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Preferred Ring Sizes of Cyclic Transition States in Bifunctional Catalysis of the Dedeuteration of Isobutyraldehyde-*2-d* by Polyethylenimines†[1a,b]

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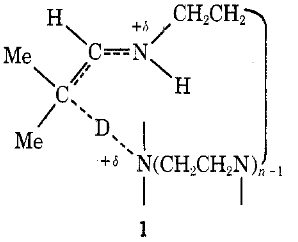
Polyethylenimines (PEI's) act as bifunctional catalysts for the dedeuteration of isobutyraldehyde-*2-d* by using primary amino groups to reversibly complex the aldehyde, partly as iminium ions, and then using other amino groups to remove deuterium from the iminium ion groups in the same molecule. The exchange of 0.05 *M* aldehyde at pH 8.5 in the presence of 1 *N* PEI's, where almost all the reaction is due to complexed aldehyde, proceeds at relative rates of 1:1.19:1.24:1.38 for PEI's with average molecular weights of 600, 1200, 1800, and 50,000, respectively. The reaction under these conditions is catalyzed by 1,4-diazabicyclo[2.2.2]octane (Dabco), which attacks the complexed aldehyde. The relative rates of attack by Dabco are 1.46:1.32:1.15:1 on aldehyde complexed to PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively. These and previous observations show that attack by internal amino groups on the complexed aldehyde is ineffective when the chain separating the amino and complexed aldehyde groups is either too long or too short. A computer-simulated polymerization process is used to estimate the detailed structure of the polymers. With data on various reference reactions this is used in an argument that the complexed aldehyde is probably dedeuterated most efficiently by amino groups that are 3–6 monomer units from the complexed aldehyde.

Earlier papers in this series described evidence that polyethylenimines (PEI's) act as bifunctional catalysts in the dedeuteration of isobutyraldehyde-*2-d*.[2,3] A primary amino group on the polymer transforms the aldehyde to an imine, which is in equilibrium with the corresponding iminium ion. Then, in the rate-controlling step of the reaction, another amino group in the polymer removes the activated α-deuterium atom *via* a transition state, such as 1, arising from the trans form of the iminium ion. Cyclic transition states are probably rather common in enzymatic reactions. The dedeuteration of acetone-d_6 by acetoacetate decarboxylase, for example, probably involves the formation of an iminium ion by the ε-amino group of a lysine unit followed by removal of deuterium by another basic group in the same molecule.[4] For these reasons it was of interest to learn what ring sizes are preferred in the formation of transition states like 1 from PEI's for which a wide variety of ring sizes are possible. We have therefore measured the catalytic activities of PEI's under various conditions and made experimental measurements and computer calculations to estimate the relative numbers and basicities of the primary, secondary, and tertiary amino groups in these PEI's.



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Results

The kinetics of the deuterium exchange of isobutyraldehyde-*2-d* were studied as described previously.[5] The reactions were stopped by acidifying the reaction mixture to neutralize the basic catalyst and liberate the aldehyde from any complex formed with the catalyst. The aldehyde was then extracted and its deuterium content was determined by proton magnetic resonance measurements. First-order rate constants obtained in the presence of various PEI's are listed in Table I. PEI-*X* is a polymer with a number-average molecular weight of *X*. Normalities refer to the number of equivalents of amino groups per liter. The aldehyde forms complexes with the catalysts in equilibria that are much faster reactions than the deuterium exchanges. In the presence of 1.0 *N* PEI's the aldehyde is very largely complexed, so that the rate constants listed in these cases are essentially those of the complexed aldehyde.

To help in estimating the catalytic efficiencies of the secondary amino groups of the PEI's, diethylamine was studied as a catalyst. Rate constants obtained in the presence of several diethylamine buffers are listed in Table II. Ultraviolet measurements showed that 0.2 *M* diethylamine transforms less than 1% of 0.07 *M* isobutyraldehyde

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† This paper contains "miniprint." See Editorial regarding miniprint on p 8A of the Jan 11, 1974, issue.

Table I
Rate Constants for Exchange of Isobutyraldehyde-2-*d* in the Presence of PEI's in Water at 35° [a]

PEI	pH	10^5k, $\sec^{-1}$
1.00 *N* PEI-600	8.49	10.2
1.00 *N* PEI-600[b]	8.50	24.1
1.00 *N* PEI-1200	8.51	12.1
1.00 *N* PEI-1200[b]	8.48	24.6
1.00 *N* PEI-1800	8.54	12.6
1.00 *N* PEI-1800[b]	8.51	23.5
1.00 *N* PEI-50,000	8.52	14.1
1.00 *N* PEI-50,000[b]	8.50	23.6
0.099 *N* $(H_2NCH_2CH_2)_2NH$	8.51	0.90
0.099 *N* PEI-146[c,d]	8.48	2.0
0.100 *N* PEI-190[c,e]	8.51	3.0
0.103 *N* PEI-600	8.47	7.5
0.153 *N* PEI-600	8.42	9.5
1.01 *N* PEI-600	7.40	8.1
1.01 *N* PEI-600	7.78	9.6
1.01 *N* PEI-600	7.91	11.1
1.01 *N* PEI-600	8.15	10.8
1.01 *N* PEI-600	8.37	9.9
1.01 *N* PEI-600	8.40	9.8
0.100 *N* PEI-50,000	8.60	6.5
0.30 *N* PEI-50,000	8.51	11.5
0.60 *N* PEI-50,000	8.52	15.0
1.00 *N* PEI-50,000	6.81	14.9
1.00 *N* PEI-50,000	7.55	22.5
1.00 *N* PEI-50,000	7.96	21.0
1.00 *N* PEI-50,000	8.56	14.9

[a] $[Me_2CDCHO]_0$ = 0.054 *M*. All concentrations listed are total concentrations, regardless of states of protonation or complexing. [b] 0.100 *M* 1,4-diazabicyclo[2.2.2]octane also present. [c] Labeled as a PEI because it is a mixture of polyethylenepolyamines; the molecular weight given is that of its principal component. [d] Eastman Technical triethylenetetramine. [e] Eastman Technical tetraethylenepentamine.

Table II
Diethylamine Catalysis of the Deuterium Exchange of Isobutyraldehyde-2-*d* in Water at 35°

$[Et_2NH]$	$[Et_2NH_2^+]$	10^5k_p, $\sec^{-1}$	$10^5k_h[OH^-]$, $\sec^{-1}$	$10^3k_{Et_2NH}$, $M^{-1}\sec^{-1}$
0.0241	0.0774	8.77	1.40	3.06
0.0247	0.164	8.42	0.76	3.10
0.0498	0.136	17.9	1.8	3.24
				Av 3.13

Table III
Titrations with *p*-Toluenesulfonic Acid at 63 ± 1% Acetic Acid–37 ± 1% Acetic Anhydride

Amine	Concn, *M*	$[p\text{-TsOH}]$,[a] *M*	Equiv of base/mol of amine
$(Me_2NCH_2CH_2)_2NMe$	0.022	0.200	2.99
$(Me_2NCH_2CH_2NMeCH_2)_2$	0.0070	0.100	3.96
$(Me_2NCH_2CH_2)_3N$[b]	0.0065	0.100	3.00
$(AcNHCH_2CH_2)_3N$[c]	0.107	0.200	1.02

[a] In glacial acetic acid. [b] The 3.7% $(Me_2NCH_2CH_2NMeCH_2)_2$ present as an impurity was assumed to take up 4 equiv of acid/mol of amine. [c] The starting material was $(H_2NCH_2CH_2)_3N$ containing 13.2% of triethylenetetramine as an impurity. The material was acetylated in the manner used for PEI's, and the impurity was assumed to leave no base that would be titrated under the conditions used.

