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Selective synthesis of diazacyclooctane-containing flexible ladder polymers with symmetrically or unsymmetrically substituted side chains

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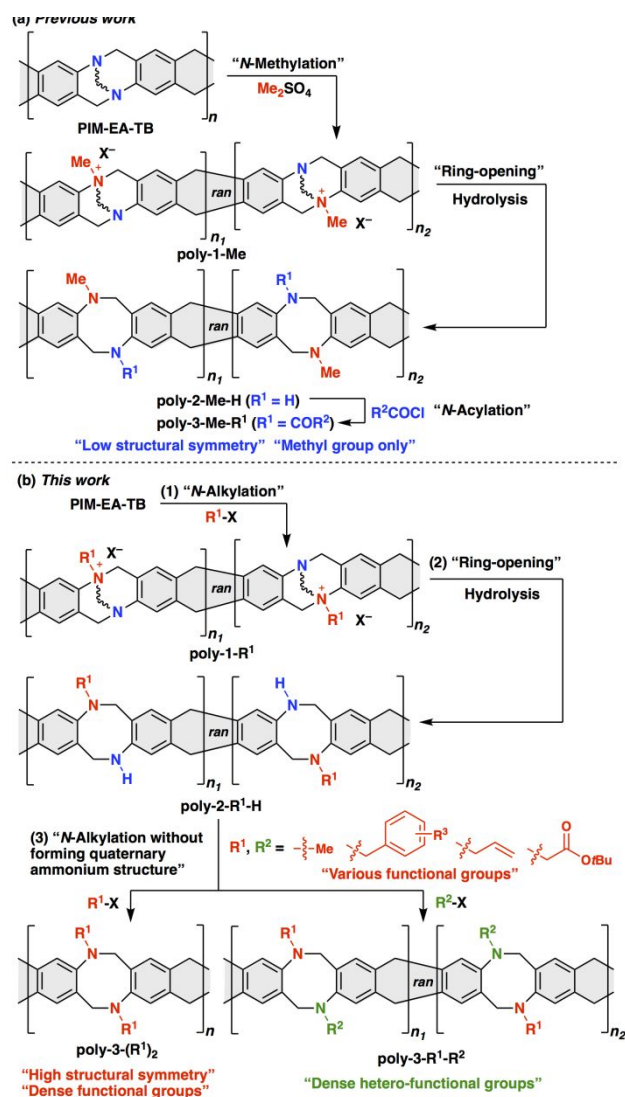
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The structure and substitution pattern of the side chains of polymers affect polymer-chain behaviors in solution and physical properties in the solid state. As a part of our studies on ladder polymers with two-dimensional conformational freedom, here we synthesize symmetrical or unsymmetrical diazacyclooctane (DACO)-containing flexible ladder polymers with various functionalities through sequential *N*-alkylation reactions for a Tröger's base-containing rigid ladder polymer.

Ladder polymers are an interesting class of polymers having more than two bonds in their main chains and potentially exhibit superb properties (*e.g.*, charge carrier conductivity and microporosity) over conventional non-ladder-type polymers.^{1–14} All existing examples of structurally well-defined ladder polymers consist of a rigid main chain with very limited conformational behavior.^{1–14} We recently reported the first successful synthesis of conformationally flexible ladder polymers by a post-polymerization reaction of a Tröger's base (TB)-containing ladder polymer (Scheme 1a).^{15,16} The post-polymerization reaction involves sequential *N*-methylation and hydrolysis for the TB unit, giving rise to a diazacyclooctane (DACO) skeleton with tertiary (*i.e.*, *N*-methylated) and secondary amine groups (Scheme 1a, poly-2-Me-H).¹⁵ The secondary amine group can readily be functionalized by various acylation reagents (Scheme 1a, poly-3-Me-R¹).¹⁵ Very recently, Tang, Xu, Li and coworkers reported that the conversion of the TB unit into a DACO unit of a polymer membrane results in the enhancement of antifouling properties and permeability as a ultrafiltration membrane for water purification.¹⁷ DACO-containing ladder polymers featuring both nitrogen functionality and two-dimensionally restricted degree of freedom of the main chain may have great potential for exhibiting various functions. However, the method for TB-to-



Scheme 1. Synthesis of DACO-containing ladder polymers by (a) the previously reported method and (b) a new method reported herein.

