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Regioisomeric Preference in Ring-Opening Polymerization of 3′,5′-Cyclic Phosphoesters of Functional Thymidine DNA Analogues

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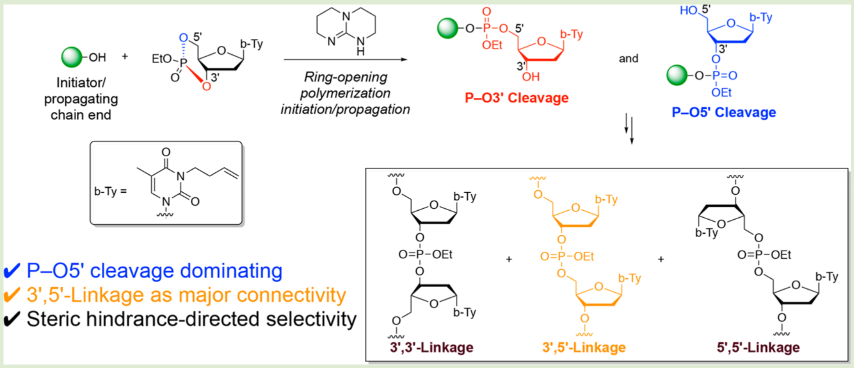
Supporting Information



ABSTRACT: Regioregularity is a crucial property in the synthesis of DNA analogues, as natural DNA is synthesized exclusively in the 5′ to 3′ direction. We have focused our attention on the determination of the regioisomeric distribution of poly(3′,5′-cyclic 3-(3-butenyl) thymidine ethylphosphate)s obtained from the ring-opening polymerization of (*R*)-3′,5′-cyclic 3-(3-butenyl) thymidine ethylphosphate. The regioisomeric preference was investigated by comparison to synthesized model compounds of 3′,3′-, 3′,5′-, and 5′,5′-linkages, where the model 3′-phosphoester linkages were to the secondary alcohol of 3-hydroxytetrahydrofuran and the model 5′-linkages derived from coupling to the primary alcohol of tetrahydrofurfuryl alcohol. From the ^{31}P resonance frequency assignments of those small molecule model compounds, ^{31}P NMR spectra revealed the major connectivity in the polymer backbone to be 3′,5′-linkages, with ≤30% of other isomeric forms. Model reactions employing a series of alcohol initiators imparting various degrees of steric hindrance, to mimic the increased steric hindrance of the propagating alcohol relative to the initiator, were then conducted to afford the corresponding ring-opened unimer adducts and to gain understanding of the regioselectivity during the ring-opening polymerization. ^{1}H−^{31}P heteronuclear multiple-bond correlation spectroscopy showed ethanol and 4-methoxybenzyl alcohol initiation to yield only the P−O5′ bond cleavage product, whereas attack by isopropyl alcohol upon (*R*)-3′,5′-cyclic 3-(3-butenyl) thymidine ethylphosphate afforded both P−O3′ and P−O5′ bond cleavage products, supporting our hypothesis that the increased steric hindrance of the propagating species dictates the regioselectivity of the P−O bond cleavage. Further model reactions suggested that the P−O5′ bond cleavage products can be detected upon the formation of dimers during the ring-opening polymerization. Overall, this work provides a fundamental understanding of the polymerization behavior of six-membered cyclic phosphoesters and broadens the scope of DNA analogues from the ring-opening polymerization of 3′,5′-cyclic phosphoesters.

