Group Interactions in Polyelectrolytes. XI. The Kinetics of *N*-Methylation of Poly(ethyleneimine)

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The *N*-methylation of polyethyleneimine (PEI) of low and high molecular weights as well as that of diethylenetriamine was investigated kinetically in 50% aqueous ethanol; during the procedure we observed deceleration due to the electrostatic effect of the neighboring charged groups. The rate equation was derived for the *N*-methylation of PEI, which proceeded in three steps with a marked deceleration beyond quarter-conversion and also beyond half-conversion. In the second and third steps of the *N*-methylation of PEI, additional energies equivalent to the electrostatic free energies due to the one and the two nearest-neighboring charged groups were required respectively, in addition to the intrinsic activation energy of the first step.

The amination of chloromethylated polystyrene with a large excess of primary and secondary amines was investigated kinetically in several organic solvents in order to establish that most of the amination with primary amines conformed to the ordinary second-order kinetics; however, the rate constant of the amination with secondary amines decreased as the amination proceeded.[1,2] Since no electrical charge forms on the polymer in this amination, the deceleration during the amination with secondary amine was ascribed to the steric obstruction by the neighboring substituted groups. On the other hand, a deceleration due to the electrostatic effect of the charge on the polymer was observed during the quarternization of the aminated chloromethylated polystyrene in 50% aqueous DMF.[2] Such a deceleration was also found in the quarternization of poly-4-vinyl pyridine with *n*-butyl bromide in tetramethyl sulfone or propyrene carbonate.[3] In these Menschutkin reactions of the polyamines, the deceleration was marked beyond half-conversion, and the reactions were treated kinetically as they proceeded in two steps. Although the *N*-methylation of ethylenediamine (EDA) with methyl iodide in water was not a Menschutkin reaction, the deceleration due to the electrostatic effect was also observed and the reaction could be described by the same kinetics as the quarternization of the aminated chloromethylated polystyrene.[4]

The *N*-methylation of diethylenetriamine (DETA), which has three amino groups, in 50% aqueous ethanol has been found to decelerate in three steps. Further, the *N*-methylation of polyethyleneimine (PEI), which has many amino groups, in 50% aqueous ethanol has also been found to proceed in three steps. These *N*-methylations have been investigated kinetically in the present study.

Experimental

Polyethyleneimine. Polyethyleneimine of a low molecular weight (PEI-L) was prepared by the cationic polymerization of ethyleneimine in dilute hydrochloric acid; the acid was removed by passing the reaction mixture through a column of Amberlite IRA-400 in the hydroxide form. The effluent was concentrated by the use of an evaporator and then lyophilized. Since this polymer was almost entirely absorbed in a column of Amberlite IRC-50 in the hydrogen form, its molecular weight was estimated to be relatively low.

Polyethyleneimine of a high molecular weight (PEI-H) was supplied by courtesy of the Nihon Shokubai Chem. Ind. Co. in a state of an aqueous solution (P-1000). The P-1000 was diluted and passed through a Dowex-50 (X-8, H-form) column and then through a Dowex-2 (X-8, OH-form) column, after which the effluent was concentrated and lyophilized.

Reagents. Commercial anhydrous ethylamine, ethylenediamine (EDA), and diethylenetriamine (DETA) of a reagent grade were treated with solid sodium hydroxide and distilled. Other organic solvents and reagents were also distilled before use. They were proved to be pure by their refractive indices. Deionized, decarbonized water was used throughout.

Kinetic Measurements. The procedure used for the kinetic measurements in the *N*-methylation of DETA and PEI was almost the same as that used for EDA.[4] The temperature of a reaction mixture, composed of an amine, methyl iodide, and a solvent, was maintained at 30±0.1 °C.

Conductometric Titration. Aqueous solutions of ethylamine, EDA, DETA, and PEI-L (0.010—0.016 amino group equivalent/l) were titrated with 0.1 M hydrochloric acid at 25+0.02 °C, and the conductivity measurements were made with the use of a Yanagimoto MY-7-type conductivity measuring set at 800 c.p.s.

