

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

5.* DIRECTION OF PROTONATION OF FURANS

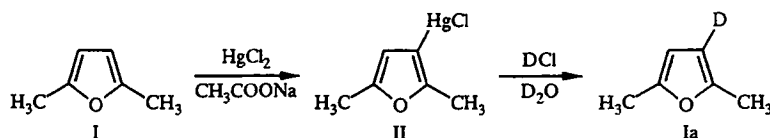
T. I. Gubina, V. I. Labunskaya, A. N. Pankratov,
S. P. Voronin, and V. G. Kharchenko

2,5-Dimethyl-3-D-furan was prepared for the first time. Its recyclization into the corresponding thiophene and selenophene was investigated. The possibility of β -C-protonation of the furan ring was confirmed by experimental and quantum chemical data.

Many studies have been dedicated to answering the question of the direction of protonation of furans in the reaction of acid hydrolysis. α -C-Protonation of the furan ring was selected *a priori* by analogy with reactions of electrophilic substitution in [2]. Finnish researchers believe that hydrolysis of 2,5-dimethyl- and 2-methoxyfurans begins with β -C-protonation of the ring [3, 4]. However, it was suggested in [5] that this hypothesis was based on incorrect determination of the structure of the products of hydrolysis of 2-methoxyfuran. The furan ions formed in the gas phase in conditions of mass spectrometry with chemical ionization (reagent gases: isobutane and methane) are described as products of α -C-protonation in [6]. Stable furanium ions were obtained from *tert*-butylfurans in the liquid phase, and 2,5-dimethylfuran was completely resinified in the same conditions in [7].

Acid-catalyzed isotope exchange is widely used for assessing the reactivity of heterocycles. In studying the rate of deuterium exchange of benzene, furan, thiophene, selenophene, and pyrrol, protonation of the β -carbon atom of the furan ring was found. Only the mobility of the α -H atoms could be measured in the deuterium exchange reaction, since hydrolytic splitting of the furan ring was simultaneously observed in the region of concentrations of H_2SO_4 greater than 30 wt. %, where exchange of protons in β positions takes place with a sufficient rate [8].

We continued the study of the mechanism of the reaction of recyclization of furans into thiophenes and selenophenes in conditions of acid catalysis. We investigated the possibility of β -C-protonation as the first stage of recyclization. 2,5-Dimethyl-3-D-furan (Ia) was investigated. Incorporation of a label in position 3 of 2,5-dimethylfuran (I) was conducted similar to the method described in [9] via mercury chloride (II) according to the following scheme:



Recyclization of compound Ia into 2,5-dimethylthiophene (III) and 2,5-dimethylselenophene (IV) was conducted with hydrogen sulfide and hydrogen selenide in absolute ethanol saturated with dry hydrogen chloride, similar to the method described in [10]. The evolution of the reaction was monitored with the GLC data, and after incorporation and preservation of the label, it was monitored by PMR spectroscopy and mass spectrometry.

*See [1] for Communication 4.

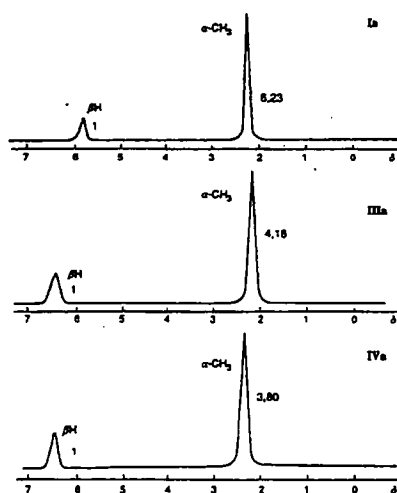
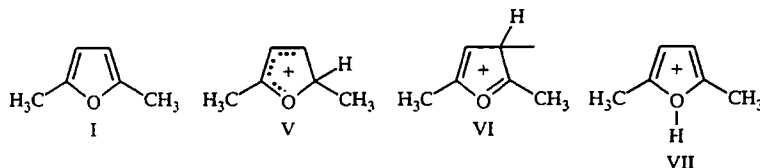


Fig. 1. PMR spectra of compounds Ia, IIIa, and IVa with relative peak areas.

