Solvent Effects and Brønsted Coefficients in Nucleophilic Substitutions at Tetraco-ordinate Sulphur

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The rate of reaction of benzenesulphonyl chloride with pyridines or primary amines has been measured in a series of solvent mixtures. The kinetic data have been plotted in a Brønsted fashion against the pK_a of the conjugate acid of the nucleophile. A large effect of the solvent composition on the Brønsted slope was observed. For primary amines the slope changes from 0·38 in pure water to 0·53 in 45% dioxan–water at 25 °C. For pyridines, in the same solvent mixtures, the slopes are 0·43 and 0·79 respectively at 0 °C. Acetonitrile–water mixtures have also been investigated. Such changes are discussed, as usual, in terms of different degree of bond formation in the transition state. However, the difficulties of this unique interpretation are also pointed out.

THE value of the extended Brønsted coefficient has been related to the bond order in the transition state of nucleophilic substitutions.[1,2] The correlation is quantitative but empirical. A relatively precise correlation between bond order and Brønsted coefficient has been suggested only for acyl transfer reactions where the value of 1·7 could be put forward corresponding to complete bond formation.[3] In general, values ranging from 0·6 to 1·5 have been considered as an indication of large bond formation [1,3–5] while values from zero to *ca.* 0·3 have been related to little bond formation.[6,7] Intermediate values have also been reported and given a mechanistic significance.[7–9] Small differences between Brønsted coefficients are not considered to be significant [7] especially when different reactions or different classes of nucleophile are being compared. Sometimes, be it for experimental difficulties [4a] or other reasons,[6c] the Brønsted coefficients are calculated with the reaction rates measured in a medium and the pK_a values measured in water where they are more readily available.[10] This is a further limit to the interpretation of Brønsted coefficients.[10,11] However, when the reaction characteristics and the experimental conditions are similar, larger confidence is given to the comparison of Brønsted coefficients.

While studying the effect of the nucleophile on the leaving group mobility for reactions at tetraco-ordinate sulphur [12] we ran preliminary experiments to check the influence of the solvent on the rate of reaction. We realised that the Brønsted coefficient might be solvent-dependent. Further experimentation, herein reported, showed in effect that Brønsted values are largely influenced by relatively small solvent changes.

RESULTS

The effect of the solvent composition on the rate of reaction and on the Brønsted coefficients was measured in a series of solvent media for the reaction of benzenesulphonyl chloride with substituted pyridines [8] or primary amines.[12] The rate data in Table 1 are the averages from 3—7 runs of different amine and/or substrate concentration. In each case the order of reaction is unity in substrate and nucleophile. The pH of the reaction mixture was determined for each run with a glass electrode and was constant, within experimental error, throughout the reaction. The neutral hydrolysis was in all cases much slower than the measured reaction and therefore did not disturb the kinetics. The alkaline hydrolysis was also negligible under all experimental conditions. The kinetic runs were always linear up to 90% reaction.

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Table 2 is a summary of pK_a values, activation parameters, and nucleophilic Brønsted coefficients (β). The reported pK_a values were measured at the same temperature at which the Brønsted coefficients were calculated. The maximum error in the Brønsted slopes is estimated to be ±0·015.

For a Brønsted relationship to remain valid and with the *same slope* on changing solvent composition, the hypothesis must be verified that a given solvent change affects all nucleophiles identically (in free-energy terms). As far as the pyridine-catalysed hydrolysis is concerned, this hypothesis is not verified since the three studied nucleophiles define quite different slopes with changing solvent composition. Since the linearity of the Brønsted relationship for

Table 1

Velocity constants for the reaction of benzenesulphonyl chloride with various nucleophiles in a number of solvent media [a, b]

