NMR, IR, GC, and TLC to an authentic sample.

(b) By a similar procedure, hexamethyldisilane (1.72 g, 11.8 mmol), methyllithium (1.4 M in ether, 0.40 mL, 0.56 mmol), and pyridine *N*-oxide (1.02 g, 10.7 mmol) were reacted in HMPT (15.0 mL). After being stirred for 24 h, the mixture was worked up and chromatographed as described above. Short-path distillation of the major fraction gave pyridine (0.694 g, 82%).

(c) Methyllithium (1.4 M in ether, 1.8 mL, 2.5 mmol) was added slowly to a solution of bis(trimethylsilyl) peroxide[7] (0.453 g, 2.54 mmol) in ether (1.0 mL) at 0 °C. After the mixture was stirred for 1 h, hexamethyldisilane (0.370 g, 2.53 mmol) and HMPT (2.0 mL) were added at 0 °C. The solution was stirred for an additional hour, and pyridine *N*-oxide (0.201 g, 2.11 mmol) in HMPT (1.0 mL) was injected. The solution was stirred at room temperature for 8 h and was quenched as described above. It was worked up and chromatographed as in a. Pyridine (0.148 g, 89%) was obtained.

***N*-Hydroxypiperidine Trimethylsilyl Ether (5).** Tetra-*n*-butylammonium fluoride was dried[15] and weighed (0.235 g). THF (5.0 mL) and hexamethyldisilane (0.132 g, 0.899 mmol) were added at −78 °C. The dry ice bath was removed, and the brown solution was stirred for 20 min after it had warmed to room temperature. *N*-Hydroxypiperidine (Alfa, 67.9 mg, 0.671 mmol) in THF (0.750 mL) was added at 0 °C to the above solution. The ice bath was removed, and the solution was stirred at room temperature for 3 h. The reaction mixture gave two spots on TLC (ethyl acetate as eluent): R_f 0.76 (faint, compound **5**); R_f 0.13 (dark, *N*-hydroxypiperidine). It was dissolved in ether and washed twice with a saturated solution of sodium bicarbonate, once with water, and once with brine. The ether solution was dried ($MgSO_4$), and the solvent was removed. GC analysis indicated that **5** was obtained in 1.4% yield and that 94% of the starting material *N*-hydroxypiperidine was recovered. Commercially available *N*-hydroxypiperidine and pure compound **5**,[17] prepared by reaction of *N*-hydroxypiperidine with chlorotrimethylsilane in triethylamine, were used as references.

Acknowledgment. We are grateful to the donors of The Petroleum Research Fund, administrated by the American Chemical Society, for partial support of this research. This project was also supported in part by BRSG Grant S07 RR7041, awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health.

Registry No. **5**, 94070-51-6; MeLi, 917-54-4; pyridine *N*-oxide, 694-59-7; pyridine, 110-86-1; hexamethyldisilane, 1450-14-2; tetrabutylammonium fluoride, 429-41-4; *N*-hydroxypiperidine, 4801-58-5.

(17) Although compound **5** can be purified by flash column chromatography on silica gel, it hydrolyzes readily when left on silica gel for longer periods of time.

Anomeric Effect in Hydrogen Abstraction Reactions of Conformationally Fixed 2-Alkoxytetrahydropyrans

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One aspect of the anomeric effect[2] is the preference for abstraction of axial hydrogens over equatorial hydrogens in oxygen heterocycles. In our previous work,[3,4] we found that the cis isomers of 2-methoxy-4-methyltetrahydropyran (*cis*-**1**) and 2-methoxy-6-methyltetrahydropyran (*cis*-**2**) were more reactive than the trans isomers by factors of 8 and 10, respectively, toward photochemical hydrogen atom abstraction. This preference can be explained[3] in terms of the anomeric effect in that the more easily cleaved C–H bond is anti-periplanar to a nonbonding electron pair on the ring oxygen. The exocyclic methoxy group adds similarly to the reactivity of both isomers.

Table I. Relative Rates of Hydrogen Atom Abstraction

compd	K_{cis}/K_{trans}	uncertainty range
1[a]	8.0	6.6–9.4
2[b]	10.0	nd[c]
3	16.0	13–19
4	10.6	9.0–12.7
5	49	28–∞
6	36	24–70

[a] Reference 3. [b] Reference 4. [c] Not determined.

