Nuclear Magnetic Resonance Investigations of Carbonium Ion Intermediates. Part I. Kinetics and Mechanism of Formation of the Vilsmeier–Haack Reagent

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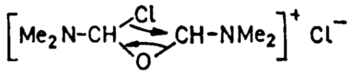
The mechanism of formation and the structure of the Vilsmeier reagent (dimethylformamide and $POCl_3$, $SOCl_2$, or $COCl_2$) has been studied by use of kinetic and structural data obtained from ^1H and ^{31}P n.m.r. spectroscopy. The rate constants and activation energies are discussed in terms of structural changes and solvent effects.

THE structure of the formylating reagent obtained from dimethylformamide (DMF) and a Lewis acid XCl (X $\equiv$ COCl, SOCl, or $POCl_2$) has been investigated and conflicting results have been reported in the literature.[1] The Vilsmeier–Haack complex may be represented by the formulae $[\mathrm{Me_2N\overset{\cdots}{-}CHCl}]^+\mathrm{OX}^-$ (I) or $[\mathrm{Me_2N\overset{\cdots}{-}CHCl}]^+\mathrm{Cl}^-$ (II). Complex (II) is formed with evolution of CO_2 or SO_2 when the Lewis acid is phosgene or thionyl chloride respectively. These structures have been proved by i.r.[2] and n.m.r.[3] measurements which eliminated the alternative representation $[\mathrm{Me_2N\overset{\cdots}{-}CH{\cdot}OX}]^+\mathrm{Cl}^-$ (III).



$\left[\mathrm{Me_2N{-}CH}\overset{\mathrm{Cl}}{\underset{\mathrm{O}}{\rightleftarrows}}\mathrm{CH{-}NMe_2}\right]^+\mathrm{Cl}^-$

(IV)

Recently a rapid exchange between (I), or (II), and DMF [see (IV)] has been tentatively suggested[4] to explain some kinetic behaviour of the Vilsmeier reagent, and these results can be extrapolated to explain the structure of the complexes between XCl and DMF in terms of equilibrating species (V).

To provide qualitative and quantitative support for the mechanism of formation of the Vilsmeier reagent, we have studied the kinetics of the reaction between DMF and $POCl_3$, $SOCl_2$, and $COCl_2$ in $CHCl_3$, $CHCl_2{\cdot}CHCl_2$, or CH_2Cl_2 as solvent, and also the ^{31}P n.m.r. spectral characteristics of the adduct.

RESULTS

The formation of (I) or (II) [or (V)] obeys mixed equilibrated second order kinetics[5] [equation (1) where $\Delta^{\frac{1}{2}} = (\beta^2 - 4\gamma)^{\frac{1}{2}}$, $\beta = -(a + b + 1/K)$, and $\gamma = ab$].

$$\ln \frac{x + \dfrac{\beta - \Delta^{\frac{1}{2}}}{2}}{x + \dfrac{\beta + \Delta^{\frac{1}{2}}}{2}} = \Delta^{\frac{1}{2}} k_1 t + \ln \frac{\beta - \Delta^{\frac{1}{2}}}{\beta + \Delta^{\frac{1}{2}}} \qquad (1)$$

The kinetics of the association between DMF and the solvent is assumed to be rapid compared with that of the reaction studied. The second-order rate constant k_1 is computed from the initial concentrations of DMF (a) and Lewis acid (b) and from the equilibrium constant K, and is expressed in l mol^{-1} s^{-1} or (mol fraction)$^{-1}$ s^{-1} according to the units of a and b. No significant differences are revealed when activation energies are computed from both series of data.* The thermodynamic and kinetic results for the action of DMF on $POCl_3$ and $SOCl_2$ are shown in Table 1, and Table 2 gives the half- and three-quarter times of the reaction.

The conditions for kinetic measurements were approximately the same as those used in organic synthesis. However, accurate determination of the rate constant k and the equilibrium constant K required respectively low (233—273 K) and high (263—293 K) temperature. The K values required for the calculation of k [equation (1)] were estimated from the same data obtained from a kinetic determination. Thus, the values of K measured in concentrated media (*ca.* 1 mol l^{-1}) have a relative meaning rather than an

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* In a previous communication,[4] the units of the rate constants are effectively l mol^{-1} s^{-1}.

[1] G. Hazebroucq, *Ann. Pharm. France*, 1966, **24**, 793.

[2] Z. Arnold and A. Holy, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2886.

[3] G. J. Martin and M. L. Martin, *Bull. Soc. chim. France*, 1963, 1637.

