ν_{CO} 1710; ^{1}H NMR δ 1.15 (s, 9 H), 1.3–2.4 (m, 8 H), 4.05 (br m, 1 H), 4.8 (br m, NH); ^{19}F NMR ϕ 155.5 (not resolved m).

4,5-Tetramethylene-2-oxazolidone (**19**): IR: ν_{NH} 3450 (sharp), 3250 (br), ν_{CO} 1750; ^{1}H NMR δ 1.3–2.2 (m, 8 H), 4 (t, J = 4, 1 H), 6.45 (s, 1 H), 7.46 (s, 5 H).

***N*-(*tert*-Butoxycarbonyl)-1-ethyl-7-azabicyclo[4.1.0]heptane (20d)**: crude product, IR ν_{CO} 1710; ^{1}H NMR δ 0.8-1.9 (m exhibiting a sharp s at 1.4, 22 H), 2,3 (m, 1 H). A 1-g (4.4 mmol) sample of **20d** was allowed to react with NR_3–2.5HF. The crude solid isolated (970 mg) exhibited only one signal in the ^{19}F NMR spectrum; its ^{1}H NMR spectrum was consistent with pure **21dT**. The structure of **21dT** was confirmed by its hydrolysis to the amine **21aT** in Olah's reagent, followed by Schotten–Baumann benzoylation to **24bT**.

***N*-(*tert*-Butoxycarbonyl)-2-fluoro-2-ethylcyclohexylamine (21dT)**: yield 90; mp 107–109 °C (CH_3CN); IR ν_{NH} 3440, ν_{CO} 1710; ^{1}H NMR δ 0.9 (2 overlapping t, J = 7), 1.4 (s) and 1.2-2,2 (m, total 22 H), 3,85 (br m, 1 H), 4,7 (br m, 1 H); mass spectrum, m/e (relative intensity) ϕ 161.6; 245 (10, $M^{+\cdot}$), 225 (2), 189 (34), 169 (4), 152 (7), 145 (7), 140 (3), 113 (10), 109 (9), 108 (16), 100 (10), 96 (4), 82 (6), 67 (5), 57 (100).

***N*-Benzoyl-7-azabicyclo[4.1.0]heptane (22b)** was purified by recrystallization from petroleum ether: mp 69–71 °C; IR ν_{CO} 1660; ^{1}H NMR δ 1.1–2.4 (m, 8 H), 2.7 (br s, 2 H), 7.6 and 8.1 (2 m, 5 H). Reaction of **22b** (1.136 g, 5.7 mmol) with NR_3–2.5HF gave 1.060 g of crude product containing primarily *trans*-*N*-benzoyl-2-fluorocyclohexylamine (**23bT**; yield 70%, as determined by integration of the ^{1}H NMR spectrum).

Registry No. 1, 25865-52-5; **2E**, 71057-05-1; **2T**, 71057-06-2; **2T**·HCl, 79121-05-4; **3**, 71057-07-3; **3**·HCl, 79102-18-4; **4**, 30031-86-8; **5E**, 79102-19-5; **5T**, 79102-20-8; **6E**, 79102-21-9; **6T**, 79102-22-0; **7aC**, 1605-06-7; **7bC**, 13866-14-3; **7aT**, 25125-72-8; **7bT**, 79102-23-1; **8aE**, 71057-09-5; **8aT**, 71057-08-4; **8bT**, 79102-24-2; **8bE**, 79102-25-3; **9C**, 58821-35-5; **9T**, 71027-98-0; **10aC**, 1485-13-8; **10aT**, 20993-60-6; **10aT** *N*-benzoyl derivative, 79102-26-4; **10dC**, 74275-05-1; **10bC**, 79102-27-5; **10eC**, 20993-62-8; **11aE**, 74275-07-3; **11dE**, 74275-06-2; **11dT**, 79102-28-6; **11bT**, 79102-29-7; **11aT**, 75197-98-7; **12a**, 75-55-8; **12b**, 21384-41-8; **13a**, 66679-40-1; **13b**, 74275-02-8; **14a**, 66679-45-6; **14b**, 74275-01-7; **15**, 23437-02-7; **16**, 25393-66-2; **17a**, 25022-23-5; **17a** *N*-benzoyl derivative, 79102-30-0; **17d**, 79102-31-1; **18aC**, 79102-32-2; **18aT**, 75213-92-2; **18bC**, 79102-33-3; **18dT**, 79102-34-4; **18dC**, 79102-35-5; **19**, 17539-96-7; **20a**, 51617-08-4; **20d**, 79102-36-6; **21bC**, 79102-37-7; **21bT**, 79102-38-8; **21dT**, 79102-39-9; **21aC**, 79102-40-2; **21aT**, 79102-41-3; **22a**, 286-18-0; **22b**, 4714-50-5; **23aC**, 79102-42-4; **23bT**, 79102-43-5; **23aT**, 75198-04-8; **23bC**, 79102-44-6; **24C**, 51650-18-1; **24T**, 38222-77-4; **25**, 79121-06-5; **26**, 57437-13-5.

