Preparation of the BSA–30 Conjugate. A solution of compound **25** (75 mg) in MeOH (10 mL) containing hydrazine (3 mL) was refluxed for 2.5 h, concentrated to a dry residue, redissolved in 5 mL of water, and applied on a column of Bio Gel P2 (200–400 mesh) equilibrated and eluted with water. Fractions (8 mL) containing the product (fraction nos. 59–69) were pooled and concentrated to a dry residue (75 mg).

The above product (10.4 mg, 10 μmol) in dry DMF (1 mL) was cooled to −30 °C. A solution of hydrochloric acid (40 μmol) in DMF (100 μL) and *tert*-butyl nitrite (15 μmol) in DMF (100 μL) was added. After 60 min at temperatures between −20 and −30 °C, a solution of sulfamic acid (5 μmol) in DMF (100 μL) was added, and the solution was maintained at −30 °C for 10 min. BSA (13 mg) in sodium borate–$KHCO_3$ buffer (pH 9.0, 5 mL) was cooled in an ice bath, and the above DMF reaction mixture was added dropwise. After gentle shaking at 4 °C for 16 h, the solution was diluted (to 10 mL) and dialyzed against deionized water for 3 days; the deionized water was replaced every 12 h. The solution was lyophilized, and the residue was dissolved in a buffer (pH 6.5, 2 mL) containing sodium cacodylate (200 μmol), CMP-NeuAc (37 mg), triton (20 μg), and Galβ1,4GlcNAc α2,6-sialyltransferase (500 mU) and incubated for 24 h. The reaction mixture was then applied on a column of sephadex G-50 (fine) equilibrated and eluted with water. The fractions containing the product (UV absorption at 220 nm) were pooled and lyophilized (7.2 mg).

Acknowledgment. The authors thank Dr. T. Fukunaga for valuable discussions, Dr. G. Reddy and Mr. F. Davidson for recording NMR spectra, and Mrs. E. Matthews for recording optical rotation.

Supplementary Material Available: Listings of the NMR data for the mono- and trisaccharide intermediates and the tri- and pentasaccharides, the 1D and 2D NOESY proton spectra of the pentasaccharides, and the NOE buildup curve for a pentasaccharide (26 pages). Ordering information is given on any current masthead page.

Conformation and Reactivity of Anomeric Radicals

Scott D. Rychnovsky,*[1] Jay P. Powers, and Teresa J. LePage[2]

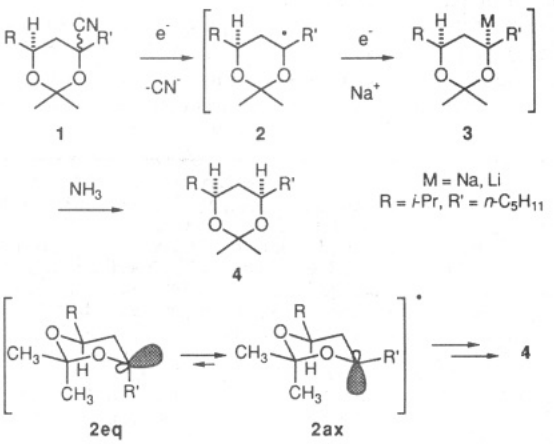
Contribution from the Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received April 22, 1992*

Abstract: Reductive decyanations of 2-cyanotetrahydropyran derivatives with sodium in ammonia show a strong preference for axial protonation. For the 2-cyanotetrahydropyran **6**, the selectivity is 119:1, and for the cyanooxadecalin **13**, which is sterically biased against axial hydrogen introduction, the ratio is 1.78:1. These stereochemical outcomes and ab initio calculations of the intermediate radical conformations are consistent with the following mechanistic model: reductive decyanation proceeds through the pyramidal, axial radical to give the configurationally stable, contrathermodynamic axial anion which is protonated with retention of configuration. Anomeric carbohydrate radicals have been described as nearly planar on the basis of electron spin resonance (ESR) spectroscopic studies, and that observation appears to be inconsistent with this model. Ab initio calculations show that though the pyramidalization at the radical center is small, the potential surface for pyramidalization is very asymmetric. Examination of the energy surface for the 2-tetrahydropyranyl radical **17** shows a 3.46 kcal/mol energy difference at UMP2/6-31G*//6-31G* on going from the axial ($\theta = -139.5°$) to the equatorial ($\theta = 149.5°$) conformer. The UMP2/6-31G*//6-31G* calculated energy differences between axial and equatorial conformers for tetrahydropyranyl radical **18** and oxadecalinyl radical **22** are qualitatively consistent with the experimentally observed reductive decyanation product ratios. The semiempirical methods AM1 and PM3 poorly model anomeric stabilization in radicals and are not useful for predicting radical conformations. Calculations show that introduction of an electron-withdrawing substituent, fluorine, in the equatorial 3-position of the tetrahydropyran radical **21c** flattens the radical center and makes the boat conformation **21b** more accessible, in good agreement with the substituent effects found in ESR studies of carbohydrate radicals.

Introduction

Radical intermediates play an ever increasing role in modern synthetic chemistry, and the stereochemistry of radical reactions is an area of considerable interest.[3] Substituted 2-tetrahydropyranyl radicals are particularly intriguing because the anisotropic interactions of the radical center with the adjacent oxygen atom dominate the stereochemical outcome of these radical reactions. These 2-tetrahydropyranyl radicals are important intermediates in a number of stereoselective transformations including radical-mediated synthesis of C-glycosides,[4] preparation of 2-deoxy-β-glycosides,[5] and synthesis of axial (2-tetrahydropyranyl)lithium[6] and 1-glycosyllithium[7] reagents. In each of these examples axial addition to the chair conformation of an anomeric radical predicts the stereochemical outcome. For example, axial (2-tetrahydropyranyl)lithium reagents are produced by reductive lithiation of 2-(phenylthio)tetrahydropyrans, and the explanation given invokes the greater stability of the intermediate pyramidal axial radicals than of the equatorial radicals.[8] A similar explanation was

Scheme I



(1) Camille and Henry Dreyfus Teacher–Scholar 1990–1995. Alfred P. Sloan Research Fellow 1992–1993.

(2) Address: 3M Center, Building 201-3N-04, St. Paul, MN 55144.

(3) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304.

(4) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980.

(5) (a) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716–8787. (b) Crich, D.; Lim, L. B. L. *Tetrahedron Lett.* **1990**, *31*, 1897–1900.

(6) (a) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6902. (b) Cohen, T.; Lin, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131. (c) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375–377. (d) Verner, E. J.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1072–1073.

(7) (a) Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355–356. (b) Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185–6188.

(8) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161 and references therein.

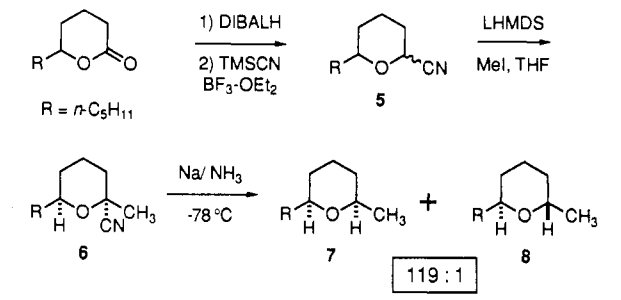
0002-7863/92/1514-8375$03.00/0

originally proposed in the axial selective coupling of anomeric radicals and alkenes to produce C-glycosides.[9] However, ESR studies on an intermediate anomeric radical demonstrated that it is nearly planar and adopts a 3,5-boat conformation.[10] Sterics were proposed to account for the stereoselectivity of the reaction. These two views of anomeric radical geometry appear to be contradictory, and we set out to develop a better understanding of geometries and energetics of anomeric radicals by combining experimental studies with semiempirical and ab initio calculations.

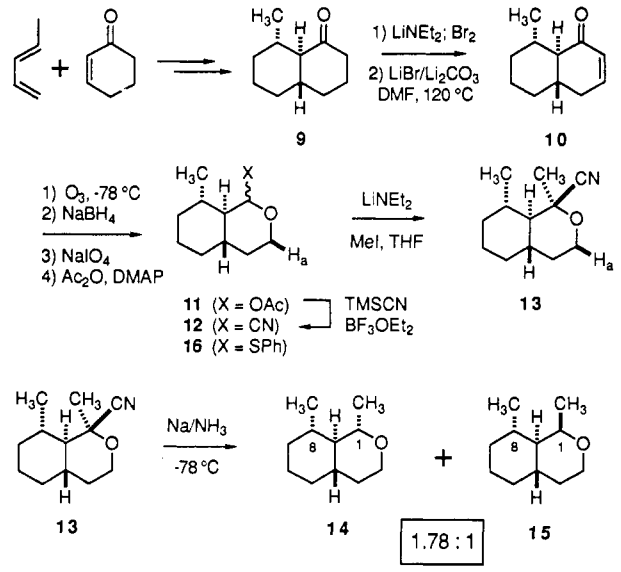
Our own interest in pyranyl radicals was stimulated by the intermediacy of 1,3-dioxan-4-yl radicals in methods we have developed for the stereoselective synthesis of polyol chains (Scheme I).[11,12] For example, in the reduction of cyanohydrin acetonides **1eq** or **1ax** by sodium or lithium in ammonia at −78 °C, initial cleavage of the C–CN bond leads to the α-oxygenated radical **2**. The product stereochemistry is set during the reduction of intermediate radical **2** to alkylsodium or alkyllithium **3**, and subsequent protonation from the axial direction gives acetonide **4** with >99:1 stereoselectivity. According to Cohen's analysis of the closely related reductive lithiation of a 2-(phenylthio)tetrahydropyran,[8] the intermediate radical **2** is nonplanar and exists as a rapidly equilibrating mixture of quasi-axial radical **2ax** and quasi-equatorial radical **2eq**. Preferential stabilization of the axial radical by overlap with the oxygen lone pair and subsequent rapid and nonselective electron transfer[8] generates the axial anion **3**. Compound **3** maintains its configuration until protonation by solvent gives acetonide **4** with retention of stereochemistry. These α-alkoxylithium reagents are known to be configurationally stable at −78 °C,[13] and the same stereochemistry results from reductive lithiation of an analogous cyanohydrin acetonide with lithium di-*tert*-butylbiphenylide in THF at −78 °C followed by protonation. These reductive decyanation reactions provide a powerful tool for stereocontrolled polyol chain synthesis.[11]

In this and other examples of reductions involving α-oxygenated radicals in 6-membered rings, the stereochemical outcome is indirect evidence for the intermediacy of the axial chair radical conformation. Yet ESR experiments seem to indicate that such radicals centers are nearly planar. If they are planar, then the cause of the stereoselectivity on reduction is not obvious and another explanation is needed. Ab initio calculations are particularly well-suited for providing structural and energetic information to clarify such a problem. Carbon centered radicals[14] are well-defined, neutral intermediates whose structure and relative stability can be predicted by ab initio calculations.[15] The structure of α-oxygenated radicals has been investigated a number of times but only on very simple systems at high levels (e.g., hydroxymethyl radical) or on complex systems at very low levels of theory.[16] Given the dramatic advances in computer capabilities in the last decade, the problem seemed ripe for a modern reinvestigation. Ab initio calculations can answer a number of questions about these intermediates. For instance, are anomeric radicals planar or pyramidal? Are the axial and equatorial radicals' minima on the energy surface? Is there an electronic bias favoring the axial radical, and what is it worth? A thorough understanding of α-oxygenated radicals will help to develop their full synthetic potential. We set out to map the energy surface of the 2-pyranyl radical pyramidalization and to determine what level of theory is required to give realistic stereochemical predictions for these synthetically useful reductive decyanations.

