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SYNTHESIS AND STRUCTURE ANALYSIS OF CYCLIC FURFURAL ACETALS

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UDC 547.278.3 + 547.72.07

Quantum chemical calculations and the PMR method are used to show that the preferable conformation of cyclic furfural acetals is a chair with an axial orientation of the furyl substituent. In 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane, the conformation equilibrium is shifted toward the trans-isomer with diaxial positions of the furyl and oxymethyl groups. The results of calculations suggest that the synthesis can lead to a cis-isomer with an axial orientation of the furyl and equatorial oxymethyl groups. It was shown experimentally that the synthesis leads to a mixture of trans- and cis-isomers. Mild conditions (room temperature, aqueous medium) lead to formation of the trans-isomer and small amounts of the cis-isomer (less than 2%). In rigid conditions (boiling in aromatic hydrocarbons), up to 20% of the cis-isomer is formed.

Effective applications of biologically active substances are provided by simple and convenient synthetic procedures. Many cyclic furfural acetals possess a wide spectrum of biological activity [1], due to which they are used as active agents in growth regulators for grain, root, cucurbit crops, etc. [2]. Thus 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane (1) shows a high growth regulating activity [3]. According to a preliminary analysis, *cis-trans*-isomerism is possible for compound 1. First, this is the result of different conformation states and configurations of substituents with respect to the symmetry plane of the acetal ring through the C(2) and CC(5) atoms. Another reason is possible rotation of the plane of the furan ring around the C(2)–C(2') bond, as shown earlier for some compounds [4]. In view of the various potential activities of compounds of this class, the problem of their preferable conformations and positions of substituents deserves special investigations.

Synthesis of isomers of furyldioxane 1 in individual form certainly involves experimental difficulties and evidently leads to a mixture of several compounds. Prior to choosing synthetic conditions, we calculated preferable geometry for a series of furyl-containing dioxacycloalkanes.

Quantum chemical analysis was performed using the software implementing different semiempirical methods for calculating molecular parameters and spatial structure optimization. The AM1 semiempirical method (AMPAC-IBM PC) was chosen as most adequately reproducing the geometry of the molecules under study as compared to known (XRD, ED) experimental data; this was confirmed by preliminary calculations for some dioxacycloalkanes [5]. Geometry optimization was carried out by the Davidson–Fletcher–Powell (DFP) method in the RHF approximation by the energy minimum. The initial data were molecular structures in internal coordinates, no restrictions on optimization were imposed, and all parameters were independent of each other.

For compound 1, possible enantiomeric structures of *trans*- and *cis*-isomers with furyl and oxymethyl substituents in the axial (*a*) or equatorial (*e*) positions (1*a-d*) as well as conformers formed due to rotation of the plane of the furan ring around the C(2)–C(2') bond (1*e,f*) were calculated. Table 1 gives the calculated enthalpies of formation of different structures.

It follows that *trans*-isomer 1*a* is the energetically preferable state, in which the furyl substituent at C(2) and

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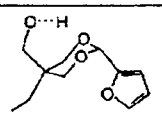
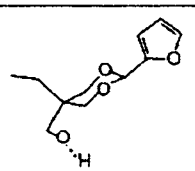
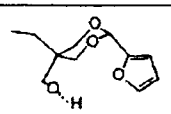
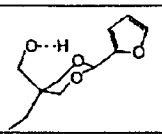
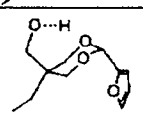
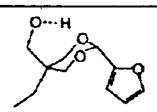
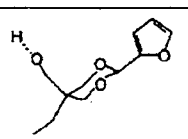
TABLE 1. Parameters of Possible Structures of 2-(Furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane

No.	Structure	ΔH_f, kcal/mole	$\Delta H_f - \Delta H_f(1a)$, kcal/mole
1*a*		-146.7	–
1*b*		-141.1	5.6
1*c*		-145.2	1.5
1*d*		-143.6	3.1
1*e*		-145.8	0.9
1*f*		-144.0	2.7
1*g*		-142.9	3.8

the oxymethyl substituent at C(5) are oriented axially. The least favorable structure is *trans*-isomer 1*b* with the *e,e*-position of these radicals (the difference in the total energies between 1*a* and 1*b* reaches 5.6 kcal/mole).

