

## STUDY OF THE MECHANISM OF RECYCLIZATION OF FURANS INTO THIOPHENES AND SELENOPHENES IN CONDITIONS OF ACID CATALYSIS.

### 6.\* EXPERIMENTS WITH LABELED ATOMS.

### QUANTUM CHEMICAL CALCULATIONS OF INTERMEDIATES OF RECYCLIZATION AND HYDROLYSIS

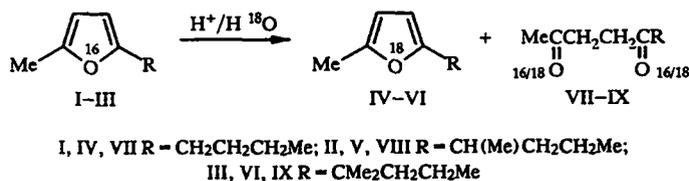
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*The reaction of 2-methyl-5-R-furans (R = Me, Bu, 2,2-pentyl-2-methylpentyl) with H<sub>2</sub><sup>18</sup>O was investigated. Furans and the corresponding 2,5-alkanediones containing the <sup>18</sup>O isotope were obtained. The general characteristics of the recyclization and isotope exchange reactions were established. A kinetic study of recyclization of 2,5-dimethylfuran with <sup>16</sup>O and <sup>18</sup>O into 2,5-dimethylthiophene was conducted. A reverse kinetic isotope effect was found. The schemes of the mechanisms of these processes were refined based on the experimental data and quantum-chemical calculations of the recyclization and hydrolysis intermediates.*

Kinetic studies of recyclization of 2,5-dialkylfurans into thiophenes and selenophenes in conditions of acid catalysis in ethanol and water-ethanol media were conducted previously [2-5]. It was found that in recyclization in the presence of a competing nucleophile — water — the processes can take place in two parallel directions: through intermediate formation of dicarbonyl compounds, and as a result of direct transformation of furans into isologs [2, 4]. The subsequent study of the kinetics of hydrolysis and recyclization of different alkyl-substituted furans showed that the rates of these reactions are differently dependent on the position and structure of the substituents and the concentration of the acid component and water [4, 5].

The results of studying the mechanism of the hydrolysis and recyclization reactions with labeled atoms are reported here.

The reaction of 2,5-dialkylfurans (I-III) with H<sub>2</sub><sup>18</sup>O was investigated in the conditions of the recyclization reaction. The composition of the reaction mixture was determined by GLC. The incorporation of the "label" was monitored with the mass spectrometric data. It was shown that substitution of the <sup>16</sup>O atom of the furan ring by the <sup>18</sup>O isotope takes place together with the hydrolysis reaction (see Fig. 1). As a result, the products of isotope exchange of furans (IV-VI) and diketones (VII-IX) were obtained.



\*See [1] for Communication 5.

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TABLE 1. Rate Constants of Hydrolysis of Furans in H<sub>2</sub><sup>16</sup>O and H<sub>2</sub><sup>18</sup>O at 35°C

Compound	$K_{\text{eff}} \times 10^{-4}, \text{sec}^{-1}$	
	H <sub>2</sub> <sup>16</sup> O	H <sub>2</sub> <sup>18</sup> O
I	2,39 ± 0,29	4,50 ± 0,15
II	1,40 ± 0,15	3,40 ± 0,11
III	0,82 ± 0,20	1,91 ± 0,09

TABLE 2. Rate Constants of Recyclization of Compounds XI and XIa at 35°C

Expt. No.	$K_{\text{XIef}} \times 10^{-4}, \text{sec}^{-1}$	$K_{\text{XIef}} \times 10^{-4}, \text{sec}^{-1}$	$K^{18}\text{O} / K^{16}\text{O}$
1	1,346 ± 0,08	2,014 ± 0,14	1,49
2	1,360 ± 0,18	2,260 ± 0,12	1,66
3	1,409 ± 0,16	1,529 ± 0,07	1,09
4	1,959 ± 0,12	1,798 ± 0,11	1,09
5	1,965 ± 0,12	2,423 ± 0,08	1,23

