Rates, Activation Parameters, and Enthalpies of Transfer of Transition States for the Reaction of Imidazole with Aromatic Sulphonyl Chlorides in Methanol and Acetonitrile

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Rates of reaction of substituted benzenesulphonyl chlorides with imidazole have been measured in methanol and acetonitrile. The increase in rate on changing solvent from protic to dipolar aprotic is relatively small (*ca.* 35 times faster in acetonitrile at 25 °C). This is due to compensation of a substantial decrease in the enthalpy of activation in the dipolar aprotic solvent by a concomitant decrease in the entropy of activation. Substituent effects on the rate of reaction as measured by ρ are equal in the two solvents. The solvent effect on the enthalpy of activation has been separated into initial-state and transition state-effects by measurements of heats of solution of the reactants in the two solvents. The lower activation enthalpy in the aprotic solvent (*ca.* 7 kcal mol^{-1}) is thus found to be caused by a combination of an endothermic enthalpy of transfer of the nucleophile (*ca.* 3 kcal mol^{-1}) and an exothermic enthalpy of transfer of the transition state (*ca.* −4 kcal mol^{-1}) from the protic to the aprotic solvent.

As a continuation of our studies of nucleophilic substitution at tetraco-ordinate sulphur,[1,2] the effect on rates and activation parameters of a change from a protic to a dipolar aprotic solvent has been investigated for the reaction of imidazole with some aromatic sulphonyl chlorides. The two solvents, methanol and acetonitrile, were chosen because of their similar dielectric constants in order to focus, as much as possible, upon protic–dipolar aprotic solvent effects.

Since a protic–dipolar aprotic solvent change generally leads to large changes in activation parameters,[3] this is also expected in the present case. To separate solvent effects on $\Delta H^\ddagger$ into initial-state and transition-state effects, the heats of solution of the reactants have been measured in the two solvents. By combining differences in enthalpy of solution with differences in enthalpy of activation, the enthalpy of transfer of the transition state from one solvent to another can be calculated.[4] Since the enthalpy of transfer of the transition state depends upon its structure and electron distribution, one may obtain further information about the nature of the substitution reaction.

EXPERIMENTAL

Materials.—The sulphonyl chlorides were fractionally distilled at reduced pressure or recrystallized from light petroleum (b.p. 60—80 °C). Imidazole was recrystallized from benzene. Acetonitrile was purified as described by Coetzee [5] (specific conductance *ca.* 3×10^{-7} ohm^{-1} cm^{-1}). Methanol was dried with molecular sieves 3A and fractionally distilled (5×10^{-7} ohm^{-1} cm^{-1}). *N*-Phenylsulphonylimidazoles were prepared from imidazole and the corresponding acid chloride in tetrahydrofuran according to Staab.[6]

Rate Measurements.—Rates were measured conductometrically with a Radiometer conductivity meter CDM3 connected to a Sargent Recorder SRL and Radiometer conductivity cell PP 1042.

The reactions were started by adding the acid chloride in acetonitrile (0·010 ml) to a solution of imidazole in acetonitrile or methanol (25 ml). Final concentration of acid chloride was in the range 4×10^{-5}—4×10^{-4}M. The concentration of imidazole was in the range 1×10^{-3}—0·1M depending upon the acid chloride and solvent. Reactions were generally run to *ca.* 3—4 half-lives. The observed first-order rate constants were calculated from the resulting conductivity–time curve by Guggenheim's method.[7] Second-order rate constants were calculated from the slopes of plots of the observed first-order rate constant against the imidazole concentration. Rate constants are estimated to be accurate to ±5% or better. Activation parameters were calculated from a least-squares treatment of ln (k/T) against T^{-1}. The estimated accuracy is *ca.* ±0·5 kcal mol^{-1} in $\Delta H^\ddagger$ and *ca.* ±2 cal mol^{-1} K^{-1} in $\Delta S^\ddagger$.

Heats of Solution.—The calorimeter was similar to that described by Arnett *et al.*[4] except that during calibration the potential drop across the standard resistance (8·5Ω) was measured with an Orion digital pH–mV meter 801. The solvent volume was generally 230 ml. Final concentration of solute was in the range 3×10^{-3}—3×10^{-2}M. The calorimeter was tested by measuring the heat of solution of KCl in water. The average of nine determinations was 4·08 kcal mol^{-1} with a standard deviation of ±0·06, which is in reasonable agreement with the reference value of 4·115 kcal mol^{-1} referred to by Fuchs.[8] As a further check the heat of solution of pyridine in methanol was found to be −0·96 kcal mol^{-1} which is in good agreement with the published value −0·95 kcal mol^{-1}.[9]

Product Analysis.—Qualitative and quantitative product analysis were carried out for the reaction of benzene- and toluene-*p*-sulphonyl chloride by comparing the u.v. spectra of the final reaction mixture with the spectra of the corresponding *N*-phenylsulphonylimidazole in an identical solution. The final mixture for the other reactions showed similar spectra. Isolation of the products were done as follows; to imidazole (0·02 mol) in acetonitrile (30 ml) was

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[1] O. Rogne, *J.C.S. Perkin II*, 1972, 489.

