

REACTION OF 2-CHLOROTETRAHYDROFURAN
AND 2,3-DICHLOROTETRAHYDROFURAN WITH PYRIDINE
AND ITS MONOSUBSTITUTED DERIVATIVES*

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The reaction of pyridine and its monosubstituted derivatives with 2-chlorotetrahydrofuran (*I*) or 2,3-dichlorotetrahydrofuran (*II*) in dimethylformamide follows the first-order rate law. The dissociation of the C_{α} -Cl bond asserts itself as the step determining the overall reaction rate. Compound *I* reacts about $2 \cdot 10^4$ times faster than compound *II*. The character of the base affects the reaction rate constant values which afford in the case of 3- and 4-monosubstituted pyridines a linear dependence of the free energy in reactions with compound *I* and *II* with the use of Jaffe σ constants, and with ρ equal to -0.31 . The σ value of the 4-aldoxime group was estimated as about -0.49 . Activation energies and entropies* were determined.

The formation of pyridinium salts from pyridine or its derivatives and the organic halo derivatives has been paid sufficient attention so far¹. The reaction depends on the alkyl halide (*i.e.*, on the readiness of dissociation of the R—X bond which is affected by the character of the halo atom X as well as the structure of the organic residue R), on the basicity of the nitrogen atom in the pyridine derivative to be quaternised (*i.e.*, on the influence of substituents attached to the pyridine ring), and on some additional factors, particularly on the medium. The factors mentioned affect not only the reaction rate but also the reaction order. The alkyl halides react usually relatively slowly and often follow the bimolecular mechanism, while substances bearing an activated halo atom such as α -halo ethers (including the present compounds *I* and *II*) react relatively fastly and follow the first-order rate law^{2-4,9}. The dependence of the reaction course on the structure of the moiety of the halo derivative has been exemplified on the reaction of substituted benzyl chlorides with pyridine⁵. In the present paper, we wish to examine the structural effect of the pyridine derivative on the reaction course and to compare the reactivity of compounds *I* and *II*.

The substitution reactions of the α -halo atom in compounds *I* and *II* might be accompanied by eliminations but under conditions of our measurements and with the

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use of pyridine as the second reaction component, only substitution has been observed and no elimination products have been found⁶.

EXPERIMENTAL

Methods

The reaction was followed by measuring the conductivity of the reaction mixture in dimethylformamide. Conductivity was converted to the concentration of the product by means of calibration curves made for all test-substances and temperatures using limit conductivity values when the reaction rate is zero and corresponds to the concentration of the product at the complete conversion. The reactants were always used in an equimolar ratio. Measurements were performed on a Type OK-102 Conductivity Meter (platinum black electrodes). The 50 ml vessel was ultrathermostatted (water). The dimethylformamide-containing vessel was charged with the pyridine derivative to be measured and the reagent was added. After a thorough agitation of the content, the time dependence of the conductivity was measured.

TABLE I
Monosubstituted Pyridine Derivatives as Test Substances

Formula	Substituent	σ	M.p., °C	B.p., °C	d_4^{25}	n_D^{25}
IV	2-Br	—	—	194	1.167 ¹⁵	1.574 ²²
V	2-CH ₃	—	—	128	0.950 ¹⁵	1.501 ²⁰
VI	3-CH ₃	-0.07	—	143—144	0.930 ¹⁵	1.504 ²⁴
VII	4-CH ₃	-0.17	—	144—145	0.957 ¹⁵	1.508 ²²
VIII	4-C ₂ H ₅	-0.15	—	163—165	0.936 ²⁰	1.446 ²²
IX	2-CO ₂ H	—	135—136 (decomp.)	—	—	—
X	3-CO ₂ H	0.35	235 (subl.)	—	1.473 ²⁰	—
XI	4-CO ₂ H	0.26	315 (decomp.)	—	—	—
XII	2-CO ₂ C ₂ H ₅	—	—	122 (13 Torr)	1.119 ²⁰	1.509 ²³
XIII	3-CO ₂ C ₂ H ₅	0.39	8—9	225	1.107 ²⁰	1.504 ²³
XIV	4-CO ₂ C ₂ H ₅	0.52	—	113 (30 Torr)	1.009 ¹⁵	1.501 ²³
XV	2-COCH ₃	—	—	192	—	1.526 ²³
XVI	3-COCH ₃	0.31	—	222—223	—	1.534 ²³
XVII	4-COCH ₃	0.52	15.5	212	—	1.524 ²³
XVIII	2-CH=NOH	—	109—110	—	—	—
XIX	4-CH=NOH	—	110—111	—	—	—