Natural products have been of interest for the replacement of petrochemical-based monomers to increase functionality, decrease the dependence on fossil fuels, and reduce potential biological and environmental adverse effects.[1−4] Natural oils,[5,6] terpenes,[7−10] carbohydrates,[11−18] and the sugar components of DNA (2′-deoxyribonucleosides)[19−24] are attractive and versatile building blocks for the construction of polymeric materials by ring-opening polymerization (ROP). Several types of cyclic monomers, such as carbonates, epoxides, phosphazenes, phosphoesters,[25,26] *H*-phosphonates, phosphonites, phosphorothioates, siloxanes, and thiocarbonates, undergo ROP from opening of cyclic monomers from either side of the ring. If such monomers are asymmetrical, the regioisomeric ROP can yield polymers with head-to-head, head-to-tail, and tail-to-tail configurations. Mikami et al. reported the regiorandom nature of glucose-derived polycarbonates from organobase catalyzed ROP of a six-membered 4,6-cyclic carbonate of glucose with the 1-, 2-, and 3-positions protected by methyl groups, as determined from electrospray ionization tandem mass spectrometric analysis by electron transfer dissociation of the polymer species.[27] In contrast, with larger and base-coordinating ethyl carbonate protecting groups, regioregular head-to-tail ROP was observed.[17] Vandenberg,[28] Penczek,[29]

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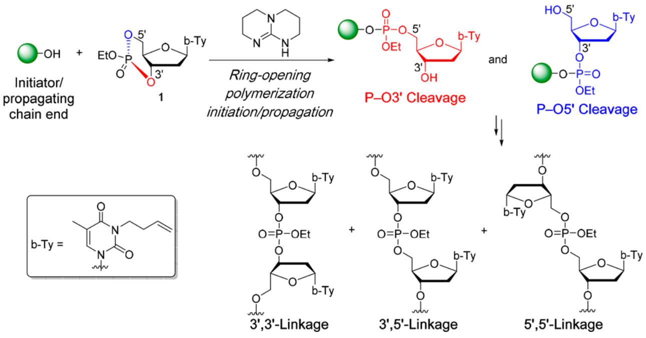
and Wurm[30] performed microstructural analyses of cyclic phosphorothioates, *H*-phosphonates, and phosphoesters to understand whether there was regioselectivity of these phosphorus-containing monomers for ROP from the spectroscopic characteristics of corresponding isomers. These studies concluded that head-to-tail configuration was the dominant connectivity when steric effects from both ring-opening directions were different, for example, primary and secondary alcohols formed from the ring-opening reactions. This selectivity was driven by differing steric effects within the phosphorus-containing five-membered cyclic monomers.[30]

We recently reported the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)-catalyzed ROP of thymidine-derived six-membered 3′,5′-cyclic phosphoester monomer **1** and, herein, advance the fundamental understanding of the ROP regiochemical selectivity. As observed by ^{31}P NMR analysis, three resonance frequencies supported the presence of populations of regioisomers. The possible regioisomeric forms of poly(3′,5′-cyclic 3-(3-butenyl) thymidine ethylphosphate) (**PCBT**) include 3′,3′-, 3′,5′-, and 5′,5′-linkages, corresponding to head-to-head, head-to-tail, and tail-to-tail configurations, respectively (Scheme 1). Initial model studies indicated that, in addition to the P substituents within the monomer,[30] the nature of the incoming nucleophile could also influence the directionality of ring opening. Therefore, we undertook extensive experimental and computational studies to better understand the mechanistic details of ring opening for these six-membered cyclic phosphoesters. Ultimately, as we aim to more closely mimic natural DNA,[31] which is synthesized exclusively in the 5′ to 3′ direction, these studies are expected to inform synthetic approaches toward regioregular DNA analogues by ROP of thymidine-derived cyclic phosphoesters.