[2] O. Rogne, *J. Chem. Soc.* (*B*), 1971, 1855.

[3] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

[4] E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, 1965, **87**, 1541.

[5] J. F. Coetzee, *Pure Appl. Chem.*, 1966, **13**, 427.

[6] H. A. Staab and K. Wendel, *Chem. Ber.*, 1960, **93**, 2902.

[7] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[8] R. F. Rodewald, K. Mahendran, J. L. Bear, and R. Fuchs, *J. Amer. Chem. Soc.*, 1968, **90**, 6698.

[9] P. Haberfield, A. Nudelman, A. Bloom, R. Romm, and H. Ginsberg, *J. Org. Chem.*, 1971, **36**, 1792.

added sulphonyl chloride (0·01 mol). When the reaction was complete imidazole hydrochloride was filtered off and acetonitrile evaporated under vacuum. The residue was dissolved in dry tetrahydrofuran, filtered, evaporated to dryness, and recrystallized from benzene–cyclohexane (1 : 3); m.p.s 83 and 78 °C for the reaction of benzene- and toluene-*p*-sulphonyl chloride respectively (lit.,[6] for *N*-phenylsulphonylimidazole 83—84 °C, for *N*-*p*-tolyl sulphonylimidazole 78—78·5 °C).

TABLE 1

Rate constants and activation parameters for the reaction of imidazole with sulphonyl chlorides, $XC_6H_4SO_2Cl$, in acetonitrile and methanol

		k/l mol^{-1} s^{-1}						$\Delta S^\ddagger$/
X	Solvent	5 °C	10 °C	15 °C	25 °C	30 °C	$\Delta H^\ddagger$/kcal mol^{-1}	cal mol^{-1} K^{-1}
p-NO_2	MeCN	22·6	27·2	31·3	41·1		4·3	−37
	MeOH	0·290	0·415		1·07	1·51	10·3	−24
m-NO_2	MeCN	10·8						
	MeOH	0·139						
p-Br	MeCN	2·96						
	MeOH	0·0420						
p-Cl	MeCN	2·53						
	MeOH	0·0355						
H	MeCN	1·65	1·88	2·36	3·20		5·0	−39
	MeOH	0·0187	0·0275		0·0883	0·129	12·3	−22
p-Me	MeCN	0·860	1·02	1·21	1·79		5·5	−39
	MeOH	0·0108	0·0168		0·0510	0·0740	12·2	−24
p-MeO	MeCN	0·282	0·364	0·461	0·660		6·6	−37
	MeOH	0·00410	0·00695		0·0225	0·0316	13·0	−22

TABLE 2

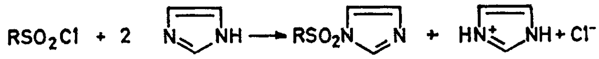
Heats of solution of sulphonyl chlorides and imidazole in methanol and acetonitrile at 25 °C

	ΔH_S(MeOH)/kcal mol^{-1}	ΔH_S(CH_3CN)/kcal mol^{-1}	$\delta\Delta H_S$ [a]/kcal mol^{-1}
Imidazole	1·76 ± 0·02 (7) [b]	4·79 ± 0·02 (6)	3·03
Benzenesulphonyl chloride	0·65 ± 0·01 (8)	0·67 ± 0·01 (10)	0·02
p-Nitrobenzenesulphonyl chloride	4·91 ± 0·05 (12)	4·25 ± 0·04 (9)	−0·66
Toluene-*p*-sulphonyl chloride	5·55 ± 0·05 (9)	5·54 ± 0·05 (8)	−0·01
p-Methoxybenzenesulphonyl chloride	5·74 ± 0·04 (13)	5·60 ± 0·04 (11)	−0·14

[a] $\delta\Delta H_s = \Delta H_s$(MeCN) − ΔH_s(MeOH). [b] Standard error of the mean and number of observations.

