Transition State Enthalpies of Transfer from Propanol to Acetonitrile in the Reaction of Imidazole with Benzoyl and Benzenesulphonyl Chlorides,

By **Otto Rogne,** Norwegian Defence Research Establishment, Division for Toxicology, P.O. Box 25, N-2007 Kjeller, Norway

Rates, activation parameters, and heats of solution of the reactants have been measured for the reaction of imidazole with benzoyl and benzenesulphonyl chlorides in propanol and acetonitrile. Enthalpies of transfer from propanol to acetonitrile of the transition state for the two reactions have been calculated. Approximate values for transfer from methanol are also given. Transition state enthalpies of transfer from propanol and methanol for substitution on carbonyl carbon are *ca.* −4 to +7 kJ mol^{-1} whereas corresponding values for substitution at sulphonyl sulphur are *ca.* −15 to −25 kJ mol^{-1}. This is taken to mean that transition states for substitution at sulphonyl sulphur are polar and polarizable structures with little localized negative charge, poor hydrogen bond acceptors, and well solvated by dipolar aprotic solvents. Corresponding transition states for substitution at carbonyl carbon resemble the tetrahedral intermediate, are good hydrogen bond acceptors, and well solvated by protic solvents.

THE relative reactivity of nucleophiles toward sulphonyl sulphur is well correlated with their relative reactivity toward carbonyl carbon in substitutions involving a similar leaving group.[1] This suggests that sulphonyl sulphur is similar in character to carbonyl carbon as an electrophilic centre.[1] To investigate further the similarity of nucleophilic substitution at the sulphonyl and carbonyl centre, enthalpies of transfer from propanol to acetonitrile of the transition state in the reaction of imidazole with benzenesulphonyl and benzoyl chlorides have been determined. Although a complete analysis also requires consideration of free energies and entropies, transition state enthalpies of transfer from one solvent to another should nevertheless reflect differences in interactions of the transition state with the two solvents, and thus give information about charge distribution and structure of the transition state.[2-4] Thus comparison of transition state enthalpies of transfer in nucleophilic substitution of imidazole at benzoyl and benzenesulphonyl chlorides may reveal similarities and differences in transition state structure for substitution at the two centres.

---

[1] J. L. Kice and E. Legan, *J. Amer. Chem. Soc.*, 1973, **95**, 3912.

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

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

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

It was originally the intention to use methanol as the protic solvent in the present work because of the similar dielectric constant of methanol and acetonitrile, and because enthalpies of transfer from methanol to acetonitrile for the reaction of imidazole with benzenesulphonyl chlorides are available.[5] The high rate of solvolysis of benzoyl chlorides in methanol made it difficult however to obtain sufficiently precise data with our apparatus, and only approximate enthalpies of transfer from methanol could be obtained.

EXPERIMENTAL

Materials.—Acid chlorides were fractionally distilled at reduced pressure or recrystallized from light petroleum (b.p. 60—80 °C). Imidazole was recrystallized from benzene. Acetonitrile was treated with calcium hydride and fractionally distilled from phosphorus pentaoxide.[6] n-Propanol was treated with calcium hydride and fractionally distilled.[6] *N*-Benzoylimidazoles were prepared according to Staab,[7] m.p. *ca.* 20 for *N*-benzoylimidazole and 69.5 °C for *N*-*p*-methylbenzoylimidazole (lit.,[7] 20—21 and 72.5—73.5 °C respectively).