Scheme II



Scheme III



The reductive decyanation of cyanohydrin acetonide **1** is very selective, with the cis acetonide **4** being favored over the trans isomer by between 100:1 and 500:1. High selectivity is very useful in a preparative reaction, but the uncertainty in accurately measuring large product ratios and thus energy differences makes it poorly suited to comparison with calculated relative enthalpies of the radical intermediates. Furthermore, small amounts of the minor isomer which might arise from impurities present in the starting material, side reactions, or unusual conformations would compromise the analysis. The ideal product ratio for comparison to calculated relative enthalpies is 1:1, where minor impurities, minor side reactions, and unusual high energy conformations can be safely ignored.

We have investigated the reductive decyanation in two new systems to explore its scope and to provide a more appropriate basis for theoretical analysis. Tetrahydropyran **6** does not have the overwhelming steric bias associated with the axial methyl group in acetonide **1**, but the expected axial protonation still leads to the thermodynamic product. In oxadecalin **13**, the steric interaction between the equatorial methyl group at C8 and the equatorial position at C2 reverses the normal steric bias; now axial protonation leads to the thermodynamically less stable product. MM2 calculations suggest that *trans*-dimethyloxadecalin **15** is more stable than *cis*-dimethyloxadecalin **14** by ~2.0 kcal/mol (vide infra), and the nearly balanced steric and stereoelectronic influences in this system provide a challenging test for stereochemical predictions.

(9) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349–1352.

(10) (a) Dupuis, J.; Giese, B.; Ruegge, D.; Fischer, H.; Korth, H. G.; Sustman, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896–898. (b) Korth, H. G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453–1459. (c) Korth, H. G.; Sustmann, R.; Groeninger, K. S.; Witzel, T.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461–1464. (d) Korth, H. G.; Sustmann, R.; Groeninger, K. S.; Leisung, M.; Giese, B. *J. Org. Chem.* **1988**, *53*, 4364–4369. (e) Korth, H. G.; Sustmann, R.; Giese, B.; Rueckert, B.; Groeninger, K. S. *Chem. Ber.* **1990**, *123*, 1891–1898.

(11) (a) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984. (b) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551. (c) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563.

(12) For a related preparation of *C*-glycosides see: Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6189–6192.

(13) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202. (b) Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011–3014.

(14) For a review see: Kochi, J. K. *Adv. Free-Radical Chem.* **1975**, *5*, 189–317.

(15) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; Chapter 6.

(16) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122–125.

Reductive Decyanations

The tetrahydropyran **6** was prepared from δ-decanolide by the sequence shown in Scheme II. Reduction of the lactone with DIBALH and in situ treatment of the aluminum lactol with TMSCN and $BF_3{\cdot}Et_2O$ gave the 2-cyanopyran **5** in 38% yield as a mixture of anomers. Deprotonation with lithium bis(trimethylsilyl)amide (LHMDS) and alkylation with MeI gave nitrile **6** in 64% yield as a single isomer. Reductive decyanation with sodium metal in NH_3/THF at −78 °C gave a mixture of reduced products **7** and **8** in quantitative yield. Analysis by capillary GC showed a 119:1 mixture of the cis isomer **7** and trans isomer **8**. An authentic sample of the trans isomer **8** was prepared in 87% yield by reductive lithiation[6] of the corresponding 2-(phenylthio)pyran and alkylation with dimethyl sulfate. The stereochemical assignment was based on literature precedent for the reductive lithiation[6] and analysis of the ^1H NMR spectra of the two isomers. The reductive decyanation was repeated three times with similar results;[17] the median product ratio was 119:1 cis to trans, which corresponds to a difference in free energy of 1.92 kcal/mol at −70 °C.

The oxadecalin cyanohydrin **13** was prepared as shown in Scheme III. A Diels–Alder reaction between piperylene and 2-cyclohexenone was catalyzed with $BF_3{\cdot}Et_2O$, and the initially formed cis-fused decalin was epimerized to the trans isomer **9** on treatment with alumina as previously described.[18] The double bond was introduced by bromination of the kinetic enolate with Br_2 and dehydrobromination by treatment with Li_2CO_3/LiBr in hot DMF.[19] The enone **10** was converted to the lactol acetate **11** by ozonolysis, $NaBH_4$ reduction, periodate cleavage of the resulting 1,2-diol, and acylation. The lactol acetate **11** was coupled with TMSCN and $BF_3{\cdot}Et_2O$ to give cyanohydrin **12** in 92% yield as a 10:1 mixture of axial and equatorial nitrile isomers as determined by proton coupling constants. Deprotonation with $LiNEt_2$ and alkylation with MeI gave cyanohydrin **13**, the axial nitrile isomer, in 90% yield. The stereochemistry of **13** was assigned by comparison of the chemical shift of proton H_a (3.77 ppm) with the corresponding proton in cyanohydrins **12**, where the axial nitrile leads to a downfield shift to 3.81 ppm versus 3.45 ppm in the equatorial nitrile isomer.

Reductive decyanation of the cyanooxadecalin **13** with sodium metal in NH_3/THF at −70 °C gave the reduced product as a 1.78:1 mixture of the axial-H isomer **14** and the equatorial-H isomer **15** in quantitative yield. The stereochemistry of the products was assigned by ^1H NMR analysis and synthesis of the minor isomer. The major isomer showed a J_{1-8a} coupling constant of 9.1 Hz, while the minor isomer showed a J_{1-8a} coupling constant of only 4.6 Hz. The former is an axial–axial coupling consistent with structure **14**, while the latter is an axial–equatorial coupling consistent with structure **15**. An authentic sample of the minor isomer **15** was prepared via the (phenylthio)oxadecalin **16**. (Phenylthio)oxadecalin **16** was prepared by treatment of acetate **11** with PhSH and $BF_3{\cdot}Et_2O$ at −78 °C.[6] Reductive lithiation and alkylation with dimethyl sulfate gave the equatorial-H isomer **15** as a single isomer, confirming the ^1H NMR assignment. The 1.78:1 ratio of axial-H **14** and equatorial-H **15** corresponds to a difference in free energy of 0.23 kcal/mol at −70 °C.

Calculated Energies

Methods. The AM1 and PM3 semiempirical NDDO methods with the half-electron formalism were used as part of the MOPAC 6.0 package.[20] Ab initio calculations were performed using the Gaussian 90[21] package on a CRAY X-MP at the Minnesota Supercomputing Center and the SPARTAN[22] package on a Silicon Graphics IRIS 4D-35. Odd-electron species were calculated using unrestricted Hartree–Fock methods (UHF) and UMP2(FC). We had difficulty getting geometry optimizations to converge in these very flexible ring systems when internal coordinates were used. SPARTAN implements a Cartesian optimization algorithm that gave efficient optimization of geometry even for the oxadecalin system.[23]

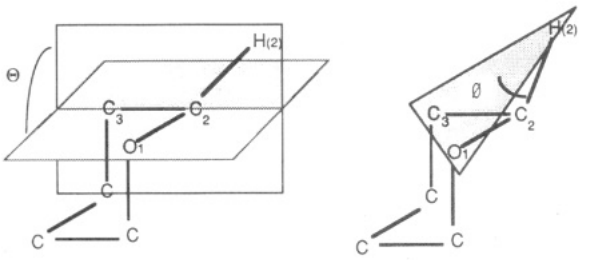


Figure 1. Improper dihedral angle θ is defined by the pyranyl atoms O1–C3–C2–H2. Specifically, θ is the angle between the plane defined by O1–C3–C2 and the plane defined by C3–C2–H2. In the pyranyl radicals, ϕ is the angle formed between the C2–H2 bond and the plane defined by O1–C3–H2.

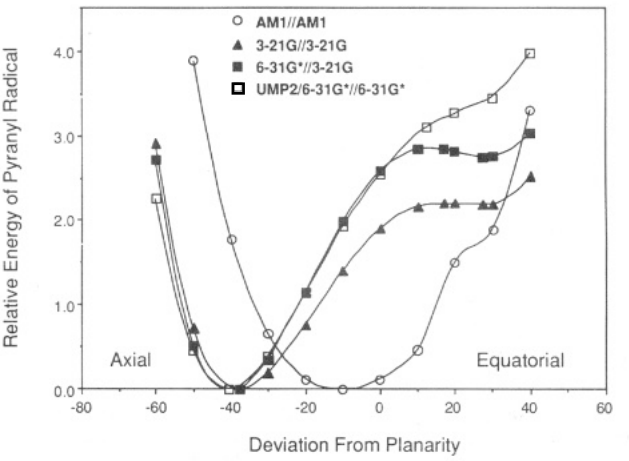


Figure 2. Relative energy of pyranyl radical **17** as a function of pyramidalization. Axial radicals have a negative angle $-(\theta + 180)°$, equatorial radicals have a positive angle $(180 - \theta)°$, and the planar radical has an angle of 0°. See Table II for tabulated data.

2-Tetrahydropyranyl Radicals. We began investigating 2-tetrahydropyranyl radicals with semiempirical AM1 and PM3 calculations using MOPAC.[24] Two different measures of pyramidalization were used in this work: the out-of-plane C–H angle ϕ and the O1–C3–C2–H improper dihedral angle θ. These angles are illustrated in Figure 1. In a planar radical $\phi = 0°$ and $\theta = 180°$, whereas in a tetrahedral radical $\phi \cong 20°$ and $\theta \cong 120°$. The dihedral angle θ was incorporated into the *Z*-matrix and constrained in 10° steps centered around 180°. The energies of the resulting minimized structures using AM1 are plotted against the deviation from planarity of the radical center in Figure 2. AM1 and PM3 calculations both predict a nearly planar 2-tetrahydropyranyl radical (**17**) with the single minimum at $\theta \approx -170°$ toward an axial radical (−10° in the figure). The equatorial radical is not a minimum on either energy surface.

The 2-tetrahydropyranyl radical **17** structure was investigated at the ab initio 3-21G level. The angle θ was constrained as before. The energies of the resulting minimized structure are plotted against the deviation from planarity in Figure 2. The plot of

(17) The ratios for three runs were 114:1, 119:1, and 122:1 by capillary GC analysis.

(18) Das, J.; Kakushima, M.; Valenta, Z.; Jankowski, K.; Luce, R. *Can. J. Chem.* **1984**, *62*, 411–416.

(19) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1965**, *30*, 2942–2947.

(20) Stewart, J. J. P. *MOPAC Version 6.0*; Frank J. Seiler Research Laboratory, United States Air Force Academy; CO 80840.

(21) Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. P. P.; Topiol, S.; Pople, J. A. *Gaussian 90*; Gaussian Inc.: Pittsburgh, PA, 1990.