Among the structures listed in Table 1 is *cis*-isomer 1*c*, whose geometry is noteworthy because the *a*-position of the furyl substituent is combined with the *e*-oxymethyl group. The difference between the calculated heats of formation for the *trans* (1*a*) and *cis* (1*c*) isomers is small (1.5 kcal/mole); this indicates that *cis*-isomer 1*c* is the most probable admixture to *trans*-isomer 1*a* in the synthesis of compound 1.

When rotated around the C(2)–C(2') bond, the furyl substituent must overcome a barrier of about 7 kcal/mole to pass from the favorable "oxygen-in" (1*a*) to the less stable (by 2.7 kcal/mole) "oxygen-out" (1*f*) position. Figure 1 gives the energy diagram for rotation of the furyl substituent in the axial position in dioxane 1.

Qualitative estimation of the occupancies of the calculated conformation states at 273-400 K for structures 1*a-g* shows that one would expect real formation of the *cis-a,e* isomer (1*c*) in addition to the *trans-a,a* compound (1*a*) and that any appreciable amount of the *trans-e,e* isomer (1*b*) is excluded.

Preliminary conclusions for the calculations of the preferable conformation and configuration of substituents in compound 1 are quite unexpected, since it is commonly accepted that the bulky substituents at the C(2) and C(5) atoms in 1,3-dioxacycloalkanes are in the diequatorial position. Thus in [6] it was stated that the oxymethyl and furyl groups in dioxane 1 are diequatorial. When the substituent at C(2) is an electronegative group, it can occupy an axial vacancy as a result of the anomeric effect [7], which, in our opinion, takes place in compound 1.

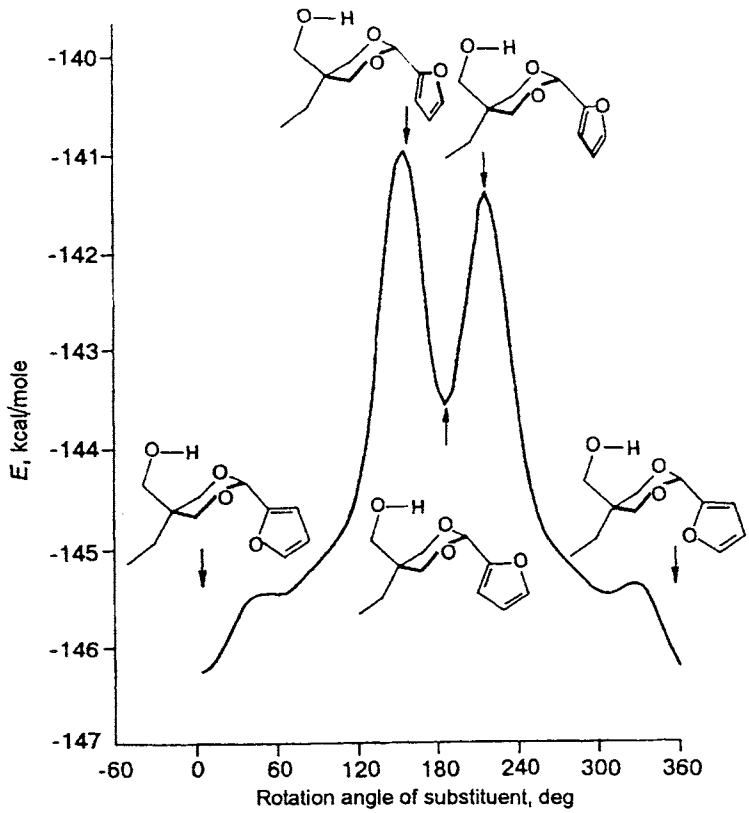


Fig. 1. Energy diagram of rotation of the furyl substituent around the C(2)–C(2′) bond.

