Tautomerism Polymerization: New Degradable Polyethers and Polythioethers from Nucleic Acid Base Derivatives

Kazuhiro Nakano, Yuri Sumitomo, and Koichi Kondo*

Department of Chemistry, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525, Japan

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ABSTRACT: Tautomerism of nucleic acid bases was applied to a new type of polycondensation which was achieved by dehydration of hydroxyethyl purines and pyrimidines or dehydrochlorination of chloroethyl purines and pyrimidines to give polyethers and polythioethers containing purine and pyrimidine bases in the main chain. The polymer was found to be decomposed to the monomer under acidic and basic condition.

Introduction

Much attention has been given in recent years to the tautomerism of nucleic acid bases that the lactam form exists predominantly over the lactim form as verified by extensive NMR spectroscopy[1] and theoretical MO calculations.[2] Synthetic application based on the tautomerism of nucleic acid bases such as pyrimidines and purines appeared in the field of dehydrating and desulfhydrating reagents which are related to the lactim to lactam tautomerism transformation.[3,4] The synthetic route to alkoxy pyrimidines is also associated with typical tautomerism cases which are realized in the reaction of uracil with primary alcohols by using Mitsunobu's reagent.[5] Furthermore, thioalkylation of thiopyrimidine or purine bases by alkyl halides conducted under basic conditions is another example of the tautomerism application to the exclusive *S*-alkylation rather than *N*-alkylation.[6] Based on these findings, Misumi *et al.* performed the synthesis of purinophanes via the thioalkylation of thiopurine.[7] Obviously, these synthetic methods suggest that a new type of polymer can be prepared from the lactam to lactim tautomerism for pyrimidine and purine monomers with appropriate bifunctionality, and the reverse course of lactim to lactam transformation may bring about the polymer degradation.

This paper describes the formation of polyethers by the intramolecular dehydration of hydroxyethyl purine and pyrimidine derivatives referred to the lactam to lactim tautomerism as well as polythioethers by the dehydrochlorination of chloroethyl purine and pyrimidine derivatives, together with the polymer degradation to the monomer level under acidic and basic conditions.

Experimental Section

Monomer Synthesis. 1-(2-Hydroxyethyl)thymine (**1**) was prepared from thymine and ethylene carbonate in DMF as described in the literature.[8] 9-(2-Hydroxyethyl)hypoxanthine (**3**) was derived from the deamination of 9-(2-hydroxyethyl)-adenine, which was similarly obtained by the reaction of adenine with ethylene carbonate.[9] 1-(2-Chloroethyl)-4-thiothymine (**5**) and 9-(2-chloroethyl)purine-6-thione (**7**) were prepared from the phosphorus pentasulfide treatment of the corresponding chloroethyl compounds[8,9] in pyridine.[10]

Polycondensation. 1-(2-Hydroxyethyl)thymine (**1**) (0.2 g, 1.2 mmol) was treated with triphenylphosphine (0.39 g, 1.5 mmol) and diethyl azodicarboxylate (0.26 g, 1.5 mmol) in DMF (28 mL) for 7 days at 90 °C. After condensation, the residue was purified two times from the DMF solution by ether reprecipitation; conversion 86%.

