Kinetics of nucleophilic vinyl substitution of geminal dihalo derivatives of furan and thiophene

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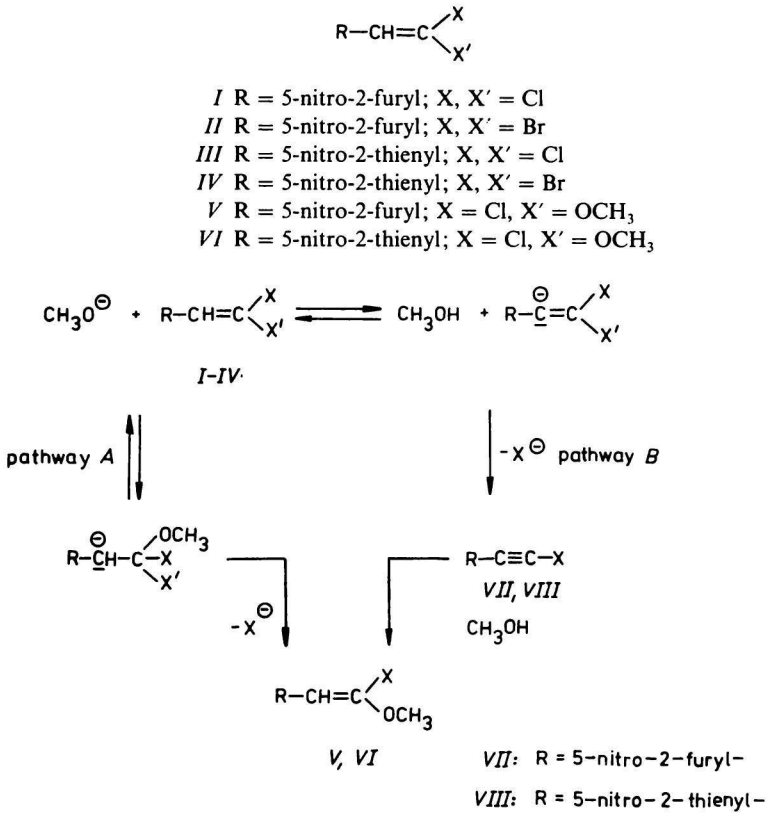
Dedicated to Professor Ing. J. Kováč, DrSc., in honour of his 60th birthday

The reactivity of 1,1-dichloro(resp. 1,1-dibromo)-2-(5-nitro-2-furyl)ethylene and analogous thiophene derivatives in the reaction with sodium methanolate was assessed by kinetic studies. Based on the obtained rate constants k_1 and k_2, isolated intermediates as well as on spectral studies the reaction mechanism of the exchange of one or both halogen atoms is discussed.

Проведено кинетическое изучение реакционной способности 1,1-дихлор(или 1,1-дибром)-2-(5-нитро-2-фурил)этилена и аналогичных производных тиофена в реакции с метилатом натрия. Исходя из полученных величин констант скоростей k_1 и k_2, выделенных промежуточных продуктов, а также на основе спектрального исследования, обсуждается механизм реакции обмена одного или обоих атомов галогена.

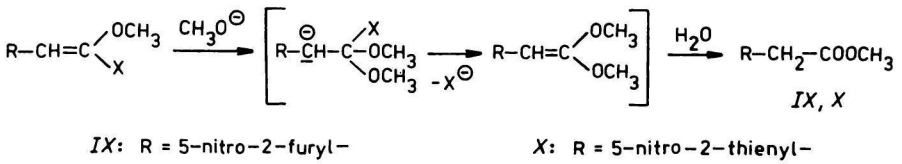
Nucleophilic vinyl substitution was systematically studied recently [1—4]. Lesser known are nucleophilic vinyl substitutions S_NV at systems having two halogen atoms attached to the vinyl carbon. These reactions were sofar studied either from the synthetic point of view [5, 6] or as in the case of 1,1-dichlorovinyl sulfones kinetically as well [7]. Geminal dihalo derivatives of 5-nitro-2-furan or 5-nitro-2-thiophene series were found to be suitable models for the study of nucleophilic vinyl displacement reaction [8—10].

