KINETICS OF ALKALINE HYDROLYSIS OF MONO- AND DIMETHYL ESTERS OF 2,3- AND 3,4-THIOPHENEDICARBOXYLIC ACIDS, CYANOTHIOPHENECARBOXYLIC ACIDS AND THEIR DIHYDROANALOGUES

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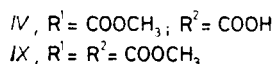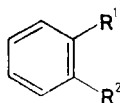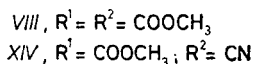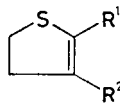[b] *Chemical Institute, Comenius University, 842 15 Bratislava*

Kinetics of alkaline hydrolysis of mono- and dimethyl esters of 2,3- and 3,4-thiophenedicarboxylic acids and their dihydroanalogues have been studied in 70% dioxane. The rate measurements have been carried out by the titrimetric method and the k_1, k_2 rate constants evaluated by the Frost–Schwemer method. The activation parameters of these reactions have been calculated. The results are compared with kinetic parameters of alkaline hydrolysis of methyl and dimethyl phthalates. The hydrolysis rate is significantly affected by the cyclic system to which the methoxy-carbonyl groups are bound, the reactivity order being: Dihydrothiophene > thiophene > benzene. Also measured were the kinetics of alkaline hydrolyses of methyl 4-cyano-3-thiophene-carboxylate and 3-cyano-2-thiophenecarboxylate and of their dihydroanalogues. No meaningful prefer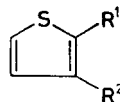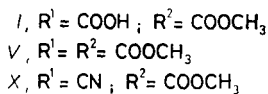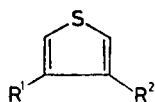ence of the hydrolysis of the group at the position 2 has been observed in case of 2,3--isomers. However, it has been confirmed that the hyper- and hypo-*ortho* transfer of electronic effects operates in the thiophene nucleus.

Relatively few of available papers deal with kinetic studies of hydrolysis of dialkyl dicarboxylates. The greatest problem of such studies was (and to a certain extent still is) connected with reliable and precise evaluation of the hydrolysis rate constants of the two steps (k_1, k_2), because the alkaline hydrolysis of diesters does not obey any simple kinetic equation of the second-order reaction but represents (from kinetic point of view) a second-order consecutive competitive reaction (the hydrolysis of the second ester group), which is rather complicated for calculation. After several un-successful attempts of various authors[1−4], Frost and Schwemer[5] published a method for sufficiently exact calculation of the k_1, k_2 rate constants. This method has been used unchanged until now[6−8]. We also have applied it to the estimation of k_1 and k_2 in this study of hydrolysis of dimethyl esters of 3,4-thiophenedicarboxylic (*V*), 2,3--thiophenedicarboxylic (*VI*), 2,5-dihydro-3,4-thiophenedicarboxylic (*VII*), 4,5-di-hydro-2,3-thiophenedicarboxylic (*VIII*), and phthalic acids (*IX*). The last compound mentioned served for comparison of the effects. However, the method was modified. In the procedure by Frost and Schwemer the $\alpha = [A]/[A]_0$ values (for the meaning

of symbols see Experimental) are plotted against time on a semilogarithmic paper (time in log scale), and from the resulting smooth curve, time values are read for fixed percentual decreases of hydroxyl ion concentration (the times t_{20}, t_{30}, ..., t_{60} correspond to 20, 30, ..., 60% conversion of the reaction, respectively). We have chosen a procedure in which each two successive experimental points were inter-related on the basis of power approximation, and the times t_{20} through t_{60} are read from the curves thus obtained. The remaining calculation procedure was considerably simplified by a program allowing to complete the calculation on an EMG-666 computer within several minutes. The α–t dependence was also graphically recorded in order to exclude erroneous experimental points.