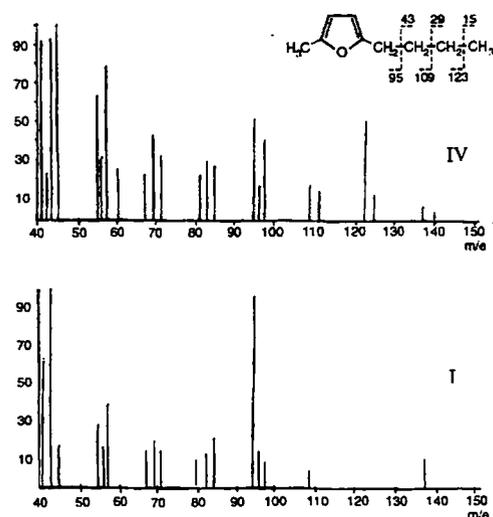
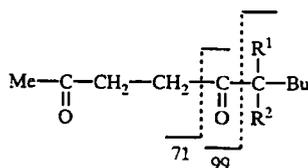


Fig. 1. Mass spectra of compound I (<sup>16</sup>O) and compound IV (<sup>18</sup>O).

Isotope exchange also takes place in the molecules of diketones VII-IX. A quantitative evaluation of the distribution of the <sup>18</sup>O isotope in their molecules was performed for compounds VII and VIII based on the ratio of the *m/e* 71-73 peak intensities corresponding to the fragment including carbonyl oxygen next to the CH<sub>3</sub> group and the *m/e* 99-101 signals characterizing the total amount of <sup>18</sup>O isotope in the diketone molecule.



The results of isotope exchange of furans IV-VI indicate that the concentration of <sup>18</sup>O isotope in these compounds is approximately the same (37-43 mole %). This is in agreement with the data on the same rate of recyclization of furans into thiophenes and selenophenes [4]. It was thus shown that in both recyclization and in isotope exchange of these compounds, the reaction rate is not a function of the steric effect of the α-substituent. At the same time, the rate of hydrolysis in the reaction of furans I-III with H<sub>2</sub><sup>18</sup>O decreases significantly in going from substance I to compound III, which is comparable to the data on hydrolysis of these compounds in H<sub>2</sub><sup>16</sup>O (Table 1).

TABLE 3. Charges on Atoms and Wiberg Indexes of Intermediates (B-C)

Intermediates	Charges on atoms					Wiberg indexes				
	C(2)	C(3)	C(4)	C(5)	O	C(2)-O	C(3)-C(2)	C(3)-C(4)	C(5)-C(4)	O-C(5)
C	0,057	0,042	- 0,225	0,372	0,084	0,898	1,000	1,754	1,138	1,383
D	0,082	- 0,042	0,244	0,149	- 0,237	0,926	0,985	1,893	0,997	1,053
E	0,061	- 0,021	- 0,244	0,304	- 0,154	1,188	0,991	1,810	1,048	0,921
F	0,338	- 0,141	- 0,137	0,097	- 0,007	1,437	1,031	1,011	1,880	0,951
G	0,310	- 0,131	- 0,156	0,038	0,004	1,464	1,025	1,010	1,822	0,942
H	0,199	- 0,108	- 0,199	0,027	- 0,098	1,175	0,976	1,004	1,842	0,974
I	0,439	- 0,176	0,025	0,349	- 0,227	0,004	1,147	1,775	0,964	1,184
J	0,419	- 0,229	0,099	0,049	- 0,292	0,003	1,202	1,719	0,966	1,053
K	0,419	- 0,211	0,072	0,161	- 0,243	0,002	1,193	1,717	0,979	1,129
L	0,419	- 0,022	- 0,276	0,373	- 0,103	1,481	0,993	0,953	2,115	0,001
M	0,420	- 0,141	- 0,160	0,319	- 0,094	1,483	1,000	1,001	1,879	0,001
N	0,223	- 0,039	- 0,195	0,378	- 0,222	1,170	0,947	0,936	2,003	0,003
O	0,437	- 0,122	- 0,022	0,433	- 0,114	0,006	1,110	1,776	1,010	1,463
P	0,358	- 0,178	- 0,050	0,429	- 0,129	0,021	2,034	0,961	1,009	1,457
Q	0,030	0,439	- 0,292	- 0,409	- 0,035	0,898	1,108	1,154	0,995	1,439

