JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

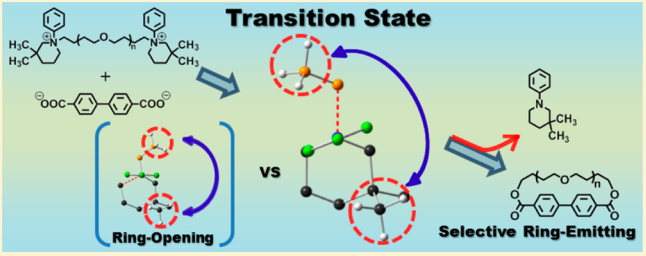
Regioselective Ring-Emitting Esterification on Azacyclohexane Quaternary Salts: A DFT and Synthetic Study for Covalent Fixation of Electrostatic Polymer Self-Assemblies

Akihiro Kimura, Shinnosuke Takahashi, Susumu Kawauchi,* Takuya Yamamoto, and Yasuyuki Tezuka*

Department of Organic and Polymeric Materials, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Supporting Information

ABSTRACT: A regioselective nucleophilic esterification upon six-membered, thus considered *unstrained*, azacyclohexane quaternary salts has been disclosed by DFT calculations using a model compound and subsequent experimental studies of nucleophilic substitution on *N*-phenyl-3,3-dimethylpiperidinium salt groups at the polymer chain ends by carboxylate anions. An exclusive ring-*emitting* esterification was proposed theoretically and confirmed experimentally to produce a simple ester group, in contrast to less robust amino-ester linkages through an alternative ring-*opening* process with *strained* five-membered ammonium salts. This reaction was subsequently applied to a prototypical process of an *electrostatic self-assembly and covalent fixation* (ESA-CF) technique to produce a ring polymer having simple ester linking units.



INTRODUCTION

The ring strain conception has served over a century after Baeyer's report[1] as a basis for understanding the chemical reactivity of cyclic compounds.[2] Ring strain has frequently or intuitively been assumed to be a principal driving force of controlling the reaction of ring systems in organic chemistry, in biochemistry, and in polymer chemistry.[2−4] Ring strain has also been elucidated through theoretical and computational means,[5] which have recently been contributing to rational interpretations of experimental results and furthermore to prediction of the unknown experimental outcome.[6] Typically, nucleophilic ring-opening reactions by strained three-, four-, and five-membered cyclic oxonium, sulfonium, and ammonium salts by various nucleophiles have been exploited in a wide range of practical chemical processes, including cationic ring-opening polymerization.[4] Carboxylates, in particular, have been employed in routine esterification processes to form ether esters, thioether esters, and amino esters.[7]

In contrast, six-membered cyclic onium salts are considered strain-free and consequently incapable of inducing any selection between ring-emitting and ring-opening paths. In addition, the nonselective reaction should produce twice the amount of ring-opening product formed by attack at *two endo*-methylene units vs the ring-emitting counterpart produced by the reaction at *one exo*-methylene unit. Indeed, regioselective nucleophilic substitution reactions of six-membered ammonium (piperidinium) salts have scarcely been documented, except for *N*-methyl cyclic ammonium derivatives, which in turn undergo exclusive attack on the methyl group rather than ethyl or other alkyl counterparts due to steric preferences.[8] It was surprising, therefore, to observe that nucleophilic substitution by a carboxylate anion on *N*-phenylpiperidinium end groups of poly(tetrahydrofuran), poly(THF), proceeded predominantly (80−90%) at the *exo* position: i.e., the *N*-adjacent methylene unit of the polymer chain. Also, the elimination of *N*-phenylpiperidine (ring-emitting) produces a simple ester linkage (Scheme 1).[9]

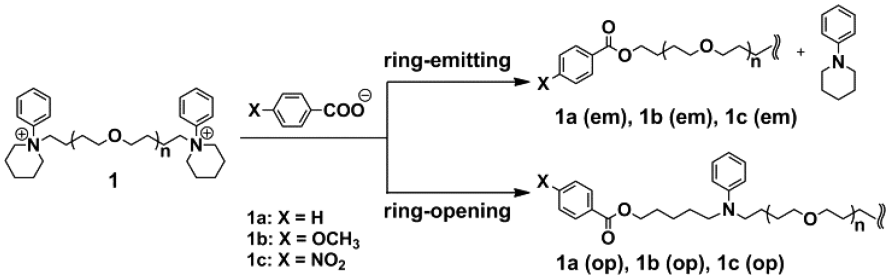
In the present study, we first conducted density functional theory (DFT) calculations in order to obtain insights into this counterintuitive observation. The DFT results showed that the observed regioselection is likely explained by the higher energy and frustrated transition state toward the ring-opening path in comparison with that toward the ring-emitting path, despite the absence of ring strain in the ground state six-membered cyclic ammonium salts. By the DFT analyses, moreover, the 1,3-diaxial steric interaction could exert a crucial influence on the energy profile of the transition states of these nucleophilic substitution reactions. Prompted by these DFT results, we conducted experimental studies to realize an exclusive ring-emitting esterification process by *N*-phenyl-3,3-dimethylpiperidinium salt groups at the polymer chain ends.

We have subsequently applied this covalent fixation process to produce a ring polymer having a simple ester linkage, which is hard to obtain through an alternative common alcohol/acid condensation or other nucleophile/electrophile esterification. The controlled conversion of ion pairs into covalent forms has so far been achieved by the ring-opening reactions of moderately strained cyclic ammonium salts with carboxylate counteranions. In addition, an *electrostatic self-assembly and covalent fixation* (ESA-CF) process thereby has successfully been employed to construct a wide variety of complex polymer

Received: January 11, 2013
Published: March 7, 2013

   dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086−3094

Scheme 1. Ring-Emitting and Ring-Opening Reactions of Six-Membered Cyclic Ammonium Salt End Groups with a Series of Carboxylate Anions



architectures (topological polymer chemistry; see Scheme S1 in the Supporting Information).[10,11] The ESA-CF process has recently been applied also as a versatile means of surface modification of solids and fabrics.[12] In these covalent fixation processes, such moderately strained five-membered pyrrolidinium[13] and six-membered bicyclic quinuclidinium salts as well as a five-membered thiolanium salt[14] have currently been applied. The regioselective ring-opening reaction took place, at the prescribed elevated temperatures, through nucleophilic substitution at the *endo* position of the *N*- and *S*-adjacent methylene units of the cyclic onium salt unit.

An alternative covalent fixation protocol through a ring-emitting process with polymer precursors having *N*-phenylpiperidinium end groups could produce simple and robust ester linkages, in contrast to amino ester groups formed through the relevant ring-opening process in the conventional ESA-CF technique.[15] Notably, moreover, a cyclic polymer including a fluorescent perylene unit, which is specifically employed for single-molecule spectroscopic studies, was prepared using a polymer precursor having *N*-phenylpiperidinium end groups; even the ring-emitting esterification of the unsubstituted *N*-phenylpiperidinium group failed to proceed selectively.[16] In this particular case, the elimination of fluorescence-quenching *N*-phenylamine groups from the polymer product was a prerequisite for performing the single-molecule spectroscopic measurements.