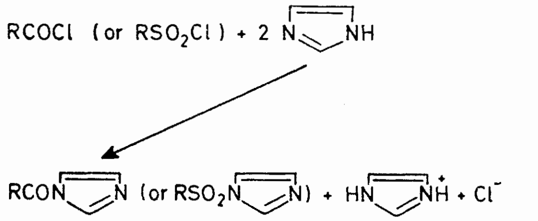
Rate Measurements.—Rates of reaction were measured conductometrically as described.[5] Final concentration of acid chlorides was in the range 4×10^{-5}—4×10^{-3}M. The concentration of imidazole was in the range 1×10^{-3}—0.1M depending upon the acid chloride and solvent. Reactiond were generally run at *ca.* 3—4 half-lives. Observed first-order rate constants were calculated from the resulting conductivity–time curve by Guggenheim's method [8] or by fitting the data to the equation $x = a(1 - e^{-kt})$ by use of an Olivetti Programma 102. Reactions were also occasionally run practically to completion and tested for first-order kinetics by conventional plots of log $(a - x)$ against time. Second-order rate constants were calculated from the slopes of plots of the observed first-order rate constants 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.* ±2 kJ mol^{-1} or better in $\Delta H^‡$ and *ca.* ±8 J mol^{-1} K^{-1} in $\Delta S^‡$. A few parallel rate measurements were also done by following the increase in absorption at 265 nm with time using a Cary 118 C spectrophotometer. Rate constants obtained spectrophotometrically were, within experimental error, identical to those measured conductometrically.

Heats of Solution.—The calorimeter proper is an LKB calorimeter flask (100 ml) fitted with a 2 000 Ω thermistor and a 50 Ω calibration heater. The flask is held in a brass cylinder which is submerged in an LKB precision thermostat. The thermistor is connected to a Wheatstone bridge powered by a mercury cell. Bridge unbalance is detected by a d.c. null voltmeter (Hewlett–Packard 419A) to which is connected a recorder (Kontron W + W) for automatic recording of the resistance–time curve. Calibration is carried out by passing current from a Keithley 225 current source through the heater for a measured time. Time is measured with an electronic time interval meter (Eldorado 255) synchronized to the passage of current by means of a relay. The resistance of the calibration heater is measured by means of a precision potentiometer and a 10 Ω standard resistor (ESI, model SR1) which is also used to standardize the current from the current source. The accuracy of the apparatus was checked by measuring the heat of solution of tris-(hydroxymethyl)aminomethane in 0.1N-hydrochloric acid at 25 °C. The mean of seven determinations was −29.75 kJ mol^{-1} with a standard deviation of ±0.08 kJ mol^{-1} which is to be compared with an accepted value[9] of −29.76 ± 0.03 kJ mol^{-1}. Two calibrations are usually made before, and two after the breaking of the sample ampoule and the mean value used. The precision in calibrations is generally about 0.5%. In the case of benzoyl chlorides in propanol the heat of the solvolysis reaction precluded calibrations after the solute had been introduced. The concentration of solute was generally in the range 0.5—5.0×10^{-2}M. The change in temperature is calculated from the resistance–time curve by graphical extrapolation (Dickinson's method).[10] Heats of solution are estimated to be accurate to ±0.5 kJ mol^{-1}.

Product Analysis.—The formation of *N*-arysulphonylimidazoles from imidazole and arenesulphonyl chlorides in organic solvents [11] was confirmed in a previous study.[5] Formation of *N*-benzoyl- and *N*-*p*-methylbenzoyl-imidazole from imidazole and the corresponding acid chloride [12] was confirmed by comparing the u.v. spectra of the final reaction mixture with the spectra of the corresponding *N*-benzoylimidazole in an identical solution. The *meta*-methyl and *para*-methoxy-compound 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.

RESULTS

The reaction between acid chlorides and imidazole in organic solvents takes place according to equation (1).[5,11,12] With imidazole in large excess over acid



(1)

chloride, the observed rates of reaction were 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 imidazole. Second-order rate constants and activation parameters for the reaction of imidazole with benzoyl and benzenesulphonyl chlorides in propanol and acetonitrile are given in Tables 1 and 2 respectively. Heats of solution of imidazole and benzoyl and benzenesulphonyl chlorides in propanol and acetonitrile are in Table 3. Differences in enthalpies of activation, $\delta\Delta H^‡$, and enthalpies of transfer from propanol

---

[5] O. Rogne, *J.C.S. Perkin II*, 1973, 823.

[6] J. A. Riddick and W. A. Bunger, 'Organic Solvents,' Wiley–Interscience, New York, 1970.

[7] H. A. Staab, M. Luking, and F. H. Durr, *Chem. Ber.*, 1962, **95**, 1275.

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

[9] E. J. Prosen, and M. V. Kildag, *J. Res. Nat. Bur. Stand.*, 1973, **77***A*, 581.

