1040. *A Comparison of the Nucleophilic Reactivity of Ethoxide, Methoxide, and Hydroxide Ions in Dioxan.*

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By an extrapolation procedure, the rates of the S_N2 reactions of sodium ethoxide, sodium methoxide, and sodium hydroxide with methyl iodide have been determined in 100% dioxan. The results show that the rates differ less in dioxan than they do in ethanol, methanol, and water, respectively. The results are compared with those of other workers who used a different solvent and substrate. Literature values for the rates of bimolecular substitutions of these reagents in their corresponding solvents are quoted and the reactivity of the hydroxide ion is discussed.

ALTHOUGH ethoxides, methoxides, and hydroxides are among the most widely used nucleophilic reagents, few comparisons of their nucleophilic reactivity under identical conditions have been reported. This is undoubtedly due partly to their strongly basic properties and partly to the virtual insolubility of the salts in aprotic solvents.

The first consideration precludes the use of simple kinetic measurements in hydroxylic solvents as a method of comparison, for proton transfer of the type $ROH + R'O^- \rightleftharpoons RO^- + R'OH$ would partly convert the added alkoxide or hydroxide into the conjugate base of the solvent.[1,2] A comparison of the rates of reaction of RO^- and $R'O^-$ then requires a knowledge of the equilibrium concentration ratio of the two nucleophilic reagents and of the proportions of products arising from their attack on a common substrate. A study of this general type has been made by Bender and Glasson[3] using (*a*) acetyl-L-phenylalanine methyl ester in alkaline methanol–water and (*b*) the ethyl ester in alkaline ethanol–water. By extrapolation of both series of results to 100% water, the relative rates were found to be 1 : 1·59 : 4·17 for hydroxide, methoxide, and ethoxide, respectively, the change of substrate from a methyl to an ethyl ester of the same acid being assumed to have no effect on the relative rates of hydrolysis.

TABLE 1.

Second-order rate constants (in l. mole^{-1} sec.$^{-1}$) for S_N2 reactions of methyl iodide in various solvents.

MeI = *ca.* 0·01M; NaOR, NaOH = *ca.* 0·02M, throughout.

Reagent	" Volume % " dioxan in solvent	60	70	80	100
NaOEt	Remainder	EtOH	EtOH	EtOH	—
	10^3k_2 at 35·2°	6·33	7·00	7·85	9·4[a]
NaOMe	Remainder	MeOH	MeOH	MeOH	—
	10^3k_2 at 35·2°	3·93	4·45	4·99	6·0[a]
NaOH	Remainder	H_2O	H_2O	H_2O	—
	10^3k_2 at 70·0°	12·5	13·3	13·9	15[a]
NaOH	Remainder	H_2O	H_2O	H_2O	—
	10^3k_2 at 51·2°	3·97	4·25	4·70	5·4[a]
NaOH	Remainder	H_2O	H_2O	H_2O	—
	10^3k_2 at 35·2°	1·34[b]	1·45[b]	1·69[b]	2·0[c]

[a] Value obtained by linear extrapolation of the (almost linear) plot of k_2 against the " volume % " of dioxan in the solvent. The extrapolated values are substantially unaltered if log k_2 is plotted against " volume % " of dioxan. [b] Value obtained by extrapolation assuming the Arrhenius equation $k_2 = A \exp(-E/\boldsymbol{R}T)$: energies of activation for sodium hydroxide in 60, 70, 80, and 100% dioxan are, respectively, 13·4, 13·4, 12·7, and 12 kcal. mole^{-1}. [c] The same value $2·0 \times 10^{-3}$ is obtained either by extrapolation of results in the last row or of the third and fourth results in the final column.

The second consideration rules out hydrocarbons and ethers as reaction media, and

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[1] (a) England, *Chem. and Ind.*, 1954, 1145; (b) Burns and England, *Tetrahedron Letters*, 1960, 24, 1.

