

Notes

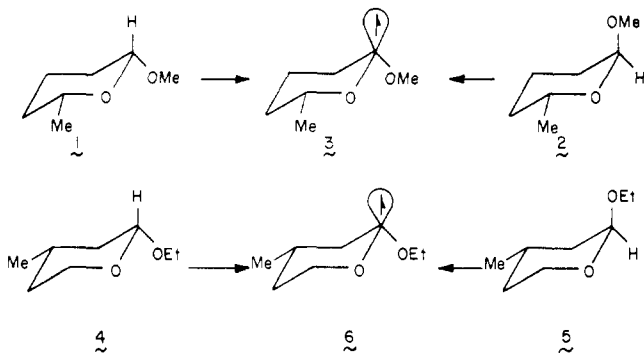
On the Conformation of 2-Alkoxytetrahydropyran-2-yl Radicals¹

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Molecular conformation has a profound effect on the rates of hydrogen atom abstraction from 2-alkoxytetrahydropyrans.^{4,5} For example,⁴ hydrogen abstraction from the conformationally biased⁶⁻⁸ (anameric⁹) 2-methoxy-4-methyltetrahydropyrans by triplet benzophenone at ambient temperature occurs ~8 times as rapidly from the *cis* isomer as from the *trans* isomer. Since both isomers gave the same product distribution it was concluded⁴ that a common free radical was formed.¹⁰ We now report an EPR study which establishes that **1** and **2** yield a common radical even at temperatures as low as -120 °C and that this radical is probably *cis*-2-methoxy-6-methyltetrahydropyran-2-yl (**3**). Similarly, hydrogen abstraction from *cis*- and *trans*-2-ethoxy-4-methyltetrahydropyrans (**4** and **5**, respectively) yields a common

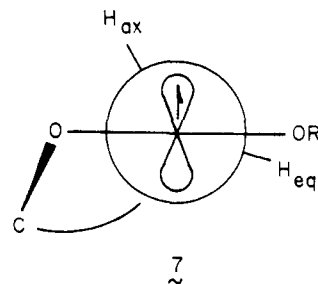


radical which is probably *cis*-2-ethoxy-4-methyltetrahydropyran-2-yl (**6**).

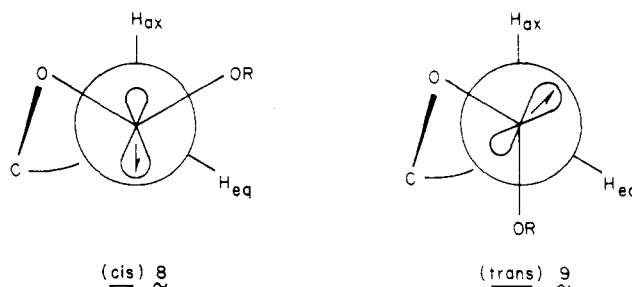
The radicals were prepared by UV photolysis of di-*tert*-butyl peroxide and the alkoxyethyltetrahydropyrans in cyclopropane directly in the cavity of a Varian E-104 EPR spectrometer. The EPR parameters are listed in Table I. They indicate that a "common" radical has been generated from each pair of isomers. The parameters did not vary significantly over a temperature range from -30 to -120 °C, the upper temperature being the limit determined by signal to noise and the lower determined by solidification of the samples. There was no trace of a second radical from **1** or **2**, but **4** and **5** gave a very weak signal which appeared to come from the radical produced by hydrogen abstraction from the methylene of the ethoxy group. For all four substrates the hydrogen atom on C-2 was the most reactive,¹¹ presumably because this C-H bond is weakened by the presence of two adjacent oxygen atoms.