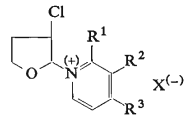
Materials

Dimethylformamide was dried by azeotropic rectification with benzene; the water content was then lower than 0.01%, as determined according to Fischer; n_D^{20} 1.4261. 2-Chlorotetrahydrofuran (*I*) was prepared by photochlorination of tetrahydrofuran³ at -25°C and distillation under diminished pressure; b.p. $30-32^\circ\text{C}/13$ Torr; n_D^{20} 1.4635; d_4^{20} 1.1932. 2,3-Dichlorotetrahydrofuran (*II*) was obtained by chlorination of tetrahydrofuran^{3,7} at $25-30^\circ\text{C}$ and distillation at 59 to $60^\circ\text{C}/16$ Torr; n_D^{20} 1.4833; d_4^{20} 1.3271. Pyridine (*III*) was dried with potassium hydroxide pellets and distilled at $114-116^\circ\text{C}$; n_D^{20} 1.5073; d_4^{20} 0.9815; $\sigma = 0$. The monosubstituted pyridine derivatives *IV-XIX* are shown in Table I. Compounds *V-XVII* were prepared in Department of Organic Chemistry, Institute of Chemical Technology, Prague; compounds *XVIII* and *XIX* were synthesized in the Research Medical Institute, Hradec Králové.

Pyridinium Derivatives

The pyridinium chlorides obtained by reaction of the chloro derivatives *I* and *II* with substituted pyridines *III-XIX* are strongly hygroscopic. In some cases, the use of ClO_4^- , I_3^- , and FeCl_4^- as anions led to stable, nonhygroscopic, and defined salts (Table II). Compound *XX* was prepared from a 20% ethanolic solution of N-[2-(3-chloro)tetrahydrofuryl]pyridinium chloride (*XXVII*) by the addition of a 10% ethanolic solution of perchloric acid; on standing, the mixture deposits

TABLE II
Stable Pyridinium Salts



Formula	R ¹ R ²	R ³ X	R' _F R _F	M.p., °C	Calculated/Found		
					% C	% H	% N
<i>XX</i>	H	H	0.53	141-143	38.20	3.88	4.93
	H	ClO ₄	0.35		37.69	3.80	4.00
<i>XXI</i>	H	H	—	90-93	19.12	1.96	2.48
	H	I ₃	—		19.02	1.95	2.05
<i>XXII</i>	H	H	0.50	132-134	28.23	2.88	3.66
	H	FeCl ₄	0.42		27.97	2.81	3.12
<i>XIII</i>	H	H	0.85	140-141	30.38	3.54	3.54
	CH ₃	FeCl ₄	0.32		30.35	3.44	3.47
<i>XXIV</i>	H	CH ₃	0.78	141-143	30.38	3.54	3.54
	H	FeCl ₄	0.30		29.87	3.41	3.36
<i>XXV</i>	CH=NOH	H	0.72	130-132	28.22	2.82	6.58
	H	FeCl ₄	0.23		28.36	2.80	6.66
<i>XXVI</i>	H	CH=NOH	0.70	126-127	28.22	2.82	6.58
	H	FeCl ₃	0.25		28.18	2.79	6.38

TABLE III

The k Constant Values in Reactions of 2-Chlorotetrahydrofuran (*I*) with Monosubstituted Pyridines along with Activation Energy E_A (kcalmol⁻¹) and Entropy ΔS_{293}^\ddagger Values