Data on the possible conformation states of a series of 2-(furyl-2′)-1,3-dioxacycloalkanes also indicate that the axial position of the furyl substituent is preferable (by 0.5-3.5 kcal/mole).

Thus the analysis of the results of calculations including only thermodynamic parameters indicates that mild conditions of synthesis (relatively low temperatures) must lead to the isomer with *a*-orientations of substituents at C(2) and C(5), which is the most stable isomer. The polarity of the solvent can also be of importance. Thus it is known that 2-substituted tetrahydropyranes change conformation preferences from nonpolar to polar solvents [7]. Major differences are observed between the effects in organic solvents and in water [7, 8].

We synthesized 2-(furyl-2′)-5-ethyl-5-oxymethyl-1,3-dioxane (1) and other cyclic acetals (2-5) by condensation of furfural with appropriate diols in aqueous media at room temperature in the presence of sulfuric acid. The target products were separated by crystallization from aqueous suspensions and emulsions formed after the components have been stirred for 0.25-0.5 h. Table 2 gives the yields and some constants for the compounds.

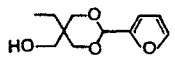
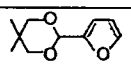
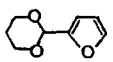
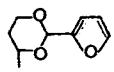
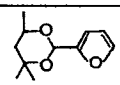
To establish the spatial structure of the compounds synthesized in these conditions, we analyzed their ^{1}H and ^{13}C NMR and IR spectra. The results of spectral studies were compared with the experimental data available for some compounds and the results of quantum chemical calculations.

It should be noted that the physicochemical constants of the furyl-containing acetals synthesized (Table 2) generally coincide with the published data. The compounds that can exist as isomers, including dioxane 1, show some differences in spectral data (^{1}H, ^{13}C NMR).

The conclusion about the conformation state of compounds 1-5 was made from quantitative estimates of the expected relative changes in nuclear magnetic shielding constants and agrees well with the available data [9, 10]. Thus the AB quadruplet with the nonequivalence $\Delta\sigma_{ae} = 0.55$ ppm for protons at C(4) and C(6) suggests that 2-(furyl-2′)-5-ethyl-5-oxymethyl-1,3-dioxane molecules predominantly have a chair conformation (Fig. 2).

In our opinion, it is very important to solve the problem of preferable configuration of substituents in compound 1. From the analysis of the PMR spectrum of this compound (Fig. 2) one can assume that the furan ring lies axially,

TABLE 2. Yields and Physicochemical Constants of Furfural Acetals

No.	Compound	Yield, %	T_b, deg (mmHg)	d_4^{20}	n_D^{20}
1		74	70*	–	–
2		89	20*	–	–
3		81	105(18)	1.2060	1.4870
4		79	126(20)	1.1181	1.4830
5		72	116(4)	1.0602	1.4807

*Melting point, deg.

since the singlet with δ = 5.45 ppm and integrated intensity of ^1H evidently belongs to the equatorial proton at C(2). In 2-substituted 1,3-dioxanes, the chemical shift of the axial proton δ = 4.3-4.5 ppm; in isomers with the equatorial proton, the chemical shift increases by 0.1-0.3 ppm downfield [11]. In compound 1, the inductive and magnetically anisotropic effect of the furan ring must lead to a shift of the resonance proton at C(2) downfield. However, in 2-methoxy-5-isopropyl-1,3-dioxane existing as *cis*- and *trans*-isomers with *e*- and *a*-positions of the methoxy group (and showing an inductive effect similar to that of the furan substituent), the axial position of the proton at C(2) with δ = 5.33 ppm differs considerably from the resonance of the equatorial proton having δ = 5.44 ppm [11]. For compounds 2-5 synthesized by the procedure described here, the chemical shift of the proton at C(2) is within 5.45-5.75 ppm.

