The Mechanism of the Vilsmeier–Haack Reaction. Part II.[1,2] A Kinetic Study of the Formylation of Thiophen Derivatives with Dimethylformamide and Phosphorus Oxychloride or Carbonyl Chloride in 1,2-Dichloroethane

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The kinetic order of the reaction of thiophen derivatives with dimethylformamide and phosphorus oxychloride in 1,2-dichloroethane depends on the reactivity of the substrate. Reactions of relatively inert substrates (such as thiophen and the methylthiophens) follows third-order kinetics, first-order in each reagent. On the other hand reactions of very labile substrates (such as 2-methoxythiophen) follow second-order kinetics, the rates being independent of the concentration and the nature of the substrate. The observed kinetics are consistent with a mechanism involving an equilibrium leading to an electrophilic complex, which then attacks the heterocyclic substrate. According to the reactivity of the substrate, the rate-determining step is either the attack of the complex on the aromatic compound or the formation of the complex. The reactions with the complex formed from dimethylformamide and carbonyl chloride follow pure second-order kinetics, first-order in substrate and first-order in complex.

ALTHOUGH many studies have been devoted to the nature of the complex formed from dimethylformamide and phosphorus oxychloride [3-8] and several hypotheses have been formulated on the mechanism of the Vilsmeier–Haack formylation,[9,10] no kinetic study of this reaction has yet been accomplished. Five-membered heteroaromatic rings, because of their high reactivity toward electrophilic substitution, are especially suitable substrates for the study of reactions with mild electrophiles.[11] Accordingly, we have undertaken a complete kinetic study of the Vilsmeier–Haack formylation of these compounds. We now report the main kinetic features of the formylation of thiophen derivatives with dimethylformamide as the amide, phosphorus oxychloride or carbonyl chloride as the halide, and 1,2-dichloroethane as the solvent.

RESULTS AND DISCUSSION

Kinetics of the Reaction with Dimethylformamide and Phosphorus Oxychloride.—The reactions were carried out by mixing equimolecular amounts of heterocyclic substrate, phosphorus oxychloride, and dimethylformamide in dichloroethane and were followed by titrating the acid present in the hydrolysed mixture. During the reaction the number of equivalents of acid drops from 4 (3 HCl and the first hydrogen of H_3PO_4) to 3, since one equivalent of acid is consumed by the dimethylamine formed.

The reactions of substrates of relatively low reactivity (thiophen, 2-methylthiophen, and 3-methylthiophen) obey third-order kinetics (i), first-order in each component.

$$\text{Rate} = k_{\text{obs}}[\text{Het}][\text{Me}_2\text{N·CHO}][\text{POCl}_3] \qquad \text{(i)}$$

Reactions of very reactive substrates (2-methoxythiophen) follow second-order kinetics, the rates being independent of the substrate concentration; the observed k values are, in this case, equal to the rate constants k_1 relating to the formation of the electrophilic adduct.

Substrates of intermediate reactivity (2-methylfuran) exhibit kinetics of order between 2 and 3. Second-order plots exhibit downward and third-order plots upward curvature, respectively.

This kinetic behaviour is consistent with a mechanism involving an equilibrium leading to an electrophilic adduct C (1), followed by an attack of the latter on the heterocyclic substrate (2), with formation of an intermediate which is finally converted into the formyl derivative by the action of water (3).

$$\text{Me}_2\text{N·CHO} + \text{POCl}_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{C} \qquad (1)$$

$$\text{Heterocycle} + \text{C} \xrightarrow{k_2} \text{intermediate} \qquad (2)$$

$$\text{Intermediate} \xrightarrow{3\text{H}_2\text{O}} \text{formyl derivative} + \text{H}_3\text{PO}_4 + 2\ \text{HCl} + \text{Me}_2\text{NH}_2\text{Cl} \qquad (3)$$

Depending on the reactivity of the substrate, the rate-determining step is either the attack of the electrophile on the aromatic compound (third-order kinetics) or the formation of the adduct C (second-order kinetics).