RESULTS AND DISCUSSION

1. Experimental Studies on the Regioselectivity in the Esterification of Azacyclohexane Quaternary Salts. We first examined the regioselectivity in the nucleophilic substitution on the *N*-phenylpiperidinium units by carboxylate anions of various nucleophilicity, including benzoate (pK_a = 4.20), *p*-methoxybenzoate (pK_a = 4.47), and *p*-nitrobenzoate (pK_a = 3.42) using poly(THF) having *N*-phenylpiperidinium salt end groups.[13] The phenyl substituent on the nitrogen atom was purposely introduced in order to circumvent the substitution reaction on this specific position (Scheme 1). An alternative methyl substituent on the nitrogen atom promotes the nucleophilic attack at this sterically favored position, even in the case with that on the strained five-membered ammonium salt.[17] It is also notable that the pyridinium end group failed to cause selective substitution at the *exo* position, instead resulting in uncontrolled reactions on the pyridinium ring unit.[18]

As the employed poly(THF)s possessing ionic end groups, having molecular weights of more than several thousands, were readily soluble in the appropriate organic media, nucleophilic substitution by various carboxylates was carried out in dry THF, where the anion is free of hydration to form a "naked" nucleophile to promote the reaction.[19] Thus, poly(THF) having *N*-phenylpiperidinium salt end groups carrying triflate counteranions (**1**/triflate), were mixed with a THF solution containing an excess amount (10 equiv) of tetra-*n*-butylammonium benzoate or tetra-*n*-butylammonium *p*-methoxybenzoate. The reaction mixture solution was refluxed to cause esterification via a nucleophilic substitution reaction. For the reaction with *p*-nitrobenzoate, on the other hand, the initial triflate counterion of **1**/triflate was replaced by *p*-nitrobenzoate to avoid side reactions.[20] The esterification products, **1a**(em,op), **1b**(em,op), and **1c**(em,op) (Scheme 1), obtained with the respective benzoate anions, were collected by reprecipitation, and the regioselectivity of the reactions was determined by means of ^{1}H NMR analysis (Figure 1). Thus, the ring-emitting/ring-opening reaction ratio (em/op) was readily estimated by comparing the signals arising from the benzoate groups at 6.9−8.3 ppm (unsubstituted benzoate at 7.4−8.1 ppm, *p*-methoxybenzoate at 6.9−8.0 ppm, or *p*-nitrobenzoate at 8.2−8.3 ppm) and methylene groups adjacent to the ester oxygen atoms at 4.3−4.4 ppm with those from the *N*-phenyl groups at 6.6−7.2 ppm. It has been confirmed that, as summarized in Table 1, concurrent ring-emitting and ring-opening reactions were observed to take place, while the regioselectivity in the nucleophilic substitution was scarcely affected by the type of benzoates having different nucleophilicities. It is notable, in particular, that the ring-emitting substitution (85−87%) prevailed despite the fact that the six-membered azacyclohexane unit is intuitively considered free of ring strain, as in the case of cyclohexane.

2. DFT Studies on the Transition States in the Esterification of Azacyclohexane Quaternary Salts. The serendipitous observation of the predominant ring-emitting esterification with azacyclohexane quaternary salts was subsequently studied by a DFT technique using a series of model compounds, where an ethyl group was introduced in place of the polymer chain for the sake of the calculations (Scheme 2). It is notable that combined experimental/theoretical studies on noncovalent self-assembly processes are of increasing current interest.[21] A restricted hybrid nonlocal density functional, R-B3LYP,[22] with the 6-31+G(d) basis set[23] has been used for the calculations. The continuum conductor-like polarizable continuum model (CPCM, COSMO)[24] was employed to include a solvent effect of THF to fit the terms with the experimental conditions. The optimized transition state structures were verified to have only one imaginary frequency indicating the reaction coordinate by harmonic vibrational frequency calculations (see the Supporting Information for details). All of the calculations were carried out by using the Gaussian 09 program.[25]

The differences in the transition state free energies ($\Delta\Delta G^{\ddagger}_{em-op}$) calculated at 339.15 K and 1 atm by using

dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086−3094

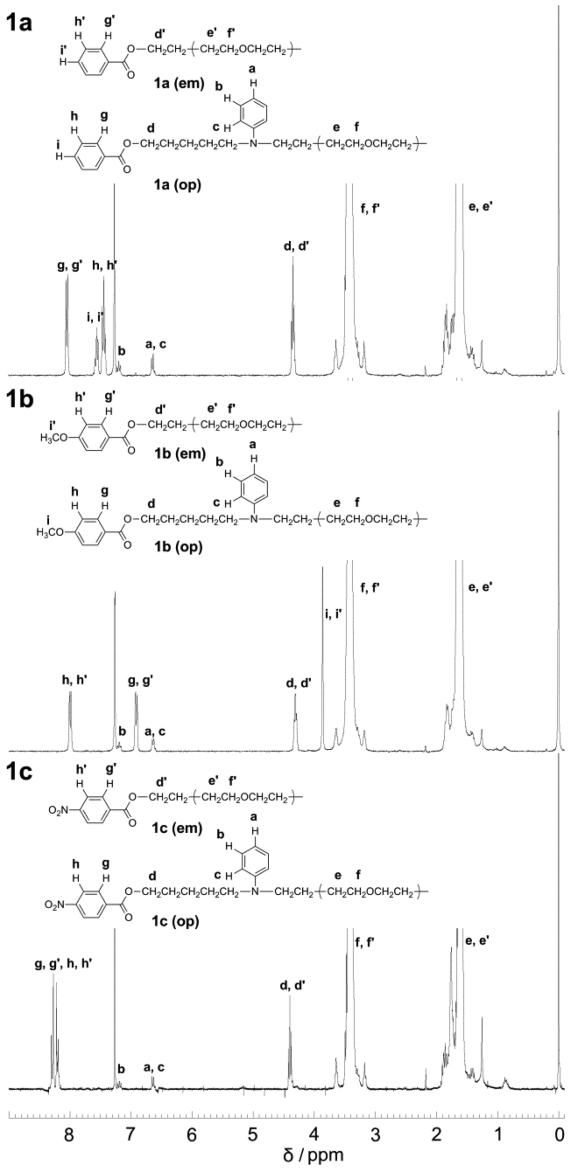


Figure 1. ^{1}H NMR spectra of (top) **1a**(em,op), (middle) **1b**(em,op), and (bottom) **1c**(em,op) ($CDCl_3$, 25 °C).

statistical thermodynamics[26] and the ring-emitting/ring-opening product ratios (em/op) estimated thereby, together with experimentally obtained values, are collected in Table 1. Thus, the calculation results for *N*-phenylpiperidinium model compound **I** with X = H of $\Delta\Delta G^{\ddagger}_{em-op}$ = −7.9 kJ/mol (corresponding to em/op = 94/6), as well as **I** with X = OCH_3 of −8.7 kJ/mol (em/op = 96/4) and **I** with X = NO_2 of −7.5 kJ/mol (em/op of 94/6) comparatively agreed with the experimental em/op ratios (and $\Delta\Delta G^{\ddagger}_{em-op}$ values estimated therefrom) for a series of telechelics **1** with X = H for 85/15 (−4.9 kJ/mol), with X = OCH_3 for 85/15 (−4.9 kJ/mol), and with X = NO_2 for 87/13 (−5.4 kJ/mol), respectively. It is notable, moreover, that the DFT results coincide with the experimental observations by the constant regioselectivity with a series of benzoates having varied nucleophilic reactivities. These results strongly suggest that the regioselectivity in the present esterification process is driven by kinetic (transition state energy) factors.