Anomeric Effect in 2-Alkoxytetrahydropyrans Studied by ^{13}C and ^{17}O NMR Chemical Shifts[1]

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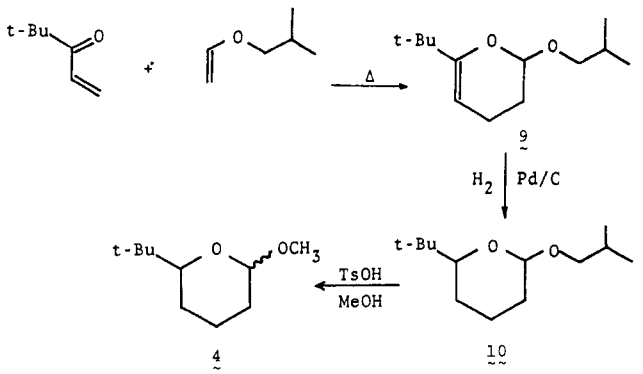
Received March 20, 1981

A series of 13 2-alkoxytetrahydropyrans has been prepared and studied by ^{13}C and ^{17}O NMR spectroscopy. Ten of these were in the form of cis and trans isomeric pairs, where the chemical shifts of isomers containing axial and equatorial alkoxy groups could be compared directly. A consistent pattern was observed, where the chemical shifts of not only the two oxygens but also the three carbons attached to oxygens were shifted "upfield" for the axial isomers. The results are interpreted in terms of three factors: a stereochemical γ-effect, back-bonding of a nonbonding orbital on the ring oxygen with the σ^* orbital of the exocyclic C–O bond, and local paramagnetic screening.

The anomeric effect is a general phenomenon of 1,3-diheteroatomic systems. In 2-alkoxytetrahydropyrans and related systems, it manifests itself primarily in a preference for axial over equatorial stereochemistry. This difference can be either configurational or conformational depending on the system under study. In systems where cis and trans isomers are possible, configurational equilibration can be used to establish free-energy differences. In simpler systems, spectral techniques such as NMR can be used to at least establish preferred geometry.

A variety of experimental techniques and theoretical calculations have been used to explain the origin of the anomeric effect.[3] The nonbonding electron pairs on oxygen are of paramount importance. Interactions between pairs on different oxygens (dipole–dipole) and also overlap of nonbonding orbitals with C–X bonds have been shown to be important. One manifestation of the latter is the conformational preference known as the exo-anomeric effect.[4]

Scheme I. Preparation of *cis*- and *trans*-6-*tert*-Butyl-2-methoxytetrahydropyrans (4)



(1) Part 7 of "^{17}O Nuclear Magnetic Resonance Studies". Part 6: Kobayashi, K.; Sugawara, T.; Iwamura, H. *J. Chem. Soc., Chem. Comm.* **1981**, 479.

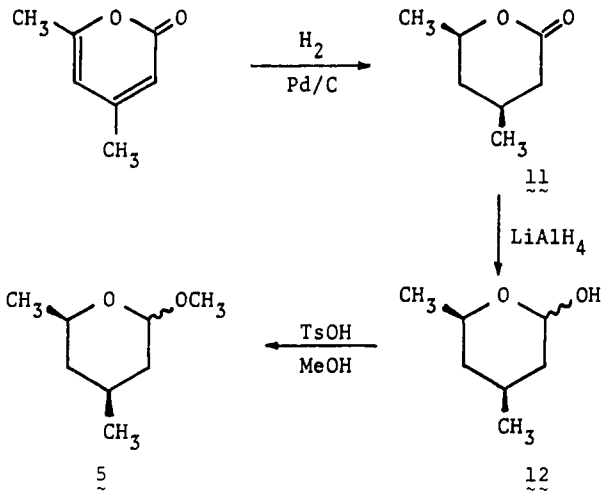
(2) IMS Invited Foreign Scholar, 1980.