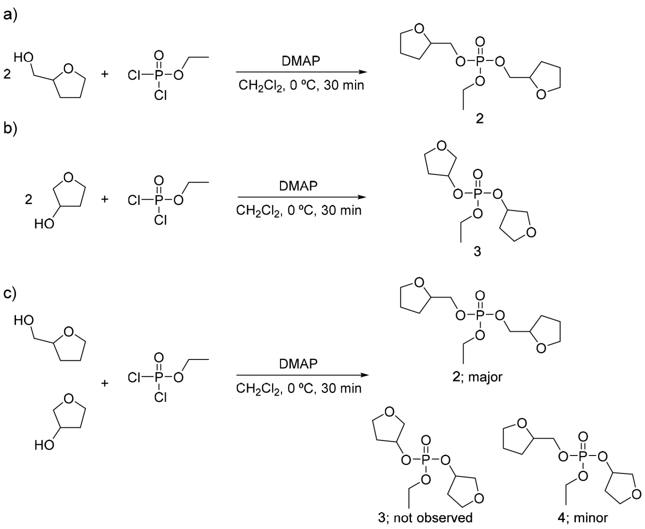
Scheme 1. Three Regioisomeric Forms from P−O3′ and P−O5′ Cleavages of 1 in TBD-Catalyzed ROP



Herein, we report a series of model reactions to investigate the regioisomeric preference in the ROPs of **PCBT**. Alcohols with varying steric effects were used to mimic the differing steric hindrances of the nucleophilic species. With increasing steric hindrance of the nucleophilic alcohol, increasing P−O3′, relative to P−O5′, cleavage products were observed in the product distribution. Density functional theory (DFT) calculations on the reaction coordinates were employed to rationalize the origin of the selectivity in the ROP systems. To the best of our knowledge, experimental and computational analyses on regiochemistries have not been extended to the ROP of 3′,5′-cyclic phosphoester monomers.

To investigate the origin of the ^{31}P NMR signals of **PCBT** and to simplify the complexity of the NMR spectra from nucleobases, 3-hydroxytetrahydrofuran and tetrahydrofurfuryl alcohol were used as models for 3′- and 5′-alcohols, respectively (Scheme 2a,b), assuming that the chemical shifts of the phosphorus atoms are influenced exclusively by the nearest environment. By reacting 2 equiv of these alcohols with 1 equiv of ethyl dichlorophosphate, **2** and **3** were obtained after purification by column chromatography. By comparing the ^{31}P NMR signals of **2** and **3** to those in the spectrum of **PCBT**, we can conclude that signals from −0.9 to −1.1 ppm and −2.7 to −2.9 ppm arise from 5′,5′- and 3′,3′-linkages, respectively (Figure 1). To determine the position of resonances corresponding to 3′,5′-linkages, model compound **4** was synthesized from the reaction of a 1:1 mixture of 3-hydroxytetrahydrofuran and tetrahydrofurfuryl alcohol with

Scheme 2. Model of (a) 5′,5′-Linkage, (b) 3′,3′-Linkage, and (c) 3′,5′-Linkage from Reacting Tetrahydrofurfuryl Alcohol and 3-Hydroxytetrahydrofuran with Ethyl Dichlorophosphate



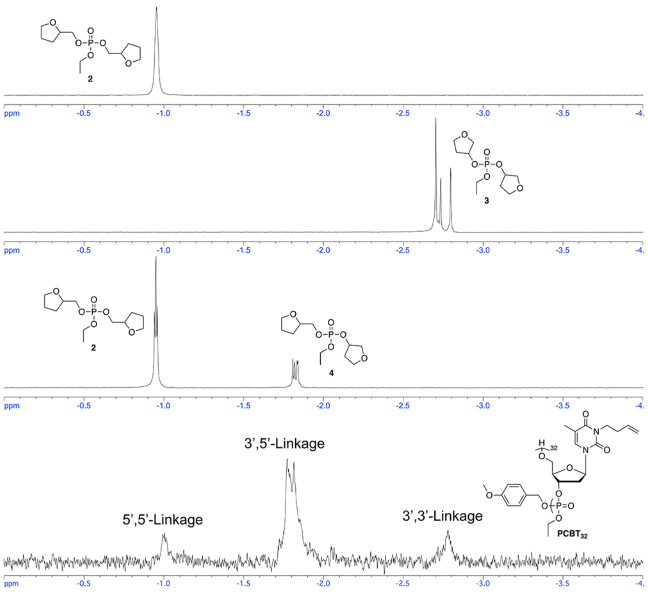
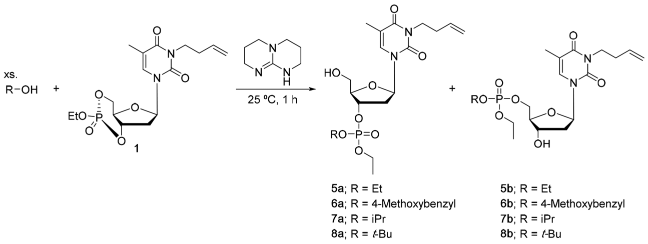


