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Nucleophilic Reactivity of Amines toward Ethylene Oxide

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The rates of reaction of ethylene oxide with a series of primary, secondary, and tertiary amines with a wide pK_a range have been studied in aqueous solution. A logarithmic plot of the rate constants against the pK_a values of the amines is a curve with individual deviations, but against the nucleophilicity parameter N_+ a straight line of slope 0.60 is obtained. These correlations are discussed with reference to the reaction mechanism.

During kinetic studies on cation-anion combination reactions, the remarkably simple relationship

$$\log k_N{}^R = \log k_{H_2O}{}^R + N_+ \tag{1}$$

was shown to correlate the rates of reaction of different cations from triarylmethyl, benzenediazonium, and phenyltropylium systems with different anions over a reactivity range of six powers of ten.[1] $k_{H_2O}{}^R$ is the first-order rate constant of the reaction of a particular cation R with water in water as solvent and $k_N{}^R$ is its second-order rate constant with the nucleophile N in a particular solvent. N_+ is the corresponding nucleophilicity parameter defined by the equation

$$N_+ = \log k_N{}^{PNMG} - \log k_{H_2O}{}^{PNMG} \tag{2}$$

where the rate constants refer to the reactions of *para*-nitro Malachite Green, *i.e.* the bis(*para*-dimethylaminophenyl)-*para*-nitrophenylmethyl cation.

Some support for the value of eqn. (1) in correlating the reactions between cations and neutral molecules and between neutral molecules has also been gathered.[2] These observations suggested that further study would yield more information about the detailed reaction process. We report here our kinetic results for the reaction of various amines and some anions with ethylene oxide, one of the cyclic ethers which has been studied for several years in these laboratories.

EXPERIMENTAL

Chemicals. Ethylene oxide, a product of *purum* grade from Fluka AG, Buchs, Switzerland, was used directly from its steel cylinder. Glycine, glycylglycine, phenylhydrazine hydrochloride, and potassium cyanide were guaranteed reagents from Fluka AG or

Merck AG, Darmstadt, BRD, and used without further purification. The hydrochlorides of ethylamine, ethylenediamine, hydrazine, semicarbazine, piperidine, and diethylamine were commercial chemicals or prepared by standard methods from the corresponding amines. They were recrystallized from appropriate solvents before use. Pyridine and triethylamine were products of *purum* grade from Fluka AG and were fractionally distilled. Water was purified by distillation and ion-exchange. Methanol, a guaranteed *purissimum p.a.* product from Fluka AG was used as received.

A stock solution of sodium hydroxide free from carbon dioxide was prepared by mixing equal weights of sodium hydroxide and water and allowing the solution to stand until a clear supernatant was obtained. A stock solution of sodium methoxide was prepared by adding freshly cut sodium to methanol.

Kinetic experiments. Ethylene oxide was passed through a capillary tube into water. This solution was mixed with the buffer solution prepared by partly neutralizing the amine hydrochloride solution with a solution of sodium hydroxide. In the case of pyridine and triethylamine the buffer solutions were prepared from amine and perchloric acid solutions. The addition reactions of cyanide anion in water and methoxide ion in methanol were studied in unbuffered solutions.

The reactions were followed by analyzing the concentration of ethylene oxide using either gas chromatography or the thiosulphate method of Roos.[3,4] The gas chromatograms were run on a Perkin-Elmer model F11 gas chromatograph equipped with a flame ionization detector and using a 2-meter column containing 10 % Silicone Gum Rubber SE-30 on Chromosorb W at 40°C with helium as carrier gas. This method was employed when the reactions of ethylamine, phenylhydrazine, semicarbazine, triethylamine, pyridine, and cyanide were studied. In the reactions of ethylamine, glycine, piperidine, diethylamine, and methoxide anion, the titrations were carried out visually to the cresol red end-point near pH 8. Potentiometric titrations were suitable for analyzing the reactions of ethylenediamine, 2-ammonioethylamine, glycylglycine, and hydrazine. Within the limits of experimental error the same value of the rate constant was obtained when both methods were employed for the analysis of ethylene oxide from the reaction of ethylamine.

Calculations. Pseudo-first-order overall rate constants were evaluated from the variation of the ethylene oxide concentration with time. Second-order rate constants were calculated by subtracting the first-order rate constants of possible side reactions from the overall rate constant and dividing the difference by the average concentration of free amine during the reaction. The aminium ions were not found to add ethylene oxide.

The rate constant for the reaction of ethylenediamine was corrected for the reaction of 2-ammonioethylamine. The uncatalyzed hydrolysis of ethylene oxide was taken into account in calculating the rate constants of reactions of phenylhydrazine, semicarbazine, and pyridine, as was the uncatalyzed reaction of chloride ion with ethylene oxide in the reactions of 2-ammonioethylamine, phenylhydrazine and semicarbazine.[4,5] In the semicarbazine buffers, the pH was so low that the contributions of acid-catalyzed hydrolysis and the reaction of chloride ion with ethylene oxide were significant.[4] The total contribution of these side-reactions was low. It amounted to less than 8 % of the overall reaction except in the case of semicarbazine for which it was about 40 %.

