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Mechanism of Levulinic Acid Formation in Acid Catalysed Hydrolysis of 2-Hydroxymethylfurane and 5-Hydroxymethylfurane-2-carbaldehyde

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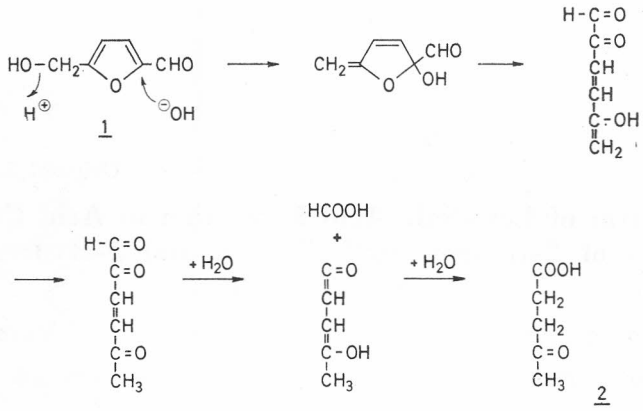
Mechanism of levulinic acid (*2*) formation in acid catalysed hydrolysis of 2-hydroxymethylfurane (*3*) and 5-hydroxymethylfuran-2-carbaldehyde (*1*) is studied by ^{13}C-NMR spectroscopy. Hydroxymethyl-derivative of dihydrofurane *5*, its anhydro-derivative *6*, and an unsaturated keto-aldehyde (*8*) are determined as intermediates in the transformation of *3* into *2* (Scheme 3). The conversion of *1* into *2* requires more drastic conditions, and the only two structures determined unambigously are *15* and *16*; the former intermediate led to polymerized material *via A-5*, analogous to polymerization of *4* via *13* and *14* (Scheme 4), while the latter decarbonylates and rearranges to afford levulinic acid (Scheme 5). Intramolecular oxygen transfer *via* cyclic intermediates (Scheme 6), embracing concerted C(1)—O and C(5)—X (X = H or CHO) bond breaking, cannot be proved.

INTRODUCTION

The formation of levulinic acid (γ-keto-valeric acid, or 4-oxo-pentanoic acid, *2*) from mono- and polysaccharides, induced by mineral acids, is a well known reaction. Tollens[1] was the first to observe in 1876 the formation of this keto-acid when heating starch or glucose with dil. sulfuric acid. Since then, industrial scale production[2-5] and broad usage[6-8] of levulinic acid were developed. From 1964 this acid is commercially available and represents a valuable C_5-synthon in the production of drugs, plastifyers, resins, *etc.*

Acid catalysed degradation of hexoses, *e. g.* D-glucose or D-fructose into levulinic acid implies, among other mechanistic peculiarities, a puzzling transformation of their 6-hydroxymethyl group into a methyl group in the final product. The intermediary formed aldehyde *1* could be converted into levulinic acid in the yields that range around 50%, apparently embracing the critical steps of the all-round process of levulinic acid formation. The first mechanistic proposal[9] for transformation of *1* into levulinic acid (*2*) is outlined in Scheme 1., and has repeatedly been referred to in the monographs.[10,11] On the other hand, when 2-hydroxymethylfurane (furfurol, *3*) is heated in aqueous solution in the presence of mineral acids, levulinic acid is obtained in much higher yields. Preparative studies of the rearrangement of furfurol

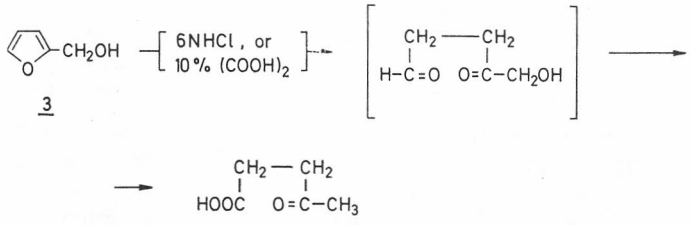
SCHEME 1.