Nucleophile	T/°C	Co-solvent	Water (mol fraction)	$\frac{k_2}{\text{l mol}^{-1}\text{ s}^{-1}}$
4-Methylpyridine	0·0		1·000	0·84, 0·849 [c]
4-Methylpyridine	0·0	MeCN	0·980	0·89
4-Methylpyridine	0·0	MeCN	0·953	1·19
4-Methylpyridine	0·0	MeCN	0·856	0·79
4-Methylpyridine	0·0	MeCN	0·693	0·38
4-Methylpyridine	0·0	MeCN	0·202	0·23
4-Methylpyridine	0·0	Dioxan	0·980	0·96
4-Methylpyridine	0·0	Dioxan	0·965	1·31
4-Methylpyridine	0·0	Dioxan	0·856	0·74
4-Methylpyridine	0·0	EtOH	0·941	0·87
4-Methylpyridine	0·0	EtOH	0·963	0·22
4-Methylpyridine	15·7		1·000	3·11
4-Methylpyridine	15·7	MeCN	0·953	3·65
4-Methylpyridine	15·7	MeCN	0·693	0·89
4-Methylpyridine	15·7	MeCN	0·202	0·48
4-Methylpyridine	30·0		1·000	8·90 [c]
4-Methylpyridine	30·0	MeCN	0·953	9·60
4-Methylpyridine	30·0	MeCN	0·693	1·78
4-Methylpyridine	30·0	MeCN	0·202	0·83
4-Methylpyridine	25·0	Dioxan	0·856	2·35
Pyridine	0·0		1·000	0·41, 0·442 [c]
Pyridine	0·0	MeCN	0·953	0·65
Pyridine	0·0	MeCN	0·693	0·13
Pyridine	0·0	MeCN	0·202	0·065
Pyridine	0·0	Dioxan	0·856	0·22
Pyridine	15·7		1·000	1·61 [c]
Pyridine	15·7	MeCN	0·953	1·90
Pyridine	15·7	MeCN	0·693	0·32
Pyridine	15·7	MeCN	0·202	0·14
Pyridine	30·0		1·000	4·62
Pyridine	30·0	MeCN	0·953	4·20
Pyridine	30·0	MeCN	0·693	0·72
Pyridine	30·0	MeCN	0·202	0·23
Pyridine	25·0	Dioxan	0·856	0·90
Ethyl pyridine-3-carboxylate	0·0		1·000	0·047, 0·051 [c]
Ethyl pyridine-3-carboxylate	0·0	MeCN	0·953	0·050
Ethyl pyridine-3-carboxylate	0·0	MeCN	0·693	0·0061
Ethyl pyridine-3-carboxylate	0·0	MeCN	0·202	0·0017
Ethyl pyridine-3-carboxylate	0·0	Dioxan	0·856	0·0084
Ethyl pyridine-3-carboxylate	15·7		1·000	0·19 [c]
Ethyl pyridine-3-carboxylate	15·7	MeCN	0·953	0·16
Ethyl pyridine-3-carboxylate	15·7	MeCN	0·693	0·020
Ethyl pyridine-3-carboxylate	15·7	MeCN	0·202	0·0042
Ethyl pyridine-3-carboxylate	30·0		1·000	0·564, [c] 0·607 [d]
Ethyl pyridine-3-carboxylate	30·0	MeCN	0·953	0·40
Ethyl pyridine-3-carboxylate	30·0	MeCN	0·693	0·052
Ethyl pyridine-3-carboxylate	30·0	MeCN	0·202	0·0096
Ethyl pyridine-3-carboxylate	25·0	Dioxan	0·856	0·035
n-Butylamine	25·0		1·000	74
n-Butylamine	25·0	MeCN	0·953	85
n-Butylamine	25·0	MeCN	0·693	43
n-Butylamine	25·0	MeCN	0·202	60
n-Butylamine	25·0	MeCN	0·000	154
n-Butylamine	25·0	Dioxan	0·856	82
n-Butylamine	25·0	MeOH	0·000	4·2
Glycine ethyl ester	25·0		1·000	6·4
Glycine ethyl ester	25·0	MeCN	0·693	1·8
Glycine ethyl ester	25·0	MeCN	0·202	1·2
Glycine ethyl ester	25·0	Dioxan	0·856	3·9

[a] Pyridines as nucleophiles; substrate concn., 2×10^{-4}—10^{-3}M; nucleophile concn., 2×10^{-3}—$3{\cdot}6 \times 10^{-1}$M. [b] Primary amines as nucleophiles; substrate concn., 5×10^{-5}—10^{-4}M; nucleophile concn., 10^{-2}—10^{-1}M. [c] Calculated with the activation parameters reported by Rogne.[8] [d] Measured by Rogne.[8]