DACO conversion still has problems to improve (Scheme 1a). First, only methyl group can be introduced on the tertiary amine group on the DACO skeleton (Scheme 1a, poly-2-Me-H and poly-3-Me-R¹).¹⁵ Second, since the substituents on two nitrogens of the resultant DACO-containing ladder polymer are different from each other, DACO-containing ladder polymers with

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structural symmetry are difficult to obtain (Scheme 1a, poly-**3-Me-R**¹).¹⁵ Hence, the development of versatile method that can overcome this synthetic limitation has been required to endow the ladder-polymer systems with various properties that enhance reactivity for labeling, grafting and crosslinking, as well as ability to control the solubility, polarity, miscibility for other polymers, and self-assembled structure. Here we report a versatile synthetic method for selectively obtaining symmetrical or unsymmetrical *N,N'*-dialkylated DACO-containing flexible ladder polymers with various functionalities through sequential *N*-alkylations for the TB and DACO units of a TB-containing ladder polymer (Scheme 1b).

Prior to investigating the structural transformation of the TB-containing ladder polymer, we examined the reactivity of a monomeric compound (**TB**) as a model (Table 1). We used alkyl halides listed in Table 1 as *N*-alkylation reagents for **TB**. The first quaternization step from **TB** to **1a** and **1c–g** proceeded quantitatively using a slightly excess amount of highly reactive alkyl halides, such as MeI (entry 1),^{18–23} BnBr (entry 4),^{18–22} 3,4,5-tri(octyloxy)benzyl bromide (entry 5), allyl bromide (entry 6),¹⁸ propargyl bromide (entry 7) and *t*-butyl bromoacetate (entry 8) in DMSO at 25 °C. The structures of the corresponding quaternized TB derivatives (**1s**) and other model compounds (**2s** and **3s**) were unambiguously characterized by one- and two-dimensional NMR and IR spectroscopy, as well as MS spectrometry (Analytical data, Figs. S7–S107, ESI⁺). Meanwhile, the quaternization reactions using 1-iodooctane (entry 2) and BnCl (entry 3) resulted in the quantitative recovery of **TB** and a low product yield, respectively.²³

The ring-opening reactions^{15,18} of **1a**, **1c–e** and **1g** using an aqueous solution of NaOH (1 M) proceeded quantitatively at 25 °C to give the corresponding low symmetrical *N*-monoalkylated DACO derivatives **2a**, **2c–e** and **2g** (entries 1, 4–6, and 8) with tertiary and secondary amine groups. While the ring-opening reaction of propargyl-appended **1f** resulted in full consumption of **1f**, the NMR spectrum of the product did not show any signal due to the terminal alkyne, which usually appears at approximately 3.8 ppm (Fig. S1, ESI⁺), suggesting that the propargyl group is not stable under the reaction conditions. Although we could not identify the product obtained from the alkaline hydrolysis of **1f**, the propargyl group was possibly hydrated to a ketone group according to spectroscopic analysis (Figs. S1–S4, ESI⁺).

The *N*-alkylation of the secondary amine groups of **2a**, **2c–e** and **2g** were conducted with alkyl halides identical to those used in the first quaternization reaction (Table 1). In general, efficient *N*-alkylation of secondary amine groups to form tertiary amines is difficult because quaternization reactions compete. Indeed, when **2a** was treated with 10 eq. of MeI in DMSO at 25 °C, bisquaternized DACO derivative **4a** was formed (Fig. S5, ESI⁺).²⁴ However, we found that undesirable quaternization reaction of the secondary amino groups can be suppressed under milder conditions. For example, when DACO derivatives **2a**, **2c** and **2d** were reacted with 2.0 eq. of MeI, BnBr and 3,4,5-tri(octyloxy)benzyl bromide, respectively, in the presence of 5.0 eq. of K₂CO₃ in CH₂Cl₂ at 25 °C, the corresponding structurally symmetrical *N,N'*-dialkylated DACO derivatives (**3a**, **3c** and **3d**) were quantitatively obtained (Table 1, entries 1, 4, 5). When allyl bromide (entry 6) and *t*-butyl bromoacetate (entry 8) were used, more harsh conditions were required to complete the reaction. Thus, **2e** and **2g** were reacted with 5.0 eq. of alkyl halides in the presence of 5.0 eq. of K₂CO₃ in DMF at 100 °C to give **3e** and **3g** quantitatively. In ¹H NMR spectroscopy, the methylene protons of the DACO skeletons in **3a**, **3c**, **3e** and **3g** (Analytical data, ESI⁺) were observed as a singlet peak, which is obviously due to ring-flipping of the DACO skeletons that occurs faster than the NMR time scale.^{15,16} The efficient three-step TB-to-DACO transformation protocol, which has been established through the present work, provides not only a model experiment for polymer reactions but also a rational synthesis of DACO derivatives with various functionalities.^{25–31}