(22) *SPARTAN© Version 2.0*; Wavefunction Inc.: 18401 Von Karman, #210; Irvine, CA 92715.

(23) Baker, J.; Hehre, W. J. *J. Comput. Chem.* **1991**, *12*, 606–610. Using the NEWZMAT utility to prepare a *Z*-matrix, M. Frisch found that at 3-21G* both oxadecalin radicals converged efficiently with Gaussian 92.

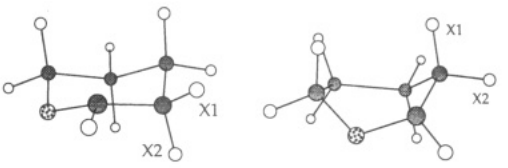
(24) Semi-empirical calculations on radicals were performed using the MOPAC keyword "UHF". The calculation thus performed is not in fact unrestricted Hartree–Fock but a half-electron formalism.

	17eq	17ts	17ax
3-21G//3-21G	2.18	2.20	0
6-31G*//6-31G*	2.70	2.88	0
UMP2/6-31G* //6-31G*	3.46	-----	0
Angles (θ, ø)	149.5, 10.5	167.7, 4.1	-139.5, 14.0

Figure 3. Equatorial and axial minima for the 2-tetrahydropyranyl radical **17** and the transition state interconverting them. The structures and angles reported were calculated at 6-31G*. The relative energies are given in kcal/mol.

	18ax	18eq
3-21G//3-21G	0	2.30
6-31G*//6-31G*	0	3.52
UMP2/6-31G* //6-31G*	0	4.09
Angles (θ, ø)	-139.5, 11.1	149.5, 8.4

Figure 4. Equatorial and axial minima for the 2-methyl-2-tetrahydropyranyl radical **18**. The structures and angles reported are the 6-31G* minima, and the energies are given in kcal/mol.



	21c		21b	
Substitution	E	θ	E	θ
$X_1, X_2 = H$	0.0,	-139.5	3.72,	-139.5
$X_1 = H, X_2 = F$	0.0,	-142.0	5.81,	-139.8
$X_1 = F, X_2 = H$	0.0,	-140.2	0.93,	-144.2

Figure 5. Chair (**21c**) and 2,5-boat (**21b**) minima for the 2-tetrahydropyranyl radical and the corresponding 3-fluoro radicals. The energies reported are UMP2/6-31G*//6-31G*, and the reported angles are from the 6-31G* minima. The relative energies are given in kcal/mol.

energy as a function of pyramidalization angle is quite different from the plot obtained from semiempirical calculations. The 2-tetrahydropyranyl radical **17** is much more pyramidal and now shows both an axial and an equatorial minimum at $\theta = -142°$ (−38°) and $\theta = 153°$ (27°), respectively. The energies of the constrained 2-tetrahydropyranyl radicals were recalculated at 6-31G*//3-21G and are plotted in Figure 2. This larger basis set only serves to accentuate the energy difference between the axial and equatorial radical. The energies of the constrained 2-tetrahydropyranyl radicals were recalculated at UMP2/6-31G*//6-31G* and are plotted in Figure 2. Second-order Møller–Plesset electron correlation does not change the potential around the axial minimum but does increase the energy of the equatorial radical enough so that it is no longer a minimum on the energy surface.

The axial and equatorial radicals were optimized at 3-21G and 6-31G*, and the 6-31G* minima are illustrated in Figure 3. At 3-21G the axial radical is more stable than the equatorial radical by 2.18 kcal/mol, and a transition state was located near the equatorial minima at $\theta = 163°$ that was 0.02 kcal/mol less stable than the equatorial radical, indicating an extremely shallow minimum. At 6-31G* the difference between the axial **17ax** and equatorial **17eq** radicals has increased to 2.70 kcal/mol, and both of them are slightly more pyramidal than at 3-21G. A transition state (**17ts**) was located between the two minima at $\theta = 168°$ that was 0.18 kcal/mol less stable than the equatorial radical. Finally UMP2/6-31G*//6-31G* single-point calculations at the axial and equatorial geometries gave a difference in energy of 3.46 kcal/mol. As the size of the basis set is increased, the 2-pyranyl radical becomes more pyramidal and the energy difference between the axial and equatorial radical increases. Depending on the level of computation, the equatorial conformer of **17** is either a very shallow minimum or an inflection point on the radical pyramidalization surface (Figure 2). We will refer to it as a minimum, though the question remains unresolved.

The reduction of 2-cyanotetrahydropyran **7** proceeds through an intermediate tertiary radical. This system was modeled with the 2-methyl-2-tetrahydropyranyl radicals **18ax** and **18eq**. AM1 calculations found axial and equatorial minima of equal energy with $\theta = \pm 170°$. PM3 calculations found axial and equatorial minima of nearly equal energy with $\theta = \pm 167°$. Ab initio calculations at 3-21G//3-21G and 6-31G*//6-31G* were carried out and the two 6-31G* minima are shown in Figure 4. The axial radical **18ax** is favored over the equatorial radical **18eq** by 2.30 kcal/mol using a 3-21G basis set, 3.52 kcal/mol using a 6-31G* basis set, and 4.09 kcal/mol at UMP2/6-31G*//6-31G*. These represent a modest increase in axial selectivity for the methyl-substituted tetrahydropyran over the unsubstituted system.

Table I. Predicted Relative Energy of Oxadecalin **14** and **15**

method	energy, **14**	energy, **15**	$E_{14} - E_{15}$ (kcal/mol)
MM2	21.21[a]	19.24[a]	1.97
AM1	−88.72[a]	−91.28[a]	2.56
PM3	−77.62[a]	−80.06[a]	2.44
3-21G//3-21G	−500.287 530[b]	−500.291 811[b]	2.69
6-31G*//3-21G	−503.039 487[b]	−503.044 965[b]	3.43

[a] Energy in kcal/mol. [b] Energy in hartrees.

Model Systems for Carbohydrate Radicals. The most extensive study of radical conformations at anomeric positions comes from the work of Giese and his colleagues on carbohydrate radicals.[10] To develop a better understanding of these anomeric carbohydrate radicals, we have examined the chair and $B_{2,5}$ boat conformations of the 2-tetrahydropyranyl radical, **21c** (X_1, X_2 = H) and **21b** (X_1, X_2 = H), respectively, and to model the effects of electron-withdrawing substituents, we have examined the corresponding axial and equatorial 3-fluoro-2-tetrahydropyranyl radicals. The energies of the boat and chair conformations of these radicals at UMP2/6-31G*//6-31G* are given in Figure 5 and Table III. In all cases the chair conformations are preferred, but introduction of the equatorial 3-fluorine (**21c**, where X_1 = F, X_2 = H) stabilizes the boat conformation **21b** (X_1 = F, X_2 = H) by 2.79 kcal/mol relative to the unsubstituted 2-tetrahydropyranyl radical. In contrast, introducing an axial 3-fluorine (**21c**, where X_1 = H, X_2 = F) stabilizes the chair conformation by 2.09 kcal/mol relative to the unsubstituted 2-tetrahydropyranyl radical. For the 2-tetrahydropyranyl radical at UMP2/6-31G*//6-31G*,

Table II. Energy of Constrained Tetrahydropyranyl Radical **17**

deviation from planarity (q)	AM1[a]	PM3[a]	3-21G//3-21G[b]	6-31G*//3-21G[b]	6-31G*//6-31G*[b]	UMP2/6-31G*//6-31G*[b]
axial radical						
−60 (−120)	−32.35	−28.10	−267.896 396	−269.385 569	−269.388 083	−270.188 219
−50 (−130)	−35.94	−31.02	−267.899 858	−269.389 055	−269.391 406	−270.191 085
−40 (−140)	−38.05	−32.70	−267.901 011[c]	−269.389 855[c]	−269.392 255[d]	−270.191 812[d]
−30 (−150)	−39.17	−33.55	−267.900 710	−269.389 323	−269.391 597	−270.191 212
−20 (−160)	−39.69	−33.83	−267.899 797	−269.388 055	−269.390 301	−270.190 003
−10 (−170)	−39.82	−33.87	−267.898 779	−269.386 731	−269.389 016	−270.188 732
0 (180)	−39.70	−33.72	−267.897 985	−269.385 779	−269.388 404	−270.187 753
10 (170)	−39.36	−33.38	−267.897 573	−269.385 357	−269.387 659[e]	−270.186 867[e]
20 (160)	−38.31	−33.11	−267.897 511	−269.385 398	−269.387 760	−270.186 620
30 (150)	−37.93	−32.46	−267.897 519	−269.385 507	−269.387 942	−270.186 309
40 (140)	−36.51	−31.33	−267.896 911	−269.385 065	−269.387 512	−270.185 481
50 (130)	−34.19	−29.42				
equatorial radical						

[a] Energy in kcal/mol. [b] Energy in hartrees. [c] Energy minimum (3-21G*); deviation from planarity = −37.7° (θ = −142.3°). [d] Energy minimum (6-31G*); deviation from planarity = −40.5° (θ = −139.5°). [e] Transition state (6-31G*); deviation from planarity = 12.3° (θ = 167.7°).

Table III. Energy of Axial and Equatorial Radicals

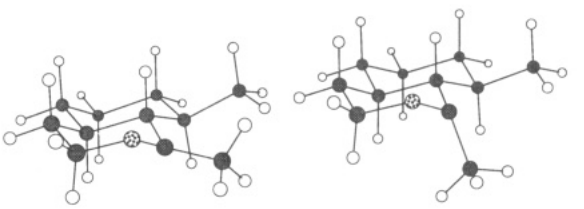
structure	AM1[a]	PM3[a]	3-21G//3-21G[b]	6-31G*//3-21G[b]	6-31G*//6-31G*[b]	UMP2/6-31G*//6-31G*[b]
17eq	*c*	*c*	−267.897 539	−269.385 525	−269.387 943	−270.186 301
17ax	−39.83	−33.90	−267.901 011	−269.389 887	−269.392 255	−270.191 812
17ts			−267.897 504	−269.385 354	−269.387 659	
18ax	−47.05	−43.01	−306.727 951	−308.433 437	−308.435 090	−309.366 845
18eq	−47.01	−43.08	−306.724 280	−308.427 710	−308.429 482	−309.360 326
21c (X_1, X_2)						
(H, H)			−267.901 011	−269.389 887	−269.392 255	−270.191 812
(H, F)			−366.221 516	−368.241 207	−368.244 981	−369.211 438
(F, H)			−366.220 914	−368.240 872	−368.244 012	−369.208 629
21b (X_1, X_2)						
(H, H)			−267.895 200	−269.382 738	−269.385 364	−270.185 878
(H, F)			*c*		−368.236 652	−369.202 180
(F, H)			−366.217 492	−368.235 517	−368.239 492	−369.207 152
22ax	−64.65	−58.16[d]	−499.665 758	−502.437 705	−502.440 557	−504.031 853
22eq	−64.77	−58.16[d]	−499.669 705	−502.439 230	−502.442 239	−504.032 921

[a] Energy in kcal/mol. [b] Energy in hartrees. [c] No local minimum was found. [d] Essentially the same geometry.

the $B_{2,5}$ boat conformation **21b** (X_1, X_2 = H) is 0.26 kcal/mol higher in energy than the previously identified equatorial radical **17eq**.