In a similar manner we measured the rate constants of alkaline hydrolysis of three theoretically possible monoesters of *ortho*-substituted thiophenedicarboxylic acids: 4-methoxycarbonyl-3-thiophenecarboxylic (*I*), 2-methoxycarbonyl-3-thiophenecarboxylic (*II*), 3-methoxycarbonyl-2-thiophenecarboxylic (*III*), and (for comparison) 2-methoxycarbonylbenzoic (*IV*) acids. As these constants are defined identically as the k_2 rate constants of alkaline hydrolysis of the diesters $V - VIII$, they could serve us for verification of accuracy of the k_2 calculation by the Frost–Schwemer

I, R¹ = COOH ; R² = COOCH₃
V, R¹ = R² = COOCH₃
X, R¹ = CN ; R² = COOCH₃

II, R¹ = COOCH₃ ; R² = COOH
III, R¹ = COOH ; R² = COOCH₃
XI, R¹ = COOCH₃ ; R² = CN
XII, R¹ = CN ; R² = COOCH₃

VII, R¹ = R² = COOCH₃
XIII, R¹ = CN ; R² = COOCH₃

VIII, R¹ = R² = COOCH₃
XIV, R¹ = COOCH₃ ; R² = CN

IV, R¹ = COOCH₃ ; R² = COOH
IX, R¹ = R² = COOCH₃
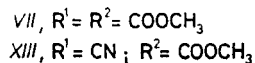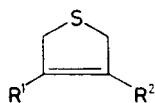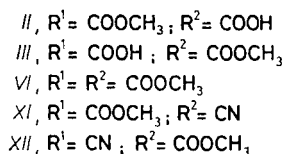
procedure, and, in the case of ester *VI*, they provide rough information about the direction of the alkaline hydrolysis of diesters with non-equivalent methoxycarbonyl groups.

In usual ways we also measured and evaluated the rate constants of alkaline hydrolysis of methyl esters of 4-cyano-3-thiophenecarboxylic (X) and 3-cyano-2--thiophenecarboxylic (XI) acids and their dihydro analogues *XIII*, *XIV*.

EXPERIMENTAL

Solvents and Solutions

The redistilled water was devoid of CO_2 (several minutes boiling and subsequent cooling under nitrogen). Dioxane (*p.a.*, Lachema, Brno) was refluxed with sodium and rectified under nitrogen, the fraction boiling at 100·5 — 101·5°C was collected. Methanol (*p.a.*) was refluxed with magnesium methoxide and rectified. The sodium hydroxide solutions were prepared by dissolution of sodium in redistilled water free of CO_2 under nitrogen and were standardized with potassium phthalate solution (phenolphthalein).

Synthesis and Purification of the Substances Used

Methyl hydrogen 3,4-*thiophenedicarboxylate* (*I*) was prepared from 3,4-thiophenedicarboxylic acid according to ref.[9]. Three recrystallizations from water gave a product melting at 116·0 to 116·5°C.

2-*Methoxycarbonyl-3-thiophenecarboxylic acid* (*II*) was prepared by partial esterification of 2,3-thiophenedicarboxylic acid according to ref.[10] and recrystallized from water, m.p. 120 — 121°C. 3-Methoxycarbonyl-2-thiophenecarboxylic acid (*III*) was prepared by partial acid-catalyzed hydrolysis of dimethyl 2,3-thiophenedicarboxylate according to ref.[10] and recrystallized from water, m.p. 103 — 104°C.

Methyl hydrogen phthalate (IV) was recrystallized from benzene; m.p. 85°C. The compounds *V*, *VI*, *VII*, *VIII*, *X*, *XI*, *XIII*, *XIV* were prepared according to ref.[11]: Dimethyl 3,4-thiophenedicarboxylate (*V*), m.p. 60 — 61°C (diethyl ether), dimethyl 2,3-thiophenedicarboxylate (*VI*), m.p. 34°C (diethyl ether). Dimethyl 2,5-dihydrothiophene-3,4-dicarboxylate (*VII*) was prepared by esterification of the corresponding dicarboxylic acid according to ref.[12] and purified by rectification (b.p. 130 — 131°C/400 Pa, $n_D^{23} = 1·5180$). Dimethyl 4,5-dihydrothiophene-2,3-dicarboxylate (*VIII*) was prepared similarly to *VII*; b.p. 127 — 129°C/400 Pa. Dimethyl phthalate (*IX*) was redistilled (b.p. 283 — 284°C, $n_D = 1·5138$). Methyl 4-cyano-3-thiophenecarboxylate (*X*) m.p. 97°C (diethyl ether). Methyl 3-cyano-2-thiophenecarboxylate (*XI*), m.p. 104 — 105°C (diethyl eter). Methyl 4-cyano-2,5-dihydrothiophene-3-carboxylate (*XIV*), m.p. 54°C (diethyl ether–petroleum ether).

