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SYNTHESIS AND NMR SPECTRA OF TETRAHYDROFURAN-2-^{13}C

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An original method was developed for the synthesis of THF labeled selectively with the ^{13}C isotope at the α-carbon atom. The effective reduction of symmetry brought about by the insertion of the isotopic label removes the excess degeneracy of the spin systems describing the multiplet structure of the ^{1}H and ^{13}C NMR spectra, making it possible to undertake a detailed analysis. Exact values for the $^{1}H–^{1}H$ spin-spin coupling constants through four bonds and also the $^{13}C–^{1}H$ and $^{13}C–^{13}C$ spin-spin coupling constants involving the α-carbon atom were determined for the first time. The isotopic chemical shifts of the protons and ^{13}C nuclei caused by replacement of the ^{12}C nucleus by ^{13}C were determined. These data can be used to construct a quantitative model of the conformational behavior of THF as a molecular system in which pseudorotation in terms of vibrations with large amplitude is realized.

Keywords: tetrahydrofuran, analysis of multiplet structure of NMR spectra, conformational analysis, high-resolution NMR spectroscopy, isotopic effects, molecular dynamics.

Five-membered saturated heterocycles, including tetrahydrofuran (THF, **1**), are important fragments of natural compounds – sugars, nucleic acids, etc. The presence of these flexible structure fragments makes the skeleton of nucleic acids, for example, sufficiently mobile to ensure rapid and reliable recognition of the substrates. To understand these processes at the molecular level it is necessary to construct a quantitative model of the conformational behavior of five-membered rings [1]. The first attempt to explain the specific character of the conformation of five-membered rings and, in particular, the anomalously high entropy of cyclopentane formation was made by Kilpatrick et al. [2] in terms of pseudorotation – a synchronous cyclic process, accompanied by the successive going out from the basal plane of the ring from one to four structural elements forming this ring, with ten pairs of canonical conformations of the "envelope" and "twist" types. In papers by Pople and co-workers [3], a convenient and sufficiently illustrative scheme was proposed for the parametrization of this process using the pseudorotation phase angle (φ) and the folding amplitude (Q).

Among five-membered heterocycles, a special place is occupied by THF. Many attempts have been made to characterize its structure with the use of practically all the principal physical methods: X-ray structural analysis at -125°C [4]; electron diffraction [5]; microwave spectroscopy [6-9]; NMR spectroscopy both in an isotropic liquid phase [10-13] and in nematic liquid-crystalline solutions [14, 15]; photoelectron spectroscopy [16]. There have been numerous attempts to calculate the pseudorotation parameters in tetrahydrofuran by

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nonempirical methods [17-19]. However, the results of these investigations are contradictory. Until now there has been no common view about the most stable conformation of THF in literature. The results depend to a considerable degree on what model was used to describe the process and even on what methods were used to process the data. In our opinion [13], the conformational process in THF must be regarded as an exceptionally fast dynamic process taking place mainly in a scheme of pseudorotation as a vibration with large amplitude. In the early papers [4, 5], the structure determination was conducted within the model with one fixed form, which was assigned the "twist" conformation ${}^3T_4$ with C_2 symmetry ($\varphi = 90°$ with the oxygen atom on the basal plane, see the designation in [13]). Meyer et al. [8] came to the conclusion that the global minimum of the pseudorotation potential is at the non-canonical conformation (C_1 symmetry, $\varphi \approx 50°$), whereas Mamleev [7] and Mel'nik [9] concluded on the basis of data from the vibrational-rotational spectra that the most stable conformation is the "twist" conformation ${}^3T_4$. Analysis of the photoelectron spectra [16] made it possible to obtain a broad band, which the authors assigned to the ${}^1E$ "envelope" configuration (C_S symmetry, $\varphi = 0$) in addition to the main ${}^3T_4$ form. The accuracy of modern quantum-chemical calculations is probably insufficient for reliable prediction of the relative stability of conformers so close in energy. The calculations results depend to a great degree on the level of the approximation employed [17-19], and in the series of the most complicated and, as could be expected, more accurate calculations by the MP2 method with aug-cc-pVXZ wave functions (X = D and T) the global minimum is at the ${}^1E$ "envelope" [19].

