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INVESTIGATION OF THE KINETICS OF THE NITRATION OF THIOPHENE DERIVATIVES

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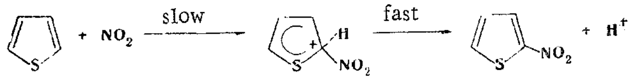
The kinetics of the nitration of thiophene derivatives with nitric acid in acetic anhydride were investigated. The nitration of 2-substituted thiophenes is a second-order reaction. The rate constants and activation parameters of the reaction were calculated. The possibility of the use of the Hammett and Yukawa–Tsuno equations for this reaction series is demonstrated. An isokinetic dependence is observed.

Some aspects of electrophilic substitution reactions in the thiophene series, including nitration, have been correlated in a monograph [1]. However, despite a detailed study of the mechanism of nitration, only one study has been devoted to the kinetics of this reaction [2]; Butler and Hendry investigated the kinetics of the nitration of thiophene with a mixture of nitric and sulfuric acids. Nitro groups enter the 4 and 5 positions in the nitration of thiophene and substituted thiophenes. 5-Nitrothiophenes are of greatest interest for the synthesis of monomers. Tirouflet and co-workers [3, 4] have shown that primarily 5-nitrothiophenes are formed in the nitration of some thiophene derivatives with a mixture of nitric acid with acetic anhydride. Having in view the subsequent use of nitro derivatives of thiophene for the synthesis of monomers, we investigated the kinetics of the nitration of thiophene and its derivatives with a mixture of nitric acid with acetic anhydride.

We investigated the yields of 5-nitro derivatives of thiophene as a function of the substrate concentration over the concentration range 0.03 to 0.85 mole/liter with nitrating mixture concentrations from 0.3 to 0.55 mole/liter at –20 to +65°C. According to the literature data [1, 5], the nitration of thiophene derivatives by the nitronium ion, in analogy with the benzene ring, proceeds through a slow step involving the formation of a σ complex with rapid splitting out of a proton:



The nitration is a second-order reaction, as determined graphically from the logarithmic dependence of the reaction rate on the concentration. It was determined experimentally that the reaction is first-order in the substrate and the nitrating agent. The overall second order of the reaction is also confirmed by the constancy of the reaction rate constants calculated from the equation for a second-order reaction for various degrees of conversion.

The rate constants calculated for a constant equimolar ratio of the reagents at various temperatures are presented in Table 1. The rate constants presented in Table 1 show that electron-donor substituents accelerate the reaction, whereas electron-acceptor substituents slow it down. The introduction of an iodine atom in the thiophene ring has little effect on the reaction rate, whereas the introduction of a bromine atom slows it down. The differences in the reaction rates for electron-acceptor substituents are due to both the activation energy and the pre-exponential multiplier. Electron-donor substituents are characterized by close values of the pre-exponential multiplier.

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TABLE 1. Rate Constants and Activation Parameters for the Nitration of 2-Substituted Thiophenes with a Mixture of Nitric Acid with Acetic Anhydride

Compound	$k \cdot 10^3$, liters·mole^{-1}·sec^{-1}				$k \cdot 10^5$, liters·mole^{-1}·sec^{-1}			E, kcal/mole	lg A
	−20°	−14°	−10°	−6°	+45°	+55°	+65°		
Thiophene		3,9±0,2	5,3±0,3	7,0±0,3				9,3±0,2	6,8±0,4
2-Ethylthiophene	3,3±±0,4	4,3±0,4	5,0±0,1					10,3±0,9	6,3±0,8
2-tert-Butylthiophene		5,0±0,2	6,5±0,3	8,4±0,5				10,0±0,6	6,2±0,5
2-Bromothiophene		2,7±0,2	3,8±0,2	5,4±0,4				11,9±0,6	5,4±0,5
2-Iodothiophene		3,9±0,3	5,4±0,4	7,4±0,7				11,0±0,2	6,95±0,2
2-Formylthiophene		0,26±±0,01	0,42±±0,01	0,67±±0,04				16,2±0,5	10,2±1,1
2-Acetylthiophene		0,19±±0,01	0,28±±0,02	0,41±±0,03				13,2±0,2	7,5±0,2
2-Nitrothiophene					0,87±±0,02	1,2±±0,03	1,5±±0,03	6,5±0,1	1,03±0,12
2-Cyanothiophene					6,3±±0,3	10,0±±1,4	15,4±±1,4	10,6±0,6	3,1±0,4

The kinetic data obtained do not contradict the assumed mechanism of bimolecular nitration of thiophene derivatives. The bimolecularity of the reaction is also confirmed by the negative entropy [6].

