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The Intrachain Aminolysis of a Terminal *p*-Nitrophenyl Ester Group by a Terminal 4-Pyridyl Group Attached to Both Ends of a Poly(oxyethylene) Chain*

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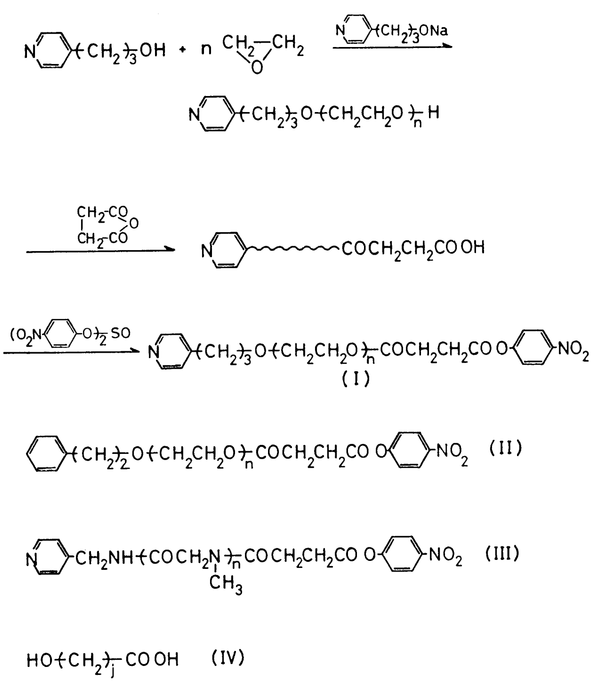
The intrachain aminolysis by a terminal 4-pyridyl group of a *p*-nitrophenyl ester group at the other terminal of a poly(oxyethylene) chain was investigated. The rate constants of the intrachain reaction were determined as a function of the degree of polymerization, n, of the poly(oxyethylene) chain over the range of 5—33 at 15, 25, and 35 °C. The rate constant was at its maximum at $n=7$ and decreased with an increase in the chain length. A comparison of the data with those obtained with polysarcosine chain showed that the intrachain reaction proceeded more effectively in the latter chain. Some thermodynamic considerations were made as to the cyclization process of a poly(oxyethylene) chain.

Many types of intramolecular reactions in which a polymeric molecule participates have been investigated. For a quantitative understanding of these reactions, including enzymic reactions, the investigation of the intramolecular reaction between two functional groups connected by a polymeric chain with a definite chain length is very useful.[1] The polymer molecules of this type can be shown schematically as an X–Y-type polymer, where X and Y denote the reactive groups. The intramolecular reaction of X and Y is different from the intermolecular one to an extent which is determined by the constraint imposed by the conformation of the polymer chain. In a previous paper of this series,[2] an intrachain aminolysis on a polysarcosine chain with a terminal *p*-nitrophenoxycarbonyl group and a terminal 4-pyridyl group was investigated. The rate constant of the intrachain reaction decreased monotonously with an increase in the chain length. This observation is not in accordance with the chain length-ring-closure probability relationship predicted by the Monte Carlo calculation of the polysarcosine chain.[3] The calculation predicted a maximum intrachain rate constant at $n=7$ (n is the number of sarcosine units). In this study, the same sort of reaction was examined with poly(oxyethylene) chains with the degrees of polymerization, n, from 5 to 33. The results were compared with those obtained with the polysarcosine chain. The poly(oxyethylene) chain was employed to connect the functional groups because; (1) it readily dissolves in water; (2) it can be synthesized by anionic polymerization and the degree of polymerization is controlled by the monomer/initiator ratio;[4] and (3) its physical properties, such as the average dimensions in solution have been widely investigated.

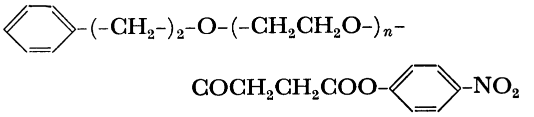
Experimental

Preparation and Characterization of Polymer Samples. Poly(oxyethylene) with a terminal *p*-nitrophenoxycarbonyl group and a terminal 4-pyridyl group (I) was synthesized as is shown in Scheme 1.[2]



Scheme 1.