The DFT-optimized ground state and transition state structures in the ring-emitting and the ring-opening routes of model compound **I** were subsequently compared in Figure 2A (**I**(gs), **I**(em) and **I**(op), respectively). Throughout the reaction, the azacyclohexane unit of **I** adopts a chair conformation with the phenyl substituent at the axial position and the ethyl counterpart (thus, corresponding to the polymer chain in **1**) at the equatorial position, respectively.[27] This specific structure was calculated to be favored also at the transition state rather than an alternative form with the phenyl group at an equatorial position, by 3.1 kJ/mol for the ring-opening and 7.1 kJ/mol for the ring-emitting products, respectively.[28] Importantly, at the transition state in the ring-opening path (**I**(op) in Figure 2A, top view), the azacyclohexane ring is distorted through the elongation of the distance between N1 and C6 to 2.125 Å from 1.539 Å at the ground state (**I**(gs) in Figure 2A, top view). In contrast, the corresponding bond distance at the transition state in the ring-emitting path remains unchanged at 1.498 Å (**I**(em) in Figure 2A, top view). In addition, the N1−C6−C5 angle at the transition state in the ring-opening path (**I**(op) in Figure 2A, top view) decreases significantly to 98.8° from 112.4° at the ground state (**I**(gs) in Figure 2A, top view). On the other hand, the corresponding angle in the ring-emitting path remains unchanged at 112.5° (**I**(em) in Figure 2A, top view). These results indicate the greater structural frustration at the transition state in the ring-opening path than that in the ring-emitting path, in which elongation of the distance between N1 and C7 (2.101 Å) does not affect the conformation of the azacyclohexane unit (**I**(op) and **I**(gs) in Figure 2A, top view). Thus, it is conceivable that the ring-emitting, rather than the ring-opening, esterification is favored on the *N*-phenylpiperidinium end group.

In order to realize an exclusive ring-emitting process by using a modified *N*-phenylpiperidinium salt derivative, we have subsequently conducted DFT calculations for a series of model compounds having a variety of substituent patterns on either the phenyl or azacyclohexane unit, to determine steric and electronic effects on the transition state (Scheme 2, **II**−**IV**). The results are collected in Table 2. The introduction of either an electron-donating or electron-withdrawing substituent at the 4-position of the phenyl substituent has little influence on the $\Delta\Delta G^{\ddagger}_{em-op}$ value (for **III** −7.9 kJ/mol, and for −9.1 kJ/mol).

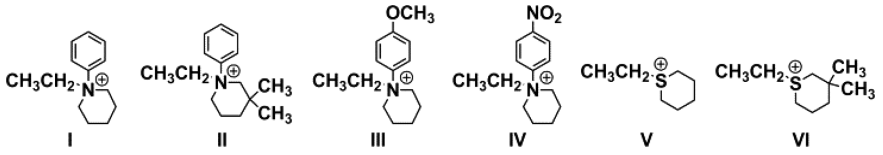
Table 1. Experimental and Calculated Ring-Emitting/Ring-Opening Product Ratios (em/op) and Transition State Free Energy Differences ($\Delta\Delta G^{\ddagger}_{em-op}$) in the Esterification on Six-Membered Azacycloalkane Quaternary Salts by a Series of Benzoate Anions

type of benzoate anion[a]			
para substituent	pK_a	ring-emitting/ring-opening experimental product ratio (em/op)[b]	calculated $\Delta\Delta G^{\ddagger}_{em-op}$ (kJ/mol)[c]
H	4.20	85/15 (−4.9)	−7.9 (94/6)
OCH_3	4.47	85/15 (−4.9)	−8.7 (96/4)
NO_2	3.42	87/13 (−5.4)	−7.5 (94/6)

[a]See Scheme 1 for the structures. [b]The calculated $\Delta\Delta G^{\ddagger}_{em-op}$ values in parentheses were obtained by using the equation $\Delta\Delta G^{\ddagger}_{em-op} = RT$ ln (op/em) with R = 8.3145 × 10^{-3} kJ/(mol K) and T = 339.15 K, which is the reflux temperature of THF as in the experimental conditions. [c]The calculated em/op values in parentheses were obtained by using the equation $\Delta\Delta G^{\ddagger}_{em-op} = RT$ ln (op/em) with R = 8.3145 × 10^{-3} kJ/(mol K) and T = 339.15 K, which is the reflux temperature of THF as in the experimental conditions.

dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086−3094

Scheme 2. Series of Model Compounds Employed for the DFT Calculations on the Transition States of Their Ring-Emitting and Ring-Opening Reactions with Carboxylate Counteranions



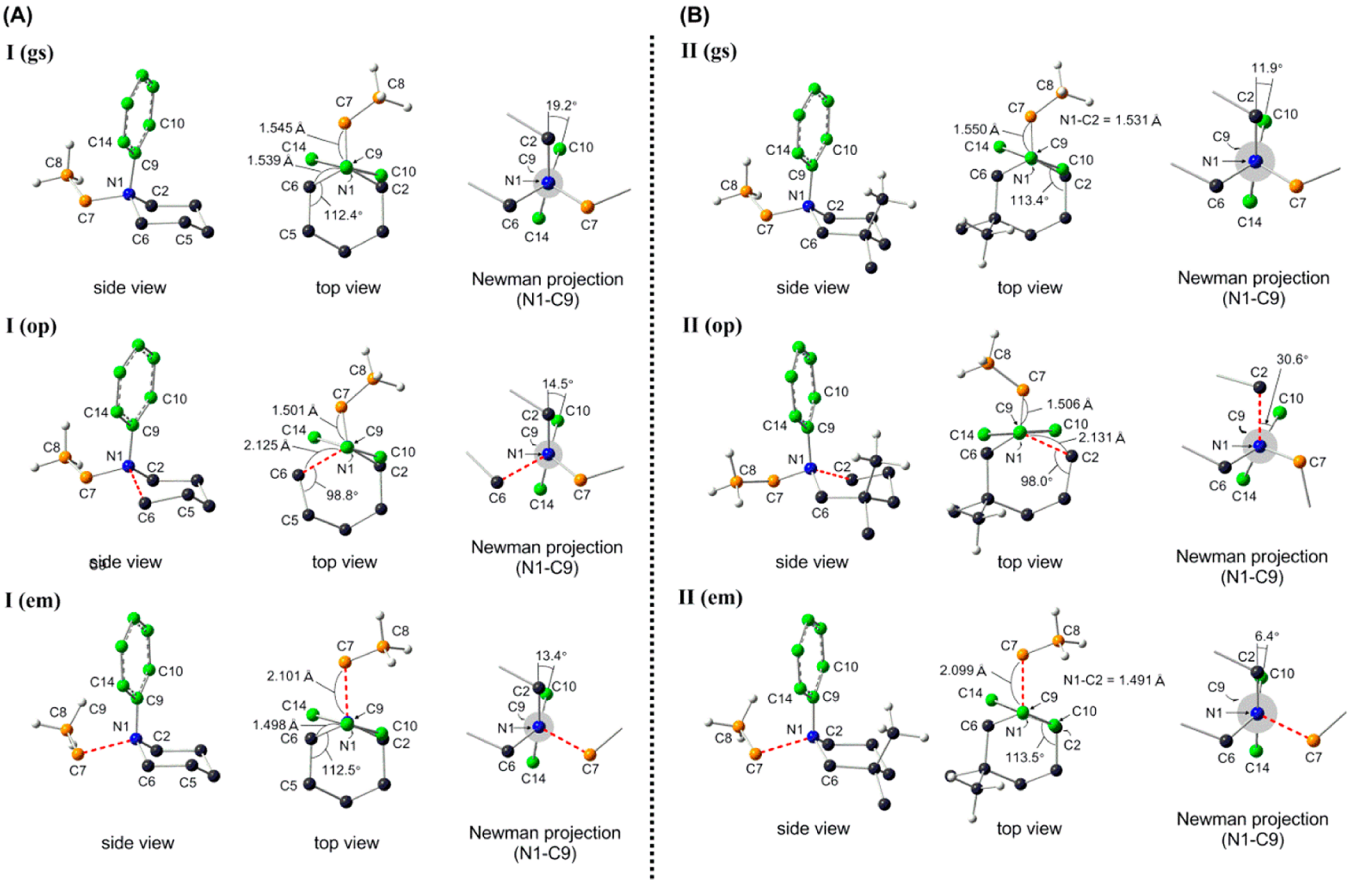


Figure 2. DFT-optimized ground state (gs) and the ring-opening (op) and the ring-emitting (em) transition state structures of the esterification by benzoate upon (A) *N*-phenylpiperidine (**I**) and (B) *N*-phenyl-3,3-dimethylpiperidine salt groups (**II**). The benzoate anion is omitted for the sake of clarity.