H. S. ISBELL, J. Res. Nat. Bur. Stand. 32 (1944) 45.

to levulinic acid ester by methanolic hydrogen chloride,[13,14] and to levulinic acid in aqueous hydrochloric acid,[15] were published in the late 50's, but these important papers were not cited[10,11] until a recent monography.[12] Crucial for the mechanism of levulinic acid formation from hexoses is the hydroxymethyl → methyl transformation with concomitant oxydation of carbonylic to carboxylic group. This apparent concertidness of a reductive and an oxydative process in the same molecule led to the following assumption, expressed in Elderfield's monography:[16] »... It is suggested that the hydroxyketoaldehyde (XIV) is an intermediate in the formation of levulinic acid, which in turn is formed by a sort of intramolecular disproportionation resembling a Cannizzaro reaction ...« (Scheme 2 — referred to as in the original[16]).

SCHEME 2



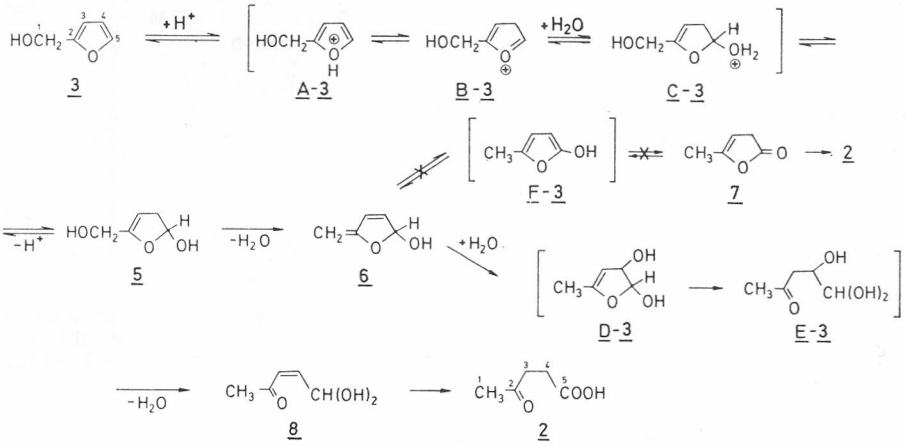
A. PUMMERER et al., Chem. Ber. 68 (1935) 480.

It is obvious, however, that the above acid catalysed *process cannot be compared* with the Canizzaro reaction, which takes place *under strongly basic conditions and includes two carbonyl groups* in a disproportionation process.

RESULTS AND DISCUSSION

The study of levulinic acid formation from monosaccharides in aqueous solution at elevated temperatures, *i. e.* under conditions used exclusively for its preparation either on the bench-[17–19] or on the industrial[2–5] scale, was described only in the early paper of Birkofer *et al.*[15] Involved in some preparative work on levulinic acid production from available natural resources,[19] we noticed that mechanistic aspects of this transformation in aqueous solution could only be conveniently followed by ^{13}C-NMR. The first results were published in a preliminary paper,[20] here we present the full account of this work.

SCHEME 3



The hydrolysis of the model compound *3* and 2-methyl congener *4* was monitored first, then the same process was examined for 5-hydroxymethylfuran-2-carbaldehyde (*1*), the actual intermediate in hydrolysis of hexoses to levulinic acid. On dissolving *3* and *4* in dil. aq. hydrochloric acid, both compounds turned within 10—15 min. at ambient temperature into oils, which were separated and analysed by ^{13}C-NMR. Compound *3* gave a mixture of the unsaturated acetal *5* and its dehydration product *6*, as well as a small quantity of an unsaturated ketone derivative, presumably *8*. Compound *4* transformed into a mixture of the hemiacetal *13* and the open-chain derivative *14*, which underwent complete polymerization above 70 °C (Scheme 3, compounds in the square brackets, assigned by letter and Scheme number, were not spectroscopically identified). Figure 1 shows the ^{13}C-NMR spectra of the mixture *5*/*6*, while Table I includes chemical shifts and multiplicities of the signals (where they could be determined unambigously) in the off resonance experiments.

