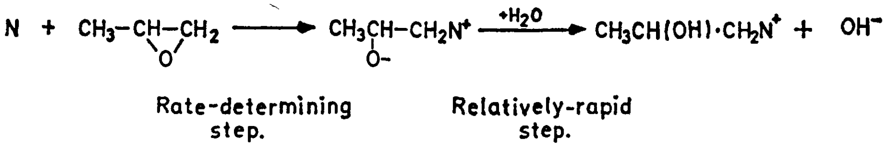
Studies on the Reaction of Aromatic Bases with Epoxides, and Anucleophilic Buffer for the Acid-catalysed Hydrolysis of Epoxides

By **J. G. Pritchard** * and **I. A. Siddiqui**, Department of Chemistry, North East London Polytechnic, Stratford, London E15 4LZ

The rates of nucleophilic reaction of pyridine and pyrazine with propylene and isobutylene oxides have been measured and compared with related data. No nucleophilic activity can be detected for tetramethylpyrazine, and this base forms an effective buffer in the pH range 3—4. A precision of 3—4% may be attained when rates of epoxide hydrolysis are measured in tetramethylpyrazine–perchlorate buffer solutions at pH 3·5. The rate coefficient for the acid-catalysed hydrolysis of 0·1M-aqueous isobutylene oxide at 25·7° is within the range 7·35 ± 0·24 l mol^{-1} s^{-1}.

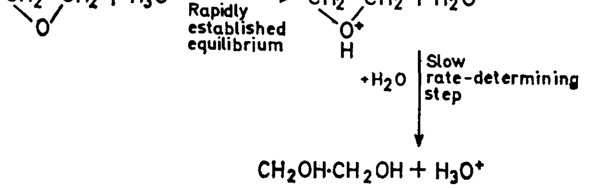
RATES of epoxide hydrolysis have been studied for pH values near 7 in solutions of non-nucleophilic buffers in order to avoid interference from the acid-catalysed reaction induced through pH drift.[1] 2,6-Dimethylpyridine, which buffers near pH 7, and closely related molecules in which the functional group is sterically shielded, were shown to be anucleophilic toward the nucleophile-sensitive propylene oxide molecule. This was demonstrated by the absence of the general bimolecular reaction of epoxides with tertiary amines (N):[2]



(1)

Perchloric acid was used a sthe buffering agent, owing to the extremely low nucleophilic activity of the perchlorate ion. Such buffer solutions have since found use in other systems in which the absence of nucleophiles is important.[3] Here we explored the relative nucleophilicities of pyridine, pyrazine, and tetramethylpyrazine towards epoxides with a view to the use of the latter amines in anucleophilic buffers suitable for the acid pH range.

The rate for the acid-catalysed hydrolysis of epoxides is proportional to concentration of epoxide and concentration of hydrogen ions over the pH range 0—6 (and to the Hammett acidity function for negative values of pH).[4,5] The reaction proceeds by way of a very small proportion of the conjugate acid of the slightly basic epoxide:[1,4,5]



(2)

(3)

Epoxides in which the reactive ring is activated by electron-releasing substituents react very rapidly by the

---

[1] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 6008.

[2] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.

[3] D. F. O'Brian, *J. Org. Chem.*, 1968, **33**, 262.

[4] J. N. Brønsted, M. Kilpatrick, and M. Kilpatrick, *J. Amer. Chem. Soc.*, 1929, **51**, 428.

[5] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 2667.

acid-catalysed path, and convenient study of their rates by normal dilatometric techniques must be made with solutions in the pH range 3—6. In this range, the reaction solution is subject to pH drift if it is not buffered. It is clearly important that constancy of pH be maintained in the course of these reactions if accurate kinetic results are to be obtained. Accurate rate data are very important to the reliability of derived energies and entropies of activation.[6,7] In this work, through the use of anucleophilic buffer, we attempt to demonstrate the highest possible precision for measurements of acid-catalysed hydrolysis rates.