[2] Baker and Neale, *J.*, 1954, 3225.

[3] Bender and Glasson, *J. Amer. Chem. Soc.*, 1959, **81**, 1590.

intermediate types of solvent such as ketones and esters will obviously be unsuitable with such alkaline reagents.

To overcome this problem we have employed a series of solvents consisting largely of dioxan (the remainder being ethanol, methanol, or water) to dissolve low concentrations of sodium ethoxide, methoxide, or hydroxide and have measured the rates of the S_N2 reactions of methyl iodide with these bases. A short extrapolation of the observed rates to 100% dioxan then gives a comparison of the nucleophilic reactivities in the same solvent. Methyl iodide was chosen as substrate because data on the nucleophilic power of reagents in the S_N2 reactions of aliphatic halides, as opposed to the bimolecular nucleophilic substitution of suitably activated aromatic halides,[4, 5] are somewhat scanty. Also, with methyl iodide, complications due to the simultaneous occurrence of S_N1 reactions or eliminations are most unlikely. Results are assembled in Table 1.

EXPERIMENTAL

Reagents and Solutions.—Methyl iodide was distilled and stored over silver wire in the dark. Standard solutions were prepared by weighing the iodide. "AnalaR" ethanol and methanol and distilled water free from carbon dioxide were used to make up the solvents. The alkoxide solutions were prepared by adding pieces of clean sodium to the appropriate solvents containing dioxan and methanol or ethanol. With aqueous solvents, "AnalaR" sodium hydroxide was added after being washed to remove carbonate from the surface of the pellets. Alkaline solutions were standardised by titration in a nitrogen atmosphere, Bromothymol Blue being used. Considerable difficulty was experienced with the purification of dioxan when used with sodium hydroxide (see below).

Mixed solvents. The term " 60 volume % " of dioxan indicates that $6x$ volumes of dioxan were mixed with $4x$ volumes of ethanol, methanol, or water at 20°.

Kinetic Measurements.—Aliquot parts of reaction mixtures were added to dilute nitric acid, and iodide ion was titrated potentiometrically with 0·01N-silver nitrate. The runs in dioxan–methanol and dioxan–ethanol were carried out in glass vessels at 35·2°, about 15 aliquot parts being analysed in each run. In all cases at least 75% of the reaction was followed. Individual constants showed a maximum deviation of 4% from the mean and duplicate runs were reproducible to within 1%. In 80% dioxan–20% methanol as solvent, sodium iodide crystallised during the reaction and the sealed-tube technique was adopted in this case. Solubility difficulties prevented use of solvents containing 90% of dioxan.

When 60% dioxan–40% water was used as solvent for reactions with sodium hydroxide, the following observations were made: (*a*) With methyl iodide alone in the solvent at 80° in glass vessels, the first-order constant for the solvolysis of methyl iodide showed a continuous downward drift and an average value of about 2×10^{-5} sec.$^{-1}$. (*b*) When sodium hydroxide was used alone under the conditions in (*a*), there was a continuous fall in titre. (*c*) When the solvent contained methyl iodide (*ca.* 0·01M) and sodium hydroxide (*ca.* 0·02M) at 51·2° in glass vessels, the second-order constant showed a continuous downward drift.

These results were probably due to a combination of attack of reagents, particularly hydroxide ion, on the glass and on the dioxan. Similar difficulties have been noted by other workers.[4, 6, 7] The "AnalaR" dioxan was purified by Vogel's method and stored under nitrogen, and the reactions were carried out in Polythene bottles at 70° and 51·2° because of the low velocity at 35·2°. Under these conditions, good second-order constants were obtained showing a maximum and random deviation of about 6% from the mean for at least 60% of the reaction. The mean value was reproducible to within 1·5%. Polythene disintegrates after a few days in a thermostat bath at 60° with a surface layer of paraffin to prevent evaporation. Rates at 35·2° were obtained by extrapolation (Table 1).