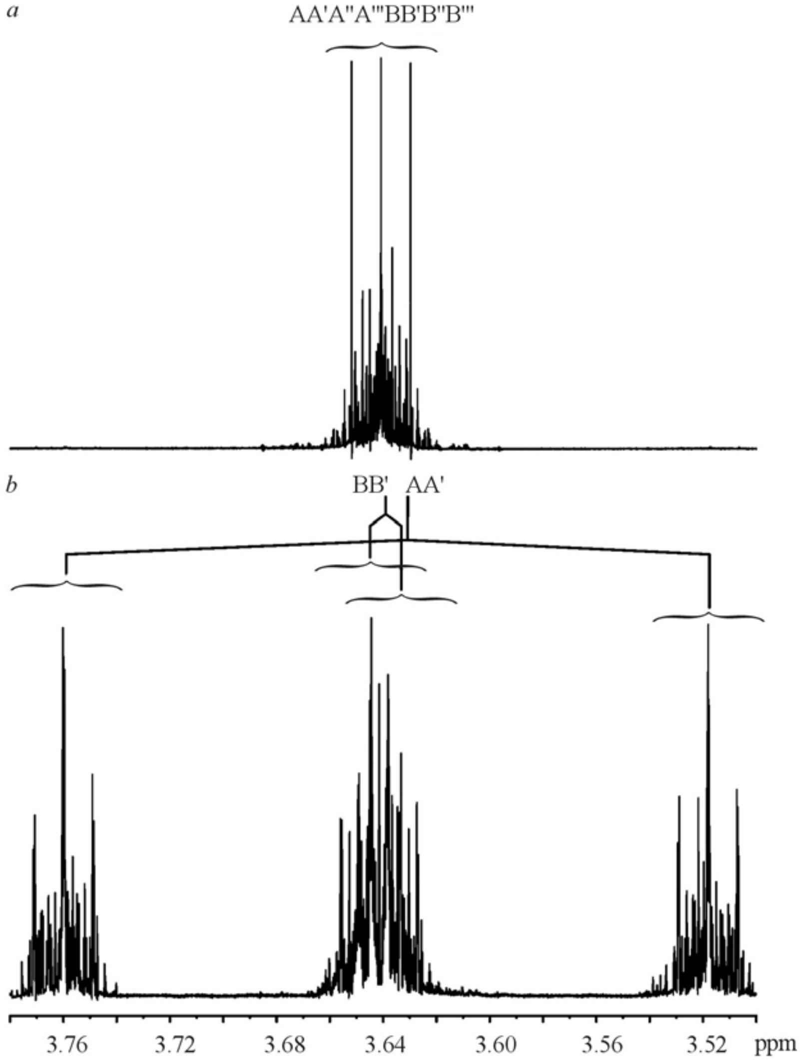


Fig. 1. The downfield part of the ${}^1H$ NMR spectrum of tetrahydrofuran (**1a**) (*a*) and tetrahydrofuran-2-${}^{13}C$ (**1b**) (*b*).

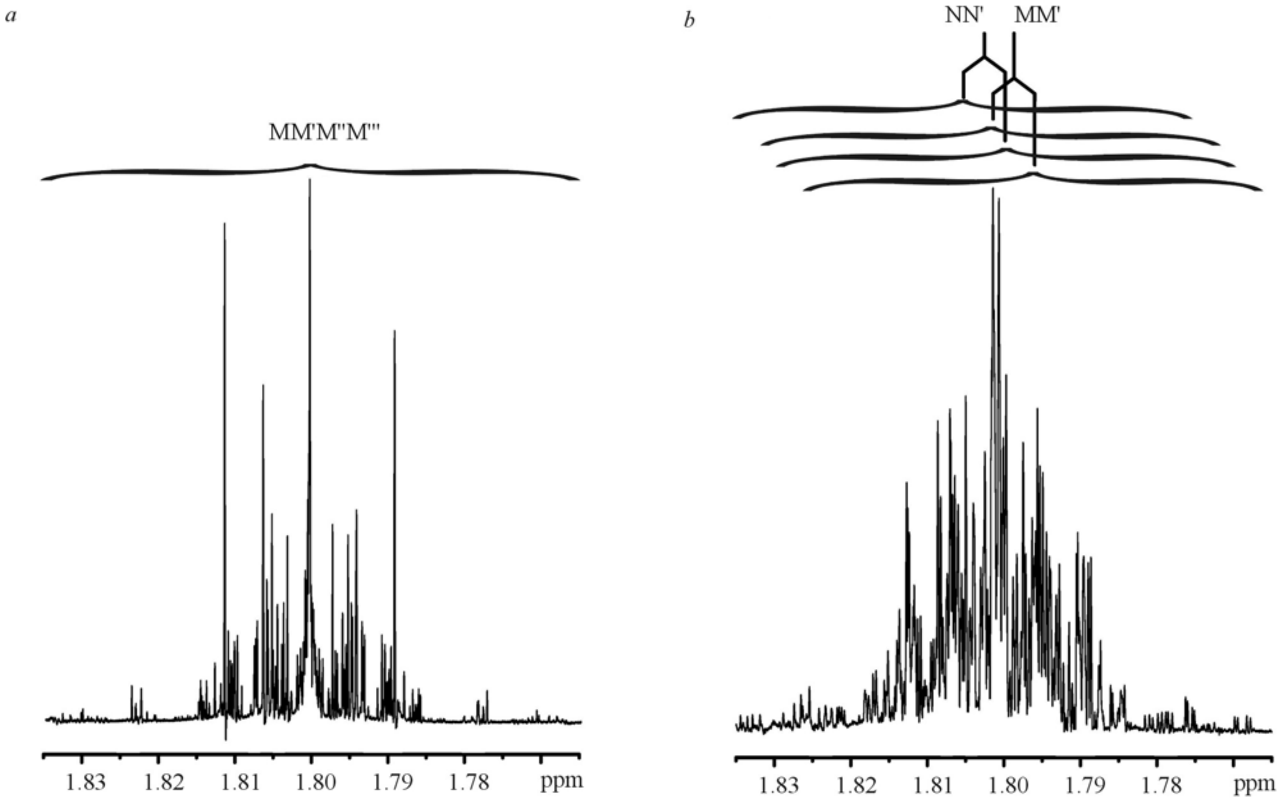


Fig. 2. The upfield part of the ^{1}H NMR spectrum of THF (**1a**) (*a*) and THF-2-^{13}C (**1b**) (*b*).