Table 1. Synthesis of structurally symmetrical *N,N'*-dialkylated DACO derivatives.

Table 2. Synthesis of *N,N'*-dialkylated DACO-containing ladder polymers.

Entry	R ¹	R ²	1a (quant.) ^a	2a (quant.) ^b	3a (quant.) ^c
1	Me	Me	poly-1a-1g	poly-1a	poly-1a
2	<i>n</i> -C ₈ H ₁₇	Me	poly-1b (0%) ^b	poly-1b	poly-1b
3	Bn	Cl	poly-1c (30%) ^b	poly-1c	poly-1c
4	1Bn	Me	poly-1c (quant.) ^b	poly-1c (93%) ^b	poly-1c (93%) ^b
5	3,4,5-OC ₈ H ₁₇	Me	poly-1d (quant.) ^b	poly-1d (>99%) ^b	poly-1d (>99%) ^b
6	allyl	Me	poly-1e (quant.) ^b	poly-1e (quant.) ^b	poly-1e (quant.) ^b
7	propargyl	Me	poly-1f (quant.) ^b	poly-1f (0%) ^b	poly-1f (0%) ^b
8	<i>t</i> -Bu	Me	poly-1g (quant.) ^b	poly-1g (99%) ^b	poly-1g (99%) ^b

^a3.0 eq. of MeI was used. ^b2.0 eq. of *n*-C₈H₁₇ was used. ^creacted for 24 h. ^d5.0 eq. of R¹X was used and reacted in DMF at 100 °C for 24 h. ^e5.0 eq. of R²X was used and reacted in DMF at 100 °C for 24 h.

With the above results in mind, we investigated the structural transformation of the polymeric systems. As a starting material, we chose **PIM-EA-TB**¹² (Table 2, ESI†, $M_n = 3.0 \times 10^4$ Da, $M_w/M_n = 1.69$), which is the most common TB-containing ladder polymer, and tested the reaction using alkyl halides that gave good results in the model reaction with **TB** (Table 1). As shown in Table 2, the first quaternization step for **PIM-EA-TB** using 5.0 eq. of MeI (entry 1), BnBr (entry 2), 3,4,5-tri(octyloxy)benzyl bromide (entry 3), allyl bromide (entry 4) or *t*-butyl bromoacetate (entry 5) in DMSO at 25 °C proceeded almost quantitatively and afforded the corresponding product (poly-**1a**, poly-**1c–e** or poly-**1g**) in a high isolation yield (Analytical data, ESI†). For the second ring-opening step, a powder sample of the product (poly-**1a**, poly-**1c–e** or poly-**1g**) was treated with an aqueous solution of NaOH (1 M) at 25 °C. The solid-state post-polymerization ring-opening reaction also took place very efficiently, giving rise to the corresponding DACO-containing ladder polymer (poly-**2a**, poly-**2c–e** or poly-**2g**) in a high isolation yield (Table 2, entries 1–5, Analytical data, ESI†).