Kinetic Measurements

The kinetic measurements of alkaline hydrolysis of the diesters were carried out by the methods described in detail in refs[5,9,13]. The required weighed amount of the diester was dissolved in 35 ml dioxane and 15 ml redistilled water free of CO_2 was added under nitrogen. In another flask, 35 ml dioxane was mixed with 15 ml NaOH solution under nitrogen (the hydroxide solution of suitable concentration was prepared by dilution of standard NaOH solution with water).

The two solutions were kept in a thermostat for 30 min and then combined (they contained equivalent amounts of diester (0.005 mol l^{-1}) and NaOH (0.010 mol l^{-1})) under inert atmosphere. At definite time intervals, 5 ml samples were withdrawn by means of a pipette and added to an excess of standard hydrochloric acid, and the solution obtained was retitrated with standard NaOH solution (phenolphthalein). The kinetic measurements of hydrolysis of the monoesters of the carboxylic acids were carried out in usual way using equivalent concentrations of ester and hydroxide. The kinetic measurements of the hydrolysis of cyanoesters were performed according to ref.[14].

RESULTS AND DISCUSSION

Evaluation of the Kinetic Measurements

The alkaline hydrolysis of diesters represents a kinetic system of consecutive competitive reactions of the 2nd order described by the equations

$$A + B \xrightarrow{k_1} C + E$$

$$A + C \xrightarrow{k_2} D + E.$$
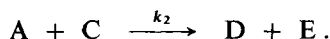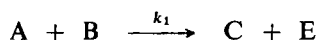
Therefrom it follows:

$$d[A]/dt = -k_1[A][B] - k_2[A][C] \qquad (1)$$

$$d[B]/dt = -k_1[A][B] \qquad (2)$$

$$d[C]/dt = k_1[A][B] - k_2[A][C], \qquad (3)$$

where A, B, C, D, and E stand for the hydroxide, diester, semiester, dianion, and the methanol formed, respectively. Let the starting concentrations of A and B be $[A]_0$ and $[B]_0$, resp. The numerical calculation can be simplified by introduction of dimensionless variables α, β, τ and the K parameter:

$$\alpha = [A]/[A]_0 \qquad \beta = [B]/[B]_0$$

$$\tau = [B]_0 k_1 t \qquad K = k_1/k_2.$$

For more details see ref.[5]. The α values were plotted against time. These experimental points were linked in the following way: The first two points were linked by a curve described by the equation $y = b_0 + b_1 x + b_2 x^2$, i.e., by quadratic approximation. The same procedure was used for the last two points. All the remaining points were treated in such way that also two further adjacent points were taken into account, i.e., four points were interlinked by a curve with the equation

$$y = b_0 + \sum_{i=1}^{3} b_i x^i \,, \tag{4}$$

but graphically only the section between the two middle points was represented. These operations were carried out by means of the EMG-666 computer with a plotter recording the graphical course, which enabled the experimentally erroneous points to be excluded. From the curve thus obtained, time data were determined corresponding to fixed percentual sections of the reaction course, *i.e.*, time points by which 10, 20, ..., 60% of the starting diester had reacted. Furthermore, time ratios were calculated for various percentual ratios of the reaction. Using the tables by Frost and Schwemer[5] we calculated the values $1/K = k_1/k_2$ from these data. From the known average $1/K$ value, the τ value was calculated for various α values. The k_1 values were obtained from the definition $\tau = [B]_0 k_1 t$, and, k_1 and $1/K$ being known, the k_2 values were determined.