Beckwith and Easton[5] have found a similar stereoelectronic effect in reactions of 1,3-dioxanes, and Malatesta and Ingold[6] have studied a variety of cyclic, bicyclic, and tricyclic ethers. The latter authors could explain their rates in terms of similar overlap, and in rigid systems where such overlap was not possible, hydrogen abstraction was not observed, even in the presence of three neighboring oxygens. Descotes and co-workers found similar preferences in dimethoxytetrahydropyrans[7] and carbohydrate derivatives.[8] The structure[9] and theoretical aspects[10] of the resulting radicals have also been studied. Griller et al.[11] have found the same effect in amines.

Although the relative reactivities of cis and trans isomers of **1** and **2** demonstrate the preference for axial hydrogen abstraction, they may not give a quantitative measure of the effect because a single methyl group may not be enough to keep the compounds in a single conformation. Thus, the cis isomers might spend some of their time in the less reactive diaxial conformation, while the trans isomers might derive some of their reactivity from the minor alternative chair conformation. This paper describes our results on conformationally fixed 2-alkoxytetrahydropyrans.

Cis and trans isomers of 2-methoxy-*cis*-4,6-dimethyltetrahydropyran (**3**), 6-*tert*-butyl-2-methoxytetrahydropyran (**5**), and 2-isobutoxy-6-*tert*-butyltetrahydropyran (**6**) were available from a previous study.[12] 2-Ethoxy-*cis*-4,6-dimethyltetrahydropan (**4**) was prepared by alkoxy exchange from **3**. These compounds should be conformationally fixed[13] and provide a quantitative measure of

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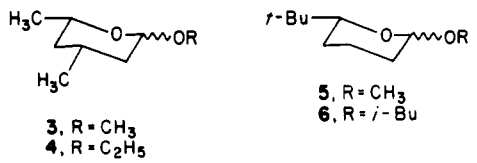


3, R = CH_3
4, R = C_2H_5

5, R = CH_3
6, R = i-Bu

the relative reactivity of axial and equatorial hydrogens. Cis/trans mixtures were irradiated in benzene, using benzophenone as initiator. The relative reactivities are given in Table I and were calculated by using eq 1. The

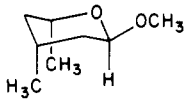
$$k_{cis}/k_{trans} = \ln (cis/cis_0)/\ln (trans/trans_0) \quad (1)$$

large and lopsided uncertainty ranges are due to the fact that this function is very sensitive to small changes in the concentration of trans, since the denominator is almost zero.

The first thing to note from Table I is that the conformationally fixed compounds (3–6) show higher ratios than do 1 and 2. The presence of ca. 3% alternative conformations in 1 and 2 would be sufficient "leakage" to convert a ratio of 13 (the average for compounds 3 and 4) into a ratio of 9 (the average for 1 and 2). It is difficult to estimate the amount of alternative conformation. Although ΔG values have been calculated for monosubstituted tetrahydropyrans,[14] the values for 1,3-diaxial interactions are not available. However, the *possibility* of 3% alternative conformation seems reasonable for 1 and 2.[15] More "leakage" would be expected in 1, since a 4-methyl has a smaller ΔG value than a 6-methyl,[14c] and indeed, 1 has the lowest ratio.

Compounds 5 and 6, with an equatorial *tert*-butyl group, showed similar ratios, but considerably higher than the other compounds. Although excited-state rate constants were not determined, the reactions proceeded at similar rates. If you assume the same lifetime for benzophenone triplet, this suggests that the equatorial hydrogens are less reactive, rather than that the axial hydrogens are more reactive.

It is tempting to attribute the difference to "leakage" from alternative conformations in the dimethyl series, in spite of the large equilibrium constants.[13] This would require that the alternative conformation in *trans*-3 have a much higher rate constant than the major conformation.



Two factors appear to be important in determining the rate of this minor conformation. The first is steric hindrance to the approach of the benzophenone triplet. This would tend to slow down the reaction. The second is steric acceleration due to the relief of two 1,3-diaxial methyl–hydrogen interactions when the anomeric hydrogen is removed.

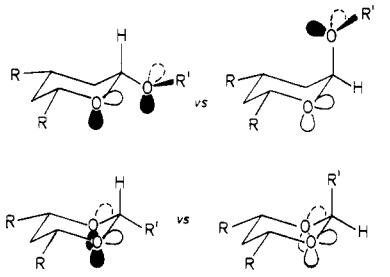
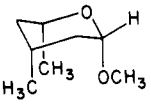


Figure 1. Stabilizing lone pairs in 2-alkoxytetrahydropyrans and 1,3-dioxanes (lone pairs antiperiplanar to reacting C–H bonds shown in black).

