; Patchornik, A. *Eur. J. Biochem.* **1974**, *42*, 151–156; (c) Huang, X.; Chan, C.-C.; Zhou, Q.-S. *Synth. Commun.* **1982**, *12*, 709–714; (d) Cohen, B. J.; Karoly-Hafeli, H.; Patchornik, A. *J. Org. Chem.* **1984**, *49*, 922–924; (e) Kim, K.; Le, K. *Synlett* **1999**, 1957–1959.
- (a) Pop, I. E.; Déprez, B. P.; Tartar, A. L. *J. Org. Chem.* **1997**, *62*, 2594–2603; (b) Dendrinios, K.; Jeong, J.; Huang, W.; Kalivretenos, A. G. *Chem. Commun.* **1998**, 499–500; (c) Dendrinios, K. G.; Kalivretenos, A. G. *Tetrahedron Lett.* **1998**, *39*, 1321–1324; (d) Adamczyk, M.; Fishpaugh, J. R.; Mattingly, P. G. *Tetrahedron Lett.* **1999**, *40*, 463–466; (e) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2001**, *42*, 4487–4489.
- (a) Andreev, S. M.; Tsiryapkin, V. A.; Samoilova, N. A.; Mironova, N. V.; Davidovich, Y. A.; Rogozhin, S. V. *Synthesis* **1977**, 303–304; (b) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 261–264; (c) Arnould, T.; Barrett, A. G. M.; Hopkins, B. T.; Zécri, F. J. *Tetrahedron Lett.* **2001**, *42*, 8215–8217.
- (a) Barrett, A. G. M.; Smith, M. L.; Zecri, F. J. *Chem. Commun.* **1998**, 2317–2318; (b) Chen, J.; Dixon, B. R.; Dumas, J.; Brittelli, D. *Tetrahedron Lett.* **1999**, *40*, 9195–9199.
- (a) Akiyama, M.; Shimizu, K.; Aiba, S.; Katoh, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1421–1425; (b) Svirskaya, P. I.; Leznoff, C. C.; Steinman, M. *J. Org. Chem.* **1987**, *52*, 1362–1364; (c) Weidner, J. J.; Parlow, J. I.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239–242; (d) Golisade, A.; Calenbergh, S. V.; Link, A. *Tetrahedron* **2000**, *56*, 3167–3172.
- (a) Brown, J.; Williams, R. E. *Can. J. Chem.* **1971**, *49*, 3765–3766; (b) Weinshenker, N. M.; Shen, C.-M. *Tetrahedron Lett.* **1972**, 3285–3288; (c) Weinshenker, N. M.; Shen, C.-M.; Wong, J. Y. *Org. Synth. Coll. Vol. VI* **1988**, 951–954; (d) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2000**, *41*, 2463–2466; (e) Disadee, W.; Watanabe, T.; Ishikawa, T. *Synlett* **2003**, 115–117; (f) Valeur, E.; Bradley, M. *Chem. Commun.* **2005**, 1164–1166.
- (a) Desai, M. C.; Stramiello, L. M. S. *Tetrahedron Lett.* **1993**, *34*, 7685–7688; (b) Sturino, C. F.; Labelle, M. *Tetrahedron Lett.* **1998**, *39*, 5891–5894.
- (a) Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, *6*, 4579–4582; (b) Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401–3404.
- (a) Kunishima, M.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. *Tetrahedron Lett.* **1999**, *40*, 5327–5330; (b) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Tani, S. *Tetrahedron* **1999**, *55*, 13159–13170; (c) Kaminski, Z. J.; Paneth, P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248–4255; (d) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275–277.
- Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **2001**, *57*, 1551–1558.
- Of course, the dehydrocondensing reaction can be performed efficiently in commonly used neutral aprotic organic solvents (Ref. 10).
- Kunishima, M.; Hioki, K.; Wada, A.; Kobayashi, H.; Tani, S. *Tetrahedron Lett.* **2002**, *43*, 3323–3326.
- For preliminary reports, see: (a) Kunishima, M.; Yamamoto, K.; Watanabe, Y.; Hioki, K.; Tani, S. *Chem. Commun.* **2005**, 2698–2700; (b) Hioki, K.; Yamamoto, K.; Tani, S.; Kunishima, M. *Pept. Sci.* **2006**, 485–486.
- (a) Kaminski, Z. J. *Biopolymers* **2000**, *55*, 140–164; (b) Blotny, G. *Tetrahedron* **2006**, *62*, 9507–9522.
- (a) Masala, S.; Taddei, M. *Org. Lett.* **1999**, *1*, 1355–1357; (b) Luo, G.; Xu, L.; Poindexter, G. S. *Tetrahedron Lett.* **2002**, *43*, 8909–8912.
- Falchi, A.; Taddei, M. *Org. Lett.* **2000**, *22*, 3429–3431.
- For polymer dehydrocondensing reagents, catalytic decarbonylation of highly toxic diisocyanatohexane was reported to give hexamethylenecarbodiimide as a linear polymeric structure (Ref. 19a). More recently, a high-loading polymer-gel carrying fluoroformamidinium salt was prepared by ring opening metathesis polymerization (ROMP) (Ref. 19b).
- (a) Wolman, Y.; Kivity, S.; Frankel, M. *J. Chem. Soc., Chem. Commun.* **1967**, 629–630; (b) Barrett, A. G. M.; Bibal, B.; Hopkins, B. T.; Köbberling, J.; Love, A. C.; Tedeschi, L. *Tetrahedron* **2005**, *61*, 12033–12041.
- de Hoog, P.; Gamez, P.; Driessen, W. L.; Reedijk, J. *Tetrahedron Lett.* **2002**, *43*, 6783–6786.
- Both the degree of polymerization and cross-linking are unclear because Poly-*O*-Trz-Cl is insoluble in any common solvents.
- The yield was calculated based on the theoretical structure.
- CDMT cannot react directly with carboxylic acid whereas DMT-MM can react with carboxylic acid leading to the formation of amides or esters (Ref. 24). Therefore, the addition of NMM to Poly-Trz-Cl to generate Poly-Trz-MM is essential for dehydrocondensation.
- Kunishima, M.; Yoshimura, K.; Morigaki, H.; Kawamata, R.; Terao, K.; Tani, S. *J. Am. Chem. Soc.* **2001**, *123*, 10760–10761.



25. With regard to the cross-linking Poly-*N*-Trz-Cl, the tertiary amino group derived from cross-linker **7** contained a chloride anion as a hydrochloride, to some extent because hydrogen chloride was produced in the synthetic process of the polymer. Therefore, first, the chloride anion was exchanged for a nitrate anion by treatment with an excess amount of an aqueous sodium nitrate, and then, the amount of chloride anion newly released from the chlorotriazino group by treatment with NMM to form Poly-*N*-Trz-MM was determined according to the method mentioned above.
26. The degree of cross-linking was defined as molar percentage of **7** per total amount of amines (**7**+**8**) employed. Since Poly-*N*-Trzs in Scheme 5 was defined as 100% cross-linking, it can be abbreviated as Poly-*N*-Trzs<sub>100</sub>.
27. Miyazawa, T.; Ensatsu, E.; Hiramatsu, M.; Yanagihara, R.; Yamada, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 396–401.