Figure 1. ^{31}P NMR spectra (202 MHz) of **2**, **3**, **4**, and **PCBT**$_{32}$ in CDCl$_3$, suggesting that the three chemical shift regions of **PCBT** correspond to 3′,3′-, 3′,5′-, and 5′,5′-linkages.

ethyl dichlorophosphate (Scheme 2c). This reaction yielded **2** as the major product, **4** as the minor product, and no evidence of **3**. This result was attributed to the higher reactivity and lower steric hindrance of primary alcohols, as **2** was a product from two primary alcohols, **4** was from a primary and a secondary alcohol, and **3** was from two secondary alcohols. The ^{31}P NMR spectrum of the 3′,5′-model compound **4** matched that of the **PCBT** signal at −1.7 to −1.9 ppm. Both 3-hydroxytetrahydrofuran and tetrahydrofurfuryl alcohol were racemic mixtures; therefore, multiple chemical shifts in ^{31}P NMR spectra could be observed for **2**, **3**, and **4** due to the combinations of diastereotopic isomers. Therefore, according to the relative integrations of the ^{31}P NMR signals in the spectra of **PCBT**,[24] about 75% connectivity in the polymer backbone was found to be 3′,5′-linkages, and similar distributions were observed for samples having number-averaged degrees of polymerization of 10, 21, and 32. This observation is consistent with the findings from ROPs of five-membered phosphorus-containing monomers, for which head-to-tail configuration dominated.[28−30]

To understand the preference of ring opening during initiation and propagation of polymerization in more detail, we performed studies on the unimer formed upon reaction with primary, secondary, and tertiary alcohols. 3′,5′-Cyclic monomer **1** was synthesized according to the previously reported procedure.[24] Reaction of 4-methoxybenzyl alcohol, the initiator used in the previous study, with **1** gave the corresponding unimer, allowing for evaluation of the monomeric product(s) from the initial ring-opening reaction. Both unimer and dimer formed when 1 equiv of 4-methoxybenzyl alcohol was added, and attempts to separate the two products with silica gel column chromatography were unsuccessful. Excess 4-methoxybenzyl alcohol was then added to suppress dimerization, but removal of the alcohol to obtain **6a** was difficult due to its high boiling point (257−259 °C at 760 Torr)[32] and poor water solubility (not removable by extraction). Due to the separation difficulty of 4-methoxybenzyl alcohol, another model reaction with a primary alcohol was performed. This model reaction utilized excess ethanol as initiator and solvent to ensure the formation of unimer (Table 1). The ^{1}H−^{31}P heteronuclear multiple bond correlation (HMBC) analysis indicated that only the product from P−O5′ bond cleavage was formed (Figure 2a). This result suggested that the initial ring-opening reaction with 4-methoxybenzyl alcohol was more favorable at the P−O5′ position. However, ^{31}P NMR spectra of **PCBT** suggested both P−O5′ and P−O3′ bond breaking took place during polymerization, which appeared to be contradictory to the ethanol model reaction. To confirm whether ethanol possesses the same ring-opening preference as 4-methoxybenzyl alcohol, a ^{31}P NMR experiment of the crude product using excess 4-methoxybenzyl alcohol was performed, showing a single resonance signal at −1.77 ppm (Figure S8). Even though isolation of **6a** from 4-methoxybenzyl alcohol was difficult, the ^{1}H−^{31}P HMBC spectra of crude mixtures revealed that the only product formed was **6a**, due to the presence of $^{4}J_{HP}$ coupling with 2′-H (Figure S9). This result indicated that P−O5′ bond cleavage was favored during the initiation by 4-methoxybenzyl alcohol, suggesting that P−O3′ cleavage took place during subsequent propagation steps. Hence, we hypothesized that increased steric hindrance of propagating alcohols, relative to the initiating benzylic alcohol, might alter the regioselectivity during ROP.