An important method for determination of the conformation and dynamic behavior of molecules is high-resolution NMR spectroscopy. The development of methods for nonempirical calculation of the spin-spin coupling constants [10, 12] made it possible to raise the problem of characterizing the THF conformational state according to the NMR spectroscopy data. In a recent paper, we proposed a more complete scheme for the assessment of the parameters of the potential energy surfaces based on experimental data for the spin-spin coupling constants, on calculated conformational dependencies of the spin-spin coupling constants, and on solution of the reverse spectroscopic structural problem [13]. Having at our disposal a limited set of experimental spin-spin coupling constants (four vicinal constants from [20]) we came to the conclusion that the main conformation for THF is the $^3T_4$ conformation.

In the present work, we set out to obtain more accurate experimental data on the spin-spin coupling constants in THF. For correct and reliable estimation of the conformation it is necessary to have numerical values of the spin-spin coupling constants between protons through four bonds ($^4J_{\mathrm{H,H}}$), accurate values of the spin-spin coupling constants through three bonds ($^3J_{\mathrm{H,H}}$), and long-range spin-spin coupling constants of protons with ^{13}C nuclei ($^nJ_{\mathrm{C–H}}$). It should be noted that it is not by accident that the $^4J_{\mathrm{H,H}}$ values had not been previously determined with sufficient accuracy. In principle, they could be determined from analysis of the ^{1}H NMR spectrum of THF, but this spectrum has such complicated multiplet structure (Figures 1*a* and 2*a*) that its interpretation is exceedingly difficult.

In our opinion the early attempt at analysis of this spectrum [10] led to insufficiently accurate results. In order to get round this problem Lambert et al. [20] realized the synthesis of a series of selectively deuterated tetrahydrofuran derivatives and studied their ^{1}H NMR spectra with spin decoupling from the deuterium. The deuterated compounds were specially selected by the authors [20] in such a way that long-range $^4J_{\mathrm{H,H}}$ constants were not observed in them. This method allows to greatly simplify the multiplet structure of the NMR spectra.

If all possible fast dynamic processes on the NMR time scale (pseudorotation and ring inversion) are taken into account tetrahydrofuran has C_{2V} symmetry and its ^{1}H NMR spectrum is described by an eight-spin system of the AA'A"A'"MM'M"M'" type.

The series of control model calculations that we conducted made it possible to conclude that the multiplet structure of the ^{1}H NMR spectra of THF is degenerately simple. This means that in spite of the abundance of transitions their position does not depend on all the possible values of the eight spin-spin coupling constants (four $^{3}J_{H,H}$ and four $^{4}J_{H,H}$). The high symmetry of the molecule creates substantial difficulties for interpretation. In order to overcome this problem we used the isotopic perturbation method that was used earlier for measurement of the spin-spin coupling constants in such highly symmetrical systems as benzene [21], cyclohexane [22-24], nortricyclene [25], benzaldehyde [26], and toluene [27]. The isotopic perturbation method is based on the fact that the symmetry of a molecule can decrease if an isotopic tag is inserted into the molecule. In the case of THF-2-^{13}C the symmetry of the molecule corresponds to the C_S point group, and the ^{1}H NMR spectra and proton-coupled ^{13}C NMR spectrum are described by an AA'BB'MM'NN'X spin system (Fig. 3). In this case, the proton sub-spectrum is no longer described by two chemical shifts, as in the case of tetrahydrofuran itself, but by four since the protons of the methylene groups at the C-2 and C-5 atoms and at the C-3 and C-4 atoms become non-equivalent in pairs. It could be expected that isotopic substitution of ^{12}C by ^{13}C would cause the same nonequivalence for the spin-spin coupling constants, for example, $^{3}J_{A–M}$ and $^{3}J_{B–N}$ or $^{4}J_{A–N}$ and $^{4}J_{B–M}$. However, the results of our early calculations showed that the effects of replacement of the heavy isotopes for the spin-spin coupling constants are extremely small (e.g., see [21, 28]). Effects of this type have been recorded reliably by experiment in only one case – during analysis of the set of acetylene isotopomers [29]. Thus, analysis of the NMR spectra of isotope-labeled molecules has made it possible in a number of cases to evaluate the spin-spin coupling constants for highly symmetrical molecular systems with high accuracy.

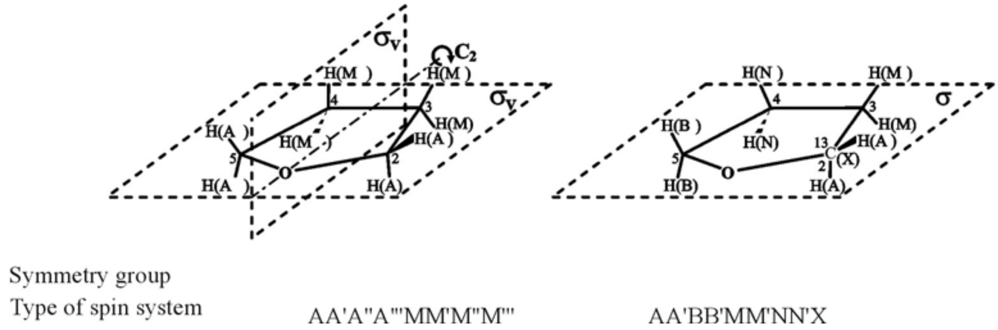
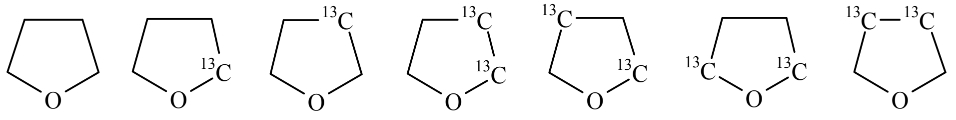


Fig. 3. Types of spin systems and symmetry of THF (**1a**) and THF-2-^{13}C (**1b**) averaged among the fast dynamic processes.