Table 2

Summary of pK_a values, activation parameters, and Brønsted coefficients in various solvent media

Nucleophile	pK_a [a]	$\Delta H^{\ddagger}$ [b,c]	$-\Delta S^{\ddagger}$ [b,d]	β [a]
Water (x = 1·000)				
4-Methylpyridine	6·40	12·2 [e]	14·0 [e]	0·43
Pyridine	5·54	12·2 [e]	15·3 [e]	
Ethyl pyridine-3-carboxylate	3·45	12·7 [e]	17·8 [e]	
n-Butylamine	10·68 [f]			0·38
Glycine ethyl ester	7·90 [g]			
MeCN–water (x = 0·953)				
4-Methylpyridine	5·93	10·9	18·0	0·49
Pyridine	5·18	9·8	23·5	
Ethyl pyridine-3-carboxylate	3·05	10·7	25·3	
n-Butylamine	10·59			
MeCN–water (x = 0·693)				
4-Methylpyridine	5·14	7·9	31·3	0·63
Pyridine	4·28	8·8	30·1	
Ethyl pyridine-3-carboxylate	2·24	11·3	27·1	
n-Butylamine	10·07			0·48
Glycine ethyl ester	7·22			
MeCN–water (x = 0·202)				
4-Methylpyridine	4·23	6·4	37·7	0·70
Pyridine	3·43	6·4	40·2	
Ethyl pyridine-3-carboxylate	1·17	8·8	38·9	
n-Butylamine	9·46			0·64
Glycine ethyl ester	6·79			
Dioxan–water (x = 0·856)				
4-Methylpyridine	5·04	6·88	33·7	0·79
Pyridine	4·35	8·46	30·3	
Ethyl pyridine-3-carboxylate	2·57	8·71	35·9	
n-Butylamine	10·15 [h]			0·53
Glycine ethyl ester	7·65 [h]			

[a] At 0 °C for pyridines; at 25 °C for primary amines. [b] At 25 °C. [c] Maximum error, 0·4 kcal mol^{-1}. [d] Maximum error, 1·4 cal mol^{-1} K^{-1}. [e] From ref. 8. [f] From ref. 14. [g] From ref. 3. [h] From ref. 4*b*.

this reaction has been established in water[8] as well as in methanol[10] we assume that it holds in aqueous mixed solvents as well. As far as primary amines are concerned, the data show that a solvent change affects the nucleophilic displacement reaction in a manner similar to that of the pyridine-catalysed hydrolysis thus supporting the analogy of the two reactions.[12] The Brønsted coefficients in Table 2 derived from only two amines cannot imply a linear relationship even though this assumption is reasonable.

The rate data are accurate to within 3% of the reported value. Thus the maximum error[13] in the activation parameters is *ca.* 0·4 kcal mol^{-1} for the enthalpy of activation and *ca.* 1·4 cal mol^{-1} K^{-1} for the entropy of activation.

DISCUSSION

The reaction mechanism both for the hydrolysis catalysed by substituted pyridines[8] and for the nucleophilic substitution by primary amines[12] of benzenesulphonyl chloride has been discussed.[12] In each case the first and slow step of the reaction is a nucleophilic displacement on sulphur yielding an unstable sulphonylammonium intermediate which can in a following fast step either lose a proton to give the corresponding sulphonamide (with primary or secondary amines) or be hydrolysed by water (with tertiary amines).

A plot of the rate of reaction against the solvent composition reaches a maximum at *ca.* 0·95 mol fraction of water for all nucleophiles and co-solvents at the lowest temperatures investigated. Only the reaction with n-butylamine shows an additional feature. At high co-solvent composition the rate again increases. Thus, a plot of the rate against solvent composition shows both a maximum and a minimum. (In no case is the number of points sufficient to determine the exact solvent composition of the maxima or minima since this at the present is beyond our scope.) A maximum in rate at changing water concentration has been found by Foon and Hambly for the neutral hydrolysis of aliphatic sulphonyl chlorides in water–dioxan mixtures at temperatures close to 0 °C.[15] The similarity between the neutral hydrolysis and the hydrolysis catalysed by pyridines is shown also by the activation parameters which in both cases decrease with decreasing water content of the solvent. Moreover, in both cases very low entropies of activation have been measured.