In contrast, the introduction of two methyl groups at the 3-position of the azacyclohexane unit (**II**) resulted in a remarkable increase of the $\Delta\Delta G^{\ddagger}_{em-op}$ value (−22.0 kJ/mol) to accelerate the ring-emitting process over the ring-opening counterpart.

The DFT-optimized ground state and transition state structures in the ring-emitting and ring-opening processes for a *N*-phenyl-3,3-dimethylpiperidinium salt group were subsequently compared in Figure 2B (**II**(gs), **II**(em), and **II**(op), respectively). First, the distorted azacyclohexane ring structure is observed at the transition state in the ring-opening path, as in the case of the unsubstituted model compound **I** (parts A and B of Figure 2, top view). In addition, the 1,3-diaxial interaction between a phenyl and a methyl group at the 3-position of the azacyclohexane unit causes a remarkable rearrangement of the spatial positions of the phenyl group around the N−Ph bond. Thus, in contrast to the nearly constant dihedral angle of C2−N1−C9−C10, namely 14.5° for **I**(op) and 13.4° for **I**(em), for the unsubstituted model compounds shown in Newman projections (N1−C9) in Figure 2A, the subsequent introduction of dimethyl groups at the 3-position of the azacyclohexane unit caused a significant increase of the dihedral angle for **II**(op) to 30.6°, against the slight decrease for **II**(em) to 6.4° as noticed in Newman projections (N1−C9) in Figure 2B. This coincides with the substantial difference in the spatial arrangement of substituent groups in **II**(op), where the group containing C8 and the 3,3-dimethyl group are placed on the same side in order to accommodate the carboxylate anion coming toward C2 from the opposite side (**II**(op) in Figure 2B, top view), whereas the spatial arrangement of substituent groups both in **II**(em) and in the ground state commonly both the group containing C8 and the 3,3-dimethyl group are placed on opposite sides (**II**(gs) and **II**(em) in Figure 2B, top view). The substantial structural rearrangement at the transition state in the ring-opening path, **II**(op), is in parallel with the enhanced steric frustration in comparison with the alternative ring-emitting process, **II**(em). Consequently, it is conceived that the exclusive ring-emitting esterification proceeds with *N*-phenyl-3,3-dimethylpiperidinium salt groups at the polymer chain ends.

dx.doi.org/10.1021/jo400058f | *J. Org. Chem.* 2013, 78, 3086−3094

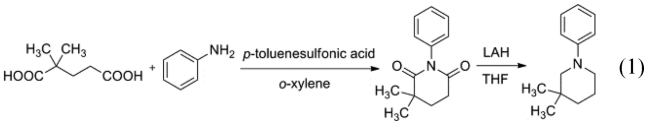
Table 2. Calculated Transition State Energy Differences ($\Delta\Delta G^{\neq}_{em-op}$) and Product Ratios (em/op) for the Ring-Emitting and Ring-Opening Reactions of *N*-Phenylpiperidinium Derivatives (I–IV), Thianium (V), and 3,3-Dimethylthianium (VI) with a Benzoate Anion

model substrate[a]	calcd $\Delta\Delta G^{\ddagger}_{em-op}$ (kJ/mol)	ring-emitting/ring-opening product ratio (em/op)[b]
I	−7.9	94/6 (85/15)[c]
II	−22.0	100/0 (100/0)[d]
III	−7.9	94/6
IV	−9.1	96/4
V	−9.1	96/4
VI	−10.1	97/3

[a]See Scheme 2. [b]The em/op and $\Delta\Delta G^{\ddagger}_{em-op}$ values were interconverted with each other by using the equation $\Delta\Delta G^{\ddagger}_{em-op} = RT \ln (op/em)$ with $R = 8.3145 \times 10^{-3}$ kJ/(mol K) and $T = 339.15$ K, which is the reflux temperature of THF as in the experimental conditions. [c]The numbers in parentheses indicate the experimental em/op for **1** reacted with benzoate (see Scheme 1). [d]The numbers in parentheses indicate the experimental em/op for **2** reacted with benzoate (see Scheme 3).

The postulated 1,3-diaxial interaction upon the regioselectivity in the esterification on the azacyclohexane quaternized salts was further supported by DFT calculations of the transition states of the relevant model compounds, namely six-membered cyclic thianium (**V**) and its 3,3-dimethyl derivative (**VI**); both are free of axial substituent groups on the sulfur atom (Figure 2B).[29] In contrast with the quaternary ammonium salts of **I** and **II** (Table 2), the transition state energy is hardly affected by the introduction of two methyl groups at the 3-position of thiacyclohexane unit (−9.1 kJ/mol for **V** and −10.1 kJ/mol for **VI** in Table 2). The DFT-estimated ring-emitting/ring-opening product ratio of 96/4 with **V** and 97/3 with **VI** should indicate concurrent ring-emitting/ring-opening esterification rather than an exclusive ring-emitting process, as the relevant DFT-estimated product ratio of 94/6 for **I** (−7.9 kJ/mol) corresponds to the experimental ratio of 85/15 for **1a**(em,op).

3. Selective Ring-Emitting Esterification by Azacyclohexane Quaternary Salts for Topological Polymer Chemistry. Prompted by the computational studies described so far, we synthesized *N*-phenyl-3,3-dimethylpiperidine by the reduction of *N*-phenyl-3,3-dimethyl-2,6-piperidinedione,[29,30] which was prepared by the reaction of 2,2-dimethylglutaric acid with aniline as shown in eq 1 below.



(1)

Poly(THF) having *N*-phenyl-3,3-dimethylpiperidinium groups (**2**/triflate) was subsequently prepared by the end-capping reaction of a living poly(THF) with *N*-phenyl-3,3-dimethylpiperidine. The nucleophilic substitution reaction of **2**/triflate by benzoate anion was conducted first to test experimentally the DFT-predicted regioselectivity. Thereafter, poly(THF) having *N*-phenyl-3,3-dimethylpiperidinium groups accompanying a biphenyldicarboxylate counteranion, **2**/biphenyldicarboxylate, was subjected to the ESA-CF cyclization process as a prototypical reaction for *topological polymer chemistry* to demonstrate the potential of the present esterification protocol (Scheme 3). The ^{1}H NMR spectra of **2** accompanying benzoate and biphenyldicarboxylate counteranions, **2**/benzoate and **2**/biphenyldicarboxylate, are shown in Figure 3 (top) for the latter and in Figure S1 (top) in the Supporting Information for the former. The introduction of the respective counteranions was confirmed by the presence of signals attributed to benzoate at 7.29–8.19 ppm and biphenyldicarboxylate at 8.20 and 7.59 ppm, in addition to those due to the *N*-phenyl-3,3-dimethylpiperidinium group at 7.47–7.66, 3.70–4.22, and 4.37–4.49 ppm. The subsequent heat treatment of the ionic complexes **2**/benzoate and **2**/biphenyldicarboxylate was performed in THF at concentrations of 2.0 and 0.2 g/L, respectively, at reflux for 5 h, as the dilution was requisite for effective intramolecular cyclization.[11] The covalently converted products, **3**(linear) and **3**(cyclic), were recovered after column chromatographic purification in 77% yield for the former and in 56% yield for the latter. The ^{1}H NMR spectra showed a triplet signal arising from the methylene protons adjacent to the ester oxygen atoms at around 4.4 ppm, while no signals assignable to the *N*-phenyl group were detectable between 6.0 and 7.2 ppm, indicating the quantitative elimination of *N*-phenyl-3,3-dimethylpiperidine (Figure 3 (bottom) and Figure S1 (bottom) in the Supporting Information).