Since hydrogen abstraction has a very low activation energy,[16] it should have an "early" transition state, and the former effect should predominate, and this minor conformation would probably react more slowly than the major one. However, a convincing argument can be made even without this assumption of an early transition state. Even taking credit for the entire 2.40 kcal/mol assigned[13] to the sum of the two 1,3-diaxial interactions being relieved, and adding in a factor of 16 (in an iterative fashion) due to the anomeric effect on hydrogen abstraction while ignoring the steric hindrance to benzophenone approach, leads to a "worst case" possibility that the minor conformer is 870 times as reactive. Still only 0.6% of the reaction of the trans isomer could come from the minor conformation, because of the extremely low concentration present.[13]

In the minor conformation of *cis*-3, an equatorial hydrogen is being removed. Thus, relief of 1,3-diaxial interactions (4.4 kcal/mol[13]) would not occur until after hydrogen abstraction was essentially complete, presumably after the "early" transition state.



Also, such relief results in a loss of the favorable anomeric effect (1.0 kcal/mol[13]). Even allowing the full 3.4 kcal/mol factor here, but applying iteratively an unfavorable factor of 16 for equatorial hydrogen abstraction, leads to the conclusion that less than 0.013% of the reaction of the cis isomer comes from the minor conformation because of the large population difference.

Thus, "leakage" does not appear to be a factor in the dimethyl series. Although conformational energies are not available for the *tert*-butyl series, such leakage apparently is not a factor there either, since the reactivity ratio is higher.

Three other possible explanations come to mind. The first is that the *tert*-butyl group hinders equatorial approach of the benzophenone triplet to the trans isomer. This seems unlikely in a 1,3-diequatorial system. The second is that the ring is distorted from the chair conformation,[17] although it seems this would be more likely to lower the reactivity of an axial hydrogen by disrupting the anomeric stabilization due to the ring oxygen. Finally, it is possible that the orientation of the exocyclic alkoxy group is somehow altered by the *tert*-butyl group. If this were to happen, overlap of the C–H bond with a non-

(13) *cis*-3 for example, should prefer the all equatorial conformation by approximately 7.1 kcal/mol. The alternative conformation has a 1,3-diaxial interaction of two methyl groups (3.7 kcal/mol),[14a] two methyl methoxy 1,3-diaxial interactions (2.2 kcal/mol each, using methyl hydroxyl as a model[14a]), and an offsetting negative anomeric effect (1.0 kcal/mol). This leads to an equilibrium constant between the two conformations of 1.4×10^5. Similarly, the trans isomer should favor the conformation with the two methyls equatorial by the same amount, since the alternative conformation has the 1,3-diaxial interaction of the two methyls, a positive anomeric effect, and two different types of methyl–hydrogen interactions with the anomeric hydrogen (worth 1.43 and 0.97 kcal/mol[14c]).

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bonding orbital on this oxygen would be destroyed and stabilization due to the exo-anomeric effect would be lost. An interesting test of this possibility would be to look at the 4-*tert*-butyl isomers, where the *tert*-butyl group would be slightly farther away.[18]

It is also of interest to compare the reactivity ratios found in our 2-alkoxytetrahydropyrans with those found in 1,3-dioxanes.[5] In the former case, in going from axial hydrogen to equatorial hydrogen, the molecule loses only the stabilization of one oxygen lone pair,[19] on the ring oxygen (see Figure 1). The exo-anomeric stabilization is still available. On the other hand, a similar change in the 1,3-dioxanes causes the loss of stabilization from both oxygens, since they are both in the ring. Nevertheless, the ratios in the 1,3-dioxanes (ca. 11), using *tert*-butoxyl radical as abstractor, are similar to our ratios for the systems other than **5** and **6**. This appears to be due to the *tert*-butoxyl system being less selective than triplet ketone. Thus, 2-methoxy-6-methyltetrahydropyran (**2**) gave a cis/trans reactivity ratio of 10 using acetophenone at room temperature[4] and a ratio of only 4 using di-*tert*-butyl peroxide at −40 °C.[6]

In conclusion, we feel that the best value for the reactivity ratio between axial and equatorial hydrogens is 10–16, and the dimethyl substituents are best for locking the ring in an undistorted conformation. The previous values, particularly for compound **1**, were too low, presumably due to conformational flexibility. The *tert*-butyl results appear to be anomalous, and the use of this substituent for conformational locking is risky.

