

REACTIONS OF CHLORINATED FURANIDINES. IX.*

THE EFFECT OF SOLVENTS
ON FORMATION AND ISOMERISATION
OF *cis*- AND *trans*-2-ALKOXY-3-CHLOROTETRAHYDROFURANS

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The effect of solvent on the course of alcoholysis of 2,3-dichlorotetrahydrofuran with tert-butanol manifests itself in the *trans*:*cis*-2-tert-butoxy-3-chlorotetrahydrofuran ratios; the amount of *cis*-isomer is highest in solvents enhancing S_N2 reactions and lowest in solvents enabling the S_N1 path. The rate of establishing the equilibrium *cis*-2-ethoxy-3-chlorotetrahydrofuran $\xrightleftharpoons[k_2]{k_1}$ *trans*-2-ethoxy-3-chlorotetrahydrofuran is directly proportional to the pK_a value of solvent (in nitromethane $k_1 = 3.14 \text{ min}^{-1}$, $K = 4.1$, in toluene $k_1 = 0.28 \text{ min}^{-1}$, $K = 5.2$). No *cis*-*trans* isomerisation takes place in basic solvents.

In the preceding paper¹ we studied, amongst other things, the effect of bulkiness of alkoxy-groups, as well as the effect of polarity of solvents, on the population of *cis*- and *trans*-2-alkoxy-3-chlorotetrahydrofurans which arise in alcoholysis of 2,3-dichlorotetrahydrofuran. It was possible to follow the effect of both factors simultaneously. Using gas-liquid chromatography, it was proved that in the mixture of *cis*- and *trans*-2-alkoxy-3-chlorotetrahydrofuran an equilibrium exists between the two isomers and one may assume that in some cases the rate at which this equilibrium is achieved will affect the *trans*/*cis* ratio already during the alcoholysis of compound *Ia*

*Ia*, R = Cl*IIa,b*, R = OC₂H₅*IIIa,b*, R = OCH(CH₃)₂*IVa,b*, R = OC(CH₃)₃*a*: *trans*-isomer, *b*: *cis* isomer

In the alcoholysis of compound *Ia* with ethanol in *N,N*-dimethylformamide, the ratio *IIa*/*IIb* = 0.573, with 1-propanol, *IIIa*/*IIIb* = 0.720, and with tert-butanol

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$IVa/IVb = 1.61$; in acetone $IIa/IIb = 0.420$, $IIIa/IIIb = 0.544$, and $IVa/IVb = 21.5$; in cyclohexane $IIa/IIb = 0.352$, $IIIa/IIIb = 0.420$, and $IVa/IVb = 6.29$. In the reaction with ethanol and 1-propanol, the *trans*-/*cis*-ratio increases with increasing polarity of solvent whereas the alcoholysis of compound *Ia* with tert-butanol is not proportional to the polarity of solvent. A more detailed analysis showed that the ratio IVa/IVb is proportional neither to polarity nor to acidity of the medium (Table I). It is necessary, therefore, to seek an explanation in different course of alcoholysis of the compound *Ia* with tert-butanol in the solvents used. In the alcoholysis of compound *Ia* with ethanol and 1-propanol, one may assume that the decisive factor will be the solvolytic reaction of compound *Ia* with these alcohols, and that the solvent will but little affect the course of alcoholysis. The reaction of compound *Ia* with tert-butanol will be difficult owing to the bulkiness of the alcohol, and hence in this case the solvent can play the decisive role. The ratio IVa/IVb in cyclohexane and tetrachloromethane is comparable with the value of IVa/IVb (about 6.5) for the alcoholysis of compound *Ia* with tert-butanol without any solvent¹. The abnormally high values of IVa/IVb (about 21) in acetone, diethyl ether and tetrahydrofuran may be explained by complex formation of compound *Ia* with these

TABLE I

The Effect of Solvents on the Equilibrium $IVa \rightleftharpoons IVb$

Solvent:	CCl_4	C_6H_{12}	$HCON(CH_3)_2$	CH_3CN	CH_3NO_2
$K(IVa/IVb)$:	6.63	6.29	1.61	1.68	2.93
Solvent:	$CO(CH_3)_2$	$(C_2H_5)_2O$	C_4H_8O	C_6H_6	C_6H_5Cl
$K(IVa/IVb)$:	21.5	21.5	20.5	3.78	3.62

TABLE II

The Effect of Solvent on the Relative Rate of Reaction of Compound *Ia* with tert-Butanol and on the Shift of the C_{α} -Cl Absorption Band in the Spectrum of *Ia*

