The Stereodependent Effect of Oxygen on the Chemical Shifts and Vicinal Coupling Constants of Tetrahydropyran

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The analysis of the ^1H NMR spectra of two selectively deuterated derivatives of tetrahydropyran at −115 °C has provided accurate values for proton chemical shifts and vicinal coupling constants about the C(2)–C(3) bond. A comparison with the corresponding parameters of cyclohexane allows a precise definition of the stereodependent effect of oxygen ($^3J_{2a3a}$, $^3J_{2e3e}$, $^3J_{2a3e}$ are reduced while $^3J_{2e3a}$ is increased) in this fundamental molecule. An explanation of the trends observed is given and the conformational and stereochemical implications of the results are discussed.

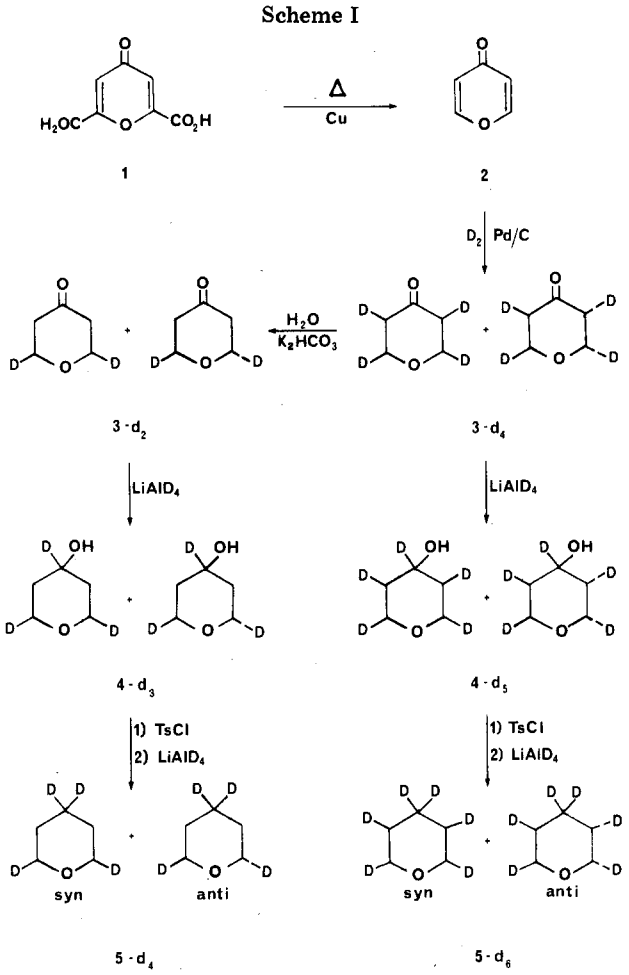
The field of conformational and stereochemical analysis of basic six-membered ring systems is often considered fundamental in organic chemistry. NMR spectroscopy ranks among the most useful tools of experimental investigation in this domain and, when appropriate reference parameters are available, its application to molecules with readily analyzable spectra has become rather straightforward.[1] Vicinal coupling constants recently published[2] for cyclohexane-d_8 have provided the reference basis for many applications through an empirically determined dependence on dihedral angles.

It is well known that heteroatoms affect the values of vicinal couplings according to their electronegativity, and many efforts have been aimed at providing information on the magnitude of this effect. In particular, approximate coupling values have been proposed for pyranoid derivatives from studies on carbohydrate derivatives,[3] but there is at present no knowledge of the quantitative effect of oxygen in $-CH_2CH_2O-$ fragments from cyclic systems and more specifically from the parent compound, tetrahydrofuran.

Because of the fundamental nature of tetrahydropyran both for theoretical reasons and for practical conformational and stereochemical applications to many classes of heterocyclic organic compounds, it appeared to us that accurate chemical shift and coupling information for this basic compound should be a necessary prerequisite to quantitative deductions which go beyond merely drawing parallels between carbocyclic and heterocyclic rings.