MALDI-TOF MS analysis further confirmed the production of the covalently converted linear and ring poly(THF)s, **3**(linear) and **3**(cyclic), respectively (Figure 4A). Thus, a series of peaks with an interval of 72 mass units corresponded to poly(THF) having the specific end groups or the linking group structure. The peak at m/z 3927.1 (Figure 4, top) matched a Na^+ adduct of **3**(linear) with a DP_n of 50 having benzoate ester end groups, in agreement with the calculated molar mass of 3926.692 Da for $(C_4H_8O) \times 50 + C_{18}H_{18}O_4$ plus Na^+. Moreover, the peak at m/z 3924.9 (Figure 4A, bottom) corresponded to **3**(cyclic) with a DP_n of 50 incorporating the biphenyldicarboxylate linking group (the calculated molar mass of 3924.676 Da for $(C_4H_8O) \times 50 + C_{18}H_{16}O_4$ plus Na^+). These molecular weights deviate by 2 mass units arising from the difference between the chemical structures of two benzoate and one biphenyldicarboxylate anion.

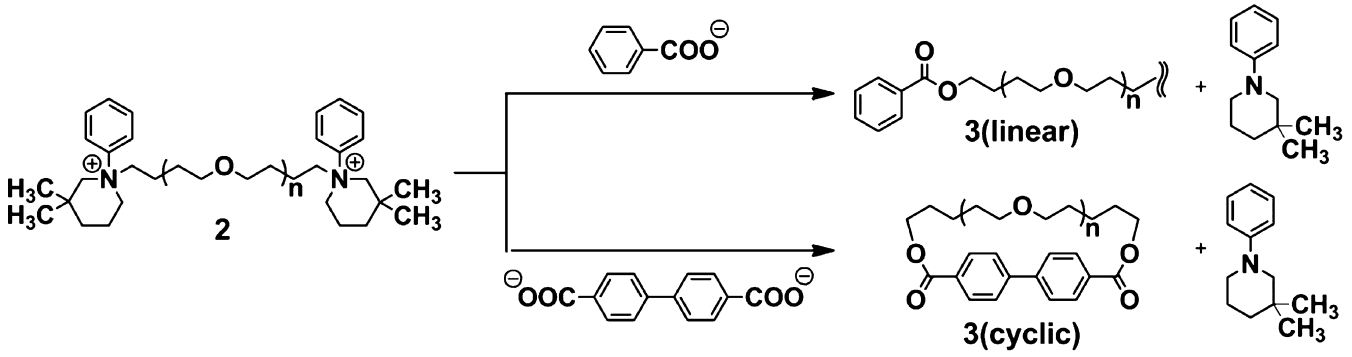
SEC traces of the covalently converted linear and ring products, i.e., **3**(linear) and **3**(cyclic), respectively, were then compared (Figure 5). Both products showed narrow size distribution (PDI) of 1.17 for the linear and 1.22 for the ring polymer products, and the linear product showed an apparent peak molecular weight M_p of 7800 as a measure of the hydrodynamic volume; this value was notably higher than that of the ring polymer product (M_p) of 5900, despite both products being derived from the common poly(THF) precursor **2**/triflate. The hydrodynamic volume ratio of the linear and ring polymer products was thus estimated to be 0.76 and was in good agreement with previous studies.[11,31] These results demonstrate effective polymer cyclization through *ring-emitting* covalent fixation by the selective elimination of *N*-phenyl-3,3-dimethylpiperidine units at both chain ends.

■ CONCLUSION

By a combination of DFT and experimental studies, we have successfully developed an exclusive ring-emitting esterification process, which provide a "click" type chemical process to form simple ester linkages applicable to a wide variety of polymer reactions, replacing the relevant ring-opening process resulting in less stable amino-ester linkages. This new covalent fixation

dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086–3094

Scheme 3. Ring-Emitting Reaction of *N*-Phenyl-3,3-dimethylpiperidinium Salt Groups at Polymer Chain Ends



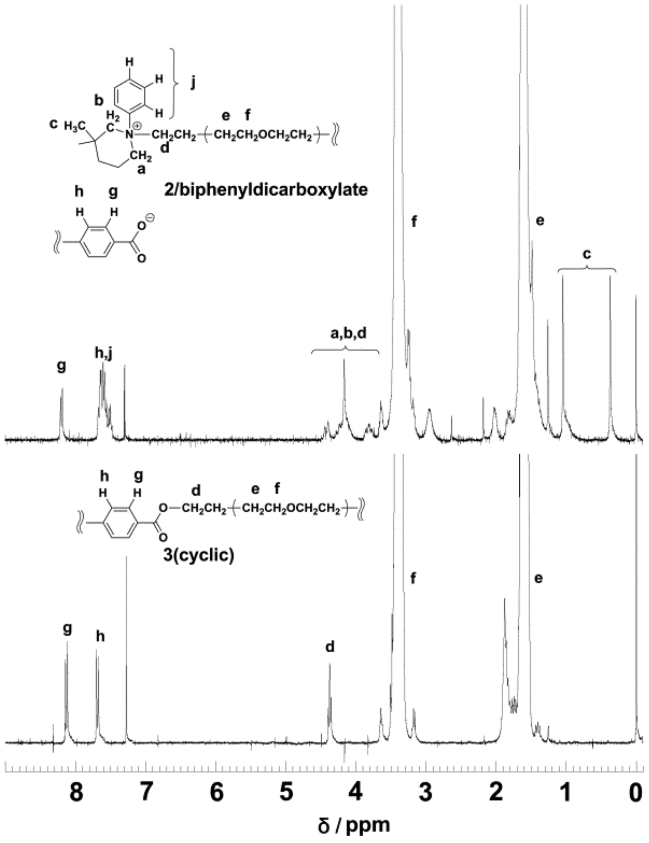


Figure 3. ^{1}H NMR (300 MHz) spectra of telechelic poly(THF) having *N*-phenyl-3,3-dimethylpiperidinium salt groups carrying a biphenyldicarboxylate counteranion, **2**/biphenyldicarboxylate (top), and the covalently linked product, **3**(cyclic) (bottom) ($CDCl_3$, 25 °C). See also Figure S1 in the Supporting Information.