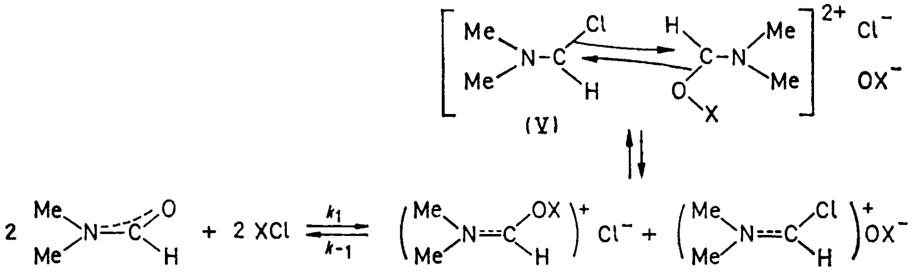
[4] G. J. Martin, S. Poignant, M. L. Filleux, and M. T. Quemeneur, *Tetrahedron Letters*, 1970, 5061.

[5] S. W. Benson, 'The Foundations of Chemical Kinetics,' McGraw-Hill, New York, 1960.

absolute one. A slight decrease of ΔH has been observed [6,7] when the concentration of Lewis acid in DMF increases.

No quantitative result is available for the reaction of phosgene and DMF because the reaction is very rapid even at 213 K and carbon dioxide is evolved as soon as the reagents come into contact; it may be assumed that the formation of (II) is complete.

The ^{31}P n.m.r. spectrum of the complex between $POCl_3$ and DMF was also studied. Just one resonance was observed for the adduct dissolved in $CHCl_2{\cdot}CHCl_2$, at +7 p.p.m. with respect to external H_3PO_4; the chemical shift of pure $POCl_3$ at the same phosphorus concentration in $CHCl_2{\cdot}CHCl_2$ is −3·5 p.p.m.



SCHEME 1

TABLE 1

Thermodynamic and kinetic results for the action of $POCl_3$ or $SOCl_2$ on DMF

		Thermodynamic data			Kinetic data		
Vilsmeier reagent	Solvent	$K_{273\,K}$/ l mol⁻¹	$\Delta G_{273\,K}$/ kcal mol⁻¹	ΔH/ kcal mol⁻¹	$10^5 k_{253\,K}$/ l mol⁻¹ s⁻¹	log A/ l mol⁻¹ s⁻¹	E_a/ kcal mol⁻¹
$DMF{-}POCl_3$	$CHCl_3$	202	−3·8	−10·1	71·7	5·5	8
	$CHCl_2{\cdot}CHCl_2$	370	−7·1	−13·7	134·7	2·6	4·2
	CH_2Cl_2	310	−6·1	−12·3	203·3	1·8	3·1
$DMF{-}SOCl_2$	$CHCl_3$	6	−0·97	−8·8	0·43	6·3	11·6
	$CHCl_2{\cdot}CHCl_2$	11·5	−1·3	−9·8	0·65	3	7·4
	CH_2Cl_2	8·3	−1·15	−10·2	1·7	1·9	6·0

All data were evaluated by least-squares analysis. Thermodynamic data were obtained at 263—293 K. Kinetic data were obtained at 233—273 K for initial [DMF] : [Lewis acid] *ca.* 1. Accuracy of ΔH and E_a *ca.* ±15%.

TABLE 2

Half- and three-quarter times for the reaction between $POCl_3$ or $SOCl_2$ and DMF

	$t_{1/2}$/min						$t_{3/4}$/min		
	$DMF{-}POCl_3$			$DMF{-}SOCl_2$			$DMF{-}POCl_3$		
T/K	$CHCl_3$	$CHCl_2{\cdot}CHCl_2$	CH_2Cl_2	$CHCl_3$	$CHCl_2{\cdot}CHCl_2$	CH_2Cl_3	$CHCl_3$	$CHCl_2{\cdot}CHCl_2$	CH_2Cl_2
213	145		9				420		28
233	23	8·5	4				70	26	12
243		6·5		3000	1320	540		20	
253	8	4	2·7	1200	840	300	27	13	8
263				660	480	180			

EXPERIMENTAL

The reagents used were carefully dried and twice distilled. The solvent and the Lewis acid were weighed in the n.m.r. tube and the spectrometer insert was maintained at a given temperature. By means of Teflon needles connected with a three-way Hamilton valve, an adequate volume of DMF was introduced under a flow of dry argon. The first integration was performed *ca.* 30 s after the starting time (introduction of DMF) the optimization of the resolution of the spectrometer having been made previously. The equilibrium constants were determined by integration of a mixture of DMF, Lewis acid, and Vilsmeier complex contained in a sealed n.m.r. tube maintained for a sufficiently long time in a thermostat. The ^1H and ^{31}P spectra were studied respectively with a Varian A60A and a JEOL C60HL spectrometer.