The kinetics of the reaction of geminal dihalo derivatives (*I—IV*) and monohalo methoxy derivatives (*V*, *VI*) activated by the presence of 5-nitro-2-furyl and 5-nitro-2-thienyl moiety, with sodium methanolate in methanol was studied. All listed compounds can undergo an exchange of one or both halogens by two pathways (*A* and *B*, Scheme 1).



Scheme 1

The exchange of the second halogen atom can proceed analogously by two pathways. Both *A* and *B* pathways can produce acetic ester, *e.g.* according to pathway *A* the following mechanism was assumed



Scheme 2

It can be seen that the halogen atom can be exchanged either by addition--elimination mechanism, designated as "direct substitution" (pathway *A*), or by elimination-addition mechanism (pathway *B*) [1, 2].

Measurements of the rates of reactions with sodium methanolate in methanol and isolated intermediates led us to the conclusion that addition-elimination pathway was possible only when X, X′ = Cl. Spectral methods (UV, ^{1}H NMR) and TLC analyses of geminal dichloro derivatives of both heterocyclic systems (furan, thiophene) confirmed the formation of acetic ester *IX*, *X* (Table 1). The alternative acetylenic intermediate (pathway *B*) could not be isolated nor proved

Table 1

^{1}H NMR spectral data

Compound	δ_i/ppm			
	H-3	H-4	H-CH_2	H-CH_3
IX	6.56 d	7.32 d	3.88 s	3.75 s
X	7.11 d	7.86 d	4.01 s	3.87 s

Table 2

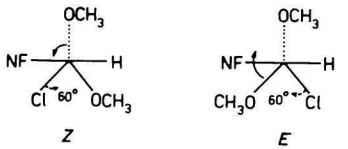
Rate constants k_1 and k_2 of the reactions of compounds *I*—*IV* with sodium methanolate in methanol at (50 ± 0.2) °C

Compound	*Z*	X	X′	k_1/(dm^3 mol^{-1} s^{-1})	k_2/(dm^3 mol^{-1} s^{-1})
I	O	Cl	Cl	0.0705 ± 0.004	0.00904 ± 0.003
II	O	Br	Br	0.534 ± 0.004	0.127 ± 0.005
III	S	Cl	Cl	0.0378 ± 0.003	0.00165 ± 0.009
IV	S	Br	Br	0.485 ± 0.002	0.086 ± 0.001
V	O	Cl	OCH_3		0.0108 ± 0.003
VI	S	Cl	OCH_3		0.00163 ± 0.002

by TLC, indicating that the exchange of the first halogen atom proceeded by addition-elimination mechanism to give stereoisomers of monosubstituted product (*V*, *VI*). Analogously the second halogen atom was exchanged.