EXPERIMENTAL

Materials.—The following pure organic chemicals were used as received: propylene oxide, n_D^{19} 1·3670 (Hopkin & Williams), isobutylene oxide, n_D^{20} 1·3748 (K & K), and pyrazine, 99·5% pure, m.p. 54·5—55·5° (Koch–Light). Other reagents were of AnalaR grade.

Tetramethylpyrazine.—Ethyl methyl ketone (490 g) was condensed with ethyl nitrite at 45° in the presence of hydrochloric acid and anhydrous copper sulphate to yield biacetyl monoxime (400 g) as white platelets from water, m.p. 76—77°.[8] Biacetyl monoxime (50 g) was condensed through reduction by stannous chloride and hydrochloric acid [9] to yield tetramethylpyrazine trihydrate (20 g) as white needles from water, apparent m.p. 85° (lit.,[10] 75°), τ (CCl_4) 7·64 (s, CH_3), 5·35 (s, H_2O). The trihydrate was held at 40° for 10 h to yield anhydrous tetramethylpyrazine, m.p. 85° (lit.,[11] 86°), τ (CCl_4) 7·64 (s, CH_3) (Found: C, 70·2; H, 8·8; N, 20·4.* Calc. for $C_8H_{12}N_2$: C, 70·6; H, 8·9; N, 20·6). G.l.c. on a 1-metre column of 10% polyethylene glycol 1000 on 100—120 mesh Diatomite C, with nitrogen at 100°, showed a single symmetrical peak with retention time 45 min.

Nucleophilic Reaction Kinetics.—Standard solutions (0·100M) of the aromatic amines were prepared and 20-ml aliquots were pipetted into a small vessel at 22 ± 1° equipped with glass and calomel electrodes connected to a Dynacap pH meter, which was standardised at pH 4·00 and 7·00 by known buffers. A measured quantity of the epoxide was added to the solution from a calibrated syringe and dissolved to give either a 0·10 or a 0·20M solution. The pH was adjusted rapidly to 9·0 by the addition of a small quantity of sodium hydroxide solution from another syringe. The increase of pH, due to reaction of epoxide with amine, was recorded. In the case of tetramethylpyrazine, which does not dissolve sufficiently to give a 0·10M solution at 22°, the experiment was carried out with the reaction vessel in a water-bath thermostatted at 50 ± 0·1°. Second-order rate coefficients for the initial bimolecular reaction were calculated from the initial slopes of hydroxide ion concentration plotted against time (*cf.* Figure 1).

pK of Tetramethylpyrazine.—A 0·1000M-aqueous solution of (anhydrous) tetramethylpyrazine at 50° was slowly titrated with 1·000M-perchloric acid solution and the pH was recorded with temperature compensation. The pH of a 50%-neutralised 0·02M-aqueous tetramethylpyrazine solution was measured for different temperatures over the range 0—50°.

Dilatometry.—Degassed aqueous solutions containing tetramethylpyrazine (0·0002—0·1M) were approximately 50% neutralised with dilute perchloric acid solution to give a pH close to 3·50 at 25·7°. Each solution was placed in the storage chamber of a dilatometer and thermostatted for 1 h at 25·7°. A few drops of the oxide were then introduced into the solution from a calibrated syringe and dissolved with minimum contact between the surface of the solution and the air. The solution was then passed to the 10-cm³ working chamber of the dilatometer and isolated by an oblique tap lubricated with silicone grease. The pH of the solution was measured before and after the dilatometric measurements by means of a Dynacap pH meter calibrated as before. Dilatometric measurements were taken from a scale attached to the Veridia-brand 0·50-mm i.d. precision-bore capillary tube of the dilatometer. Reactions were followed generally up to at least 80%. The Guggenheim treatment was used in each case to determine the pseudo-first-order rate coefficient (k_1) from a smoothed plot of the diminution in volume with time: $\log_{10}(x_2 - x_1) = -k_1t/2{\cdot}303 + \text{constant}$, where x_1 and x_2 are values of volume change corresponding to times t and $t + \Delta t$ after the start of the measurements, and Δt is a selected time interval. A typical plot gave the straight line: $\log_{10}(x_2 - x_1) = -0{\cdot}0627t + 0{\cdot}972$ for $t = 25$ min and t varied over the range 0—20 min (last result in Table 2). Some runs were made in the absence of tetramethylpyrazine, and the effect of the additional presence of pyrazine was also examined.