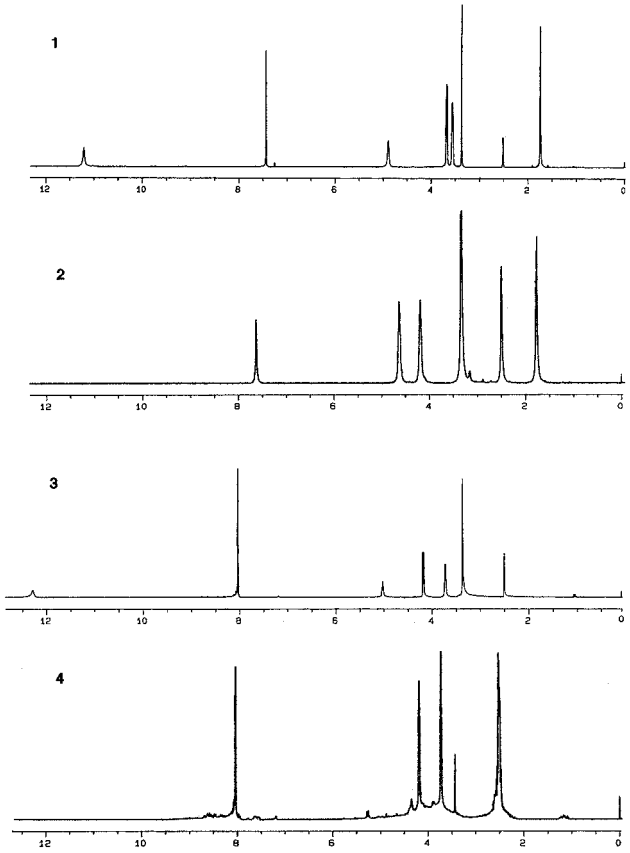

Figure 1. NMR spectra for **1**−**4**.

9-(2-Hydroxyethyl)hypoxanthine (**3**) was similarly treated in hexamethylphosphorous triamide (HMPA) and purified two times from the HMPA solution by ether reprecipitation; conversion 52%. 1-(2-Chloroethyl)-4-thiothymine (**5**) (0.21 g, 1 mmol) was treated with *t*-BuOK (0.16 g, 1,4 mmol) in 1-methyl-2-pyrrolidone (NMP) (10 mL) for 4 days at 60 °C. After condensation, the residue was purified two times from the NMP solution by methanol reprecipitation; conversion 27%. Similarly, 9-(2-chloroethyl)purine-6-thione (**7**) was treated in NMP and purified two times from the NMP solution by methanol reprecipitation; conversion 54%.

Time of Flight (TOF) Mass Spectroscopy Measurement. The matrix sinapinic acid solution, which was prepared from 30% aqueous acetonitrile and 0.1% trifluoroacetic acid,[11] was mixed with polymer, applied to a flat metal probe, dried, and used for the measurement.

NMR Spectra. NMR spectra of all the compounds were measured in DMSO-d_6 so that each spectrum includes H_2O and DMSO signals at 3.45 and 2.49 ppm, respectively.

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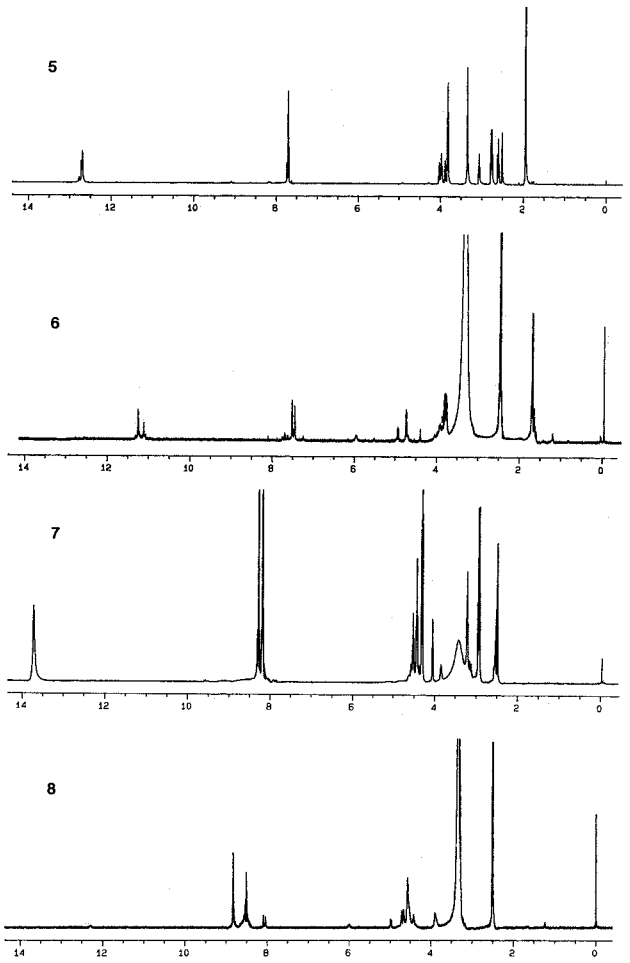


Figure 2. NMR spectra for **5**−**8**.