Interference from Solvolysis of Methyl Iodide in Aqueous Media.—The kinetics of hydrolysis of methyl iodide in pure water, with and without added hydroxide, have been extensively

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[4] Bunnett and Davis, *J. Amer. Chem. Soc.*, 1954, **76**, 3011; 1958, **80**, 4337.

[5] Bevan and Hirst, *J.*, 1956, 254.

[6] Fairclough and Hinshelwood, *J.*, 1937, 538.

[7] Foster and Hammett, *J. Amer. Chem. Soc.*, 1946, **68**, 1736; Beste and Hammett, *J. Amer. Chem. Soc.*, 1940, **62**, 2481.

studied by Moelwyn-Hughes.[8] The solvolytic reaction occurring concurrently when hydroxide is added should cause a slight upward drift of the observed second-order constants. In dioxan–water, interference by water solvolysis should be less serious for the following reasons: (*a*) the water concentration is reduced; (*b*) the rate of the solvolytic reaction (between two uncharged reagents) should, according to Hughes and Ingold's theory of solvent action,[9] decrease as more dioxan is added; and (*c*) for the same reason the rate of substitution by hydroxide ion should increase.

At 70°, the specific rate ratio, k_2/k_1, for substitution by hydroxide ion and for solvolysis in pure water is about 300, whereas from our results, the same ratio in 60% dioxan–40% water is about 1700. However, the relative proportions of these reactions depend also on the concentration of sodium hydroxide, an increased proportion of solvolysis occurring at lower concentrations. We have calculated that the percentage of solvolysis occurring under our conditions was never more than 3%, and no corrections for this effect were made.

DISCUSSION

The results in Table 1 give the relative rates 1 : 3·0 : 4·7 for hydroxide, methoxide, and ethoxide, respectively, reacting with methyl iodide in dioxan at 35·2° C. With mixed solvents the rate is increased slightly in all cases by increasing the proportion of dioxan in the mixture, an observation which is in agreement with the predictions of Hughes and Ingold's theory of solvent action. It is noteworthy, however, that a qualitatively opposite result was obtained for the reaction of allyl chloride with potassium hydroxide (*ca.* 0·17M) in 40% and 60% aqueous dioxan at 64·9° (where the rate is twice as fast in the more aqueous solvent) by Vernon [10] who attributed the anomaly to the greater polarity of the transition state in S_N2 substitutions of allyl halides.

From rates and Arrhenius parameters quoted by Moelwyn-Hughes,[8,11] the rates of reaction of methyl iodide with hydroxide in water, methoxide in methanol, and ethoxide in ethanol are found to be $2{\cdot}15 \times 10^{-4}$, $9{\cdot}08 \times 10^{-4}$, and $3{\cdot}14 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$, respectively (ratio 1 : 4·22 : 14·6) at 35·2°. These are all less than the values in Table 1 for 60% dioxan–40%-water, -methanol, or -ethanol, and it seems likely that the rate of the reaction of each of these anions with methyl iodide shows a continuous increase as the solvent is changed from pure water, methanol, or ethanol to pure dioxan. However, the rate changes by different factors over the complete range of solvent variation in the three cases: 9·3 for the change of water, 6·6 for the change of methanol, and 3·0 for the change of ethanol to pure dioxan in each case. Again this is qualitatively the expected result if the polarity order is water > methanol > ethanol.

In Table 2 a critical selection of literature data on the relative rates of attack of ethoxide and methoxide ions, dissolved in their parent solvents, on various halides is assembled. Data for the attack of hydroxide ion in water on halides are meagre because of solubility difficulties and are not included. The rate ratio is always greater than in dioxan, as expected, and seems very roughly constant over a wide range of halides. Insofar as there are differences between halides these seem to bear no systematic relation to their structure.

