KINETICS OF THE FORMYLATION OF THIOPHENE DERIVATIVES WITH N,N-DIMETHYLFORMAMIDE

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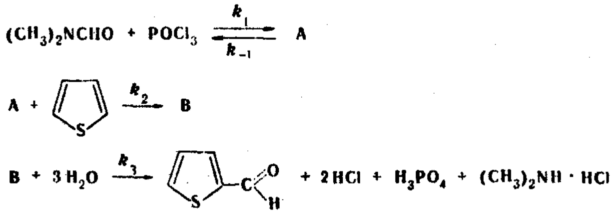
The kinetics of the formylation of five thiophene derivatives in the presence of phosphorus oxychloride and the formylation of thiophene in the presence of thionyl chloride were investigated. The effect of the condensing agent on the reaction rate is shown, and the rate constants and the activation parameters are calculated. The isokinetic dependence and the Hammett dependence of the reactivities on the structure were established for this reaction series. The effect of the solvent on the formylation was studied.

The formyl derivatives of thiophene serve as a foundation for the production of dyes [1, 2], and many of them have bactericidal and fungicidal properties [3] and are effective combustion retardants [4]. Alcohols [5, 6] and amines [7] of the aliphatic series can be synthesized from them.

Formyl derivatives of thiophene are obtained chiefly via the Vilsmeier–Haack reaction. This reaction has been investigated only in the case of formylation of thiophene, 2-methylthiophene, and 3-methylthiophene in the presence of phosphorus oxychloride [8, 9]. The following mechanism was proposed in the indicated studies:



(1)

(2)

(3)

where A is the complex of N,N-dimethylformamide (DMF) with phosphorus oxychloride, B is the DMF + $POCl_3$ + substrate intermediate, k_1 is the rate constant for the forward reaction to form complex A, k_{-1} is the rate constant for the reverse reaction involving decomposition

TABLE 1. Rate Constants and Activation Parameters for the Formylation of Thiophene Derivatives in Dichloroethane in the Presence of Phosphorus Oxychloride

Compound	$k^* \cdot 10^5$, liter^2·mole^{-2}·sec^{-1}					ln A	ε_a, kJ/kmole
	60°	70°	80°	90°	100°		
Thiophene		1.33±0.07	2.97±0.12	4.12±0.21		10,24±1.20	61.13±3.35
Thiophene†			0.31±0.01	0.82±0.03	1.26±0.03	21,16±1.75	99.23±1.26
2-Iodothiophene		0.78±0.05	1.50±0.06	2.70±0.20		10,83±0.69	64.48±2.09
2-Ethylthiophene	33.8±2.0	69.0±10.0	100.0±14.0			11.65±2.24	80.39±6.28
2-Bromothiophene			0.41±0.01	0.90±0.03	1.53±0.10	11.35±1,36	71.60±4.19
2-tert-Butylthiophene		141.0∓9.0	237.0±10.0	380.0±28.0		11.07±0,66	51.50±2.09

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*The average values of the constants calculated from the kinetic curves at various degrees of conversion are presented.

†The reaction was investigated in the presence of thionyl chloride.

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TABLE 2. Effect of the Solvent on the Rate Constant for the Formylation of 2-Ethylthiophene in the Presence of Phosphorus Oxychloride

t, °C	$k \cdot 10^4$, liter^2-mole^{-2}-sec^{-1}			
	acetonitrile $\varepsilon^{20}=37.5$, $n_D^{20}=1.3416$	dichloroethane $\varepsilon^{20}=10.36$, $n_D^{20}=1.4451$	chloroform $\varepsilon^{20}=4.806$, $n_D^{20}=1.4180$	benzene $\varepsilon^{20}=2.284$, $n_D^{20}=1.5011$
60	5,37	3,38	3,99	1,17
70	10,12	6,88	6,80	2,35
80	18,40	9,98	8,78	4,55

of complex A, k_2 is the rate constant for the formation of intermediate B, and k_3 is the rate constant for the hydrolysis of complex B to give the formyl derivative of thiophene.

The rate constants for the formation of complex A at several temperatures ($k = 15 \cdot 10^{-4}$ liter-mole^{-1}-sec^{-1} at 40°C) and the observed rate constant for the overall reaction to form 2-methyl-5-formylthiophene, as well as the k_2 constants for the other two compounds, were determined. The disparate data presented do not make it possible to estimate the reactivitie of thiophene and substituted thiophenes in the formylation reaction.