In the present work, we have used selective enrichment with the heavy isotope of carbon ^{13}C. In THF one isotopomer **1a** not containing a ^{13}C label, two isotopomers **1b**,**c** containing one labeled atom, and four isotopomers **1d-g** containing two labeled carbon atoms are possible (Fig. 4).

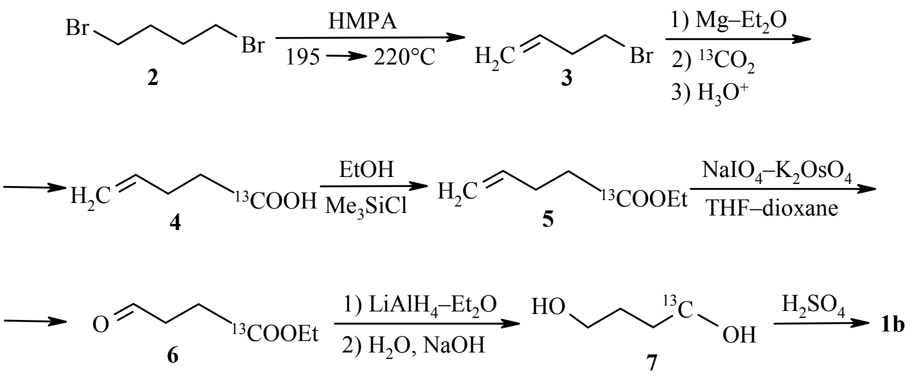


1a **1b** **1c** **1d** **1e** **1f** **1g**

Fig. 4. The $^{12}C/^{13}C$-isotopomeric forms of THF **1a-g**.

The main form of THF with the natural content of the carbon isotope is isotopomer **1a** (mass fraction 95.469%) alongside which there are relatively insignificant amounts of isotopomers **1b**,**c** (2.216% of each) and negligibly small amounts of the isotopomers **1d-g** with two labeled carbon atoms (total 0.099%). In the NMR spectra of normal THF the isotopomeric forms **1b**,**c** can be observed as relatively weak satellite signals. Their recording involves considerable difficulties on account of overlap with the stronger signals of the main isotopomer **1a** (Fig. 4).

In the present work, we have synthesized THF-2-^{13}C (**1b**) and interpreted the multiplet structure of its ^{1}H and ^{13}C NMR spectra. The insertion of the isotopic tag was the key stage of our synthesis. For this, thoroughly dried $^{13}CO_2$ was brought into reaction with an equimolar amount of "solid" Grignard reagent, which was obtained after vacuum distillation of the solvent from a solution of the Grignard reagent (obtained from 4-bromo-1-butene and magnesium) in ether. The starting 4-bromo-1-butene was obtained with a high yield by dehydrobromination by the modified method [30] of thermolysis of 1,4-dibromobutene in HMPA solution.



The double bond was used as latent protection of the second functional group required for cyclization. In fact, the double bond at the γ-position does not interfere with Grignard synthesis from the corresponding alkyl bromide. We then planned to oxidize this double bond (in penten-4-oic-1-^{13}C acid) to an aldehyde group by the action of periodate in the presence of catalytic amounts of osmate [31]. However, control tests revealed complications during the isolation of the 4-oxobutanoic-1-^{13}C acid formed here at the level of semimicro quantities (with loads in the order of 5-10 mmol). This problem was solved by conversion of the carboxyl group into an ester group. Then, both the aldehyde and the ester group were reduced to alcohol groups with lithium aluminum hydride. At the final stage the butane-1,4-diol-1-^{13}C was cyclized with conc. H_2SO_4. Control of the isotopic purity of the ^{13}C-enriched compounds showed that at all stages of the synthesis it corresponded to the degree of enrichment of the employed source of the isotopic tag (from 98.5 to 99.2% according to the high-precision ^{13}C NMR spectra).

The ^{1}H NMR spectrum of the THF-2-^{13}C (**1b**) obtained in this way (Figs. 1*b* and 2*b*) differ significantly from the spectrum of the THF with natural content of the ^{13}C isotope (Figs. 1*a* and 2*a*). The most significant differences are observed in the downfield part of the spectrum, i.e., in the region where the signals for the H-2 protons of the isotopomer **1b** are observed.