2,5-Dimethyl-3-D-thiophene (IIIc) and 2,5-dimethyl-3-D-selenophene (IVa) were obtained as a result of recyclization of furan Ia. The deuterium label in the β positions of the heterocycles of compounds IIIa and IVa were calculated with the ratio of the areas of the α -CH₃ and β -H signals in the PMR spectra. The analysis of the data obtained showed that compound IIIa loses 60.7% and compound IVa loses 73.3% of the deuterium label (Fig. 1). Compounds IIIa and IVa were also prepared by back synthesis as a result of deuterium exchange of thiophene III and selenophene IV. The stability of their deuterium label was investigated in the recyclization conditions, and it was found that in the experimental conditions the D-label in compounds IIIa and IVa is totally preserved. Loss of the label during recyclization of 2,5-dimethyl-3-D-furan thus indicates that the β position of the ring is one of the reaction sites during the reaction.

A quantum chemical calculation of the 2,5-dimethylfuran molecule (I) and its protonated forms in the α -(V) and β -(VI) positions of the furan ring and the oxygen atom of (VII) was performed to answer the question of the direction of protonation (Tables 1 and 2).



The data in Table 2 show that from a thermodynamic point of view, both types of C-protonation are possible, although α -C-protonation is energetically more advantageous (by ~ 7 kcal/mole). The initial O-protonation is energetically less favorable.

A significant positive charge on the α -carbon atom (respectively in position 5 and 2) appears both in α - and in β -C-protonation of the furan ring, and this promotes subsequent attack of the nucleophile. Protonation at the oxygen atom insignificantly alters the distribution of the electron density in the ring, the Wiberg index of the C₍₂₎-O and C₍₅₎-O bonds decreases slightly, and weak negative charges appear on the C₍₂₎ and C₍₅₎ atoms, which reduces the possibility of attack by the nucleophile (Table 1).

EXPERIMENTAL

The evolution of the process was monitored 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 m, the diameter was 3 mm, the thermostat temperature was 160°C, and the argon carrier gas flow rate was 2 liter/h.

The PMR spectra were recorded on a Varian FT-80A spectrometer (80 MHz) in deuteriochloroform using HMDS as the internal standard.

TABLE 1. Charges on Atoms, Wiberg Indexes of 2,5-Dimethylfuran (I), and Products of Its α -C- (V), β -C- (VI), and O-Protonation (VII)

Molecule	Charges on atoms				
	C(2)	C(3)	C(4)	C(5)	O
I	-0,047	-0,175	-0,175	-0,048	-0,062
V	0,053	0,055	-0,232	0,359	-0,087
VI	0,318	-0,135	-0,138	0,018	-0,039
VII	-0,035	-0,043	-0,043	-0,035	0,073

Molecule	Wiberg indexes				
	C(2)—O	C(2)—C(3)	C(3)—C(4)	C(4)—C(5)	O—C(5)
I	1,095	1,658	1,198	1,658	1,095
V	0,897	1,002	1,736	1,154	1,377
VI	1,452	1,031	1,012	1,829	0,943
VII	0,857	1,811	1,068	1,811	0,857

TABLE 2. Thermodynamic Characteristics of 2,5-Dimethylfuran and Its Protonated Forms

Molecule	ΔH_f^{298} , kcal/mole	S, cal/mole·K	ΔS , cal/mole·K	ΔG_f , kcal/mole	$\Delta \Delta G^*$, kcal/mole
I	-21,75	85,11	-399,05	-7,47	—
V	153,36	83,49	-418,06	172,78	-201,85
VI	153,59	87,83	-413,72	179,02	-194,85
VII	184,14	86,66	-415,06	209,91	-164,72

* $\Delta \Delta G$: change in the isobaric-isothermal potential calculated for the reaction $F + H^+ = FH^+$ (F = furan), $\Delta \Delta G = \Delta G_{FH} - (\Delta G_F + \Delta G_H)$.