Table IV
Tertiary Amine Content of PEI's as Determined by the Acetylation–Titration Method

PEI	% tertiary[a]
PEI-600	21.6
PEI-1200	25.2
PEI-1800	26.0
PEI-50,000	26.5

[a] The number of tertiary amino groups divided by the total number of amino groups and multiplied by 100.

Table V
Thermodynamic pK_a Values in Water at 25°

Amine	pK_1	pK_2	pK_3
$(Me_2NCH_2CH_2)_2NMe$	9.32	8.24	
$(Me_2NCH_2CH_2)_3N$	9.42	8.34	6.66
$(Me_2NCH_2CH_2NMeCH_2)_2$	9.16	8.17	4.62

to carbinolamine (or any other adduct). In view of this fact and the earlier observation that secondary amines do not give any detectable catalysis of the dedeuteration of isobutyraldehyde-2-*d* *via* iminium ion formation,[6] these exchange reactions were assumed to follow eq 1, where k_p is

$$k_p = k_{Et_2NH}[Et_2NH] + k_h[OH^-] \qquad (1)$$

the pseudo-first-order rate constant obtained in a given run. (The catalysis constant for water[5] is so small that such catalysis may be neglected in all the runs described in the present paper.) As shown in Table II, the corrections for hydroxide ion catalysis (calculated from the catalysis constant for hydroxide ions[5]) do not exceed 16% of the total reaction, and the values obtained for k_{Et_2NH} are reasonably constant.

One method of determining the fraction of the amino groups in PEI's that are tertiary is to treat the material with excess acetic anhydride to transform the primary and secondary amino groups to amide groups and then to titrate the remaining basic groups with *p*-toluenesulfonic acid in acetic acid–acetic anhydride.[7] It seems possible that, if too many tertiary amino groups are located near each other in the polymer, the protonation of some of them will so decrease the basicity of the remaining ones that the number of amino groups determined will be smaller than the number actually present. To test this possibility, four model compounds were titrated, and the averages of the results obtained are shown in Table III. The potentiometric titration curves obtained were essentially the same as those obtained in titrations of acetylated PEI's, except that the end points were slightly sharper in the case of the model compounds. The number of tertiary amino groups determined is correct in every case except that of tris(2-dimethylaminoethyl)amine, where only three of the four amino groups present were protonated during the titration. We therefore conclude that a tertiary amino group in a PEI will not be protonated in the titration if the three nearest amino groups are protonated, but that protonation of a tertiary amino group is not prevented by protonation of two of the three nearest amino groups (*cf.* the first two compounds in Table III). The tertiary amino contents of PEI's listed in Table IV were determined by the standard acetylation–titration method and have not been corrected for the possibility that some of the tertiary amino groups escaped titration. Essentially the same results were obtained in several cases where the acetylation was varied from the standard 4 hr to as little as 15 min and as much as 6 hr.

The pK_a values of three of the model compounds were determined by potentiometric titration in aqueous solution, with the results shown in Table V.

Discussion

The rate constants for the dedeuteration of 0.053 *M* isobutyraldehyde-2-*d* in the presence of ethylenediamine and its five N-ethylated derivatives, all at concentrations of

0.10 *M*, at pH 8.5 and 35° range from $0.20 \times 10^{-5}\ \text{sec}^{-1}$ for the unsubstituted compound to $0.55 \times 10^{-5}\ \text{sec}^{-1}$ for the triethyl derivative.[2,3] The relative reactivities are a complicated function of the fraction of the aldehyde that is complexed, the fraction of the amine that is protonated at pH 8.5, the amount of reaction that involves two molecules of catalyst, and other factors. The rate of dedeuteration in the presence of ethylenediamine around pH 8.5 increases to a maximum at diamine concentrations around 0.03 *M*, decreases to a minimum around diamine concentrations of 0.10 *M*, and then increases with increasing concentrations of diamine.[8] These and similar observations show that the relative catalytic activities of ethylenediamine and its N-ethylated derivatives are functions of the concentrations of aldehyde and diamine used. The fact that diethylenetriamine is about 60% more efficient than the best of the N-ethylated ethylenediamine catalysts may suggest that bifunctional catalysis has become important, but there are a number of possible alternative explanations. In fact, in view of the evidence that the exchange of isobutyraldehyde *via* iminium-ion formation involves only the trans iminium ions[6,9-13] and that more than six carbon (or other) atoms are needed between the primary amino group and the basic catalyzing group for bifunctional catalysis *via* a trans iminium ion,[13] it seems unlikely that diethylenetriamine is acting bifunctionally. All the compounds listed as PEI's in Table I have pairs of amino groups separated by a large enough number of atoms that a molecular model of a transition state for bifunctionally catalyzed dedeuteration *via* a trans iminium ion may be constructed without obvious major strain. In view of all the additional evidence described, particularly for PEI-1800,[2,3] it seems likely that bifunctional catalysis is significant for all these PEI's. The reactions in all cases will include a component from free aldehyde and a component from complexed aldehyde, with all the bifunctionally catalyzed reaction being included in the latter component. Therefore, in order to learn more about the bifunctionally catalyzed reaction, we shall give particular attention to the relative reactivities determined in the presence of 1.0 *N* PEI's, where the complexed aldehyde is responsible for almost all the observed reaction.

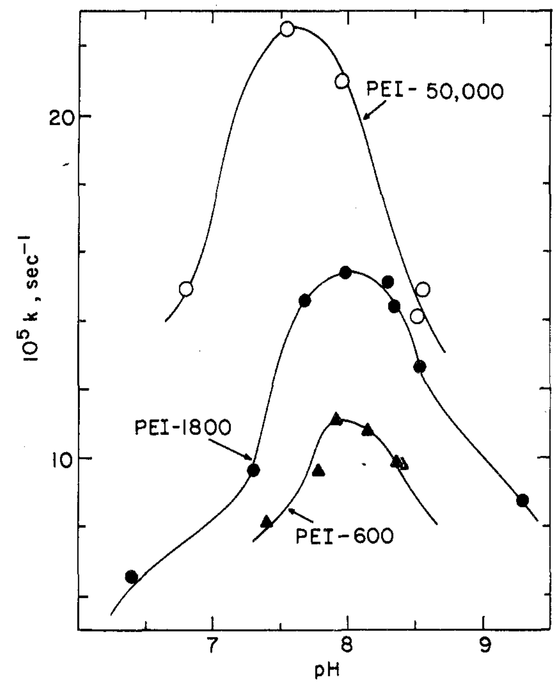


Figure 1. Plot of rate constants for dedeuteration of isobutyraldehyde-2-*d* in water at 35° in the presence of, ▲, 1.01 *N* PEI-600; ●, 0.97 ± 0.03 *N* PEI-1800; ○, 1.00 *N* PEI-50,000.