Substituent Compound	T °C	k s ⁻¹	E_A ΔS_{293}^\ddagger	Substituent Compound	T °C	k s ⁻¹	E_A ΔS_{293}^\ddagger
4-CH=NOH <i>XIX</i>	20	1.92 ± 0.05	6.1 ± 0.2	4-H	20	1.28 ± 0.07	5.7 ± 0.5
	15	1.32 ± 0.01	-36.8 ± 0.7	<i>III</i>	15	0.87 ± 0.04	-39.0 ± 1.7
	10	1.09 ± 0.03			10	0.72 ± 0.06	
3-CH ₃ <i>VI</i>	20	1.43 ± 0.03	5.8 ± 0.3	4-CO ₂ H	20	1.10 ± 0.06	5.6 ± 0.2
	15	0.98 ± 0.08	-38.4 ± 1.0	<i>XI</i>	15	0.74 ± 0.02	-39.6 ± 0.7
	10	0.81 ± 0.07			10	0.61 ± 0.04	

crystals of compound *XX*. Crystals of compound *XXI* were obtained from an aqueous solution of compound *XXVII* and KI₃. Compounds *XXII*–*XXVI* were prepared from the corresponding N-substituted pyridinium chlorides dissolved in a minimum amount of boiling ethanol and a hot saturated ethanolic solution of ferric chloride; on cooling down, the mixture deposited crystals. The purity of preparations was checked by thin-layer chromatography on silica gel CH 40–100 (Lachema, Brno, Czechoslovakia) in the solvent system 1-butanol–conc. hydrochloric acid–ac-

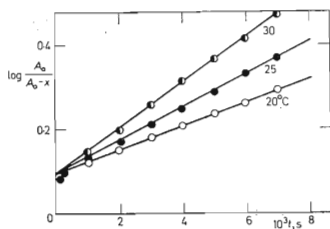


FIG. 1

Conversion Dependence for the System 2,3-Dichlorotetrahydrofuran (*II*) and Pyridine (*III*), $A_0 = 2.06 \cdot 10^{-2} \text{ mol l}^{-1}$

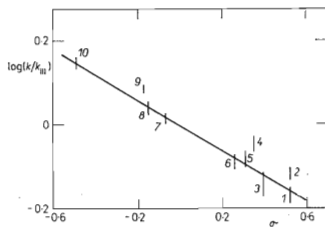


FIG. 2

Correlation of Relative Rates of the Pyridinium Salt Formation from 2-Chlorotetrahydrofuran (*I*) and 2,3-Dichlorotetrahydrofuran (*II*) with Monosubstituted Pyridines, Based on Pyridine (*III*)

Designations of pyridine derivatives: 1 *XVII*, 2 *XIV*, 3 *XIII*, 4 *X*, 5 *XVI*, 6 *XI*, 7 *VI*, 8 *VIII*, 9 *VII*, 10 *XIX* (the σ constant determined).

tone (3 : 1 : 1). The spots of compounds *XXI*–*XXVI* are coloured; the spot of compound *XX* exhibits fluorescence under ultraviolet light. Compounds listed in Table II (except for compound *XXI*) along with melting point values and elemental analyses did not contain any contaminations. The R_F values in Table II are accompanied by R'_F values of the analogous compounds substituted on the nitrogen atom by hydrogen.

TABLE IV

The k Constant Values in Reactions of 2,3-Dichlorotetrahydrofuran (*II*) with Monosubstituted Pyridines along with Activation Energy E_A (kcalmol⁻¹) and Entropy ΔS_{303}^\ddagger Values