1: 1.78 (s, 3H, 5-CH_3), 3.56 (m, 2H, CH_2), 3.66 (m, 2H, CH_2), 4.89 (s, 1H, O*H*), 7.43 (s, 1H, 6-*H*), 11.21 (s, 1H, N*H*) ppm. **2**: 1.77 (s, 3H, 5-CH_3), 4.19 (m, 2H, CH_2), 4.63 (m, 2H, CH_2), 7.62 (s, 1H, 6-*H*) ppm. **3**: 3.72 (m, 2H, CH_2), 4.18 (m, 2H, CH_2), 5.02 (s, 1H, O*H*), 8.02 (d, 2H, 2-H, 8-*H*), 12.28 (s, 1H, N*H*) ppm. **4**: 3.74 (m, 2H, CH_2), 4.25 (m, 2H, CH_2), 8.11 (d, 2H, 2-*H*, 8-*H*) ppm. **5**: 1.95 (s, 3H, 5-CH_3), 2.75−4.15 (m, 4H, CH_2CH_2), 7.69 (s, 1H, 6-*H*), 12.69 (s, 1H, N*H*) ppm. **6**: 1.96 (s, 3H, 5-CH_3), 3.37−3.85 (m, 4H, CH_2CH_2), 7.56 (s, 1H, 6-*H*) ppm. **7**: 2.93−4.44 (m, 4H, CH_2CH_2), 8.19 (s, 1H, 8-*H*), 8.29 (s, 1H, 2-*H*), 13.73 (s, 1H, N*H*) ppm. **8**: 4.42−4.71 (m, 4H, CH_2CH_2), 8.57 (s, 1H, 8-*H*), 8.84 (s, 1H, 2-*H*) ppm.

Degradation. All the polymers were decomposed in 1 N HCl or NaOH aqueous solution at room temperature for 6−14 days. After evaporation, the powder sample was analyzed by mass, NMR, and IR measurements.

Results and Discuussion

Polymerization. When 1-(2-hydroxyethyl)thymine (**1**) and 9-(2-hydroxyethyl)hypoxanthine (**3**) were treated with Mitsunobu's reagent (triphenylphosphine (Ph_3P)/diethyl azodicarboxylate (DEADC), poly(4,1-(3-methyl-2-oxopyrimidine)diyloxyethylene) (**2**) and poly(9,6-purinediyloxyethylene) (**4**) were obtained in conversions of 86 and 52%, respectively. The formation of the polymer was confirmed by NMR and IR spectra. Amido protons (**1**, 11.21; **3**, 12.28 ppm) disappeared in both polymers as well as hydroxy protons (**2**, 4.89; **3**, 5.02 ppm) (Figure 1). IR spectra showed that the O−H stretching vibration (**1**, 3288; **3**, 3219 cm^{-1}) disappeared and that a new strong C=N stretching vibration appeared (**2**, 1610; **4**, 1697 cm^{-1}), together with a C−O stretching vibration (**2**, 1288; **4**, 1250 cm^{-1}) to exhibit the ether bonding formation (Figure 3). These findings indicate that the lactam to lactim transformation in the