In Figure 1 are plots of the rate constants for deuterium exchange of 0.054 *M* isobutyraldehyde-2-*d* *vs.* pH in the presence of 1.0 *N* PEI-600, PEI-1800, and PEI-50,000. Whether one compares the rate constants at a given pH, such as 8.5, where the largest amount of data exists, or at the respective maxima for the various PEI's, the catalytic activities are seen to increase with increasing molecular weight of the PEI's. This increasing reactivity of the complexed aldehyde suggests either that as the molecular weight of the PEI increases the complexed aldehyde becomes increasingly reactive toward attack by a base (*e.g.*, because of a larger fraction of it being present as iminium ions), or that there is an increase in the number and/or basicity of internal amino groups that can attack complexed aldehyde, or that both of the preceding factors are important. In view of the results obtained when Dabco was present in the reaction solution, the first alternative seems unlikely. The effect of 0.200 *N* Dabco on the exchange rate in the presence of 1.00 *N* PEI's increases in the order PEI-50,000 < PEI-1800 < PEI-1200 < PEI-600. This sequence is reasonably explained by assuming that aldehyde complexed to PEI-600 is somewhat more reactive than that complexed to PEI-50,000 because a somewhat larger fraction of it is complexed as iminium ions, but it is also possible that aldehyde complexed to the larger PEI's is more sterically hindered. A larger fraction of iminium ions would be expected in the aldehyde complexed to the lower molecular weight PEI's because these have a larger fraction of primary amino groups, which can yield imines and iminium ions, in contrast to the secondary amino groups, which yield carbinolamines, imidazolidines, and perhaps larger ringed heterocycles. The greater rate of deuterium exchange of aldehyde complexed to the higher molecular weight PEI's is therefore most plausibly explained in terms of the larger number of amino groups in the same molecule that are capable of removing deuterium from those isobutyraldehyde-2-*d* molecules that are complexed as iminium ions. However, the reactivity of complexed aldehyde is not simply proportional to the number of other amino groups present in the molecule (even if a correction is made for differences in susceptibilities of complexed aldehyde to attack by bases as judged from the effect of Dabco on exchange rates). Aldehyde that is complexed to PEI-1800 must have about three times as many amino groups in the same molecule with it as does aldehyde that is complexed to PEI-600, and yet the PEI-1800-complexed aldehyde is only about 24% more reactive. PEI-50,000-complexed aldehyde is only 5–90% (depending on the pH at which the comparison is made) more reactive than PEI-1800-complexed aldehyde, in spite of having about 30 times as many amino groups. If we make the plausible assumption that an amino group (of a given basicity, etc.) separated from a complexed aldehyde by a given number of atoms has about the same rate constant for deprotonating it in one PEI as in a PEI of much different molecular weight, it follows that most of the amino groups in PEI-50,000 are separated from the average complexed aldehyde by such a long chain of atoms that they rarely collide with it and are thus quite inefficient at deprotonating it.

In order to get an improved understanding of how the ability of an amino group to deprotonate complexed aldehyde depends on the length of the intervening chain of atoms, we used computer and other techniques to estimate certain aspects of the detailed structures of the PEI's, as described in more detail in the Appendix. We carried out computer simulations of ethylenimine polymerization, using constraints to make some properties of

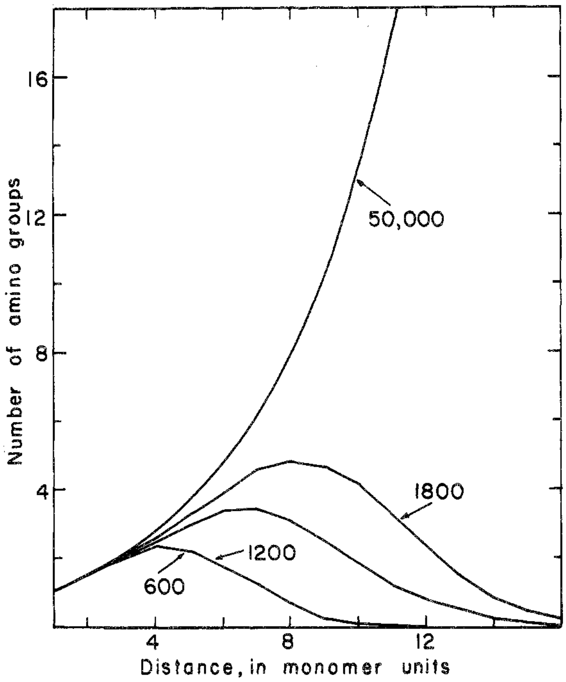


Figure 2. Estimated total number of amino groups at each distance from the average primary amino group in polyethylenimines with average molecular weights of 600, 1200, 1800, and 50,000.

the polymers resemble those observed experimentally but otherwise assuming random reaction. We then estimated the number of primary, secondary, and tertiary amino groups at each possible distance from the average primary amino groups. The estimated total number of amino groups at each distance from the average primary amino group in PEI-600, PEI-1200, PEI-1800, and PEI-50,000 is plotted in Figure 2.

To discuss internal attack on complexed aldehyde simply in terms of the number of amino groups at various distances away that are available for attack neglects several important factors. Other factors being equal, the most basic amino groups will attack most rapidly. However, at the pH's where bifunctional catalysis is most clearly significant, many of the amino groups of a PEI are protonated, and the most basic amino groups will be protonated to the greatest extent. Furthermore, in view of the fact that trimethylamine dedeuterates isobutyraldehyde-*2-d* 20 times as rapidly as triethylamine does, in spite of being only about one-seventh as basic,[5] allowance should also be made for differences in steric hindrance and any other factors that influence the ease with which a base removes α deuterium from an N-substituted isobutylideniminium ion. In order to allow for such factors we subdivided the amino groups in PEI's in aqueous solution at pH 8.5 into a number of categories and estimated the rate constant for the attack of each on *N*-methylisobutylideniminium ions. As described in detail in the Appendix, data on model compounds were used to estimate the basicities of the various types of amino groups in the unprotonated PEI's and the effect of protonation of nearby amino groups on these basicities. Then Brønsted relationships were assumed for the rate constants for dedeuteration of *N*-methylisobutyliden-*2-d*-iminium ions by these various types of amino groups. Rate constants for dedeuteration by the different types of amino groups were then calculated from their respective basicities and the Brønsted relationships. From these results the estimated average rate constants for dedeuteration by the primary, by the secondary, and by the tertiary amino groups of each of the PEI's were calculated. It was then assumed that the *relative* magnitudes of these rate constants for attack on the *N*-methylisobutyliden-*2-d*-iminium ion are the same as those for attack on the isobutyliden-*2-d*-iminium ions formed from any given PEI. This permits us to combine the estimated rate constants and the estimated numbers of primary, secondary, and tertiary amino groups at each of the possible number of units away from the average primary amino group to obtain the relative rate constants that would be expected, for a given PEI, for dedeuteration of complexed aldehyde *via* transition states with each of the possible rings if there were no ring-size effect. A plot of the estimated relative rate constants[14] for attack on complexed aldehyde by the primary, secondary, and tertiary amino groups at each of the possible distances from the average primary amino group in PEI-1800 is shown in Figure 3. The estimated amount of catalysis by tertiary amino groups is seen to be quite small compared with that estimated for primary and secondary amino groups, which are less hindered and, on the average, more basic. The three curves in Figure 3 may be summed to get the total relative rate constants that would be expected if there were no ring-size effect. Before comparing such a summed curve with that for another PEI, a correction was made for differences in ease of removal of deuterium from complexed aldehyde as evidenced by reactivities toward added Dabco. That is, the estimated rate constants for PEI-600, PEI-1200, and PEI-1800 were multiplied by 1.46, 1.32, and 1.15, respectively, since the effects of Dabco on the rate of exchange of aldehyde complexed to PEI-600, PEI-1200, and PEI-1800 are greater by 46, 32, and 15%, respectively, than on the rate of exchange of aldehyde complexed to PEI-50,000 (Table I). A plot of the relative rate constants (relative to that for the average tertiary amino group in PEI-50,000) is shown in Figure 4. (To put the entire plot for PEI-50,000 on the same graph would make those for the smaller polymers too small to see clearly.)