Results

N-*Methylation of Diethylenetriamine (DETA).* In the *N*-methylation of DETA with methyl iodide in 50% aqueous ethanol, the second-order rate constant (k), computed on the basis of Eq. (1), decreased as the reaction proceeded:

$$kt = \frac{1}{a-b}\ln\frac{b(a-x)}{a(b-x)} \equiv \overline{kt} \tag{1}$$

where a and b are the initial concentrations of the methyl iodide and the amino group respectively, and where x is the concentration of hydrogen iodide formed after time t. The course of the *N*-methylation is shown in Fig. 1, where β $(=x/b)$ is the fractional conversion and where $\overline{kt}$ represents the right-hand term of Eq. (1). The white circles in the figure represent the observed values of β, and the black circles, the values of $\overline{kt}$. The plot of $\overline{kt}$ *vs.* t could be represented approximately by three straight lines which intersect each other at $\beta \approx 0.4$ and $\beta \approx 0.65$. The apparent rate constants given by the slopes of these lines $(k_n' = \Delta\overline{kt}/\Delta t)$ were:

$$k_1' = 5.66\times10^{-2},\quad k_2' = 2.03\times10^{-2}$$
$$k_3' = 8.83\times10^{-4}\ \text{l/mol min}$$

Although such reactions of compounds with two

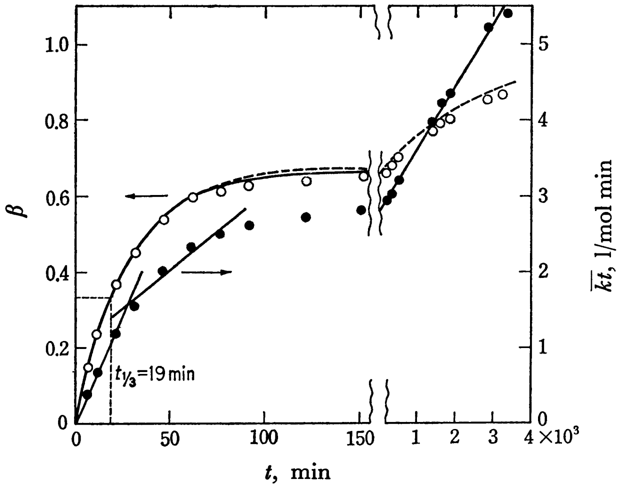

Fig. 1. N-Methylation of DETA with methyl iodide in 50% aq. ethanol at 30 °C. (a=0.3922, b=0.0362 mol/l)
—— Curve I, calculated on the basis of Eq. (5)
---- Curve II, calculated on the basis of Eq. (6).

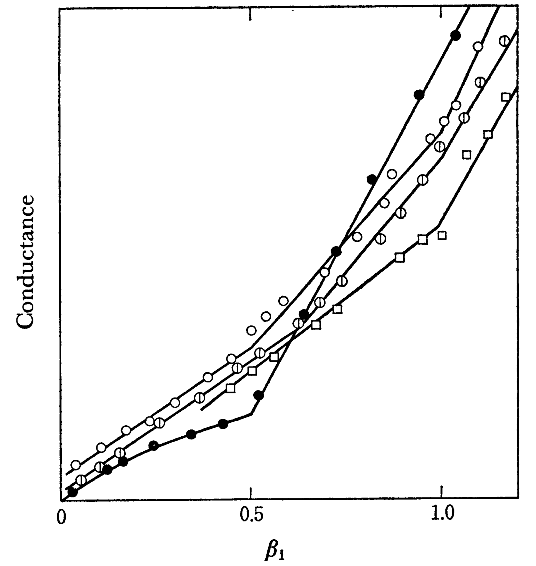

Fig. 2. Conductometric titration of PEI-L(●), DETA-(◐), EDA(○), and ethylamine(□) with hydrochloric acid.