Because of the complexity of the ^1H NMR spectrum of tetrahydropyran and the need to obtain very accurate coupling constants we have prepared stereospecifically deuterated derivatives with simpler spectra and because ring inversion is rapid at normal room temperature[4] we have analyzed the spectra at low temperatures in order to obtain parameters characteristic of the noninverting chair conformation of this molecule.

Scheme I



Results

As illustrated in Scheme I, γ-pyranone (**2**) obtained from chelidonic acid (**1**)[5] was deuterated with deuterium gas in the presence of palladium on carbon to give a mixture of syn and anti isomers[6] of tetrahydropyranone-*cis*-2,3,*cis*-5,6-d_4 (**3**-d_4) which were reduced with lithium aluminum deuteride to give the alcohols **4**-d_5 which were converted to tetrahydropyran-4,4,*cis*-2,3,*cis*-5,6-d_6 (**5**-d_6). Protonic exchange of the α deuterium in **3**-d_4 gave a mixture of syn and anti isomers tetrahydropyranone-2,6-d_2 (**3**-d_2) which were reduced to the alcohols **4**-d_3 followed by transformation to tetrahydropyran-2,4,4,6-d_4 (**5**-d_4).

Spectral Analysis. Deuterium decoupled, 100 MHz, ^1H NMR spectra of **5**-d_6 are shown in Figure 1. At 25 °C the spectrum contains two equally intense multiplets centered at 3.46 (α protons) and 1.45 ppm (β protons) while the spectrum at −115 °C reveals that a marked change, associated with the slowing down of ring inversion,[4] has taken place to give three multiplets of relative intensity 1:1:2 with increasing field.

Analysis of these spectra is not straightforward because both the syn and anti isomers of **5**-d_6 exist as a mixture of two equally populated conformations (**6**–**9**) differing only by the location of the deuterium atoms. If both sides of the molecules of **5**-d_6 were independent of each other, the time-averaged spectrum observed at 25 °C should consist of only four lines resulting from the superposition of AX patterns. Clearly this is not observed and the additional splitting may be due to a combination of several factors: (a) the presence of isotopic impurities[7] of the type

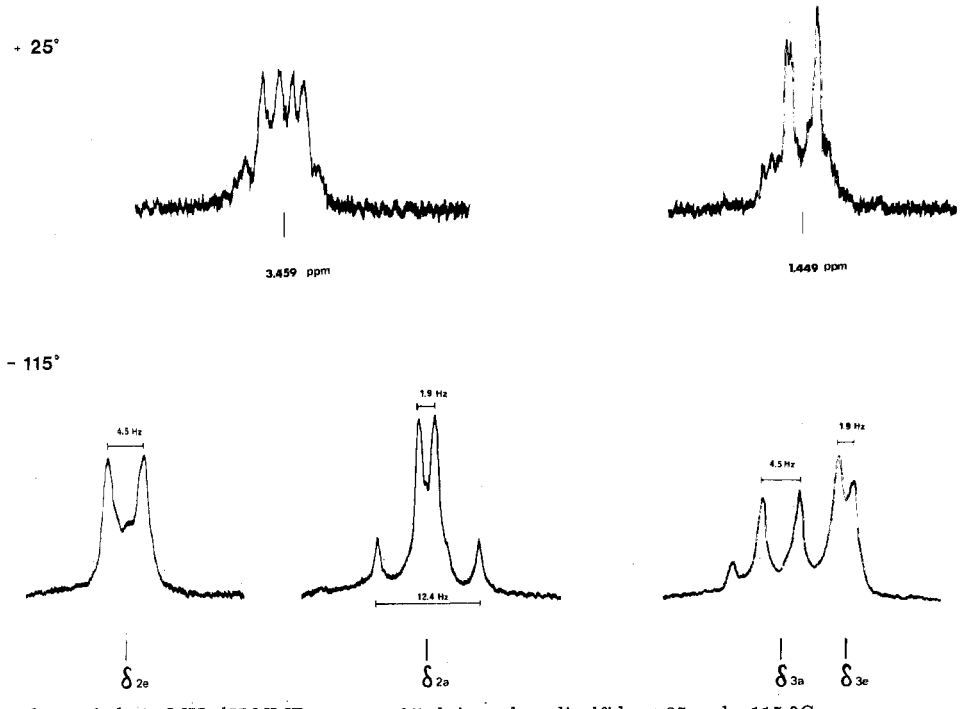
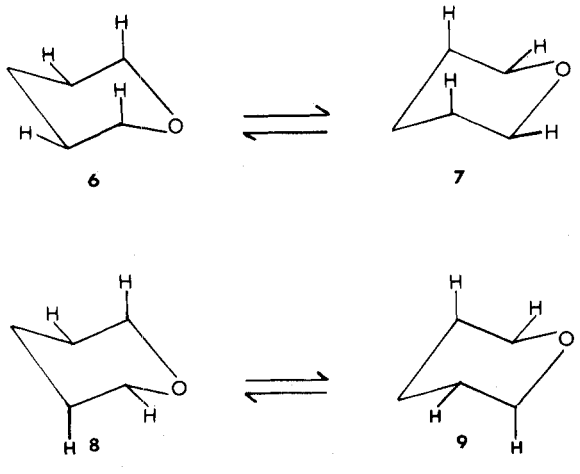