Oxadecalinyl Radicals. Before attempting to predict the stability of the axial and equatorial radicals in the oxadecalin system, we needed to examine the relative stabilities of the two products, the axial-H isomer **14** and the equatorial-H isomer **15**. The calculated energies of these two isomers were evaluated using a variety of theoretical techniques, and these energies are reported in Table I. The MM2 force field is parameterized for systems of this type and is expected to give the best answer, but the other methods are in remarkably good agreement as all of the calculated energies except that from 6-31G*//3-21G fall within a 0.72 kcal/mol range. As expected, the equatorial-H isomer **15** is the more stable, and the best value is probably between 2.0 and 2.7 kcal/mol.

The relative stability of the axial oxadecalin radical **22ax** and equatorial oxadecalin radical **22eq** were examined by semiempirical and ab initio methods (Figure 6). A preliminary investigation using the AM1 method gave two nearly planar minima on the radical energy surface with the equatorial radical favored by 0.12 kcal/mol. PM3 calculations found only a single minimum with θ = −177.8°. Axial and equatorial minima were located using a 3-21G basis set, and the equatorial radical **22eq** was found to be more stable than the axial radical **22ax** by 2.46 kcal/mol. A 6-31G* single-point calculation at these geometries shows a difference of only 0.95 kcal/mol, favoring the equatorial radical. The Cartesian geometry optimization and direct UHF-SCF methods in the SPARTAN ab initio program allowed us to locate axial and equatorial 6-31G*//6-31G* minima. These are shown in Figure 6. The equatorial radical **22eq** is now favored over the axial radical **22ax** by 1.05 kcal/mol, showing little relative change from the 6-31G*//3-21G energies. Electron correlation is expected to further stabilize the axial conformation (Figure 2). The UMP2/6-31G*//6-31G* calculations for **22ax** and **22eq** were performed using Gaussian 92, and the results are shown in Figure 6 and Table III.[25] The UMP2/6-31G*//6-31G* energies for **22eq** and **22ax** favor the equatorial conformer by 0.67 kcal/mol.



	22ax	22eq
3-21G//3-21G	2.46	0.0
6-31G*//3-21G	0.95	0.0
6-31G*//6-31G*	1.05	0.0
UMP2/6-31G* //6-31G*	0.67	0.0
Angles (θ, ø)	-145.7, 9.2	142.6, 10.7

Figure 6. Equatorial and axial minima for the oxadecalinyl radical **22**. The structures and angles reported are the 6-31G* minima. The relative energies are reported in kcal/mol.

Discussion

α-Alkoxy Radical Calculations. Previous calculations on the 2-tetrahydropyranyl radical **17** by a simple perturbation approach

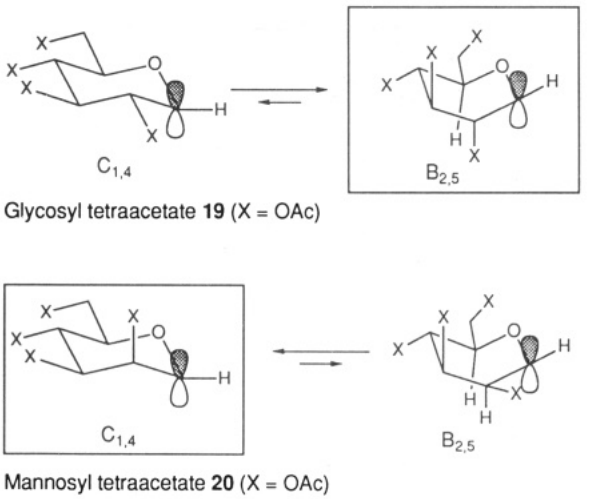
(25) These calculations were not possible using SPARTAN on a Silicon Graphics 4D-35 and were performed by M. Frisch using Gaussian 92 on a Silicon Graphics 4D-320.

found that the axial radical was expected to be more stable than the equatorial radical.[16] Initial calculations using AM1 (Figure 2) or PM3 predict a nearly symmetric potential for radical **17** centered around an essentially planar radical. When ab initio methods are used, the results are quite different. The 3-21G potential for the radical **17** is clearly asymmetric with an axial minimum at $\theta = -142°$ and a very shallow equatorial minimum at $\theta = 153°$. A distinct double minimum is apparent in the 6-31G*//3-21G potential (Figure 2). The 6-31G* axial **17ax** and equatorial **17eq** minima are shown in Figure 2. At UMP2/6-31G*//6-31G*, the difference in energy between the axial and equatorial radicals has increased to 3.46 kcal/mol and the equatorial radical is not a minimum on the UMP2 energy surface (Figures 2 and 3). The asymmetric shape of the inversion potential for this radical is qualitatively well-described at 3-21G, although the difference in energy between the axial and equatorial radical almost doubles on going to higher calculational levels. The best predicted structure for tetrahydropyranyl radical **17** is nonplanar with the axial radical favored over the equatorial radical by ~3 kcal/mol. Semiempirical methods predict no anomeric stabilization for pyranyl radical **17**—apparently the model does not reproduce anomeric effects.

Is the conformation of these radicals dominated by steric or electronic effects? The more stable conformation of the 2-tetrahydropyranyl radical, **17ax**, has an equatorial hydrogen at the anomeric position, whereas the less stable conformation, **17eq**, has an axial hydrogen at the anomeric position, and steric interactions alone predict that the **17ax** should be the more stable conformation. Steric interactions also predict that **18ax** with an equatorial methyl group should be more stable than **18eq** with an axial methyl group, as observed in our calculations. However, the magnitude of the energy differences is not at all what one would predict based on a purely steric model. At UMP2/6-31G*//6-31G*, the increased preference for an equatorial substituent at the anomeric position on going from a hydrogen in compound **17** to a much larger methyl substituent in compound **18** is only 0.63 kcal/mol, which is only a small fraction of the overall energy difference between conformers. For comparison, the pseudo-*A*-value for a methyl group at the 2-position of a tetrahydropyran using MM2 is ca. 2.6 kcal/mol. Although steric interactions clearly play a role, electronic interactions are responsible for the large conformational preference for axial radicals in compounds **17** and **18**.

How far can calculations be trusted to predict the structure and energy of α-alkoxy radicals? There is little direct information about the 2-tetrahydropyranyl radical structure and energy. The ESR spectrum of tetrahydropyranyl **17** has been interpreted as due to a slightly pyramidal radical undergoing rapid chair–chair interconversion.[26] Hydrogen abstraction to form 2-alkoxy-2-tetrahydropyranyl radicals shows a large kinetic anomeric effect,[27] but the 2-alkoxy-2-tetrahydropyranyl radicals are more pyramidal than the simple tetrahydropyranyl radical **17**,[28] and the influence of a second oxygen on the radical center makes comparison with the present calculations problematic.

A much more thoroughly studied system is the hydroxymethyl radical, which has been examined by ESR spectroscopy[29] and ab initio calculations.[30] Analysis of the ESR hyperfine coupling constant $a(^{13}C)$ and $a_\alpha(H)$ using an INDO simulation suggests a slightly pyramidal structure ($\phi = 4°$).[26c] The optimized 6-31G* geometry has a more pyramidal structure with $\phi = 11.6°$,[30a] and the optimized geometry at MP2(full)/6-31G* has a more planar structure with $\phi = 9°$.[30c] Substantial uncertainty is associated with pyramidalization angles determined experimentally. Yet accurately calculating the exact degree of pyramidalization when such a shallow potential is present is probably not possible.[31] It appears that the 6-31G* geometries overestimate pyramidalization of these radicals and that introducing electron correlation improves the match with experiment. Yet the exact pyramidalization angle is less important than the shape of the energy surface for predicting the stereochemical behavior of radicals like **17**. Rotation around the HO–CH bond of hydroxymethyl interconverts the two hydrogens on carbon. This rotational barrier and the transition from axial radical **17ax** to equatorial radical **17eq** both involve rotating the oxygen lone pairs out of alignment with the singly occupied orbital, so it is not surprising that the barriers are similar in magnitude. The rotation in hydroxymethyl was shown to have a 4 kcal/mol activation energy by variable-temperature ESR measurements.[29b] This rotational barrier has been calculated at a variety of levels: 2.23 kcal/mol at 3-21G//3-21G, 2.78 kcal/mol at 6-31G*//6-31G*, 4.39 kcal/mol at MP2/6-31G**//6-31G*, and 3.99 kcal/mol at MP3/6-31G**//6-31G*.[30a] This trend closely follows that found for the pyranyl radical in the present work, where the difference in energy between the axial and equatorial radical increases on going from 3-21G//3-21G to UMP2/6-31G*//6-31G*. We can use this trend to predict that UMP3 calculations on the pyranyl radical **17** would narrow the gap between the axial and equatorial conformations and that the best answer is probably between the 6-31G*//6-31G* and the UMP2/6-31G*//6-31G* values. The best calculated value for the hydroxymethyl rotation barrier of 3.99 kcal/mol at MP3/6-31G**/6-31G* is in excellent agreement with the experimental value of 4 kcal/mol, demonstrating that theoretical methods are capable of predicting reasonable energy surfaces for α-alkoxy radicals.



Glycosyl tetraacetate **19** (X = OAc)

Mannosyl tetraacetate **20** (X = OAc)

Figure 7. Conformations of glycosyl tetraacetate (**19**) and mannosyl tetraacetate (**20**) determined by ESR spectroscopic studies (ref 10a).

Modeling Carbohydrate Radical Conformations. The most extensive study of anomeric radical conformations comes from the work of Giese and his colleagues on carbohydrate radicals. They assign a nearly planar $B_{2,5}$ boat conformation by analysis of the ESR spectrum for the 1-tetraacetoxyglucosyl radical **19**,

(26) (a) Hudson, A.; Root, K. D. J. *Tetrahedron* **1969**, *25*, 5311–5317. (b) Beckwith, A. L. J.; Tindal, P. K. *Aust. J. Chem.* **1971**, *24*, 2099–2116. (c) Dobbs, A. J.; Gilbert, B. C.; Norman, R. O. C. *J. Chem. Soc. A* **1971**, 124–135.

(27) (a) Hayday, K.; McKelvey, R. D. *J. Org. Chem.* **1976**, *41*, 2222–2223. (b) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609–614. (c) Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455–1459. (d) McKelvey, R. D.; Iwamura, H. *J. Org. Chem.* **1985**, *50*, 402–404.

(28) (a) Brunton, G.; Ingold, K. U.; Roberts, B. P.; Beckwith, A. L. J.; Krusic, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 3177–3179. (b) Malatesta, V.; McKelvey, R. D.; Babcock, B. W.; Ingold, K. U. *J. Org. Chem.* **1979**, *44*, 1872–1873. (c) McKelvey, R. D.; Sugawara, T.; Iwamura, H. *Magn. Reson. Chem.* **1985**, *23*, 330–334.

(29) (a) Hudson, A. *J. Chem. Soc. A* **1969**, 2513–2514. (b) Krusic, P. J.; Meakin, P.; Jesson, J. P. *J. Phys. Chem.* **1971**, *75*, 3438–3453. (c) Laroff, G. P.; Fessenden, R. W. *J. Chem. Phys.* **1972**, *57*, 5614–5615. (d) Bernhard, W. A.; Horning, T. L.; Mercer, K. R. *J. Chem. Phys.* **1984**, *88*, 1317–1320.