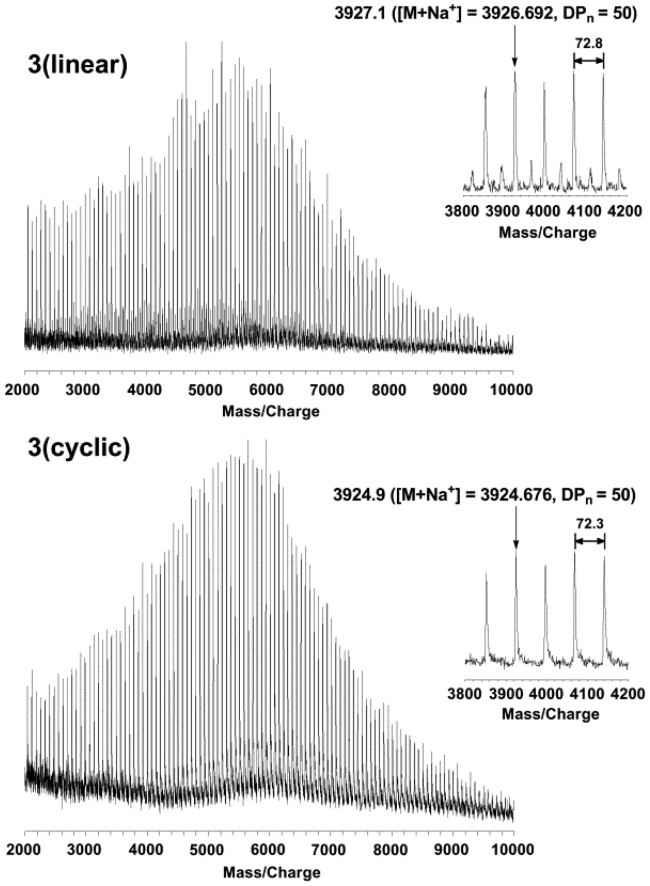


Figure 4. MALDI-TOF mass spectra of the linear polymer product obtained by the telechelic poly(THF) having *N*-phenyl-3,3-dimethylpiperidinium salt groups with benzoate counteranions, 3(linear) (top), and the ring polymer product obtained with a biphenyldicarboxylate counteranion, 3(cyclic) (bottom). (MALDI-TOF mass; linear mode, matrix: dithranol with sodium trifluoroacetate. DP_n denotes the number of monomer units in the product.).

protocol is significant in practice, not only for topological polymer chemistry but also for versatile polymer reactions and surface modifications, since the esterification is one of the most important chemical reactions, ubiquitous not only in bioprocesses but also in polymer and other materials productions.

EXPERIMENTAL SECTION

Materials. Poly(THF) having six-membered cyclic *N*-phenylpiperidinium salt groups (**1**/triflate) was prepared according to the method reported previously.[32] Tetra-*n*-butylammonium *p*-methoxybenzoate was synthesized by neutralization of *p*-methoxybenzoic acid (>99.0%) with tetra-*n*-butylammonium hydroxide (40% in water). Sodium *p*-nitrobenzoate and disodium biphenyldicarboxylate were prepared by neutralization of *p*-nitrobenzoic acid (>99.0%) and biphenyldicarboxylic acid (>97.0), respectively, with sodium hydroxide (NaOH, >95.0%). Sodium benzoate (>99.5%), 2,2-dimethylgulutaic acid (>98.0%), *p*-toluenesulfonic acid hydrate (99%), and lithium aluminum hydride (>98.0%) were used as received. Other reagents were used as received otherwise noted. Wakosil C-300 was used as received for flash chromatography.

Reaction of Poly(THF) having *N*-Phenylpiperidinium Salt End Groups (1/triflate) with *p*-Methoxybenzoate. The reactions of poly(THF) having *N*-phenylpiperidinium salt end groups (**1**/triflate) with a series of benzoate anions were performed by the

dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086−3094

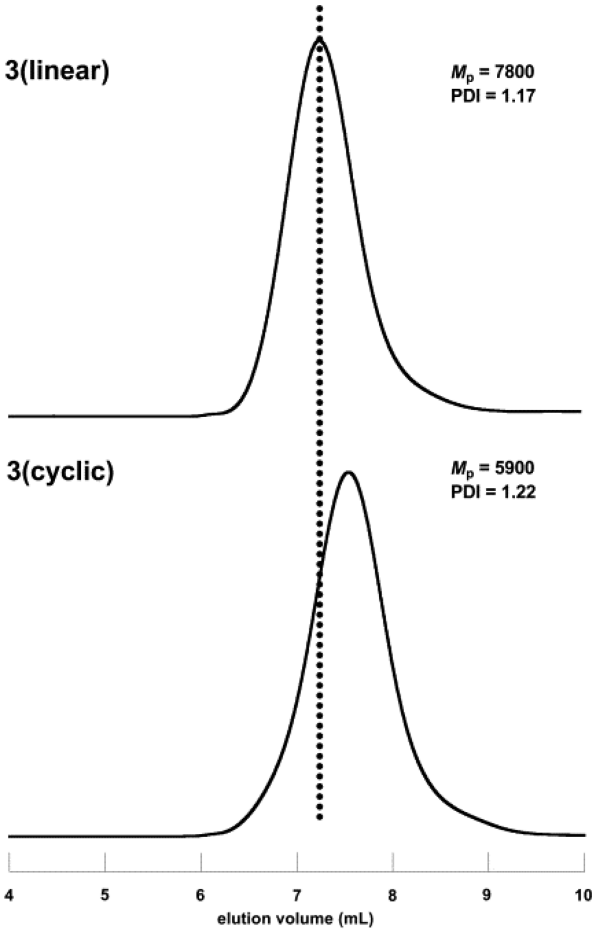


Figure 5. SEC traces of the linear polymer product obtained by telechelic poly(THF) having *N*-phenyl-3,3-dimethylpiperidinium salt groups with benzoate counteranions, **3**(linear) (top), and the ring polymer product obtained with a biphenyldicarboxylate counteranion, **3**(cyclic) (bottom) (THF as eluent at late flow 1.0 mL/min, with a TSK G3000HXL column).

procedure reported previously with unsubstituted benzoate.[9] Thus, a weighed amount of **1**/triflate (50 mg) and tetra-*n*-butylammonium *p*-methoxybenzoate (39.4 mg) was dissolved in THF (50 mL), and the resulting solution was refluxed for 3 h. Thereafter, most of the solvent was removed under reduced pressure, and the concentrated solution was passed through a plug of silica gel with *n*-hexane/acetone (2/1 v/v). Reprecipitation from acetone into ice-cooled water and subsequently from acetone into dry ice/acetone cooled *n*-hexane afforded an esterification product, **1b** (34.6 mg, M_n(NMR) = 4900, M_p(SEC) = 6300, PDI = 1.11), in 69% yield.

Reaction of Poly(THF) having *N*-Phenylpiperidinium Salt End Groups (1/triflate) with *p*-Nitrobenzoate. The counteranion exchange reaction of **1**/triflate was first performed to give **1**/*p*-nitrobenzoate by the following procedure. An acetone solution (2.0 mL) of **1**/triflate (200 mg, 44 μmol) was added dropwise into an ice-cooled aqueous solution (100 mL) containing sodium 4-nitrobenzoate (420 mg, 50 equiv) with vigorous stirring. The precipitate that formed was collected by filtration and dried under reduced pressure. The reprecipitation procedure was repeated, and 156 mg of a crude product (**1**/*p*-nitrobenzoate, with 91% ion-exchange rate) was collected, with a trace amount of water retained to avoid uncontrolled reactions.

The esterification reaction with **1**/*p*-nitrobenzoate was performed as follows. A weighed amount of **1**/*p*-nitrobenzoate (50 mg) was dissolved in THF (250 mL), and the resulting solution (0.2 g/L) was refluxed for 3 h. A large amount of THF was used to prevent the side reaction between the nitro group and azacycloalkane quaternary salt. Thereafter, most of the solvent was removed under reduced pressure, and the concentrated solution was passed through a plug of silica gel with *n*-hexane/acetone (2/1 v/v). Reprecipitation from acetone into ice-cooled water and subsequently from acetone into dry ice/acetone cooled *n*-hexane afforded an esterification product, **1c** (18.5 mg, M_n(NMR) = 6100, M_p(SEC) = 5900, PDI = 1.21).