Ethylene oxide was polymerized in dioxane by using a mixture of 3-(4-pyridyl)-1-propanol (3 part) and its sodium salt (1 part).[4] All the polymerization procedures, including the preparation of the catalyst solution, were carried out in a vacuum line. After the reaction mixture had been allowed to stand for a week at 60 °C, the reaction tube was opened and an excess amount of succinic anhydride was added immediately. After a few hours, a three-fold excess of bis(*p*-nitrophenyl)sulfite was added and the mixture was left overnight at 25 °C. The polymer sample was then separated from the low-molecular-weight compounds by preparative gel-chromatography using a Sephadex LH-20 column equilibrated with dioxane. The fractions containing polymer samples were freeze-dried from dioxane. A polymer sample with a terminal phenyl group instead of a pyridyl group (II) was synthesized by using phenethyl alcohol as the initiator.



(II)

Polymers with degrees of polymerization higher than 40 were precipitated from the polymer mixture with ether.

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* Intrachain Reaction of a Pair of Reactive Groups Attached to Polymer Ends. Part VI.

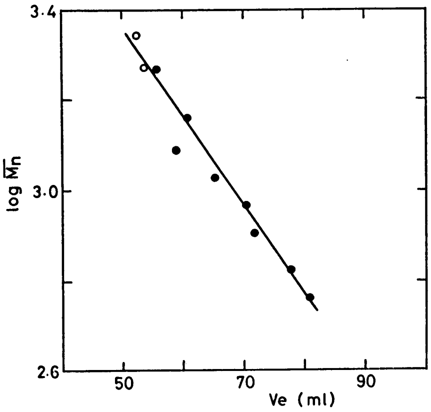


Fig. 1. Relation between the number-average molecular weight of poly(oxyethylene) and the elution volume at the peak position. The number-average molecular weight was calculated according to Eq. 1 (●) or determined by vapor-pressure osmometry (○).

The number-average molecular weight of the ether-precipitated polymers was measured by means of vapor-pressure osmometry. The low-molecular-weight samples, which were freeze-dried from the dioxane solution, usually contained trace amounts of a residual solvent and so were not suitable for the molecular-weight determination by the above method. Therefore, their molecular weight was determined on the basis of the elution volume in the gel chromatogram. Plots of the elution volume against the number-average molecular weight calculated by Eq. 1[4] are shown in Fig. 1. The

$$\bar{n} = [\text{Monomer}]/[\text{Initiator}]. \tag{1}$$

molecular weights measured by vapor-pressure osmometry are also plotted against the elution volume (open circles). Since the experimental points of different kinds (open and closed circles) lie on the same line, the following relation should hold between the elution volume, V_e, and the number-average degree of polymerization, $\bar{n}$:

$$V_e = 104 - 31 \log \bar{n}. \tag{2}$$

In the following part, the discussion will be based on the degree of polymerization calculated by Eq. 2. The number-average degrees of polymerization for polymers carrying a terminal phenyl group were determined in a similar way. The results of the polymer characterization are summarized in Table 1.

TABLE 1. CHARACTERIZATION OF POLYMER SAMPLES

Initiator	$\bar{n}$ Calcd by Eq. 1	Determined by VPO	Determined by GPC
3-(4-Pyridyl)-1-propanol	5.2		4.8
	7.0		6.9
	9.7		11
	12.7		12
	15.6		17
	20.0		27
	25.7		24
	36.3		33
	31.7	35	40
	35.0	38	43
β-Phenetyl alcohol	4.6		2.4
	9.2		14
	13.4		13
	18.5		18
	18.1	28	27

The agreement of the molecular weights calculated from Eq. 1 with the observed values suggests a Poisson-type molecular-weight distribution for the polymer samples.[4] The narrow molecular-weight distribution was actually indicated by the elution diagram.

The amount of pyridyl group incorporated into a polymer end was estimated by means of the absorbance of the pyridyl group (260 nm, $\varepsilon = 2.01 \times 10^3$) for the ether-precipitated high-molecular-weight polymers. The ratios of the observed amount to the calculated amount for the complete incorporation were 0.88 ($\bar{n}=42$) and 0.95 ($\bar{n}=80$). These data show that the incorporation is nearly quantitative.

Measurements. The aminolysis reactions were carried out at pH 6.1 (phosphate buffer, $\mu=0.067$).[2] The reaction was followed by recording the absorbance (320 nm) of the *p*-nitrophenol liberated. The concentration of the terminal ester group was adjusted to about 5×10^{-5} M. At this dilute concentration the contribution from the intermolecular reactions can be ignored (see below). The iodometry[5] showed no evidence of the formation of poly(oxyethylene) micelles at this concentration. The fraction of free pyridyl groups at pH 6.1 has been estimated to be about 0.93,[2] irrespective of the reaction temperature.