RESULTS

The reaction between sulphonyl chlorides and imidazole in organic solvents takes place according to equation (1).[6,10] This was confirmed as described for benzene- and


(1)

toluene-*p*-sulphonyl chloride. The other sulphonyl chlorides are assumed to react in the same way. This assumption is reasonable in view of the similar u.v. spectra of the final reaction mixture and the consistency of the rate data.

With imidazole in large excess over acid chloride, the observed rates of reaction were always of the first order. Plots of the observed first-order rate constants against concentration of imidazole were linear, showing that the reactions are of the first order in nucleophile. In a few cases a small upwards curvature was noticed in these plots at imidazole concentrations >0·1M. This was not investigated further but could indicate a third-order term in the rate law.

The rates of reaction of the sulphonyl chlorides with imidazole at 5 °C are well correlated by the Hammett equation. When the ordinary σ values,[11] except for *p*-MeO which as before is taken as −0·45,[12] are used, a least-squares correlation give ρ values, standard error, and correlation coefficients of 1·41 ± 0·07 (r 0·994) and 1·43 ± 0·08 (r 0·992) for methanol and acetonitrile respectively.

TABLE 3

Enthalpy of transfer of reactants, $\delta\Delta H_s^r$, and transition states, $\delta\Delta H^t$, and differences in enthalpy of activation, $\delta\Delta H^\ddagger$, for the reaction of imidazole with sulphonyl chlorides in methanol and acetonitrile

	$\delta\Delta H_s^r$/ kcal mol^{-1}	$\delta\Delta H^\ddagger$/ kcal mol^{-1}	$\delta\Delta H^t$/ kcal mol^{-1}
Imidazole + *p*-$NO_2C_6H_4SO_2Cl$	2·37	−6·0	−3·6
Imidazole + $C_6H_5SO_2Cl$	3·05	−7·3	−4·2
Imidazole + *p*-$MeC_6H_4SO_2Cl$	3·02	−6·7	−3·7
Imidazole + *p*-$MeOC_6H_4SO_2Cl$	2·89	−6·4	−3·5

The heats of solution in methanol and acetonitrile of imidazole and four of the sulphonyl chlorides were determined as described (Table 2). Although these values are

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[10] T. C. Bruice, 'Methods in Enzymology,' eds. S. P. Colowick and N. O. Kaplan, Academic Press, New York, 1963, vol. VI, p. 606.

[11] P. R. Wells, *Chem. Rev.*, 1963, **63**, 171.

[12] O. Rogne, *J. Chem. Soc.* (*B*), 1971, 1334.

not very accurate, they are sufficient for the present purpose considering the uncertainties in the $\Delta H^{\ddagger}$ values. Table 3 gives the total change in heat of solution of the reactants $\delta\Delta H_s{}^r$, the difference in activation enthalpies $\delta\Delta H^{\ddagger}$, and the enthalpy of transfer of the transition state $\delta\Delta H^t = \delta\Delta H_s{}^r + \delta\Delta H^{\ddagger}$.[4]

Since enthalpies of activation are available for the reaction of pyridine with benzenesulphonyl chloride in methanol[12] and aqueous acetonitrile[13] (10% H_2O, mole fraction $H_2O = 0{\cdot}202$), the heat of solution of pyridine and benzenesulphonyl chloride was also measured in aqueous acetonitrile. These data together with the calculated enthalpies of transfer from methanol to 10% H_2O–MeCN are in Table 4.

TABLE 4

Heats of solution of reactants and enthalpies of transfer of transition state and reactants for the reaction of pyridine with benzenesulphonyl chloride in methanol and 10% H_2O–MeCN at 25 °C. All values in kcal mol^{-1}

	MeOH	10% H_2O–MeCN
$\Delta H_s(PhSO_2Cl)$	0·65	0·96
ΔH_s(pyridine)	−0·95 [a]	−0·77
$\Delta H^{\ddagger}$	10·6 [b]	6·4 [c]
$\delta\Delta H_s{}^r$	0·49	
$\delta\Delta H^{\ddagger}$	−4·2	
$\delta\Delta H^t$	−3·7	

[a] From ref. 9. From ref. 12. [c] From ref. 13.

DISCUSSION

The products, kinetics, and substituent effects in the reaction of imidazole with aromatic sulphonyl chlorides are consistent with a nucleophilic substitution on the sulphur atom. The mechanism of this reaction could be either a direct S_N2 process, or an addition–elimination process involving a pentaco-ordinate intermediate.[14,15] Both types of mechanism have been suggested for reactions of benzenesulphonyl chloride with amines.[1,2,16] However, in the case of an addition–elimination mechanism for the present reactions, formation of the intermediate is expected to be rate determining.[16] Thus, the rate constants reported here refer, in any case, to attack of imidazole on the sulphur atom.