Figure 1. Deuterium decoupled 100 MHz ^{1}H NMR spectra of **5**-d_6 in carbon disulfide at 25 and −115 °C.



–CHDCHD– trans and –CHDCH$_2$– suggested by the mass spectrum, (b) second-order effects arising from appreciable four-bond coupling between magnetically equivalent equatorial protons, and (c) a possible but small long-range isotope.[6] Fortunately, the more meaningful ^{1}H NMR parameters are revealed from the low-temperature spectrum and a detailed analysis of the averaged spectrum at 25 °C is not necessary.

The spectrum of **5**-d_6 at −115 °C, on the other hand, appears to be much simpler since signals from isotopic impurities no longer coincide with those of the main product. In fact, the eight intense lines observed can readily be identified as two apparent AX patterns (one with a splitting of 4.5 Hz and the other of 1.9 Hz) expected for the two possible cis arrangements about the C(2)–C(3) bond (namely $H_{2e}H_{3a}$ and $H_{2a}H_{3e}$) when both sides of the molecules are treated as independent of one another, except for line broadening effects. First-order analysis and the knowledge that H_{2a} absorbs at higher field[8] than H_{2e} lead to the identification of the environment of protons on C(3) as written at the bottom of Figure 1 where it is shown that H_{3e} absorbs at higher field than H_{3a}.

The symmetry properties of conformations **6**–**9** suggest that second-order effects should be largest for the syn conformers **6** and **7** for which appreciable four-bond couplings are expected between the magnetically equivalent equatorial protons. On the other hand, the anti conformers **8** and **9** are expected to show little second-order effect because of the absence of magnetic equivalence and relatively small axial–equatorial four-bond coupling constants.[9,10] Computer simulations of AA′XX′ or ABXY patterns for the various forms have demonstrated convincingly that the anti isomer gives a first-order spectrum at −115 °C for which any small coupling between H_{2e} and H_{6a} would only broaden the spectral lines. Furthermore, the calculated spectra for **6** and **7** are slightly perturbed by second-order effects but since they represent only 50% of total intensity, the superposition of spectra for the syn and anti isomers gives a resultant spectrum for which the second-order effects only broaden the base of each peak so that separations measured from the experimental spectrum effectively are equal to the coupling constants expected for the two cis arrangements of protons about the C(2)–C(3) bond of tetrahydropyran. Isotopic impurities present in small amount would also affect the spectrum mostly at the base of the spectral lines of **5**-d_6.

In addition to the intense doublet with the 1.9-Hz splitting, the signal identified by δ_{2a} in the spectrum at −115 °C (Figure 1) shows another, less intense, doublet possessing a 12.4-Hz splitting. Owing to the lack of exclusive cis selectivity[7] of the catalytic reduction in Scheme I, it is reasonable to assign this doublet to trans species (isotopic impurities) and consequently to conclude that $^3J_{2a3a}$ = 12.4 Hz. Careful examination of the high-field signal shows that the other half of the trans AX pattern is symmetrically disposed about δ_{3a}. One component of the doublet is readily visible at the left of the multiplet whereas the upfield component falls under a line from the cis species to give the most intense line of that multiplet. Since J_{2e3e} is small, the other trans AX pattern is not resolved.