TABLE I

Rate measurement of hydrolysis of dimethyl 3,4-thiophenedicarboxylate in 70% dioxane. Starting concentrations: Diester 5 mmol l^{-1}, NaOH 10 mmol l^{-1}. Concentration of NaOH for the titration 10·1 mmol l^{-1}, concentration of HCl 10·64 mmol l^{-1}, volume of HCl 5 ml, sample volume 5 ml, temperature 35·00 ± 0·05°C

Time s	$[OH^-]$ mmol l^{-1}	$\alpha = [OH^-]/[OH^-]_0$
224	8·741	0·874
332	8·378	0·838
439	7·953	0·795
596	7·549	0·755
740	7·287	0·729
892	7·166	0·717
1 153	6·620	0·662
1 354	6·196	0·620
1 532	5·893	0·589
1 726	5·630	0·563
2 001	5·327	0·533
2 318	5·065	0·507
2 854	4·742	0·474
3 637	4·176	0·418
4 157	4·014	0·401
5 283	3·570	0·357
5 876	3·368	0·337

Typical calculation course is shown in Tables I and II with compound V as the example. The activation parameters of the alkaline hydrolyses of mono- and diesters of carboxylic acids were calculated from the Eyring equation. By evaluation of rate constants of two independent experiments at identical conditions we determined the maximum error of the measurement as the percentual difference of these two values measured. The relative error of the measurement was calculated by means of the relation given in ref.[15].

The standard errors of activation parameters were calculated on the basis of the parameters of the linear regression by which these parameters were determined. The standard deviations in these correlations express the magnitude of error of the determination of the activation enthalpy and activation entropy.

The experimental kinetic parameters of alkaline hydrolysis of monomethyl esters of thiophenedicarboxylic acids and phthalic acid are presented in Table III and those of the dimethyl esters in Table IV. From data of Table III it follows that the velocity of alkaline hydrolysis of monoesters of the dicarboxylic acid studied decreases in the order: $III > I > II > IV$, i.e., methyl hydrogen phthalate reacts the most slowly. The isomer III is hydrolyzed about twice as fast as II. All the rate constants measured have relatively low values, which is due to a strong electron-donating effect of $-COO^-$ group on the hydrolysis rate of methoxycarbonyl group. This effect is so dominant that hardly any serious conclusions can be made about relative reactivites of the methoxycarbonyl groups at different positions of thiophene ring or at benzene and thiophene rings. Although the differences between the individual rate constants are indistinct, some conclusions can be made when taking into account the thermodynamic values obtained. The relatively low value found for the activation enthalpy of the alkaline hydrolysis of I can explain the inferior transfer of negative effect

TABLE II

Calculation of rate constants of alkaline hydrolysis of dimethyl 3,4-thiophenedicarboxylate (V)

R_X %	t s	Percentages compared	t_{rel}	$1/K^a$	τ	$k_1{}^a$ $dm^3\ mol^{-1}\ s^{-1}$
20	426	60/20	9·544	6·76	0·269	0·1264
30	919	60/30	4·424	4·53	0·486	0·1059
40	1 464	60/40	2·775	5·09	0·810	0·1106
50	2 418	60/50	1·681	4·96	1·331	0·1102
60	4 064	50/20	5·677	8·68^b	2·251	0·1108
—	—	50/30	2·632	4·14	—	—

^{a} The average for $1/K$ is 5·10, the average for k_1 and k_2 being 0·1128 and 0·0221 $dm^3\ mol^{-1}\ s^{-1}$, respectively. ^{b} Not involved into the average due to large deviation.

of COO^- group from the hypo-*ortho* position at thiophene ring as compared with the hyper-*ortho* positions of isomers *II* and *III*. Therewith connected is the smaller "retardation" proper of the hydrolysis reaction rate by the COO^- anion as compared with *II* and *III*. It is only due to high negative value of the activation entropy of hydrolysis of *I*, that merely average reaction rate is actually measured and its value lies between those of *III* and *II*.