In the reactions of cyanide ion with ethylene oxide, the hydrolysis of cyanide ion was taken into account using a pK_a value of 9.14 for hydrocyanic acid.[6] The rate was corrected for small contributions from the uncatalyzed hydrolysis of ethylene oxide and its reaction with hydroxide ion.[4]

RESULTS

The work of Eastham *et al.* has shown that ethylene oxide reacts with amines in aqueous solutions of pH range from 4 to 14 without any significant basic catalysis or catalysis by hydrogen or ammonium-type ions. In agreement with this, the rates of the reactions studied in the present work were found to be strictly first-order in ethylene oxide and amine. The pH of the aqueous amine buffer solutions was adjusted to or near the pK_a value of the

Table 1. Rate constants for the reaction of ethylene oxide with amines in water at 25°C.

Amine	Initial concn of amine, M	pH	pK_a [a]	k_{amine} M^{-1} s^{-1}	N_+ [d]
1. Ethylamine	0.313	11.00	10.97	1.08×10^{-3}	4.88
2. Ethylenediamine	0.463	10.71	10.18	1.30×10^{-3}	5.04
3. Glycine	0.300	9.76	9.76	1.12×10^{-3}	4.95
4. Glycylglycine	0.313	8.29	8.25	5.07×10^{-4}	4.25
5. Hydrazine	0.313	8.23	8.20	1.81×10^{-3}	5.60
6. 2-Ammonioethylamine	0.313	7.45	7.42	4.35×10^{-4}	3.39
7. Phenylhydrazine	0.156	5.30	5.27 [b]	7.41×10^{-4}	4.36
8. Semicarbazine	0.313	3.89	3.89	3.57×10^{-5}	3.32
9. Piperidine	0.313	11.45	11.42	5.60×10^{-3}	6.25
10. Diethylamine	0.313	10.70	10.67	1.35×10^{-3}	5.87
11. Triethylamine	0.302	10.77	10.75 [c]	5.46×10^{-4}	
12. Pyridine	0.310	5.54	5.52	1.90×10^{-4}	

[a] Ref. 8. [b] Ref. 9. [c] Ref. 6. [d] Ref. 2.

aminium ions, *i.e.* within the range 3.9 to 11.4. The results are collected in Table 1. Close agreement is found between our reaction rate constants for diethylamine, triethylamine, and pyridine and those measured dilatometrically by Eastham *et al.*, 1.1×10^{-3}, 5.2×10^{-4}, and 2.0×10^{-4} M^{-1} s^{-1}, respectively.[7]

Data for the reaction of ethylene oxide with some other nucleophiles than amines are collected in Table 2. Gee *et al.* have measured the rate of the reaction of methoxide ion in methanol at 29.8°C in 0.263 M sodium methoxide solution.[10] Because direct comparison with our other results was ambiguous, we repeated the experiments at 25°C using a lower concentration of the salt. Our result agrees with their value of 2.14×10^{-4} M^{-1} s^{-1} when the different experimental conditions are taken into account.

Table 2. Rate constants for the reactions of ethylene oxide with nucleophiles at 25°C.

Nucleophile	Solvent	Initial conc. of nucleophile, M	k_1 s^{-1}	k_2 M^{-1} s^{-1}	pK_a	N_+ [g]
13. Hydroxide ion	water	2.04×10^{-2}		1.22×10^{-4} [a,b]	15.75 [e]	4.5
14. Phenoxide ion	water	3.05×10^{-2}		9.50×10^{-5} [a]	10.00 [f]	
15. Cyanide ion	water	4.66×10^{-2}		3.38×10^{-4}	9.14 [d]	3.8
16. Azide ion	water			9.00×10^{-5} [c]	4.59 [d]	
17. Water	water		6.18×10^{-7} [a]		−1.74	0.0
18. Methoxide ion	methanol	3.73×10^{-3}		2.11×10^{-4}	15.5 [e]	7.5
19. Methanol	methanol		4.99×10^{-8} [a]		−1.39	0.5

[a] Ref. 4. [b] Ref. 5. [c] Ref. 11. [d] Ref. 6. [e] Ref. 8. [f] Ref. 12. [g] Ref. 1.