It is therefore reasonable to conclude that first-order analysis of the low-temperature spectrum of **5**-d_6 provides accurate vicinal coupling constants and that second-order effects broaden the lines. Accordingly the experimental error in the coupling constants is within 0.2 Hz.

Figure 2 shows the deuterium decoupled, 100 MHz, ^{1}H NMR spectrum of **5**-d_4. The parameters obtained from the

Table I. ^{1}H NMR Parameters for Deuterated Derivatives of Tetrahydropyran and Cyclohexane

Parameter	Tetrahydropyran[a]	Cyclohexane[b]	Coupling differences
J_{2a3e}	1.9 Hz	3.65 Hz	−1.7 Hz[c]
J_{2e3e}	1.5	2.96	−1.5
J_{2a3a}	12.4	13.12	−0.7
J_{2e3a}	4.5	3.65	+0.8
$\Delta\nu_{2e2a}$	+0.527 ppm[d,e]	+0.479 ppm[e]	
$\Delta\nu_{3e3a}$	−0.074	+0.479[f]	
R	2.17	2.16	

[a] From the analysis of 5-d_4 and 5-d_6 in this work. [b] Values taken from ref 2 for cyclohexane-d_8. [c] The sign is negative when the coupling constant is smaller in tetrahydropyran than in cyclohexane. [d] Chemical shift differences were measured directly from the spectrum of 5-d_6. [e] The sign is positive when the axial proton chemical shift is smaller than the equatorial proton chemical shift. [f] Obviously C(2) and C(3) are identical for cyclohexane.

spectral analysis of 5-d_6 have enabled the computer simulation shown. The calculated spectrum consists of the sum of two equally intense ABX patterns whereby long-range coupling constants were considered to broaden the lines.[6-8] The X regions of each ABX system (B in Figure 2) are well separated from each other and their analysis provided an accurate value for J_{2e3e} = 1.5 Hz in addition to confirming the magnitude of 12.4 Hz for J_{2a3a}.

The fact that the chemical shift difference between H_{3a} and H_{3e} is quite small has made the analysis of the AB part of the spectrum (A in Figure 2) more difficult because several lines are closely spaced and one of the subspectra has an effective chemical shift difference smaller than J_{AB}.[11] The solid and broken lines of the stick diagram under the calculated spectrum identify the two ABX patterns.

Table I contains a summary of the pertinent ^{1}H NMR parameters characteristic of tetrahydropyran together with those for cyclohexane.[2]

Discussion

It is well known that among the various factors[12] affecting vicinal coupling constants, dihedral angles and the orientation of electronegative substituents[13] are most significant. Tetrahydropyran possesses some of the desired geometrical properties enabling a valuable test of existing concepts. Consequently, at the outset, it is important to define the geometrical properties of its chair conformation as precisely as possible.

Although the chair conformation of cyclohexane is well characterized,[14a] the extent of possible chair deformation for tetrahydropyran is not known with much certainty.[14b,c] In the last years the need for similar information concerning various six-membered cyclic compounds has led to the formulation of the R-value method[15,16] whereby a ratio R is defined for a $-CH_2CH_2-$ fragment such that

$$R = \frac{J_{trans}}{J_{cis}} \qquad J_{trans} = \tfrac{1}{2}(J_{aa} + J_{ee}) \qquad J_{cis} = \tfrac{1}{2}(J_{ae} + J_{ea})$$

Deviations from R = 2.16 (cyclohexane) are interpreted in terms of puckering (increase of R) or flattening (decrease of R) of the ring.

For tetrahydropyran R = 1.91 (J_{trans} = 7.4 and J_{cis} = 3.87 Hz)[15a] has been calculated from averaged couplings at ambient temperature. Using the individual vicinal coupling constants reported in Table I, the value R = 2.17 (J_{trans} = 6.95 and J_{cis} = 3.20 Hz) is calculated. The difference between these results lies outside the experimental error of our work and since isotope effects are unlikely for vicinal coupling constants,[17] we are tempted to suggest that part of the difference might lie in the limited accuracy of the averaged couplings obtained from the analysis of the averaged AA′XX′ spectrum[15a] of tetrahydropyran-*4,4*-d_2.