The Equilibrium of Complex Formation.—The equilibrium constant for the formation of the electrophilic complex from dimethylformamide and phosphorus oxychloride in dichloroethane has been determined by measuring spectrophotometrically the equilibrium concentration of the 'free' dimethylformamide. The

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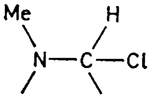
K values, determined at five different temperatures, are in Table 1. The van't Hoff plot is linear; the thermodynamic parameters ($\Delta H = -13{\cdot}7$ kcal mol^{-1}, $\Delta S = -38{\cdot}6$ cal mol^{-1} K^{-1}) have been calculated by a least-squares procedure. The rate constants (k_1) for the formation of the complex were evaluated from experiments carried out under pseudo-first-order conditions by use of a large excess of $POCl_3$. The k_1 values were calculated from the equilibrium constant $K = k_1/k_{-1}$ and the slopes of the plots of $C_{eq}/C_{eq} - x$ against time, which yield $k_1 + k_{-1}$. The 'true' second-order rate constants were calculated by dividing the first-order constants by the initial concentration of phosphorus oxychloride (Table 1). The activation parameters were $\Delta H^{\ddagger} = 15{\cdot}8$ kcal mol^{-1}; $\Delta S^{\ddagger} = -20{\cdot}7$ cal mol^{-1} K^{-1}. The values reported are in serious disagreement with those determined by Martin and his co-workers,[7] who studied the formation of the complex between dimethylformamide and $POCl_3$ in chloroform or methylene dichloride at temperatures ranging from −60 to −20 °C by n.m.r. spectroscopy. The discrepancy of the values is large and cannot be ascribed entirely to the different experimental conditions; we cannot explain these differences.

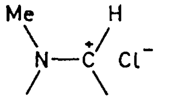
TABLE 1

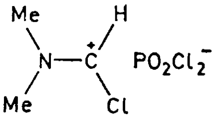
Formation of the $Me_2N{\cdot}CHO{-}POCl_3$ complex in 1,2-dichloroethane

Equilibrium constant		Rate constant	
t/°C	K/l mol^{-1}	t/°C	$10^4 k_1$/l mol^{-1} s^{-1}
29·6	28·4	25·0	4·95
34·4	21·0	29·6	7·90
39·0	15·0	35·0	11·7
44·2	9·8	40·0	15·0
49·0	7·2		

Among the structures previously suggested for the complex between dimethylformamide and phosphorus oxychloride are the covalent structure (I) and the ionic structures (II) and (III).

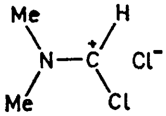

(I)


(II)


(III)

Structure (I) has been discarded by arguments based on i.r. spectra, and an ionic structure is generally accepted. Earlier researchers[3,4] inclined towards the structure (II) but recently structure (III) gained in favour on the basis of chemical,[5,8] spectroscopic,[6] and thermodynamic[12] evidence.

The kinetics observed are consistent with the hypothesis of a complex in equilibrium with the reagents but this, by itself, does not permit us to choose among structures (I)—(III). Information useful for this purpose can be obtained by a comparison of the k_2 values for equation (2) with the k values obtainable in the reaction with the complex formed by dimethylformamide and carbonyl chloride. When these substances are mixed in an inert solvent, carbon dioxide is given off and the equilibrium is completely shifted towards the right with formation of a crystalline complex, the structure of which is unequivocally[12] (IV) [the cation is the same as in structure (III)].


(IV)

Determination of k_2.—The constants k_2 for step (2) of the formylation of 2- and 3-methylthiophen have been determined from equation (4) where S_0 is the initial concentration of the heteroaromatic substrate, x the concentration of the product (determined experimentally by an acid–base titration), and C_t is the instantaneous concentration of the electrophilic complex, derivable from the expression (5), where A_0 is the initial concentration of both dimethylformamide and phosphorus oxychloride.

$$dx/dt = k_2(S_0 - x)(C_t) \qquad (4)$$

$$K_{eq} = C_t/(A_0 - x - C_t)^2 \qquad (5)$$

The rates dx/dt were determined at several points from the plots of x against t by the tangent method; the k_2 values were hence calculated from equation (4) (Table 2).

TABLE 2

Rate constants for the formylation of thiophen derivatives

Substrate	Reagent	T/°C	$10^4 k_2$/l mol^{-1} s^{-1}
Thiophen	$Me_2N{\cdot}CHO{-}POCl_3$	58	0·024
2-Methylthiophen	$Me_2N{\cdot}CHO{-}POCl_3$	40	0·63
2-Methylthiophen	$Me_2N{\cdot}CHO{-}POCl_3$	50	1·81
2-Methylthiophen	$Me_2N{\cdot}CHO{-}POCl_3$	58	3·45
3-Methylthiophen	$Me_2N{\cdot}CHO{-}POCl_3$	40	0·27 [a]
3-Methylthiophen	$Me_2N{\cdot}CHO{-}COCl_2$	40	0·89 [a]

[a] Overall rate constants. The isomeric ratio 2-formyl : 5-formyl was 6·1 for the reaction with $POCl_3$ and 5·9 for the reaction with $COCl_2$.