Table 1. Model Reaction of Various Alcohols with 1 to Give Unimers



entry	R	**a**/**b** (molar ratio)
1	Et	100:0
2	4-methoxybenzyl	100:0[a]
3	iPr	76:24[b]
4	*t*-Bu	NR[c]

[a]Determined by the crude ^{31}P NMR spectrum. [b]Determined by the isolated yields. [c]No reaction at both ambient temperature and reflux conditions.

To verify our hypothesis of steric hindrance-directed ring-opening preference, excess isopropyl alcohol was used as the nucleophilic solvent to provide increased steric hindrance relative to 4-methoxybenzyl alcohol and ethanol (Table 1). Two isomers, **7a** and **7b**, were formed from the model reaction of **1** with isopropyl alcohol, but the separation was challenging. Even though thin layer chromatography showed complete separation of **7a** and **7b** with 30:70 acetone/hexanes as the eluent (Figure S10a), integration from ^{1}H and ^{31}P NMR spectra of **7b** suggested about 20 mol % of **7a** remained in the **7b** fraction (Figure S5c). Use of 25:75 acetone/hexanes eluent did not improve the separation (Figure S10b). The low R_f values indicated longer retention time in the silica gel column, and this phenomenon led to mixing of **7a** and **7b** due to longitudinal diffusion (the B-term described in the van Deemter equation).[33] Despite incomplete separation, spectroscopic data of the mixture nevertheless provided evidence for the formation of both **7a** and **7b** upon reaction of **1** with isopropyl alcohol. Due to the slower kinetics of isopropyl alcohol during the initiation step, oligomerization was observed even when excess initiator was used, and the oligomers complicated the analysis of the ^{31}P NMR spectrum of the crude mixture. Thus, the unimers were separated from the oligomers and used to calculate the relative ratio of **7a** and **7b**. These model reactions successfully demonstrated that steric hindrance determines the regioselectivity of ROP of **1**, from preferential P−O5′ cleavage to mixtures of P−O5′ and P−O3′ bond breaking, giving rise to the 3′,3′- and 5′,5′-linkages in **PCBT**. Further increasing steric hindrance by using *tert*-butyl alcohol as the nucleophile resulted in no reaction at both ambient temperature and upon reflux of the mixture.

To further mimic the propagating species present during ROP for the model reaction and explore if the P−O3′ linkages observed in **PCBT** are due to the nature of the propagating alcohol, excess tetrahydrofurfuryl alcohol was used to conduct the TBD-catalyzed ring-opening reaction of **1** in dichloromethane (Table 2, entry 1). Only **9a** from P−O5′ cleavage was observed (Figure S11), suggesting the steric effect that primarily alters regioselectivity arises from the substituent(s) at the 3′-position (similar to *syn*-pentane interaction). Therefore, the model reaction of **1** with **5a** as the nucleophile was then performed, and the inseparable dimeric mixture of **10a** and **10b** was obtained (Table 2, entry 2). The ^{1}H−^{31}P HMBC