When the acidic solution of *5* or *6* was heated at cca 70 °C, complete conversion into levulinic acid took place. It is conceivable that if formed, the intermediary angelica lactone *7* could undergo [1,5s]-sigmatropic shift[21]

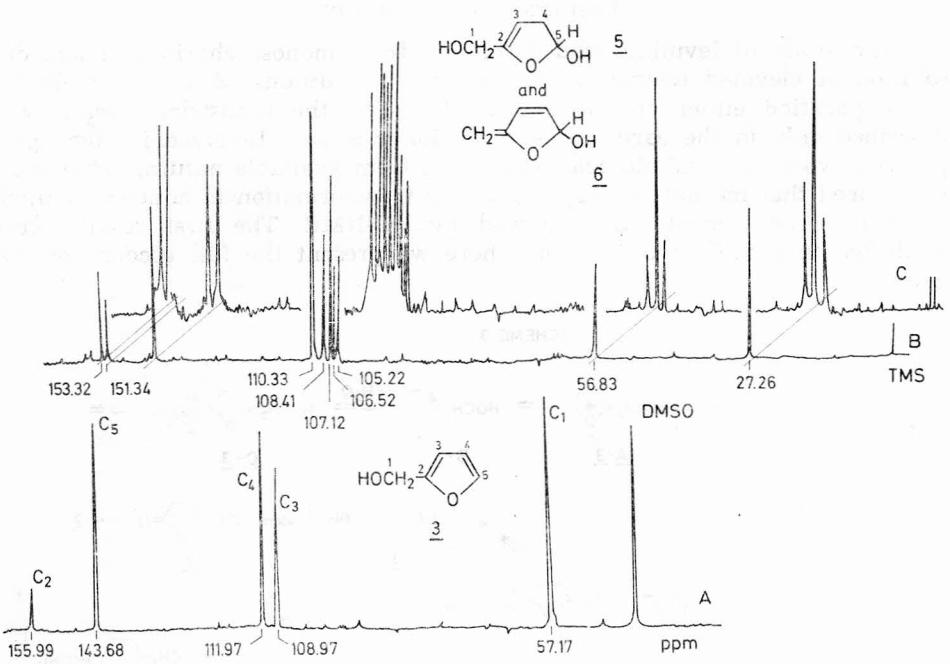


Figure 1. A. — ^{13}C-NMR spectrum of *3*, B. — ^{13}C-NMR spectrum of mixture *5/6*, isolated by extraction in chloroform, after 10 min. reaction of *3* in dil. (1 : 4) hydrochloric acid at 70 °C, C — off resonance spectrum of the same *5/6* mixture.

TABLE I

^{13}C-NMR Chemical Shifts (in ppm) for Compounds 1, 2, 3—16[a,b]

Compound	C_1	C_2	C_3	C_4	C_5	C_6
1	58.3 (t)	153.6 (s)	113.0 (d)	128.4 (d)	163.4 (s)	181.2
2	29.6 (q)	208.3 (s)	37.9 (t)	27.9 (t)	177.3 (s)	
3	57.2 (t)	156.0 (s)	109.0 (d)	112.0 (d)	143.7 (d)	
4	11.9 (q)	151.1 (s)	104.6 (d)	109.5 (d)	139.9 (d)	
5	56.8 (t)	153.3 (s)	110.3 (d)	27.3 (t)	107.1 (d)	
6	108.4 (t)	151.3	105.2	141.4 (d)	106.5 (d)	
7	13.9 (q)	153.2 (s)	99.5 (d)	34.1 (t)	170.0 (s)	
8	27.2	206.4	126.6	137.3	108[g]	
9	78.4	143.7	108.5	28.3	108.1	
10	30.0	208[g]	39.9	66.5	108[g]	
11	27.8	208[g]	128.3	135.1	110[g]	
12	29.5 (q)	206.9 (s)	38.0 (t)	28.0 (t)	173.4 (s)	51.6
13	12.1 (q)	153.0 (s)	105.2 (d)	28.6 (t)	105.0 (d)	
14	27[g]	206.2[d]	35.2[e]	36.1[e]	205.5[d]	
15	65.2 (t)	113.4 (s)	26.9 (t)	125.4	153.5	192.2
16	26.8	207.5[e]	128.8	138.7	209.8[e]	184.6

[a] Numbering of C-atoms is exemplified on the formulas of compounds *1*, *2*, *3* and *16* in Schemes 3 and 5.
[b] Multiplicities of signals in the off resonance experiments are given in parentheses.
[c, d, e] Assignments may be interchanged.
[f] Signals of the methoxy group carbons appear between 55—58 ppm.
[g] Assignments are ambiguous, more than one signal being present in the narrow region.

leading to aromatic structure *F-3*, which actually represents its enolic form (Scheme 3). To examine this pathway, independently prepared 7 was treated under the same conditions; neither the presence of its enolic form nor the formation of levulinic acid was observed (Figure 2).