From the values given in Table IV it follows that the rate constants of the first step of alkaline hydrolysis, k_1, of diesters *V—IX* decrease in the order: *VII* $\gg$ *VIII* > > *VI* > *V* > *IX*, *i.e.*, regardless of positions of methoxycarbonyl groups, the reactivity in the various cyclic systems decreases in the order: Dihydrothiophene > > thiophene > benzene. In compounds *VII* and *VIII* mutual interactions of two methoxycarbonyl groups are realized through a double bond which obviously ensures a more efficient transfer of electronic effects as compared with the aromatic system. It is, however, an unexpected result, that the k_1 value of compound *VIII* is three times smaller than k_1 of *VII*. In this case the sulphur atom probably plays an important role in the transfer of the effect of methoxycarbonyl group. A similar decrease of the transfer of the effect of COO^- from position 2 to 3 was observed

TABLE III

Kinetic parameters of alkaline hydrolysis of monoesters of thiophenedicarboxylic acids and phthalic acid in 70% (v/v) dioxane

Compound	Serial No.	Temperature °C	$k \cdot 10^{3a}$	$\Delta H^{\neq b}$	$-\Delta S^{\neq c}$
I	1	25	10·5	55·0	98
	2	35	22·8		
	3	45	45·4		
II	4	25	5·9	61·8	80
	5	35	14·2		
	6	45	30·0		
III	7	25	12·7	60·2	79
	8	35	30·1		
	9	45	62·1		
IV	10	25	5·1	57·3	97
	11	35	9·9		
	12	45	23·3		

[a] Max. error $\pm 3\%$; [b] max. deviation ± 2 kJ mol^{-1}; [c] max. deviation ± 20 J K^{-1} mol^{-1}.

TABLE IV
Kinetic parameters of alkaline hydrolysis of diesters of dicarboxylic acids in 70% (v/v) dioxane

Compound	Serial No.	Temperature °C	$k_1 \cdot 10^{3a}$	$k_2 \cdot 10^{3b}$	k_1/k_2	$\Delta H_1^{\ddagger c}$	$\Delta H_2^{\ddagger d}$	$-\Delta S_1^{\ddagger e}$	$-\Delta S_2^{\ddagger f}$
V	13	25	46·7	8·8	5·29	58·2	59·4	75	80·5
	14	35	112·8	22·1	5·10				
	15	45	217·9	42·4	5·14				
VI	16	25	115·0	7·4	15·54	60·9	69·0	58	54
	17	35	293·1	21·3	13·77				
	18	45	574·8	45·4	12·66				
	19[g]	45	24·3	0·9	27·52				
VII	20	10	151·7	9·2	16·42	52·7	51·2	74	103
	21	20	340·4	19·4	17·57				
	30	30	710·5	41·6	17·07				
	23[h]	25	494·5	28·8					
VIII	24	20	111·4	9·3	11·97				
IX	25	25	28·0	3·6	7·88	54·3	71·7	93	51
	26	35	57·3	12·0	4·78				
	27	45	118·4	23·3	5·09				

[a] Max error ±5%; [b] max. error ±5%; [c] max. deviation ±4 kJ mol^{-1}; [d] max. deviation ±5 kJ mol^{-1}; [e] max. deviation ±20 J K^{-1} mol^{-1}; [f] max. deviation ±20 J K^{-1} mol^{-1}; [g] the hydrolysis was carried out in 80% (v/v) methanol; [h] the rate constants calculated from the $\Delta H^{\ddagger}$ and $-\Delta S^{\ddagger}$ values.

in the hydrolysis of compound *III*. The fact that k_1 of compound *V* is higher than k_1 of *IX* indicates that the overall effect of the system on the hydrolysis is more significant than the character of the "single" bond through which the transfer is realized in the case of compound *V* (hypo effect — see below). High k_1 values were also found in the hydrolysis of dimethyl 2,3-furanedicarboxylates[9].

The rate constants k_2 show substantially smaller differences in accordance with the facts discussed in connection with the values obtained from the hydrolyses of compounds *I—IV*. The k_2 order of decreasing reactivity is *VII > VIII > V ≈ ≈ VI > IX*, i.e., qualitatively practically identical with the order of k_1 values. Correctness of the k_2 rate constants calculated by the Frost–Schwemer method can be simply verified by comparing these constants with the rate constants of alkaline hydrolyses of the respective monoesters of dicarboxylic acids which were carried out at identical conditions, the constants being identically defined in accordance with Eq. (2). Comparison of the *k* values from Table III (Ser. Nos 1, 2, 3) with the k_2 values from Table IV (Ser. Nos 13, 14, 15) shows that the respective deviations in the values of rate constants are 16%, 3%, 7%. This result is acceptable from experimental point of view and indicates that the application of the Frost–Schwemer method to the calculation of k_1 and k_2 is justified.