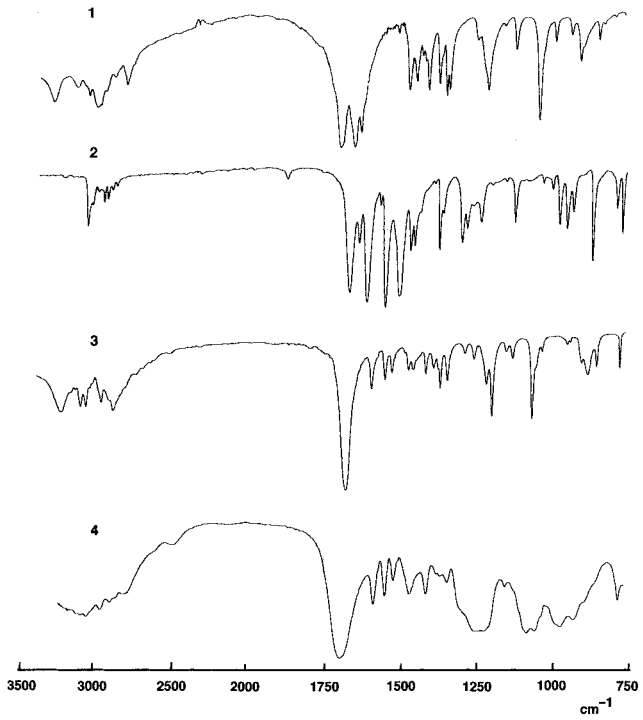
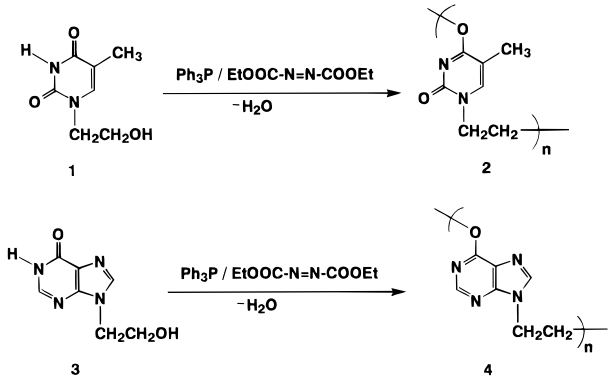
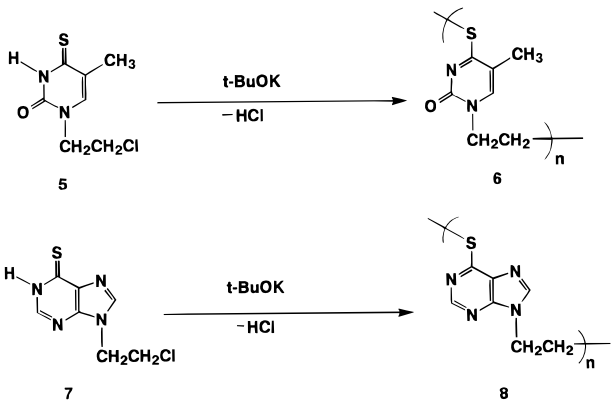


Figure 3. IR spectra (KBr method) for **1**−**4**.

Scheme 1



Scheme 2



pyrimidine and purine rings took place during the intramolecular dehydration to give the polymer (Scheme 1). Such a polycondensation may be referred to as a tautomerism polymerization.

On the treatment of **5** and **7** with a strong base such as *t*-BuOK, intramolecular dehydrochlorination took place to give poly(4,1-(3-methyl-2-oxopyrimidine)diylthioxyethylene) (**6**) and poly(9,6-purinediylthioxyethylene) (**8**) in conversions of 27 and 54%, respectively (Scheme 2).