(30) (a) Saebo, S.; Random, L.; Schaefer, H. F. *J. Chem. Phys.* **1983**, *78*, 845–853. (b) Fossey, J.; Sorba, J. *J. Mol. Struct. (THEOCHEM)* **1989**, *186*, 305–319. (c) Curtiss, L. A.; Kock, L. D.; Pople, J. A. *J. Chem. Phys.* **1991**, *95*, 4040–4043.

(31) For example, see the discussion on methylene in Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; pp 194–208.

but the corresponding 1-tetraacetoxymannosyl radical **20** exists in a chair form (Figure 7).[10] The importance of good overlap between the α-alkoxy radical and the 2-acetoxy substituent in controlling conformation has been emphasized and has been attributed to a "quasi-homo-anomeric stabilization".[32] It has recently been shown that only very electronegative groups at the 2-position force an anomeric glucosyl radical to adopt a boat conformation: a 2-acetate or 2-fluoro substituent leads to a $B_{2,5}$ boat conformation, but 2-tosylamido, 2-methyl, and 2-H glucosyl radicals adopt a $C_{1,4}$ chair conformation.[10c] We modeled these conformations by comparing the calculated energies of fluorine-substituted boat and chair 2-tetrahydropyranyl radicals **21c** and **21b** (Figure 5). At UMP2/6-31G*//6-31G*, both of the fluorine-substituted pyranyl radicals and the unsubstituted pyranyl radical prefer the chair conformation, but introducing an equatorial fluorine substituent (**21c**, where X_1 = F, X_2 = H) stabilizes the boat conformation **21b** (X_1 = F, X_2 = H) by 2.79 kcal/mol relative to the unsubstituted system. Introducing an axial fluorine substituent (**21c**, where X_1 = H, X_2 = F) stabilizes the chair conformation by 2.09 kcal/mol relative to the unsubstituted system. Conformations with good orbital overlap between the radical and the carbon–fluorine bond (i.e., **21c** (X_1 = H, X_2 = F) and **21b** (X_1 = F, X_2 = H)) are more stable. This is consistent with the experimentally observed conformations of 2-acetoxy carbohydrate radicals, and it is plausible that the introduction of further electronegative substituents would bias the theoretical model in favor of a $B_{2,5}$ boat conformation.

Pyramidalization angles from ESR analysis are usually reported as the average out-of-plane C–H angle φ, which is a measure of the α-H overlap with the radical center as illustrated in Figure 1. Pyramidalizations reported as angle φ may appear misleadingly small because they vary at about one-third the rate of conventional torsion angles for the same motion. Thus a tetrahedral sp^3 center will have a $\phi \approx 20°$. The pyramidalization of 1-tetraacetoxyglucosyl radical **19** seems smaller when reported as angle $\phi = 3.9°$ than when reported as the corresponding improper dihedral angle $\theta \approx -168°$. Recent ESR studies have shown that the 1-tetraacetoxyglucosyl radical **19** is not typical of less highly substituted tetrahydropyranyl radicals and that the corresponding anomeric 2-deoxyglycosyl radical is much more pyramidal with $\phi = 7.0°$ ($\theta \approx -159°$).[10e] In the 6-31G* structures for the 2-tetrahydropyranyl radicals **21c** and **21b** (Figure 5), the 3-fluoro-substituted tetrahydropyranyl radicals with good radical–fluorine overlap, **21c** (X_1 = H, X_2 = F) and **21b** (X_1 = F, X_2 = H), are 2–4° more planar than corresponding unsubstituted tetrahydropyranyl radicals, in agreement with the observed trend. Carbohydrate radicals carry many electron-withdrawing substituents, and conclusions about carbohydrate ring conformations and radical pyramidalizations should be used with caution in less highly substituted systems.

Reductive Decyanation Reactions. The pyranyl radicals studied herein clearly prefer an axial chair conformation even if pyramidalization is not fully sp^3. Giese has pointed out that the approach of incoming reagents to chair conformation carbohydrate radicals usually occurs from the more hindered axial face as predicted by arguments for stereoelectronic control, presumably due to favorable overlap with the oxygen lone pair in the developing transition state.[4] In our reductive decyanation reactions, the incoming reagent is an electron of negligible size, and so the equilibrium conformation of the radical is expected to dominate the stereoselectivity.

The reductive decyanation of 2-cyanotetrahydropyran **6** gives a 119:1 ratio of axial and equatorial protonated products **7** and **8**, which corresponds to a difference in free energy of 1.92 kcal/mol at −70 °C. The calculated difference in enthalpy for the model intermediates, axial radical **18ax** and equatorial radical **18eq**, is 3.52 kcal/mol at 6-31G*//6-31G* and 4.09 kcal/mol at UMP2/6-31G*//6-31G*. The ab initio minimum values agree with the experimental values qualitatively but not quantitatively. As previously discussed, with a difference in energy of this magnitude other conformations such as boat (e.g., **21b**, where X_1 = H, X_2 = H) and twist boat may become important as precursors to the minor isomer, the precisely defining the origin of all the minor isomer is not possible. These effects would bring the experiment and theory into better agreement, but the general trend favoring the axial radical is clearly evident in the calculations.

How well do various theoretical methods predict steric strain? Comparison of the oxadecalin reduction products **14** and **15** provides some insight into how different calculational methods handle steric strain (Table I). All of the different methods are in reasonable agreement with each other except 6-31G*//3-21G which overestimates the steric strain. This is consistent with what is known about 6-31G* calculations, which have been found to overestimate the gauche-anti conformational preference in butane by 25%.[33] The overweighing of steric factors should be kept in mind when comparing steric and electronic effects using 6-31G* calculations.

The oxadecalin system provides a better quantitative test of calculational methods than the 2-methyltetrahydropyran system because the energies of the intermediate radicals are more nearly balanced and the calculations were performed on the exact system rather than a model. The reductive decyanation of 2-cyanotetrahydropyran **13** gives a 1.78:1 ratio of axial and equatorial protonated products **14** and **15**, which corresponds to a difference in free energy of 0.23 kcal/mol at −70 °C, favoring the axial conformer. Calculations on the axial oxadecalin radical **22ax** and equatorial oxadecalin radical **22eq** predict that the equatorial radical will be more stable than the axial radical by 1.05 kcal/mol at 6-31G*//6-31G*. When electron correlation is included, the energy difference still favors the equatorial radical but by only 0.67 kcal/mol, within 1 kcal/mol of the experimental value. The geometries do not change very much on going from 3-21G to 6-31G*, but the stabilization of the axial radical **22ax** increases by more than 1 kcal/mol relative to the equatorial isomer **22eq**. Only by including correlation does the full magnitude of the axial stabilization become apparent. The AM1 calculations also predict a product ratio close to the experimental value, but this is apparently dumb luck. AM1 makes the same prediction for both the methylpyranyl system and the oxadecalin system (that the axial and equatorial isomers will have equal energies) and gets it right half the time. AM1 should successfully predict the product ratio of any reductive decyanation that gives a 1:1 mixture of isomers, but for more challenging cases ab initio methods which include electron correlation are preferred.

Conclusions

The calculated relative energies of axial and equatorial anomeric radicals are in good qualitative agreement with the stereochemical results of the reductive decyanation reactions reported here and the reductive lithiations previously reported by Cohen.[6,8] These studies lend strong support to the previously proposed mechanistic scheme where the stereochemistry of radical reduction is largely determined by the conformational preference of the anomeric radicals. The apparent contradiction between the stereochemical outcome for these reductions and the ESR results for carbohydrates can be reconciled by the soft potential calculated for radical pyramidalization, shown in Figure 2, and the flattening effect of increasing electronegative substitution, illustrated in Figure 5.

Anomeric radicals are shown by ab initio methods to be pyramidal with a shallow but clearly asymmetric potential. The simple axial 2-tetrahydropyranyl radical **17ax** is predicted to be more stable than the equatorial radical **17eq** by 2.70 kcal/mol at 6-31G*//6-31G* and 3.46 kcal/mol at UMP2/6-31G*//6-31G*. The semiempirical methods AM1 and PM3 poorly model anomeric stabilization in radicals and are not useful for predicting radical conformations. The electron-withdrawing substituents present in anomeric carbohydrate radicals significantly perturb

(32) Korth, H.-G.; Praly, J.-P.; Somsak, L.; Sustmann, R. *Chem. Ber.* **1990**, *123*, 1155–1160.

(33) At HF/6-31G* level, the trans conformer is more stable than the gauche conformer by 0.96 kcal/mol compared to an experimental value of 0.77 kcal/mol: Krishnan, R. *J. Chem. Phys.* **1984**, *91*, 1383–1387.

the radicals' conformational behavior relative to unsubstituted 2-tetrahydropyranyl radicals.

Experimental Section[34]

6-Pentyltetrahydropyran-2-carbonitrile (5). δ-Decanolide (2.0 g, 11.7 mmol, 1.0 equiv) was added to a flame-dried flask with 150 mL of CH_2Cl_2. The solution was cooled to −78 °C, followed by slow addition of 1.0 M DIBALH in cyclohexane (14.3 mL, 14.3 mmol, 1.2 equiv). The solution was stirred for 1 h, followed by the addition of TMSCN (3.13 mL, 23.4 mmol, 2.0 equiv) and $BF_3{\cdot}Et_2O$ (5.77 mL, 46.8 mmol, 4.0 equiv). The mixture was stirred for 30 min and quenched by the addition of 50 mL of saturated $NaHCO_3$. The solution was diluted with 100 mL of 1 M NaOH, extracted (3 × 100 mL of CH_2Cl_2), washed (1 × 100 mL of brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 4% Et_2O/hexanes followed by 8% Et_2O/hexanes) gave 812 mg (4.48 mmol, 38%) of product as a 2.6/1 trans/cis mixture. IR (neat, mixture): 2934, 2862, 1458, 1441, 1379, 1200, 1123, 1089, 1051, 888 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), trans isomer: δ 4.82 (apparent doublet, J = 2.2 Hz, 1 H), 3.70 (m, 1 H), 1.95–1.70 (m, 4 H), 1.70–1.15 (m, 10 H), 0.89 (t, J = 6.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), trans isomer: *C* 118.1; *CH* 74.7, 65.0; CH_2 35.9, 31.8, 30.8, 28.6, 24.9, 22.6, 19.8; CH_3 14.0. MS (EI): m/z 181.1455 (M^+), 163, 158, 152, 138, 124, 82, 55. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 72.72; H, 10.36.