Results and Discussion

Evaluation of Rate Constants of the Intrachain Reaction. The intrachain aminolysis was carried out at 15, 25, and 35 °C. Figure 2 shows a typical first-order plot for the reaction at 25 °C. The rate of the reaction depends unambiguously upon the chain length. The slope affords an apparent rate constant, k_{obsd}, which should consist of these three terms:

$$k_{\text{obsd}} = k_1 + k_s + k_2[\text{Pyr}], \tag{3}$$

where k_1, k_s, and k_2 denote the rate constants for the intrachain aminolysis, spontaneous hydrolysis, and

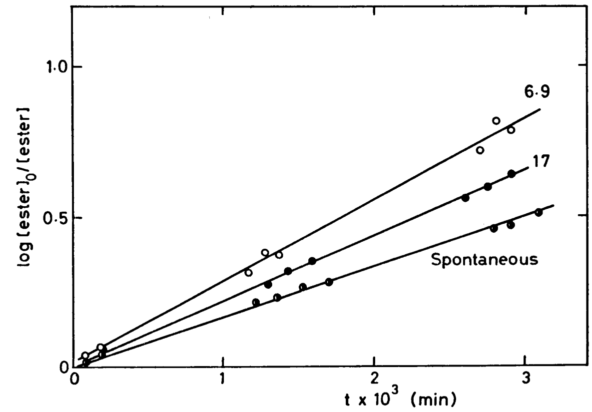


Fig. 2. Typical first-order plot for the reaction of polymer (I) having different chain lengths; 25 °C, pH=6.1. Numbers in the Figure indicate the number-average degrees of polymerization of poly(oxyethylene) chain. The bottom line represents the spontaneous hydrolysis of the polymer (II) ($n=18$).

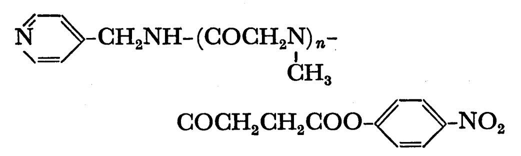
TABLE 2. RATE CONSTANTS FOR SPONTANEOUS HYDROLYSIS (k_s) AND INTERMOLECULAR REACTION BY PYRIDINE (k_2)

	$\bar{n}$	Temp (°C) 15	25	35
k_s	2.4	0.9×10^{-4}	2.9×10^{-4}	5.9×10^{-4}
(min^{-1})	7.4	0.9		
	12.5	1.0	3.5	5.4
	17.5	1.4	3.6	4.6
	27.4	1.2	3.5	4.7
	average	1.1×10^{-4}	3.3×10^{-4}	5.1×10^{-4}
k_2	2.4	2.0×10^{-2}	4.3×10^{-2}	1.3×10^{-1}
(M^{-1} min^{-1})	7.4	2.1		
	12.5	1.8	7.5	1.2
	17.5		4.4	1.5
	27.4	2.1	4.8	1.2
	average	2.0×10^{-2}	5.3×10^{-2}	1.3×10^{-1}

intermolecular aminolysis respectively. The concentration of the terminal pyridyl group is denoted as [Pyr]. The k_s value was determined from the spontaneous hydrolysis of the phenyl-terminated polymer (II) under the same conditions. The k_2 value was estimated from the pyridine-catalyzed aminolysis of the polymer (II). The results are collected in Table 2. The k_s and k_2 values were not affected by the chain length, indicating the same inherent reactivity of the terminal ester groups attached to poly(oxyethylene) with different chain lengths. The value of k_2 is so small that the contribution from the intermolecular reaction can be ignored when the polymer concentration is as low as 5×10^{-5} M.

The rate constant of the intrachain aminolysis, k_1, was calculated according to Eq. 3; it is plotted in Fig. 3 as a function of the degree of polymerization of the poly(oxyethylene) chain. It is interesting to note that the intrachain reaction is most efficient at $\bar{n}=7$. Undoubtedly the conformational constraints imposed by the poly(oxyethylene) chain caused this marked dependence on the chain length. The presence of the optimum chain length has been expected as a result of some conformational calculations and has actually been observed in some intrachain reactions.[3,6,7] The chain-length dependence of k_1 was more marked at higher temperatures. This trend indicates that the cyclic conformations, which are necessarily taken up to substantiate the intrachain reaction, have a large entropy at the optimum chain length resulting in the high intrachain reactivity. This view is consistent with the thermodynamic consideration (see below).