TABLE 4. Thermodynamic Characteristics of Intermediates in Reactions of 2,5-Dimethylfuran with a Nucleophile H<sub>2</sub>X (X = O, S)

Intermediate	H <sub>f</sub> 298. kcal/mole	S. kcal/mole	DG <sub>f</sub> . cal/mole
C	92,87	102,32	130,59
D	142,44	96,19	175,82
F	92,47	101,83	130,41
H	147,31	110,35	176,47
I	387,62	100,51	430,52
J	418,72	102,63	454,83
L	385,58	108,38	461,87
M	379,96	107,37	480,79
O	450,86	94,13	479,07
P	458,96	91,95	487,81

TABLE 5. Change in the Isobaric-Isothermal Potential ( $\Delta\Delta G$ ) in Addition of Protons and Nucleophiles to 2,5-Dimethylfuran

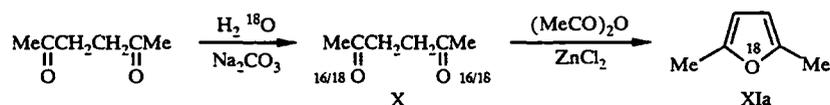
Process	$\Delta\Delta G$ , kcal/mole	Process	$\Delta\Delta G$ , kcal/mole
A + H <sub>2</sub> O - C	8,46	D + H <sup>+</sup> - J	-18,76
B + H <sub>2</sub> S - F	0,75	F + H <sup>+</sup> - L	24,72
A + H <sub>2</sub> S - D	8,11	G + H <sup>+</sup> - M	-1,54
B + H <sub>2</sub> S - G	2,20	A + H <sup>+</sup> - O	-60,77
C + H <sup>+</sup> - I	2,11	B + H <sup>+</sup> - P	-80,77

The GLC data showed that the concentration of diketones VII-IX does not change when the length of the reaction increases, i.e., their cyclization into furans does not take place.

The results obtained thus suggest that isotope exchange can only take place according to a recyclization mechanism and confirm the presence of two directions of transformation of furans under the effect of nucleophiles in water-ethanol acid media.

Based on the results of kinetic studies of recyclization of furans into thiophenes and selenophenes in absolute ethanol, it was previously shown that the reaction takes place according to a mechanism of specific acid catalysis and is second-order in the concentration of the acid [3]. This suggested that cleavage of the twice protonated form of the substrate takes place in the limiting stage of recyclization. The kinetics of recyclization of samples of 2,5-dimethylfuran containing <sup>16</sup>O (XI) and <sup>18</sup>O (XIa) isotope into 2,5-dimethylthiophene (XII) were investigated to demonstrate this, and the <sup>16</sup>O/<sup>18</sup>O isotope effect was determined. We know that the strength of the bond between two atoms is a function of the mass of the corresponding atom, and in the case of breaking of C-<sup>16</sup>O and C-<sup>18</sup>O bonds, it was hypothesized that a primary isotope effect would be obtained.