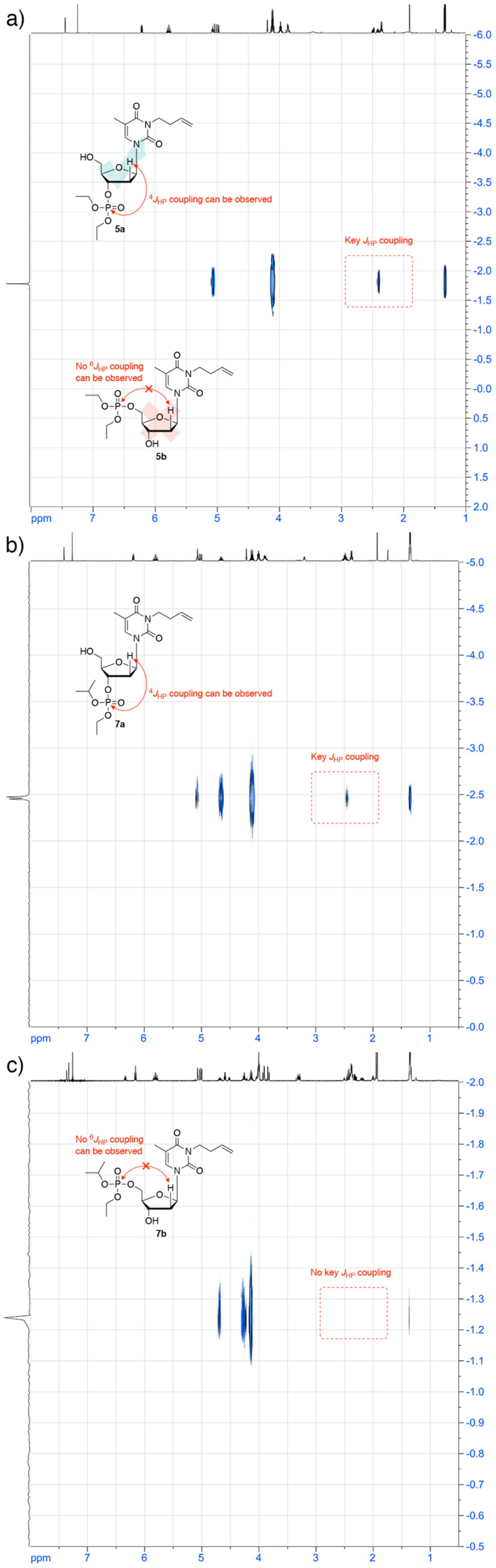
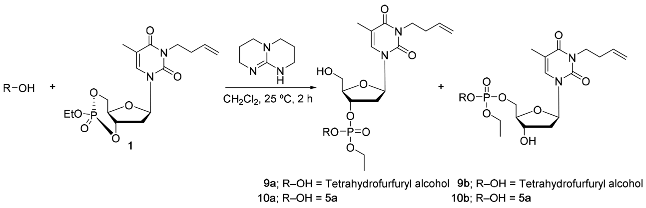


Figure 2. ^{1}H−^{31}P HMBC (500 MHz for ^{1}H) of (a) **5a**, (b) **7a**, and (c) **7b** in $CDCl_3$, indicating preferential P−O5′ bond breaking during initiation when ethanol was used, but both P−O5′ and P−O3′ cleavages occurred upon reaction of **1** with isopropyl alcohol.

Table 2. Model Reaction of Various Alcohols with 1 for the Propagating Step



entry	R−OH	a/b (molar ratio)
1	tetrahydrofurfuryl alcohol	100:0
2	**5a**	89:11[a]

[a] Determined by integration values in the ^{1}H NMR spectrum.

