

REACTIONS OF CHLORINATED FURANIDINES. XI.*
NUCLEOPHILIC SUBSTITUTION ON C₍₂₎ ATOM
IN 2-ALKOXY-3-CHLOROTETRAHYDROFURANS

M. KRATOCHVÍL, V. ZEZULA and B. ŠIMÁK

Department of Organic Chemistry,
Purkyně-University, Brno

Received April 19th, 1971

In non-catalysed substitutions of 2-alkoxy-3-chlorotetrahydrofurans only O-acids can react at C₍₂₎-atom. The reaction of *cis*-2-ethoxy-3-chlorotetrahydrofuran with 1-butanol, followed as a monomolecular process ($k = 0.0939 \text{ min}^{-1}$), takes place approximately three times more rapidly than the reaction of the *trans*-isomer, dependent (as shown by the role of retarders of the isomerisation) on the attainment of *trans* \rightleftharpoons *cis* equilibrium.

The investigation of the reactions at C_α of cyclic ethers also comprises the reactivity of the exocyclic C_α-O bond. Kankaanperä and Mikki described¹ the results of a kinetic study of acid catalysed hydrolysis of 2-methoxytetrahydrofurans with a water-alcohol mixture; in addition to 2-hydroxytetrahydrofuran they also identified 2-alkoxytetrahydrofuran in the reaction mixture. From the results of the isomerisation of *cis*-2-ethoxy-3-chlorotetrahydrofuran (*Ib*) in various solvents it is evident that no appreciable reaction takes place on temporarily liberated C_α with C-acids serving as solvents². It is understandable that the exchange of the ethoxy group by stronger O-acids (acetic acid, ethylene chlorohydrin) takes place easily because the processes are autocatalysed. It is also shown that ethanol too, when serving as a solvent, appreciably accelerates the isomerisation of substance *I* without any additional catalysis (at 1 : 1, 1 : 2, and 1 : 3 dilutions k_{rel} is equal to 1.00, 1.92, and 2.22, respectively), and that after its substitution by 1-butanol *cis*- and *trans*-2-butoxy-3-chlorotetrahydrofurans (*Ila, b*) could also be identified in the reaction mixture. This communication is therefore directed to the course of the non-catalysed trans-acetalisation of 2-ethoxy-3-chlorotetrahydrofuran. The process followed is not simple: In addition to the establishment of equilibria during the exchange of alkoxy groups, an isomerisation of the starting *Ib* to the *trans*-isomer *Ia* may take place. The *Iib* formed can also disappear during the attainment of the equilibrium with its *trans*-isomer *Ila*; eventually, mainly at higher temperatures, it is not excluded that thermic dealkoxylation of the reactants may also take place.

Isomerisation of compound *I* was investigated in paper³; present knowledge was completed by the study of the effect of dilution of the system with cyclohexane (1 : 1, 1 : 3, and 1 : 10) on the rate of the change *Ib* \rightleftharpoons *Ia*. The determined value of the rate constant ($k = 1.65 \cdot 10^{-2} \text{ min}^{-1}$, $k_r = 2.50$ at 140°C, ratio of dilution 1 : 1) is charged by an error caused by thermal dealkoxylation, which after 1 : 1 dilution and heating at 140°C for 60 minutes is approx. 4%. With increasing dilution with cyclohexane the isomerisation rate *Ib* \rightleftharpoons *Ia* diminishes. At a 1 : 3 dilution equilibrium is not attained even after 8 hours heating, and at 1 : 10 dilution the isomerisation rate is

* Part X: This Journal 36, 3051 (1971).

practically zero. In contrast to this it was shown that when substance *I* was diluted with a C-acid (nitromethane) the isomerisation rate remains unchanged². The part of the isomerisation $Ib \rightleftharpoons Ia$ which is an accompanying process of the transacetalisation of substance *I* with 1-butanol is demonstrated in Fig. 1 on the basis of the maximum on the curve of the dependence of the concentration of *Ib* on time; it is slower than the exchange of the ethoxy group. The differences in the transacetalisation rates of *Ia* and *Ib* with 1-butanol at 120°C ($k_{cis} = 9.39 \cdot 10^{-2} \text{ min}^{-1}$, $k_{trans} = 3.08 \cdot 10^{-2} \text{ min}^{-1}$) also point to this conclusion.