The configuration of the substituents at C(5) was established from the chemical shift of the proton resonance of the ethyl group. The triplet with δ = 0.8 and the quadruplet with δ = 1.2 ppm belong to the methyl and methylene

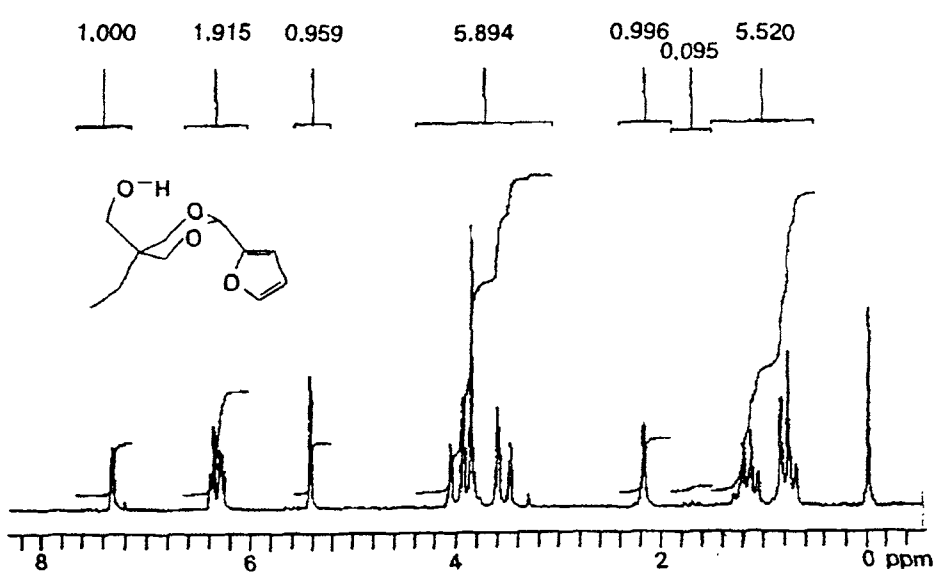


Fig. 2. PMR spectrum of 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane synthesized at room temperature.

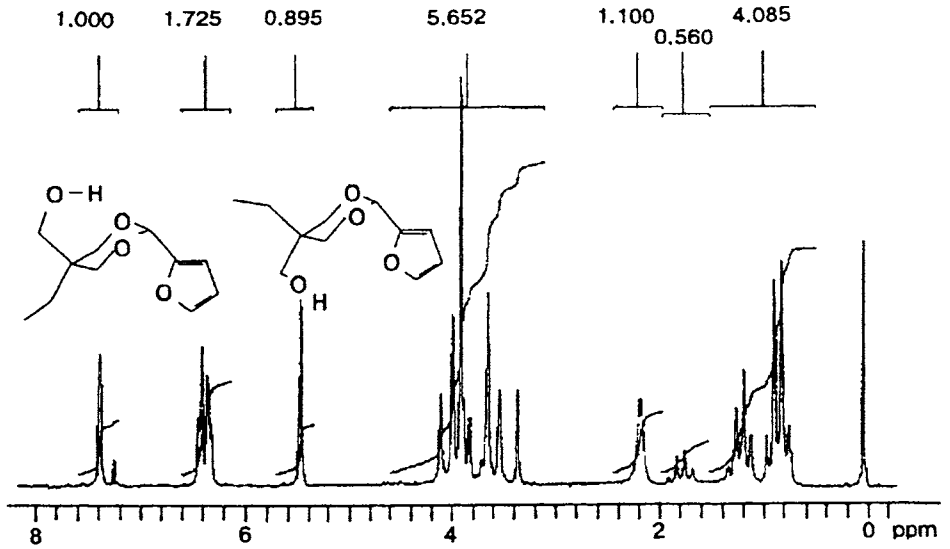


Fig. 3. PMR spectrum of 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane isomers isolated from the reaction mixture in the known synthesis [12].

groups, respectively. The above values of chemical shifts suggest that the ethyl group is equatorial. The alternative axial position of the ethyl group must lead to a 1.7-1.8 ppm downfield shift of the signal of the methylene group of the ethyl radical [11], which is absent in the spectrum of compound 1. The quadruplet of the methylene group with a chemical shift of 1.75 ppm appears in the spectrum of compound 1 synthesized by the known procedure [12]. In this case, we isolated a mixture of isomers whose PMR spectrum is presented in Fig. 3. Another feature of the spectrum of this sample is the presence of signals with δ = 3.3 and 3.75 ppm and different intensity ratio and multiplicity for the signal of the methyl group with δ = 0.8 ppm. These changes in the spectrum are attributed to the presence of isomer admixtures to 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane obtained by the procedure using benzene or toluene as a solvent at 80-100°C [12].