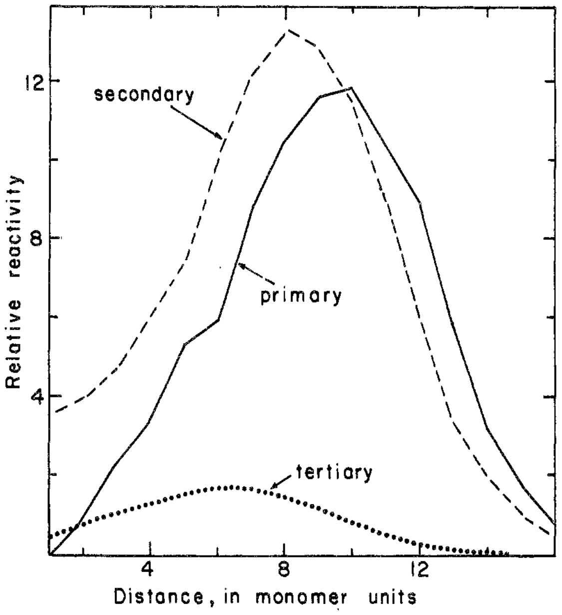


Figure 3. Estimated reactivities (relative to that of a tertiary amino group), in dedeuteration of $Me_2CDCH{=}N^+H-$ groups, of the primary, secondary, and tertiary amino groups at various distances from the average primary amino group in PEI-1800.

If there were no ring-size effect, the relative rate constants for the exchange of complexed aldehyde would be essentially equal to the relative areas under the curves shown in Figure 4. Thus, aldehyde complexed to PEI-1200, PEI-1800, and PEI-50,000 would exchange 2.0, 2.7, and 70 times as fast as aldehyde complexed to PEI-600.

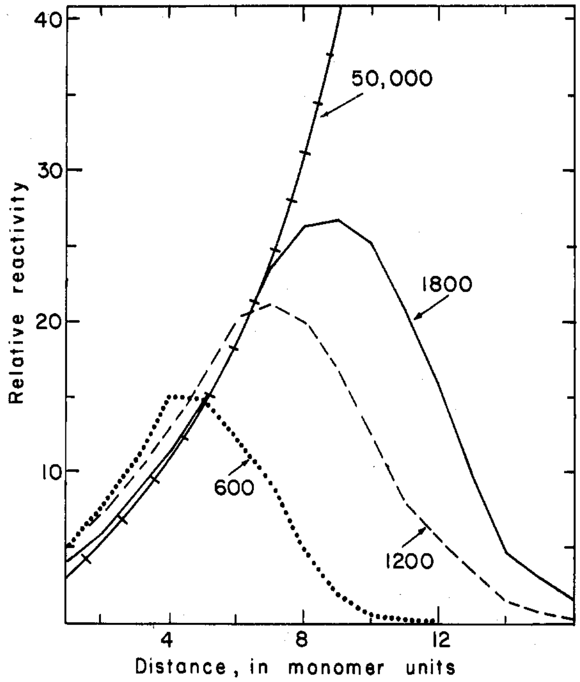


Figure 4. Estimated reactivities (relative to that of the average tertiary amino group in PEI-50,000), in dedeuteration of internal $Me_2CDCH{=}N^+H$- groups, of amino groups at various distances from the average primary amino group in four PEI's.

These figures are quite different from the observed ratios of 1.19, 1.24, and 1.38, which may be calculated from the data on runs using 1.0 *N* PEI's at pH 8.5 in Table I. We assume that these differences would largely disappear if each of the rate constants for reaction *via* a transition state with a given ring size were multiplied by the proper ring-size factor.

There are, of course, an infinite number of sets of ring-size factors that will give the desired agreement, but they are not all equally plausible. We have assumed that whatever value of *n* makes 1 the most favorable transition state, the next most favorable one will be one with one more or one less ethylenimine unit in the ring. More precisely, we have assumed that the ring-size factors will be a Gaussian function of ln *n*, as shown in eq 2. In this equation *r*, the ring-size factor, is the number by which the relative rate constants, such as those plotted in Figure 4, should be multiplied to correct them for the ring-size effect; n_{op} is the value of *n* in the optimum transition state; and *C* is a constant that controls the sharpness of the Gaussian function. A logarithmic function is used so that

$$\ln r = -C\left(\ln \frac{n_{op} - 1}{n - 1}\right)^2 \qquad (2)$$

r will be undefined for negative values of *n* but still positive for any large *n*. A function of $n - 1$ is used to make *r* zero for an *n* value of 1, since models of the appropriate transition state 1 can be constructed only with obvious enormous strain. With n_{op} restricted to integers, a very large value of *C* corresponds to essentially all the reaction proceeding *via* the transition state in which *n* is equal to n_{op}. An n_{op} value of 5.5, for example, corresponds to the transition states for which *n* is 5 and 6 being about equally favorable. A very small value of *C* corresponds to essentially identical ring-size factors for all values of *n*, which, as explained earlier, corresponds to much greater relative catalytic activity for the larger PEI's than that found experimentally.

We determined how well the observed relative reactivities of aldehyde complexed to the four polymers could be fit (as measured by the standard per cent deviations) by various pairs of values of n_{op} and *C*. The results are shown in Figure 5, in which two contour lines have been drawn, one at a standard deviation of 17% and the other at a standard deviation of 40%. It is seen that for any value of *C* from one to infinity there are values of n_{op} that permit our data to be fit with standard deviations of 40% or less. For this reason, we feel that all we can say about *C* is that its value is probably not much less than 1.0. The plot is much more restrictive as to the probable value of n_{op}, however. If a 40% standard deviation from the experimental values is taken as satisfactory, n_{op} must be in the range 3–6. If it is demanded that the standard deviation not exceed 17%, n_{op} is probably either 4 or 5.

