Tetrahedron Letters No.48, pp. 4223-4224, 1970. Pergamon Press. Printed in Great Britain.

# KINETICS AND MECHANISM OF THE VILSMEIER FORMYLATION OF THIOPHEN DERIVATIVES[1]

Paolo Linda, Gianlorenzo Marino, and Sergio Santini
Istituto di Chimica Organica - Università di Perugia - Italy

(Received in UK 23 July 1970; accepted for publication 10 September 1970)

In continuation of our studies on the electrophilic substitutions of five-membered heteroaromatic systems[1], we have undertaken a kinetic study of the formylation of thiophen derivatives by dimethylformamide and phosphorus oxychloride and we wish to report the preliminary results obtained.

In spite of the interest aroused by this reaction, it is surprising that no kinetic studies of it have been reported to date.

The reaction has been studied in an inert solvent, dichloroethane, and the rate has been followed by titrating volumetrically the acid present in the hydrolyzed mixture.

Reactions of thiophen and 2-methylthiophen follow third order kinetics, first order in each component:

$$\text{rate} = k_{obs}\,[\text{het}]\,[\text{DMF}]\,[\text{POCl}_3]$$

These kinetics are in agreement with a mechanism involving a rapid pre-equilibrium leading to an electrophilic adduct, followed by a slow attack of the latter on the heterocyclic substrate, with formation of an intermediate which is then converted to the final aldehydic product by the action of water:

$$(1)\quad \text{DMF} + \text{POCl}_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{electrophilic adduct}$$

(2) electrophilic adduct + heterocycle $\xrightarrow{k_2}$ intermediate

(3) (intermediate $\xrightarrow{H_2O}$ formyl derivative)

Such a mechanism leads to the observed kinetics when $k_2 << k_1, k_{-1}$.

These kinetic results substantiate the current hypotheses on the mechanism of this reaction[2,3].

The constant for the equilibrium (1) has been determined to be 42.5 at 25° and 7.2 $l.mole^{-1}$ at 49°, using a spectrophotometric technique. A kinetic study of the formation of the adduct has been also made and the second order rate constants $k_1$ determined at various temperatures.

With very reactive substrates, such as 2-methoxythiophen, step (2) is very fast and step (1) becomes rate-determining: the reaction then follows a second order kinetics and the observed rate constant is equal to the rate constant $k_1$ relative to the formation of the electrophilic adduct. 2-Methylfuran, a substrate of intermediate reactivity[4], exhibits kinetics of order between 2 and 3.

Rate measurements on 2-methyl-5-deuterothiophen, have shown the existence of a small kinetic isotope effect ($k_H/k_D = 1.18 \pm 0.02$). There appears to be no way of deciding if such a small effect is a primary (i.e., indicating a partial weakening of the C-H bond in the transition state) or a secondary one.

A full account of this work will be published in due course.

We thank the "Consiglio Nazionale delle Ricerche" for financial support.

### References

1) Part XIII of the series: Electrophilic substitutions in five-membered heteroaromatic systems. Part XII: S.Clementi, P.Linda and G.Marino, J.Chem.Soc., (B), in the press.

2) H.H.Bosshard and H.Zollinger, Helv.Chim.Acta, 42, 1659 (1959)

3) M.R. de Maheas, Bull.Soc.Chim.France, 1989 (1962).

4) S.Clementi and G.Marino, Tetrahedron, 25, 4599 (1969).