Product Studies.—Attempts to isolate a product from the reaction of propylene oxide with aqueous pyridine under conditions close to those used for the kinetics yielded only pyridine perchlorate after neutralisation of the reaction mixture with perchloric acid and crystallisation. No quarternary ammonium salt could be isolated.

The hydrolysis of isobutylene oxide to isobutylene glycol has been adequately checked previously by mass spectrometry [12] and by direct isolation in the laboratory.[12,13]

RESULTS AND DISCUSSION

Nucleophilic Reaction Rates.—Some rates of production of hydroxide ions by reaction of propylene and isobutylene oxides with pyridine and pyrazine are shown in Figure 1. The reactions were started at pH 9, at which the amines are entirely in the form of their un-ionised free bases. Table 1 lists initial second-order rate coefficients, initial rates being considered because hydroxide ions catalyse the hydrolysis of the oxides.

Propylene oxide is the more reactive substrate with respect to both amines. The slower reaction of isobutylene oxide is due partly to the steric effect of the additional methyl substituent and consequent un-

---

* Microanalysis by Mr. R. A. Tingey of these laboratories.

[6] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 7.

[7] K. Wiberg, 'Physical Organic Chemistry,' John Wiley, London, 1964, p. 378.

[8] *Org. Synth.*, Coll. Vol. 2, 1947, p. 204.

[9] F. B. Kipping, *J. Chem. Soc.*, 1929, 2889.

[10] G. R. Ramage and J. K. Landquist, in 'Chemistry of Carbon Compounds,' E. H. Rodd, ed., Elsevier, London, vol. IVB, 1959, p. 1321.

[11] D. T. Cromer, A. J. Ihde, and H. L. Ritter, *J. Amer. Chem. Soc.*, 1951, **73**, 5587.

[12] F. A. Long and J. G. Pritchard, *J. Amer. Chem. Soc.*, 1956, **68**, 2663.

[13] H. Moureu and M. Dodé, *Bull. Soc. chim. France*, 1937, **4**, 281, 637.

availability of the β-carbon site, and partly to deactivation of the carbon of the oxide ring toward nucleophilic reagents caused by the additional electron-releasing substituent.[12] Our result for the rate of reaction of pyridine with propylene oxide is in agreement with previous results for pyridine and ethylene oxide,[14] and for 3-methylpyridine and propylene oxide.[15] Pyridine is about twice as nucleophilic as hydroxide ion. However, pyrazine reacts at least 50 times slower than pyridine here. Allowing a statistical factor of 2 for the two nucleophilic nitrogens in pyrazine, we can conclude that the functional nitrogen in this compound is at least 100 times less nucleophilic than in pyridine. As the functional groups in these two amines have identical geometries,[16] this substantial difference in nucleophilic activity may be interpreted in terms of a relationship of the Brønsted type between nucleophilicity and basicity. Pyridine (I) is a weak base with p*K* 5·2, whereas pyrazine (II) is a much weaker base with p*K* estimated as 0·65.[17]

