PMR Analysis and Conformation of 2,5-Bis-(3,4,5-trimethoxyphenyl)-3,4-dimethyltetrahydrofuran Isomers (1)

Kyösti V. Sarkanen and Adrian F. A. Wallis (2)

Department of Chemical Engineering, University of Washington, Seattle, Washington 98195

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In connection with phenol oxidation studies (3), we have obtained and assigned configuration to four isomers of 2,5-bis-(3,4,5-trimethoxyphenyl)-3,4-dimethyltetrahydrofuran (**1-4**) which are related to naturally-occurring lignans. Continuing interest in the conformation of the mobile tetrahydrofuran ring systems, particularly those of furanose sugars (4), prompts us to report the pmr spectra of the isomers (**1-4**) and to relate these data to their most probable conformations in solution.

Hall *et al.* (5) have provided an excellent discussion of the applicability of the nmr method to the assignment of conformation of furanoses in solution. They consider the ten twist (T) and ten envelope (V) conformers to be related in a "cycle of pseudorotation" where each ring atom becomes out of the plane of the others in turn, and the most-populated conformations may be represented by a segment of the cycle. With the aid of Dreiding models, the approximate torsion angles between the H_2, H_3, and H_4, H_5 proton pairs in each of the tetrahydrofuran conformers in the cycle have been determined and are presented in Table I. Substituents projecting behind the plane of the paper are designated "α" and those out from the plane "β".

In the pmr spectra of the isomers (**1-4**) (Table II), the H_2, H_3 and H_4, H_5 proton pairs are well separated in chemical shift and are thus amenable to first-order analyses. Use of the Karplus relationship (6) between pmr coupling constants and torsion angles gives an indication of the favorable conformations of isomers (**1-4**).

The pmr doublet at 4.67 ppm of the all-*trans* isomer (**1**) is assigned to the benzylic protons at C_2 and C_5 split by the vicinal methine protons with coupling constants $J_{2,3} = J_{4,5} = 8.6$ Hz, which is consistent with torsion angles for $H_{2\beta}$-$H_{3\alpha}$ and $H_{4\beta}$-$H_{5\alpha}$ approximating 150°. This is provided by conformations $^2T_3$-$^4T_5$, each of which have all-pseudoequatorial substituents. For other examples of all-*trans* tetrahydrofurans analogous to isomer (**1**), $^3T_4$ conformers having pseudoaxial substituents have been proposed (7). In addition, Buys *et al.* (8) have found the halogen atoms in *trans*-3,4-dihalogenotetrahydrofurans to be pseudoaxial and to occupy the most puckered part of the ring. A contributing factor to the axial nature

Ar = 3,4,5-trimethoxyphenyl

of the substituents in these compounds is the dipole-dipole interactions due to adjacent polar groups, which would be absent in isomer (**1**). Furthermore, the possibility of compound (**1**) having pseudoaxial substituents is unlikely due to the severe 1,3-diaxial aryl-methyl interactions which would be imposed in these conformations, *e.g.* $^3T_4$.

The second symmetrical isomer (**2**) displays a benzylic pmr doublet at 4.55 ppm, and the coupling constants $J_{2,3} = J_{4,5} = 5.9$ Hz are in accordance with torsion angles averaging 120°. This is satisfied by forms $^3T_2$-$^5T_4$ and $^2T_3$-$^4T_5$, and isomer (**2**) probably exists largely in these two groups of conformers. This is in line with an earlier proposal (9) that the preferred tetrahydrofuran conformations are those where the oxygen is one of the in-plane atoms, as this would tend to reduce the non-bonded interactions between vicinal substituents.

The unsymmetrical isomer (**3**) exhibits two separate benzylic and methyl pmr signals. Because the C_4 methyl and C_5 aryl groups are *cis*-oriented, the aryl group is not free to rotate about the C_4-Ar bond, which constrains the C_4 methyl to lie above the plane of the aromatic ring and H_5 to be in the plane of the ring. The C_4 methyl and H_5, therefore, are shielded and deshielded respectively and are assigned to the doublets at 0.70 and 5.11 ppm. Decoupling experiments have confirmed these assignments and have shown the center of the H_3 and H_4 multiplets to be at 1.83 and 2.24 ppm. The pmr spectrum of isomer (**3**) is

TABLE I

Cycle of Pseudorotation for Tetrahydrofurans (1)-(4)