Since the substituent affects the reaction rate, it was assumed that a correlation should exist between the rate constants and the σ_p substituent constants [7]. A quantitative relationship between the structure and reactivity in the nitration reaction was found from the Hammett dependence, as well as from the Yukawa–Tsuno equation [8].

It is apparent from Fig. 1 that there is a good correlation between the logarithm of the ratio of the rate constant for the nitration of 2-substituted thiophene to the rate constant for the nitration of thiophene and the Hammett σ_p constants. For this reaction series ρ is -6.729 ± 1.591 with correlation constant $r = -0.99$ (with respect to the Hammett equation) and -4.010 ± 1.794 with coefficient $r = 0.99$ (with respect to the Yukawa–Tsuno equation). The large absolute value of the ρ constant indicates transmission of the electronic effects of the substituents in the thiophene ring.

At the same time, deviation from the regression line of this reaction series is observed for alkyl substituents; this can be explained by the different effect of these substituents on the reaction center (Fig. 2).

The isokinetic temperatures were determined from the dependences of $\Delta H^{\neq}$ on $\Delta S^{\neq}$ (Fig. 2) and $\log k_{263}$ on $\log k_{253}$ (Fig. 3) for this reaction series. The existence of an isokinetic dependence was also confirmed by intersection (in pairs) of the lines in coordinates of log k and 1/T and by the dependence of ρ on 1/T. The isokinetic temperature is found in the range 263-319°K. Deviation of the isokinetic temperature to the average experimental temperature is observed.

The enthalpies and entropies obtained for the investigation reaction series constitute evidence for the combined effect of the entropy and enthalpy factors.

EXPERIMENTAL

The starting 2-iodothiophene [9], 2-ethylthiophene [10], 2-cyanothiophene [11], 2-formylthiophene [12], and nitro derivatives of the thiophene [13-16] were synthesized by known methods. The purity of the reaction products was verified by chromatographic and polarographic methods.

Method for Investigation of the Kinetics. The calculated amounts of the nitrating mixture and the substrate were placed in a three-necked flask equipped with a thermometer, a gas-inlet tube for stirring of the reaction mixture with argon, and a condenser. The nitrating mixture was prepared by mixing 100% nitric acid and acetic anhydride at −10°C. The course of the reaction was monitored from the accumulation of the desired nitro derivative. Analysis was performed with an LR-60 polarograph with a dropping mercury electrode at 0 to −2 V. The base electrolyte was a solution of 40% alcohol and a 20% acetate buffer with pH

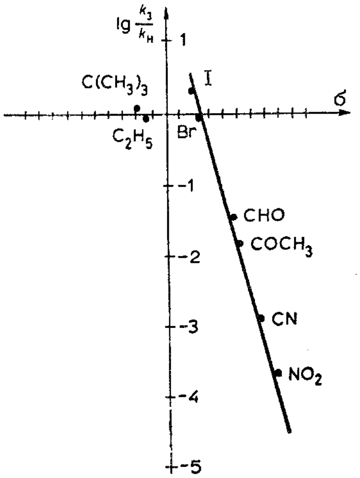

Fig. 1

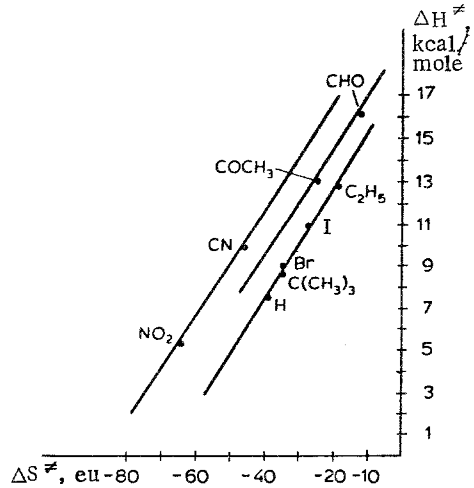

Fig. 2

Fig. 1. Dependence of the logarithm of the ratios of the rate constants for the nitration of 2-substituted thiophenes (k_3) to the rate constant for the nitration of thiophene (k_H) on the Hammett σ_p constants for the nitration of thiophene derivatives.