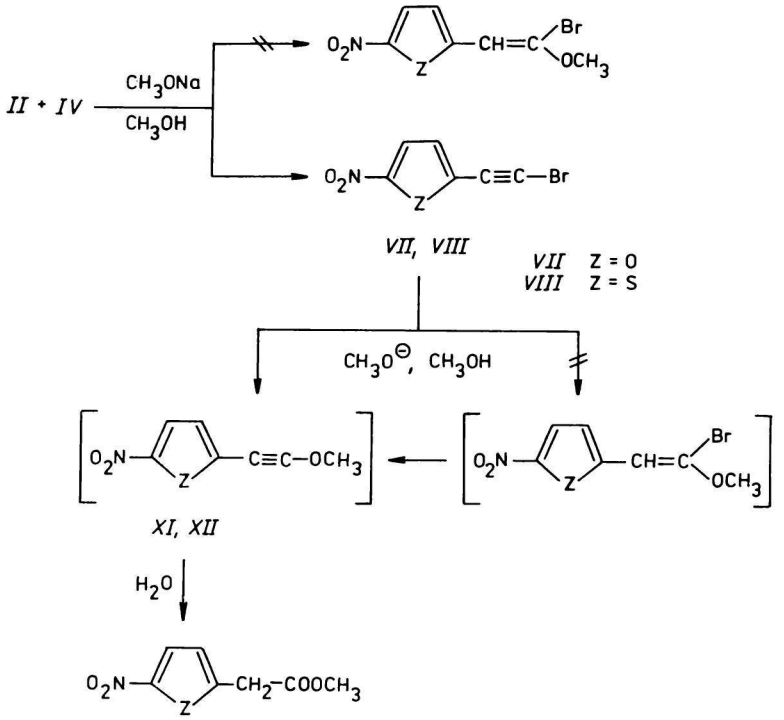
The reaction rate of the second exchange was slower (k_1 and k_2 of derivatives *I* and *III*, Table 2) due to the positive mesomeric effect of OCH_3 group and its conjugation with the easily polarizable vinyl double bond, activated by withdrawing 5-nitro-2-furyl or 5-nitro-2-thienyl group (*V*, *VI*). Data in Table 2 also document the higher reactivity of geminal dihalo derivatives of furan confirming thus better transfer of electronic effects through furan ring in accord with earlier data [11, 12].

The S_NV reaction of 1-chloro-1-methoxy-2-(5-nitro-2-furyl)ethylene (*V*) and of its thiophene analogue (*VI*) with sodium methanolate in methanol was conducted in the same manner. The starting compounds represent an intermediate in the reaction of geminal dihalo derivatives and were both isolated as *Z* isomers. In the furan series the reaction rate constant k_2 of this S_NV reaction was found to be $1.08 \times 10^{-2}\,dm^3\,mol^{-1}\,s^{-1}$, in thiophene series it was $1.63 \times 10^{-3}\,dm^3\,mol^{-1}\,s^{-1}$. Reaction rates given in Table 2 testify that for derivative *I* the value of k_2 found for the exchange of the second chlorine matches closely that of k_2 (Table 2, derivative *V*) determined in the reaction of pure *Z* isomer of methoxychloro derivative, the same being true in the thiophene series (Table 2, derivatives *III* and *VI*). The comparison demonstrates that the halogen exchange in *V* and *VI* proceeds equally well in both stereoisomers, as it would be expected from the intrinsic stereochemical possibilities of Ad—E mechanism [1, 2]



The picture changed when geminal dibromo derivatives of both series (*II*, *IV*) were acted upon by sodium methanolate in methanol. Measured rate constants k_1 and k_2 did not correspond to those measured for dichloro derivatives. ^{1}H NMR spectra of reaction mixtures revealed that the reason was a different reaction mechanism, namely the formation of bromoacetylene as an intermediate, instead of the expected monobromo methoxy derivative, which was the result of hydrogen bromide elimination by strongly basic CH_3O^- anion (Scheme 3).

Reaction rate constant k_1 (Table 2, derivative *II* and *IV*) thus characterizes the formation of bromoacetylene derivative [9]. In furan series k_1 was higher than in thiophene series (Table 2). The exchange of bromine atom in bromoacetylene (*VII*, *VIII*) can be performed according to tentative Scheme 2. The measured rate constants k_2 for compounds *II* and *IV* thus characterize either the direct bromine exchange by substitution at the acetylenic carbon leading to methoxyacetylene *XI*, *XII* or the indirect exchange *via* methanol addition under the formation of *V*, *VI* (X = Br) followed by its transformation to *XI*, *XII*. Values of k_2 for *II* and *IV* are orders of magnitude higher than those for derivatives *I* and *III*. This would suggest that bromoacetylenes *VII* and *VIII* are more reactive than monochloro methoxy derivatives *V*, *VI* in the reaction with methanolate anion.



Scheme 3

In conclusion we may say that the mechanisms of exchange of chlorine and bromine in *I*—*IV* are different, though leading ultimately to the same end product — a methyl ester of acids *IX* and *X*.