An important feature of this multiplet is splitting on the large constant $^{1}J_{C,H}$ (see the splitting scheme in Fig. 1). This signal can also be observed with high amplification in the ^{1}H NMR spectrum of THF with the natural ^{13}C content (the "outer satellite"). However, full interpretation of the complex multiplet structure requires all the remaining signals of the isotopomer **1b**: the "inner satellites" in the regions of the ^{1}H NMR spectrum from 1.76 to 1.84 ppm (the H-3,4 protons, see Fig. 2*b*) and from 3.61 to 3.67 ppm (the H-5 protons, Fig. 1*b*), and also the corresponding multiplet of the proton-coupled ^{13}C NMR spectrum. Interpretation of all the components of the multiplet structure of the NMR spectrum of the isotopomer **1b** (824 lines in the ^{1}H NMR spectrum and 273 lines in the proton-coupled ^{13}C NMR spectrum) was achieved by means of the LACX iteration software [31, 32] within a spin system of the AA'BB'MM'NN'X type, taking into account the chemical equivalence of the protons of the methylene groups and the weak coupling of the three types of nuclei (the α- and β-methylene protons and the ^{13}C nucleus). The scheme employed for factorization of the Hamiltonian proved adequate for effective convergence of the iteration process. The vicinal $^3J_{H,H}$ constants from [20] and the long-range $^4J_{H,H}$ constants for related derivatives of cyclopentane (see [33-35]) were used as the initial approximation. The final values of the spin-spin coupling constants $^nJ_{H,H}$ and $^nJ_{C,H}$ and the isotopic chemical shifts of the protons due to replacement of the ^{12}C nuclei by ^{13}C are presented in the Table 1.

Important information about the structure of the minor isotopomeric forms is carried by the ^{13}C NMR spectra, which have a significantly simpler multiplet structure than the ^{1}H NMR spectra. Figure 5 shows the upfield part of the ^{13}C NMR spectrum of 2-^{13}C-enriched THF, corresponding to the β-carbon atoms. The reference point here is the C-3 signal of the minor form **1c**, which is present in an insignificant amount in the investigated mixture of isotopomers. The splittings of the β-carbon atoms of the C-3 form **1d** and the C-4 form **1e** at the labeled atom C-2 are clearly seen in the spectrum presented in Fig. 5. In this spectrum there are also relatively large isotopic chemical shifts of C-3 of form **1d**, due to replacement of ^{12}C by ^{13}C at the C-2 carbon atom ($^1\Delta\delta_{C\text{-}3}$), and of C-4 of form **1e** due to replacement of ^{12}C by ^{13}C at the C-2 carbon atom ($^2\Delta\delta_{C\text{-}4}$). Analogous signals are observed in the downfield part of the ^{13}C NMR spectrum in the region of the α-carbon atoms. These parameters of the NMR spectra are also presented in the Table 1.

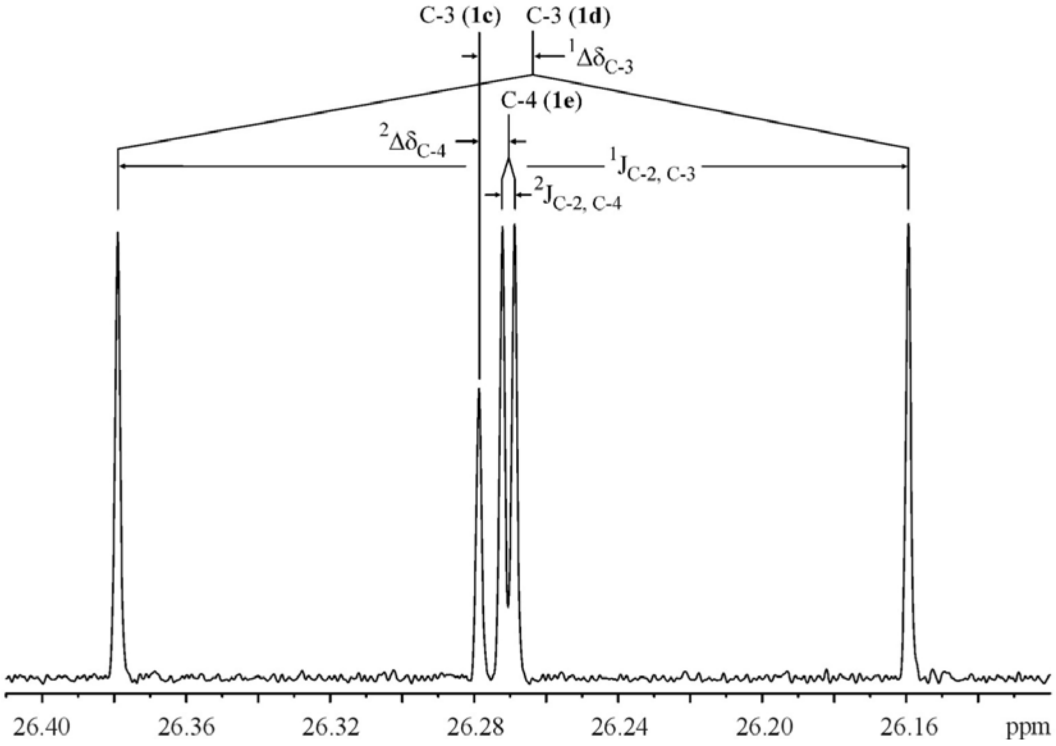


Fig. 5. The ^{13}C NMR spectrum of 2-^{13}C-enriched THF (**1b**). The labeling scheme of the signals for the C-3 and C-4 carbons of isotopomers **1c-e** is presented.