A particularly interesting model compound is dimethyl 2,3-thiophenedicarboxylate (*VI*) with two non-equivalent methoxycarbonyl groups. With this compound there arises the question whether the Frost–Schwemer method can be applied to a system containing two non-equivalent groups. Furthermore, from the reactivity point of view, there also arises the question if one of the methoxycarbonyl groups present in *VI* is more reactive than the other group (e.g., the group at the position 2 can be more reactive than that at the position 3, as it is the case with the alkoxycarbonyl groups in furane ring[9]).

Application of the Frost–Schwemer method to calculation of hydrolysis rate constants of unsymmetrical diesters has only been described in a single paper[16] so far. Cambon and Jullien studied an extensive series of diesters of alkyl substituted cyclopropanedicarboxylic acids. The relative errors given by the authors for the calculated rate constants k_1 and k_2 are 5% and 8%, resp. (for symmetrical diesters, i.e., diesters with equivalent alkoxycarbonyl groups). With non-symmetrical diesters the situation is far more complex, e.g., the hydrolysis of compound *VI* can be represented by Scheme 1. An exact solution of the problem of hydrolysis of diesters with non-equivalent alkoxycarbonyl groups would thus necessitate determination of four rate constants $(k_1', k_2', k_1'', k_2'')$. Since in the above-mentioned paper[16] all diesters with non-equivalent groups contained one methoxycarbonyl group bound to a secondary carbon atom and the other to a tertiary carbon, the authors — with respect to a distinct difference between reactivities of ester groups bound in this way — neglected the contribution of k_1'' and k_2'' (k_1'' expresses the hydrolysis rate of the less reactive methoxycarbonyl group) and carried out the whole calculation with application

SCHEME 1
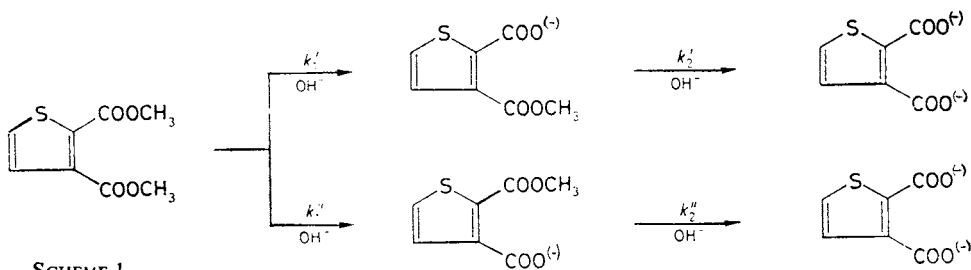
of the Frost–Schwemer method. For this simplification they calculated the enhanced relative errors in k_1 and k_2, viz. 10% and 30%, respectively. This means that the Frost–Schwemer method can be applied even to the cases where the methoxycarbonyl groups differ more distinctly in their reactivities.

Theoretical analysis of Scheme 1 shows that the Frost–Schwemer method can also be used in the cases where the two ester groups exhibit roughly the same reactivity, i.e., $k_1' = k_1''$. The $k_{2,exp}$ value (i.e., the k_2 value experimentally found) will then lie (theoretically) in the middle of the interval $k_2' \leftrightarrow k_2''$. Shifts of the $k_{2,exp}$ value to k_2' or k_2'' can then be considered to be a measure of non-equivalence of methoxy-carbonyl groups of the starting diester. The k_2' and k_2'' values can be experimentally determined by measurements of the rate constants of the corresponding monoesters III and II, because they are identically defined. Any extremely large shift from the middle of the interval means that the esters groups differ so much in their re-activities that practically only the more reactive one is transformed and the system is reduced to k_2' (or k_2'') as it was the case with the dimethyl esters of alkyl substituted cyclopropanedicarboxylic acids[16]. It was important for us (and this fact can be generalized) that this method enabled experimental estimation of relative reactivity, i.e., which of the ester groups present is substantially more reactive, and gave thus direct evidence of kinetic preference of one of the groups. In the case of compound VI, the rate constant values obtained by measurements of alkaline hydrolysis of the semi-esters II and III (Table III, Ser. Nos 4−9) correspond to the k_2' and k_2'' values, and the k_2 rate constant corresponds to $k_{2,exp}$ (Table IV, Ser. Nos 16−18), which enables estimation of the shift of $k_{2,exp}$ from the middle value of the interval $k_2' \leftrightarrow k_2''$. For the rate constants denoted by Ser. Nos 16, 17, and 18 these shifts make 28%, 5%, and 2%, respectively.