The rate maximum was attributed[15] to a break-up of the water structure by the added co-solvent. Such explanation is likely to be true since the maximum is detectable only at the lowest temperatures (Table 1), where water presents a more organised solvent structure. Foon and Hambly, however, considered this fact a consequence of the greater availability of water for nucleophilic attack. Therefore in their opinion the rate change resulted from a change in the concentration of free nucleophile. On the other hand in our system water does not enter the rate equation and therefore its influence must be related to solvation factors. Owing to the similarity of behaviour, we can assume that also in the neutral hydrolysis the maximum in rate is due to solvation factors even though in the latter case the effect of water as solvent cannot be easily discerned from its effect as nucleophile (the order of reaction in water is greater than two for most sulphonyl derivatives and gradually increases as the water content increases).[15a]

Even though the polarity of the solvent medium is certainly important for the reaction of sulphonyl chlorides with neutral reagents since the reaction involves charge separation,[16] the experimental evidence shows that the dielectric constant or the polarity of the medium are insufficient to explain the data. In pure ethanol, a protic solvent like water, the reaction of benzenesulphonyl chloride with n-butylamine is in effect slower than in water (in accord with the smaller dielectric constant of ethanol); however, in acetonitrile, a polar aprotic solvent, the reaction is faster than in water, its smaller dielectric constant notwithstanding. Moreover, no meaningful relationship can be found when the rate of reaction is reported against the dielectric constant or the polarity (*Y*- or *Z*-values)[17] of the various solvent mixtures. Clearly the data can be explained only by specific solvation models[18,19] where the specific solvation by water prevails or obscures the polarity of the solvent medium.

An interesting feature emerging from the data presented here is the solvent effect on the nucleophilic Brønsted coefficient. Even though it is generally recognized that solvent effects influence reaction rates and equilibrium constants or in general any 'extra-thermodynamic' relationship,[11] there is no specific study of solvent effects on the nucleophilic Brønsted coefficient. Matsui and Tokura recently reported modified Brønsted plots (log *k* against carbon basicities) in different solvents (acetone, nitrobenzene, and tetrahydrofuran) for the quaternization of dimethylanilines with methyl iodide.[20] It seems to us that in general there is a tendency to believe that limited variations in the solvent nature do not effect the nucleophilic Brønsted coefficient or at least that the differences are so small as to be without any mechanistic significance. Limited variations in Brønsted coefficient in fact have never been discussed, owing to the well known inherent limitations and dangers of such relationships in mechanistic interpretations.[7,10] A trend is usually recognized: that in an aprotic solvent the slope should be larger than in a protic solvent. This is in fact what we find on changing the solvent composition. However, the vari-

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ation of β with the solvent are large relatively to apparently small variations in the solvent nature. For the hydrolysis of benzenesulphonyl chloride catalysed by pyridines at 0 °C, the Brønsted coefficient changes from 0·43 in pure water to 0·79 in 45% dioxan–water (corresponding to 0·86 mol fraction of water). The value of 0·45 was measured by Rogne in pure water at 25 °C and given a mechanistic significance: 'sulphur, being highly polarizable, would be able to form bonds at a larger distance than carbonyl carbon, where 0·8 is generally found'.[8] Since polarizability (a gas-phase property) cannot change with changing solvent composition such a comment is unwarranted.

It must be noticed that a change in Brønsted coefficient is found not only for the hydrolysis catalysed by pyridines but also for the direct displacement with primary amines. Thus, such changes cannot be attributed to the particular type and/or pK_a range of the amines used as nucleophiles but to the substrate. Therefore, from consideration of the largest (0·79) and the smallest (0·38) value of Table 2, it appears that benzenesulphonyl chloride presents different degrees of bond formation according to the solvent and nucleophile. Further experimentation will show whether the same trend is found with other neutral or charged nucleophiles.