Alternatively, k_2 values were calculated by the following empirical procedure. It was observed that, until about 50% reaction, the plots of C_t against x are linear [equation (6)]. Hence, from equations (4) and (6), we obtain (7), which gives by integration equation (8).

$$C_t = C_0 - mx \qquad (6)$$

$$dx/dt = k_2(C_0 - mx)(S_0 - x) \qquad (7)$$

$$k_2 m[S_0 - (C_0/m)]t = \ln \frac{S_0 - x}{(C_0/m) - x} \qquad (8)$$

The k_2 values obtained graphically from the plots of $\log (S_0 - x)/[(C_0/m) - x]$ against time are in excellent agreement with the values determined by the tangent procedure (Table 3).

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The reaction–time curves are not sigmoid since the formation of the complex, although not instantaneous, is nevertheless much faster than the reaction between the complex and the substrate. Some experiments were carried out by premixing dimethylformamide and phosphorus oxychloride and allowing them to reach the equilibrium before adding the substrate: the results were the same, within experimental error, as those obtained when all the three reagents were mixed at the same time.

Reaction with the Dimethylformamide–Carbonyl Chloride Complex.—Carbon dioxide is evolved and the electrophilic complex, having an unequivocal structure, can be isolated as crystals. The reactions between this complex and the heteroaromatic compounds follow

$$v = k_2\,[\text{Substrate}]\,[\text{Me}_2\text{N·CHO–COCl}_2\text{ complex}] \qquad \text{(ii)}$$

pure second-order kinetics (ii). The rate constants and the isomer distribution for the reaction with 3-methylthiophen are reported in Table 2 and compared with the data obtained in the reaction with $POCl_3$ and dimethylformamide. The isomer distribution is practically the same in the two reactions, showing that the electrophilic species involved exhibit similar steric requirements.

A difference in k values exists, although not very large; it could be ascribable either to different structures of the cations or to different anions bonded to the same cation $Me_2N{\cdot}CHCl^+$ in the ion-pair. We hope to be able to collect further information which will permit us to give a definitive answer to this problem. The reaction with the $COCl_2$–$Me_2N{\cdot}CHO$ complex, in view of its very simple kinetics, appears promising for studies of structure–reactivity correlations.

EXPERIMENTAL

Materials.—Thiophen, 2-methylthiophen, 3-methyltiophen, 2-methoxythiophen, and 2-methylfuran were from previous studies. Dimethylformamide, 1,2-dichloroethane, toluene, and phosphorus oxychloride were fractionated through a Todd column in a nitrogen atmosphere. Commercial carbonyl chloride (20% solution in toluene) was used without further purification.

Product Analysis.—All the substrates examined gave, under kinetic conditions, the expected aldehydes in very high yield, as checked by g.l.c. analysis of the products. Thiophen gave thiophen-2-carbaldehyde, 2-methylthiophen gave 5-methylthiophen-2-carbaldehyde, 3-methylthiophen gave a mixture of 85·8% of 3-methylthiophen-2-carbaldehyde and 14·2% of 4-methylthiophen-2-carbaldehyde with $Me_2N{\cdot}CHO$–$POCl_3$ and, respectively, 86·2 and 13·8% with $Me_2N{\cdot}CHO$–$COCl_2$.

Kinetic Procedures.—*Formation and equilibrium constants of the* $Me_2N{\cdot}CHO$–$POCl_3$ *complex.* Stock solutions of dimethylformamide and phosphorus oxychloride, preheated at the proper temperature, were mixed and the reaction of complex formation was followed directly in the spectrophotometer by measuring the decrease in dimethylformamide concentration at 240 nm. A ten-fold excess of $POCl_3$ with respect to the dimethylformamide concentration (*ca.* 1×10^{-2}M) was used and the pseudo-first-order constants, graphically evaluated, were converted into second-order constants (Table 1) by dividing them by the initial concentration of $POCl_3$ (*ca.* 10^{-1}M).

For the determination of the equilibrium constant, preheated solutions of dimethylformamide and phosphorus oxychloride in 1,2-dichloroethane were mixed in a thermostatted cell, and allowed to reach equilibrium. The equilibrium concentration of the 'free' *NN*-dimethylformamide was determined by measuring the absorbance at 240 nm.