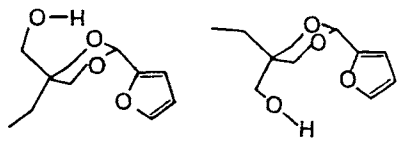
The absence of an additional signal near the singlet of the equatorial proton at C(2) with δ = 5.45 ppm suggests that the isomerism is due to a change in the configuration of substituents at C(5), the configuration of substituents at C(2) remaining unaltered.

It is noteworthy that the two isomers differ significantly in the nonequivalence of H_a and H_e at C(4) and C(6). Thus according to the spectrum of the nearly pure *trans*-isomer (Fig. 2), $\Delta\sigma_{ae}$ = 0.55 ppm; for the second isomer, this value is significantly smaller, $\Delta\sigma_{ea}$ = 0.15 ppm. It is known that such a decrease in $\Delta\sigma_{ae}$ may be associated with a transition of compound 1 from the chair to flexible asymmetric bath conformation [6]. The shift of the conformation equilibrium to the preferable chair conformation with the *a,a*-position of substituents may be promoted by formation of intramolecular hydrogen bonds. Indeed, the IR spectrum of compound 1 contains a narrow absorption band of OH vibrations in the region of 3460 cm^{-1}.

Since the PMR spectrum (Fig. 3) has a quadruplet of the methylene group of the ethyl radical with δ = 1.75 ppm, lying in the *a*-position, the singlet of the *e*-oxymethyl group must be shifted upfield with respect to the same singlet of the *a*-oxymethyl group [13]. Indeed, the singlet of the *a*-oxymethyl group is observed at δ = 3.85 ppm (Figs. 2 and 3), and the *e*-oxymethyl group gives rise to a quadruplet at δ = 3.35 ppm in the spectrum of the isomer mixture (Fig. 3). The signals with δ = 3.75 ppm belong to the protons at the C(4) and C(6) isomers. Changes in the intensity and multiplicity of the signal of the methyl group in the region with δ = 0.8 ppm are attributed to an overlap of the triplets of the methyl groups of the ethyl radical in the isomers.

Based on the analysis of the PMR spectra (Figs. 2 and 3), we concluded that the synthetic procedure developed by us gave 2-(furyl-2')-5-ethyl-5-oxymethyl-1,3-dioxane with a chair conformation, which is a *trans*-isomer with a diaxial position of the furyl at C(2) and oxymethyl at C(5) substituents (structure 1*a*). The synthetic procedure published

earlier [12] gives a mixture of *trans*- and *cis*-isomers in the ratio 1*a* : 1*c* = 5 : 1. The *cis*-isomer has a chair conformation; the furyl group is in the axial position, and the oxymethyl group is in the equatorial position (1*c*).



Ia Ic

The experimental data confirm the results of calculations and the conclusion about the predominant formation of the *trans*-isomer of compound 1 with the *a,a*-position of the furyl and oxymethyl substituents in mild conditions (structure 1*a*, Table 1). Performing the synthesis at an elevated temperature (boiling benzene, toluene) creates favorable conditions for the formation of *cis*-isomer 1*c*, which is thermodynamically less stable, along with isomer 1*a*.