(3) For pertinent reviews, see: (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965; Chapter 6. (b) Szarek, W. A.; Horton, D., Eds. "Anomeric Effect. Origin and Consequences"; American Chemical Society: Washington, DC, 1979; ACS Symp. Ser No. 87.

(4) Lemieux, R. U.; Koto, S. *ACS Symp. Ser.* **1979**, *No. 87*, 17.

0022-3263/81/1946-4948$01.25/0

Scheme II. Preparation of *cis,cis*- and *trans,cis*-2-Methoxy-4,6-dimethyltetrahydropyrans (5)



As a further probe of the anomeric environment, we have chosen ^{17}O NMR chemical shifts. Several cis and trans pairs of 2-alkoxytetrahydropyrans were synthesized, and the results were supplemented by ^{13}C NMR chemical shifts.

Results

Five cis and trans pairs of 2-alkoxytetrahydropyrans (**2–5**, **8**) were prepared and separated. In one case, only cis isomer **7** was available. Two monosubstituted alkoxytetrahydropyrans, **1** and **6**, were also prepared for reference. Most of these were known compounds, prepared according to literature methods (see Experimental Section). However, two (**4** and **5**) of the pairs were new and were synthesized as shown in Schemes I and II, and as detailed in the Experimental Section.

The typical ^{17}O NMR spectra are shown in Figure 1. ^{13}C and ^{17}O chemical shifts for the 2-alkoxytetrahydropyrans are collected in Table I. The ^{17}O shifts are presented in parts per million downfield from water. The ^{13}C shifts are relative to Me_4Si. ^{17}O NMR spectroscopy of relatively large organic molecules is handicapped by low natural abundance (0.037%) and line broadening due to ^{17}O quadrupole relaxation.[5,6] In order to partly overcome the latter effect by minimizing the Einstein–Stokes equation ($\tau_c = 4\pi a^3\eta^*/3kT$) to narrow the resonance lines under usual conditions, we found toluene to be the solvent of choice at higher temperatures. This hydrocarbon is among the least viscous solvents (η = 0.271 cP at 100 °C) as compared to other hydrocarbons and haloalkanes.

The ^{17}O assignments are based on two factors. It is known that methyl ethers appear at higher field than ethyl ethers and that secondary and tertiary ethers appear at increasingly lower field.[5] Thus, the exocyclic methoxy oxygens are assigned to the high-field peak. These all fall into the narrow range of 23–34 ppm. A similar assignment of the more shielded exocyclic oxygen in 2-ethoxy derivatives can be made when they carry an additional methyl group at position 6. Now the comparison is between primary and secondary ethers. This just leaves two compounds, **2** and **7**, where both oxygens bear a primary substituent. A tentative assignment, given in Table I, is based on the unique observation that in all of the unambiguous cases, the peak due to the ring oxygen is taller than that of the alkoxy oxygen. This difference in peak width may be due to anisotropic tumbling, with the exocyclic oxygen somehow relaxing at a faster rate than the endocyclic oxygen. Finally, the chemical shifts appear to form a self-consistent set. The carbons were assigned in a similar way. The same two compounds **2** and **7** presented a similar problem. The O–CH_2 peaks appear close together, and the assignments could easily be reversed. However, this would not affect the discussion which follows.