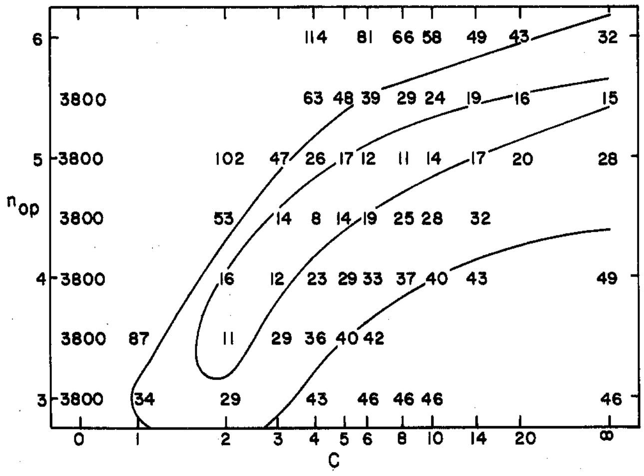


Figure 5. Per cent standard deviations in the fit to the observed catalytic activities of four PEI's obtained using eq 2 and various values of n_{op} and *C*.

The preceding conclusions are relatively insensitive to some of the details of the treatment used. In alternative treatments we assumed that the number of amino groups at a given distance from the average primary amino group agreed with the number calculated for an infinitely large polymer out to 20 ethylenimine units (instead of 13, as in the treatment that gives Figure 5), neglected catalysis by amino groups more than 20 units away, replaced the terms $n_{op} - 1$ and $n - 1$ in eq 2 by $n_{op} - 2$ and $n - 2$, and took the reactivity of tertiary amino groups as the same in all the polymers. Although these alternative treatments were not carried out in as much detail, in no case was there any evidence that *C* is significantly smaller than 1.0 or that n_{op} is outside the range 3–6. The range 3–6 of n_{op} corresponds to a ring size of 13–22 atoms for the optimum cyclic transition state. Models of transition states of the type of 1 can be constructed without obvious strain in bond lengths or bond angles (but perhaps with unfavorable nonbonded interactions and torsional strains around single bonds) for any value of *n* equal to 3 or more. Bifunctional catalysis by 1-dimethylamino-8-amino-2-octyne, which should give a transition state with a 13-membered ring, has been observed.[13] The compounds $H_2N(CH_2)_mNH_2$, where *m* was 11 and 12 (corresponding to cyclic transition states with 16- and 17-membered rings), did not appear to be bifunctional catalysts,[13] but this may result from the greater energy required to achieve the necessary gauche conformations in a polymethylene chain. The range 13–22 atoms obtained for the optimum cyclic transition state in the present case may depend significantly on the polyethylenimine nature of most of the ring. It would take more data to learn how extrapolatable the present results are to compounds with other types of relatively flexible chains between the primary amino group and the other basic group in bifunctional catalysts for deuterium exchange *via* the trans form of aldiminium ions.

Experimental Section

Reagents. Polyethylenimines with average molecular weights of 600 (Montrek-6, lot no. 534-1-47), 1200 (Montrek-12, lot no. 534-2-2), and 1800 (Montrek-18, lot no. TA09028BON) were obtained from the Dow Chemical Co. as viscous, colorless liquids containing less than 3% water. PEI-50,000 (Montrek-600, lot no. 01047BOI, said to have a number-average molecular weight of 40,000–60,000) was obtained as a "~33% solution in water." The elemental analysis agreed best with a 34.6% solution of PEI containing 0.88%[15] hydrochloric acid.

Anal. Calcd for 34.6% $(C_2H_5N)_x$–0.88% HCl–64.5% H_2O: C, 19.30; H, 11.29; N, 11.25; Cl, 0.86. Found: C, 19.52; H, 11.28; N, 11.11; Cl, 0.86.

Volhard analysis showed 0.19, 0.24, and 0.51 wt % chloride in the PEI-600, -1200, and -1800, respectively. These amounts were taken as hydrochloric acid already in the samples, and they were therefore added to the per cents of tertiary amino group determined by acetylation and titration[7] to give the results shown in Table IV.

The *N,N*-bis(2-dimethylaminoethyl)methylamine (Ames Laboratories) used was found by glpc to be at least 99.8% pure. After purification by recrystallization of their hydrochlorides, *N,N'*-bis(2-dimethylaminoethyl)-*N,N'*-dimethylethylenediamine (Ames) and tris(2-dimethylaminoethyl)amine [prepared by methylation of tris(2-aminoethyl)amine][16] were found by glpc to be >99.8 and 96.3% pure, respectively; the 3.7% impurity in the latter tetramine was the former tetramine.

Both Eastman Technical triethylenetetramine and tetraethylenepentamine showed a large number of peaks on glpc.

p*K* Determinations. The p*K* values listed in Table V were determined by potentiometric titration of aqueous amine solutions in the concentration range 0.02–0.03 *M* with 1.00 *M* hydrochloric acid using a Radiometer Model 26 pH meter and G202B glass and K401 reference electrodes. Values of pK_1, pK_2, and pK_3 (when determinable) were calculated, using a computer program, so as to minimize the sum of the squares of the deviations of the calculated from the observed pH values for at least eight experimental points. Equation 3 was used to calculate activity coefficients.[17] The reliability of the p*K* values obtained probably stands in the order $pK_1 > pK_2 > pK_3$ because of the uncertainties in calculating the activity coefficients of multicharged ions at the higher ionic strengths present when the diprotonated and triprotonated amines were the principal amine species present.

$$\log \gamma = -0.509Z^2\left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}} - 0.2\mu\right) \qquad (3)$$

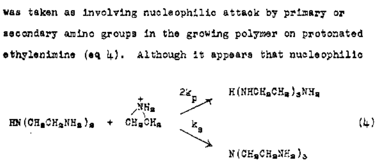
Acknowledgment. We thank Drs. Frank C. Schmalstieg, F. E. Rogers, and R. E. Notari for preliminary studies in the area of this investigation, the Dow Chemical Co. for gifts of the polyethylenimines used, and the Instruction and Research Computer Center of The Ohio State University for making its facilities available.

Registry No.—Isobutyraldehyde-2-*d*, 4303-51-9.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the mini-

Appendix

Estimation of Distribution of Various Types of Amino Groups.—For the purpose of estimating the environment of the average primary, secondary, and tertiary amino groups in the various PEI's, the polymerization of ethylenimine was taken as involving nucleophilic attack by primary or secondary amino groups in the growing polymer on protonated ethylenimine (eq 4). Although it appears that nucleophilic



$$HN(CH_2CH_2NH_2)_2 + \overset{\overset{+}{N}H_2}{CH_2CH_2} \begin{matrix} \xrightarrow{2k_p} H(NHCH_2CH_2)_3NH_2 \\ \xrightarrow{k_s} N(CH_2CH_2NH_2)_3 \end{matrix} \qquad (4)$$

attack by ethylenimine is even more important,[18,19] allowance for such a pathway would have complicated our treatment greatly, and it is not clear that it would have changed the results significantly. Although both ethylenediamine and diethylenetriamine are used in the polymerization