It can be seen that the $^nJ_{C,C}$ spin-spin coupling constants that we recorded first are close in value to the corresponding $^nJ_{C,C}$ constants in cyclopentane (see [23]). In all cases the isotopic chemical shifts that we obtained in THF are negative, which agrees with the current theoretical model for NMR parameters of this type (for more detail, see [23, 24, 29]).

Analysis of the NMR spectra of the synthesized THF-2-^{13}C made it possible to refine the existing experimental data on the vicinal $^{3}J_{H,H}$ constants and to determine for the first time a whole series of previously unknown parameters of the NMR spectra required for the construction of a quantitative model of the conformational dynamics of THF.

TABLE 1. The Parameters of the ^{1}H and ^{13}C NMR Spectra in the Series of Isotopomers of THF **1a-f***

Isotopomer	Parameter	Experimental value *[2]
1a	$\delta_{H\text{-}2}$	3.641
	$\delta_{H\text{-}3}$	1.800
1b*[3]	$^{1}\Delta\delta_{H\text{-}2}$	–1.541 (0.002)
	$^{2}\Delta\delta_{H\text{-}3}$	–0.399 (0.002)
	$^{3}\Delta\delta_{H\text{-}4}$	–0.171 (0.002)
	$^{3}\Delta\delta_{H\text{-}5}$	–0.084 (0.002)
	$\delta_{C\text{-}2}$	68.282
	$^{2}J_{2,2'}$	-8.130 (0.120)
	$^{2}J_{3,3'}$	-12.010 (0.120)
	$^{3}J^{cis}_{2,3}$	7.607 (0.002)
	$^{3}J^{trans}_{2,3}$	6.163 (0.003)
	$^{3}J^{cis}_{3,4}$	8.773 (0.002)
	$^{3}J^{trans}_{3,4}$	6.149 (0.002)
	$^{4}J^{cis}_{2,4}$	0.022 (0.003)
	$^{4}J^{trans}_{2,4}$	-0.494 (0.003)
	$^{4}J^{cis}_{2,5}$	-0.161 (0.002)
	$^{4}J^{trans}_{2,5}$	-0.161 (0.002)
	$^{1}J_{C\text{-}2,H\text{-}2}$	145.094 (0.001)
	$^{2}J_{C\text{-}2,H\text{-}3}$	-2.471 (0.001)
	$^{3}J_{C\text{-}2,H\text{-}4}$	3.288 (0.001)
	$^{3}J_{C\text{-}2,H\text{-}5}$	3.864 (0.001)
1c	$\delta_{C\text{-}3}$	26.266
1d	$^{1}\Delta\delta_{C\text{-}2}$	-9.470 (0.030)
	$^{1}\Delta\delta_{C\text{-}3}$	-5.650 (0.020)
	$^{1}J_{C\text{-}2,C\text{-}3}$	33.150 (0.010)
1e	$^{2}\Delta\delta_{C\text{-}2}$	-3.330 (0.030)
	$^{2}\Delta\delta_{C\text{-}4}$	-7.530 (0.03)
	$^{2}J_{C\text{-}2,C\text{-}4}$	0.510 (0.010)
1f	$^{2}\Delta\delta_{C\text{-}5}$	-4.640 (0.020)

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*The values of the chemical shifts δ_H and δ_C are given in parts per million, the isotopic chemical shifts $^{n}\Delta\delta_H$ and $^{n}\Delta\delta_C$ are given in parts per billion, the spin-spin coupling constants are given in Hz (0.16 M solution in CD_3CN, 303 K, Bruker AV-600).

*[2] The standard deviations for the isotopic chemical shifts and spin-spin coupling constants are given in parentheses.

*[3] The mean-square deviation of 1097 frequencies of the transitions of the calculated spectra and lines of the experimental spectra amounts to 0.016 Hz.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-360 (360 MHz for ^{1}H nuclea and 90 MHz for ^{13}C nuclei), Bruker AV-600 (600 MHz for ^{1}H nuclei and 150 MHz for ^{13}C nuclei), and JNM-ECA-600 (600 MHz for ^{1}H nuclei) spectrometers. The ^{13}C NMR spectra for determining the isotopic purity of the ^{13}C-enriched products and the ^{1}H NMR spectra of the target product were recorded in enhanced accuracy mode at the narrow frequency bands with data sampling times from 24 to 30 sec and digital resolution in the transformed spectrum from 0.002 to 0.003 Hz. The use of such rigorous parameters makes it possible to secure the sufficient accuracy required for subsequent interpretation of the complex multiplet structure of these spectra and for the adoption of sound decisions about the values and signs of the long-range spin-spin coupling constants and isotopic effects caused by the replacement of ^{12}C by ^{13}C.

Reagents and deuterated solvents from Aldrich and Merck were used. The solvents ethanol, ether, THF, hexane, and chloroform were submitted to further purification before use in the reaction and/or before chromatography.

The Ba^{13}CO$_3$ with 98% purity in ^{13}C produced by Matheson was used as source of the isotopic tag. Precise measurements of the intensities of the signals of the ^{13}C-enriched carboxylic acid **3** showed that the actual content of the ^{13}C isotope in the Ba^{13}CO$_3$ used in this work was 99.2%. The carbon dioxide ^{13}CO$_2$ was obtained by the action of phosphoric acid on Ba^{13}CO$_3$ [36] followed by thorough separation of the ^{13}CO$_2$ from traces of water (for greater detail, see below).