The "simple" explanation for these results is that **3** and **6** are planar at the radical center. Provided the methyl group attached to the pyran ring is able to hold the ring in a pseudochair conformation, then the half-filled orbital will almost eclipse the axial hydrogen attached to C-3, H_{ax} , while the equatorial hydrogen on this carbon, H_{eq} , will lie almost in the

nodal plane. This is indicated in structure **7**, and it means that $a^{H_{ax}}$ will be large and $a^{H_{eq}}$ will be small. This is consistent with the experimental data and is also what has been observed with the cyclohexyl radical.¹³ However, this "simple" explanation ignores the fact that dialkoxyalkyl radicals, whether cyclic or acyclic, are not planar at the radical center.¹⁵⁻¹⁸ This non-



planarity has been most unequivocally demonstrated by measurements of $a^{13C_{\alpha}}$ in such radicals.¹⁵⁻¹⁸ That **3** and **6** are also significantly nonplanar is suggested by the relatively small magnitude of $\Sigma a^{H_{\beta}}$ ($= a^{H_{ax}} + a^{H_{eq}}$) for these two radicals. That is, it is well established that in series of structurally related radicals, $\Sigma a^{H_{\beta}}$ decreases as the deviation of the radical center from planarity increases.¹⁹ Comparison of $\Sigma a^{H_{\beta}}$ for **3** (31.5 G) and **6** (32.85 G) with the value of ~49 G reported^{16,17,20} for their parent, tetrahydropyran-2-yl, therefore suggests that **3** and **6** are nonplanar. Furthermore, because the two β -hydrogens produce very dissimilar hyperfine splittings, it is clear that the exocyclic alkoxy group in **3** and **6** must lie in the pseudoequatorial position, i.e., **8**. The alternative conformation, **9**, with an axial alkoxy can be ruled out because the



semi-occupied orbital would then nearly bisect the $H_{ax}C_3H_{eq}$ angle and this would cause $a^{H_{ax}}$ and $a^{H_{eq}}$ to be of similar magnitude. In addition, since the H_{ax} and H_{eq} hyperfine splittings in **3** and **6** show no measurable temperature dependence, we conclude that the *cis* conformation (**8**) is relatively "stiff" and is not easily distorted.²¹ That is, not only is there no *cis* → *trans* inversion (i.e., **8** ≠ **9**),²² but also **8** does not vibrate appreciably about its preferred conformation.

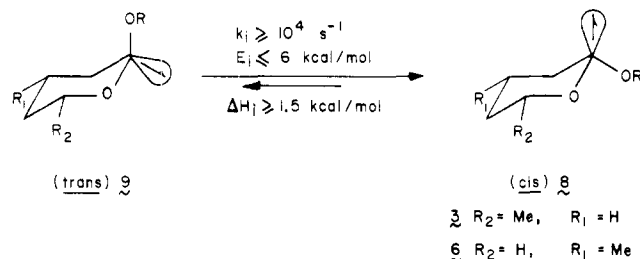
On the other hand, the barrier to the *trans* → *cis* inversion at the **3** and **6** radical centers cannot be large or the *trans* and *cis* parent molecules would yield different radicals. Under optimum experimental conditions we would have been able to detect either of the *trans* radicals in the presence of a 20-fold excess of their *cis* counterparts. If the *trans* radicals are indeed discrete species that invert to the *cis* form, the rate constant for inversion, k_i , must be greater than 10^4 s^{-1} even at a temperature of -120 °C. Since ΔS^\ddagger_i for this inversion will be close to zero, the barrier for the presumed *trans* radical → *cis* radical inversion, E_i , must be less than or equal to ~6 kcal/mol.

Table I. EPR Parameters for Methyl-2-alkoxytetrahydropyran-2-yl Radicals in Cyclopropane at -98°C ^a

radical precursor	<i>g</i>	<i>a</i> ^H (1 H)	<i>a</i> ^H (1 H)	<i>a</i> ^H (3 H)
1	2.0028 ₅	27.32	4.12	0.75
2	2.0028 ₇	27.44	4.14	0.74
4 ^b	2.0029 ₀	28.92	3.99	
5 ^b	2.0028 ₈	28.94	3.86	

^a Hyperfine splittings are in gauss. The number of hydrogens producing each splitting are given in parentheses. ^b A trace of a second radical is also present which appears to have *a*^H(1 H) = 14.5 G, *a*^H(3 H) = 22.5 G, and *g* = 2.0029.