Compound XIa was synthesized according to the following scheme:

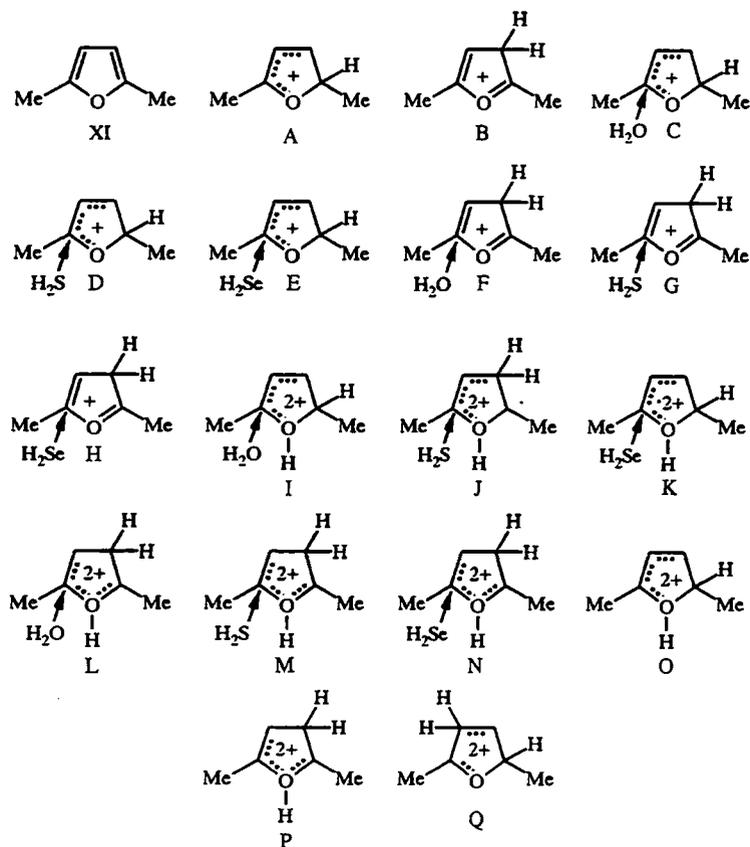


The percentage concentration of "label" in compounds X and XIa was determined with the mass spectrometric data and was 50 and 40 mole %, respectively.

The reaction rate of recyclization of compounds XI and XIa into thiophene XII was estimated by the change in the concentration of the starting furans based on GLC data. The internal standard method (toluene was used as the internal standard) was used to calculate the concentration of the components. The calculated rate constants of recyclization of compounds XI and XIa are reported in Table 2. We found that compound XIa is recyclized into thiophene XII with a slightly higher rate than compound XI. Contrary to expectations, a reverse kinetic effect,  $K^{18}\text{O}/K^{16}\text{O} = 1.312 \pm 0.2$ , was obtained.

Cases of a reverse kinetic effect are described in the literature for reactions including transfer of a proton from oxygen or to oxygen and decomposition of protonated intermediates [6]. For this reason, our results could indicate that the limiting stage of recyclization is cleavage of the form of the substrate protonated at the oxygen.

We performed quantum-chemical calculations of the intermediates formed during recyclization and hydrolysis of 2,5-dimethylfuran XI (A-C) to explain the experimental data obtained and refine the schemes of the mechanisms of recyclization and hydrolysis.



By gradually making the 2,5-dimethylfuran molecule more complex, we examined the redistribution of the electron density and the bond orders and determined the standard heats of formation, entropy, and the change in the isobaric-isothermal potential of formation of the forms reported above (Tables 3-5).