Solvent	Rel. rate	cm^{-1}	Solvent	Rel. rate	cm^{-1}
Cyclohexane	1.0	655	Diethyl ether	3.2	648
Benzene	1.8	650	Nitromethane	5.2	647
Acetone	2.7	653	N,N-Dimethylformamide	5.2	645

solvents; this complex affords by S_N1 mechanism preferentially the *trans*-isomer, analogously to other findings². The lowest values of the ratio IVa/IVb were found for the reaction in *N,N*-dimethylformamide, acetonitrile and nitromethane. The explanation of this fact may be found in the interference of these solvents with the mechanism of the reaction of compound *Ia* with tert-butanol: these solvents may enhance the proportion of S_N2 mechanism by orienting their molecules around the $C_\alpha-Cl$ bond. In benzene and chlorobenzene, IVa/IVb values are lower than in cyclohexane and tetrachloromethane, and therefore we may assume that, in these solvents, in the course of alcoholysis of compound *Ia* with tert-butanol a formation of a π -complex of α -carboxonium ion with aromatic ring takes place. Measurement of relative rates of the reaction of compound *Ia* with tert-butanol (Table II) confirms these assumptions. A study of the effect of solvents on compound *Ia* by means of infrared spectroscopy revealed a shift of the absorption band of $C_\alpha-Cl$ towards higher wavelengths, which is also in accord with the anticipated effect of solvent on the reaction centre of the substrate. The rate of establishing the *cis*- \rightleftharpoons -*trans*-equilibrium was followed for compounds *Iib* and *Iia* at 100°C, 120°C and 140°C. A similar

TABLE III

The Effect of Solvents on the Equilibrium and Rate Constant of Isomerisation $Iib \xrightleftharpoons[k_2]{k_1} Iia$ at 120°C

Solvent	pK_a	K	k_1, min^{-1}	$-\Delta G, \text{kcal mol}^{-1}$
Cyclohexane	40	5.3	0.25	1.30
Toluene	35	5.2	0.28	1.29
Acetonitrile	25	5.1	1.56	1.27
Acetone	20	4.9	2.28	1.24
Nitromethane	11.0	4.1	3.14	1.10
Diethyl malonate	8.0	4.5	6.46	1.17

TABLE IV

The Effect of Temperature on Equilibrium and Rate Constant of Isomerisation $Iib \rightarrow Iia$ in Nitromethane

$t, ^\circ\text{C}$	100	120	140
K	5.4	4.1	3.75
k_1, min^{-1}	0.99	3.14	9.45

measurement for compounds *IVb* and *IVa* was complicated by the fact that the reaction of *Ia* with tert-butanol affords in all cases less than 40% of *IVb*.

The rate of isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ increases in the presence of sulphuric, hydrochloric or a Lewis acid³⁻⁵ (in the presence of saturated zinc chloride in diethyl ether the equilibrium was achieved in 10 minutes at 80°C; $K = 4.26$). The isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ is faster also in protic solvents (Table III); on the other hand, the solvents of basic character (diethyl ether, tetrahydrofuran, N,N-dimethylformamide, nitrobenzene) retard or even stop the isomerisation. The drop in the isomerisation rate in acidic solvents with growing pK_a value of solvents has a trend shown in Table III. On the basis of measured rates of isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ in various solvents, or without solvent, we tried to comprehend the path of this reaction, making some simplifying assumptions. (The rate constants were computed for a simple reversible first order reaction⁶, disregarding the slow pyrolysis of the starting compound⁷ or a possible acid-catalysed decomposition of acetals of the tetrahydrofuran series^{8,9}.) In the isomerisation of compound *I**b*** to *I**a*** in nitromethane, the rate constant is constant for shorter time intervals ($k_1 = 3.14 \text{ min}^{-1}$), however, after 25 minutes $k_1 = 4.77 \text{ min}^{-1}$, and after 30 minutes $k_1 = 6.14 \text{ min}^{-1}$; in these intervals the composition of the reaction mixture is similar to the equilibrium composition, and probably the rate of the side-reaction – the thermal dealkoxylation – manifests itself in the calculation of the rate constants under aforementioned simplifying assumptions. Also the accuracy of equilibrium constant determinations is affected by the same factors. Despite simplifications and limitations made above we were able to find the trend of the rate and equilibrium constant dependence on the pK_a value of solvent. Table IV shows the effect of temperature on equilibrium and rate constant in the isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ in nitromethane. The activation energy[†] of this reaction, $E^* = 17.46 \pm 0.29 \text{ kcal mol}^{-1}$, the frequency factor, $\log A = 6.43 \text{ s}^{-1}$, and the change of entropy of activation, $\Delta S^\ddagger = -29.63 \text{ e.u.}$ The compound *I**b*** isomerises to *I**a*** at 120°C also without solvent, $k_1 = 0.47 \text{ min}^{-1}$, $K = 2.6$. The calculated changes of the free enthalpy of isomerisation (Table III) correspond to the values published for isomerisation of 2,5-dialkoxytetrahydrofurans¹⁰ and for similar reactions in the tetrahydropyran series¹¹, so that the isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ may be also ascribed to the anomeric effect in these compounds. From Table IV we may see that the value of equilibrium constant of isomerisation $I_{IIb} \rightleftharpoons I_{IIa}$ drops with increasing temperature; thus increase of the energy of the system results in higher concentration of the less stable *cis*-isomer in the equilibrium mixture. It is possible to assume three ways of isomerisation. The thermal decomposition of compound *I**b*** and retro-addition of ethanol on 2,3-dihydro-4-chlorofuran would hardly be a possible path for formation of compound *I**a***, except under assumption that the electrophilic addition of ethanol on 2,3-dihydro-4-chlorofuran is a *cis*-addition. A preliminary NMR study¹² of basicity of both oxygen atoms in molecule by means of complex formation of compounds *I**a*** and *I**b*** with