reactive groups as the N-methylation of ethylenediamine (EDA)[4] and the alkaline hydrolysis of dimethyl succinate[5] could be treated as two-step reactions which decelerate markedly beyond $\beta=1/2$, the N-methylation of DETA, which has three reactive groups, may be treated as a three-step reaction which decelerates markedly at $\beta=1/3$ and $\beta=2/3$. The rate equation of this reaction is the same as that of the alkaline hydrolysis of triethyl citrate,[5] and the rate constants are given by:

$$k_1 = \frac{1}{[(3-2k_2/k_1)a-b]t}\ln\frac{1-\alpha}{1-(3-2k_2/k_1)\beta} \tag{2}$$

$$k_2 = \frac{\ln\dfrac{1-[3(2-k_3/k_2)/(4-k_3/k_2)\chi_1/b]}{1-[3(2-k_3/k_2)/(4-k_3/k_2)\beta]}\times\dfrac{1-\alpha}{1-\chi_1/a}}{[(2-k_3/k_2)a-(4-k_3/k_2)b/3](t-\tau_1)} \tag{3}$$

$$k_3 = (kt-C)/t \tag{4}$$

$$C = \ln[(1-\chi_2/a)/(1-\chi_2/b)] - k_2(a-b)\tau_2$$

where $\alpha=x/a$ and $\beta=x/b$; τ_1 is the time when the concentration of the first changed group (x_1) reaches approximately $b/3$, and χ_1 is the value of x at that time. C in Eq. (4) is a constant in a given reaction system. The calculated values of these constants were:

$k_1 = 6.08\times10^{-2}$, $k_2 = 4.77\times10^{-2}$,
$k_3 = 8.83\times10^{-4}$ l/mol min.

Further, when $a\gg b$, the course of this reaction can be calculated on the basis of the following two equations in the given ranges of β.
In the range of $\beta=0-2/3$:

$$\beta = \frac{2}{3} - \frac{3k_1-4k_2}{3(3k_1-2k_2)}\,e^{-3k_1at} - \frac{k_1}{3k_1-2k_2}\,e^{-2k_2at} \tag{5}$$

In the range of $\beta=1/3-1$:

$$\beta = 1 - \frac{2(k_2-k_3)}{3(2k_2-k_3)}e^{-2k_2a(t-t_{1/3})} - \frac{2k_2}{3(2k_2-k_3)}\,e^{-k_3a(t-t_{1/3})} \tag{6}$$

where $t_{1/3}$ is the value of t when $\beta=1/3$. The plot of β against t calculated on the basis of Eq. (5) is represented by the solid line (Curve I) in Fig. 1, from which $t_{1/3}$ is determined to be 19 min. The plot of Eq. (6) is represented by the broken line (Curve II) in the figure. The observed values represented by the white circles fall substantially on Curves I and II.

N-*Methylation of Polyethyleneimine (PEI).* Shepherd and Kitchener[6] reported that, although the pH titration curve of PEI of a relatively low molecular weight (number of monomeric units, n=35—40) could be described according to Katchalsky's theory[7] as a polybase with an intrinsic pK_0 value of 10 in a certain range of degree of ionization (β_I) (β_I=0.3—0.5), the titration curve deviated greatly from the theory in the $\beta_I>0.5$ range because of the intense electrostatic interaction due to two near-neighboring charged groups.

Figure 2 shows the results of conductometric titration of PEI-L (PEI of low molecular weight) with hydrochloric acid, in which a distinct inflexion point appears at β_I=0.5. The figure also shows the results for EDA and DETA, the inflexion points for which appear at β_I=0.5 and β_I=0.65 respectively, in addition to the points at β_I=1.0. For ethylamine, which has a single amino group, a distinct point appears only at β_I=1.0. These results for EDA and DETA are in accordance with the results of the N-methylation of the amines. The pH titration and the conductometric titration of PEI with a large molecular weight ($n\approx700$) were reported by Saber and Shams,[8] who found inflection points of the titration curves at β_I=0.6.

In view of the above-mentioned facts, the N-methylation of PEI is expected to decelerate markedly beyond $\beta=1/2$. On the other hand, it was found that the alkaline hydrolysis of polymethyl acrylate in 29% aqueous acetone decelerates at $\beta=1/4$, 1/2, and 3/4.[5,9] In the present study, PEI of low and high molecular weights (PEI-L and PEI-H) was N-methylated with methyl iodide, first in water; the results are shown in Fig. 3. The rate of the N-methylation becomes