At this point we must ask ourselves whether the measured Brønsted coefficients really reflect different extents of bond formation. The linearity of the Brønsted plot[8] for the hydrolysis of benzenesulphonyl chloride catalysed by pyridines suggests that base dissociation is a good model process for the reaction. Basicity was considered to be an increasingly potent factor as the positive charge on the electrophilic centre increased. Tetrahedral suphur is an example of an electrophilic centre which is positively charged in transition states.[21] However, one might be justified in thinking that the model is incomplete when one considers that apparently minor solvent modifications which should not influence the transition-state structure are responsible for large changes in Brønsted coefficient. In effect, if one plots the Brønsted coefficients against the water mol fraction for water–acetonitrile mixtures, one can see that the largest variations occur at the smallest co-solvent concentrations. In addition, Table 2 shows that the relative pK_a values (ΔpK_a) are almost constant in all solvent mixtures. Therefore the changes in Brønsted coefficient are due only to changes in $\Delta \log k$ (relative rates of reaction). In fact the best model process would be that corresponding to the equilibria between the same series of nucleophiles and a tetraco-ordinate sulphur compound. It is likely that solvation factors influence in a different manner sulphur and hydrogen basicities. Unfortunately sulphur basicities for tetraco-ordinate sulphur are not yet known. (A few data relative to dico-ordinate sulphur are available in other solvent media.[22]) On the other hand, provision being made for the well known limitation,[1,11,23] a large number of examples seems to point to the validity of the Brønsted coefficient. Therefore for the time being we must still consider the change in bond order at changing solvent composition as a possible explanation of the Brønsted coefficients reported in Table 2.

This interpretation is in contrast with the assumption that transition-state configurations remain unchanged in the studied range of water-rich solvents.[6,19] On this assumption are based the specific solvation models of Hudson and Loveday[18] and Hyne.[19] In solvolytic (S_N1) reactions,[19] where the bond to the leaving group is completely or almost completely broken, it might be assumed that the bond distance is not modified by the solvent. The Brønsted coefficient should always be close to zero in all water-rich solvents. For S_N2 reactions, for particular substrates which are conceivably strongly solvated by water both in the ground and transition states, as might be the case of sulphonyl derivatives whose electrophilic atom bears a double positive charge, it is not unreasonable that solvation factors change the degree of bond formation. If this is so, the same behaviour should be found for substrates such as some derivatives of P^V and S^{IV}.

Very little is known about solvent structure, especially in mixed solvents, and about specific solvent interactions. Therefore we consider that the most important result emerging from our data is that large variations in Brønsted coefficients are possible for relatively small[19] modifications in the solvent nature. The next step is to find out if this behaviour is general or is linked to specific substrate characteristics.

EXPERIMENTAL

Materials.—Reagent grade acetonitrile was refluxed over anhydrous potassium carbonate and fractionated. Commercial benzenesulphonyl chloride was fractionated under vacuum (b.p. 113—116°/10 mmHg). The preparation and/or purification of dioxan, water, and amines has been described.[4b]

Kinetics.—The reactions with pyridines were followed conductimetrically with a Metrohm E 101 apparatus equipped with a platinum conductivity cell. In a typical run 25 ml of the pyridine solution was placed in a jacketted reaction vessel. To start the reaction a solution (0·05 ml) of the substrate at the appropriate concentration in acetonitrile (or dioxan) was injected into the reaction vessel with stirring.

The reactions with primary amines were followed at *ca.* 240 nm either with a Durrum stopped-flow apparatus for the fastest reactions or with an Unicam SP 800 recording spectrophotometer. The ethyl ester of glycine was generated *in situ*.[4b]

pH and pK_a *Determinations.*—The pK_a values were determined by potentiometric technique *via* a half-neutralization procedure. When necessary the end point for the weakest amines was determined by conductimetric measurements run in parallel. pH measurements were performed with a Metrohm Herisau pH meter equipped with an XL

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glass electrode. While the linearity of the response of the glass electrode has been demonstrated for water–dioxan solvent mixtures,[24] we have assumed a similar linearity for water–acetonitrile mixtures.

Owing to its high pK_a, a fraction of n-butylamine is always protonated. The reported concentrations of unprotonated n-butylamine were calculated from its pK_a in each solvent mixture and the pH measured for each amine concentration. Such values should be free from liquid-junction potential errors since such errors in measurements of pH and pK_a cancel each other.[25]

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