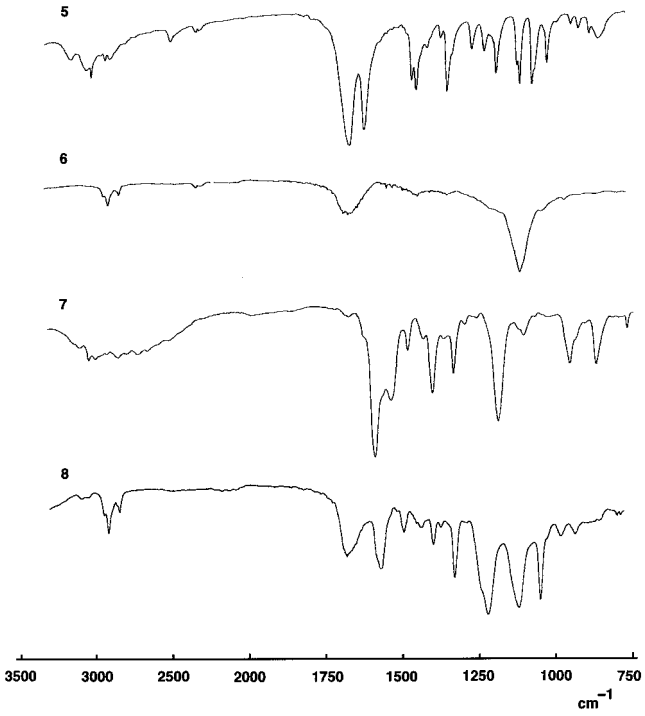


Figure 4. IR spectra (KBr method) for **5**−**8**.

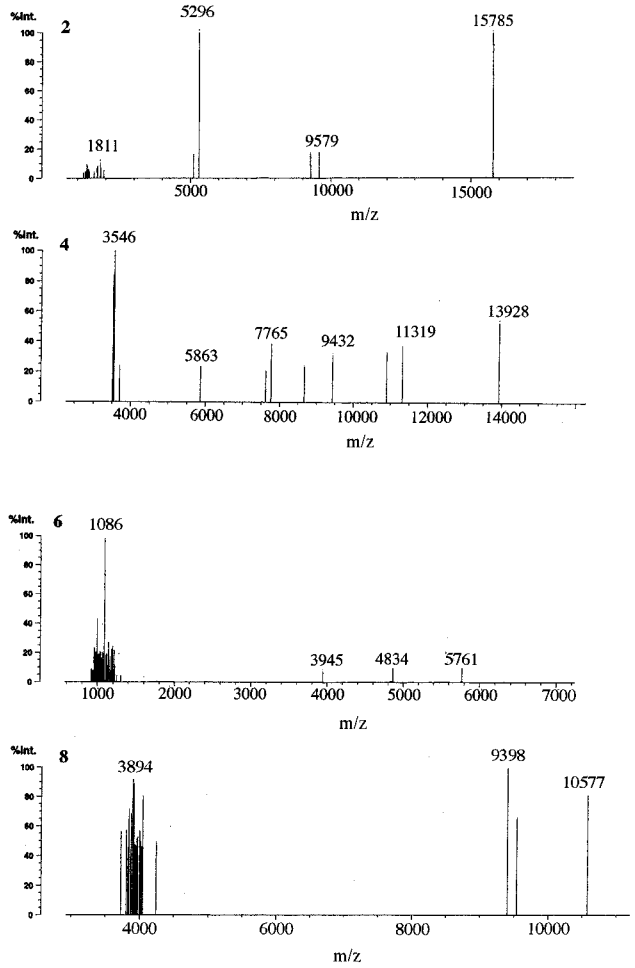


Figure 5. Mass spectra for **2**, **4**, **6**, and **8**.

The low conversion and molecular weight (*vide infra*) of **6** were interpreted in terms of another dehydrochlorination of the 1-chloroethyl group which was related to the formation of 1-vinyl-4-thiothymine corresponding to the weak ABX type vinyl proton signals[3] at 4.76−7.49 and two NH proton signals at 11.15−11.28 ppm