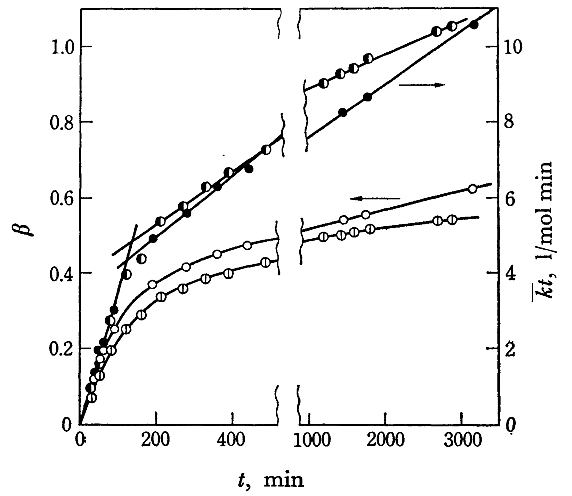

Fig. 3. N-Methylation of PEI with methyl iodide in water at 30 °C.
(PEI-L, $a=0.0831$, $b=0.0277$ mol/l; PEI-H, $a=0.984$, $b=0.0171$ mol/l)
◑,◐: PEI-L, ○,●: PEI-H.

very slow beyond half-conversion, as is to be expected; however, the plots of $\overline{kt}$ *vs.* t in the figure indicate additional intersecting points at $\beta=0.25$—0.3.

In the N-methylation of PEI in water, the complete kinetic measurements beyond $\beta=0.5$ were practically difficult because of its very slow rate; the solubility of methyl iodide in water was low, and its concentration was low. Therefore, PEI was also N-methylated in 50% aqueous ethanol; when the concentration of methyl iodide was increased, the N-methylation proceeded nearly to completion. The results are shown in Figs. 4 and 5, where white and black circles represent the observed values of β and $\overline{kt}$ respectively. The plot of $\overline{kt}$ *vs.* t is represented approximately by three straight lines which intersect each other nearly at $\beta=1/4$ and $\beta=1/2$. The plot in the range of $\beta=0.5$—0.85 is a straight line showing no inflection point, though an intersecting point at nearly $\beta=3/4$ in addition to those at $\beta=1/4$ and 1/2 was observed in the case of the alkaline hydrolysis of polymethyl acrylate.

The numerical values of k_n' obtained as the slopes of the $\overline{kt}$ *vs.* t plots in Figs. 3, 4, and 5 are tabulated in Table 1. The values of k_n' are almost the same for PEI-L and PEI-H both in water and in 50% aqueous ethanol. This fact suggests, first, that the magnitude of the electrostatic effect of neighboring charged groups on the reactivity of amino groups of PEI at a given β value is almost independent of the molecular weight of PEI. Second, a limited number of neighboring charged groups affect the reactivity, because the N-methylation of PEI as well as EDA and DETA is composed of a limited number of steps. Third, the dielectric constant of the microscopic environment surrounding the reactive groups is almost the same for the N-methylation both in water and in 50% aqueous ethanol.

Table 1. Rate constant k_n', l/mol min, in the N-methylation of PEI with methyl iodide at 30 °C

Solvent PEI	Water		50% aq. Ethanol	
	PEI-L	PEI-H	PEI-L	PEI-H
$k_1'\times10^2$	3.45	3.48	3.18	3.28
$k_2'\times10^3$	6.09	7.80	5.70	5.40
$k_3'\times10^4$	(8.10)[a]	(13.6)[a]	6.96	12.8

a) ( ) shows less acurate measurements.

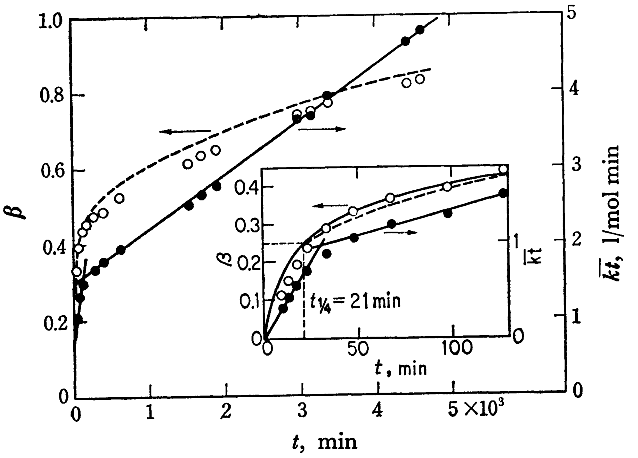

Fig. 4. N-Methylation of PEI-L with methyl iodide in 50% aq. ethanol at 30 °C. ($a=0.3922$, $b=0.0398$ mol/l)
—— Curve I, calculated on the basis of Eq. (12)
---- Curve II, calculated on the basis of Eq. (17).