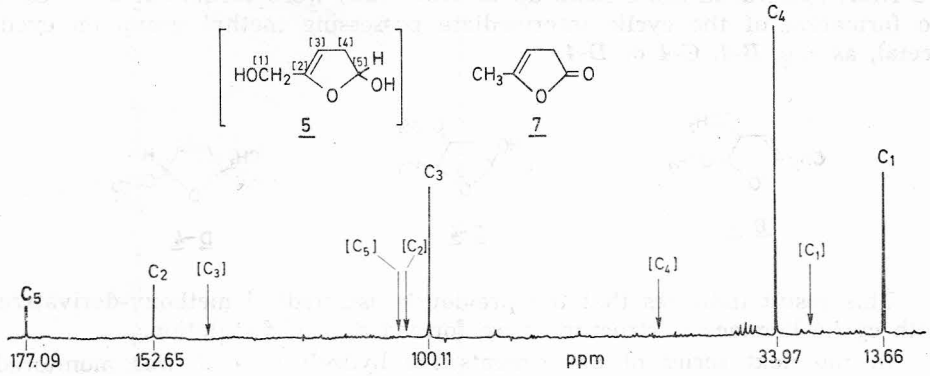
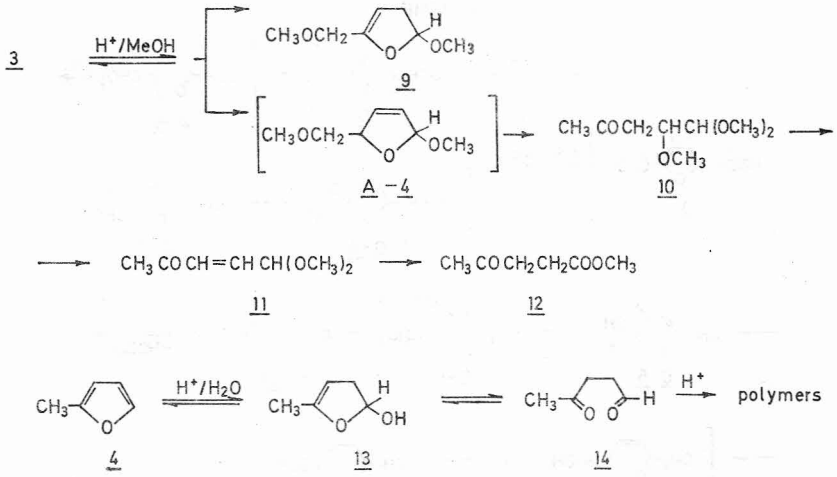


Figure 2. ^{13}C-NMR spectrum of 7 in dil. (1 : 4) hydrochloric acid, positions for signals (in brackets) of *5* are indicated.

SHEME 4.

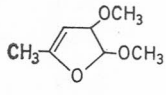


Since the ^{13}C-NMR spectrum of 7 unambigously revealed that this compound exists in its carboxylic form, an earlier statement, that *4* exists in the enolic form, based on UV-spectroscopic data,[22] should be corrected.

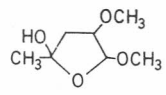
When we repeated acid catalysed methanolysis of *1* under conditions described for preparative scale experiments,[14] ^{13}C-NMR monitoring revealed accumulation of the open-chain intermediates *10* and *11* along with the final ester *12* (Scheme 4). Birkofer *et al.*[15] isolated *A-4*, presumably the first intermediate formed, which subsequently transformed into the open-chain compounds *10—12*, (Scheme 4).

Some ethoxy congeners of these compounds were identified by Horton and others[23,24] during the work on acid catalysed degradation of a 2,3-unsaturated sugars.