Experimental

^{1}H NMR spectra were determined by the 80 MHz Tesla spectrometer, model BS 487 C in deuteriochloroform or CD_3COCD_3; UV spectra were measured on a Zeiss spectrophotometer Specord UV VIS in the range 200—800 nm of ethanolic solutions or on the Specord M 40 in the range 250—450 nm of chloroform solutions, the concentrations used were (4—6) × 10^{-5} mol dm^{-3}.

The following model compounds were synthesized:

1,1-Dichloro-2-(5-nitro-2-furyl)ethylene was prepared by the reaction of 5-nitro-2--furaldehyde with the *in situ* generated dichloroketene (from dichloroacetic acid chloride and triethylamine) according to Ref. [8]. The same procedure was applied to prepare the

thiophene analogue. The requisite ethylene was obtained in 76.5 % yield, m.p. = 72.5 °C. UV (methanol), λ_{max} = 367 nm, log (ε/(m^2 mol^{-1})) = 2.17. ^{1}H NMR ($CDCl_3$), δ/ppm: 7.37 (d, H-4), 7.03 (d, H-3), 6.85 (s, H-A), $J_{3,4}$ = 3.9 Hz.

1,1-Dichloro-2-(5-nitro-2-thienyl)ethylene was obtained in 80 % yield, m.p. = = 88—90 °C. UV (methanol), λ_{max} = 378.5 nm, log (ε/(m^2 mol^{-1})) = 2.14. ^{1}H NMR (CD_3COCD_3), δ/ppm: 8.02 (d, H-4), 7.34 (d, H-3), 7.6 (s, H-A), $J_{3,4}$ = 4.5 Hz.

1,1-Dibromo-2-(5-nitro-2-furyl)ethylene as well as its thiophene analogue was prepared according to Ref. [8] starting from the corresponding 5-nitro-2-furaldehyde and 5-nitro-2-thiophenecarbaldehyde, respectively, and triphenylphosphine, tetrabromomethane, and zinc dust in dichloromethane solution. 1,1-Dibromo-2-(5-nitro-2-furyl)ethylene was obtained in 75 % yield, m.p. = 78 °C. UV (methanol), λ_{max} = 370 nm, log (ε/(m^2 mol^{-1})) = 2.02. ^{1}H NMR ($CDCl_3$), δ/ppm: 7.33 (d, H-4), 7.14 (d, H-3), 7.48 (s, H-A), $J_{3,4}$ = 3.9 Hz.

1,1-Dibromo-2-(5-nitro-2-thienyl)ethylene, yield = 70 %, m.p = 113.5—114.5 °C. UV (methanol), λ_{max} = 382.5 nm, log (ε/(m^2 mol^{-1})) = 2.03. ^{1}H NMR ($CDCl_3$), δ/ppm: 7.34 (d, H-4), 7.15 (d, H-3), 7.48 (s, H-A), $J_{3,4}$ = 4.4 Hz.

1-Chloro-1-methoxy-2-(5-nitro-2-furyl)ethylene

To the intensely stirred solution of 1,1-dichloro-2-(5-nitro-2-furyl)ethylene (2.08 g; 0.01 mol) in 2.5 cm^3 of acetone was at 5 °C dropwise added a solution of sodium methanolate in methanol (prepared by dissolving 0.34 g of Na in 5 cm^3 of methanol). After the whole volume has been added, the mixture was further stirred for 15 min. The progress of reaction was monitored by TLC. After the consumption of the starting material the reaction was terminated by the addition of 0.98 cm^3 of 36 % hydrochloric acid in 5 cm^3 of methanol, the solvent evaporated to give a mixture of both isomers (determined by ^{1}H NMR). Pure *Z* isomer was isolated on a silica gel column (100—150 μm, eluant benzene), yield = 0.55 g (28.2 %), m.p. = 54—55 °C. UV (methanol), λ_{max} = = 376 nm, log (ε/(m^2 mol^{-1})) = 2.03. ^{1}H NMR ($CDCl_3$), δ/ppm: *E* isomer: 7.23 (d, H-4), 6.63 (d, H-3), 5.78 (s, H-A), 3.88 (s, CH_3); *Z* isomer: 7.35 (d, H-4), 6.85 (d, H-3), 5.90 (s, H-A), 3.98 (s, CH_3).