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°C, column length of 1.5 m, 30.5% SE stationary phase, and helium carrier gas flow rate of 0.9 g/liter.

Compounds I, III, and IV were synthesized by the methods in [10].

The quantum chemical calculations by the RMZ SCF LCAO MO method [11, 12] were performed with the MOPAC program [13, 14] with complete optimization of the geometry (Broyden—Fletcher—Goldfarb—Shanno procedure [15, 16]), using the Thiel fast minimization algorithms [16]. The condition was set that the gradient norm would not exceed 0.02 kcal/mole/Å. Preliminary optimization was conducted by the MMC method [17] with the POMODEL software package [17]. In calculating the rotational contributions to the thermodynamic functions, the symmetry number was set equal to 1.

The values of the change in the isobaric-isothermal potential in formation of the substances ΔG_f was calculated from the ratio:

$$\Delta G_f = \Delta H_f - T\Delta S_f,$$

where the standard entropy of formation ΔS_f was calculated with the equation:

$$\Delta S_f = S - \sum_i S_i,$$

where S_i is the entropy of formation of the elements constituting the molecule in their standard states [18], found with consideration of the diatomic character of the hydrogen, oxygen, and rhombic sulfur molecules; $T = 298.15$ K.

Synthesis of 2,5-Dimethyl-3-chloromercurofuran (II). A round-bottom, 1000-ml flask equipped with a mechanical stirrer was filled with 480 ml of water, 20 g (0.21 mole) of compound I, 20 g of sodium acetate, and 43 g (0.16 mole) of diva-

lent mercury chloride. The reaction mixture was stirred at a temperature of 50°C for 4.5 h. Sediment of compound II precipitated, was filtered off, washed with water, dried, and used without purification in synthesis of compound IIIa. Yield of 29.4 g (53%).

Synthesis of 2,5-Dimethyl-3-D-furan (Ia). A round-bottom, 100-ml flask was filled with 12.7 g (0.038 mole) of compound II, 14.8 g of a solution of DCl in D₂O (1:3), and stirred at room temperature for 3 h. The target product was then distilled from the flask, collecting the fraction with bp = 90-100°C, it was dried over calcined sodium sulfate, and stillled again, bp = 94-96°C; $n_D^{20} = 1.4305$. Yield of 1.9 g (51%). PMR spectrum, δ , ppm: 2.31 (s, CH₃); 5.3 (s, β -H). Mass spectrum: 96 (M⁺); 97 (M + 1).

Synthesis of 2,5-Dimethyl-3-D-thiophene (IIIa). A 30-ml flask equipped with a reflux condenser was filled with 1.5 g (0.013 mole) of 2,5-DMT, 4.53 g (0.074 mole) of CH₂COOD, and 2.27 g (0.02 mole) of CF₃COOD. The reaction mixture was held at 50°C for 20 h, then neutralized with a saturated solution of soda and extracted with ether. The ether extracts were washed with water and dried with calcined sodium sulfate. The ether was eliminated, and the residue was vacuum distilled. Bp = 76-78°C (150 mm Hg); $n_D^{20} = 1.5155$. Yield of 1.3 g (80%). PMR spectrum, δ , ppm: 2.25 (s, CH₃); 6.3 (s, β -H). Mass spectrum: 112 (M⁺); 113 (M + 1); 114 (M + 2).

Synthesis of 2,5-Dimethyl-3-D-selenophene (IVa). Synthesis was conducted similar to synthesis of IIIa, starting with 2.07 g (0.013 mole) of compound IV, 4.53 g (0.074 mole) of CH₃COOD, and 2.27 g (0.02 mole) of CF₃COOD. Yield of 1.53 g (73%), bp = 88-89°C (70 mm Hg); $n_D^{20} = 1.5440$. PMR spectrum, δ , ppm: 2.37 (s, CH₃); 6.58 (s, β -H).