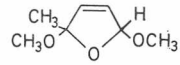
It is particularly noteworthy that careful examination of time depended ^{13}C-NMR spectra, in some cases up to 5000 scans were accumulated, revealed no formation of the cyclic intermediate possessing methyl group on cyclic acetal, as *e. g. B-4, C-4* or *D-4.*



B-4



C-4

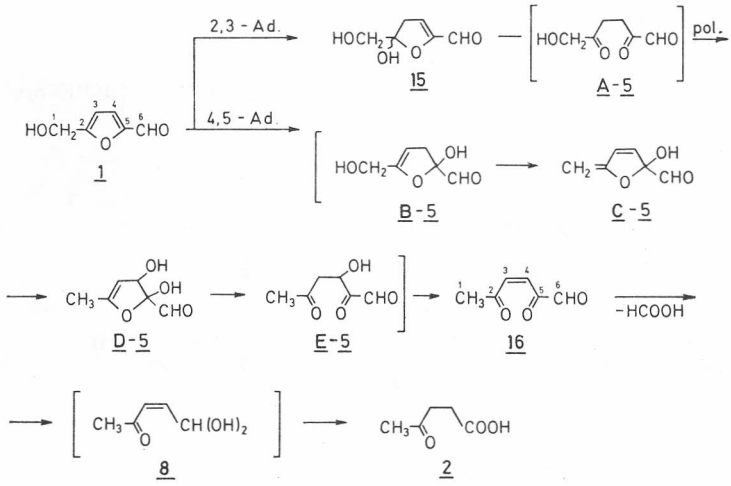


D-4

This result indicates that the previously isolated[13,14] methoxy-derivatives with cyclic hemiacetal structure were formed during distillation.

In the next series of experiments the hydrolysis of *1* was monitored. It required a slightly higher temperature ($> 100\ ^{\circ}C$), and the formation of the two intermediates (*15* and *16*) was demonstrated (Scheme 5, compounds in the square brackets, assigned by letter and Scheme number, are not spectroscopically identified, Table I).

SCHEME 5.

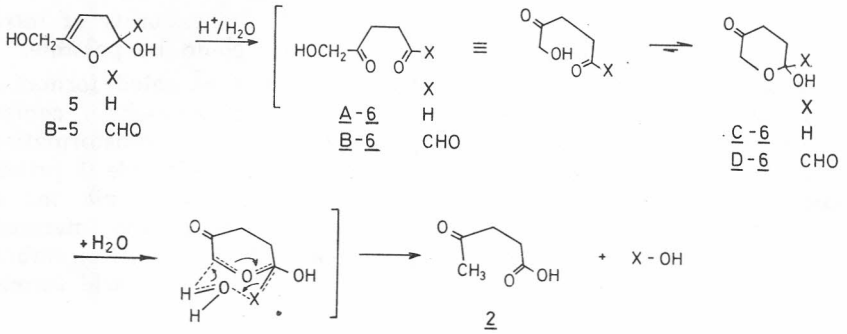


Obviously, the first one (*15*) resulted from the regioselective 2,3-addition of water on *1*, and presumably polymerized *via A-5* similarly as *4* polymerizes *via 13* and *14*. The »correct« 4,5-addition of water on *1* should give *B-5* which could then undergo a similar sequence of transformations as *5*, including decarbonylation step of the detectable intermediate *16*.

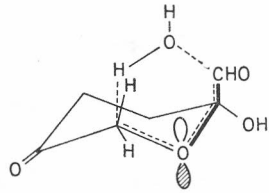
There remains, however, another possibility of levulinic acid formation from the intermediary *5*, or its counterpart *B-5*, as outlined in Scheme 6. This is an attractive way of explaining the formal disproportionation of

C-6 or *D-6* which has been already mentioned in a wrong context.[16] This mechanism requires intramolecular acetalysation of *A-6*, or ketalisation of *B-6*, leading in both cases to 6-membered intermediates *C-6* or *D-6*. Such unsubstituted cyclic hemiacetals are known to predominate in equilibrium with respective open-chain forms.[25] We were not able, however, to notice in the ^{13}C-NMR spectra of the reaction mixtures any significantly intensive signals that could be assigned to the intermediates *A-6*/*B-6* and *C-6*/*D-6*. Assuming that their steady-state concentrations were beyond the sensitivity of the instrumental technique, there still remains another assumption to be confirmed; in the intermediates *C-6* and *D-6* an anomalous C(1)-O bond cleavage should occur to form levulinic and formic acid, or water molecule. Since such a process is difficult to envisage as the heterolytic one, we presume concerted, water assisted, cleavage of the C(1)-O and C(5)-X bonds (Sheme 6).