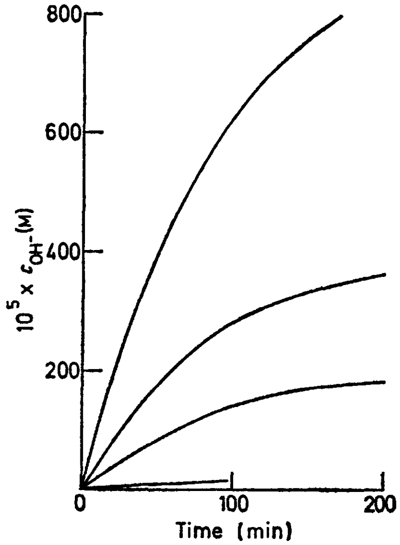
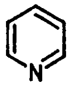


FIGURE 1 Concentration of hydroxide ions (C_{HO^-}) formed from reaction of 0·1M-pyridine with (highest gradient) 0·1M-propylene oxide, (next highest) 0·2M-isobutylene oxide, and (next highest) 0·1M-isobutylene oxide; and (lowest gradient) 0·1M-pyrazine with 0·1M-propylene oxide

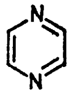
TABLE 1

Second-order rate coefficients for reaction of nucleophiles with epoxides in aqueous solution

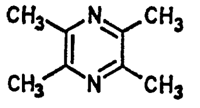
Nucleophile	Epoxide	Rate coefficient, ($l\ mol^{-1}\ s^{-1}$)
Pyridine	Propylene oxide	1.6×10^{-4} (22°)
Pyridine	Isobutylene oxide	2.9×10^{-5} (22°)
Pyrazine	Propylene oxide	2.9×10^{-6} (22°)
Pyrazine	Isobutylene oxide	2.8×10^{-7} (22°)
Tetramethylpyrazine	Isobutylene oxide	$<10^{-9}$ (22°)
Pyridine	Ethylene oxide [14]	2.0×10^{-4} (25°)
3-Methylpyridine	Propylene oxide [15]	1.6×10^{-4} (20°)
Hydroxide ion	Ethylene oxide [1]	1.0×10^{-4} (25°)
Hydroxide ion	Propylene oxide [1]	8.7×10^{-5} (25°)
Water	Propylene oxide [12]	1.0×10^{-8} (25°)
Water	Isobutylene oxide [12]	2.0×10^{-8} (25°)



(I)
Pyridine
p*K* 5·2



(II)
Pyrazine
p*K* 0·65



(III)
Tetramethylpyrazine
p*K* 3·5

Examples of the tertiary ammonium products of reaction (1) are known, but they must be prepared in the tertiary amine as solvent.[18] In alcohol[19] or water, derivatives of *N*-(2-hydroxyethyl)aminium salts evidently decompose (to aminium salt, and alkoxyglycol or glycol) sufficiently rapidly to preclude their isolation. Thus, the reaction between tertiary amines and ethylene oxide derivatives may be regarded as a catalysed alcoholysis in alcohol as solvent[19] and a catalysed hydrolysis in water.

Tetramethylpyrazine in 0·1M-aqueous solution produced no detectable hydroxide ions with 0·2M-isobutylene oxide at 50° during 3 h at pH 9·2. If we allow a possible error, or compensated drift, of 0·05 of a pH unit, the rate coefficient for reaction (1) at 20—25° could not exceed 10^{-9} l mol^{-1} s^{-1} and is most likely far smaller. This figure corresponds to a half-life of *ca.* 150 years for the above concentrations of reactants, so the test is quite sensitive. Tetramethylpyrazine is thus at least 10 times less nucleophilic towards epoxides than water mol for mol (Table 1). The p*K* of tetramethylpyrazine (III) has been variously reported as 3·55 (27°),[17] 3·6 (25°),[20] and 2·8 (25°),[21] *i.e.* intermediate between the values for pyridine and pyrazine. The structure of tetramethylpyrazine is planar and centrosymmetric, as for pyrazine.[11,16] Hence, the anucleophilicity of tetramethylpyrazine must be due mainly to the hindering of reaction at both of its nucleophilic centres by the methyl substituents.