[10] I. Wadsø, *Science Tools*, 1966, **13**, 33.

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

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

TABLE 1

Rate constants and activation parameters for the reaction of imidazole with aroyl chlorides, XC_6H_4COCl, in acetonitrile and propanol

X	Solvent	5 °C	10 °C	15 °C	20 °C	25 °C	30 °C	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}
				k/l mol^{-1} s^{-1}					
p-MeO	MeCN	11.1	14.1	17.9		28.6		30	−117
	PrOH	0.450		0.958		1.83	2.47	45	−88
p-Me	MeCN	37.8	45.5	57.0		86.6		26	−117
	PrOH	1.77	2.38		4.54	6.34	8.04	41	−92
m-Me	MeCN	68.4	85.4	106		154		26	−117
	PrOH	3.15	4.23	5.79		10.4	14.0	39	−92
H	MeCN	91.6	115	151		209		26	−113
	PrOH	4.37	6.07	8.12	10.9	14.4	19.8	39	−92

TABLE 2

Rate constants and activation parameters for the reaction of imidazole with arenesulphonyl chlorides, $XC_6H_4SO_2Cl$, in acetonitrile [a] and propanol

X	Solvent	15 °C	25 °C	35 °C	40 °C	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J mol^{-1} K^{-1}
			k/l mol^{-1} s^{-1}				
p-MeO	MeCN		0.660			27	−155
	PrOH	0.00610	0.0139	0.0298	0.0418	55	−96
p-Me	MeCN		1.79			23	−163
	PrOH	0.0145	0.0315	0.0648	0.0932	53	−96
H	MeCN		3.20			21	−163
	PrOH [b]	0.0217	0.0473	0.0954		52	−96
p-NO_2	MeCN		41.1			18	−155
	PrOH	0.412	0.744	1.32	1.78	41	−109

[a] Data in acetonitrile from ref. 5. [b] 0.0324 at 20, 0.0665 at 30 °C.

to acetonitrile of reactants, $\delta\Delta H_S^r$, and transition states,[2] $\delta\Delta H^t = \delta\Delta H_S^r + \delta\Delta H^‡$, are in Table 4. Corresponding values for transfer from methanol are in Table 5.

TABLE 3

Heats of solution in kJ mol^{-1} in propanol and acetonitrile at 25 °C

Compound	ΔH_S(PrOH)	ΔH_S(MeCN)	$\delta\Delta H_S$
Imidazole	10.0	20.7	10.7
PhCOCl	3.6	3.6	0
m-MeC_6H_4COCl	4.5	5.0	0.5
p-MeC_6H_4COCl	4.4	4.9	0.5
p-$MeOC_6H_4COCl$	6.4	4.4	−2.0
$PhSO_2Cl$	5.2	2.8 [a]	−2.4
p-$MeC_6H_4SO_2Cl$	25.8	23.2 [a]	−2.6
p-$MeOC_6H_4SO_2Cl$	26.1	23.4 [a]	−2.7
p-$NO_2C_6H_4SO_2Cl$	25.6	17.8 [a]	−7.8

[a] From ref. 5.

TABLE 4

Enthalpies of transfer in kJ mol^{-1} from propanol to acetonitrile of reactants and transition states in the reaction of imidazole with acid chlorides at 25 °C

Acid chloride	$\delta\Delta H^‡$	$\delta\Delta H_S^r$	$\delta\Delta H^t$
PhCOCl	−13	10.7	−2
m-MeC_6H_4COCl	−13	11.2	−2
p-MeC_6H_4COCl	−15	11.2	−4
p-$MeOC_6H_4COCl$	−15	8.7	−6
p-$NO_2C_6H_4SO_2Cl$	−23	2.9	−20
$PhSO_2Cl$	−31	8.3	−23
p-$MeC_6H_4SO_2Cl$	−30	8.1	−22
p-$MeOC_6H_4SO_2Cl$	−28	8.0	−20