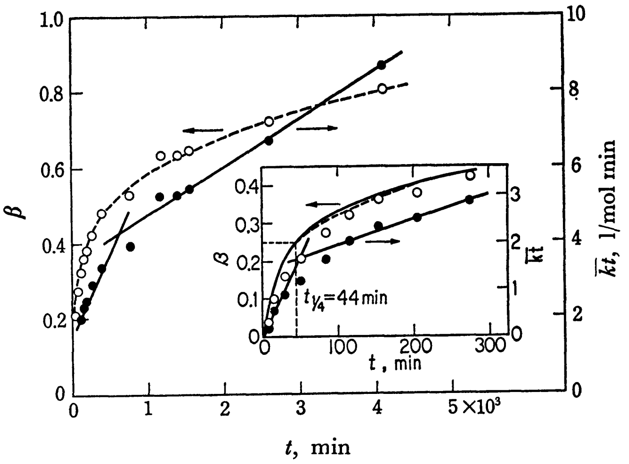

Fig. 5. N-Methylation of PEI-H with methyl iodide in 50% aq. ethanol at 30 °C. ($a=0.1976$, $b=0.0205$ mol/l)
—— Curve I, calculated on the basis of Eq. (12)
---- Curve II, calculated on the basis of Eq. (17).

Discussion

Kinetics of the N-*Methylation of PEI.* Since the N-methylation of PEI, unlike that of DETA, decelerates at $\beta=1/4$ and $\beta=1/2$, a somewhat different kinetic treatment is needed if we are to describe the former. In the following model compound composed of four reactive groups, the reactivity of X_2Y_2 is assumed to be the same as that of X_3Y namely $k_3=k_4$, since the reactivity of amino groups of PEI did not change in the $\beta>1/2$ range.

$$\underset{\mu_0}{Y_4} \xrightarrow{k_1} \underset{\mu_1}{X_1Y_3} \xrightarrow{k_2} \underset{\mu_2}{X_2Y_2} \xrightarrow{k_3} \underset{\mu_3}{X_3Y} \underset{(=k_3)}{\xrightarrow{k_4}} \underset{\mu_4}{X_4}$$

where X and Y represent the changed and unchanged groups respectively and where μ_0 and μ_n, represent the concentrations of the unchanged compound (Y_4) and the partially-changed one (X_nY_{4-n}), n groups of which have been changed at time t. These concentrations are given by the following:

$$\left.\begin{aligned} \mu_0 &= M - x_1 = (b/4) - x_1 \\ \mu_n &= x_n - x_{n+1} \end{aligned}\right\} \tag{7}$$

where M is the initial concentration of the compound ($M=\sum_{n=0}^{4}\mu_n$) and where x_n is the concentration of the nth changed group at time t ($x=\sum_{n=1}^{4}x_n$).

The over-all rate of this reaction is given by the equation:

$$\mathrm{d}x/\mathrm{d}t = \sum_{n=1}^{4} \mathrm{d}x_n/\mathrm{d}t = (a-x)\sum_{n=1}^{4}(4-n+1)k_n\mu_{n-1} \tag{8}$$

The rate constants of this reaction, k_n, are given by the following equations on the assumption that $\sigma=4$ and $k_3=k_4$ (k_σ) in Eq. (6) of Ref. 5:

$$k_1 = \frac{1}{[(4-3k_2/k_1)a-3b/4]t}\ln\frac{1-\alpha}{1-(16/3-4k_2/k_1)\beta} \tag{9}$$

$$k_2 = \frac{\ln\dfrac{1-[2(3-2k_3/k_2)/(3-k_3/k_2)\chi/b]}{1-[2(3-2k_3/k_2)/(3-k_3/k_2)]\beta}\times\dfrac{1-\alpha}{1-\chi_1/a}}{[(3-2k_3/k_2)a-(3-k_3/k_2)b/2](t-\tau_1)} \tag{10}$$

$$k_3 = (\overline{k}t - C)/t \tag{11}$$

where C is a constant in a given reaction system; τ_1 is a time when $x_1=b/4$, and χ_1, a value of x at that time.