Finally, *N*-alkylation of the *N*-H groups of the ring-opened polymers was carried out with the same alkyl halides that were used in the initial quaternization step of the **PIM-EA-TB**, where the reaction solvent and temperature were set in accordance with the reaction conditions used for the model compound (Table 1). Thus, DACO-containing ladder polymer poly-**2a**, poly-**2c** or poly-**2g** was treated with 5.0 eq. of MeI (entry 1), BnBr (entry 2) or 3,4,5-tri(octyloxy)benzyl bromide (entry 3) in the presence of 5.0 eq. of K_2CO_3 in CH_2Cl_2 at 25 °C. For the *N*-alkylation with relatively less reactive allyl bromide (entry 4) and *t*-butyl bromoacetate (entry 5), the reactions were conducted in DMF at 100 °C. Although ¹H and ¹³C NMR spectroscopic analysis of the reaction mixture indicated the quantitative conversion of *N*-H groups into *N*-R¹ groups of the DACO rings (Table 2, poly-**3s**), the purification process including washing and repeated reprecipitation resulted in low isolation yields of the polymer products.

We determined the chemical structures of the ladder polymers (poly-**1s**, poly-**2s** and poly-**3s**) from the comparison between the NMR spectrum of each polymer and that of the corresponding model compound (Analytical data, ESI†). As an example, the ¹H NMR spectra of poly-**3s** (black lines) and its model compound **3s** (blue lines) are shown in Fig. 1. The NMR signals of the polymers are broadened but are unambiguously assignable as those arising from each functional group (red, pink and green marks). Furthermore, the values of chemical shift observed for poly-**3s** and **3s** are very similar to one another.

We have shown the symmetrical *N,N'*-dialkylation of the DACO-containing ladder polymers, which would be beneficial for modifying their chemical and physical properties in solution and in the solid state. Furthermore, the versatile synthetic protocol would also give opportunities for post-functionalization to the DACO ring with reactive functional groups that allow *e.g.*, thiol-ene click reaction, hydrosilylation and ester-exchanging reaction.³² For example, by a procedure similar to that for a model reaction (Scheme 2a, Figs. S101–S107, ESI†), we successfully synthesized from poly-**2g**

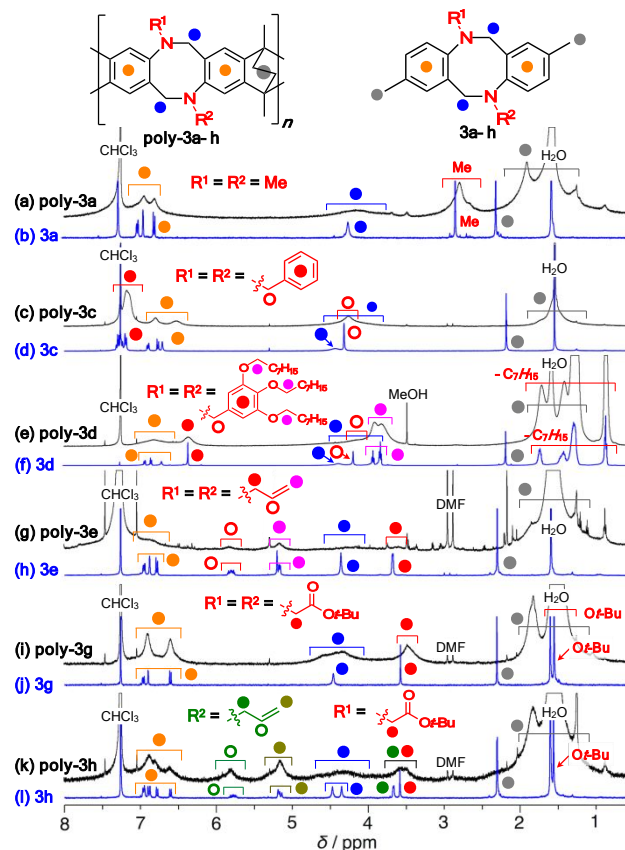
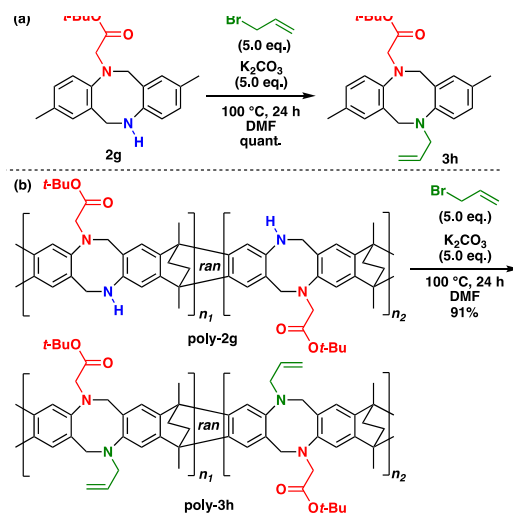