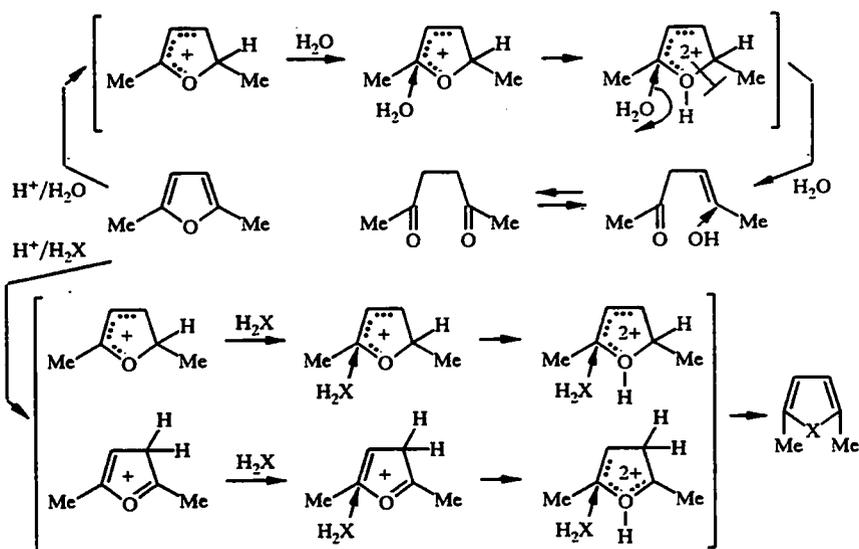
It was shown in a previous communication [1] that the probabilities of  $\alpha$ -C- and  $\beta$ -C-protonation as the initial stage of recyclization are comparable. As the second stage of the process, we examined the attack of the  $C_{(5)}$  atom in the ring by a nucleophile ( $H_2O$ ,  $H_2S$ ,  $H_2Se$ ) (intermediates C-E) used in the literature [1-4]. It was found that addition of the nucleophile does not weaken any bond. This only occurs on repeated protonation of the ring at the oxygen (forms I-K). A comparison of the results of calculations of monoprotonated intermediates F-H and the products of double protonation of M-O led to similar conclusions. With respect to the possibility of double  $\alpha$ - and  $\beta$ -C-protonation, it was found that this pathway is not promising (form Q).

Since the calculations showed that repeated protonation at the oxygen is the determining factor of ring rupture, we also considered the version of double protonation without addition of a nucleophile. It was found that bond loosening takes place immediately after addition of a second proton to the oxygen, which causes opening of the ring (intermediates O, P).

The nucleophile can thus also be added after ring opening. The calculations of the thermodynamic parameters (Tables 4 and 5) showed that addition of a second proton at the oxygen is favorable both before and after addition of the nucleophile  $H_2X$  ( $X = O, S$ ) in the  $\alpha$  position of the ring. In addition, successive  $\alpha$ -C- and O-protonation, which results in form I, is thermodynamically more advantageous in the hydrolysis reaction than  $\beta$ -C- and O-protonation (form L). Both  $\alpha$ - and  $\beta$ -protonation with subsequent O-protonation (forms J, K, M, N) are favorable for recyclization (Table 5).

The difference in the distribution of the electron density in the furan ring as a function of the type of nucleophile should be noted (Table 3). Attack of position 5 of the  $\alpha$ -protonated form of the substrate by a molecule of water has a weak effect on the change in the electron density in intermediate C, preserving the structure of the quasi-diene molecule — genetically close to the product of hydrolysis. Attack by hydrogen sulfide or selenide causes localization of the  $C_{(3)}-C_{(4)}$  double bond (forms D, E). Loosening of  $C_{(2)}-O$  and  $C_{(5)}-O$  bonds takes place on repeated protonation in intermediates I-J and L-N (Table 3).

In summarizing the experimental and calculated data, we can conclude that double protonation is unnecessary both in hydrolysis and in recyclization of furans. For hydrolysis,  $\alpha$ -C- and O-protonation is required; for recyclization, in addition to the above, the variant of  $\beta$ -C and O-protonation is also probable. Addition of the nucleophile can take place both before and after cleavage of the furan ring. The basic difference in these processes is in the degree of nucleophilicity of the reagents used:  $H_2O < H_2O^{18} < H_2S < H_2Se$ . The thiophenes and selenophenes formed during recyclization are stable in acid medium, in contrast to furan.



The data obtained indicate the closeness of the schemes of the mechanisms of hydrolysis and recyclization of furans in the ring-opening stage.