The solvent effect upon the rates of reaction is apparent from Table 1. Since the enthalpy of activation is different in the two solvents, the relative rates are temperature dependent. Thus the rates increase in the dipolar aprotic solvent by a factor of *ca.* 80 at 5 °C and *ca.* 35 at 25 °C. These relatively small effects on the rates are due to compensation of a substantial lowering of $\Delta H^{\ddagger}$ in the aprotic solvent by a concomitant decrease in $\Delta S^{\ddagger}$. This is in agreement with what is generally observed for protic–aprotic solvent effects for molecule–molecule reactions.[3]

The effect of substituents on rate does not show any protic–aprotic solvent dependence as is apparent from the ρ values which are within experimental error equal in the two solvents. This suggests that there is no large change in the electronic characteristics of the substituents or the reaction centre as a result of a protic–dipolar aprotic solvent change. As mentioned, the enthalpy of activation in acetonitrile is *ca.* 6—7 kcal mol^{-1} lower than in methanol. To separate this solvent effect on $\Delta H^{\ddagger}$ into initial-state and transition-state effects, the enthalpy of transfer of the reactants, $\delta\Delta H_s$, was determined (Table 2). As can be seen $\delta\Delta H_s$ of imidazole from methanol to acetonitrile is endothermic, which may be attributed to stabilization in methanol through hydrogen bonding. The other $\delta\Delta H_s$ values for the sulphonyl chlorides are small and insignificant in comparison with imidazole. Thus the total enthalpy of transfer of the reactants, $\delta\Delta H_s{}^r$ (Table 3) are all endothermic due to the dominating contribution from imidazole. The enthalpy of transfer of the transition state, $\delta\Delta H^t$, is obtained from the equation $\delta\Delta H^t = \delta\Delta H_s{}^r + \delta\Delta H^{\ddagger}$.[4] These values, as can be seen from Table 3, are all exothermic. Thus the observed decrease in $\Delta H^{\ddagger}$ of *ca.* 7 kcal mol^{-1} for the reaction of imidazole with sulphonyl chlorides in acetonitrile relative to methanol may be accounted for by a decreased solvation of the nucleophile by *ca.* 3 kcal mol^{-1} and increased solvation of the transition state by *ca.* 4 kcal mol^{-1} in the aprotic solvent.

In the reaction of pyridine with benzenesulphonyl chloride (Table 4) $\delta\Delta H^{\ddagger}$ is almost completely accounted for by increased solvation of the transition state in the aprotic solvent. The enthalpy of transfer of the transition state is also, within experimental error, the same for pyridine and imidazole as nucleophile.

In spite of the energetic advantage of the dipolar aprotic solvent for these reactions, the observed rate increase is, as mentioned above, modest. This is probably due to a dominating contribution from an unfavourable entropy of transfer of the transition state from methanol to acetonitrile.[9,17]

The present results show that the transition state for the reaction of aromatic sulphonyl chlorides with tertiary amines is considerably better solvated by a dipolar aprotic solvent than a protic solvent. In this respect these reactions are similar to the Menschutkin reaction.[9,18] Unlike the reaction of benzyl chlorides with pyridine,[9] however, there is no significant variation of $\delta\Delta H^t$ with the substituents in the substrate. The superior ability of dipolar aprotic solvents, compared with protic solvents, to solvate large polarizable transition states with well dispersed charges[3] seem to suggest a transition state

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[13] L. J. Stangeland, L. Senatore, and E. Ciuffarin, *J.C.S. Perkin II*, 1972, 852.

[14] L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, 1970, **92**, 3035.

[15] W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, 1970, **92**, 2731.

[16] E. Ciuffarin, L. Senatore, and M. Isola, *J.C.S. Perkin II*, 1972, 468.

[17] R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley, London, 1971, p. 50.

[18] M. H. Abraham, *J. Chem. Soc.* (*B*), 1971, 299.

for the present reactions more like that expected for a concerted one-step mechanism than for an addition–elimination mechanism. In the latter case the transition state would probably resemble the intermediate,[19] have more developed and localized charges, and be better solvated by methanol. An uncertainty in this interpretation is, however, introduced by the polarizability of sulphur and its ability to accommodate negative charge. A more definite answer could be obtained from comparison of enthalpies of transfer of transition states and compounds suitable as transition state models. Such data are, however, not available.

I thank Mrs. I. Heggen for experimental assistance.

[2/2575 *Received*, 14*th November*, 1972]

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[19] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.