Fig. 1. ¹H NMR (500 MHz) spectra of (a) poly-**3a**, (b) **3a**, (c) poly-**3c**, (d) **3c**, (e) poly-**3d**, (f) **3d**, (g) poly-**3e**, (h) **3e**, (i) poly-**3g**, (j) **3g**, (k) poly-**3h** and (l) **3h** in $CDCl_3$ at 25 °C.



Scheme 2. Synthesis of unsymmetrically functionalized (a) DACO derivative **3h** and (b) DACO-containing ladder polymer poly-**3h**.

unsymmetrical *N,N'*-dialkylated DACO-containing ladder polymer poly-**3h** carrying different reactive *N*-alkyl groups (*e.g.*, allyl and ester groups) on the DACO ring (Scheme 2b, Figs. S145–147, ESI†). The ¹H NMR spectra of **3h** and poly-**3h** (Fig. 1k,l) clearly showed the signals arising from the ester groups (red marks) and allyl groups (green marks). This hetero-functional polymer would serve as a useful ladder-polymer platform for applications such as labeling, grafting and crosslinking.

Conclusions

In summary, we have demonstrated a versatile synthetic method for symmetrical or unsymmetrical *N,N'*-dialkylated DACO-containing ladder polymers. This method involves optimized three-step post-polymerization reactions for a TB-containing rigid ladder polymer, *i.e.*, (1) *N*-alkylation of a TB unit, (2) ring-opening reaction of the resultant quaternized TB unit into a DACO unit, and (3) selective *N*-alkylation of secondary amino group of the resultant DACO unit (Scheme 1b). Accordingly, it becomes possible to develop ladder polymers with a high density of various side chain functionalities, enabling the tuning of the physical and chemical properties of the DACO-containing ladder polymers in terms of *e.g.*, solubility, polarity, self-assembling properties, miscibility for other polymers and affinity for other materials. Notably, the DACO-containing ladder polymers consist of a unique main-chain, which is flexible while the motion is restricted two-dimensionally. We expect that the combination of the main-chain dynamics and chemical design of the side chains would lead to a new aspect of this new class of ladder polymer. Studies along this line are underway in our group.

Conflicts of interest

There are no conflicts to declare.

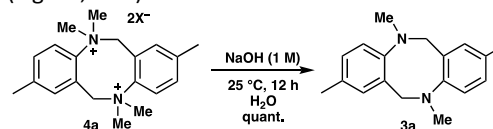
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Notes and references

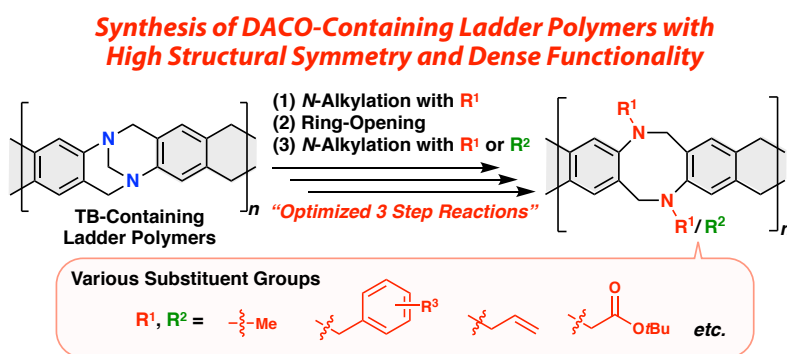
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- We found that by the simple treatment of **4a** with an aqueous solution of NaOH (1 M), selective demethylation of **4a** takes place quantitatively to give neutral **3a**. This means that over methylation does not hamper the formation of the tertiary amine compound (Fig. S6, ESI⁺).



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Graphical Abstract



We report a versatile synthetic method for selectively obtaining symmetrical or unsymmetrical *N,N'*-dialkylated DACO-containing flexible ladder polymers with various functionalities.