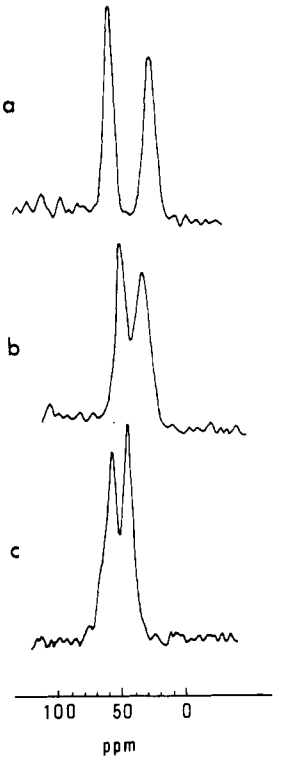
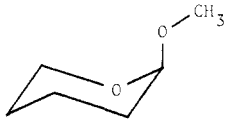
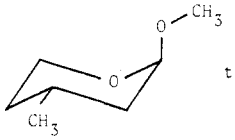
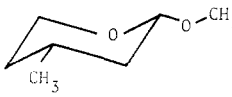
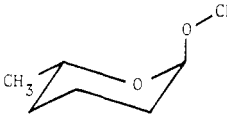
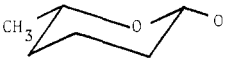
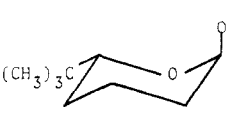
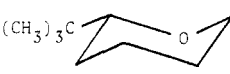
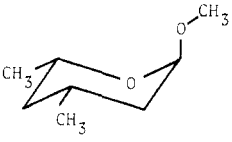
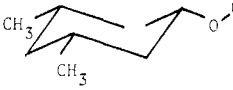
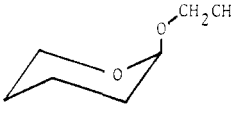
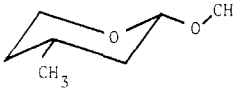
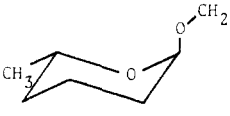
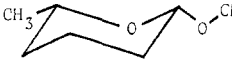


Figure 1. ^{17}O NMR spectra at 10.78 MHz of (a) *trans*-6-*tert*-butyl-2-methoxytetrahydropyran (*trans*-**4**), (b) *cis*-2-methoxy-4-methyltetrahydropyran (*cis*-**2**), and (c) 2-ethoxytetrahydropyran (**6**).

Examination of the chemical shifts in Table I shows several trends. First of all, where both cis and trans isomers were available, *both* the ring oxygen and the alkoxy oxygen were shielded more in the trans isomer, where the alkoxy group is exclusively or predominantly axial. This effect had the average size of 13 ppm for the ring oxygen and was in the range 5–10 ppm for the exocyclic oxygen. Second, the ^{13}C signals for *all three* carbons attached to oxygen appear at higher field in the trans isomers than the corresponding carbons in the cis isomers. This effect was largest at C-6 (average 6.8 ppm), intermediate at C-2 (average 4.7 ppm), and smallest at the alkoxy carbon (average 1.3 ppm). Monosubstituted compounds **1** and **6**, which would have the alkoxy group about 80% axial,[7] fit into the same pattern, with the 4-methyl-substituted analogues as pure equatorial and axial forms for comparison.[8] Finally, substitution at C-6 systematically affected the chemical shift difference between cis and trans isomers for the ring oxygen. With no substituent the difference was 10.3 ppm, with a methyl group the difference was 13.9–14.2 ppm, and with the bulkiest *tert*-butyl group the difference was 22.7 ppm.

(5) Christ, H. A.; Diehl, P.; Schneider, H. R.; Dahl, H. *Helv. Chim. Acta* **1961**, *44*, 865. Sugawara, T.; Kawada, Y.; Katoh, M.; Iwamura, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3391.
(6) Klemperer, W. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 246. Sugawara, T.; Kawada, Y.; Iwamura, H. *Kagaku no Ryoiki* **1980**, *34*, 35.
(7) Eliel, E. L.; Giza, C. A. *J. Org. Chem.* **1968**, *33*, 3754.
(8) Anderson, C. B.; Sepp, D. T. *J. Org. Chem.* **1968**, *33*, 3272; *Tetrahedron* **1968**, *24*, 1707.