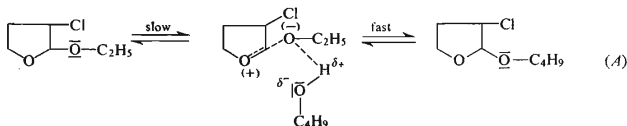
The evaluation of kinetic data has shown that for the calculation of the rate constant of the reactions of substance *Ia,b* with 1-butanol the relationship for a first order reversible reaction is satisfactory. The values of rate and equilibrium constants are as follows (ratio of components 1 : 2):

Temperature, °C	k , min^{-1}	A , min^{-1}	ΔS^\ddagger , e.u.	K
<i>Ia</i>				
100	0.0107	$7.11 \cdot 10^5$	-34.29	2.03
120	0.0308	$8.19 \cdot 10^5$	-34.02	2.21
140	0.0705	$8.19 \cdot 10^5$	-34.12	2.15
<i>Ib</i>				
120	0.0939	$2.50 \cdot 10^6$	-31.80	1.98

From the data we deduce that substance *Ib* reacts with 1-butanol approximately three times faster than the *trans*-isomer *Ia*: The primary process of the transacetalisation of *I* – similarly as in the isomerisation³ $Ia \rightleftharpoons Ib$ – is the labilisation of the $C_\alpha-O_{exo}$ bond, which is easier in *cis*-isomer. The role of a pseudoreagent may be assigned to the *trans*-isomer. Therefore it seems sensible to follow the role of the *cis*-isomer during the transacetalisation of compound *I* with 1-butanol, especially when it was demonstrated that in the presence of solvents retarding isomerisation of 2-alkoxy-3-chlorotetrahydrofurans (dimethylformamide, tetrahydrofuran, etc.²) substance *I* does not react with 1-butanol in tetrahydrofuran (1 : 2, 1 : 3).

The view that the reaction starts with dealkoxylation of *I* for which *cis*-isomer has a suitable arrangement, could not be demonstrated by Wamhoff with NMR spectroscopy⁴. In addition to this it is questionable whether the formed 4-chloro-2,3-dihydrofuran, as a β -chlorovinyl ether, would add the liberated ethanol (in the course of the isomerisation), or 1-butanol (in the course of transacetalisation), by a more rapid process than elimination, if the suitable conditions were not induced by acid catalysis. The conditions are not given for the E2 type, while E1, starting with the formation of the carboxonium-alkoxide ion pair, would have a higher

activation energy than the supposed S_N1 reaction. On the basis of the demonstrated first order of the reaction it can be postulated that the mechanism is an asynchronous heterolysis of the $C_\alpha-O_{exo}$ bond, similar to the S_N1 type (equation (A)).



For the proposed course the fact that the transacetalisation of substance *I* with cyclohexanol takes place at a comparable rate only at a temperature exceeding 140°C is significant. In comparison with the molecules of 1-butanol, sterically more demanding molecules of cyclohexanol have a more limited chance. Another fact connected with the mentioned conditions is that the reaction gives both isomeric 2-cyclohexyl-3-chlorotetrahydrofurans after 60 minutes (in the ratio of *trans* : *cis* equal to 10 : 1), while alcoholysis of 2,3-dichlorotetrahydrofuran with cyclohexanol at 20°C gave only the *trans*-isomer³. The indicated role of 1-butanol as an O-acid is further evident from a dilution study: a) Dilution of the system *Ib*-1-butanol (1 : 1) with cyclohexane caused a slowing down of the transacetalisation; however, not to a proportion corresponding to a reaction of a higher order. b) The increase of the concentration of 1-butanol in the reaction system containing *Ia* and *Ib* in a 9 : 1 ratio does not practically affect the transacetalisation rate at 1 : 1 and 1 : 2 dilution; at a 1 : 4 excess the reaction rate decreases (relative rate after 30 minutes is $k^{1:4}/k^{1:1} = 0.89$,

after 50 min it is 0.97). At 70°C (measured after 75 minutes) a mutual exchange of alkoxyls between *I* and 2-n-butoxytetrahydrofuran also takes place, during which we suppose an analogous mechanism: of the two reactants 2-n-butoxytetrahydrofuran more easily forms a pair of ions of which the carboxonium ion selects during the coordination of the nucleo-