DISCUSSION

The logarithm of the rate constant for the reactions of ethylene oxide with the nucleophiles is plotted as a function of the basicity of the nucleophile in Fig. 1. When the reactions in water (circles) only are considered, the data show (despite some individual variations) a decreasing dependence of the rate on the basicity of the nucleophile with increasing basicity. A similar levelling out of the reaction rate has been observed in the reactions of acetate esters [8] and substituted *N*-acetylpyridinium ions.[13] The phenomenon has been cited as evidence that the transition state occurs early along the reaction coordinate so that no significant change in the charge of the nucleophile occurs. The explanation warrants consideration, but it is well to remember that our knowledge of the relationship between carbon and hydrogen basicities is very limited. The reactions of oxirans are promoted by acid catalysis, and the catalyzed reactions are believed to proceed *via* transition states in which both partial bonds are long. The spontaneous reactions of oxirans are evidently facilitated by hydrogen or other bonds to the oxygen atom. The speculation is consistent with the interpretation that when the enhanced rate of oxiran reactions is caused by increased catalytic activity or by increased nucleophilicity of the nucleophile, the transition state has a looser structure. The above-mentioned catalytic effect in the stretching of the carbon-oxygen bond of the oxiran thus gives the reaction mechanism a more S_N1-like character.

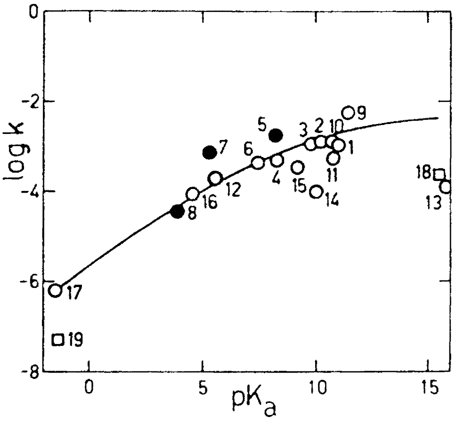

Fig. 1. Dependence of the rate constant for the reaction of ethylene oxide with nucleophiles on the basicity of the nucleophile. Notation as in Tables 1 and 2.

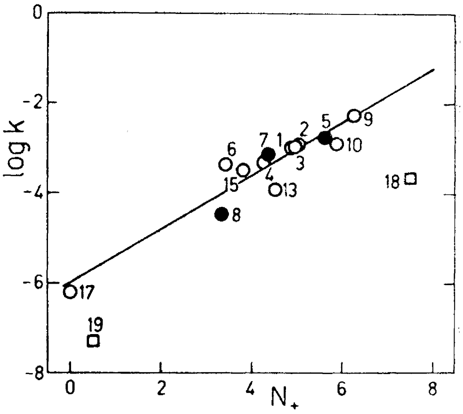

Fig. 2. Logarithm of the rate constant for the reaction of ethylene oxide with nucleophiles as a function of the parameter N_+. Numbers refer to the same nucleophiles as in Fig. 1.

There are several deviations from the rate-basicity curve. Hydroxide anion shows its characteristic negative deviation as does phenoxide ion.[13] Clearly the anions of strong acids like chloride, $k = 8.0 \times 10^{-6}$ M^{-1} s^{-1} at 30°C,[4] and bromide, $k = 7.0 \times 10^{-5}$ M^{-1} s^{-1} at 35°C,[11] also deviate from the plot.

When studying the reaction of Malachite Green with nucleophiles, Dixon and Bruice found that the Brønsted plots for α-effect nucleophiles (black points in Fig. 1) and for primary amines of similar pK_a fall on different lines,[14] and that the magnitude of the α-effect decreases with decreasing pK_a.[15] If the ratio k(hydrazine)/k(glycylglycine) is taken as a measure of the α-effect,[16] a value of 3.6 is obtained for the reactions of ethylene oxide. This low value is consistent with the gentle Brønsted slope of about 0.2 for the reaction rates of primary amines 1 – 4.

The logarithm of the rate constant for each reaction is plotted in Fig. 2 as a function of the nucleophilicity parameter N_+ where this is known. Comparison with Fig. 1 indicates that the rates in aqueous solution show no curvature and that the hydroxyl anion lies close to the line. The low reaction rate of methanol and methoxide anion in methanol (squares) is easily understood from the first paragraph of this discussion. These deviations arise from the low hydrogen bond donor ability of methanol compared with that of water.

Regression analysis of the data obtained in aqueous solution yields the equation

$$\log k_N = 0.60\,N_+ - 6.01 \tag{3}$$

with a regression coefficient of 0.944. It has been noted that N_+ values are inherent properties of nucleophiles alone[17] and independent of the electrophilic component of the reaction system. Moreover, it has been suggested that the N_+ values are related to the desolvatation energy of the nucleophiles: the higher the N_+ value, the less is the amount of energy required for the reaction.[1] Thus eqn. (1) with unit slope correlates reactions which are controlled by the desolvation of the nucleophiles, *i.e.* typical S_N2 reactions. Consequently, a slope of less than unity directs attention to the changes occurring in ethylene oxide itself during the formation of the transition state. Points for clean S_N1 reactions would surely fall on a line with zero slope. When more data have been collected we hope to discuss the question of whether this kind of analysis of reaction rates can be used as a measure of reaction mechanism.

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