Experimental. Melted 1,1,1-trimethylolpropane 134 g (1 mole) is placed in a chemical glass, and 96 g (1 mole) of freshly distilled furfural is poured in with stirring. The mixture is placed on a water bath, 10 cm^3 of the 10% solution of sulfuric acid is poured in at room temperature, and the mixture is stirred for 0.1-0.15 h. When the mixture becomes clouded, signaling the start of crystallization of the product, 200 cm^3 of water is added. A precipitate settles out. The precipitate is washed with a 5-10% aqueous solution of sodium carbonate to neutral or weak alkaline reaction, then filtered and dried at room temperature. The yield of compound 1 is 74%. Compounds 2-5 were obtained by an analogous procedure. Dioxanes 3-5 are formed as viscous oily liquids and are distilled in vacuum for purification. The PMR spectra of the compounds were recorded on a "Tesla-467" spectroscope at an operating frequency of 100 MHz in chloroform and HMDS as internal standard. The presence of the furyl substituent in the compounds is confirmed by two multiplets in the PMR spectra: one at 6.1-6.3 ppm with an integrated intensity of 2H, which belongs to the protons at C(3′) and C(4′) of the furyl heterocycle, and the other is a multiplet of the proton at C(5′) at 7.25-7.40 ppm with an integrated intensity of ^1H. In the IR spectra, the absorption bands at 3120, 1620, and 1510 cm^{-1} refer to the stretching vibrations of the C–H bond and the ring of the furyl group.

For compounds 1-5, the name, notation, yield (%), PMR (δ, ppm) and IR (cm^{-1}) data are given below:

2-(Furyl-2′)-5-ethyl-5-oxymethyl-1,3-dioxane (1), 74;

0.8 t (3H, CH_3), 1.18 qu (2H, CH_2), 2.2 s (1H, OH), 3.75 dd (4H, $2CH_2$), 3.85 s (2H, CH_2OH), 5.45 s (1H, OCHO);

IR spectrum (ν, cm^{-1}): 3620, 3492, 3120, 2910, 2860, 2330, 1600, 1450, 1405, 1360, 1300, 1195, 1150, 1090, 1000, 950, 920, 810, 750;

^{13}C NMR spectrum (δ, ppm): 6.83 C(9), 23.55 C(5), 37.07 C(8), 61.82 C(7), 72.36 C(4) and C(6), 96.25 C(2), 107.57 C(11), 110.24 C(12), 142.60 C(13), 150.64 C(10);

2(Furyl-2′)-5,5-dimethyl-1,3-dioxane (2), 89;

0.70 s (3H, *e*-CH_3), 1.18 s (3H, *a*-CH_3), 3.55 dd (4H, $2CH_2$), 5.40 s (1H, OCHO);

IR spectrum (ν, cm^{-1}): 3120, 2970, 2860, 1640, 1515, 1470, 1435, 1400, 1370, 1320, 1265, 1225, 1160, 1115, 1030, 980, 940, 920, 890, 820, 750;

2-(Furyl-2′)-1,3-dioxane (3), 81;

1.0-1.5 m (1H, *a*-CH_2), 1.65-2.25 m (1H, *e*-CH_2), 3.60-4.20 m (4H, $2CH_2O$), 5.45 s (1H, OCHO);

IR spectrum (ν, cm^{-1}): 3120, 2970, 2860, 1620, 1520, 1475, 1435, 1380, 1245, 1160, 1110, 1030, 960, 930, 890, 870, 805, 750;

2(Furyl-2′)-4-methyl-1,3-dioxane (4), 79;

1.20 d (3H, CH_3), 1.4-2.0 m (2H, CH_2), 3.80 dt (2H, CH_2O), 4.0-4.25 m (1H, CH), 5.5 s (1H, OCHO);

2-(Furyl-2′)-4,4,6-trimethyl-1,3-dioxane (5), 72;

1.1 d (3H, CH_3), 1.2 s (3H, *e*-CH_3), 1.3 s (3H, *a*-CH_3), 1.45 d (2H, CH_2), 3.8-4.2 m (1H, CH), 5.7 s (1H, OCHO);

IR spectrum (ν, cm^{-1}): 3135, 2980, 2950, 2880, 1620, 1510, 1440, 1380, 1360, 1325, 1270, 1240, 1220, 1170, 1105, 1080, 1025, 965, 940, 910, 830, 750.

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