Comparison with the Intrachain Reaction on a Polysarcosine Chain. To compare the present data with those obtained with other polymer chains, the chain-length dependence of k_1/k_2, the intrachain rate constant relative to the intermolecular one, was examined. The rate-constant ratio eliminates the ambiguity arising from the different inherent reactivities of the terminal groups. The rate-constant ratios are shown in Fig. 4, together with the data obtained with the polysarcosine chain (III)[2] and the polymethylene chain (IV).[6] The data for the polymethylene chain have been obtained by the intramolecular esterification (lactone formation) of ω-hydroxycarboxylic acid in a benzene solution at 80 °C.[7] For the other two poly-



(III)

$HO\text{-}(\text{-}CH_2\text{-})_j\text{-}COOH$ (IV)

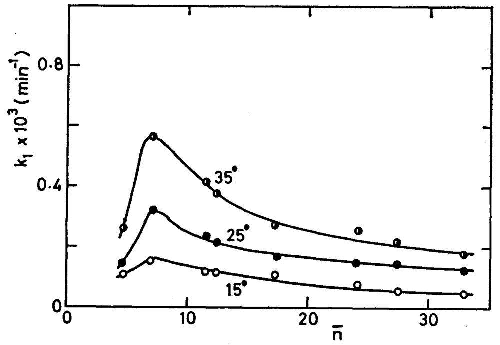


Fig. 3. Dependence of the rate constant of intrachain aminolysis k_1 on the degree of polymerization of poly(oxyethylene) at three different temperatures, pH=6.1.

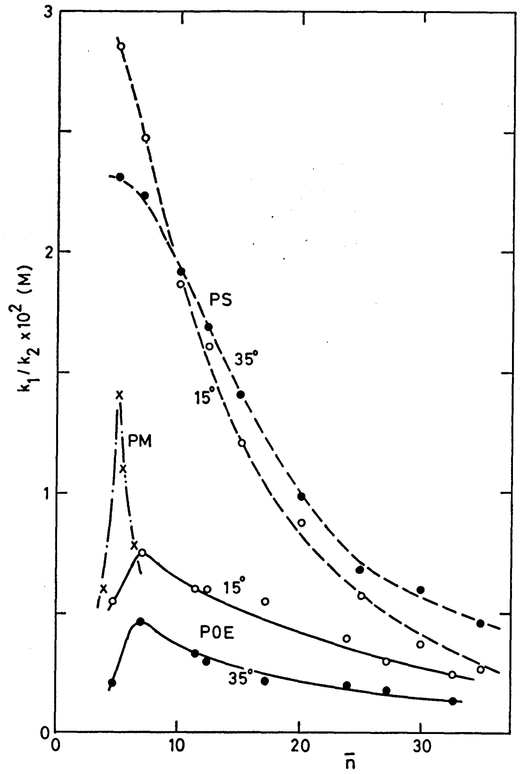


Fig. 4. Comparison of the rate-constant ratio of intrachain and intermolecular aminolyses k_1/k_2 among three polymers, *i.e.*, poly(oxyethylene) (POE), polysarcosine (PS), and polymethylene (PM). For polymethylene chains, $\bar{n}$ was calculated as $\bar{n}=(j/3)-2$.

mers, the reaction was an intrachain aminolysis. Obviously the polysarcosine and polymethylene chains are more efficient in the intrachain reaction; in other words, they take cyclic conformations more easily than poly(oxyethylene) chain. This finding is somewhat unexpected, since the latter chain appears to be more flexible due to the presence of oxygen atoms in the main chain, which are sterically less hindered than others. A Monte Carlo calculation may provide information concerning the ease of cyclization of these chains.[8] It is interesting that the population of the cyclic conformations of the poly(oxyethylene) chain increases with decreasing the temperature, whereas it increases with polysarcosines having larger chain lengths than $\bar{n}=10$ with a rise in temperature. This difference indicates the difference in the thermodynamic properties of the two chains.

Activation Parameters. The Arrehenius plots of the rate constants of the intrachain aminolysis are shown in Fig. 5. The activation parameters (ΔH_1^*, ΔS_1^*) were derived from the slope and the intercept of each straight line in Fig. 5. These parameters contain contributions from the conformational change requied for the cyclization (ΔH_c^*, ΔS_c^*) and those from the electronic change accompanying the reaction (ΔH_e^*, ΔS_e^*) as

$$\Delta H_1^* = \Delta H_c^* + \Delta H_e^*,$$
$$\Delta S_1^* = \Delta S_c^* + \Delta S_e^*. \tag{4}$$

ΔH_e^* and ΔS_e^* should be independent of the chain length. The electronic contributions can be evaluated from the activation parameters for the intermolecular reactions, ($\Delta H_2^*=14.4$ kcal/mol, $\Delta S_2^*=-15.3$ eu). Following the discussion reported previously,[2] the enthalpy for the electronic change of the intrachain reaction is equal to that of the intermolecular reaction, and the electronic entropy of the intrachain reaction is smaller by the bimolecular encounter term ($\Delta S_b^*=-3.6$ eu) than that of the intermolecular reaction. Thus, the following relations hold:

$$\Delta H_e^* = \Delta H_2^*,$$
$$\Delta S_e^* = \Delta S_2^* - \Delta S_b^*. \tag{5}$$