The small shift of $k_{2,exp}$ from the middle value indicates that the methoxycarbonyl groups bound at the positions 2 and 3 of thiophene nucleus can be considered ap-proximately equally reactive in the alkaline hydrolysis in 70% dioxane, and the cal-culation can be carried out by the Frost–Schwemer method with the allowance for the fact that the k_1 value measured corresponds to the sum of identical k_1' and k_1'', and the k_2 measured to the sum of k_2' and k_2'' which need not have identical values.

The higher percentual shift at lower temperature agrees with the general rule that selectivity of positions decreases with increasing temperature. The same conclusion can be drawn from the temperature dependence of the k_1/k_2 ratio (Table III, Ser. Nos 16−18 *cf.* with 13−15).

The identity of the positions 2 and 3 is confirmed kinetically also by the measurements carried out in the case of alkaline hydrolysis of monoesters of thiophenecarboxylic acids[17,18]. In 80% methanol the ratio of alkaline hydrolysis rate constants of methyl 2- and 3-thiophenecarboxylates is equal to $0.263/0.206 = 1.27$, hence the position 2 is more reactive than the position 3 by only $1/4$.

The above conclusion about close reactivities of methoxycarbonyl groups at positions 2 and 3 of thiophene nucleus is confirmed by further experimental results. From Table V (Ser. Nos 34, 35, 41, 42) it follows that in the case of isomeric cyanoesters *XI*, *XII* the differences between the rate constant values are only 44% at 20°C and

TABLE V

Kinetic parameters of alkaline hydrolysis of methyl cyanothiophenecarboxylates in 80% (v/v) methanol

Compound	Serial No.	Temperature °C	$k \cdot 10^{3a}$	$\Delta H^{\neq b}$	$-\Delta S^{\neq c}$
X	28	20	5·2	68	57
	29	30	14·1		
	30	40	32·7		
	31[d]	25	8·1		
	32[e]	25	235·8		
	33[d]	10	1·9		
XI	34	20	22·9	58·8	76
	35	30	57·1		
	36	40	113·6		
	37[d]	25	35·9		
	38[e]	25	1 093·2		
	39[d]	10	9·7		
XII[f]	40	9·90	5·2	68·6	46
	41	19·98	15·9		
	42	30·06	38·4		
XIII	43	10	100·0		
XIV	44	10	76·5		

[a] Max. error $\pm 2\%$; [b] standard deviation ± 3 kJ mol^{-1}; [c] standard deviation ± 20 J K^{-1} mol^{-1}; [d] the rate constant calculated from $\Delta H^{\neq}$ and $-\Delta S^{\neq}$ values; [e] the reaction was carried out in 70% (v/v) dioxane; [f] the data taken from ref.[18].

49% at 30°C, *i.e.*, the position 2 is more reactive than the position 3 by the factor of 1·5. It is logical that a change to substantially more reactive system — 70% dioxane (*cf.* Ser. Nos 34, 35, 41, 42 with 16—18) — can make the selectivity difference between the positions 2 and 3 even smaller.

Another interesting finding is the rapid increase in the k_1/k_2 ratio of compound *VI* as compared with that of compound *V*, the corresponding k_2 values being practically the same for both of them. The almost three times higher k_1 value of *VI* as compared with k_1 of *V* can be explained by different magnitude of transfer of electronic effects through the C_2—C_3 bond (the so-called hyper-*ortho* position) and C_3—C_4 bond (hypo-*ortho* position). Partial localization of the double bond results in the transfer of electronic effects through the C_2—C_3 bond being about twice as efficient than that through the C_3—C_4 bond. Several authors[19-24] dealt with the problem of the transfer of substituent effects in thiophene nucleus and estimated the ratio of transfer reaction constants to be $\varrho_{2,3}/\varrho_{3,4} = 2·05$. In our case a similar comparison of the transfer of effects can be obtained by dividing the respective constants k_1 of *VI* and k_1 of *V*, providing that the hydrolysis rate constants of methyl 2- and 3-thiophenecarboxylates are approximately the same, as we have stated above