2-Methyl-6-pentyltetrahydropyran-2-carbonitrile (6). Nitrile **5** (831 mg, 4.59 mmol, 1.0 equiv) was dissolved in 30 mL of dry THF in a flame-dried flask. The solution was cooled to −78 °C, followed by the addition of 1.2 M lithium bis(trimethylsilyl)amide (4.6 mL, 5.51 mmol, 1.2 equiv). The solution was stirred for 45 min, followed by the addition of MeI (1.04 mL, 16.8 mmol, 5.0 equiv). The solution was stirred for 30 min, allowed to warm to room temperature (~30 min), and quenched with 10 mL of saturated NH_4Cl. The solution was extracted (2 × 20 mL of Et_2O), washed (1 × 20 mL of saturated $NaHCO_3$, 1 × 20 mL of H_2O), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 6% Et_2O/hexanes) gave exclusively the trans product (575 mg, 2.94 mmol, 64%) as a clear oil. IR (neat): 2990, 2937, 2862, 1457, 1377, 1278, 1213, 1189, 1123, 1101, 1080, 1063, 981 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (dddd, J = 8.8, 6.7, 4.7, 2.9 Hz, 1 H), 1.90–1.75 (m, 3 H), 1.66 (m, 1 H), 1.55 (s, 3 H), 1.54–1.10 (m, 10 H), 0.87 (t, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 120.1, 71.5; *CH* 75.4; CH_2 35.8, 35.7, 31.5, 29.9, 24.7, 22.3, 20.6; CH_3 27.6, 13.7. MS (EI): m/z 195.1628 (M^+), 168, 124, 110, 96, 81, 71, 68, 55, 43. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.78; H, 10.84. Found: C, 73.78; H, 11.02.

***cis*-2-Pentyl-6-methyltetrahydropyran (7).** A solution of nitrile **6** (112 mg, 0.574 mmol, 1.0 equiv) in 400 μL of THF was run down the side of a flask containing a blue solution of sodium (210 mg, 9.1 mmol, 16.0 equiv) in 15 mL of NH_3 at −78 °C. The mixture was stirred at −78 °C for 1 h and quenched with 1 g of solid NH_4Cl, and the NH_3 was allowed to evaporate from an ice bath. The residue was diluted with 30 mL of Et_2O, washed (1 × 30 mL of H_2O), dried ($MgSO_4$), and concentrated from an ice bath under reduced pressure to give the product (99 mg, 0.58 mmol, quantitative) as a clear volatile liquid. GC analysis (by comparison to an authentic sample of the trans compound) showed that the product was a 119/1 cis/trans mixture of isomers. IR (neat): 2931, 2859, 1455, 1369, 1201, 1085, 1053 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.40 (dqd, J = 12.6, 6.6, 1.7 Hz, 1 H), 3.24 (dddd, J = 10.5, 7.3, 4.8, 2.2 Hz, 1 H), 1.78 (m, 1 H), 1.60–1.21 (m, 12 H), 1.16 (d, J = 6.0, 3 H), 1.2–1.1 (m, 1 H), 0.88 (t, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *CH* 77.9, 73.7; CH_2 36.6, 33.4, 31.9, 31.2, 25.3, 23.8, 22.6; CH_3 22.2, 14.0. MS (EI): m/z 170.1684 (M^+), 99, 81, 55. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.78, H, 12.93.

6-Pentyl-2-(phenylthio)tetrahydropyran. δ-Decanolide (4.0 g, 23.5 mmol, 1.0 equiv) was added to a flame-dried flask with 60 mL of CH_2Cl_2. The solution was cooled to −78 °C, followed by addition of 1.0 M DIBALH in cyclohexane (25.9 mL, 25.9 mmol, 1.2 equiv) via a dropping funnel over a period of 5 min. The solution was stirred for 1 h, followed by addition of a mixture of thiophenol (2.9 mL, 28.2 mmol, 1.2 equiv) and $BF_3{\cdot}Et_2O$ (7.22 mL, 58.7 mmol, 2.5 equiv) via cannula. The mixture was stirred for 10 min, and the reaction was quenched by the addition of 35 mL of 5% aqueous NaOH. The mixture was allowed to warm to room temperature and extracted (3 × 100 mL of Et_2O), washed (1 × 50 mL of 1 M NaOH, 1 × 50 mL of brine), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 1% Et_2O/hexanes) gave a 1.5/1 trans/cis mixture of isomers (3.83 g, 14.5 mmol, 62%) as a clear oil. IR (neat, mixture): 3059, 2934, 2859, 1584, 1480, 1456, 1439, 1191, 1115, 1082, 1042, 1024, 740, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), trans isomer: δ 7.48 (m, 2 H), 7.24 (m, 3 H), 5.65 (apparent doublet, J = 4.6 Hz, 1 H), 4.1 (m, 1 H), 2.0–1.2 (m, 14 H), 0.83 (t, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) trans isomer: *C* 136.0; *CH* 130.5, 128.6, 126.3, 85.3, 69.3; CH_2 36.0, 31.7, 31.6, 31.1, 25.1, 22.6, 14.0; CH_3 13.9. MS (CI, CH_4): m/z 263.1468 (M^+), 265, 264, 263. Anal. Calcd for $C_{16}H_{24}OS$: C, 72.68; H, 9.16. Found: C, 72.45; H, 8.94.

***trans*-2-Pentyl-6-methyltetrahydropyran (8).** 6-Pentyl-2-(phenylthio)tetrahydropyran (160 mg, 0.606 mmol, 1.0 equiv) in 400 μL of THF was run down the side of a flask containing 10 mL of a ~0.2 N solution of lithium di-*tert*-butylbiphenylide (~2.0 mmol, 3.3 equiv) at −78 °C. The solution was stirred at −78 °C for 1 h, followed by the addition of Me_2SO_4 (378 μL, 0.40 mmol, 6.6 equiv). The mixture was stirred for 5 min, followed by the addition of 5 mL of saturated NH_4Cl. The solution was allowed to warm to room-temperature (~30 min), extracted (2 × 25 mL of Et_2O), washed (1 × 25 mL of 1.0 M NaOH), dried ($MgSO_4$), and concentrated from an ice bath under reduced pressure. Purification by flash chromatography (SiO_2, 1% CH_2Cl_2/hexanes followed by 5% EtOAc/hexanes) gave 89.9 mg (0.53 mmol, 87%) of product as a clear oil. GC analysis (by comparison to an authentic sample of the cis compound) showed the product was a 52/1 trans/cis mixture of isomers. IR (neat): 2932, 2859, 1460, 1379, 1264, 1202, 1132, 1088, 1041, 1009 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (qdd, J = 6.4, 3.1, 1.8 Hz, 1 H), 3.68 (m, 1 H), 1.67–1.50 (m, 5 H), 1.39–1.18 (m, 9 H), 1.13 (d, J = 6.4 Hz, 3 H), 0.86 (t, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *CH* 71.0, 66.5; CH_2 32.9, 31.8, 31.7, 29.8, 25.5, 22.6, 18.4; CH_3 19.8, 14.0; MS (EI): m/z 170.1670 (M^+), 99, 81, 55. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.40; H, 12.91.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1(2*H*)-naphthalenone (9). 3,4,4aβ,5,8,8aα-Hexahydro-8α-methyl-1(2*H*)-naphthalenone[18] (495 mg, 3.02 mmol) was dissolved in 4 mL of EtOAc and subjected to catalytic hydrogenation (balloon) over $Pd/BaSO_4$ (5% Pd on $BaSO_4$, 30 mg) for 24 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 494 mg (2.97 mmol, 98%) of the product as a clear oil. IR (neat): 2958, 2927, 2856, 1715, 1448, 1373, 1310, 1297, 1260, 1202, 1107, 1085, 1056, 1033, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.37–2.26 (m, 2 H), 2.03 (m, 1 H), 1.78 (m, 1 H), 1.73–1.60 (m, 6 H), 1.44–1.31 (m, 2 H), 1.23–1.05 (m, 2 H), 0.88 (m, 1 H), 0.87 (d, J = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 213.5; *CH* 62.1, 46.0, 30.2; CH_2 43.3, 34.8, 34.3, 33.7, 28.0, 25.3; CH_3 21.0; MS (EI): m/z 166.1353 (M^+), 151, 110, 97, 95, 81, 67, 55, 41. Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.92. Found: C, 79.58; H, 10.97.

2-Bromo-3,4,4aβ,5,6,7,8,8aα-octahydro-8α-methyl-1(2*H*)-naphthalenone. To a solution of diisopropylamine (805 mg, 7.96 mmol, 1.2 equiv) in 25 mL of THF was added *n*-butyllithium in hexanes (3.90 mL, 7.96 mmol, 1.2 equiv) at 0 °C. The solution was stirred for 5 min and then cooled to −78 °C, and a solution of **9** (1.103 g, 6.63 mmol, 1.0 equiv) in 5 mL of THF was added by cannula. After the solution was stirred for 30 min, Br_2 (1.27 g, 7.96 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 min and then poured into 100 mL of 0.5 N HCl and allowed to warm to room temperature. The mixture was extracted (3 × CH_2Cl_2), washed ($NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 4% Et_2O/hexanes) gave the axial (2α) bromide as a clear oil (764 mg, 3.13 mmol, 47%), and the equatorial (2β) bromide (579 mg, 2.37 mmol, 36%) as fine white crystals. **2α-Bromo-3,4,4aβ,5,6,7,8,8aα-octahydro-8α-methyl-1(2*H*)-naphthalenone.** IR (neat): 2982, 2920, 2851, 1713, 1448, 1432, 1369, 1340, 1299, 1206, 1194, 1138, 1084, 1024, 1014 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.31 (dd, J = 3.0, 3.0 Hz, 1 H), 2.77 (dd, J = 10.5, 11.5 Hz, 1 H), 2.27–2.14 (m, 2 H), 1.87 (dddd, J = 14.5, 12, 11.5, 4.5 Hz, 1 H), 1.75–1.58 (m, 4 H), 1.37 (qdd, J = 11.5, 4.5, 3.0 Hz, 1 H), 1.30–1.14 (m, 3 H), 1.02–0.94 (m, 1 H), 0.92 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): *C* 206.2; *CH* 55.2, 53.1, 45.4, 29.9; CH_2 35.2, 34.4, 33.8, 28.1, 25.0; CH_3 20.4. MS (EI): m/z 244.0450 (M^+), 165, 123. Anal. Calcd for $C_{11}H_{17}OBr$: C, 54.09; H, 7.02. Found: C, 53.83; H, 7.13. **2β-Bromo-3,4,4aβ,5,6,7,8,8aα-octahydro-8α-methyl-1(2*H*)-naphthalenone**: mp 101–102 °C. IR (CCl_4): 2927, 1729, 1658, 1564, 1549, 1254, 1008 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.64 (ddd, J = 13.0, 6.5, 1.0 Hz, 1 H), 2.62 (dddd, J = 13.0, 6.5, 4.0, 2.5 Hz, 1 H),

(34) Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ). Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagent silica gel 60 (230–400 mesh). THF and ether were distilled from potassium/benzophenone ketyl. CH_2Cl_2, diisopropylamine, and toluene were distilled from CaH_2. Air and/or moisture sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*CH*), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals the number of carbon atoms are given in parentheses.

2.06 (qd, J = 13.0, 4.0 Hz, 1 H), 1.89–1.65 (m, 6 H), 1.59–1.50 (m, 1 H), 1.43 (ddddd, J = 13.0, 11.5, 11.0, 3.0, 2.5 Hz, 1 H), 1.22 (m, 1 H), 1.09 (m, 1 H), 0.92 (m, 1 H), 0.90 (d, J = 6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 202.3, 61.2, 57.2, 45.3, 39.8, 34.21, 34.2, 33.6, 30.8, 25.0, 20.7. MS (EI): m/z 244.0452 (M^+), 229. Anal. Calcd for $C_{11}H_{17}OBr$: C, 54.09; H, 7.02. Found: C, 53.92; H, 6.97.