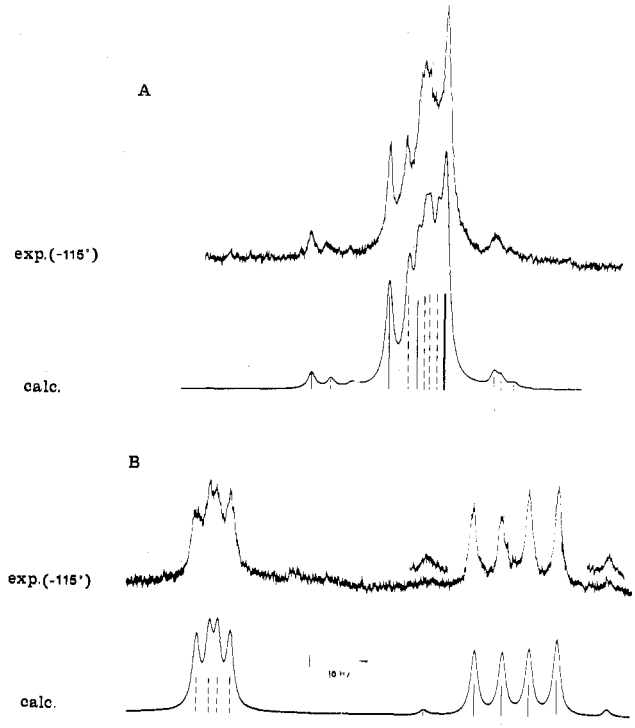
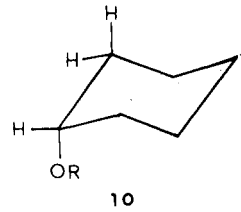


Figure 2. Deuterium decoupled 100 MHz ^{1}H NMR spectrum of 5-d_4 in carbon disulfide at −115 °C. (A) Experimental and calculated portion of the β protons. (B) Experimental and calculated portion of the α protons. The stick diagram identifies the lines of each of two ABX pattern comprising the spectrum.

It is of considerable interest to observe that our R value (2.17) for tetrahydropyran is very similar to the value R = 2.20 for 1,4-dioxane[15] and that both numbers are very close to the value R = 2.16 characterizing cyclohexane.

Table I further reveals that all the vicinal coupling constants change in a somewhat synchronous manner when oxygen replaces a methylene group (three couplings decrease while one increases). The net changes in J_{trans} and J_{cis} cancel each other and maintain R constant.

We now turn our attention temporarily to the concepts proposed to rationalize the stereodependence of the electronegativity effects of oxygen on vicinal couplings. Two different approaches using six-membered rings as substrates have been used. In one investigation Booth[18] determined the effect of axial and equatorial substituents on vicinal coupling which was found to be stereodependent whereby the decrease is maximum when the O–C–C–H relationship is trans coplanar as illustrated in structure **10.**



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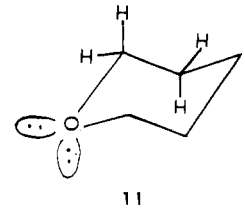

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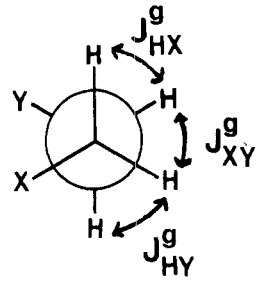
Later, work by Anteunis[19] and Crabb and co-workers[10] revealed that the stereodependent effect of oxygen is even more subtle when the heteroatom is part of the ring as in heterocycles of structure 11. It has been suggested[19] that, in addition to the above effect, eclipsing of a lone pair on oxygen with an adjacent C–H significantly raises vicinal couplings involving this proton. However, since eclipsing is expected to be small in six-membered cyclic compounds

existing in a chair conformation, the predominant effect of oxygen should be through the β proton trans to it, namely H_{3e}.