DISCUSSION

Our results show that the order of the reaction is one with respect to DMF and one with respect to the Lewis acid, and the slow step may be considered as an acid–base association. No quantitative data are available for phosgene but it may be assumed that the activation energy is low in this case.

For a given solvent, the reaction is faster and the activation energy decreases in the sequence $SOCl_2 > POCl_3 > COCl_2$. The influence of solvent is significant; activation energy decreases from $CHCl_3$ to $CHCl_2{\cdot}CHCl_2$ and CH_2Cl_2. In fact the solvent has the same importance as the Lewis acid because substitution of $CHCl_3$ by CH_2Cl_2 (for a given Lewis acid) is equivalent to the

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[6] R. C. Paul, S. Sharda, and B. R. Sreenathan, *Indian J. Chem.*, 1964, **2**, 97.

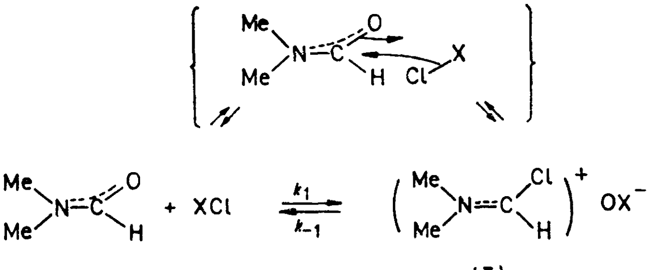
[7] R. C. Paul, S. C. Ahluwalia, and S. S. Pahil, *Indian J. Chem.*, 1965, **3**, 300.

substitution of $SOCl_2$ by $POCl_3$ (for a given solvent). Thus, the slightest proton-donating solvent (*i.e.* CH_2Cl_2) favours the formation of the complex which is also more stable.

It may be assumed that solvation is also effective in the transition state and the suggested mechanism takes this fact into account. The enthalpies of activation[8] of the complexation of DMF by $SbCl_5$, $AlCl_3$, $GaCl_3$, and $TiCl_4$ fall in the range 10—28 kcal mol^{-1}. Fratiello *et al.*[8] suggest that the strongest complex is associated with a high value of the difference in the chemical shift $\Delta\delta_{\mathrm{CHO}}$ = 0·9 p.p.m. but conclude that the rate-determining step in the complexation is a modification of the first co-ordination sphere of the ion. From the observed signal separation in the Vilsmeier complexes ($\Delta\delta_{\mathrm{CH}}$ = 2·5, 2, and 1·9 p.p.m. for $COCl_2$, $POCl_3$, and $SOCl_2$ respectively) and the values of the activation energies, it is likely that the behaviour is not the same for our system.

The phosphorus resonance of the DMF–$POCl_3$ adduct may be interpreted in the same way as our previous ^1H n.m.r. measurements.[3] The absence of spin–spin coupling between ^{31}P and the low-field proton is a proof of the absence of pure structure (III). The chemical shift of the Vilsmeier complex (+7 p.p.m.) also argues against the presence of a covalent bond between phosphoryl chloride and the remainder of the molecule [such as in (III)]. The chemical shifts for analogous[9,10] compounds [$POCl_3$ (in tetrachloroethylene) —3·5, $ROP(O)Cl_2$ —6·4 to —5·6, $(EtO)_2P(O)Cl$ —2·8, and $(EtO)_3P(O)$ or $FP(O)Cl_2$ 0 p.p.m. (relative to PO_4H_3 85%)] indicate that the relatively great shielding observed for the adduct is in good agreement with an electron-donating atom on the phosphorus nucleus such as $^{-}OP(O)Cl_2$ which would exist in $[(Me)_2NCHCl]^{+}O{\cdot}POCl_2^{-}$.

The possibility of a rapid equilibrium between (I) and (III), largely displaced towards (I) (Scheme 2), cannot be eliminated and we shall discuss this point in a future paper[11] in connection with the hindered rotation about C–N bonds and exchange phenomena.[4]



(I)

SCHEME 2

Finally, we think that the synthetic results alleged to support the structure (III),[12,13] may be explained by a variation of the anion in the ion-pair. The solvent effects on the activation energies seem to be convincing arguments in this respect.

[2/650 *Received*, *20th March*, 1972]

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[8] A. Fratiello, D. P. Miller, and R. Schuster, *Mol. Phys.*, 1967, **12**, 111.

[9] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, ' High Resolution N.M.R. Spectroscopy,' Pergamon, London, 1965, vol. 2, p. 1054.

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[11] G. J. Martin and S. Poignant, to be published.

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