Table I. ^{13}C and ^{17}O NMR Chemical Shifts of 2-Alkoxytetrahydropyrans

compd	atoms	δ(^{13}C)	atoms	δ(^{17}O)
 1	C(2)	99.2	O(1)	42
	C(6)	60.8	*exo*-O	23
	OCH_3	54.0		
 trans-2	C(2)	98.0	O(1)	39
	C(6)	59.1	*exo*-O	25
	OCH_3	53.8		
 cis-2	C(2)	102.7	O(1)	49
	C(6)	64.4	*exo*-O	32
	OCH_3	55.1		
 trans-3	C(2)	98.3	O(1)	60
	C(6)	64.3	*exo*-O	23
	OCH_3	53.7		
 cis-3	C(2)	103.0	O(1)	74
	C(6)	71.6	*exo*-O	33
	OCH_3	55.0		
 trans-4	C(2)	98.6	O(1)	52
	C(6)	75.4	*exo*-O	23
	OCH_3	53.8		
 cis-4	C(2)	103.6	O(1)	75
	C(6)	83.3	*exo*-O	34
	OCH_3	54.9		
 trans-5	C(2)	98.5	O(1)	60
	C(6)	64.2	*exo*-O	24
	OCH_3	53.8		
 cis-5	C(2)	102.7	O(1)	74
	C(6)	70.7	*exo*-O	31
	OCH_3	55.1		
 6	C(2)	98.0	O(1)	44
	C(6)	62.3	*exo*-O	56
	OCH_2	61.2		
 cis-7	C(2)	101.5	O(1)	51
	C(6)	64.4	*exo*-O	62
	OCH_2	63.3		
 trans-8	C(2)	96.9	O(1)	67
	C(6)	64.4	*exo*-O	55
	OCH_2	61.9		
 cis-8	C(2)	101.8	O(1)	81
	C(6)	71.5	*exo*-O	60
	OCH_2	63.1		

Discussion

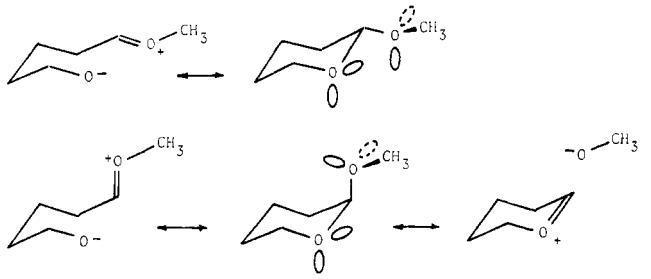
To our knowledge, this is one of the first reports of differences in ^{17}O chemical shifts due to oxygen stereochemistry.[1,9,10] Differences similar to ours for ^{13}C have been noted previously in carbohydrates,[11a] and an upfield shift has been noted for ^{1}H and ^{13}C antiperiplanar to a nonbonding orbital on tertiary nitrogen.[11b] Having both sets of ^{13}C and ^{17}O data available for a single series of compounds presents a unique opportunity for interpretation.

(9) Block, E.; Bazzi, A. A.; Lambert, J. B.; Wharry, S. M.; Andersen, K. K.; Dittmer, D. C.; Patwardhan, B. H.; Smith, D. J. H. *J. Org. Chem.* **1980**, *45*, 4810.

(10) Coderre, J. A.; Mehdi, S.; Demou, P. C.; Weber, R.; Traficante, D. D.; Gerlt, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 1870.

(11) (a) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley: New York, 1972; Chapter 8. de Hoog, A. J. *Org. Magn. Reson.* **1974**, *6*, 233. Gast, J. C.; Atalla, R. H.; McKelvey, R. D. *Carbohydr. Res.* **1980**, *84*, 137. (b) Blackburne, I. D.; Katritzky, A. R.; Takeuchi, Y. *Acc. Chem. Res.* **1975**, *8*, 300 and references therein. Vierhapper, F. W.; Eliel, E. L.; Zúñiga, G. *J. Org. Chem.* **1980**, *45*, 4844.

In discussions of the exo-anomeric effect, Lemieux and co-workers considered overlap between nonbonding orbitals on oxygen and antiperiplanar C–O bonds.[4] They show hybrid orbitals for both lone pairs, even though Sweigart and Turner showed by photoelectron spectroscopy that one orbital is probably a p orbital.[12] Such overlap leads to a preferred conformation for both α and β orientations. The following resonance forms can be used to show such overlap.

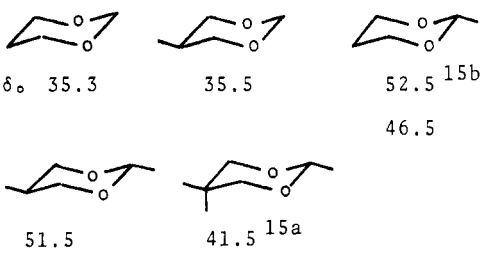


In the equatorial orientation, only overlap of the exocyclic oxygen and the ring C–O bond is important. The ionic resonance form suggests a shorter exocyclic C–O bond (observed) and a shift in electron density from the exocyclic oxygen to the ring oxygen. When the methoxy group is axial, the ionic resonance forms tend to cancel each other out. One would tend to shift electron density in one direction, while the other tends to shift in the opposite direction. A similar effect is suggested for bond lengths.[13]

Heavy-atom chemical shifts are often correlated with charge densities.[6] If such overlap as above and its consequential electron distribution were dominating ^{17}O chemical shifts, we would expect the ring oxygen to be more shielded and the exocyclic oxygen to be more deshielded for our cis isomers. However, *both* oxygens are more deshielded in our cis isomers.

