Hydrogen bonding and conformation in *cis*- and *trans*-2-alkoxy-3-hydroxytetrahydrofurans

W. W. ZAJAC, JR.,¹ F. SWEET,² AND R. K. BROWN Department of Chemistry, University of Alberta, Edmonton, Alberta Received July 14, 1967

Infrared spectra show both free and hydrogen bonded hydroxyl absorption in several *trans*-2-alkoxy-3-hydroxytetrahydrofurans. The extent of non-bonded hydroxyl is greater than that of bonded hydroxyl. Suggestions are made of possible conformations which might account for the infrared data.

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Introduction

Relatively little consideration has been given to the correlation of conformation with physical and chemical properties in cyclopentane and even less to the saturated five-membered ring heterocycles (1, 2). Having previously synthesized a series of 2-alkoxy-3-hydroxytetrahydrofurans (3), we undertook an investigation of the conformations of these compounds. Of the physical methods available, infrared spectroscopy (4) and proton nuclear magnetic resonance are particularly well-suited for the conformational studies of 2-alkoxy-3-hydroxytetrahydrofurans. The present paper reports the results of an examination of the hydrogen bonding in these molecules to obtain information concerning their conformation. Proton magnetic resonance studies will be presented in a later paper.

Experimental

Infrared spectra were obtained with a Perkin–Elmer model 421 grating spectrophotometer. Carbon tetrachloride, used as solvent, was dried and distilled from phosphorus pentoxide. Concentrations of the alcohols were 0.005 *M* or less and 1 cm or 2 cm cells were used, depending upon concentration of the solutions. Generally, successive dilutions were made to ensure that intramolecular and not intermolecular hydrogen bonding was being observed. The instrument was calibrated in the 3600 cm^{-1} region with carbon dioxide. Spectra for ethylene glycol were also obtained. The values for free and bonded hydroxyl agreed with literature values to ± 2 cm⁻¹ (5).

The 2-alkoxy-3-hydroxytetrahydrofurans were prepared according to published directions. The remaining compounds listed in Table I were prepared as described in the accompanying references.

3-Hydroxytetrahydrofuran (item 3, Table I) was pre-

pared by a more productive route than previously reported (8, 9). 2-Chloro-3-hydroxytetrahydrofuran was obtained in 62% yield according to published directions (18) by addition of hypochlorous acid (19) to 2,5-dihydrofuran (Aldrich Chemical Co.); b.p., 80° at 4 mm, 101° at 14 mm; n_D^{25} , 1.4789 (lit. b.p., 102-103° at 14 mm (18); 99-103° at 12 mm, n_D^{20} , 1.4883 (20)).

The above chlorohydrin (9.5 g, 0.078 mole) was dissolved in 50 ml of dry 1,2-dimethoxyethane (distilled from lithium aluminium hydride) contained in a 200 ml round bottom flask equipped with a magnetic stirrer, reflux condenser, and drying tube. To this was added slowly 3.97 g (0.093 mole) of sodium hydride (a 56% dispersion in mineral oil) while the flask was kept at $0-5^{\circ}$ with an ice bath. After hydrogen evolution had ceased the mixture was refluxed for 12 h, during which time sodium chloride precipitated. The mixture was cooled and diluted with ether to complete precipitation of the chloride and excess sodium hydride and then filtered by gravity. The filtrate was freed from solvents on a spinning band column and the residue was distilled giving 6.3 g (94%) of 3,4-epoxytetrahydrofuran; b.p., 45° at 14 mm; n_D^{25} , 1.4439; (lit. b.p., $143-145^{\circ}$; n_{D}^{20} , 1.4442 (20)). This was shown to contain only one component when subjected to gas-liquid chromatography using a Burrell model K-2 Kromo-Tog equipped with a 2.5 m column packed with 20% butanediol succinate on Gas-Chrom P (60-80 mesh); column temperature, 125°; helium carrier gas at a flow rate of 60 ml/min.

The above epoxide (2.0 g, 0.023 mole) in 25 ml of dry ether was added slowly to a mixture of 0.40 g (0.01 mole) of lithium aluminium hydride in 50 ml of ether at room temperature. After addition was complete (\sim 30 min), the solution was diluted with 25 ml of ether and the mixture stirred overnight at room temperature. The mixture was then cooled to about -10° with a dry ice – acetone bath and the complex decomposed by the successive addition of 1 ml of water, then 3 ml of 15% aqueous sodium hydroxide, followed by 1 ml of water. The mixture was filtered free of solids, and the solid washed with ether, then with chloroform. The combined filtrate and washings were dried over MgSO4 and freed from solvent by fractional distillation and the residue was distilled to give 1.9 g (96%) of 3-hydroxytetrahydrofuran boiling at 87° at 24 mm; n_D^{24} , 1.4482; (lit. b.p., 84–88° at 24 mm, n_D^{20} , 1.4507 (8); 82-88° at 24 mm, n_D^{25} , 1.4497 (21)). Gasliquid chromatography showed that this alcohol contained a trace of impurity which was not unreacted

¹On leave during 1965–1966 from Villanova University, Villanova, Pennsylvania. ²Doctoral candidate in the Department of Chemistry,

²Doctoral candidate in the Department of Chemistry, University of Alberta, Edmonton, Alberta.