## EXPERIMENTAL

The evolution of the reactions was controlled and the products were identified on a Tsvet-101 chromatograph with a flame-ionization detector. Apiezon-L applied in the amount of 15% on Chromaton N-AW-DMCS was used as the stationary phase. The column length was  $1\text{ m} \times 3\text{ mm}$  and  $3\text{ m} \times 3\text{ mm}$ , the thermostat temperature was  $160^\circ\text{C}$ , and the helium carrier gas flow rate was 2 liters/h.

The mass spectra were made on an MAT III chromatograph—mass spectrometer with electron ionizing energy of 80 eV, emission current of 270 mA, source temperature of  $300^\circ\text{C}$ , column length of 1.5 m, SE 30.5% as stationary phase, and helium as carrier gas.

The quantum-chemical calculations were made by the RMZ SCF MO LCAO method with the MOPAC software package similar to [1].

Compounds I-III and XI were synthesized by the methods in [7].

**General Method of Reaction of Compounds I-III with  $H_2^{18}O$ .** A 50-ml reactor thermostated at  $35^\circ\text{C}$  was filled with 25 ml of 3.2 N solution of hydrogen chloride in absolute ethanol, 1 ml of  $H_2^{18}O$  water, and 0.072 mole of furan I-III. The reaction mixture was stirred for 45 min, neutralized with saturated sodium bicarbonate solution, extracted with ether, and dried with calcined sodium sulfate. The ether was eliminated, and the residue was redistilled.

**Synthesis of 2,5-Hexanedione-<sup>18</sup>O (X).** A 50-ml round-bottom flask equipped with a reflux condenser was filled with 5 g (0.05 mole) of 2,5-hexanedione, 3.1 g (0.16 mole) of H<sub>2</sub><sup>18</sup>O, and 0.3 g (0.0027 mole) of anhydrous sodium carbonate, and was heated in a water bath at 45-50°C for 2 h. The reaction mixture was extracted with ether and dried with calcined sodium sulfate. The ether was eliminated and the residue was vacuum distilled. Yield of 3.16 g (63%). Bp = 77-78°C (15 mm Hg);  $n_D^{20} = 1.4230$ . Mass spectrum: 114 (M<sup>+</sup>); 115 (M + 1); 116 (M + 2).

**Synthesis of 2,5-Dimethylfuran-<sup>18</sup>O (XIa).** A 30-ml round-bottom flask with a reflux condenser was filled with 3.16 g (0.028 mole) of compound X, 3.19 g (0.043 mole) of acetic anhydride, and 0.132 g (0.0014 mole) of zinc chloride and heated in a water bath at 50°C for 5 min. The mixture was left at room temperature for 30 min. Then it was extracted with ether and dried with calcined magnesium sulfate. The ether was eliminated and the residue was distilled. Yield of 1.53 g (57%). Bp = 85-100°C;  $n_D^{20} = 1.4465$ . Mass spectrum: 96 (M<sup>+</sup>); 98 (M + 1).

**Determination of the Kinetic Isotope Effect of Recyclization of 2,5-Dimethylfuran with 2,5-Dimethylthiophene XII.** The reaction of furans XI and XIa with hydrogen sulfide was conducted in two reactors thermostated at 35°C, equipped with a magnetic stirrer, reflux condenser, and bubbler. Then 20 ml of a 2.2 N solution of hydrogen chloride in absolute ethanol was placed in each one and saturated with hydrogen sulfide for 1 h. After saturation, weighed portions of 0.002 mole of compounds XI and XIa and 0.15 g (0.001 mole) of toluene (internal standard) were added to each reactor. Samples 0.5 ml in volume were collected from the reaction mixture at fixed times, neutralized with 2 ml of saturated sodium carbonate, and extracted with 0.5 ml of ether. The concentration of components in the sample was determined by GLC, using the internal standard method for the calculations. The experiment was conducted five times. The rate constants of the compared reactions were calculated with the tangent of the slope of the corresponding anamorphoses. The value of the kinetic isotope effect was  $K^{18}O/K^{16}O = 1.312 \pm 0.2$  (Table 2).

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