DISCUSSION

The kinetics, products, and relative rates for the present reactions are consistent with a bimolecular nucleophilic substitution on the carbonyl and sulphonyl centre respectively. These reactions may occur by a concerted one-step mechanism, S_N2, or an addition–elimination mechanism involving a tetrahedral or pentaco-ordinate intermediate respectively. Although the existence of tetrahedral intermediates in reactions of carboxylic acid derivatives is well established,[13,14] there still seems to be questions whether reactions of carboxylic acid chlorides with amines are best described by a one- or a two-step mechanism.[15] In the case of a two-step mechanism for the present reactions it does, however, seem reasonable to assume that the addition step is rate determining in view of the good leaving ability of the chloride ion. Likewise, if substitutions on sulphonyl

TABLE 5

Approximate enthalpies of transfer from methanol to actonitrile for the reaction of imidazole with benzoyl chlorides and previously obtained values for the reaction of imidazole with benzenesulphonyl chlorides.[a] All values in kJ mol^{-1}

Acid chloride	$\delta\Delta H^‡$	$\delta\Delta H_S^r$	$\delta\Delta H^t$
PhCOCl	−3	13.4	10 [b]
m-MeC_6H_4COCl	−5	13.8	9 [b]
p-MeC_6H_4COCl	−8	13.4	5 [b]
p-$MeOC_6H_4COCl$	−8	12.1	4 [b]
p-$NO_2C_6H_4SO_2Cl$	−25	10.0	−15
$PhSO_2Cl$	−30	13.0	−17
p-$MeC_6H_4SO_2Cl$	−28	12.6	−15
p-$MeOC_6H_4SO_2Cl$	−27	12.1	−15

[a] From ref. 5. [b] Estimated accuracy ±4 kJ mol^{-1}.

---

[13] S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

[14] W. P. Jencks, ' Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.

[15] A. Kivinen, ' The Chemistry of Acyl Halides,' ed. S. Patai, Interscience, New York, 1972, ch. 6.

sulphur occur by an addition–elimination mechanism, the addition step is expected to be rate determining for reactions of sulphonyl chlorides with amines.[16,17] Thus the second-order rate constants, and hence the enthalpy of activation, may be assumed to refer to attack of imidazole on the carbonyl and sulphonyl centre respectively.

Enthalpies of transfer from propanol to acetonitrile of the various reactants are given in Table 3. The endothermic value for imidazole may be attributed to better solvation and stabilization through hydrogen bonding of imidazole in propanol relative to acetonitrile. Enthalpies of transfer for the acid chlorides are small compared to imidazole. An exception is *para*-nitrobenzenesulphonyl chloride which shows a relatively large exothermic enthalpy of transfer from propanol to acetonitrile compared to the other acid chlorides. This is consistent with the fact that polarizable solutes, such as nitro-substituted aromatics, are usually better solvated by dipolar aprotic than by protic solvents.[4] Because of the dominating contribution from imidazole the total enthalpy of transfer of the reactants is endothermic and, except for the reaction of imidazole with *para*-nitrobenzenesulphonyl chloride, lie in the range 8—11 kJ mol^{-1} (Table 4).

By combining the enthalpy of transfer of the reactants with the difference in enthalpy of activation in the two solvents, the enthalpy of transfer of the transition state from propanol to acetonitrile is obtained [2] (Table 4). It is evident that transition state enthalpies of transfer for the reaction of imidazole with benzenesulphonyl chlorides are considerably more exothermic than those for the corresponding reactions of benzoyl chlorides. Thus for the unsubstituted, the *p*-Me, and the *p*-MeO substituted acid chloride, the differences are 21, 18, and 14 kJ mol^{-1} respectively. This suggests that the transition state for the attack of imidazole on sulphonyl sulphur is considerably better solvated by acetonitrile relative to propanol than the corresponding transition state for attack of imidazole on carbonyl carbon. The more negative $\Delta S^{\ddagger}$ for the sulphonyl compared to the carbonyl reactions in acetonitrile relative to propanol is also consistent with an increased solvation of the transition state for the former reaction in acetonitrile.