Experimental Section

Compounds **3**, **5**, and **6** were available from a previous study.[12] Compound **4** was prepared from **3** by alkoxy exchange according to the method of Eliel and Giza.[14b] A typical irradiation is described below. In the GC analyses for the dimethyl series, tridecane was used as an internal standard and a 3 mm o.d. × 3.5 m column of 5% Carbowax 20M on 60/80 mesh Chromosorb W (AW DCMS) was used. For the *tert*-butyl compounds, pentadecane was the internal standard and a 3 mm o.d. × 2 m column of 5% QF-1 on 80/100 Chromosorb W AW was used. Calculations were based on the averages of at least three injections for each sample. In most cases, replicate analyses were within 0.5% of the mean, although occasionally 1% variations occurred. Uncertainty ranges were calculated on a "worst case" basis. Thus, extreme values for all four terms in eq 1, based on the observed variations, were used to maximize and minimize the function.

Photodegradation of *cis*- and *trans*-6-*tert*-Butyl-2-methoxytetrahydropyran (5). A solution of 25.2 mg of **5** (33% cis), 29.3 mg of benzophenone, and 11.5 mg of pentadecane in 4 mL of spectral grade benzene was placed in a Pyrex test tube. The sample was sealed with a rubber septum, degassed by three freeze–pump–thaw cycles, and the headspace filled with nitrogen. After analysis, the sample was irradiated with a 450-W high-pressure Xenon lamp with stirring for 50 min and, after further analysis, for an additional 40 min at which time consumption of the cis isomer was 76%, while only 1% of the trans isomer was missing. Trans consumption was corrected for a 2.5% yield of trans from cis–trans isomerization. This yield was determined by irradiation of a sample of pure *cis*-**6**. Such correction was not applied to compounds **3** and **4**, since such isomerization was shown previously[4] to occur largely through abstraction from C-6, and in the dimethyl series, this would produce new diastereomers. Indeed, small additional peaks showed up at reasonable positions in the gas chromatograms.

Acknowledgment. R.D.M. would like to thank the Japan Society for the Promotion of Science for a fellowship to allow him to carry out this research at IMS.

Registry No. *cis*-**3**, 79297-69-1; *trans*-**3**, 79233-93-5; *cis*-**4**, 94110-47-1; *trans*-**4**, 94160-55-1; *cis*-**5**, 79233-92-4; *trans*-**5**, 79233-91-3; *cis*-**6**, 16822-20-1; *trans*-**6**, 16831-17-7; benzophenone, 119-61-9.

(18) Jeffrey, G. A. in ref 2a, p 50.

(19) We continue our practice of using hybrid orbitals on oxygen, despite photoelectron spectroscopic results showing two different ionization potentials.[20] Although consideration of p- and s-type orbitals may be useful for explaining the energetics of ionization, which involves primarily the HOMO, we feel that consideration of hybrids is a convenient device which may take into account stabilizing factors from more than one MO in the transition states leading to our radicals.

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Unusual Rearrangement and Eliminative Cleavage of a Tetrachloronorbornenecarboxamide[1]

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In connection with a study requiring 2,2-disubstituted 7-methylenenorbornanes, we prepared the tetrachlorodimethoxy endo carboxamide **1**. Our attempts to relate **1** to the corresponding carboxylic acid have led to a base-promoted transformation of unusual complexity and extent, which we now report. Depending on the reaction conditions, **1** is converted either to **5** or to **8** or to a mixture of **5** and **8** (Scheme I). The tricyclic α'-alkoxy lactam **5** is concluded to be a reversibly formed side product in the ultimate transformation of **1** to **8** by ethanolic hydroxide because the ratio of **5** to **8** diminishes with time under the conditions shown and because of the separately observed conversion of isolated **5** into **8** by ethanolic hydroxide.

To account for the first stage of this transformation, the production of **5**, we have postulated the mechanism shown in Scheme II and formulated the exchange **3** → **5** as proceeding through a base-promoted elimination leading to a strained intermediate, **4**. α'-Alkoxy lactams as a class are known[2-4] and, among other synthetic routes, have been shown to result from the corresponding lactamols by acid-catalyzed treatment with alcohols.[3] Such a transformation under acidic conditions may proceed mechanistically through a lactamol's ring-chain tautomer, the keto amide.[3,4] However, our alkaline conditions would seem to offer little opportunity for exchanging α' substituents by opening and reclosing the lactam once it has been established, and the inertness of the corresponding exo carboxamide toward base argues an initiatory role for lactam formation in **1**. One such alkaline mechanism would account for **5** by alkoxide attack on **3** to give **6**, which might then add alkoxide (exo) and reclose. This sequence would avoid "violating" Bredt's rule[5] but appears incompatible with the observed conversion of **5** to **8** by hydroxide in that it predicts extensive saponification and loss of

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