Study of the Stability of the Deuterium Label in Compounds IIIa, IVa. A reactor thermostated at 35°C and equipped with a magnetic stirrer was filled with 1.3 g (0.011 mole) of compound IIIa or IVa and 30 ml of absolute ethanol saturated with dry hydrogen chloride (2.4 mole/liter). The mixture was stirred and a 10-ml sample was collected at fixed intervals (40, 80, 120 min), neutralized with a solution of soda, and extracted with ether. The ether was eliminated. Control was performed with the PMR and mass spectral data.

General Method of Recycling of 2,5-Dimethyl-3-D-furan (Ia) into 2,5-Dimethyl-3-D-thiophene (IIIa) and 2,5-Dimethyl-3-D-selenophene (IVa). A two-neck reactor thermostated at 35°C and equipped with a magnetic stirrer was filled with 30 ml of absolute ethanol saturated with dry hydrogen chloride (2.4 mole) and saturated for 1 h with hydrogen sulfide (hydrogen selenide). Then 1 g (0.01 mole) of compound Ia was added to the solution. The reaction mixture was stirred, while continuing to feed in hydrogen sulfide or selenide, for 5 h. At the end of the reaction, the solution was neutralized with a solution of soda and the product was extracted with ether. The ether extracts were washed with water and dried with calcined sodium sulfate. The ether was eliminated and the residue was vacuum distilled. Compound IIIa: yield of 0.6 g (53%); bp = 76-78°C (150 mm Hg); $n_D^{20} = 1.5162$. Compound IVa: yield of 0.4 g (33%); bp = 88-90°C (70 mm Hg); $n_D^{20} = 1.5448$.

This research was supported by the Russian Fund for Fundamental Research.

REFERENCES

1. T. I. Gubina, V. I. Labunskaya, G. K. Kornienko, L. A. Borodina, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, No. 5, 624 (1995).
2. E. J. Stamhuis, W. Drendt, and H. van den Berg, *Rec. Trav. Chim.*, **83**, 167 (1994).
3. P. Salomaa, A. Kankaanpera, E. Nikanden, K. Kaipainen, and R. Aaltonen, *Acta Chem. Scand.*, **27**, 153 (1973).
4. A. Kankaanpera and R. Aaltonen, *Acta Chem. Scand.*, **26**, 2920 (1972).
5. J. E. Garst and G. L. Schmir, *J. Org. Chem.*, **39**, 2920 (1974).
6. V. I. Kadentsev, L. I. Belen'kii, N. G. Kolotyorkina, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 1, 85 (1982).
7. U. E. Wiersum and H. Wynberg, *Tetrahedron Lett.*, No. 31, 2951 (1967).
8. K. Schwetlick and K. J. Unverferth, *J. Prakt. Chem.*, **314**, 603 (1972).
9. A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Yu. I. Ranneva, and S. A. Giller, *Khim. Geterotsikl. Soedin.*, No. 5, 643 (1966).
10. S. P. Voronin, T. I. Gubina, S. A. Trushin, I. A. Markushina, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, No. 11, 1458 (1989).
11. J. J. P. Stewart, *J. Comput. Chem.*, **10**, No. 2, 209 (1989).
12. J. J. P. Stewart, *J. Comput. Chem.*, **10**, No. 2, 221 (1989).

13. J. J. P. Stewart, MOPAC, A Semi-Empirical Molecular Orbital Program, QCPE (1983), Program N 455.
14. T. Clark, Computer Chemistry. Practical Handbook of Calculations of the Structure and Energy of Molecules [Russian translation], Mir, Moscow (1990).
15. D. K. Agrafiotis and H. S. Rzepa, J. Chem. Res. Synop., No. 3, 100 (1988).
16. W. Thiel, J. Mol. Struct. Theor. Chem., **163**, 415 (1988).
17. U. Burkert and N. L. Allinger, Molecular Mechanics [Russian translation], Mir, Moscow (1986).
18. D. R. Stull, E. F. Westrum, and G. C. Sinke, The Chemical Thermodynamics of Organic Compounds, Wiley, New York (1969).