Using these relations, the activation parameters for the conformational change were calculated and plotted as a function of the degree of polymerization of the poly(oxyethylene) chain (Fig. 6). The activation enthalpy for conformational change is negative, irrespective of the chain length, indicating that cyclic conformations are of a lower conformational energy than linear ones. The chain-length dependence of the conformational enthalpy shows a tendency opposite to that observed in the rates of intrachain reactions; *e. g.*, at the optimum chain length ($\bar{n}=7$), the activation enthalpy is at maximum. It is, therefore, feasible to say that the chain-length dependence of the intrachain reaction of poly(oxyethylene) is governed mainly by the conformational entropy. This finding contrasts with that obtained for polysarcosine, where the conformational enthalpy was a dominant factor in the intrachain reaction.[2] As may be seen from Fig. 7, the compensation plot for ΔH_c^* and ΔS_c^* falls on a straight line, giving an isokinetic tempera-

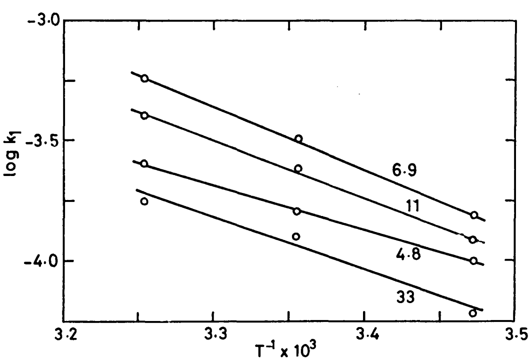


Fig. 5. Typical Arrhenius plot of the rate constants of intrachain aminolysis of poly(oxyethylene). Numbers in the Figure are the degree of polymerization of poly(oxyethylene).

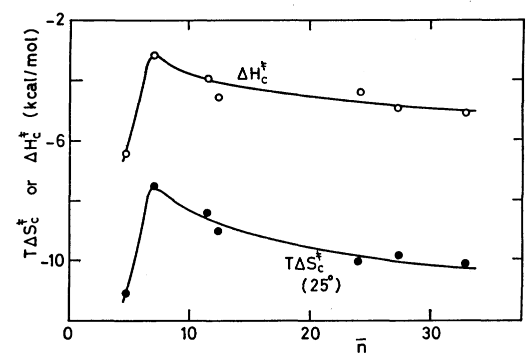


Fig. 6. Activation parameters for the conformational change accompanied with the intrachain reaction of poly(oxyethylene), plotted against the degree of polymerization.

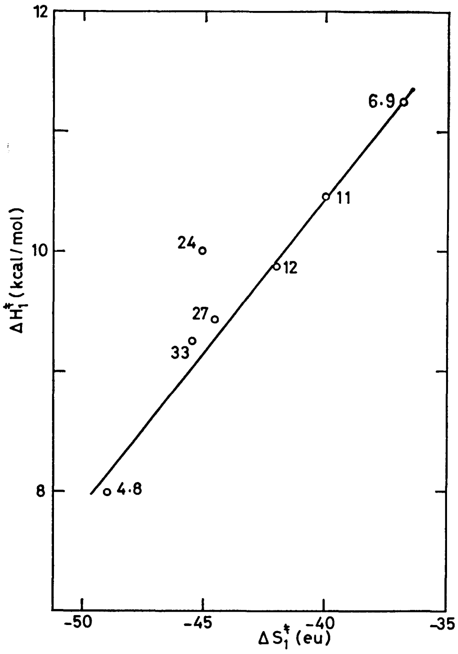


Fig. 7. Compensation plot of the activation parameters. Numbers in the Figure show the degree of polymerization of poly(oxyethylene).

ture of 2 °C. A similar relation has also been observed in the intrachain aminolysis of polysarcosine[2] and in the intrachain charge-transfer complex of polysarcosine.[9,10] Therefore, it is likely that some conformational mechanism operates to compensate for the entropy loss accompanying the cyclization, hence stabilizes the cyclized conformation. The solvation of the polymer chain has been suggested to play an important role in the compensation mechanism.[10] However, the details of the solvent effect still remain unclear in the present case.

To conclude, an optimum chain length was observed in the intrachain reaction between two terminal groups of the poly(oxyethylene) chain. Intrachain reactions on the poly(oxyethylene) chain took place less efficiently than those on polysarcosine and polymethylene chains.

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