Anucleophilic Buffer.—Figure 2 shows the titration curve for 0·1M-tetramethylpyrazine at 50°. A reasonable buffering effect occurs over the pH range 3—4. Calculations based on the pH-titre data show that the tetramethylpyrazinium ion is *ca.* 10% hydrolysed in 0·1M-solution; however, the point of half neutralisation at pH 3·33 ± 0·02 is not measurably affected by hydrolysis and corresponds to the p*K* for 50°. The respective mean p*K* values (±0·02) measured for tetramethylpyrazine at 40, 30, 20, 10, and 0° were 3·38, 3·43, 3·50, 3·54, and 3·60. Tetramethylpyrazine readily forms aqueous solutions of up to 0·05M concentration at 20—25°, and solutions containing up to 0·1M-total base can be obtained at this temperature when the base is half neutralised.

---

[14] A. M. Eastham, B. deB. Darwent, and P. E. Beaubein, *Canad. J. Chem.*, 1951, **29**, 575.

[15] J. Hansson, *Svensk. Kem. Tidskv.*, 1955, **67**, 246.

[16] V. Schomaker and L. Pauling, *J. Amer. Chem. Soc.*, 1939, **61**, 1769.

[17] A. S. Chia and R. F. Trimble, jun., *J. Phys. Chem.*, 1961, **65**, 863.

[18] L. C. King, N. W. Berst and F. N. Hayes, *J. Amer. Chem. Soc.*, 1949, **71**, 3498.

[19] R. M. Laird and R. E. Parker, *J. Chem. Soc.* (*B*), 1969, 1062.

[20] L. F. Wiggins and W. S. Wise, *J. Chem. Soc.*, 1956, 4780.

[21] D. A. Keyworth, *J. Org. Chem.*, 1959, **24**, 1355.

Nucleophiles of all types * react with epoxides by a noncatalysed simple bimolecular path [2,4,22,23] and by an acid-catalysed reaction in which the nucleophile attacks the epoxide conjugate acid.[1,4,22,24] Therefore, in order to observe the acid-catalysed hydrolysis of an epoxide free from interference by reactive species other than water, it is essential to exclude from the reaction solution any nucleophile that is more powerful than water mol for mol. Water is present at a concentration of 55M in dilute aqueous solutions, and a 0·1M concentration of an equally powerful nucleophile may be expected to interfere kinetically by *ca.* 0·2%. Interference due, for example, to pyrazine might be detectable because this base is at least 10 times more nucleophilic than water towards epoxides. No interference should be detectable for tetramethylpyrazine, and we conclude that this base should form a good buffer with perchlorate for the study of acid-catalysed hydrolysis rates and related uses in the pH range 3—4.

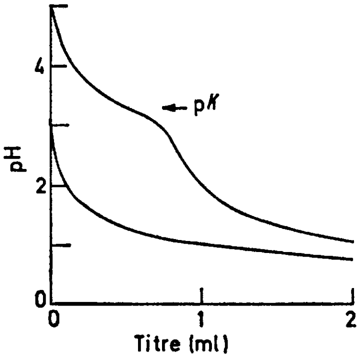


FIGURE 2 Titration of 10 ml of 0·1M-tetramethylpyrazine with 1M-perchloric acid at 50° (upper curve) and blank titration (lower curve)

TABLE 2

First-order rate coefficients (k_1) for acid-catalysed hydrolysis of 0·1M-isobutylene oxide in the presence of tetramethylpyrazine and perchlorate at pH 3·50 and 25·7°

Total TMP (M)	Initial pH	Final pH	$10^3 \times k_1$ (s^{-1}) Observed	Corrected [a]
	3·45	3·52	2·24	2·00
	3·45	3·33	2·40	2·14
	3·40	3·35	2·43	1·93
	3·40	3·34	2·58	2·05
0·002	3·43	3·42	2·66	2·27
0·002	3·50	3·50	2·35	2·35
0·003	3·50	3·53	2·22	2·22
0·01	3·50	3·50	2·30	2·30
0·02	3·50	3·50	2·38	2·38
0·03	3·50	3·50	2·38	2·38
0·05	3·50	3·50	2·30	2·30
0·1	3·50	3·50	2·40	2·40