Considering the practical importance of the Vilsmeier—Haack reaction, we investigated the kinetics of the formylation of thiophene, 2-ethylthiophene, 2-tert-butylthiophene, 2-bromothiophene, and 2-iodothiophene under comparable conditions. On the basis of the rate constants obtained (k_{obs}) we estimated the effect of substituents in thiophene on its reactivity. To ascertain the effect of the condensing agent on the reaction rate, the formylation of thiophene was carried out in the presence of both phosphorus oxychloride and thionyl chloride.

The partial reaction orders in the substrate, DMF, and phosphorus oxychloride were determined from the dependence of the rate of formylation on the concentration of each component; the initial concentration of the substance from which the reaction order was determined was 0.1 to 0.8 mole/liter vis-à-vis a sevenfold to tenfold molar excess of the other components. The reaction orders in the substrate, DMF, and phosphorus oxychloride were found to be unity on the basis of both the Ostwald—Noyes method and the van't Hoff method [10]. The overall reaction order in all cases was three.

The rate constants for the formylation of all of the investigated compounds were calculated from the experimental data using the equation below, where c_s is the concentration of the substrate in moles per liter.

$$v = k_{obs} \cdot c_s \cdot c_{DMF} \cdot c_{POCl_3},$$

The data in Table 1 show that the introduction of electron-donor substituents in the ring leads, as expected, to activation of the thiophene ring, whereas the introduction of halogens leads to deactivation of the ring. The condensing agent has an appreciable effect on the reaction rate. Thus at 80°C thiophene reacts considerably more rapidly in the presence of phosphorus oxychloride than in the presence of thionyl chloride, and the reaction proceeds with a lower activation energy.

The results of the kinetic measurements do not contradict the mechanism presented above, according to which the rates of reactions (1), (2), and (3) can be represented by the equations

$$v_1 = k_1 \cdot c_{DMF} \cdot c_{POCl_3} - k_{-1} \cdot c_A,$$
$$v_2 = k_2 \cdot c_A \cdot c_s,$$
$$v_3 = k_3 \cdot c_B \cdot c_{H_2O}.$$

From the conditions of quasi-steady-state concentrations of complexes A and B the rate of formylation can be expressed by the equation

$$v_{obs} = \frac{k_2 \cdot k_1}{k + k_2 \cdot c_s} \cdot c_{DMF} \cdot c_{POCl_3} \cdot c_s.$$

The $k_2 \cdot c_s$ value can be disregarded, since $v_3 \gg v_2$, and hence

$$v_{obs} = k_2 \cdot Kp \cdot c_{DMF} \cdot c_{POCl_3} \cdot c_s = k_{obs} \cdot c_{DMF} \cdot c_{POCl_3} \cdot c_s.$$

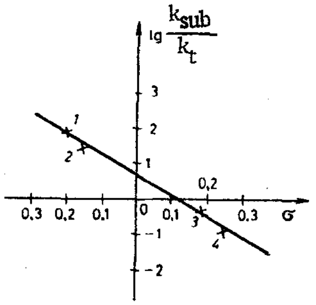

Fig. 1

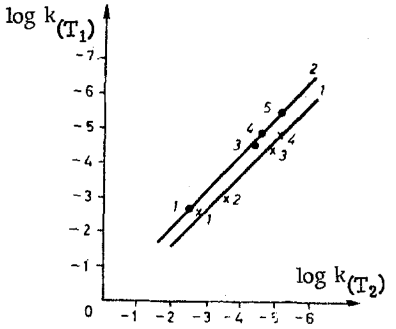

Fig. 2

Fig. 1. Dependence of the logarithm of the ratio of the rate constants of substituted thiophenes (k_{sub}) to the rate constant of thiophene (k_t) on the Hammett σ constants for the formylation of thiophene derivatives: 1) 2-tert-butylthiophene; 2) 2-ethylthiophene; 3) 2-iodothiophene; 4) 2-bromothiophene.

Fig. 2. Isokinetic Dependence for the formylation of thiophene derivatives: 1) T_1 = 353°K, T_2 = 343°K; 2) T_1 = 353°K, T_2 = 363°K; 1) 2-tert-butylthiophene; 2) 2-ethylthiophene; 3) thiophene; 4) 2-iodothiophene; 5) 2-bromothiophene.

If one converts the observed rate constants of the overall reaction for second order ($k_1 = k \cdot c_{POCl_3}$), their values will turn out to be an order lower than the rate constants for the formation of complex A [8]. From these considerations one may assume that the formation of complex B is the rate-determining step.