Synthesis of *N*-Phenyl-3,3-dimethyl-2,6-piperidinedione. To a refluxing *o*-xylene (125 mL) solution of 2,2-dimethylglutaric acid (16.7 g, 0.10 mol) and *p*-toluenesulfonic acid (0.40 g, 2.1 mmol) was slowly added an *o*-xylene (10 mL) solution of aniline (11.1 g) over 2 h. The mixture was further refluxed for 24 h, and the resulting water was azeotropically removed. The reaction mixture was cooled to 0 °C and washed three times with water. The organic phase was evaporated to dryness under reduced pressure, and the residue was suspended in acetone with sonication. The suspension was filtered through a filter paper, and the filtrate was evaporated to dryness under reduced pressure. A CH_2Cl_2 solution of the residue was filtered through a plug of silica gel with CH_2Cl_2 to afford a solid substance, which was recrystallized from an acetone solution by vapor diffusion of *n*-hexane to allow isolation of *N*-phenyl-3,3-dimethyl-2,6-piperidinedione (7.50 g) in 33% yield.

Preparation of *N*-Phenyl-3,3-dimethylpiperidine. A THF solution (15 mL) of *N*-phenyl-3,3-dimethyl-2,6-piperidinedione (2.73 g, 12.6 mmol) was added to a THF (135 mL) solution of lithium aluminum hydride (0.96 g, 25 mmol) at 25 °C, and the mixture was refluxed for 1 h. Water (200 mL) and ethyl acetate (200 mL) were added to the reaction mixture at 0 °C, and the organic phase that separated was filtered, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel with chloroform to allow isolation of *N*-phenyl-3,3-dimethylpiperidine (0.91 g) in 38% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 1.00 (s, 6H; $-CH_3$), 1.35 (t, J = 6.1 Hz, 2H; $-CH_2CH_2C(CH_3)_2-$), 1.67−1.76 (m, 2H; $-NArCH_2CH_2-$), 2.82 (s, 2H; $-NArCH_2C(CH_3)_2-$), 3.07 (t, J = 5,6 Hz, 2H; $-NArCH_2CH_2-$), 6.78 (t, J = 7.3 Hz, 1H; Ar-*H* para to N), 6.90 (d, J = 7.8 Hz, 2H; Ar-*H* ortho to N), 7.23 (t, J = 8.2 Hz, 2H; Ar-*H* meta to N). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ 22.4, 26.9, 31.0, 37.4, 49.7, 62.6, 116.5, 118.7, 128.9, 152.6. H−H and C−H COSY spectra are given in the Supporting Information (Figures S2 and S3, respectively).

Synthesis of Poly(THF) Having *N*-Phenyl-3,3-dimethylpiperidinium Salt End Groups (2/triflate). **2**/triflate was prepared according to the previous report for the preparation of **1**/triflate[31] with slight modification. Thus, triflic anhydride (17 μL, 0.10 mmol) was added to THF (15 mL), and polymerization was allowed to proceed for 11 min at 25 °C with stirring. Thereupon, a THF solution (0.20 mL) of distilled *N*-phenyl-3,3-dimethylpiperidine (0.20 mg, 1.1 mmol) was added, and the solution was stirred for another 30 min. Unreacted THF was then removed under reduced pressure, and the residue was reprecipitated from acetone into dry ice/acetone cooled *n*-hexane to afford **2**/triflate (556 mg, M_n(NMR) = 5600, PDI = 1.17).

Synthesis of a Linear Poly(THF) with Simple Ester Linkages (3(linear)). The counteranion exchange reaction of **2**/triflate was first performed to give **2**/benzoate by the following procedure. An acetone solution (1.5 mL) of **2**/triflate (100 mg, 18 μmol) was added dropwise into an ice-cooled aqueous solution (50 mL) containing sodium benzoate (129 mg, 50 equiv) with vigorous stirring. The precipitate that formed was collected by filtration and dried under reduced pressure. The reprecipitation procedure was repeated, and 64 mg of a crude product (**2**/benzoate with 81% ion-exchange rate) was collected, with a trace amount of water retained to avoid uncontrolled reactions.

The esterification reaction with **2**/benzoate was performed as follows. A weighed amount of **2**/benzoate (50 mg) was dissolved in THF (50 mL), and the resulting solution was refluxed for 3 h. Thereafter, most of the solvent was removed under reduced pressure, and the concentrated solution was passed through a plug of silica gel with *n*-hexane/acetone (2/1 v/v). Reprecipitation from acetone into ice-cooled water and subsequently from acetone into dry ice/acetone cooled *n*-hexane afforded linear poly(THF) with simple ester linkages, **3**(linear) (39 mg, M_n(NMR) = 8300, M_p(SEC) = 7800, PDI = 1.17).

dx.doi.org/10.1021/jo400058f | J. Org. Chem. 2013, 78, 3086−3094

Synthesis of a Ring Poly(THF) with Simple Ester Linkages (3(cyclic)). The counteranion exchange reaction of **2**/triflate was performed to give **2**/biphenyldicarboxylate by the following procedure. An acetone solution (2.0 mL) of **2**/triflate (200 mg, 36 μmol) was added dropwise into an ice-cooled aqueous solution (100 mL) containing disodium biphenyldicarboxylate (511 mg, 50 equiv) with vigorous stirring. The precipitate that formed was collected by filtration and dried under reduced pressure. The reprecipitation procedure was repeated, and 162 mg of a crude product (**2**/biphenyldicarboxylate with 84% ion-exchange rate) was collected, with a trace amount of water retained to avoid uncontrolled reactions.

The covalent fixation of **2**/biphenyldicarboxylate was performed as follows. A weighed amount of **2**/biphenyldicarboxylate (50 mg) was dissolved in THF (250 mL), and the resulting solution (0.2 g/L) was refluxed for 3 h. Thereafter, most of the solvent was removed under reduced pressure, and the concentrated solution was passed through a plug of silica gel with *n*-hexane/acetone (2/1 v/v). Reprecipitation from acetone into ice-cooled water and subsequently from acetone into dry ice/acetone cooled *n*-hexane afforded a ring poly(THF) with simple ester linkages, **3**(cyclic) (28 mg, M_n(NMR) = 7200, M_p(SEC) = 5900, PDI = 1.22).

Measurements. ^{1}H NMR spectra were obtained at 300 MHz using $CDCl_3$ as a solvent. Proton chemical shifts (ppm) were referenced to the signal of tetramethylsilane. Size exclusion chromatography (SEC) measurements were performed with a refractive index detector and with THF as an eluent at a flow rate of 1.0 mL/min at 40 °C. MALDI-TOF mass spectra were recorded with a nitrogen laser (λ 337 nm) and pulsed ion extraction. The spectrometer was operated at an accelerating potential of 20 kV with a linear-positive ion mode. THF solutions of a polymer sample (1 mg/mL), dithranol (20 mg/mL), and sodium trifluoroacetate (10 mg/mL) were mixed (50/50/50 in μL), and a 1 μL portion of the mixture was deposited onto a sample target plate. Mass values were calibrated by the three-point method using insulin plus H^+ at m/z 5734.62, insulin β plus H^+ at m/z 3497.96, and α-cyanohydroxycinnamic acid dimer plus H^+ at m/z 379.35.