[a] Corrected where necessary to pH 3·50 through the observed initial pH value and the expression $\log k_1 = -0{\cdot}98\,\text{pH} + \text{constant}$.[5]

Acid-catalysed Hydrolysis Rates.—Table 2 gives results for experiments on the hydrolysis of isobutylene oxide for initial pH values aimed at 3·50. The first four results obtained with no added buffer show that drifts of *ca.* 0·1 of a pH unit occur during the course of the hydrolysis. The more important results are the series of eight obtained in the presence of tetramethylpyrazine–perchlorate buffer, and these show that the pH is well controlled. A graph of the rate coefficients *versus* salt concentration barely shows any systematic trend, but rather a general scatter. On the basis of simple transition-state theory, no major salt effect on the overall acid-catalysed reaction would be expected, because neither the forward nor the backward reaction in the preliminary equilibrium step (2), nor the rate-determining step (3), involves reaction between two charged species. Application of Gosset's $t = 3{\cdot}50$ for the eight results gives the limits $2{\cdot}325 \times 10^{-3} \pm 0{\cdot}077 \times 10^{-3}$ s^{-1} for the first-order rate coefficient at pH 3·50 and 25·7° with 99% confidence. These limits correspond to ±3·3% of the absolute value and are close to the outside limits of the data. The correction due to the concomitant noncatalysed hydrolysis, $1{\cdot}1 \times 10^{-6}$ s^{-1}, is negligible.[12] The second-order rate coefficient for the acid-catalysed reaction at 25·7° is therefore $7{\cdot}35 \pm 0{\cdot}24$ l mol^{-1} s^{-1}. (Previously, without close pH control, the value 6·8 l mol^{-1} s^{-1} was obtained as the mean of several runs at 25·0° for solutions with different pH in the range 3—6.[12])

The expected deviation in rate due to an unavoidable error of, say, ±0·004—0·008 of a pH unit is ±1—2%, even with strict buffering. Under much more accurately reproducible conditions in other pH ranges, the degree of reproducibility of the dilatometric method and its results has been shown to be ±1—2% for reaction half-lives in the range 15—60 min (rising to ±5% for half-lives of a day or so).[1,25] Therefore, in our experiments here, we should expect a degree of reproducibility in the range ±2—4%, which we appear in fact to have achieved.

A drift of 0·1 of a pH unit could lead to an error of up to *ca.* 30% in the reaction rate. When the first four results in Table 2 (obtained without buffer) are corrected to pH 3·50 from the observed initial pH values, they indicate the range $2{\cdot}03 \times 10^{-3} \pm 0{\cdot}11 \times 10^{-3}$ s^{-1} for the first-order rate coefficient, with outside limits ±5%. The mean value here is *ca.* 13% lower than that determined above. The results are far worse if the correction is made from pH values which have drifted away from the initial values.

When 0·1M-pyrazine is added to the buffered reaction mixture, as a test of the effect of an interfering nucleophile on the dilatometry, the apparent rate is 30% too low in spite of apparently effective buffering by tetramethylpyrazine.

[1/2458 *Received, 22nd December,* 1971]

---

* We should note that no acid-catalysed reaction has been observed in the case of amines with p*K* values in the range 6—12 because these amines are in the form of their positive aminium ions in the acid pH range.[14]

[22] A. M. Eastham and G. A. Latremouille, *Canad. J. Chem.*, 1952, **30**, 170.
[23] P. L. Nichols, jun., and J. D. Ingham, *J. Amer. Chem. Soc.*, 1955, **77**, 6547.
[24] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[25] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4162.