SCHEME 6.



In the reactive conformation of hemiacetal *D-6* p-type lone pair on the ring oxygen and σ-orbital of C—X bond are in the *antiperiplanar* position. Thus, stereoelectronic requirements[26] are fulfilled for concerted C(5)-X bond breaking. Group X, however, cannot be a proton according to the present knowledge, since proton abstraction (oxydation) of hemiacetals is energetically highly unfavourable when performed thermally.[27,28] When X=CHO, concerted decarbonylation and C(1)-O bond breaking in *D-6* seems stereoelectronically favoured process. Approval of the concertedness of a chemical reaction is a difficult task, however, in our case it is even more so since the reacting species is an unstable intermediate.



D-6

Therefore, we have undertaken additional experiments, attempting to prove indirectly the mechanistic pathway outlined in Scheme 6, by proving

the intramolecularity of the oxygen transfer from CH_2OH group in *1* and *5*, and consequently from CH_2OH group in hexoses to the carboxylic group in the levulinic ocid.

To prove the possibility of exchange of both carbonylic and carboxylic oxygen atoms in levulinic acid with water at an elevated temperature, *via* corresponding enolic forms, an H/D exchange experiment was performed. Complete exchange was observed at the methyl and methylene groups, *i. e.* at C(1) and C(3) which flank the carbonyl group in 2, while the protons of the methylene group α- to the carboxyl group remained unexchanged (see Experimental). This result indicated that, once ^{18}O-atom is introduced into a carboxyl group its exchange with water at elevated temperature *via* enolization and the addition-elimination will be slow.

Levulinic acid exchanges at 90 °C and at pH 2—2.5 at both oxygen functions, its ketone carbonile oxygen undergoes a much faster exchange than the carboxylic oxygens. Detailed mechanistic and kinetic study on levulinic acid fragmentation and $^{16}O/^{18}O$ exchange is under way.[29] Only with all these data in hand the final answer on the possibility of intramolecular oxygen transfer within a cyclic hemiacetal could be possible.

In conclusion, it could be stated that this work revealed formation of dihydrofurane *5*, its dehydro-derivative *6*, and the open-chain compound *8* as the most stable intermediates in acid catalysed transformation of furfurol *3* into levulinic acid. The conversion of the aldehyde *1* proceeded *via* analogous intermediates *B-5* and *16*, and presumably *via* the same final intermediate *8*. So far it was not possible to prove the intermediacy of, otherwise energetically favourable, cyclic acetales *C-6* or *D-6*, embracing intramolecular oxygen transfer in the course of the levulinic acid formation.

EXPERIMENTAL

^{13}C-NMR spectra were recorded with a JEOL FX 90 Q Fourier transform spectrometer operating at 22.5 MHz at the desired temperature in 5 mm tubes. The sweep width used was 5200 Hz, the pulse width 5 μs (90° pulse), the acquisition time 1.5 or 2 s, and the digital resolution 0.056 p. p. m. Chemical shifts were measured (accuracy of the chemical shift, ± 0.1 p. p. m.) relative to internal dimethylsulfoxyde, set at 39.6 p. p. m. down-field of tetramethylsilane; or 1,4-dioxane (66.6 p. p. m.); or to internal Me_4Si. Mass spectroscopic measurements were performed on a Varian MAT-CN 7 instrument.

Compound *3* was purchased from Aldrich (Janssen) and used without further purification. Compound *1* was prepared according to ref. 30., and purified by distillation, b.p. 140—145 °C/3 mm Hg, compound *7*, according to ref. 31, and purified by distillation, b. p. 64—66 °C/20 mm Hg, compound *2* was obtained from various sources during an earlier preparative study.[19]

^{13}C-NMR Monitoring of the Conversion of 2-Hydroxymethylfuran (3) into Levulinic Acid (2)

Compound *3* (500 μL) was dissolved in dil. (1 : 4) hydrochloric acid (2 mL) and stirred in a closed vessel for 30 min. at ambient temperature. After a few minutes, yellow, oily drops separated from the solution. After 30 min of stirring, half-volume of the resulting emulsion was removed, extracted with chloroform (0.5 mL), organic phase separated, dried briefly over Na_2SO_4, and placed in the NMR tube. The accumulated signals of *5* and *6*, besides the traces of starting *3*, were identified. Then, the solution was heated in the NMR tube for 10 min. at 70 °C; this treatment led to formation of levulinic acid (*2*), no other signals were observed out of the noise-level.