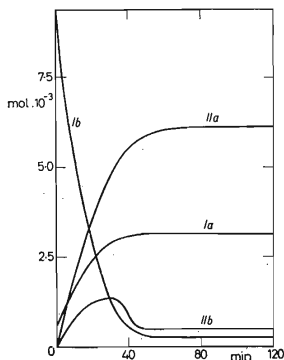


FIG. 1

Time Dependence of the Concentration of Reactants during the Transacetalisation of Substance *Ib* with 1-Butanol (1 : 1, temp. 120°C)

phile between the butoxide anion and the atom of the exocyclic oxygen in *I*. In the resulting reaction mixture 2-*n*-butoxy-3-chlorotetrahydrofuran was proved in addition to the starting compounds.

Therefore we suppose that the transacetalisation of 2-ethoxy-3-chlorotetrahydrofuran with 1-butanol also takes place without an acid catalysis, predominantly as a monomolecular phenomenon with $E_A = 13.36$ kcal/mol and $\Delta S^\ddagger = -31.80$ e.u. The *cis* isomer reacts three times faster than the *trans* isomer and it is the protagonist of this nucleophilic substitution.

EXPERIMENTAL

Chemicals: 2-Ethoxy-3-chlorotetrahydrofuran (*I*) and 2-butoxy-3-chlorotetrahydrofuran (*II*) were prepared according to³; substance *Ia* (96%, the rest is *Ib*) b.p. 55°C/8 Torr, n_D^{20} 1.4386, substance *Ib* (91%, the rest of it is *Ia*) n_D^{20} 1.4468. Mixture *Ia,b* has b.p. 88–90°C/20 Torr, n_D^{20} 1.4429. 2-Ethoxytetrahydrofuran³, b.p. 124°C/758 Torr, n_D^{20} 1.3952. *trans*-2-Cyclohexyloxy-3-chlorotetrahydrofuran obtained on alcoholysis of 2,3-dichlorotetrahydrofuran³ has b.p. 113.5°C/8 Torr, n_D^{20} 1.4695. 2-Acetoxy-3-chlorotetrahydrofuran, b.p. 104–105°C/15 Torr. 2-(β -Chloroethoxy)-3-chlorotetrahydrofuran, b.p. 111°C/15 Torr, n_D^{20} 1.4752, was identical with the substance prepared according to⁵, 2-*n*-butoxytetrahydrofuran, b.p. 45°C/15 Torr, n_D^{20} 1.4239.

Methods: The reactions were carried out in sealed thermostated ampoules, and stopped by cooling them with dry ice. The analyses were carried out with a gas chromatograph Chrom 2 with a steel column 85 cm long, provided with FID and an air thermostat; as a filling poly(ethylene-glycol adipate) was used, wetting was 10% on Rysorb BLK, granulation 0.2–0.31 mm, weight of the filling 17.1 g, nitrogen pressure 0.32–0.34 kPa/cm², hydrogen flow 65 ml/min, air flow 850 ml/min. The method of evaluation is the same as in the paper². The calculation of the rate constants was carried out using a computer and in some instances by a mathematic or graphic method.

We thank Dr J. Pichler for his suggestions and for the kinetic treatment of the data, and Dr J. Patočka for the evaluation of the results of our measurements by means of a computer. Our thanks are also due to Miss J. Ondrová who carried out a part of the gas chromatographic measurements.

REFERENCES

1. Kankaanperä A., Mikki K.: Suomen Kemistilehti B 41, 42 (1968).
2. Zezula V., Kratochvíl M.: This Journal, in press.
3. Zezula V., Kratochvíl M.: This Journal 35, 1746 (1970).
4. Wamhoff H.: Private communication.
5. Kratochvíl M.: This Journal 25, 1356 (1960).

Translated by Ž. Procházka.