of ethylenimine[19,20] reaction by the mechanism used would pass through the latter in either case. We therefore carried out a computer-simulated polymerization starting with diethylenetriamine and assuming that the reactivity of any amino group in the growing polymer depends only on whether the amino group is primary, secondary, or tertiary. Since quaternary nitrogen is known to be virtually absent from the polymer, the tertiary amino groups were assigned a relative reactivity of zero. This leaves only one parameter, k_p/k_s, the reactivity of any primary amino group relative to that of any secondary amino group. Each simulated polymerization was carried out with a given value of k_p/k_s, which was used with a random number generator to decide which amino group in the growing polymer with *n* ethylenimine units attacked ethyleniminium ions to give the polymer with *n* - 1 units. To simulate PEI-600, PEI-1200, and PEI-1800, polymers with 14, 28, and 42 amino groups (molecular weights 576, 1176, and 1780, respectively) were generated. After 50 polymers of a given type had been generated using a given value of k_p/k_s, the fractions of the amino groups in these polymers that were primary, secondary, and tertiary were calculated, and then the fraction of tertiary amino groups was corrected by subtracting those tertiary amino groups that would not be protonatable in acetic acid solution (because the amino group in question would have three protonated tertiary amino groups adjacent to it) to get the fraction of analyzable tertiary amino groups. When the value 4.0 was used for k_p/k_s the calculated fractions were all smaller than the experimental values and when 2.5 was used they were larger. The value 3.0 gave calculated fractions of analyzable tertiary amino groups of 22.4, 24.0, and 25.0% for PEI-600, PEI-1200, and PEI-1800, which are probably within the experimental uncertainty of the observed values of 21.6, 25.2, and 26.0%, respectively. The PEI-50,000 polymer is much too large for the computer simulated polymerization method used to be practical. However, a total tertiary amine content of 29% was estimated by extrapolation of the observed contents of analyzable tertiary amino groups for the smaller PEI's and the estimates of 0.4, 1.0, and 1.5% unanalyzable tertiary amino groups in PEI-600, PEI-1200, and PEI-1800, respectively. This value is near the 30% total tertiary amine content that may be calculated from the k_p/k_s value of 3.0 and the expression $2/[3 + \sqrt{4(k_p/k_s) + 1}]$ for the fraction of total tertiary amine in an infinitely large PEI, which may be derived on the following basis.

If P and S represent primary and secondary amino groups the following relations are evident. As the molecular weight

$$d[P]/dt = k_s[S] \qquad (5)$$

$$d[S]/dt = k_p[P] - k_s[S] \qquad (6)$$

$$\frac{d[S]}{d[P]} = \frac{k_p[P]}{k_s[S]} - 1 \qquad (7)$$

of the polymer approaches infinity the ratio $d[S]/d[P]$ must approach $[S]/[P]$. The fraction of tertiary amino groups may then be calculated from eq 7 and the fact that there would be essentially equal numbers of primary and tertiary amino groups in an infinitely large PEI molecule.

Let us estimate the number of amino groups of various kinds that are at each of the various possible distances from the average primary amino group in an infinitely large PEI. If *f* is the fraction of amino groups that are primary then the fraction tertiary is also *f* and the fraction secondary is 1 - 2*f*. It then follows that if E is one of the ethylene units that joins the amino groups the fraction of N-E bonds that are of the type P-E is *f*/2, the fraction of T-E bonds is 3*f*/2, and the fraction of S-E bonds is 1 - 2*f*. If the bonds are arranged randomly one might at first think that the fraction of P-E that leads on to give the partial structure P-E-S would be 1 - 2*f*. However, this ignores the fact that since we are dealing with a very large polymer the structure P-E-P, which would simply be ethylenediamine, is impossible. When this restriction is made, the fraction of the amino groups one unit away from the average primary that are secondary, which we shall denote s_1, is $(2-4f)/(2-f)$, and t_1 is $3f/(2-f)$. In calculating p_2, s_2, and t_2, the fractions of the amino groups two units away that are primary, secondary, and tertiary, respectively, we allow for the impossibility of the structures P-E-S-E-P and $P\text{-}E\text{-}T(E\text{-}P)_2$. The total number

$$p_2 = 2t_1f(2-f)/(4-f^2)$$

$$s_2 = s_1^2 + 6t_1(1-2f)/(4-f^2)$$

$$t_2 = s_1t_1 + 12t_1f/(4-f^2)$$

of amino groups two units from the average primary (a_2), that is, the sum $p_2 + s_2 + t_2$, is just $s_1 + 2t_1$. In fact, in general a_{n+1} is equal to $a_n + 2t_n$. Detailed calculations of random distributions of amino groups gave values of a_1, a_2, a_3, and a_4. If it were not for the disturbance in the calculations arising from the nonexistence of P-E-P, P-E-S-E-P, etc., the ratio a_{n+1}/a_n would always have the value 1+*f*. Because of these disturbances, which decrease with increasing *n*, the ratios a_1/a_2, a_2/a_3, and a_3/a_4 are 1.509, 1.380, and 1.334, respectively, when *f* is 0.29. We

extrapolated to larger values of *n* by assuming that a_4/a_5 differed from the limiting value 1.29 by half as much as a_3/a_4 did, and then that a_5/a_6 differed from 1.29 by half this amount, etc. With the added assumption that s_n/t_n, which was relatively constant over the range *n* = 1 to 3, does not change, values of p_n, s_n, and t_n may be calculated for any *n* (although we did not use values for any *n* larger than 20).

The number of amino groups at each distance from the average primary amino group in PEI-50,000 was assumed to be the same as for an infinitiely large polymer for distances up to 13 monomer units away (where less than 10% of the amino groups in PEI-50,000 have been accounted for). A plot of these numbers, which were calculated as described in the preceding paragraph, and the numbers obtained by counting amino groups in the polymers generated by computer simulation for PEI-600, PEI-1200, and PEI-1800 is shown in Figure 2. The agreement between the four curves, up to the points where those for the smaller polymers begin to fall off, supports both the treatments used, which were based on considerably different assumptions. It was then assumed that the rest of the curve for PEI-50,000, beyond an *n* value of 13, was fit by an equation of the type shown in eq 8, in which *n* is the number of units away and the *c*'s

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$$f(n) = c_1(n + c_2)^2/(c_3 + e^{c_4 n}) \qquad (8)$$

are disposable parameters. For each of the three required functions (for values of p_n, s_n, and t_n) values of the four parameters were obtained by imposition of four restraints. It was required that $f(n)$ have the same value for $n = 1$ and $n = 13$ as obtained from the treatment of the infinite polymer described in the preceding paragraph. It was also required that the total area under the plot of $f(n)$ vs. n be equal to the number of amino groups of the given type in the polymer and that the area under the plot between $n = 1$ and the maximum in the plot be plausible in light of the areas of the similar curves for the smaller polymers. Thus, for example, in the case of tertiary amino groups, 47% of the total are found between $n = 1$ and the maximum in the case of PEI-600, 45% in the case of PEI-1200, and 44% in the case of PEI-1800. For PEI-50,000 the figure was assumed to be 43%, and corresponding figures of 61% and 53% were similarly taken for the primary and secondary amino groups. These restraints gave c_1, c_2, c_3, and c_4 values of 2.56, 1.08, 110, and 0.150 for the p_n curve, 6.75, 1.75, 103, and 0.193 for the s_n curve, and 4.96, 1.84, 76.9, and 0.221 for the t_n curve. The resulting estimated numbers of primary, secondary, and tertiary amino groups at various distances from the average primary amino group are plotted in Figure 6.