$$k_1(VI)/k_1(V)\,(25°C) = 115·0/46·7 = 2·46$$

$$k_1(VI)/k_1(V)\,(35°C) = 293·1/112·8 = 2·59$$

$$k_1(VI)/k_1(V)\,(45°C) = 574·8/217·9 = 2·64 .$$

From the values obtained it follows that the transfer of the effect of methoxy-carbonyl group from the position 2 to 3 (and *vice versa*) is about 2·5 times as efficient as that from the position 4 to 3. Although the calculation of activation parameters from the rate constants obtained by the Frost–Schwemer method is loaded with relatively large error due to relative errors in k_1 and k_2, the activation enthalpy and entropy values can still be used for semiquantiative analysis of both reaction steps. From data of Table IV it follows that the entropy factor plays a substantial role in these hydrolyses. Large negative values of the activation entropy, $-\Delta S^*$, indicate that the transition state is highly ordered, and the molecule can react (in these cases) probably only in a certain conformation. This conclusion is also supported by quantum-chemical calculations of thiophene derivatives. Large reactivity differences between aromatic compounds derived from thiophene and benzene (in contrast to the dihydrothiophene analogues) are due to substantially different activation enthalpy values.

The rate measurements of alkaline hydrolysis of the kyanoesters *X — XIV* in 70% dioxane (Table V, Ser. Nos 32, 38) gave — in accordance with expectation — relati-

vely high rate constant values as compared with those obtained in 80% methanol (Table V, Ser. Nos 31, 37), and also the roughly three times lower reactivity of compound X than those of XI and XII was expected. It is interesting to compare the reactivities (k_1) of cyanoesters and diesters measured in 70% dioxane (Table IV, Ser. Nos 13, 16 and Table V, Ser. Nos 32, 38), where the $k(X)/k_1(V)$ and $k(XI)/k_1(VI)$ rate constant ratios for the 3,4- and 2,3-isomers are $235\cdot8/46\cdot7 = 5\cdot05$ and $1\,093\cdot2/ /115\cdot0 = 9\cdot51$, respectively. These considerable differences of reactivity can be explained by a stronger electron-withdrawing effect of cyano group and by a bulkiness of methoxycarbonyl group that hinders the attack of hydroxide ion at the adjacent ester group.

Mutual comparisons of reactivity of the cyanoesters derived from thiophene $(X - XII)$ and those derived from dihydrothiophene $(XIII, XIV)$ at the same reaction conditions (80% methanol; 10°C, Table III, Ser. Nos 33, 39, 40 and 43, 44) give the following order: $XIII > XIV \gg XI > XII > X$ which fully reflects the experience gained from carrying out the hydrolyses of diesters in 70% dioxane, *e.g.*, compound $XIII$ is hydrolyzed faster than X by the factor of 53.

LIST OF SYMBOLS

$\Delta H^{\neq}$	the activation enthalpy, kJ mol^{-1}
$\Delta H_1^{\neq}$	the activation enthalpy of the 1st reaction step, kJ mol^{-1}
$\Delta H_2^{\neq}$	the activation enthalpy of the 2nd reaction step, kJ mol^{-1}
k	the rate constant, dm^3 mol^{-1} s^{-1}
k_1	the rate constant of the 1st reaction step, dm^3 mol^{-1} s^{-1}
k_2	the rate constant of the 2nd reaction step, dm^3 mol^{-1} s^{-1}
R_X	the hydroxide amount reacted, %
$\Delta S^{\neq}$	the activation entropy, J K^{-1} mol^{-1}
$\Delta S_1^{\neq}$	the activation entropy of the 1st reaction step, J K^{-1} mol^{-1}
$\Delta S_2^{\neq}$	the activation entropy of the 2nd reaction step, J K^{-1} mol^{-1}
t_{rel}	ratio of the time values corresponding to the percentages compared
τ	the time value corresponding to R_X

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