4aβ,5,6,7,8,8aα-Hexahydro-8α-methyl-1(4*H*)-naphthalenone (10). To a flame-dried flask under N_2 was added LiBr (57.7 mg, 0.666 mmol, 1.5 equiv) and Li_2CO_3 (82.1 mg, 1.11 mmol, 2.5 equiv) in 1 mL of dry DMF.[19] The mixture was allowed to stir for 2 min, followed by addition of a 7.2/1 (2β/2α) mixture of bromides (109 mg, 0.444 mmol, 1.0 equiv) in 2 mL of DMF. The resulting milky white solution was sealed with a glass stopper and Teflon-brand tape and heated to 120 °C with rapid stirring. After 5 h the mixture was allowed to cool to room temperature and then was quenched with the addition of 10 mL of 5% acetic acid. The mixture was extracted (3 × 10 mL of Et_2O), washed (1 × 10 mL of brine, 3 × 10 mL of H_2O), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 5% Et_2O/hexanes) gave the enone (58.8 mg, 0.358 mmol, 81%) as a clear oil, and recovered 2α bromide (3.7 mg, 15.2 μmol, 3%) as fine white crystals. IR (neat): 3032, 2919, 2853, 1681, 1455, 1387, 1372, 1297, 1245, 1200, 1165, 1132, 845, 752, 710 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (ddd, J = 10.0, 6.0, 2.0 Hz, 1 H), 5.86 (dd, J = 10.0, 3.0 Hz, 1 H), 2.30 (m, 1 H), 2.12–2.05 (m, 1 H), 1.82–1.60 (m, 7 H), 1.24–1.10 (m, 1 H), 1.07 (d, J = 6.5 Hz, 3 H), 0.95 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): 202.5, 146.7, 130.2, 57.2, 40.4, 35.5, 34.8, 33.7, 30.7, 24.9, 22.2. MS (EI): m/z 164.1201 (M^+), 149, 121, 108, 95, 68. Anal. Calcd for $C_{11}H_{16}O$: C, 80.43; H, 9.83. Found: C, 80.43; H, 9.65.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1-ol. Enone **10** (747 mg, 4.55 mmol, 1.0 equiv) was dissolved in 20 mL of CH_2Cl_2/MeOH (1/1) and cooled to −78 °C. Ozone was bubbled through the solution until a dark blue-green color persisted. The solution was degassed with N_2, followed by the addition of $NaBH_4$ (345 mg, 9.10 mmol, 2.0 equiv). The solution was allowed to warm to room temperature, followed by removal of CH_2Cl_2 under reduced pressure and dilution with 10 mL of EtOH (abs). The resulting solution was cooled to 0 °C, followed by addition of $NaBH_4$ (1.723 g, 40.55 mmol, 10.0 equiv). The solution was stirred for 3 h and quenched with 75 mL of saturated NH_4Cl. The solution was extracted (5 × 40 mL of EtOAc) and concentrated under reduced pressure. The concentrated solution was then diluted with 50 mL of 0.5 M H_2SO_4 and 100 mL of THF. The acidic solution was stirred for 30 min, followed by addition of $NaIO_4$ (4.866 g, 20.2 mmol, 5.0 equiv). The solution was stirred for 24 h, quenched with solid $NaHCO_3$ to neutral pH, extracted (4 × 100 mL of Et_2O), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (12.5% EtOAc/hexanes) gave the product (453 mg, 2.66 mmol, 58%) as a 4.6/1 (1β/1α) mixture of isomers as white crystals: mp 50–51 °C. IR (CCl_4, mixture): 3386, 2919, 1611, 1549, 1528, 1444, 1131, 1087, 1047, 987, 954 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 1β isomer): δ 5.23 (apparent triplet, J = 3.0 Hz, 1 H), 4.10 (ddd, J = 12.6, 11.2, 2.5 Hz, 1 H), 3.59 (ddd, J = 11.2, 4.9, 1.6 Hz, 1 H), 2.84 (dd, J = 3.3, 1.4 Hz, 1 H), 1.90–1.57 (m, 4 H), 1.51–1.22 (m, 4 H), 1.12–0.89 (m, 3 H), 0.82 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 1β isomer): *C*H 91.6, 51.5, 32.6, 32.4; *C*H$_2$ 65.0, 35.7, 33.7, 33.0, 25.5; *C*H$_3$ 18.7. MS (EI): m/z 170.1315 (M^+), 152 (M − H_2O), 124, 109, 96, 95, 82, 81, 68, 67, 55. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66. Found: C, 70.61; H, 10.49.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1β-yl Acetate (11). 3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1-ol (348 mg, 2.05 mmol, 1.0 equiv) was dissolved in 20 mL of CH_2Cl_2 at 0 °C, followed by addition of acetic anhydride (0.967 mL, 10.3 mmol, 5.0 equiv), Et_3N (1.43 mL, 10.3 mmol, 5.0 equiv), and DMAP (250 mg, 2.05 mmol, 1.0 equiv). The solution was stirred for 45 min and then allowed to warm to room temperature. The solution was diluted with 100 mL of H_2O, extracted (4 × 25 mL of CH_2Cl_2), washed (1 × 100 mL of saturated $NaHCO_3$), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10% EtOAc/hexanes) gave 410 mg (1.93 mmol, 94%) of pure product as a clear oil. IR (neat): 2920, 2849, 1747, 1467, 1446, 1373, 1260, 1232, 1204, 1172, 1156, 1133, 1099, 1048, 1040, 1009, 969, 928, 905, 891 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.13 (d, J = 3.0 Hz, 1 H), 3.79 (ddd, J = 12.5, 11.5, 3.0 Hz, 1 H), 3.68 (ddd, J = 11.5, 5.0, 1.5 Hz, 1 H), 2.09 (s, 3 H), 1.69–1.56 (m, 4 H), 1.50 (m, 1 H), 1.38 (m, 1 H), 1.40–1.21 (m, 2 H), 1.06 (ddd, J = 11.0, 11.0, 3.0 Hz, 1 H), 1.05–0.91 (m, 2 H), 0.81 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): *C* 170.2; *C*H 91.2, 50.2, 33.3, 32.2; *C*H$_2$ 61.6, 35.6, 33.5, 32.4, 25.4; *C*H$_3$ 21.0, 18.7. MS (EI): m/z 212.1424 (M^+), 166 (M − AcOH). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.50. Found: 67.92; H, 9.65.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1-carbonitrile (12). Acetate **11** (561 mg, 2.64 mmol, 1.0 equiv) was added to a flame-dried flask in 6 mL of dry CH_2Cl_2. The solution was stirred at room temperature, followed by addition of BF_3·Et_2O (38 mg, 0.26 mmol, 0.1 equiv) and TMSCN[35] (1.586 mL, 11.88 mmol, 4.5 equiv) via syringe. The solution was allowed to stir for 15 min, and the reaction was quenched with $NaHCO_3$. The mixture was extracted (4 × 20 mL of CH_2Cl_2), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 5% Et_2O/hexanes) gave the axial (1β) nitrile isomer (397 mg, 2.21 mmol, 84%) and the equatorial (1α) nitrile isomer (40 mg, 0.222 mmol, 8.4%) as clear oils. **3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1β-carbonitrile.** IR (neat): 2926, 2857, 1465, 1446, 1378, 1338, 1260, 1171, 1106, 1092, 1047, 996, 860 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.83 (d, J = 4.9 Hz, 1 H), 3.91 (ddd, J = 12.0, 5.2, 1.4 Hz, 1 H), 3.81 (ddd, J = 12.3, 12.0, 2.1 Hz, 1 H), 1.78–1.64 (m, 3 H), 1.59–1.30 (m, 5 H), 1.19 (ddd, J = 10.8, 10.5, 4.9 Hz, 1 H), 1.04 (m, 2 H), 0.89 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 116.3; *C*H 67.4, 49.4, 35.5, 32.2; *C*H$_2$ 64.9, 35.0, 32.8, 32.2, 25.0; *C*H$_3$ 18.5. MS (EI): m/z 179.1312 (M^+), 152, 137, 109, 95, 81, 67, 55, 41. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.59; H, 9.39. **3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1*H*-2-benzopyran-1α-carbonitrile.** IR (neat): 2888, 1540, 1506, 1455, 1418, 1364, 1330, 1274, 1236, 1188, 1153, 1131, 1065, 1042, 968, 929 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.0 (ddd, J = 11.5, 4.7, 2.2 Hz, 1 H), 3.89 (d, J = 9.7 Hz, 1 H), 3.45 (ddd, J = 11.5, 11.2, 3.1 Hz, 1 H), 1.78–1.60 (m, 3 H), 1.55–1.10 (m, 8 H), 1.16 (d, J = 5.8, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 119.6; *C*H 69.2, 50.4, 39.9, 35.0; *C*H$_2$ 67.9, 36.4, 33.4, 32.0, 25.6; *C*H$_3$ 20.7. MS (EI): m/z 179.1304 (M^+), 162, 152, 137, 123, 109, 95, 81, 67, 55, 41. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.72; H, 9.47.

3,4,4aβ,5,6,7,8,8aα-Octahydro-1α,8α-dimethyl-1*H*-2-benzopyran-1β-carbonitrile (13). Diethylamine (275 μL, 2.65 mmol, 1.2 equiv) was added to 5 mL of THF in a flame-dried flask. The solution was cooled to 0 °C, followed by the addition of *n*-BuLi (1.33 mL of a 2.04-M solution in hexanes, 2.71 mmol, 1.2 equiv). The solution was allowed to stir for 35 min followed by addition via cannula of 1β-nitrile **12** (397 mg, 2.21 mmol, 1.0 equiv) in 5 mL of THF. After equilibration for 1 h MeI (627 mg, 4.42 mmol, 2.0 equiv) was added by syringe, and the solution was allowed to warm to room temperature (~1 h). The reaction was quenched with saturated NH_4Cl, extracted (3 × 15 mL of Et_2O), and dried ($MgSO_4$). Concentration under reduced pressure gave the product as a single isomer (386 mg, 2.0 mmol, 90%) without further purification. IR (neat): 2924, 2857, 1462, 1446, 1383, 1264, 1174, 1103, 1071, 852 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (ddd, J = 11.9, 4.7, 1.4 Hz, 1 H), 3.77 (ddd, J = 11.9, 12.2, 2.2 Hz, 1 H), 1.70 (s, 3 H), 1.74–1.63 (m, 3 H), 1.60–1.32 (m, 5 H), 1.19, (m, 1 H), 1.06 (m, 1 H), 1.05 (d, J = 6.7 Hz, 3 H), 1.00 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 118.6, 74.5; *C*H 55.7, 37.7, 33.7; *C*H$_2$ 64.9, 34.4, 32.4, 31.3, 25.2; *C*H$_3$ 29.2, 22.6. MS (EI): m/z 193.1463 (M^+), 178, 165, 150, 137, 123, 122, 109, 107. Anal. Calcd for $C_{12}H_{19}ON$: C, 74.57; H, 9.91. Found: C, 74.81; H, 10.00.