■ ASSOCIATED CONTENT

Supporting Information

A scheme showing polymer topologies by the ESA-CF protocol, a figure giving the ^{1}H NMR of linear polymer products, and tables giving DFT results on energies, imaginary frequencies, and optimized geometries (R-B3LYP/6-31+G(d)). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: skawauch@polymer.titech.ac.jp (S.K.); ytezuka@o.cc.titech.ac.jp (Y.T.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Prof. M. Kakimoto for access to NMR facilities. We thank the Academy for Global Leadership (A.K.) and Challenging Research President's Honorary Award (T.Y.) of the Tokyo Institute of Technology, Mizuho Foundation for the Promotion of Sciences (T.Y.), The Kurata Memorial Hitachi Science and Technology Foundation (T.Y.), and KAKENHI (23106709, T.Y.; 23685022, T.Y.; 23350050, Y.T.) for financial support. The DFT calculations were carried out on a TSUBAME 2.0 supercomputer at the Global Scientific Information and Computing Center of the Tokyo Institute of Technology.

■ DEDICATION

Dedicated to Professor Eric J. Goethals in honor of his 75th birthday.

■ REFERENCES

(1) Baeyer, A. v. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269−2281.

(2) Greenberg, A.; Liebman, J. F., *Strained Organic Molecules*; Academic Press: New York, 1978.

(3) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N., *Stereochemistry of Organic Compounds*, 2nd ed.; Wiley: New York, 1994. (b) Florkin, M.; Storz, E. H., *Comprehensive Biochemistry: Metabolism of Cyclic Compounds*; Elsevier: Amsterdam, London, New York, 1968. (c) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731−734. (d) Coulembier, O.; Raquez, J.-M., *Handbook of Ring-Opening Polymerization*; Wiley-VCH: Weinheim, Germany, 2009. (e) Xia, Y.; Boydston, A. J.; Yao, Y.; Kornfield, J. A.; Gorodetskaya, I. A.; Spiess, H. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 2670−2677. (f) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147−6176.

(4) McGrath, J. E., Ed. *Ring-Opening Polymerization: Kinetics, Mechanisms, and Synthesis*; American Chemical Society: Washington, DC, 1985; ACS Symposium Series *285*.

(5) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450−4458.

(6) (a) Morokuma, K. *Proc. Jpn. Acad., Ser. B* **2009**, *85*, 167−182. (b) Kerkines, I. S. K.; Morokuma, K.; Iordanova, N.; Viggiano, A. A. *J. Chem. Phys.* **2010**, *132*, 044309. (c) Pancharatna, P. D.; Hoffmann, R. *Inorg. Chim. Acta* **2006**, *359*, 3776−3784. (d) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *134*, 1078−1084. (e) Schwarz, W. H. E.; Schmidbauer, H. *Chem. Eur. J.* **2012**, *18*, 4470−4479.

(7) (a) Otera, J., *Esterification: Methods, Reactions, and Applications*; Wiley-VCH: Weinheim, Germany, 2003. (b) Otera, J.; Nishikido, J. *Esterification, Methods, Reactions and Applications*; Wiley-VCH: Weinheim, Germany, 2010.

(8) (a) Cerichelli, G.; Illuminati, G.; Lillocci, C. *J. Org. Chem.* **1980**, *45*, 3952−3957. (b) Cerichelli, G.; Luchetti, L. Ring-Opening Reactions. *Tetrahedron* **1993**, *49*, 10733−10738.

(9) Adachi, K.; Takasugi, H.; Tezuka, Y. *Macromolecules* **2006**, *39*, 5585−5588.

(10) (a) Tezuka, Y., Ed. *Topological Polymer Chemistry-Progress of cyclic polymers in synthesis, properties and functions*; World Scientific: Singapore, 2013. (b) Tezuka, Y. *Polym. J.* **2012**, *44*, 1159−1169.

(11) Oike, H.; Imaizumi, H.; Mouri, T.; Yoshioka, Y.; Uchibori, A.; Tezuka, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9592−9599.

(12) Foston, M.; Hubbell, C.; Park, D.-H.; Cook, F.; Tezuka, Y.; Beckham, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 1849−1852.

(13) Oike, H.; Imamura, H.; Imaizumi, H.; Tezuka, Y. *Macromolecules* **1999**, *32*, 4819−4825.

(14) Tezuka, Y.; Shida, T.; Shiomi, T.; Imai, K. *Macromolecules* **1993**, *26*, 575−580.

(15) (a) Ballester, P.; Tadayoni, B. M.; Branda, N.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3685−3686. (b) Hammett, L. P.; L., P. H. *J. Am. Chem. Soc.* **1933**, *55*, 4079−4089. (c) Eliel, E. L.; Anderson, R. P. *J. Am. Chem. Soc.* **1952**, *74*, 547−549.

(16) Habuchi, S.; Satoh, N.; Yamamoto, T.; Tezuka, Y.; Vacha, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1418−1421.

(17) Oike, H.; Hatano, H.; Tezuka, Y. *React. Funct. Polym.* **1998**, *37*, 57−63.

(18) Cunliffe, A. V.; Hartley, D. B.; Kingston, S. B.; Richards, D. H.; Thompson, D. *Polymer* **1981**, *22*, 101−107.

(19) Weber, W. P.; Gokel, W. G. *Phase Transfer Catalysis in Organic Chemistry*; Springer-Verlag: Heidelberg, Germany, 1977.

(20) According to the ^{1}H NMR, the oxygen atom of the nitro group also reacted with the cyclic ammonium when an excess of *p*-nitrobenzoate was used.

(21) (a) Zhao, G.-J.; Northrop, B. H.; Stang, P. J.; Han, K.-L. *J. Phys. Chem. A* **2010**, *114*, 3418−3422. (b) Cheng, C.-L.; Zhao, G.-J. *Nanoscale* **2012**, *4*, 2301−2305.

(22) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(23) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261. (c) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654−3665. (d) Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1984**, *80*, 3265−3269. (e) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acc.* **1973**, *28*, 213−222. (f) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209−214. (g) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294−301. We have also carried out single-point calculations for minima in the case of the six-membered ring by using a larger basis set (6-311++G(d,p)). As a result, in this case, the 6-31+G(d) basis set is enough to support the conclusions, because the obtained free energy difference between emitting and opening reactions (−5.2 kJ/mol) does not alter the result of the 6-31+G(d) basis set (−7.9 kJ/mol seen in Table 1).
(24) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.
(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C.01*; Gaussian, Inc., Wallingford, CT, 2009.
(26) Knox, J. H., *Molecular Thermodynamics*; Wiley: New York, 1971.
(27) Juaristi, E., Ed. *Conformational Behavior of Six-Membered Rings: Analysis, Dynamics, and Stereoelectronic Effects*; VCH: New York, 1995.
(28) The 1,3-diaxial interaction energies of H-Ph and H-Et are 6.3 and 4.0 kJ/mol, respectively.
(29) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316−2323.
(30) Bret, G.; Harling, S. J.; Herbal, K.; Langlade, N.; Loft, M.; Negus, A.; Sanganee, M.; Shanahan, S.; Strachan, J. B.; Tumer, P. G.; Whiting, M. P. *Org. Process Res. Dev.* **2011**, *15*, 112−122.
(31) Oike, H.; Mouri, T.; Tezuka, Y. *Macromolecules* **2001**, *34*, 6592−6600.
(32) Tezuka, Y.; Goethals, E. J. *Macromol. Chem. Phys.* **1987**, *188*, 783−789.