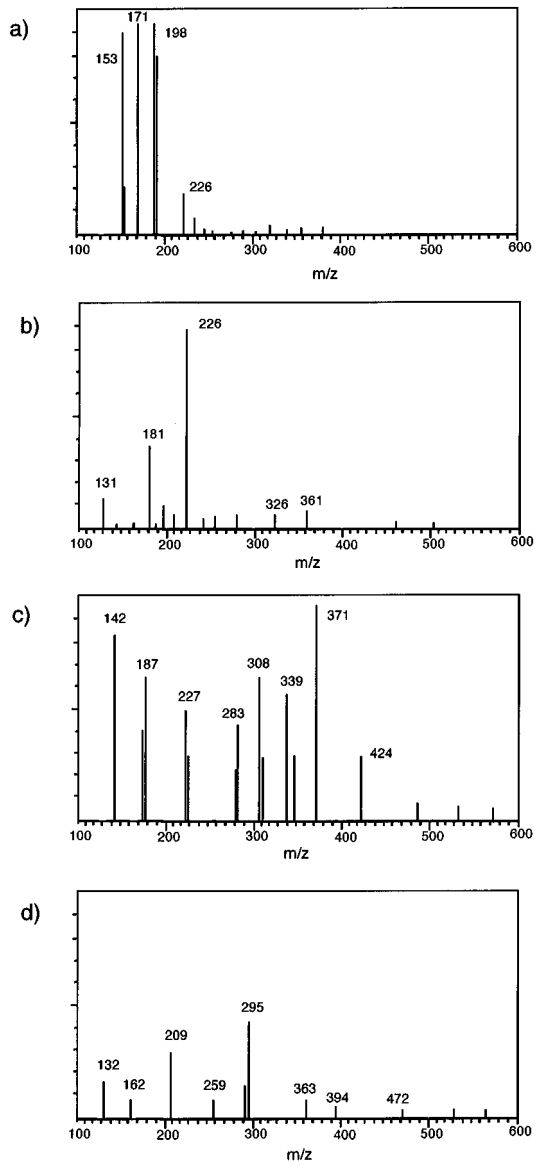


Figure 6. LC−mass spectra for degradation products of (a) **2**, (b) **4**, (c) **6**, and (d) **8**, eluted with methanol.

for the different conformers as shown in the NMR spectra (**6** in Figure 2). The ratio of polymer formation to vinylation was estimated to be about 2:3 from the proton signal intensity at around 7.5 ppm. **7** also underwent similar vinylation but to lesser a degree compared with **5** due to the large purine ring hindering the vinylation. In the NMR spectra of **6** and **8**, thioamide proton signals (**5**, 12.69; **7**, 13.73 ppm) disappeared (Figure 2), a weak thioamide N−H stretching vibration at around 3200 cm^{-1} in the IR spectra also disappeared, and a strong C═N stretching vibration appeared at 1683 cm^{-1}, indicating that the thiolactam to thiolactim transformation took place during the dehydrochlorination (Figure 4).

TOF mass spectroscopy using sinapinic acid as the matrix material, which has been developed for determining the molecular masses of proteins,[11] was found to be quite useful for the molecular weight determination of the polymer, which exhibits maximum M_n for **2**, **4**, **6**, and **8** at 1.57×10^4 ($n = 103$), 1.39×10^4 ($n = 86$), 5.7×10^3 ($n = 34$), and 1.06×10^4 ($n = 60$), respectively (Figure 5).

All the polymers are soluble in DMF, DMSO, NMP, and acidic and basic aqueous solutions. The film of **2** cast from the DMF solution was too brittle to be used for the degradation test.