Enthalpies of transfer from one solvent to another are the resultant of several types of solute–solvent interactions, such as electrostatic interactions, hydrogen bonding, and dispersion forces, and to solvent–solvent interactions.[4] By a suitable choice of solvents it is however possible to reduce the number of likely interaction mechanisms, and thus simplify the interpretation.[4,18] To minimize electrostatic contributions in the present case it would, as mentioned, have been preferable to use methanol as the protic solvent. An estimate of the transition state enthalpies of transfer from methanol may be obtained from the data in Table 5. Transition state enthalpies of transfer from methanol to acetonitrile are seen to be *ca.* 5—10 kJ mol^{-1} more endothermic than the corresponding values for transfer from propanol. These differences, which represent the transition state enthalpies of transfer from propanol to methanol, do not to any significant extent affect the transition state enthalpies of transfer of the sulphonyl relative to the corresponding carbonyl compounds, which are *ca.* −20 to −25 kJ mol^{-1} (Table 5). Thus the conclusion that the imidazole–sulphonyl chloride transition state is considerably better solvated than the corresponding imidazole–benzoyl chloride transition state by a dipolar aprotic relative to a protic solvent is not significantly affected by the particular choice of propanol as the protic solvent. It seems reasonable to attribute this difference in solvation to differences in hydrogen bond and dispersion force interactions of the two transition states with the protic and aprotic solvent respectively.

Transition states for substitution at carbonyl carbon are considered to resemble a tetrahedral intermediate with negative charge localized on the carbonyl oxygen atom.[4] Such transition states are good hydrogen bond acceptors and therefore well solvated by protic solvents.[4] This view is supported by solvent activity coefficients and relative rates,[4,19] and by transition state enthalpies of transfer in alkaline ester hydrolysis.[20,21] The transition state enthalpies of transfer for the benzoyl chloride reactions are consistent with this picture, especially when the dielectric constant of the solvents is comparable, as for methanol–acetonitrile (Table 5), when the transfer enthalpies are endothermic. The protic–aprotic transition state enthalpies of transfer observed for the imidazole–benzoyl chloride reactions are, however, much less endothermic than those observed in alkaline ester hydrolysis.[20,21] This is reasonable since the latter reactions involve anionic transition states, whereas those in the present reactions are neutral. In sharp contrast to the transition state enthalpies of transfer for the benzoyl chloride reactions are those for the corresponding sulphonyl chloride reactions. The latter are exothermic and, as mentioned, *ca.* 20 kJ mol^{-1} more exothermic than for the corresponding benzoyl compounds. This suggests that transition states for substitution at sulphonyl sulphur are large, polar, and polarizable, and have little localized negative charge. Such structures would be poor hydrogen bond acceptors and well solvated by dipolar aprotic solvents.[4] Transition states for substitution at sulphonyl sulphur do therefore not resemble hypothetical pentaco-ordinate intermediates with negative charge localized on the sulphonyl oxygens, but are more as expected for an S_N2 transition state. Similar transition state enthalpies of transfer to those for the

---

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

[17] E. Maccaroni, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, 1974, **39**, 3286.

[18] B. G. Cox, G. R. Hedwig, A. J. Parker, and D. W. Watts, *Austral. J. Chem.*, 1974, **27**, 477.

[19] M. Balakrishnan, G. Venkova Rao, and N. Venkatasubramanian, *J.C.S. Perkin II*, 1974, 6.

[20] P. Haberfield, J. Friedman, and M. F. Pinkston, *J. Amer. Chem. Soc.*, 1972, **94**, 71.

[21] R. Fuchs, C. P. Hagan, and R. F. Rodewald, *J. Phys. Chem.*, 1974, **78**, 1509.

sulphonyl chloride reactions are also observed in the S_N2 reaction of pyridine with benzyl chlorides.[3]

A two-step mechanism for substitution at sulphonyl sulphur involving a pentaco-ordinate intermediate cannot, however, be ruled out since the intermediate, and therefore presumably the transition state,[22] could have the negative charge accommodated by a low-lying sulphur *d*-orbital,[23] instead of localized on an oxygen atom as in the formally analogous tetrahedral intermediate in substitutions at carbonyl carbon. Such a transition state would probably also be a poor hydrogen bond acceptor, and could be well solvated by dipolar aprotic solvents.

I thank Mrs I. Heggen for experimental assistance.

[5/237 *Received, 4th February*, 1975]

---

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

[23] E. Ciuffarin, and A. Fava, *Progr. Phys. Org. Chem.*, 1968, **6**, 81.