Estimation of the Basicity and Reactivity of the Various Types of Amino Groups.--In estimating the average reactivity of the various types of amino groups in the PEI's, it is useful to subdivide the various P-E, S-E, and T-E bonds into subcategories, depending on the nature of neighboring amino groups. When P-E bonds lead to a secondary amino group they will be denoted Ps and when they lead to tertiary amino groups, Pt. There will be no Pp, which could exist only in ethylenediamine. Similarly, pSt represents an S-E bond in which the E is attached to a tertiary and the S to a primary amino group (through an ethylene unit). The T-E bonds are merely subdivided into Tp, Ts, and Tt categories; a more complete subdivision (like that used for S-E bonds) would be too complicated and also less worthwhile since it happens that tertiary amino groups are so weakly basic and so hindered that they contribute relatively little to internal basic catalysis. From the fraction of the amino groups in a given PEI that are primary, secondary, and tertiary the total number of P-E, S-E, and T-E bonds may be calculated. The first of these will be equal to the sum Ps + Pt, the second to pSs + pSt + sSp + sSs + sSt + tSp + tSs + tSt, and the third to Tp + Ts + Tt. This gives three equations for the 13 unknowns. Four more, such as Tp = Pt and sSp = pSs, come from symmetry considerations. Two more, such as Ps = pSs + pSt, come from material balance

requirements. The remaining equations come from assumptions of random distribution. For example, the relative number of primary amino groups that have secondary and tertiary amino groups as their nearest neighbors was assumed to be proportional to the relative number of bonds from secondary and tertiary amino groups that are available to form bonds (through ethylene groups) to primary amino groups. The resulting relationship (eq 9) reflects the fact that a

$$\frac{\mathrm{Ps}}{\mathrm{Pt}} = \frac{\mathrm{Sx} - \mathrm{Ps}}{\mathrm{Tx}} \qquad (9)$$

secondary amino group that already has a primary as one nearest neighbor is not free to take another as a nearest neighbor, since the resulting P-E-S-E-P (diethylenetriamine) cannot be a part of the PEI's we are studying. In eq 9 Sx is the total of all the S-E bonds and Tx the total of the T-E bonds.

In order to subdivide the amino groups into additional useful categories on the basis of whether they or their neighbors would be protonated at pH 8.5, where the kinetic studies being discussed were carried out, we needed estimates of basicities. From the p*K* values for the conjugate acids of the ethylamines and of ethylenediamine and diethylenetriamine and their N-alkylated derivatives,[21] it was noted

that replacement of a β-hydrogen by a β-amino substituent decreases the p*K* of a substituted ammonium ion by about 1.23 and that an ∈-amino substituent decreases the p*K* by about 0.17. Similarly, protonation of an amino substituent decreases the p*K* by about 2.55 in the β position and about 0.68 in the ∈ position. Since the nearest neighboring amino group is a β-substituent and the next-nearest neighboring amino group an ∈-substituent in a PEI, these generalizations were applied to the PEI's and the effect of more distant substituents ignored. Titrations of 1 *N* polymers with standard acid to pH 8.5 in the presence of 0.054 *M* isobutyraldehyde showed that 34.4, 32.1, 27.9, and 22.3% of the amino groups were protonated under these conditions in PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively. The presence of protonated amino groups means that our categories of bonds must be expanded to include $\mathrm{P^+t}$, $\mathrm{Ts^+}$, $\mathrm{sS^+p}$, etc., but our generalizations concerning basicity show that there should be no significant number of protonated tertiary amino groups nor of pairs of adjacent protonated amino groups. This permits the easy estimation of the basicity of the unprotonated secondary amino group associated with a $\mathrm{pSs^+}$ bond, for example. This amino group has two nearest neighbor amino groups, of which one is protonated,

and one next-nearest neighbor amino group, which must not be protonated (because it is adjacent to a protonated amino group). Correction of the p*K* value for diethylammonium ions (10.64)[21] for the effect of two β and one ∈ amino substituent and for protonation of one of the β substituents gives 5.46 as the p*K* that measures the basicity of the unprotonated secondary amino group in $\mathrm{pSs^+}$. In other cases, such as that of the secondary amino group in pSt, we know how many next-nearest neighbor amino groups there are but not how many of them are protonated, and with the outside amino group in sSs, for example, we do not even know how many next-nearest neighbor amino groups there are. In such cases the number of next-nearest neighbors was taken to be half-way between the extreme possibilities (1 and 3 in the case of sSs), and unrestricted amino groups were assumed to be protonated to the same fractional extent as the polymer as a whole. Thus the correction for protonation of the two next-nearest neighbor amino groups of pSt in PEI-1800 is 2(0.68)(0.279). Combination of this correction with the p*K* value for diethylammonium ions and corrections for the nearest and next nearest neighbor amino groups gives a p*K* of 7.46 as a measure of the basicity of the secondary amino group in pSt. The fractions of the bonds to amino groups in the PEI's at pH 8.5 that are of the various types (pSt, $\mathrm{Tp^+}$, etc.) were calculated by use of a set of simultaneous equations. A number of these were based on demands of symmetry and material balance as in the

case of the equations used to solve for the similar fractions for the unprotonated polymer. Additional equations came from the definitions of the estimated p*K* values; one of the most simply estimated *K* values is equal to $[\mathrm{H^+}]\mathrm{Pt}/\mathrm{P^+t}$. From the results it was possible to calculate the fraction of protonation of the PEI. The method described gave too small a calculated fraction of protonation for each PEI. Therefore the p*K* values were arbitrarily increased (by 0.62, 0.61, 0.29, and 0.01 in the cases of PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively) until agreement was obtained.

To estimate the relative reactivities of the various types of amino groups in the internal removal of deuterons from $\mathrm{Me_2CDCH{=}\overset{+}{N}H}$- groups their relative reactivities toward the N-methylisobutylidene-2-*d*-iminium ion were first estimated. The linearity of a plot (slope 0.84) of log *k* for attack of various bases on this ion vs. log *k* for their dedeuteration of isobutyraldehyde-2-*d* shows that isobutyraldehyde is a good model for its N-methyliminium ion in this reaction.[10] From the line in this plot, the value 93.4 M^{-1} for the equilibrium constant for the formation of N-isobutylidenemethylamine,[8,10] the value 3.57×10^{-11} *M* for the acidity constant of methylammonium ions,[10] and the value 1.32×10^{-7} *M* for the acidity constant of N-isobutylidenemethylammonium ions,[22] we obtain eq 10, in which k_B is the rate constant for attack