Conformer	2β-3α	H-C-C-H Torsion Angles for Isomers (1) 4β-5α	(2) 4α-5β	(3) 4β-5β	(4) 4α-5α
^0V	90°	150°	90°	30°	30°
$^0T_2$	90°	150°	90°	30°	30°
V_2	90°	120°	120°	0°	0°
$^3T_2$	90°	90°	150°	30°	30°
^3V	90°	90°	150°	30°	30°
$^3T_4$	90°	90°	150°	30°	30°
V_4	90°	90°	150°	30°	30°
$^5T_4$	90°	90°	150°	30°	30°
^5V	120°	90°	150°	30°	30°
$^5T_0$	150°	90°	150°	30°	30°
V_0	150°	90°	150°	30°	30°
$^2T_0$	150°	90°	150°	30°	30°
^2V	150°	120°	120°	0°	0°
$^2T_3$	150°	150°	90°	30°	30°
V_3	150°	150°	90°	30°	30°
$^4T_3$	150°	150°	90°	30°	30°
^4V	150°	150°	90°	30°	30°
$^4T_5$	150°	150°	90°	30°	30°
V_5	120°	150°	90°	30°	30°
$^0T_5$	90°	150°	90°	30°	30°

analogous to that of the related lignan veraguensin (10).

The pmr coupling constants 8.3 and 8.0 Hz for the H_2 and H_5 doublets of isomer (**3**) are consistent with the torsion angles for $H_{2\beta}$-$H_{3\alpha}$ and $H_{4\beta}$-$H_{5\beta}$ of 150° and approaching 0°, respectively. Conformations $^5T_0$-$^4T_5$ satisfy these requirements, although forms ^4V and $^4T_5$ are not favorable due to steric interaction between the aryl groups. Thus, $^5T_0$-$^4T_3$, centered about conformer ^2V where the $H_{4\beta}$-$H_{5\beta}$ torsion angle is 0°, probably represent the most-populated conformations. A similar conformational equilibrium was deduced for furanoses of analogous stereochemistry, using the "Dihedral Angle Estimation by the Ratio Method" (11).

The pmr spectrum of isomer (**4**) also shows two separate signals for both the benzylic and methyl protons. Using the same argument as that for the other unsymmetrical isomer (**3**), the low-field benzylic proton and the high-field methyl protons are assigned to H_5 and the C_4 methyl group respectively, which are deshielded and shielded by the C_5 aromatic ring. The H_3 and H_4 pmr signals have the same chemical shift in deuteriochloroform (2.47 ppm), but in deuterobenzene solution the H_3 and H_4 multiplets are centered at 2.33 and 2.19 ppm, respectively (12). By superimposing a signal corresponding to that of H_3, the low-field methyl and high-field benzylic proton doublets collapse to singlets, and likewise irradiation of the H_4 signal collapses the other doublets. This confirms the above assignments for the methyl and benzylic protons.

Conformers $^5T_0$-$^4T_5$ are in agreement with the observed pmr coupling constants $J_{2,3}$ = 8.5 Hz for tetrahydrofuran (4). However, inspection of models shows that in the forms $^5T_0$ and V_0, the *cis* C_3, C_4, and C_5 substituents experience steric interactions and are thus not favorable. In contrast to the pmr coupling constant for the *cis* protons in isomer (**3**) where $J_{4,5}$ = 8.0 Hz, that of isomer (**4**) is small (4.0 Hz), and corresponds to a torsion angle of about 60°. The conformers $^2T_0$-$^4T_5$ in the pseudorotation cycle have torsion angles $H_{4\alpha}$-$H_{5\alpha}$ of

TABLE II

PMR Data for Tetrahydrofurans (**1-4**) (a,b)

	Me_3	Me_4	H_3	H_4	H_2	H_5
(**1**)	1.10 (d) J = 6.5 Hz			1.77 (m)	4.67 (d) J = 8.6 Hz	
(**2**)	1.08 (d) J = 6.3 Hz			2.36 (m)	4.55 (d) J = 5.9 Hz	
(**3**)	1.12 (d) J = 5.9 Hz	0.70 (d) J = 6.5 Hz	1.83 (m)	2.24 (m)	4.43 (d) J = 8.3 Hz	5.11 (d) J = 8.0 Hz
(**4**)	1.05 (d) J = 6.1 Hz	0.64 (d) J = 6.7 Hz		2.47 (m)	4.67 (d) J = 8.5 Hz	5.48 (d) J = 4.0 Hz
(**4**) (c)	0.93 (d)	0.67 (d)	2.33 (m)	2.19 (m)	4.67 (d)	5.38 (d)

(a) Measured at 60 MHz in ppm for 10% solutions in deuteriochloroform containing TMS as an internal standard. (b) s, d, m, = singlet, doublet, and multiplet, respectively. (c) Measured at 100 MHz for a 5% solution in deuteriobenzene.

30° which would give a pmr coupling constant $J_{4,5} \sim 6$ Hz. It may be that the strain inherent in compound (**4**) due to the *cis* C_3, C_4, and C_5 substituents causes distortion of the molecule so that the $H_{4\alpha}$-$H_{5\alpha}$ dihedral angle has a resultant value of approximately 60°. More study is clearly required to obtain a better understanding of the conformational equilibria in tetrahydrofuran systems.

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(2) Present address: Division of Applied Chemistry, CSIRO, Box 4331, Melbourne, Victoria 3001, Australia.

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