1-Chloro-1-methoxy-2-(5-nitro-2-thienyl)ethylene

The compound was prepared by the procedure analogous to that used for the furan derivative. Yield = 0.9 g (41.8 %) of yellow crystalline solid (*Z* isomer), m.p. = = 96—98 °C. UV (methanol), λ_{max} = 394 nm, log (ε/(m^2 mol^{-1})) = 2.09. ^{1}H NMR ($CDCl_3$), δ/ppm: *Z* isomer: 7.81 (d, H-4), 6.92 (d, H-3), 6.16 (s, H-A), 3.87 (s, CH_3); *E* isomer: 7.78 (d, H-4), 6.78 (d, H-3), 6.02 (s, H-A), 3.98 (s, CH_3).

Kinetic measurements

Standard solutions used: 0.01 M hydrochloric acid
0.01 M sodium hydroxide
0.04 M sodium methanolate

Standardization procedure

The exact concentration of 0.01 M sodium hydroxide was determined by oxalic acid using phenolphthalein as indicator; exact concentration of 0.01 M hydrochloric acid by NaOH using Cooper indicator, the exact concentration of 0.04 M sodium methanolate was determined by 0.01 M-HCl using Cooper indicator, prepared according to the following procedure: 0.02 g of methyl red, 0.1 g of bromocresol green dissolved in 100 cm^3 of 96 % ethanol. The acidic--basic transition is accompanied by red-to-blue colour change.

Procedure

For kinetic studies samples were prepared as 0.02 mol dm^{-3} methanolic solutions in 100 cm^3 standard flasks, sodium methanolate as 0.04 M solution in a 100 cm^3 standard flask. Before the experiment was started samples were kept thermostated at (50 ± 0.2) °C (thermostat U-10), then mixed in a 200 cm^3 flask to produce a reaction mixture with the 0.01 mol dm^{-3} concentration of the component and 0.02 mol dm^{-3} concentration of sodium methanolate (a 100 % excess), taking into account the temperature-dependent volume contraction. At regular intervals 5 cm^3 samples of reaction mixture were taken, added to 20 cm^3 of 0.01 M-HCl to stop the reaction and the unreacted hydrochloric acid was after the addition of an indicator titrated by 0.01 M-NaOH solution. Thus obtained values of the consumption of NaOH were used to calculate the concentrations in the taken volume of the reaction mixture using the formula $c_A = c_B - c_{B,\infty}$ where c_A is the concentration of substance at the given time, c_B concentration of sodium methanolate at the same time, $c_{B,\infty}$ concentration of CH_3ONa in the time $t = \infty$.

Concentration c_B was calculated from the equation

$$c_B = (V_{HCl} \cdot c_{HCl} \cdot f_{HCl} - V_{NaOH} \cdot c_{NaOH} \cdot f_{NaOH}) \times 0.2$$

$c_{B,\infty}$ Value was determined at $t = 24$ h. Plotting the values $\log\{c_A\}$ against the time furnished two linear intersecting plots, from which k_1 and k_2 were calculated. In that case the c_B value used in calculating k_1 at the intersection was already $c_{B,\infty}$, whereas in calculation of k_2 it was the starting value.

Second order rate constants were calculated according to the expression

$$k \cdot t = \frac{1}{a-b} \ln \frac{b(a-x)}{a(b-x)}$$

where a = starting concentration of the sample $c_{A,0}$ in mol dm^{-3}
b = starting concentration of CH_3ONa $c_{B,0}$ in mol dm^{-3}
x = difference in concentration of the sample at t_0 and t $(c_{A,0} - c_A)$

In the same manner the rate constants k_2 for the reaction of 1-chloro-1-methoxy-2-(5-nitro-2-furyl, resp. 2-thienyl)ethylene with sodium methanolate were determined.

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