David et al. have interpreted the anomeric effect in terms of superjacent orbital control.[14] The polarization of the C–O bonds causes a reduction in the σ-electron density at the carbon atom. To compensate for this, they consider back-donation of electron density from the p-type lone-pair orbital of oxygen to the σ^* orbital of the adjacent C–X bond. Such overlap would tend to shift electron density which was localized on oxygen into a region between oxygen and carbon. This represents a net shift from oxygen to carbon. This overlap is expected to be more important when the electronegative substituent is axial. Although the anomeric carbons are shielded more in our axial isomers by 4.7 ppm, the oxygens appear at higher fields too by 13 ppm. Hence, we need to turn to something other than simple electron density to explain our oxygen results.

Delseth and Kintzinger and Eliel et al.[15] have demonstrated a steric aspect to the γ effect on ^{17}O chemical shifts in 1,3-dioxanes and related compounds. They found that a γ-methyl group (5-position) anti to oxygen deshielded oxygen by 0.3–5 ppm, while a γ-methyl group gauche to oxygen shielded it by 10–11.4 ppm. Hence, the difference between anti and gauche is 11.7–15 ppm. The ring carbons 4 and 6 on our tetrahydropyran rings are γ-anti to the



2-alkoxy oxygen in the equatorial isomers (cis) and γ-gauche in the axial isomers. If the effect were additive, this could be causing a 23–30-ppm (twice 11.7–15 ppm) upfield shift in the 2-alkoxy oxygen for axial (trans) isomers. In the absence of such a steric effect, the ring oxygen would appear at higher field as observed, and the exocyclic oxygen would appear at lower field by 13–25 ppm [=(23–30) – (5–10)] in the axial isomers, compared to the equatorial isomers.

The net shift, with the steric effect factored out, can now be ascribed to the anomeric effect. Local paramagnetic screening is considered to be dominant in controlling ^{17}O NMR chemical shifts. Karplus and Pople's equation for the paramagnetic term in the chemical shift expression may be cast in the form[16] of eq 1. Here $\sum Q$ is defined

$$\sigma_p^A = -\frac{e^2h^2}{2m^2c^2}\langle r^{-3}\rangle_{2p}(\Delta E)^{-1}\sum Q \qquad (1)$$

in terms of the element of the charge density and bond order matrix, and $\langle r^{-3}\rangle_{2p}$ refers to the mean inverse cube of the radius of the 2p orbitals on atom A in question, which is approximated by $(Z_{2p}/2a^\circ)^3/3$, where Z_{2p} is effective nuclear charge for 2p electrons and a° is the Bohr radius. ΔE is a mean or effective excitation energy and may be approximated by the lowest allowed transition associated with the atom in question. While we understand that these parameters are not fully independent variables, we are tempted to see which term may correlate to the experimentally found trends best. In the ^{17}O NMR chemical shifts of ring-substituted anisoles,[17] for example, the decrease in shielding with increasing electron withdrawal can be explained by the increase in the effective nuclear charge for 2p electrons and/or in the orbital terms $\sum Q$. In the case of aliphatic alcohols and ethers, the downfield shift parallels the decrease in their ionization potentials, demonstrating the importance of the ΔE term.[5]

In the present system, back-donation from the ring oxygen to the exocyclic oxygen in the axial isomers should cause an increase in the effective excitation energy (ΔE) of the n electrons at the ring oxygen and a decrease for the exocyclic oxygen. Since ΔE appears in the denominator of the Karplus and Pople equation, the ring oxygen should be more shielded and the exocyclic oxygen less shielded in the axial isomers. This is what is observed, when the steric γ effect is substracted out.

The trend that the chemical shift differences for both oxygens between anomers increase as we go from hydrogen to methyl to *tert*-butyl at position 6 is also consistent with more facile back-donation of the lone pair of electrons at the ring oxygen to the σ^* orbital of the exocyclic bond, since the ionization potential of the ring oxygen decreases in this order with higher alkyl substitution.

In conclusion, conformational and configurational assignments of 2-alkoxytetrahydropyrans are conveniently made by ^{17}O chemical shifts, and the anomeric effect in

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more complicated systems could be studied by this highly informative method.