Systematic investigations of experimental results[20] and theoretical calculations[21] have revealed that gauche couplings are not affected equally by the presence of heteroatom-containing substituents in 1,2-disubstituted ethane derivatives. It has been suggested[20b] that, for the gauche conformer (12), J_{HX}^{g} increases with increasing electronegativity of Y when X is kept constant and equal to C whereas both J_{HY}^{g} and J_{XY}^{g} decrease.



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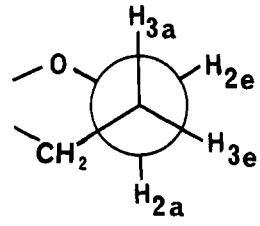

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The coupling data given in Table I are readily interpretable in terms of the above generalizations. Specifically, it is observed that the magnitudes of J_{2a3e} and J_{2e3e}, both involving H_{3e} trans to oxygen, are reduced appreciably, J_{2a3a} is decreased slightly whereas J_{2e3a} is slightly larger in tetrahydropyran. Structure 13 shows that J_{2e3a} is analogous to J_{HX}^{g} in 12 and consequently the observed increase of 0.8 Hz is normal[20] and in accord with recent theoretical predictions.[21]

Although a small flattening of the tetrahydropyran chair relative to that of cyclohexane and the associated reduction of the $H_{2e}H_{3a}$ dihedral angle by about 3° would also account for the observed increase in J_{2e3a}, it is felt that the close R values (Table I), the rather similar bond lengths[22] for C–O (1.41 Å) and C–C (1.54 Å) as well as essentially equal internal bond angles (about 112°), the similar torsional strain as reflected by the barriers to rotation about C–C and C–O segments (e.g., about 3.4 and 2.7 kcal/mol, respectively), together with the plausibility of the above discussion suggest that the observed couplings changes are a consequence mainly of the stereodependence of the electronegativity effect of the oxygen atom.

It is relevant to compare the slight decrease in J_{2a3a} (from 13.1 to 12.4 Hz) reported in Table I to that observed when a second oxygen is present as in 1,4-dioxane. The effect of the second oxygen (reduction from 12.4 to 11.7 Hz)[23] is very similar to that of the first and since the R values suggest nearly identical dihedral angles for all three molecules it can be concluded that ring oxygen atoms cause only a small additive decrease in the axial–axial coupling constant (i.e., linear relationship in $E_X + E_Y$[20b]).

The chemical shifts of the various protons also show an interesting stereodependence relative to oxygen. Table I shows that $\Delta\nu_{2e2a}$ is of comparable magnitude[24] for both cyclohexane and tetrahydropyran in accord with an earlier demonstration[8] that the axial proton next to the oxygen atom absorbs at higher fields than the equatorial proton as is the case for cyclohexane. Analysis of the spectrum of 5-d_6 (Figure 1) shows clearly that the reverse is true for the β-methylene protons whereby H_{3a} absorbs at lower field than H_{3e}. This chemical shift reversal has been noted previously in other compounds[25,26] and its origin has been attributed to an appreciable upfield shift of H_{3e} as a result of electronic polarization favored by the trans coplanar relationship of H_{3e} with the oxygen atom.

It is significant that accurate vicinal coupling constants and chemical shifts determined for benzocycloheptene and 5-oxabenzocycloheptene[6] show trends similar to those reported in Table I. Although small differences do exist between the results for the two series (probably because the seven-membered chair is more puckered than the six-membered chair), the stereodependent effect of oxygen is analogous.

Hence the stereodependence of coupling constants and chemical shifts observed for tetrahydropyran should also persist to a large extent in other pyranoid derivatives, especially carbohydrates for which modified Karplus equations,[3,27,28] ignoring this effect, continue to be used in conformational and stereochemical studies. Our results further demonstrate that factors affecting vicinal coupling constants in heterocyclic compounds are complex and suggest that many attempts to extract quantitative geometrical information must be judged with skepticism.

Thus the individual coupling constants determined for tetrahydropyran constitute a complementary set of fundamental parameters on which rapid qualitative and stereochemical deductions in many heterocyclic compounds can be based. Furthermore, the insight gained through the above discussion provides the necessary quantitative framework on which the limitations of such conclusions can be formulated confidently.