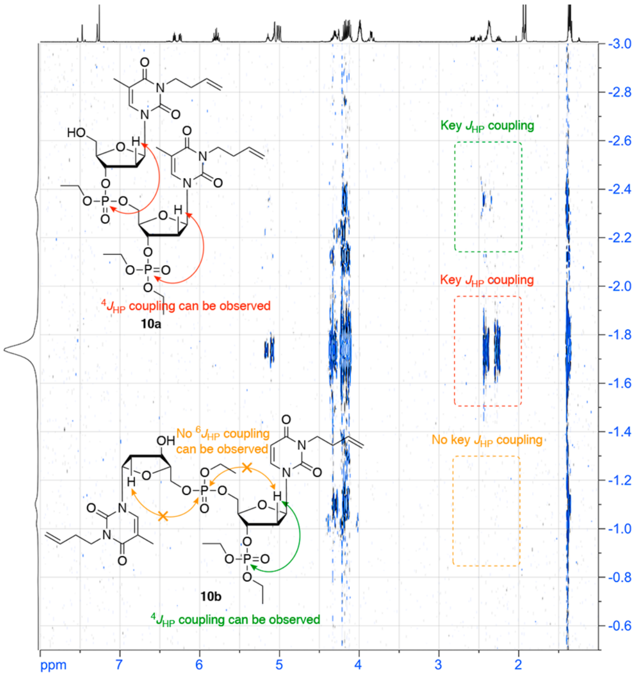


Figure 3. ^{1}H−^{31}P HMBC spectrum (500 MHz for ^{1}H) of the mixture of **10a** and **10b**.

spectrum (Figure 3) revealed peaks around −2.2 and −1.0 ppm in the ^{31}P NMR spectrum, which corresponded to the **5a** unit and the phosphotriester linkage connecting the dimer, respectively. More interestingly, the ^{31}P NMR spectrum of the mixture (Figure S7) not only indicated the presence of the products from P−O3′ and P−O5′ cleavages, but also suggested the occurrence of pseudorotation that yielded diastereomers, and thus, two sets of peaks from **10b** were observed in the ^{31}P NMR spectrum.

This steric hindrance-directed selectivity provides new insight into the mechanism of TBD-catalyzed ROP[34] of cyclic phosphoesters and further supports one previously proposed mechanism by Simón and Goodman.[35] Two mechanisms for TBD catalysis, including nucleophilic and acid−base catalysis in lactone ROP, were investigated by DFT calculations. In the nucleophilic catalytic mechanism, TBD reacted with monomers first to open the ring, and alcohols reacted subsequently. In contrast, the acid−base catalytic mechanism suggested that alcohols, monomers, and TBD reacted in situ in the transition state prior to ring-opening of cyclic monomers, that is, the

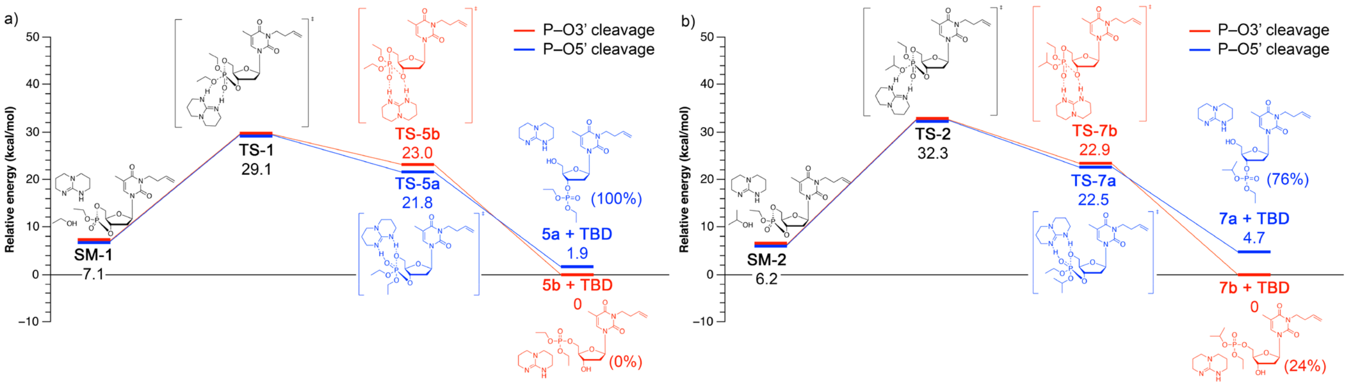


Figure 4. DFT calculations on the reaction coordinates of ring-opening reactions (acid−base catalytic mechanism) of **1** with (a) ethanol and (b) isopropyl alcohol. The molar percentages of each product are indicated in parentheses.

alcoholic initiators participated in the ring-opening process. In our system, if the TBD-catalyzed ROPs of **1** took place through the nucleophilic catalytic mechanism, steric changes in alcohol should not reflect on the selectivity, because the cyclic monomer would open prior to alcohol involvement. Hence, our finding that the steric hindrance of alcohols dictates ROP regioselectivity is consistent with the acid−base catalytic mechanism for the TBD-catalyzed ROP of **1**.