The sample of THF-2-^{13}C (**1b**) for recording the NMR spectra was prepared by dissolving 7 mg of the compound in 0.68 ml of acetonitrile-d$_3$ (containing 0.1% of TMS as internal standard), after which the solution was degassed by threefold repetition of the freezing–evacuating–unfreezing cycle in a 5-mm ampoule, and the ampoule was then sealed off. The spectra were recorded at 303 K. The isotopic chemical shifts ($\Delta\delta$) are given in parts per billion (ppb). The data of ^{13}C-INADEQUATE and 2-D COSY, HSQC, and HMBC experiments were used for the assignment of the signals of compounds **3**, **4**, and **1b**,**d**,**e** [37].

4-Bromo-1-butene (3). HMPTA (15 ml, 83 mmol) was added with vigorous stirring to 1,4-dibromobutane (9.77 ml, 82 mmol) heated to 195°C in an argon atmosphere over 20 min. The temperature of the reaction mixture was then brought to 220°C, and the mixture was kept at this temperature for a further 20 min. The volatile reaction products were collected at a pressure of 2 mm Hg in a trap with phosphorus(V) oxide, cooled to -80 to -90°C. By repeated refreezing under high vacuum it was possible to isolate 4.95 g (yield 45%) of 4-bromo-1-butene. ^{1}H NMR spectrum (600 MHz, CDCl$_3$), δ, ppm (J, Hz): 2.60 (2H, qt, J_q = 6.9, J_t = 1.3, 3-CH$_2$); 3.39 (2H, t, J = 7.0, 4-CH$_2$); 5.10 (1H, dq, J_d = 10.2, J_q = 1.3, *trans*-H-1); 5.12 (1H, dq, J_d = 17.1, J_q = 1.5, *cis*-H-1); 5.78 (1H, ddt, J_d = 10.2, J_d = 17.1, J_t = 6.6, H-2). ^{13}C NMR spectrum (150.9 MHz, CDCl$_3$), δ, ppm: 32.0 (C-4); 37.0 (C-3); 117.5 (C-1); 135.2 (C-2).

Penten-4-oic-1-^{13}C Acid (4). 1,2-dibromoethane (three drops) was added to magnesium (0.64 g, 26.5 mmol) in ether (5 ml) in an atmosphere of argon. After 10 min, 4-bromo-1-butene (**3**) (2.7 ml, 26.0 mmol) was added over 30 min, and the reaction mixture was then stirred for a further 2 h. The reaction mixture was frozen with liquid nitrogen and degassed by threefold repetition of the evacuating (on vacuum apparatus to a residual pressure of 10^{-4} mm Hg)–unfreezing–freezing cycle.

Finely ground Ba^{13}CO$_3$ (4.76 g, 24.0 mmol) was evacuated in a 500-ml flask to a pressure of 10^{-4} mm Hg for 45 min, after which previously degassed 85% phosphoric acid (35 ml) was added to it drop by drop with stirring. The released ^{13}CO$_2$ was refrozen in a trap cooled with liquid nitrogen. The compound was degassed again and dried from traces of moisture, for which purpose the ^{13}CO$_2$ was refrozen three times in a new trap cooled with liquid nitrogen, while the gas was passed through a spiral trap cooled to ~ -80°C.

The reaction flask with the Grignard reagent was cooled with liquid nitrogen and all the obtained ^{13}CO$_2$ was refrozen in it. Without removing the vacuum the reaction flask was heated on a bath with a mixture of alcohol and liquid nitrogen at -80°C and was kept under these conditions for 1 h. After this, the temperature of the bath was gradually raised to 0°C over 30 min. The reaction flask was filled with nitrogen, ether (20 ml) was added, after that water (5 ml) and 5% hydrochloric acid (5 ml) were added drop by drop. The ether layer was separated, and the target compound was extracted with a 5% aqueous NaOH solution (3×5 ml). The combined aqueous layer was acidified to pH 0 with hydrochloric acid and extracted with ether (4×7 ml). After distillation of the solvent, 1.7 g (70%) of penten-4-oic-1-^{13}C acid (**4**) was obtained.

^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.379 (2H, tq, $J_t = 1.37$, $J_q \approx 6.2$, 3-CH_2); 2.455 (2H, ddt, $J_d = 6.84$, $J_d = 1.48$, $J_t = 7.25$, 2-CH_2); 5.018 (1H, dq, $J_d = 10.24$, $J_q = 1.38$, *trans*-H-5)*;* 5.075 (1H, dq, $J_d = 17.12$, $J_q = 1.63$, *cis*-H-5); 5.835 (1H, ddt, $J_d = 10.24$, $J_d = 17.12$, $J_t = 6.36$, H-4); 11.32 (1H, br. s, COOH). ^{13}C NMR spectrum (150.9 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 28.456 (d, $J_d = 1.63$, $\Delta\delta < 0.2$, C-3); 33.339 (d, $J_d = 55.47$, $\Delta\delta = 13.3$, C-2); 115.696 (s, C-5); 136.254 (d, $J_d = 3.58$, $\Delta\delta < 0.2$, C-4); 179.641 (s, intensity ~100, C-1 (^{13}C-satellite: d, $J_d = 55.47$, $\Delta\delta = -1.9$)]. According to data from the high precision ^{13}C NMR spectrum the degree of enrichment of the carboxyl carbon was 99.2%.