The Hammett equation was used to quantitatively evaluate the relationship between the structure and reactivity within the limits of the given reaction series.

The graphical solution of the Hammett equation is presented in Fig. 1. The average ρ value found by the method of least squares is −6.475 ± 0.385, while correlation coefficient r is −0.973. According to the data in [11], ρ = −7.3 for the formylation of 2-methoxy-, 2-ethyl-, 2-methyl-, 2-phenyl-, and 3-methylthiophenes with the phosgene—DMF complex in chloroform. Consequently, the formylation of DMF in the presence of phosphorus oxychloride will be less selective than with the phosgene—DMF complex. It follows from the relationship between the logarithms of the rate constants at two different temperatures (Fig. 2) that an isokinetic dependence is observed in the investigated reaction series. The ϰ value of 0.92 and the close values of the preexponential factors make it possible to classify, within a certain approximation, this reaction series as an isoentropic series.

To ascertain the effect of the nature of the solvent on the rate of the investigated reaction we recorded the kinetic curves of the formylation of 2-ethylthiophene with DMF in the presence of phosphorus oxychloride in acetonitrile, dichloroethane, chloroform, and benzene. The indicated solvents do not react with thiophene derivatives, DMF, and phosphorus oxychloride and dissolve the starting compounds and the final products.

The overall third order of the reaction is retained when the formylation of 2-ethylthiophene is carried out in various solvents. The rate constants found are presented in Table 2. A rectilinear dependence between the logarithms of the rate constants and the polarity, polarizability, electrophilicity, and nucleophilicity parameters of the solvents [13] was not observed. In addition, there is a general tendency for an increase in the reaction rate as the dielectric constant of the solvent increases. A rectilinear relationsip between the logarithms of the formylation rate constants and two solvent parameters, viz., the polarity and the polarizability, was found. The correlation equation has the form

$$\lg k_{obs} = a + bY + cP,$$

where

$$Y = \frac{\varepsilon - 1}{2\varepsilon + 1}, \quad P = \frac{n^2 - 1}{n^2 + 2}.$$

At 60°C, $a = -3.21$, $b = 1.51$, and $c = -3.42$; at 70°C, $a = -3.35$, $b = 1.80$, and $c = -2.20$; at 80°C, $a = -2.59$, $b = 1.23$, and $c = -3.54$.

The deviation between the rate constants found and the values calculated from the equation presented above does not exceed 10%.

Thus, the formylation of the investigated thiophene derivatives with DMF in the presence of phosphorus oxychloride is described by a third-order kinetic equation with activation energies of 51-99 kJ/kmole. A relationship between the reactivities and the Hammett σ constants is observed in the investigated reaction series. The existence of a linear relationship between the logarithms of the rate constants and the parameters that characterize the nonspecific interaction between the solvent molecules was established when formylation was carried out in different solvents.

EXPERIMENTAL

2-Formylthiophene [14], 2-iodothiophene [15], and 2-ethylthiophene [16] were synthesized by previously described methods. The thiophene, 2-bromothiophene, 2-tert-butylthiophene, phosphorus oxychloride, and DMF were purified by distillation. The purity of the products was determined by chromatography with a LKhM-72 chromatograph with a flame-ionization detector on a 25% SKT stationary phase applied to Chromaton N-AW (0.2-0.25 mesh). The column was 3 m long and had a diameter of 4 mm; the column temperature ranged from 155 to 175°C. Various dimethyl esters of dicarboxylic acids were used as references. The parameters of the equations were found by the method of least squares [17].

Method for Investigation of the Kinetics. A 25-ml test tube equipped with a reflux condenser fitted with a calcium chloride tube was charged with the substrate, DMF, and phosphorus oxychloride in a molar ratio of 1:1:1 in the determination of the overall reaction order and the dependence on the temperature. The overall volume of the charge was ∿2 ml. The test tube was placed in a thermostat in which the temperature was maintained with an accuracy of ±0.1°C. The reaction was stopped by rapid cooling of the test tube and the addition of excess water to the reaction mixture. The reaction products were extracted with diethyl ether. In individual experiments it was shown that three to five extractions were sufficient for complete extraction. The ether extracts were analyzed by chromatography. The reaction rate was determined by graphical differentiation of the kinetic curves of the dependence of the degree of conversion of the substrate to the aldehyde on the time.

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