Experimental Section

Spectral Measurements. ^{13}C spectra were obtained on a JEOL FX-100 spectrometer at 25.00 MHz using an external deuterium lock. Toluene solutions were used (ca. 40%), and the spectra were referenced to Me_4Si by setting the toluene ortho carbons equal to 128.9 ppm. A spectral width of 4000 Hz and 8192 data points were used. Approximately 100 transients were accumulated by using 45° pulses, 5-s repetitions, and 5-mm tubes.

The ^{17}O measurements were made at natural abundance levels (0.037%) on a Varian FT-80A spectrometer at 10.782 MHz. For an 8000-Hz spectral width, 320 data points in the time-domain spectra were used, the Fourier number being set at 16 384. The spectra were run on ca. 40% toluene solutions in 10-mm tubes. The number of transients accumulated with 90° pulses and an acquisition time of 0.03 s had to be in the range of 10^5–10^6 to get spectra of reasonable s/n ratios. Chemical shifts were measured as frequency shifts from the radio-frequency synthesizer frequency (8.530 000 MHz) and expressed in parts per million relative to the oxygen of neutral water. Oxygen chemical shifts are considered to be accurate to ±2 ppm. The sample temperature was set at ca. 100 °C.

Compounds. 2-Methoxytetrahydropyran (**1**),[18] 2-ethoxytetrahydropyran (**6**),[18] *cis*-2-ethoxy-4-methyltetrahydropyran (**7**),[19] 2-methoxy-4-methyltetrahydropyran (**2**),[19] and 2-methoxy-6-methyltetrahydropyran (**3**)[20] were prepared directly from literature methods.

2-Isobutoxy-6-*tert*-butyltetrahydropyran (10). 2-Isobutoxy-6-*tert*-butyl-2*H*-dihydropyran (**9**) was prepared according to the method of Anderson and Sepp[8] by using *tert*-butyl vinyl ketone.[25] This was then hydrogenated according to the literature,[8] except that 59 h at 60 °C was required. The reaction went poorly at room temperature. A mixture of cis and trans isomers was obtained in 97% yield, which could be partially separated by spinning-band distillation: impure trans isomer, bp 76.5–80 °C (4.5–5.0 mm); cis isomer, bp 80.5 °C (5.4 mm) [lit.[8] bp 82.5 °C (5 mm)].

6-*tert*-Butyl-2-methoxytetrahydropyran (4). The isobutoxy group was exchanged for methoxy according to the general method of Eliel and Giza.[7] A solution of 14.9 g of **10**, 20 mg of *p*-toluenesulfonic acid and 100 g of methanol was stirred at room temperature for 24 h. The sample was concentrated and distilled to give 7.3 g (61%) of a mixture of cis and trans isomers: bp 85–87 °C (26 mm); mass spectrum, m/e calcd for $C_{10}H_{20}O_2$ 172.1463, obsd 172.1447 (best fit within the limits of $C \leq 13$, $N \leq 1$, and $O \leq 4$). A portion of the mixture was separated by gas chromatography. Trans isomer: ^1H NMR (CCl_4) δ 0.88 (s, 9 H, *t*-Bu), 1.2–1.8 (m, 6 H, ring), 3.27 (s and m, 4 H, OCH_3 and CH–O), 4.40 (br s, 1 H, $w_{1/2}$ = 6 Hz, anomeric). Cis isomer: ^1H NMR (CCl_4) δ 0.92 (s, 9 H, *t*-Bu), 1.0–2.0 (m, 6 H, ring), 2.87 (br d, 1 H, J = 10 Hz, CH–O), 3.33 (s, 3 H, OCH_3), 4.13 (br d, 1 H, J = 9 Hz, anomeric).