Ethyl Penten-4-oate-1-^{13}C (5). Trimethylchlorosilane (2.7 ml, 23.3 mmol) was slowly added (over 15 min) to a mixture of penten-4-oic-1-^{13}C acid (**4**) (0.78 g, 7.7 mmol) and alcohol (6 ml). The reaction mixture was refluxed for 3 h and was purified by flash chromatography on silica gel with $CHCl_3$ as eluent. After slow distillation of the solvent 0.82 g (82%) of the ester **5** was obtained. ^1H NMR spectrum (360 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.21 (3H, t, $J = 7.2$, $OCH_2C\underline{H}_3$); 2.25-2.34 (4H, m, 2,3-CH_2); 4.04 (2H, dq, $J_d = 3.1$, $J_q = 7.2$, $OC\underline{H}_2CH_3$); 4.93 (1H, dd, $J_d = 1.3$, $J_d = 10.2$, *trans*-H-5); 4.97 (1H, dd, $J_d = 1.5$, $J_d = 17.2$, *cis*-H-5); 5.76 (1H, ddt, $J_d = 10.2$, $J_d = 17.2$, $J_t = 6.4$, H-4).

Ethyl 4-Oxobutanoate-1-^{13}C (6). A solution of $NaIO_4$ (2.46 g, 11.5 mmol) in water (18 ml) was added to an alcohol solution of ethyl penten-4-oate-1-^{13}C (**5**) (0.82 g, 6.3 mmol) and then with stirring $K_2OsO_4 \cdot 2H_2O$ (30 mg) and THF (2 ml) was added. The mixture was stirred at room temperature for a further 1 h and extracted four times with ether. The extract was washed six times with small portions of a saturated solution of Na_2SO_3 and dried with $MgSO_4$. After evaporation of the solvent 0.54 g (65%) of the ester **6** was obtained. ^1H NMR spectrum (360 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.33 (3H, t, $J_t = 7.1$, $OCH_2C\underline{H}_3$); 2.53 (2H, q, $J_q = 6.84$, 2-CH_2); 2.71 (2H, q, $J_q = 6.1$, 3-CH_2); 4.08 (2H, dq, $J_d = 3.1$, $J_q = 7.1$, $OC\underline{H}_2CH_3$); 9.70 (1H, s, CHO).

Butane-1,4-diol-1-^{13}C (7). $LiAlH_4$ (1.25 g, 33.0 mmol) was slowly added with stirring to a solution of compound **6** (0.54 g, 4.1 mmol) in ether (17 ml) and THF (3 ml). The reaction mixture was refluxed for 6 h and treated successively with water (1.25 ml, 0.07 mol) and with a 10% solution of NaOH (4.23 ml). The obtained clotted mass was extracted with boiling THF in Soxhlet apparatus for 8 h. The compound was chromatographed on a column of silica gel in chloroform. After slow distillation of the solvent 0.20 g (62%) of butane-1,4-diol-1-^{13}C (**7**) was obtained. ^1H NMR spectrum (360 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.64-1.74 (4H, m, 2,3-CH_2); 3.68 (2H, dt, $J_d = 141.2$, $J_t = 5.8$, 1-CH_2); 3.68 (2H, t, $J_t = 5.8$, 4-CH_2).

Tetrahydrofuran-2-^{13}C (1b). With cooling to 0°C and vigorous stirring, conc. H_2SO_4 (0.03 ml) was added to butane-1,4-diol-1-^{13}C (**7**) (0.20 g, 2.7 mmol). The flask containing the reaction mixture was then quikly connected to freezing apparatus, cooled to liquid nitrogen temperature, and degassed under high vacuum (10^{-4} mm Hg) with threefold repetition of the evacuating–unfreezing–freezing cycle. The reaction mixture was heated to 90-100°C, and the volatile compounds were refrozen in a receiver cooled with liquid nitrogen. Compound **1b** was purified by refreezing twice over KOH and with calcium hydride. The tetrahydrofuran-2-^{13}C (**1b**) was stored in the gas phase in a 250-ml glass gasholder at room temperature. The reaction product creates a pressure of 38 mm Hg (yield 20%). ^1H NMR spectrum (600 MHz, CD_3CN), δ, ppm (*J*, Hz): 1.762-1.834 (4H, m, 2,3-CH_2); 3.502-3.776 (2H, dm, $J_d = 145.089$, 1-CH_2); 3.622-3.658 (2H, m, 4-CH_2). ^{13}C NMR spectrum (150.9 MHz, CD_3CN), δ, ppm (*J*, Hz): 26.267 (d, $J_d = 33.15$, $\Delta\delta = -9.47$, C-2); 26.269 (d, $J_d = 0.51$, $\Delta\delta = -7.53$, C-3); 115.696 (s, C-5); 68.309 (s, intensity ~100, C-1 (^{13}C-satellite from C-2: d, $J_d = 33.14$, $\Delta\delta = -5.6$. ^{13}C-satellite from C-3: d, $J_d = 0.51$, $\Delta\delta = -3.3$. ^{13}C-satellite from C-4: s, $\Delta\delta = -4.6$)). According to the high-precision ^{13}C NMR spectrum the degree of enrichment in ^{13}C amounted to 98.5%.

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