When $a\gg b$, on the assumption that the rate is substantially controlled by k_1 and k_2 in a range of $\beta=0$—1/2, β as a function of t is given by Eq. (12), which is the same equation as Eq. (3) in Ref. 9:

$$\beta = 1/2 - \frac{2k_1-3k_2}{2(4k_1-3k_2)}\,\mathrm{e}^{-4k_1at} - \frac{k_1}{4k_1-3k_2}\,\mathrm{e}^{-3k_2at} \tag{12}$$

In the range of $\beta=1/4$—1, the rate is given by Eq. (13), assuming that it is controlled by k_2 and k_3 ($=k_4$):

$$\mathrm{d}x/\mathrm{d}t = a[3k_2\mu_1 + k_3(2\mu_2+\mu_3)] \tag{13}$$

On the assumption that $x_1=b/4$ and then $x=b/4+x_2+(x_3+x_4)$, μ_n is given by the following:

$$\left.\begin{aligned} &\mu_1 = x_1 - x_2 = b/4 - x_2 \\ &\mu_2 = x_2 - x_3,\quad \mu_3 = x_3 - x_4 \\ &2\mu_2 + \mu_3 = 2x_2 - (x_3+x_4) = b/4 + 3x_2 - x \end{aligned}\right\} \tag{14}$$

The combination of Eqs. (13) and (14) yields:

$$\mathrm{d}x_2/\mathrm{d}t = 3ka\mu_1 = 3k_2a(b/4-x_2) \tag{15}$$

$$\mathrm{d}x/\mathrm{d}t = a[(3k_2+k_3)b/4 - 3(k_2-k_3)x_2 - k_3x] \tag{16}$$

By integrating Eqs. (15) and (16) we obtain:

$$\beta = 1 - \frac{3(k_2-k_3)}{4(3k_2-k_3)}\,\mathrm{e}^{-3k_2a(t-t_{1/4})} - \frac{3k_2}{2(3k_2-k_3)}\,\mathrm{e}^{-3k_3a(t-t_{1/4})} \tag{17}$$

where $t_{1/4}$ is the time when $\beta=1/4$. The over-all course of the reaction may be described by a combination of Eqs. (12) and (17).

Table 2. Rate constant k_n, l/mol min, in the N-methylation of PEI, DETA, and EDA with methyl iodide at 30 °C

Solvent Amine	50% aq. Ethanol			Water EDA
	PEI-L	PEI-H	DETA	
$k_1\times10^2$	6.25	6.07	6.08	6.12
$k_2\times10^3$	9.00	9.15	47.7	13.0
$k_3\times10^4$	6.96	12.8	8.83	
k_2/k_1	0.14	0.15	0.78	0.21
k_3/k_1	0.011	0.021	0.015	

Table 3. Electrostatic free energies, kcal/mol, in the N-methylation of PEI, DETA, and EDA at 30 °C

Amine	PEI-L	PEI-H	DETA	EDA
$(\Delta G_{\mathrm{el}}^{\ne})_2$	1.2	1.1	0.2	0.9
$(\Delta G_{\mathrm{el}}^{\ne})_3$	2.7	2.3	2.6	

In Table 2 are tabulated the numerical values of k_n in the N-methylation of PEI-L and PEI-H in 50% aqueous ethanol, together with those in the N-methylation of DETA and EDA. The plots of β *vs.* t in the N-methylation of PEI, which are computed on the basis of Eq. (12), are the solid lines (Curve I) in Figs. 4 and 5, from which $t_{1/4}$ is determined to be 21 min for PEI-L and 44 min for PEI-H. The plots computed on the basis of Eq. (17) are represented by the broken lines (Curve II). The observed values represented by the white circles in the figures fall substantially on the curves; this suggests that the assumption used in the derivation of the rate equations is reasonable.