An aliquote (0.3 mL) of the original aqueous solution was heated in the NMR tube for 10 min. at 70 °C, during which time the oil that separated was completely redissolved; the spectra reveal a complete transformation into levulinic acid.

^{13}C-NMR Monitoring of the Conversion of 5-Hydroxymethylfuran-2-aldehyde (1) to Levulinic Acid (2)

Compound *1* (100 μL) was dissolved in a mixture of dil. (1 : 1) hydrochloric acid (300 μL) and DMSO-d_6 (100 μL), placed in the NMR tube and the spectra run at ambient temperature and increasing the temperature by 10 °C within 10—15 min. Notable accumulation of signals for intermediates *15* and *16* was observed above 70 °C. At 90—100 °C, they slowly disappeared and only signals of levulinic acid were recorded.

When a similar experiment was performed maintaining lower temperatures (30—60 °C), very slow (days long) accumulation of signals for *15*, *16* and *8* occurred. When the same transformation was performed in the NMR probe at 120 °C, extensive polymerization occured and only signals of levulinic acid were detectable.

^{13}C-NMR Monitoring of the Conversion of 2-Methylfuran (4) into a Mixture 13/14

Compound *4* and a solvent mixture, consisting of dioxan-water-conc. hydrochloric acid (7 : 3 : 10), were mixed in the ratio 1 : 1. From the resulting solution an oily phase soon separated; this emulsion was stirred for 24 hrs, then extracted with chloroform. The organic extract was dried (Na_2SO_4), evaporated *in vacuo*, residual product mixture dissolved in DMSO-d_6, and the ^{13}C-NMR spectra were run.

A sample of this mixture was redissolved in the above solvent mixture and heated for 2 hrs at 100 °C. No traces of ^{13}C-signals of levulinic acid were detectable; on prolonged heating a complete polymerization occured.

H/D Exchange in Methyl Levulinate (12)

A. Compound *12* (19.2 mg, 0.15 mmol), and D_2O (414 mg, 20.6 mmol, Merck, min. 99.75% D) were placed in the NMR tube. *B*. The same quantities as in *A*, only 6% DCl in D_2O was used instead of D_2O.

Both samples, *A* and *B*, were thermostated at 99—100 °C, and ^{1}H-NMR spectra were run at cca 15 min. intervals. The spectrum of sample *A* did not show any H/D exchange, while in sample *B* the exchange was complete after cca 30 min; the signals at 2.20 ppm (s, CH_3CO), and at 2.72 (t, —$COCH_2$—) disappeared, while the triplet at 2.60 (for —CH_2COO) collapsed to a singlet of unaltered intensity (related to CH_3OD singlet at 3.71 ppm, as internal standard).

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SAŽETAK

Mehanizam nastajanja levulinske kiseline u kiselinom kataliziranoj hidrolizi 2-hidroksimetilfurana i 5-hidroksimetilfuran-2-karbaldehida

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^{13}C-NMR spektroskopijom proučavan je mehanizam nastajanja levulinske kiseline (*2*) u kiselinom kataliziranoj hidrolizi 2-hidroksimetilfurana (*4*) i 5-hidroksimetilfuran-2-karbaldehida (*1*). Kao intermedijari u prelazu *3* u *2* određeni su hidroksimetil-derivat dihidrofurana *5*, njegov anhidro-derivat *6*, i nezasićeni keto--aldehid *8* (Shema 4). Za prevođenje *1* u *2* potrebni su žešći uvjeti, a jedina dva jednoznačno utvrđena intermedijara u tom procesu su *15* i *16*; prvi od njih daje polimerizirani materijal preko daljeg intermedijara *A-5* (analogno polimerizaciji *4* preko *13* i *14* (v. Shema 4), dok drugi dekarbonilira i prelazi u levulinsku kiselinu (Shema 5). Nije bilo moguće dokazati intramolekulski prenos kisika preko cikličkih intermedijara (Shema 6.), koji pretpostavlja usklađeno kidanje veza C(1)—O i C(5)—X (X = H ili CHO).