Similarly, our failure to detect a trans radical at the highest temperatures reached allows a lower limit of ~ 1.5 kcal/mol to be placed on ΔH_1 for the cis-trans equilibrium. These ex-



perimentally derived conclusions are fully consistent with the results of a theoretical study of 2-alkoxytetrahydropyran-2-yl radicals.²³

The preference of these radicals for the cis conformation is too large to be entirely attributed to steric factors since these factors probably amount to little more than 0.6 kcal/mol.^{6,7} The conformational preference of the radicals stands in sharp contrast to that of their parent molecules for which the trans structure having the OR group axial is preferred by ca. 0.35–0.74 kcal/mol.^{6,7} Since an equatorial preference is usually observed in monosubstituted cyclohexanes, an axial preference is anomalous and is commonly referred to as the "anomeric effect".^{8,24,25} In the 2-alkoxytetrahydropyrans it arises because of interactions between the lone pairs of the ring oxygen and the exocyclic C₂-O and C₂-H bond orbitals.²⁶ In radicals 3 and 6 the alkoxy group adopts the equatorial position. This allows stabilization²⁷ of the radical center by conjugative delocalization to the p-type lone pair on the ring oxygen.²⁸ That is, in the cis conformation the radical will be stabilized by electron delocalization to the p-type lone pairs of both of the adjacent oxygen atoms, but in the trans conformation only the exocyclic oxygen can provide this stabilization.²⁸ We attribute the more rapid hydrogen abstraction from *cis*- than from *trans*-2-methoxy-4-methyltetrahydropyran⁴ to the fact that the *cis* isomer is thermodynamically less stable than the *trans* and that it can *directly* yield the thermodynamically more stable *cis* radical.

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Registry No.—1, 932-80-9; 2, 7429-28-9; 3, 69239-32-3; 4, 17230-09-0; 5, 17230-10-3; 6, 69239-33-4; di-*tert*-butyl peroxide, 110-05-4.

References and Notes

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- (10) A pair of rapidly interconverting radicals would, of course, yield the same result.
- (11) This conclusion arises from the fact that all of the radicals that could be formed by hydrogen abstraction are sterically unhindered. These radicals will therefore decay by radical-radical reactions which will all occur with the same rate constant since they will all be diffusion controlled.¹² Even if one or more of the radicals formed initially decays by a rapid unimolecular rearrangement, the "secondary" radical it produces will decay by a radical-radical reaction.
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- (22) It must be admitted that an inversion at the radical center which is rapid on the ESR time scale at all temperatures, though highly improbable, cannot be unambiguously ruled out by the present results. Chemical trapping experiments are planned which will, we believe, confirm that all radical-derived products arise entirely from the *cis* conformer.
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- (28) The role that such overlap plays in producing nonplanarity at the radical center has been discussed in ref 17 and 29.
- (29) See, e.g., R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, **95**, 7182 (1973); P. J. Krusic and R. C. Bingham, *ibid.*, **98**, 230 (1976); F. Bernardi, N. D. Epitios, W. Cherry, H. B. Schlegel, M. H. Whangbo, and S. Wolfe, *ibid.*, **98**, 469 (1976). See also F. Bernardi, W. Cherry, S. Shaik, and N. D. Epitios, *ibid.*, **100**, 1352 (1978).

Revised Structures of Pleniradin and Baileyin and Their Bearing on the Biogenesis of Helenanolides¹

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One of us has proposed² a biogenetic scheme for the class of sesquiterpene lactones known as helenanolides which is depicted in Scheme I. It was speculated that the formation of these compounds is initiated by enzyme-mediated anti-Markownikoff cyclization of a *cis*-1(10),*trans*-4,5-germacra-