5-Hydroxy-3-methylhexanoic Acid Lactone. This compound was prepared differently from the literature method[23] so that only the cis isomer (**11**) would be obtained. A mixture of 59.4 g of 4,6-dimethylcoumalin,[24] 200 mL of *tert*-butyl alcohol, and 0.50 g of 10% PD/C was stirred for 19 h at room temperature. The hydrogen pressure went from 85 to 22 kg/cm^2. The mixture was filtered, concentrated, and distilled to give 57.6 g (93.9%) of product, bp 77–78 °C (2 mm) [lit.[23] bp 75–77 °C (2 mm)]. The proton NMR was consistent with the cis isomer.[23]

2-Methoxy-4,6-dimethyltetrahydropyran (5). The general method of Babcock et al. was used.[20] An ether solution of lithium aluminum hydride (37 mL, 1.7 M) was added dropwise under nitrogen to a stirred solution of 32.1 g of lactone **11** in 100 mL of dry ether at −5 °C over a 70-min period. The solution was allowed to warm to room temperature and stirred for 2 h. Then, 2.5 mL of water, 2.5 mL of 15% NaOH, and 7.5 mL of water were added. Some Celite was added, and the mixture was filtered under vacuum. The ether solution was dried (Na_2SO_4) and concentrated to give 23.3 g (72%) of crude hemiacetal **12**.

Hemiacetal **12** was dissolved in 100 mL of methanol, 40 mg of *p*-toluenesulfonic acid was added, and the mixture was stirred at room temperature for 72 h. A small amount of sodium methoxide in methanol was added, and the mixture was purified by spinning-band distillation to give 4.40 g of the trans,cis isomer, 3.18 g of a mixture of isomers, and 2.02 g of the cis,cis isomer. All fractions boiled at 66 °C (50 mm). The total yield was 9.59 g (24% overall). Trans,cis isomer: ^{1}NMR (CCl_4) δ 0.87, 1.03 (2 d, 3 H each, J = 6 Hz, CH_3's), 1.20–2.20 (m, 5 H, ring), 3.27 (s, 3 H, OCH_3), 3.73 (m, 1 H, CH–O), 4.58 (br, 1 H, $W_{1/2}$ = 6 Hz, anomeric). Cis,cis isomer: ^1H NMR (CCl_4) δ 0.96, 1.17 (2 d, 3 H each, J = 6 Hz, CH_3's), 1.1–1.8 (m, 5 H, ring), 3.33 (s and m, 4 H, OCH_3 and CH–O), 4.15 (dd, 1 H, J = 1.5, 9 Hz, anomeric). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.19. Found for trans,cis isomer: C, 66.41; H, 11.18. Found for cis,cis isomer: C, 66.53; H, 11.14.

2-Ethoxy-6-methyltetrahydropyran (8). A mixture of 11.8 g of 2-ethoxy-6-methyl-2*H*-dihydropyran,[21] ca. 1.0 g of Raney nickel W-2 which had been stored for 40 days in absolute ethanol,[22] and 50 mL of dry ether was hydrogenated for 42 h at 55 °C and 99 kg/cm^2 of H_2. The mixture was filtered through Celite and concentrated to give 12.2 g (102%) of cis product, bp 85–86 °C (82 mm). The proton NMR was consistent with the cis isomer.[7]

A cis/trans mixture was obtained by adding 25 mL of absolute ethanol and 10 mg of *p*-toluenesulfonic acid and stirring for 24 h. A small amount of sodium ethoxide in ethanol was added, and the mixture was concentrated and distilled to give 4.6 g (39%) of a trans-rich mixture [bp 84–85 °C (82 mm)][7] from which a small sample of *trans*-**8** was obtained by preparative gas chromatography.

Separation of Isomers. Mixtures of cis and trans isomers were separated either by spinning-band distillation or preparative gas chromatography. A Perkin-Elmer 251 Auto Annular Still was used for distillation. For preparative gas chromatography a 0.25 in. × 6 ft column of 10% silicone DCQF-1 on Chromosorb W AW was used, with helium as the carrier. In all cases, for both distillation and gas chromatography the trans isomer was more volatile, and emerged first.

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Registry No. **1**, 6581-66-4; *trans*-**2**, 7429-28-9; *cis*-**2**, 932-80-9; *trans*-**3**, 17230-08-9; *cis*-**3**, 17230-07-8; *trans*-**4**, 79233-91-3; *cis*-**4**, 79233-92-4; *trans*-**5**, 79233-93-5; *cis*-**5**, 79297-69-1; **6**, 4819-83-4; *cis*-**7**, 17230-25-0; *trans*-**8**, 17230-10-3; *cis*-**8**, 17230-09-0; **9**, 16831-16-6; *cis*-**10**, 16822-20-1; **11**, 24405-13-8; **12**, 6900-26-1; 2-ethoxy-6-methyl-2*H*-dihydropyran, 52438-71-8; 4,6-dimethylcoumalin, 675-09-2.

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