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22

CANADIAN JOURNAL OF CHEMISTRY, VOL. 46, 1968 TABLE I

Infrared spectral data								
			$\nu_{\rm OH}$ in cm ⁻¹			<i>г</i> он О іп Å		
Item	Compound	_	Free (ϵ)	Bonded (e)	$\Delta \nu^*$	Ref. 5†	Ref. 12‡	Reference
1	HO 32 ¹ O OR	$\begin{array}{l} R = CH_{3} \\ R = C_{2}H_{5} \\ R = CH(CH_{3})_{2} \\ R = C(CH_{3})_{3} \end{array}$	3628 (30) 3628 (43) 3629 (43) 3628 (40)	3604 (24) 3604 (32) 3604 (35) 3604 (35) 3604 (35)	24 24 25 24	2.5 2.5 2.5 2.5 2.5	2.9 2.9 2.9 2.9 2.9	This work This work This work This work
2	HO OCH ₃		3620 (<5)	3565 (80)	55	2.0	2.2	This work
3	но ³ 2 ¹ 0 но		3628 3625 3624 (60)	3612 3599 (32)	13 25	2.9 2.5	3.9 2.9	8 9 This work
4	OCH3		3627					10
5	HO (2) OH		3620	_				5
6	но ССН3			3570	59	1.9	2.1	10
7	ноон		3633	3572	57	1.9	2.1	5

 $^*\Delta\nu = \nu_{\text{free}} - \nu_{\text{bonded}} : \nu_{\text{free}} \text{ taken as 3 629 cm}^{-1} (13).$ †Calculated from $\Delta\nu = (250/r) - 74.$ ‡Calculated from $\Delta\nu = [42.5/(r - 1.4)] - 3.5.$

epoxide. Pure 3-hydroxytetrahydrofuran was obtained by gas-liquid chromatography using an Aerograph Autoprep model A-700 with a 20 ft \times 1/4 in. (O.D.) column filled with 25% Carbowax 20 M on Gas-Chrom P (60-80 mesh) with helium as the carrier gas at a flow rate of 110 ml/min.

Results and Discussion

The infrared spectra were obtained in carbon tetrachloride at concentrations below 0.005 M, conditions which suppress intermolecular hydrogen bonding (4-7).

In Table I are recorded the infrared absorption frequencies in the hydroxyl stretching region. Also included are the literature data for 3-hydroxytetrahydrofuran (8, 9), cis- and transcyclopentane-1,2-diol (5) and cis- and trans-2methoxycyclopentanol (10). The data (items 1 and 2, Table I), clearly show that both the cisand trans-2-alkoxy-3-hydroxytetrahydrofurans have an hydroxyl group which is intramolecularly bonded to oxygen. Although the extinction coefficients are good only to $\pm 10\%$, the figures show a somewhat higher proportion of the conformer with a free hydroxyl group in the trans compound, while the cis isomer is essentially devoid of unbonded hydroxyl.

It has been established that no intramolecular hydrogen bonding occurs in either trans-2methoxycyclopentanol (10) or in trans-cyclopentane-1,2-diol (5), the minimum distance between hydroxyl hydrogen of one substituent and oxygen of the second substituent being too large for such bonding (>3.3 Å). Yet in our trans-2-alkoxy-3-hydroxytetrahydrofurans con-



siderable bonding does occur. Since the 3hydroxyl and 2-alkoxy groups are *trans*, no bonding is possible between them. Accordingly, hydrogen bonding must occur between the hydroxyl group at position-3 and the ring oxygen.

Barker et al. (8) have reported only free hydroxyl absorption for 3-hydroxytetrahydrofuran (item 3, Table I) whereas Eugster and Allner (9) detected both free and bonded hydroxyl absorption for this compound. We have obtained the infrared spectrum of 3-hydroxytetrahydrofuran and found both free and bonded hydroxyl absorption in roughly the same proportion as found by Eugster and Allner.³ There is a discrepancy between the value reported by the latter authors (9) for bonded hydroxyl (3612 cm^{-1}) and that found in our work (3599 cm^{-1}). This we have been unable to resolve. It is noteworthy that our value gives a $\Delta \nu$ of 25 cm⁻¹ which is consistent with the Δv values found for the trans-2-alkoxy-3-hydroxytetrahydrofurans.