Reaction of heteroaromatic substrates with $POCl_3$ *and dimethylformamide.* The reaction mixture for each kinetic experiment was prepared in a 25 ml volumetric flask by dissolving a weighed sample of the heteroaromatic compound with *ca.* 15 ml of 1,2-dichloroethane, then adding the calculated volumes of stock solutions (in the same solvent) of dimethylformamide and phosphorus oxychloride, and finally diluting with the solvent to the mark and shaking. The concentrations used were equal for all the three reagents (*ca.* 0·1M). The flask was placed in a thermostatic bath and 2 ml samples were removed at intervals and quenched in water. After at least 2 h (time necessary to complete the hydrolysis) the acid was titrated with 0·1M-sodium hydroxide solution (Bromocresol Green). A typical kinetic run is reported in Table 3. For the determination of the total order of the reaction, several experiments (with equimolecular concentrations of the reactants) were carried out, the absolute initial concentration being varied. The order was then calculated from the Noyes equation (9). For

$$n = 1 + [(\log t'_{\frac{1}{2}} - \log t_{\frac{1}{2}})/(\log C - \log C')] \qquad (9)$$

the determination of the partial orders, the concentration of dimethylformamide or the substrate was changed over a ten-fold range, the concentration of the other two reagents being kept constant. The orders were determined by the differential method from the plots of log $\Delta x/\Delta t$ against log a, where a is the initial concentration of the reagent considered. The order with respect to $POCl_3$ was determined by difference from the total order. Formylation of 2-methoxythiophen follows second-order kinetics: a typical run is reported in Table 4.

TABLE 3

Formylation of 2-methylthiophen; typical kinetic run [2-Methylthiophen] = [$Me_2N{\cdot}CHO$] = [$POCl_3$] = 0·167M; temperature 58·0 °C

t/ min	0·0985M-NaOH (ml)	% Reaction	10^2x	10^3k_{obs} / $l^2\ mol^{-2}\ s^{-1}$	10^4k_2 / $l\ mol^{-1}\ s^{-1}$
0	13·60				
155	13·15	13·2	2·20	1·91	3·27
310	12·78	24·1	4·02	1·70	3·60
415	12·52	31·8	5·31	1·89	3·41
1195	11·85	51·5	8·60	1·73	3·47
1435	11·70	55·8	9·32	1·78	3·50
1855	11·62	58·4	9·75	1·62	3·50
2665	11·38	65·4	10·09	1·64	3·52

Average $k_2 = 3{\cdot}47 \times 10^{-4}\ l\ mol^{-1}\ s^{-1}$; tangent method.
Average $k_2 = 3{\cdot}71 \times 10^{-4}\ l\ mol^{-1}\ s^{-1}$; integration method.

Reaction with the carbonyl chloride–dimethylformamide complex. Chloromethylenedimethylammonium chloride $[Me_2N{:}CHCl]^+Cl^-$ was synthesised in a flask equipped with a mechanical stirrer, a condenser, a dropping funnel, and an inlet tube for nitrogen. All operations were carried out under nitrogen. A solution of carbonyl chloride (20% in toluene) in slight excess with respect to dimethylformamide was added dropwise with stirring to an ice-cooled solution of dimethylformamide in toluene.

TABLE 4

Formylation of 2-methoxythiophen; typical kinetic run [2-Methoxythiophen] = [$Me_2N{\cdot}CHO$] = [$POCl_3$] = 0·115M; temperature 25·0 °C

t/min	0·0978M-NaOH (ml)	% Reaction	10^2x	10^4k_2/l mol^{-1} s^{-1}
0	9·50			
45	9·30	8·7	1·00	4·81
90	8·90	21·3	2·45	4·44
155	8·70	33·8	3·86	4·62
215	8·48	43·5	5·00	5·04
300	8·28	51·0	5·85	4·90
420	8·08	60·2	6·92	5·08

Average $k_2 = 4{\cdot}81 \times 10^{-4}$ l mol^{-1} s^{-1}.

After complete evolution of carbon dioxide [check with $Ba(OH)_2$] the white precipitate was washed thoroughly with anhydrous toluene and filtered off with reduced pressure.

Kinetic stock solutions in 1,2-dichloroethane were prepared by dissolving the complex in the same apparatus used for the preparation in order to avoid contact with moisture.

The reactions of thiophen derivatives with ($[Me_2N{:}CHCl]^+Cl^-$) were carried out in a volumetric flask, by use of a procedure similar to that described in the previous paragraph. A ten-fold excess of substrate was used and the reaction was followed by titrating the acid present in the water-quenched mixture. Total hydrolysis requires ½ h.

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