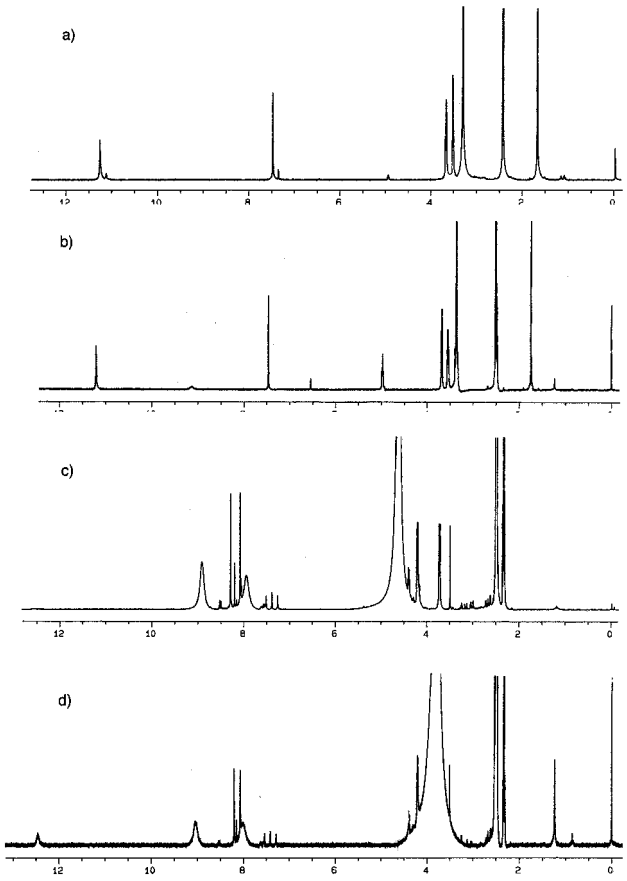


Figure 7. NMR spectra for degradation products: (a) **2** treated in 1 N HCl aqueous solution for 6 days at room temperature; (b) **2** treated in 1 N NaOH aqueous solution for 6 days at room temperature; (c) **4** treated in 1 N HCl aqueous solution for 6 days at room temperature; (d) **4** treated in 1 N NaOH aqueous solution for 6 days at room temperature.

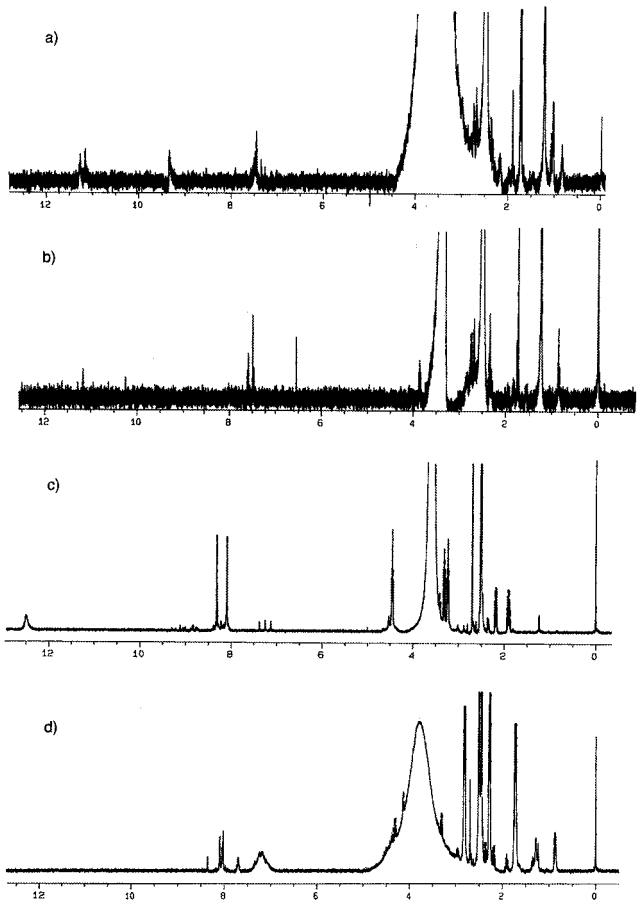
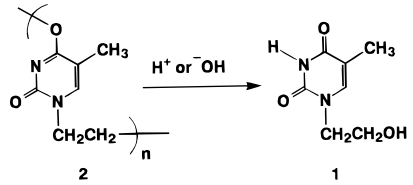
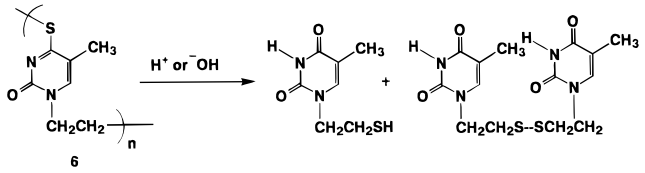


Figure 8. NMR spectra for degradation products: (a) **6** treated in 1 N HCl aqueous solution for 16 days at room temperature; (b) **6** treated in 1 N NaOH aqueous solution for 6 days at room temperature; (c) **8** treated in 1 N HCl aqueous solution for 16 days at room temperature; (d) **8** treated in 1 N NaOH aqueous solution for 6 days at room temperature.

