J|A|C|S
COMMUNICATIONS

Published on Web 03/26/2005

Structural Evidence that Alkoxy Substituents Adopt Electronically Preferred Pseudoaxial Orientations in Six-Membered Ring Dioxocarbenium Ions

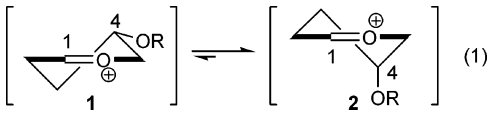
Stephen Chamberland, Joseph W. Ziller, and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92697-2025

Received February 8, 2005; E-mail: kwoerpel@uci.edu

An electronegative substituent can exert considerable influence over reactivity in tetrahydropyrans. For example, remote hydroxyl substituents accelerate glycoside hydrolysis when they are axial.[1] In addition, we reported a dramatic contrast in selectivity for nucleophilic substitution reactions of tetrahydropyran acetals with remote alkyl or alkoxy substituents.[2] These counterintuitive results inspired us to enhance our understanding of how the spatial orientation and electronic nature of an alkoxy substituent influence the structure of an oxocarbenium ion intermediate.[3]

The conformations of the intermediates in these reactions can only be surmised based on product analysis, but computational efforts offer insight into their structure. From their theoretical investigations on the likely intermediates involved in glycosylation reactions, Bowen and Miljković concluded that an electronegative C-4 substituent in tetrahydropyrylium ion **2** adopts a pseudoaxial orientation (eq 1).[4] This arrangement best promotes effective

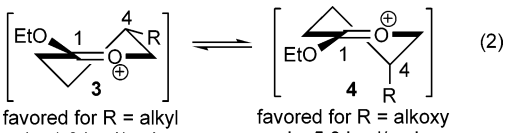


1 **2** (1)

through-space electrostatic stabilization of the carbocation.[5] Electronically neutral alkyl substituents cannot stabilize these cationic intermediates, so the conformational preferences parallel those of uncharged systems. Although the theoretical studies support and explain the selectivities we documented,[2] no experimental proof of the structures of these intermediates exists. Consequently, the selectivities we observed may reflect the relative reactivities of the conformers in solution and not their comparative ground-state energies.

To address this problem directly, we sought evidence of the conformational preferences of these intermediates in the ground state. Establishing the ground-state preference among low-energy conformers by observing a highly reactive oxocarbenium ion intermediate would be difficult because its lifetime under conditions normally used in organic synthesis is extremely short ($\sim 10^{-12}$ s).[6] Because dioxocarbenium ions are more stable than oxocarbenium ion intermediates, investigation of these ions might provide information about their short-lived counterparts provided that they are structurally similar.[7]

Establishing the structural homology between ephemeral oxocarbenium ions and isolable dioxocarbenium ions was paramount. A computational examination (MP2/6-31G*)[8] of C-4 alkyl- and C-4 alkoxy-substituted dioxocarbenium ions **3** and **4** revealed that they exhibit conformational preferences similar to those of cations reported by Bowen and Miljković (eq 2).[4] Accordingly, we prepared



3 **4** (2)

favored for R = alkyl by 1.0 kcal/mol

favored for R = alkoxy by 5.3 kcal/mol

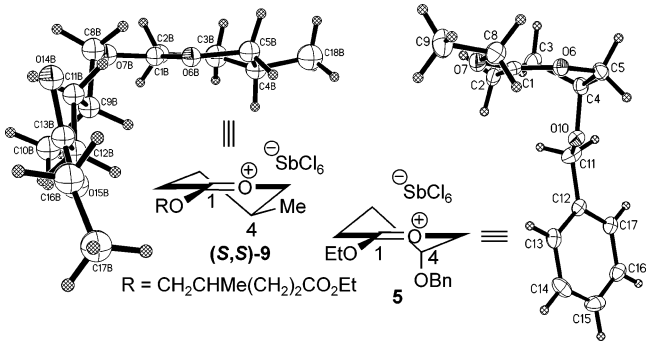
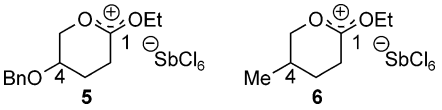
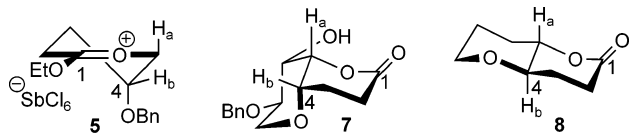


Figure 1. Crystal structures of dioxocarbenium ions **5** and **9**.