Electrostatic Interaction between Neighboring Groups in the N-*Methylation of PEI.* Since almost the same values of k_1 were obtained for PEI-L, PEI-H, DETA, and EDA, k_1 is taken to reflect the intrinsic reactivity of the amino group. The k_2 values of PEI are close to that of EDA, but different from that of DETA. However, the values of k_3 are almost the same for PEI-L, PEI-H, and DETA. The electrostatic free energies in these reactions, $(\Delta G_{\mathrm{el}}^{\ne})_n$, are given by:

$$(\Delta G_{\mathrm{el}}^{\ne})_n = RT\ln(k_0/k_n) \tag{18}$$

where k_0 is the intrinsic rate constant, $k_0=k_1$. The numerical values of $(\Delta G_{\mathrm{el}}^{\ne})_n$ are shown in Table 3.

When the electrostatic interactions are assumed to be operative among only a few neighboring groups, $(\Delta G_{\mathrm{el}}^{\ne})_n$ may be represented by:

$$(\Delta G_{\mathrm{el}}^{\ne})_n = (Ne^2/D)\sum_i Z_i\overline{r_i} \tag{19}$$

where N is the Avogadro number: e, the unit of electrical charge; D, the dielectric constant ($D=81$); Z_i, the number of the electrical charge in the ith groups apart from the reactive group, and $\overline{r_i}$, the average distance between the reactive group and the ith group.

By setting the distance between the nitrogen atoms of EDA at 3.7 Å, $(\Delta G_{\mathrm{el}}^{\ne})_2$ is calculated on the basis of Eq. (19) to be 1.1 kcal/mol, which is close to the value given in Table 3 calculated on the basis of Eq. (18).

However, the $(\Delta G_{el}^{\neq})_2$ value of DETA given in Table 3 is rather smaller than that given on the basis of Eq. (19), 0.6 kcal/mol, which is calculated by setting the distance between the end nitrogen atoms of the amine at 7.4 Å. The $(\Delta G_{el}^{\neq})_3$ of DETA is calculated to be 2.2 kcal/mol on the basis of Eq. (19) by assuming that the reactive group is affected electrostatically by the charges on the two end nitrogen atoms; this value is close to that given in Table 3. These results suggest that, in the *N*-methylation of polyethylene polyamine as well as DETA, the electrostatic contribution of the charge on the second-neighboring amino group is rather small, probably because the distance between these groups is so long that the effect of the second neighbors is cancelled by their counter ions. This can explain partly why the kinetic scheme of the *N*-methylation of PEI is somewhat different from that of the alkaline hydrolysis of polymethyl acrylate, in which the effect of the second-neighbors is distinct. The $(\Delta G_{el}^{\neq})_2$ value of PEI, which is close to that of EDA, is equivalent to the electrostatic free energy due to one first-neighboring charged group. The $(\Delta G_{el}^{\neq})_3$ of PEI, which is close to that of DETA, is equivelent to the electrostatic free energy due to two first-neighbors.

PEI, which is obtained by cationic polymerization, has a branched structure; the analysis of PEI indicates that approximately a quarter of all the amino groups are tertiary amino groups which correspond to branching points.[10] Consequently, in comparison with polymethyl acrylate, which has a linear structure, the structure of PEI is rather complex; however, the kinetics of the *N*-methylation of PEI has revealed that a limited number of neighboring groups interact electrostatically. In the *N*-methylation of PEI, composed of three steps, the first step is principally controlled by the intrinsic free energy of activation; however, the second step requires an additional free energy equivalent to the electrostatic effect of one nearest-neighboring group, and the third step requires an additional free energy equivalent to the effect due to two nearest-neighbors.

If the tertiary amino group of PEI, whose fraction is about 1/4, is finally *N*-methylated among all the species of amino groups, the reaction in the final stage will be accompanied by a larger $\Delta G_{el}^{\neq}$, because the tertiary group is apparently surrounded by three first-neighboring groups. Since the probability of this case is 1/4, and since its fractional contribution to the *N*-methylation of the total amino groups is 1/16, the deceleration due to this kind of interaction is significant, probably in the $\beta > 0.9$ range (at most). Actually, no such deceleration was observed, at least not in the range of measurements up to $\beta = 0.85$.

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