DFT was used to calculate the energies of the acid−base catalytic mechanism for starting materials (SM), transition states (TS), and final products at the B3LYP/6-31+G* level of theory to rationalize the origin of steric hindrance-directed regioselectivity (Figure 4). Products from P−O3′ cleavage (the red route in Figure 4) were more thermodynamically stable than from P−O5′ cleavage (the blue route in Figure 4) in both model reactions, but a smaller amount, if any, of such a product was obtained experimentally. These calculations combined with experimental results suggested that the reaction is kinetically, rather than thermodynamically, controlled at ambient temperature. On the other hand, despite the transition states for P−O3′ cleavage (red route) in both reactions being higher in energy compared to P−O5′ cleavage, the energy difference between the transition states for the two routes resulting from isopropyl alcohol initiation (0.4 kcal/mol) was smaller than that from ethanol initiation (1.2 kcal/mol). This lower differential energy barrier for P−O3′ versus P−O5′ bond cleavage from the transition states following nucleophilic attack by isopropyl alcohol supports the finding of 24% **7b**, the product from P−O3′ cleavage. Together, these DFT calculations applied toward an acid−base catalytic mechanism explained the origin of the regioisomeric ratios being dependent on the steric hindrance of the attacking nucleophiles. We expect the ROP of **1** might possess different regioselectivity when different catalysts are used, as the reaction mechanism might vary with different catalysts. However, in our trials with TBD, 1,8-diazabicyclo[5.4.0]undec-7-ene, $Sn(Oct)_2$, $(i\text{-}Bu)_3Al$, and methanesulfonic acid, only TBD successfully initiated the ROP.

In summary, we have verified the regioselectivity of the ROP of **1** into **PCBT** and validated our hypothesis with model reactions to establish the steric hindrance-based origin of the selectivity. From syntheses of model compounds **2**−**4** with 3′,3′-, 5′,5′-, and 3′,5′-linkages, we concluded that signals resonating in the ^{31}P NMR spectra of **PCBT** from −2.7 to −2.9 ppm, from −0.9 to −1.1 ppm, and from −1.7 to −1.9 ppm arose from 3′,3′-, 5′,5′-, and 3′,5′-linkages, respectively. Further model reactions employing different alcohols, including 4-methoxybenzyl alcohol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, and **5a**, revealed that the preference of P−O3′ and P−O5′ cleavages was dictated by steric hindrance. DFT calculations on the reaction coordinates of the ethanol and isopropyl alcohol model reactions demonstrated that the transition state energy difference between the two routes was the major reason for changes in product distribution. Overall, this work provides a fundamental understanding of the polymerization behavior of six-membered 3′,5′-cyclic phosphoesters and broadens the scope of designing different DNA analogues. The ring-opening preference of the six-membered cyclic phosphotriester thymidine analogues presented here affords polymerization primarily in the 3′-to-5′ direction, opposite relative to the 5′-to-3′ polymerization of DNA in Nature. Notably, both systems yield head-to-tail linkages as the major connectivity. We anticipate the exploration of reasons behind the varying ring opening preferences in our ROP system will further the development of a next generation of 3′,5′-cyclic monomers that mimics natural DNA.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.7b00858.

> Experimental procedures, spectroscopic data for all new compounds including ^{1}H, ^{13}C, ^{31}P NMR spectra, IR spectra, and mass spectrometry results, as well as details of computational chemistry (PDF).

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Notes

The authors declare no competing financial interest.

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