Experimental Section

The VPC analyses and separations were carried out on a Varian Aerograph A90-P3 instrument using a 0.25 in. × 15 ft SE-30 column (A) and a 0.375 in. × 20 ft SE-30 column (B) and helium as carrier gas. Mass spectral analyses were performed on an Hitachi Perkin-Elmer Model RMU-6D instrument operating at 70 and 6 eV.

Routine analytical ^{1}H NMR spectra were recorded on a JEOL C-60H spectrometer operating at 60 MHz in the external lock mode. The low-temperature ^{1}H NMR spectra were obtained at 100 MHz using a JEOL JNM-4H-100 spectrometer. Solutions containing a small quantity of Me_4Si were degassed and sealed. Deuterium decoupling, when required, was effected by means of the JEOL Hetero Spin Decoupler Model JNM-SD-HC.

Temperatures were monitored by means of a JEOL temperature control unit Model JES-VT-3 and determined accurately with a calibrated thermocouple placed inside a solvent-containing dummy NMR tube.

The computer spectral simulations were obtained with a LAOCN-3 program,[29] a CDC CYBER 74 computer, and a CALCOMP plotter at our University Computer Centre.

γ-Tetrahydropyranone-*2,3,5,6-d*$_4$ (3-*d*$_4$). To a solution of 1.5 g of γ-pyranone (2) prepared from commercial chelidonic acid[5] (1) (Aldrich) in 30 ml of D_2O was added 200 mg of Pd/C (5%) catalyst in a flask which was then attached to a compact deuteration apparatus.[6] The reduction with deuterium gas was allowed to proceed for 8 h, after which deuterium gas uptake had ceased. The solution was then filtered on diatomaceous earth, saturated with NaCl, and extracted three times with 30 ml of dichloromethane. The organic solution was then dried over $MgSO_4$ and stripped of its solvent. About 1.2 g (80%) of product was isolated on column B; it showed a VPC retention time identical with that of nondeuterated γ-tetrahydropyranone.

The product was further characterized by its 100-MHz, deuterium decoupled, ^{1}H NMR spectrum in $CDCl_3$: doublet (3.6 Hz, 2 H) at 2.49 ppm and doublet (3.6 Hz, 2 H) at 3.97 ppm. The isotopic composition obtained from a mass spectrum at 6 eV is d_6 = 3%, d_5 = 11%, d_4 = 75%, d_3 = 9%, d_2 = 2%.

γ-Tetrahydropyranone-*2,6-d*$_2$ (3-*d*$_2$). To 100 ml of an aqueous solution of K_2CO_3 (pH 11.0) were added 900 mg of 3-d_4. After being stirred for 48 h, the solution was saturated with NaCl and extracted six times with 25 ml of chloroform. The organic solution was then dried over $MgSO_4$ and the solvent was evaporated. VPC analysis showed a retention time identical with that of 3-d_4. The 100-MHz ^{1}H NMR spectrum in $CDCl_3$ showed a doublet (6.0 Hz, 4 H) at 2.49 ppm and a broadened triplet (6.0 Hz, 2 H) at 3.95 ppm. A mass spectrum showed the following isotopic composition: d_4 = 5%, d_3 = 8%, d_2 = 82%, d_1 = 5%.

γ-Tetrahydropyranol-2,3,4,5,6-d_5 (4-d_5). A solution of 3.90 g of 3-d_4 in 30 ml of anhydrous ether was slowly added to a suspension of 1.65 g of $LiAlD_4$ in 65 ml of ether. After 6 h, the excess deuteride was destroyed with 10% H_2SO_4; the organic phase was then separated and the aqueous phase was extracted with chloroform. The combined organic phases were washed with a $NaHCO_3$ solution and water and then dried over $MgSO_4$. The solvent was then stripped. About 2.68 g (70%) of alcohol was obtained.

The identity of the product was determined to be 4-d_5 through characterization by its tosylate derivative (see below).