Fig. 2. Relationship between the enthalpy and entropy for the nitration of 2-substituted thiophenes.

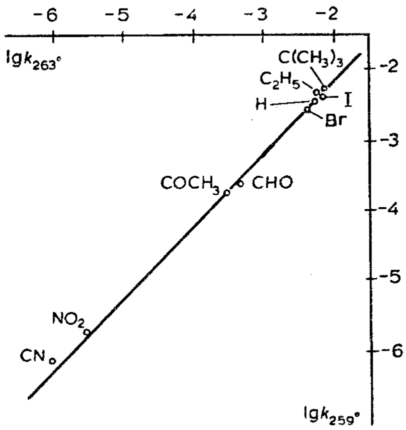

Fig. 3. Isokinetic dependence for the nitration of 2-substituted thiophenes.

3.7. The samples were selected directly in the base electrolyte in 0.01-0.001 g amounts. The percentage of the nitro derivative was determined from a calibration graph. The parameters of the linear equations were calculated by the method of least squares [17].

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CATALYTIC REDUCTIVE DEHALOGENATION OF THIOPHENE DERIVATIVES

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A method for the preparation of 3-substituted derivatives of thiophene by reductive dehalogenation of 2,5-dihalo-substituted thiophenes in the presence of a palladium complex is proposed. The dehalogenation reaction is a stepwise process. The presence of an acyl group in the 3 position increases the rate of the process.

β-Substituted thiophenes are intermediates in the synthesis of physiologically active substances. According to the prevailing opinion [1], β-substituted thiophenes are more active than α-substituted thiophenes vis-à-vis equal or lower toxicities. However, the accessibility of β-substituted thiophenes that have free α positions is limited, since their direct preparation from thiophene is impossible in view of the fact that the reactivities of both α positions of the thiophene ring exceed the reactivities of the β positions by approximately three orders of magnitude with respect to electrophilic substitution [2].

One of the methods for the preparation of thiophenes that are functionally substituted in the β position is the use of α,α'-dihalo derivatives for the introduction of a substituent with subsequent elimination of the halogens. Various dehalogenation methods are used for this purpose. The noncatalytic methods include removal of the halogens by the action of copper in propionic acid (this method is suitable only for the elimination of halogen atoms that are activated by the presence of a nitro or carbonyl group) [3, 4]. Other noncatalytic methods include dehalogenation by means of copper in quinoline [5], the action of sodium telluride in methanol [6], etc. Catalytic dehalogenation is realized by hydrogenation in the presence of palladium [7]. This method, in addition to certain advantages, has certain disadvantages: Large amounts of the catalyst must be used, products of partial hydrogenation of the ring are formed, and the selectivity is low. Even when halogen is removed from the side chains of thiophene derivatives, the yields of products range from 30 to 40% [8].

The good results obtained in the dehalogenation of chlorobenzenes and substituted chlorobenzenes in the presence of a chloride complex of palladium applied to silica gel containing γ-aminopropyl groups [9] compelled us to investigate the suitability of this catalyst for the preparation of β-substituted thiophenes from α,α'-dihalo-β-substituted thiophenes. In model experiments it was established that chlorine is split out from 2,5-dichlorothiophene (I) under mild conditions (20°C, 1 atm abs. H_2, NaOH) to give 2-chlorothiophene (II) and thiophene (III) in the presence of a palladium chloride complex applied to modified silica gel. Hydrogenolysis of the C—Cl bond proceeds selectively without hydrogenation of the thiophene ring. The process takes place via a consecutive scheme:

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