There is surprisingly close agreement between the values obtained by us (1 : 3·0 : 4·7) for the relative reactivity of hydroxide, methoxide, and ethoxide and those of Bender and Glasson [3] (1 : 1·59 : 4·17), for the two sets of results refer to different substrates and, especially, to different solvents, dioxan and water, which are at opposite ends of the polarity scale. Nevertheless it would be unwise, in our opinion, to infer that the nucleophilic reactivity of hydroxide ion is never less than that of methoxide by a factor of more than three or of ethoxide by more than five. There is good evidence [4] for the low reactivity of hydroxide in its reaction with 1-chloro-2,4-dinitrobenzene in dioxan–water and we have

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[8] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1949, *A*, **196**, 540; 1953, *A*, **220**, 386.

[9] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell, Ithaca, N.Y., 1953, p. 347.

[10] Vernon, *J.*, 1954, 4462.

[11] Moelwyn-Hughes, " Physical Chemistry," Pergamon, London, 1957, p. 1208.

TABLE 2.

Rates of reaction of halides with ethoxide in ethanol and methoxide in methanol. Rate constants (in l. mole^{-1} sec.$^{-1}$) have been calculated at 25° C from Arrhenius parameters wherever possible.

	Ethoxide in ethanol			Methoxide in methanol			Rate
Halide	t (° C)	k_2	Ref.	t (° C)	k_2	Ref.	factor
Methyl iodide	25	$1{\cdot}10 \times 10^{-3}$	11	25	$2{\cdot}55 \times 10^{-4}$	11	4·32
Methyl bromide	25	$1{\cdot}57 \times 10^{-3}$	12	25	$2{\cdot}86 \times 10^{-4}$	11	5·49
Ethyl iodide	70·2	$1{\cdot}51 \times 10^{-2}$	13	70·2	$6{\cdot}83 \times 10^{-3}$	1(a)	2·22
o-Fluoronitrobenzene	25	$9{\cdot}2 \times 10^{-4}$	14	25	$1{\cdot}16 \times 10^{-4}$	15	7·93
p-Fluoronitrobenzene	25	$8{\cdot}13 \times 10^{-4}$	16	25	$2{\cdot}14 \times 10^{-4}$	16	3·80
o-Chloronitrobenzene	25	$7{\cdot}5 \times 10^{-7}$	17	25	$1{\cdot}2 \times 10^{-7}$	18	6·25
p-Chloronitrobenzene	25	$1{\cdot}84 \times 10^{-6}$	19	25	$4{\cdot}0 \times 10^{-7}$	18	4·60
1-Chloro-2,4-dinitrobenzene	25	$8{\cdot}08 \times 10^{-2}$	16	25	$2{\cdot}6 \times 10^{-2}$	16	3·11
1-Fluoro-2,4-dinitrobenzene	0	8·97	16	0	1·85	16	4·85
1-Chloro-2,6-dinitrobenzene	50	$1{\cdot}47 \times 10^{-2}$	20	50	$7{\cdot}37 \times 10^{-3}$	18	2·00

evidence [21] for a rate ratio of about 20 in the reaction of hydroxide and methoxide with the same aromatic halide in methanol–water. The nucleophilic reactivity of hydroxide in water towards ethylene oxide [22] is also exceptionally small.

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[13] Fraser, M.Sc. Thesis, Wellington, N.Z., 1956.

[14] Bevan, *J.*, 1953, 655.

[15] Rouche, *Bull. Sci. Acad. roy. Belg.*, 1921, 534; " Tables of Chemical Kinetics," 1954 Suppl., National Bureau of Standards, Washington, D.C., p. 243.

[16] Burns, M.Sc. Thesis, Wellington, N.Z., 1960.

[17] Riklis, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1511.

[18] Miller and Williams, *J.*, 1953, 1475.

[19] Bevan, *J.*, 1951, 2340.

[20] Bevan, Hughes, and Ingold, *Nature*, 1953, **171**, 301.

[21] Alet, M.Sc. Thesis, Wellington, N.Z., 1958.

[22] Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, p. 302.