γ-Tetrahydropyranol-2,4,6-d_3 (4-d_3). Compound 4-d_3 was obtained from 3-d_2 by a procedure identical with that described above. The identity of the product was confirmed through the identification of its tosylate derivative (see below).

Tetrahydropyran-2,3,4,4,5,6-d_6 (5-d_6). A solution of 1.73 g of alcohol 4-d_5 in 15 ml of anhydrous pyridine was added to a solution of 4.0 g of *p*-toluenesulfonyl chloride (freshly recrystallized from petroleum ether) in 20 ml of pyridine and left standing for 48 h at 0 °C. Water (40 ml) and 55 ml of ether were then added and the organic phase was isolated. The aqueous solution was then extracted five times with 30 ml of ether. The combined ethereal solution was then washed successively with 3 N HCl, a saturated solution of $NaHCO_3$, and water, after which it was dried over $MgSO_4$ and stripped of its ether. The product was recrystallized from absolute ethanol and 3.17 g (90%) of pure tosylate was obtained, mp 55–56 °C (lit.[5] 56 °C).

The pure tosylate was then dissolved in 15 ml of anhydrous tetrahydrofuran and added slowly to a suspension of 700 mg of $LiAlD_4$ in 25 ml of tetrahydrofuran. After 90 h of reflux, 15 ml of water and 10% H_2SO_4 were added to destroy the deuteride left. The solution was then extracted five times with 30 ml of pentane and the organic phase was washed with a solution of $NaHCO_3$ and water. After drying over $MgSO_4$, the solution was concentrated by controlled distillation to about 7 ml. The product (5-d_6) was then obtained pure by preparative VPC using column B at 55 °C. It possessed a retention time equal to that of nondeuterated tetrahydropyran.

The product was then characterized by its ^1H NMR spectrum in carbon disulfide (Figure 1) and its isotopic composition was determined from its mass spectrum at 6 eV: d_8 = 2%, d_7 = 14%, d_6 = 64%, d_5 = 16%, d_4 = 3%.

Tetrahydropyran-2,4,4,6-d_4 (5-d_4). Compound 5-d_4 was prepared from 4-d_3 by a procedure identical with that described above. Purification by VPC provided pure 5-d_4 which showed a retention time identical with that of 5-d_6 and a ^1H NMR spectrum in carbon disulfide in accord with its proposed structure (Figure 2).

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Registry No.—2, 108-97-4; *syn*-3-d_2, 58241-27-3; *anti*-3-d_2, 58241-28-4; *syn*-3-d_4, 58267-59-7; *anti*-3-d_4, 58267-60-0; *syn*-4-d_3, 58241-29-5; *anti*-4-d_3, 58241-30-8; *syn*-4-d_5, 58241-31-9; *anti*-4-d_5, 58267-61-1; *syn*-5-d_4, 58241-32-0; *anti*-5-d_4, 58241-33-1; *syn*-5-d_6, 58267-62-2; *anti*-5-d_6, 58267-63-3; tetrahydropyran, 142-68-7.

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Expoxidation of Olefins with Molecular Oxygen in the Presence of Cobalt Complexes

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The epoxidation of *tert*-butylethylene, norbornylene, and 1,1-dineopentylethylene using molecular oxygen has been studied in the presence of cobalt(III) acetylacetonate. Epoxidations under these conditions show an induction period and other characteristics of a radical chain process, being inhibited by hydroquinone and promoted by azobisisobutyronitrile. A mechanistic scheme is presented in which the reaction between cobalt(III) acetylacetonate and oxygen initiates radical chain processes. β-Peroxyalkyl radicals are the key intermediates in the oxidation. Epoxide formation under these conditions bears a resemblance to the autoxidation of olefins studied by Mayo and co-workers. The olefins in this study were specifically chosen to preclude the formation of hydroperoxides. The results, thus, emphasize the caution which must be exercised in attributing the formation of epoxides solely to hydroperoxide intermediates in metal-catalyzed oxidations.

The oxidation of olefins catalyzed by transition metal complexes has become a subject of renewed interest, provoked by the desire to find evidence for the direct activation of molecular oxygen by metal complexes.[1-3] In most