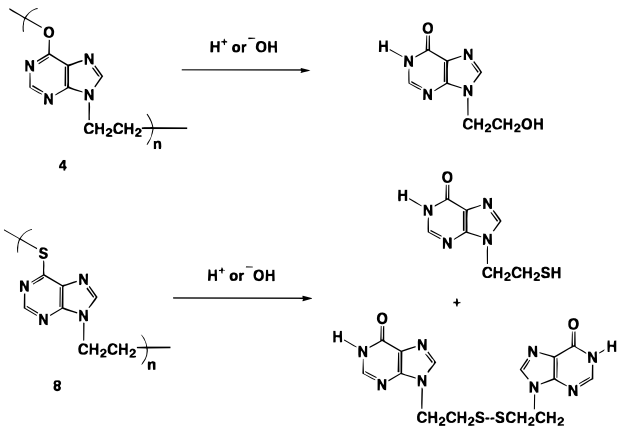
Scheme 3



Scheme 4



Scheme 5



Degradation. All the polymers were cleaved into dimers and trimers in 1 N HCl or NaOH aqueous solution for 6−16 days at room temperature. **6** and **8** were not fully cleaved in 1 N HCl for 6 days, but in 16 days, while others were cleaved in 6 days. The NMR spectra (Figure 7a,b) of the degradation products from **2** in 1 N HCl and NaOH aqueous solution were so close to that of the monomer that further detailed analysis by LC−mass spectroscopy revealed the mass of 171 (detected by the protonated form) to be consistent with the mass of monomer **1** (Figure 6). These findings indicate that **2** was cleaved precisely to the monomer level (Scheme 3)

Inspection of NMR data from other degradation products revealed that they were likely to include a structure similar to the corresponding monomer, but the fine structure was slightly different from that of the native monomer (Figures 7 and 8). Polymer **6** which was cleaved in acidic and basic conditions gave rise to a structure similar to that of the thymine moiety, which could be proved by the signals corresponding to the amide proton, 6-H, the methyl proton, and S−H at around 11.3, 7.5, 1.6, and 1.5 ppm, respectively, as observed in the magnified NMR spectra (Figure 8a,b). Such NMR data and the LC−mass peaks of 187 and 371 (Figure 6c) seem to include the monomer with the mercaptoethyl group at the 1-position and the dimer linked with disulfide bonding (Scheme 4).

In the case of purine type polymers **4** and **8**, the degradation was complicated since various degradation products were produced. The presence of the proton signal at around 12.5 ppm may come from the amide proton corresponding to the hypoxanthine moiety which both appeared in **4** in basic and **8** in acidic degradation, whereas no such a signal was detected in the reversed condition (Figures 7c,d and 8c,d). In either case, signals at around 1.5 ppm for the degradation products from **8** may be assigned to S−H, although it was difficult to find the hydroxyethyl O−H signal. Other broad signals at around 9, 8, and 4.5 ppm still remain undetermined though they were subjected to the cleavage of the purine ring. LC−mass peaks at 181 and 394 (Figure 6b,d) were considered to correspond to the hypoxanthine monomer and the dimer (Scheme 5).

Conclusion

Dehydration of (hydroxyethyl)thymine and hypoxanthine was found to give the polyether based on the lactam to lactim transformation, and dehydrochlorination of chloroethylated thiothymine and purine gave the polythioether. Degradation to the corresponding monomer was also possible based on the reverse lactim to lactam transformation, which was clearly realized in the pyrimidine polymer.

These polymer preparations and degradations can be also applied to nucleosides such as thymidine, uridine, and inosine. Such an investigation is now in progress.

References and Notes

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