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Comparison of the extinction coefficients for 3-hydroxytetrahydrofuran and the *trans*-2alkoxy-3-hydroxytetrahydrofurans shows that introduction of the alkoxy group at position-2 causes an *increase* in the proportion of the conformer having a bonded hydroxyl (free/ bonded = 60/32 in the former vs. 30-43/24 in the latter).

Kuhn (5) has shown that the hydrogen bond is stronger the larger the difference $(\Delta \nu)$ between the non-bonded and bonded absorption frequencies. Comparison of $\Delta \nu$ for each pair of *cis-trans* isomers listed in Table I shows that $\Delta \nu$ is greater for the *cis*- than for the *trans*-2alkoxy-3-hydroxytetrahydrofuran. This further corroborates the original assignment of configuration made for these compounds based on nuclear magnetic resonance data (3). Using either the equation derived by Kuhn (5) or the modified equation by Brutcher and Bauer (12) relating the Δ_{ν} to the hydrogen bonded distance between H and O, it is seen that these distances are greater in the *trans* compounds than they are in the *cis* isomers. These are in reasonable agreement with the distances found in accurate scale models. For these simple calculations we chose 3629 cm⁻¹ as the absorption frequency of the non-bonded secondary hydroxyl group as suggested by Cole and Jeffries (13).

To account for the free and bonded hydroxyl absorption found for the trans-2-alkoxy-3hydroxytetrahydrofurans, two possible situations arise. In the first of these we envisage two molecular conformations4-one in which the hydroxyl group is in a position which permits hydrogen bonding (a in Scheme I) and one in which such bonding is not possible (b in Scheme I). Each of these two conformations can be obtained by rotation about the C_1 — C_2 bond. Clockwise rotation⁵ of C_2 (sighting from C_1 to C₂), which is accompanied by anticlockwise rotation of C1, removes the hydrogen-oxygen eclipsing interaction and both the hydroxyl and alkoxy groups assume a quasiaxial (or axial)⁶ orientation (a in Scheme I). Hydrogen bonding with the ring oxygen is possible in this conformation. The reverse rotation about C_1 — C_2 , which also decreases eclipsed hydrogen-oxygen interaction, places the two substituents in a quasiequatorial (or equatorial) arrangement (b in Scheme I). In this conformation no intramolecular hydrogen bonding can occur. One

³Both free and bonded hydroxyl absorption has been found for the analogous heterocycle, 3-hydroxytetrahydrothiophene and some of its derivatives (11).

⁴Nuclear magnetic resonance data suggests that the molecule is probably not in the simple envelope conformation.

⁵For convenience in this part of the discussion we have numbered the tetrahydrofuran as shown in Scheme I with the carbon atom adjacent to the oxygen, and bearing the alkoxy group, labelled C_1 and the vicinal carbon (bearing the OH group) as C_2 , etc. Names and numbering of the ring atoms of compounds in Table I follow the normal rules.

rules. ⁶We assume the half chair conformation. The infrared data do not permit one to discern between the axial and quasiaxial arrangement. The same is true for the equatorial and quasiequatorial conformation.

might expect the latter conformation to be less stable because of gauche oxygen-oxygen interaction at C_1 and C_2 which is about 0.35 kcal/ mole in the cyclitols (14). Furthermore, the anomeric effect (15) should tend to stabilize the former conformation (a in Scheme I) in which the substituents are quasiaxial (or axial). Hence conformer a should be more stable than conformer b. Use of the extinction coefficients for the bonded and non-bonded hydroxyl groups (item 1, Table I) to calculate the proportion of the two conformers suggested above is not justified since it is known that bonded hydroxyl has a higher extinction coefficient than does free hydroxyl (16, 17). However, it is clear from the extinction coefficients that if one assumes that free and bonded hydroxyls are due only to the two conformers above, conformer b (free hydroxyl) is in greater proportion.

The alternate possibility, which might account for the hydrogen bonding data, assumes that essentially one conformer exists (i.e. a, Scheme I) because of the reasons cited above (gauche O,O interaction; anomeric effect). Rotation about the C_2 —O bond would then permit both free and bonded hydroxyl (a and a') with the conformer a' in greater abundance. It should be pointed out that the OH - - - O distance (Table I) of 2.5 Å to 2.9 Å indicates no particularly strong hydrogen bond. If this second alternative (a and a') is the one which is responsible for the observed bonded and free hydroxyl, then it follows that the hydrogen bonding in the trans-2-alkoxy-3-hydroxytetrahydrofurans is a consequence of the conformational preference for a, which in turn is due to the anomeric effect and minimization of O,O gauche interaction.

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