3,4,4aβ,5,6,7,8,8aα-Octahydro-1,8α-dimethyl-1*H*-2-benzopyran (14 and 15). A solution of nitrile **13** (167 mg, 0.863 mmol, 1.0 equiv) in 4 mL of THF was cooled to −78 °C and transferred via cannula to a blue solution of sodium (250 mg, 10.9 mmol, 12.6 equiv) in 30 mL of NH_3 at −78 °C. The solution was stirred at −78 °C for 1 h and quenched with 1.5 g of solid NH_4Cl, and the NH_3 was allowed to evaporate from an ice bath. The residue was diluted with 15 mL of Et_2O and 30 mL of H_2O, extracted (3 × 20 mL of Et_2O), dried ($MgSO_4$), and concentrated from an ice bath at reduced pressure to yield the pure reduction product (147 mg, 0.874 mmol, quantitative) as a 1.78/1 mixture of **14** and **15**. Purification by flash chromatography (SiO_2, 2% Et_2O/hexanes) gave 78 mg of **14** (0.463 mmol) and 48.4 mg of **15** (0.288 mmol) as clear volatile liquids. **3,4,4aβ,5,6,7,8,8aα-Octahydro-1α,8α-dimethyl-1*H*-2-benzopyran (14).** IR (neat): 2919, 2854, 1477, 1462, 1445, 1382, 1255, 1163, 1141, 1115, 971, 849 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.92 (ddd, J = 11.1, 4.5, 1.8 Hz, 1 H), 3.47 (ddd, J = 11.1, 10.5, 3.3 Hz, 1 H), 3.20 (dq, J = 9.1, 6.1 Hz, 1 H), 1.71–1.55 (m, 3 H), 1.50–1.29 (m, 2 H), 1.31 (d, J = 6.1 Hz, 3 H), 1.29–1.0 (m, 4 H), 0.99 (d, J = 6.2 Hz, 3 H), 0.752 (ddd, J = 10.4, 9.3, 9.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C*H 78.1, 54.8, 41.3, 34.2; *C*H$_2$ 67.8, 37.8, 34.1, 33.9, 25.9; *C*H$_3$ 23.7, 23.4. MS (EI): m/z 168.1507 (M^+), 153, 122, 109, 95, 81, 67. Anal. Calcd for $C_{11}H_{20}O_1$: C, 78.51; H, 11.98. Found: C, 78.71; H, 12.22. **3,4,4aβ,5,6,7,8,8aα-Octahydro-1β,8α-dimethyl-1*H*-2-benzopyran (15).** IR (neat): 2918, 2853, 1446, 1374, 1325, 1291, 1259, 1175, 1146, 1137, 1112, 1104, 1081, 1066, 1026, 838, 652 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (qd, J = 6.7, 4.6 Hz, 1 H), 3.68 (ddd, J = 12.5, 11.7, 2.2 Hz, 1 H), 3.65 (ddd, J = 11.7, 4.7, 1.1 Hz, 1 H), 1.71–1.58 (m, 3

(35) Reetz, M. T.; Chatziiosifidis, I.; Kunzer, H.; Muller-Starke, H. *Tetrahedron* **1983**, *39*, 961–965.

H), 1.50-1.20 (m, 4 H), 1.17 (d, J = 6.7 Hz, 3 H), 1.12-0.89 (m, 4 H), 0.82 (d, J = 5.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 69.9, 60.0, 50.9, 36.0, 34.0, 33.9, 33.2, 32.8, 25.7, 18.8, 11.8. MS (EI): m/z 168.1503 (M^+), 153, 122, 109, 95, 81, 67, 55, 41. Anal. Calcd for $C_{11}H_{20}O_1$: C, 78.51; H, 11.98. Found: C, 78.67; H, 11.83.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1β-(phenylthio)-1H-2-benzopyran (16). Acetate **11** (51.2 mg, 0.240 mmol, 1.0 equiv) was dissolved in 2 mL of CH_2Cl_2 in a flame-dried flask and cooled to -78 °C under N_2. Thiophenol (32 mg, 0.288 mmol, 1.2 equiv) and $BF_3{\cdot}Et_2O$ (85 mg, 0.601 mmol, 2.5 equiv) were added via syringe, and the solution was allowed to stir for 15 min. The reaction was quenched with $NaHCO_3$, extracted (3 × 10 mL of CH_2Cl_2), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 1% Et_2O/hexanes) gave the product (59.9 mg, 0.228 mmol, 95%) as a clear oil, which upon standing gave fine white crystals: mp 49.5-50 °C. IR (neat): 3058, 2951, 2923, 2845, 1583, 1478, 1459, 1439, 1374, 1302, 1258, 1077, 1045, 1023, 992, 952, 748, 691 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (m, 2 H), 7.30-7.19 (m, 3 H), 5.53 (d, J = 4.3 Hz, 1 H), 4.31 (ddd, J = 12.2, 11.6, 2.5 Hz, 1 H), 3.69 (ddd, J = 11.6, 3.7, 1.2 Hz, 1 H), 1.72-1.64 (m, 3 H), 1.60-1.48 (m, 3 H), 1.43-1.31 (m, 3 H), 1.10-0.91 (m, 2 H), 0.91 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): C 136.0; CH 131.4, 128.9, 126.7, 88.6, 52.8, 34.8, 34.2; CH_2 60.41, 35.6, 34.1, 33.6, 25.6; CH_3 18.7; MS (CI, CH_4): m/z 263.1458 ($M + H^+$). Anal. Calcd for $C_{16}H_{22}OS$: C, 73.24; H, 8.46. Found: C, 73.42; H, 8.33.

3,4,4aβ,5,6,7,8,8aα-Octahydro-1β,8α-dimethyl-1H-2-benzopyran (15). (Phenylthio)benzopyran **16** (47 mg, 0.177 mmol, 1.0 equiv) was dissolved in 2 mL of THF in a flame-dried flask and cooled to -78 °C. An ~0.2 N solution of lithium di-*tert*-butylbiphenylide in THF at -78 °C was added by cannula into the solution containing **16** until a dark green color persisted (~1.9 mL, 0.372 mmol, 2.1 equiv). The solution was stirred for 10 min, followed by the slow addition of Me_2SO_4 (334 μL, 3.5 mmol, 20 equiv). The solution was stirred an additional 10 min, followed by the addition of 5 mL of saturated NH_4Cl. The mixture was allowed to warm to room temperature, diluted with 15 mL of H_2O, extracted (3 × 10 mL of Et_2O), dried ($MgSO_4$), and concentrated from an ice bath under reduced pressure. Purification by flash chromatography (SiO_2, 2% Et_2O/hexanes) gave 33.2 mg of an inseparable mixture of the axial methylated product **15** (38%) and a protonated side product (61%). Spectroscopic data and the GC retention time for compound **15** matched those of the minor isomer in the reductive decyanation of **13**.

Acknowledgment. Support has been provided by the Minnesota Supercomputer Institute, the McKnight Land-Grant Professorship Program, and the National Science Foundation Presidential Young Investigator Program. Additional support was provided by the Eastman Kodak Company and Eli Lilly and Company as a 1991 Lilly Grantee. We thank Dr. Michael J. Frisch of Lorentzian Inc. for carrying out the UMP2 calculations on **22ax** and **22eq**.

Note Added in Proof. The stereochemical outcome of dissolving metal reductions on cyclic and acyclic ketones has recently been examined by ab initio methods: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656-1661.

Supplementary Material Available: Geometries of 6-31G* unconstrained minima for **17ax, 17eq, 17ts, 18ax, 18eq, 21c, 21b, 22ax**, and **22eq** (12 pages). Ordering information is given on any current masthead page.

Imidazole Buffer-Catalyzed Cleavage and Isomerization Reactions of Dinucleotides: The Proposed Mechanism Is Incompatible with the Kinetic Measurements

Albert Haim

Contribution from the Department of Chemistry, State University of New York, Stony Brook, New York 11794. *Received November 20, 1991. Revised Manuscript Received June 24, 1992*

Abstract: It is shown that the mechanism and the kinetic model proposed for the imidazole-catalyzed cleavage and isomerization reactions of dinucleotides (Breslow, R.; Huang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 9621. Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 4473) are incompatible with the kinetic measurements.

The difficulties in proceeding from kinetic measurements to mechanistic elucidation have been discussed extensively.[1] Errors and ambiguities in mechanistic interpretations are not uncommon.[2] A case in point relates to recent studies on dinucleotides. To account for their kinetic measurements of the cleavage and isomerization reactions of 3',5''-uridylyluridine (3',5''-UpU), of its 2',5'' isomer (2',5''-UpU), and of 3',5''-adenyladenine, Breslow and co-workers (AB,[3] BH[4]) proposed a mechanism and a kinetic model. Recently, Menger[5] noted several shortcomings in Breslow's papers but did not take issue with the discrepancies between the functional dependences measured experimentally and those predicted by the proposed mechanism. The purpose of the present contribution is to point out that Breslow's proposed mechanism is incompatible with some of the observed functional dependences, that the kinetic model does not reproduce the reported rate constants, and that the proposed reactions of the postulated intermediate common to cleavage and isomerization are inconsistent with the kinetic measurements.

The rate of cleavage was found to have a "clean" first-order dependence upon total imidazole concentration and a bell-shaped dependence upon state of protonation.[6] The rate of isomerization was reported to "show no deviation from linearity in buffer concentration" and to be "near-linear" in state of protonation.[7] For each set of measurements at variable total buffer concentration but constant state of protonation, the measured pseudo-first-order rate constants were treated by linear least-squares to obtain the buffer-independent contributions at each value of the state of protonation. The extrapolated contributions at zero buffer con-

(1) (a) See for example: Lewis, E. S.; Bunnett, J. F. In *Techniques of Chemistry*, 3rd ed.; Lewis, E. S., Ed.; Wiley-Interscience: New York, 1974; Vol. VI, Chapters 1 and 8. (b) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.

(2) (a) Haim, A. *Inorg. Chem.* **1966**, *5*, 2081. (b) Haim, A. *J. Phys. Chem.* **1979**, *11*, 339. (c) Seaman, G. C.; Haim, A. *J. Am. Chem. Soc.* **1984**, *106*, 1319. (d) Haim, A. *Int. J. Chem. Kinet.* in press.

(3) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 4473.

(4) Breslow, R.; Huang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 9621.

(5) Menger, F. M. *J. Org. Chem.* **1991**, *56*, 6251.

(6) We adopt the definition that state of protonation is $[ImH^+]/[Im]_t$: Breslow, R.; Labelle, M. *J. Am. Chem. Soc.* **1986**, *108*, 2655.

(7) (a) For the experiments with no imidazolium chloride added, the rate decreases with increasing imidazole concentration. (b) In one instance, the change in rate with buffer is not linear: for $[Im]/[ImH^+] = 0$, the values of the pseudo-first-order rate constants are 0.19, 1.13, and 0.91 ($\times 10^{-3}$ h^{-1}) at buffer concentrations of 0.8, 1.3, and 2.0 M, respectively.[4]

0002-7863/92/1514-8384$03.00/0