$$\log k_B' = 0.84 \log k_B + 2.04 \qquad (10)$$

of a base on isobutyraldehyde-2-*d* and k_B' is the rate constant for attack of the same base on N-methylisobutylidene-2-*d*-iminium ions. From the observed values of k_B for methylamine,[23] dimethylamine,[8] trimethylamine,[8] diethylamine, and triethylamine,[8] values of k_B' were calculated. The value for trimethylamine was 13 times that for triethylamine and the value for dimethylamine was twice that for diethylamine, presumably because of steric effects. We therefore assumed that k_B' for ethylamine is about 80% of that for methylamine and obtained a k_B' value of 0.49 $M^{-1}\,\mathrm{sec}^{-1}$. Since Brønsted β values around 0.5 (0.49 for pyridines and 0.53 for phenoxide ions) have been observed for attack of bases on isobutyraldehyde-2-*d*,[8] the value for attack on the N-methyliminium ion was assumed to be 0.5(0.84). We therefore assumed that the rate constants for all our primary amines would fall on a Brønsted line through the point for ethylamine, those for secondary amines on a line through the point for diethylamine, and those for tertiary amines on a line through the point for triethylamine, all these lines having slopes of 0.42. For each of the possible types of amino groups one of the Brønsted lines and the appropriate p*K* value, whose estimation has already been described, may be used to obtain a value of k_B'. From these results the average rate constant for the primary, secondary, and tertiary groups in each polymer

were calculated. For example, we had five categories of unprotonated primary amino groups, those associated with Pt, pSs, pSt, $\mathrm{pSs^+}$, and $\mathrm{Ps^+}$ bonds. For these amino groups in PEI-600, k_B' values of 0.160, 0.296, 0.296, 0.153, and 0.0252 $M^{-1}\,\mathrm{sec}^{-1}$, respectively, had been estimated. Since these five categories constitute 8.9, 1.3, 1.0, 0.3, and 1.3%, respectively, of the total primary amino groups in PEI-600, the average value of k_B' for all the primary amino groups (including the 87.2% that are protonated and therefore inactive) is 0.0217 $M^{-1}\,\mathrm{sec}^{-1}$. The estimated average values of k_B' for the three kinds of amino groups in each of the four polymers are listed in Table VI. The differences in the estimated average reactivities of amino groups of a given type in the different polymers are seen to be much smaller than the differences in molecular weights. The values in Table VI refer to attack on the N-methyliminium ion, but we assumed that the *relative* values of k_B' will be the same for attack on any iminium ion

derived from isobutyraldehyde-2-*d*. We then used the data on the effect of Dabco on rates of exchange in the presence of PEI's to correct for differences in the susceptibilities of complexed aldehyde to attack by bases as a function of the PEI to which the aldehyde is complexed.

Table VI

Estimated Average Rate Constants for the Dedeuteration of $\mathrm{Me_2CDCH{=}NHMe^+}$ by Amino Groups in PEI's[a]

Polyethylenimine	$10^3 k$, $M^{-1}\,\mathrm{sec}^{-1}$		
	Primary	Secondary	Tertiary
PEI-600	21.7	24.5	3.83
PEI-1200	22.1	25.9	4.75
PEI-1800	28.7	23.8	4.46
PEI-50,000	34.0	22.9	4.23

[a] In water at 35°.

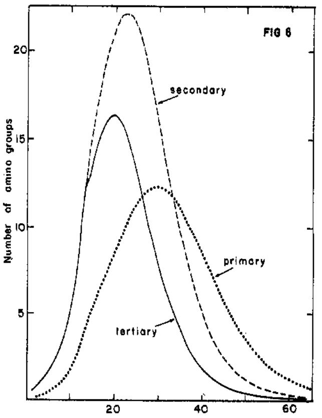

Figure 6.--Estimated numbers of primary, secondary, and tertiary amino groups at various distances from the average primary amino group in PEI-50,000.

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[23] The last part of the next to the last sentence of ref 10 should read "value of 1.55 or 2.52 x 10^{-3} $M^{-1}\,\mathrm{sec}^{-1}$, depending on which C_2 value is used." We used the average of these two values.

printed and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-863.

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Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decane Ring System[1]

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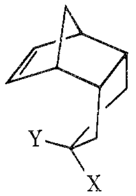
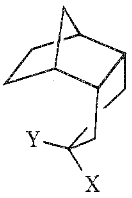
The tosylates of *endo*-5,6-trimethylene-2-norbornen-9-ol have been prepared and solvolyses carried out in acetic acid. This has led to *exo*-tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-ol. Solvolysis of the tosylate of this compound leads to a degenerate rearrangement with migration of the C_4–C_8 bond.

Participation of π electrons in the solvolysis of norbornyl derivatives has led to new norbornyl-type ring systems in many cases.[3] We were interested in the solvolysis of *endo*-5,6-trimethylene-2-norbornen-9-yl tosylates (2, 4) as a source of new ring systems.[4] Compound 3 was prepared by treatment of 4-hydroxycyclopentene with cyclopentadiene, oxidation of the product with chromium trioxide in pyridine, and reduction with lithium aluminum hydride.[5] Treatment of 4 with tetraethylammonium acetate and saponification of the resulting acetate yielded 1. Hydrogenation of 1 and 3 led to the known saturated alcohols,[6] which served to prove the configuration at C_9 was well as confirm the structure of the ring skeleton. Rate data for the acetolysis of 2 and 4 are given in Table I.



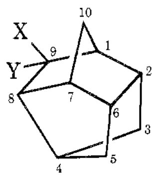
	X	Y
1	OH	H
2	OTos	H
3	H	OH
4	H	OTos
8	Cl	H



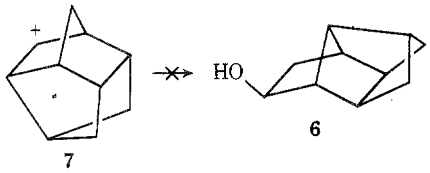
	X	Y
2a	OTos	H
4a	H	OTos

The exo/endo rate ratio of 27 at 25° is probably indicative of a small rate enhancement of the exo isomer due to participation of the π electrons. An alternate explanation of steric hindrance to ionization[6] of the endo isomer 4 seems unreasonable. The analogous saturated tosylates 2a and 4a exhibit an exo/endo acetolysis rate ratio of 0.62 at 25°.[6] It does not appear likely that introduction of the double bond would drastically change the relative rates for steric reasons. The rate for acetolysis of the saturated endo tosylate[6] 4a is 7.19×10^{-7} sec^{-1}, while that of the unsaturated is 2.49×10^{-7} sec^{-1}. The decrease in rate of the unsaturated endo tosylate 4 compared to the saturated could be largely attributed to the electron-withdrawing character of the double bond. The exo-unsaturated tosylate 2 exhibits a rate of 66.4×10^{-7} sec^{-1}, while the saturated analog 2a has a rate of 4.48×10^{-7} sec^{-1}. The fact that the unsaturated tosylate solvolyzes 15 times faster than the saturated is most reasonably explained by participation of the double bond.

Both exo and endo isomers gave excellent straight lines for first-order kinetics to over 80% of reaction. Examination of the products from acetolysis at 75° shows a 2:1 ratio of acetate to olefinic products from both 2 and 4. Dicyclopentadiene was the only olefinic product. The acetate from 4 after saponification showed 70% of 1 and 30% of rearranged alcohol 5. The product resulting from sapon-



	X	Y
5	OH	H
9	OTos	H
10	H	OH
11	H	OTos
13	D	OH



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