phenol has shown that the exocyclic oxygen is more basic than the endocyclic one, and therefore we need not consider the isomerisation by ring opening and re-cyclisation. These findings are, besides, in accord with the course of hydrolysis of 2-alkoxytetrahydrofurans (with the exception of 2-tert-butoxytetrahydrofuran¹³); however, it is possible to assume that the catalytically acting solvent attacks the exocyclic oxygen under formation of an oxonium ion. The formation of a suitable solvent shell around the reaction center may, in the extreme, contribute to the formation of an ion pair and its momentary re-combination into the more favourable arrangement. The freed alkoxy group is — as the most basic partner — preferred to the conjugated base of the solvent. This may explain the fact that in the reaction mixture it was not possible to prove the presence of a tetrahydrofuran derivative substituted in the α -position with conjugated base of the solvent. When an acid is used as solvent the conjugated base of which is capable to compete with the alkoxide ion, a new product occurs in the reaction mixture: using n-butanol as solvent, it was possible to identify in the reaction mixture — besides compounds *Ila* and *Ilb* — the *cis*- and *trans*-2-n-butoxy-3-chlorotetrahydrofurans.

EXPERIMENTAL

The analyses were performed on a vapour phase chromatograph Chrom II; the conditions were already described¹. The IR-spectra were recorded on a Zeiss UR 10 double beam spectrophotometer in potassium bromide cells of 0.03 cm thickness.

Preparation of Starting Compounds

A mixture of *cis*- and *trans*-2-alkoxy-3-chlorotetrahydrofurans was prepared by a standard procedure¹. Mixture of compounds *Ila* and *Ilb*, rich in the *cis*-isomer, was obtained by the alcoholysis of compound *Ia* (75 g; 0.5 mol) with a threefold excess of anhydrous ethanol. The arising hydrogen chloride was neutralised with anhydrous sodium carbonate and the product was purified by distillation under reduced pressure. The resulting mixture, b.p. 60–60.5°C/30 Torr, n_D^{20} 1.14437 contained 27% of *Ila* and 73% of *Ilb*.

Alcoholysis of *Ia* in Solvents

To a mixture of tert-butanol (ethanol or isopropanol) (0.029 mol) and a given solvent (0.048 mol) (Table I) was added compound *Ia* (1 ml). To neutralize the hydrogen chloride formed, anhydrous sodium carbonate (1 g) was added. The reaction was carried out at about 19°C and the crude reaction mixture was analysed after 48 hours.

The relative reaction rates of compound *Ia* with tert-butanol were determined from the ratio of unreacted *Ia* and the sum of *IVa* and *IVb* in the reaction mixture after 30 minutes, using chlorobenzene (0.1 ml) as internal standard. The concentration of reactants and solvents was the same as in the preceding experiment.

Isomerisation Procedure

A mixture of compound *Ila* (27%) and *Ilb* (73%) was mixed with a twofold molar amount of solvent (cyclohexane, toluene, acetonitrile, acetone, nitromethane, diethyl malonate, diethyl ether,

tetrahydrofuran, N,N-dimethylformamide, nitrobenzene) and with chlorobenzene (0.1 ml) which was used as internal standard. This mixture was pipetted (0.1 ml) into glass ampoules which were sealed and thermostated at 120°C (100° or 140°C). At time intervals, the samples were removed, quenched in solid carbon dioxide and analysed by vapour phase chromatography.

Determination of equilibrium constants: The reaction mixture was heated till constant ratio *Ila/I Ib* was achieved, and then analysed by vapour phase chromatography. The equilibrium constant was determined as the ratio of the peak areas. The equilibrium was approached from both sides, the required pure *trans*-isomer was isolated by preparative vapour phase chromatography¹.

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