Substituent Compound	T °C	$10^4 k$ s ⁻¹	E_A ΔS_{303}^\ddagger	Substituent Compound	T °C	$10^4 k$ s ⁻¹	E_A ΔS_{303}^\ddagger
4-CH=NOH <i>XIX</i>	30	1.79 ± 0.03	14.5 ± 0.3	4-CH ₃ <i>VII</i>	30	1.56 ± 0.05	14.5 ± 0.3
	25	1.28 ± 0.02	-28.4 ± 1.0		25	1.10 ± 0.03	-28.6 ± 0.7
	20	0.88 ± 0.02			20	0.76 ± 0.03	
4-C ₂ H ₅ <i>VIII</i>	30	1.42 ± 0.04	15.3 ± 0.2	3-CH ₃ <i>VI</i>	30	1.33 ± 0.05	14.9 ± 0.5
	25	1.05 ± 0.02	-26.2 ± 0.7		25	0.95 ± 0.04	-27.6 ± 1.6
	20	0.70 ± 0.02			20	0.65 ± 0.04	
4-CO ₂ H <i>XI</i>	30	1.02 ± 0.06	13.8 ± 0.3	3-COCH ₃ <i>XVI</i>	30	1.06 ± 0.07	14.5 ± 0.1
	25	0.72 ± 0.06	-31.8 ± 1.0		25	0.75 ± 0.05	-29.4 ± 0.3
	20	0.50 ± 0.07			20	0.52 ± 0.08	
3-CO ₂ H <i>X</i>	30	1.16 ± 0.3	14.3 ± 0.3	3-CO ₂ C ₂ H ₅ <i>XIII</i>	30	0.89 ± 0.09	14.4 ± 0.1
	25	0.83 ± 0.04	-29.9 ± 1.0		25	0.63 ± 0.08	-30.1 ± 0.3
	20	0.57 ± 0.07			20	0.44 ± 0.09	
4-CO ₂ C ₂ H ₅ <i>XIV</i>	30	0.96 ± 0.07	14.5 ± 0.1	4-COCH ₃ <i>XVII</i>	30	0.84 ± 0.08	14.6 ± 0.2
	25	0.68 ± 0.07	-29.6 ± 0.3		25	0.59 ± 0.09	-29.5 ± 0.7
	20	0.47 ± 0.08			20	0.41 ± 0.06	
<i>III</i>	30	1.27 ± 0.04	14.6 ± 0.1	2-Br <i>IV</i>	30	1.65 ± 0.05	14.5 ± 0.1
	25	0.89 ± 0.06	-28.7 ± 0.3		25	1.15 ± 0.02	-28.5 ± 0.3
	20	0.62 ± 0.04			20	0.81 ± 0.03	
2-CH ₃ <i>V</i>	30	1.21 ± 0.03	14.6 ± 0.1	2-CO ₂ H <i>IX</i>	30	0.93 ± 0.06	14.8 ± 0.1
	25	0.85 ± 0.04	-28.8 ± 0.3		25	0.65 ± 0.07	-29.7 ± 0.3
	20	0.59 ± 0.06			20	0.45 ± 0.07	
2-CO ₂ C ₂ H ₅ <i>XII</i>	30	0.80 ± 0.08	14.1 ± 0.1	2-COCH ₃ <i>XV</i>	30	0.79 ± 0.07	14.3 ± 0.2
	25	0.57 ± 0.10	-31.2 ± 0.3		25	0.55 ± 0.10	-30.6 ± 0.7
	20	0.40 ± 0.09			20	0.39 ± 0.08	
2-CH=NOH <i>XVIII</i>	30	1.10 ± 0.05	14.8 ± 0.5				
	25	0.77 ± 0.05	-28.3 ± 1.7				
	20	0.49 ± 0.06					

RESULTS AND DISCUSSION

The conversion dependence exemplified on the reaction of compound *II* with compound *III* (Fig. 1) demonstrates that the reaction is of the first order with respect to compound *II*. An analogous dependence was obtained in all the remaining cases. The reactions follow the scheme given in an earlier paper³; the order-determining step is the dissociation of the C_{α} -Cl bond. The character of the base asserts itself in the next step which competes with the reverse process of dissociation and thus participates on the overall reaction rate. The values of the rate constant *k* determined from six measurements for each reaction are shown in Tables III and IV along with the corresponding activation energy and entropy. The σ constant values⁸ shown in Table I are used for the linear correlation. Results of correlation in the case of 3- and 4-monosubstituted derivatives are shown in Fig. 2 which may be used to estimate the ρ value for the reaction of compound *I* as well as *II* (-0.31 in both cases). With the use of rate constants in reactions of compound *XIX*, the σ value of the 4-CH=NOH group was estimated as -0.49 ± 0.04 . The relation of reactivities of compound *I* and *II* is obtained by comparison of rate constant values in the corresponding reactions of these substrates at 20°C; the ratio $k_I/k_{II} = (2.16 \pm 0.05) \cdot 10^4$ may be inferred for compounds listed in Table III.

It may be seen from Fig. 1 that for the time $t = 0$ certain conversion value is greater than zero. Explanation of this effect may be based on dissociation of compound *II* which is in equilibrium with the elimination products, namely, 2,3-dihydro-4-chlorofuran, and hydrogen chloride, neutralisation of the latter by the pyridine base proceeds very fastly. Such an observation^{9,10} has been made also in some other reactions of compound *II*. The behaviour of compound *I* is analogous. From extrapolation of the linear portion of conversion plots for $t = 0$, there was calculated the eliminated amount of the reagent $15.5 \pm 0.5\%$ with compound *I* and $9.1 \pm 0.3\%$ with compound *II* (at 20°C, without dilution).

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