dioxocarbenium ion salts **5** and **6** intended to resemble the intermediates leading to highly selective *C*-glycosylation reactions[2] of acetals.[9,10] In this Communication, we provide structural evidence that a C-4 alkoxy substituent assumes a pseudoaxial orientation in dioxocarbenium ion **5**, illustrating the conformational preference we believe led to high selectivity in our previous work with related oxocarbenium ions.[2]



The lowest-energy structure for **5** predicted by theory is the major conformation in solution and in the solid state. Spectroscopic analysis (^{1}H NMR, 500 MHz, CD_2Cl_2) of **5** reveals a sextet[11] (δ 4.28 ppm, J = 2.0 Hz) corresponding to the C-4 methine proton. This multiplicity can only exist when the C-4 substituent is pseudoaxial. These coupling constants can also be compared to coupling constants reported for the C-4 methine protons of the structurally reminiscent and conformationally rigid lactone rings in decalones **7** and **8**.[12] Even more powerful than the spectroscopic data is the X-ray crystal structure which unambiguously proves the pseudoaxial orientation of the C-4 alkoxy substituent in tetrahydropyrylium ion **5** (Figure 1).



H_b, sextet, J = 2.0 Hz, J_{ab} = 2.0 Hz

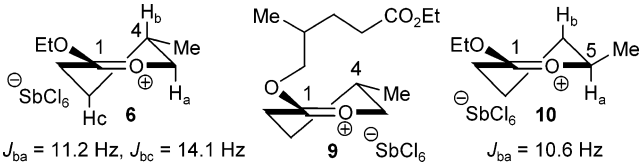
J_{ab} = 2.1 Hz

J_{ab} = 9.7 Hz

A similar strategy of crystallographic analysis for C-4 methyl-substituted cation **6** was unsuccessful. On the other hand, the pseudoequatorial orientation of the C-4 methyl substituent in a derivative (**9**) resulting from nucleophilic attack of **6** by its δ-lactone precursor was confirmed by X-ray crystallography (Figure 1).[13] In addition, cation **6** was compared to a similar dioxocarbenium ion salt, **10**−$SbCl_6$. Childs first reported the preparation of **10** and used

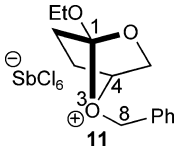
10.1021/ja050830i CCC: $30.25

X-ray crystallography to establish that the C-5 methyl substituent was pseudoequatorial.[14] We also prepared this salt[9] and compared coupling constant data obtained for the pseudoaxial C-5 methine proton of **10** to the C-4 methine proton of **6** using high-field ^{1}H NMR spectroscopy (500 MHz, CD_2Cl_2). Two large coupling constants corresponding to the two vicinal diaxial relationships involving H_b were present in the solution conformer of **6**. These coupling constants suggest that the methyl substituent is pseudoequatorial, in direct contrast to the preferred pseudoaxial orientation of the C-4 alkoxy substituent in cation **5**.



J_{ba} = 11.2 Hz, J_{bc} = 14.1 Hz J_{ba} = 10.6 Hz

We believe that the orientation of the C-4 alkoxy substituent in **5** is a result of electrostatic effects,[4] not anchimeric assistance.[15] Even though it provides the same selectivity hypothesized to arise from through-space cation stabilization, the attraction between the C-4 substituent and C-1 in **5** does not necessitate the formation of a covalent bond. Anchimeric assistance would afford bridged bicyclic cation **11**. Examination of the X-ray structure of **5** reveals that 3.301 Å separates C-1 and O-3. Within a structure such as **11**, the median carbon−oxygen bond length in the trivalent oxonium ion comprising C-1, C-4, C-8, and O-3 should be approximately 1.5 Å.[16] In addition, oxonium ion **11** is not an energy minimum according to computational methods.[8] In combination with the X-ray, spectroscopic, and computational data we present for dioxocarbenium ion **5**, the selectivity trend we observed within a series of nucleophilic substitution reactions of C-4 halogen-substituted acetates (trans selectivity decreases down the series F > Br > Cl > I)[2a] is most consistent with conformational stability derived from through-space electrostatic interactions present in the intermediate, oxocarbenium ion **2**.[4]



11

Additional stability in dioxocarbenium ion **5** may originate from the gauche relationship between vicinal electronegative atoms O-1 and the benzyloxy substituent. This coincidence could partially explain the observed conformational preference, but it is not likely the sole determinant. The gauche effect[17] can be substantial in charged systems, such as protonated 2-fluoroethanol,[18] and may influence the conformational preferences we and others observe in tetrahydropyrans.[2,19] It cannot, however, explain the predilection for a C-4 or a C-5 alkoxy substituent in an eight-membered ring oxocarbenium ion to be axial.[20] For this reason, the electrostatic stabilization hypothesis[4] remains the most plausible explanation for the enhanced stability of oxocarbenium ion conformers possessing axial electronegative substituents.

The preferred axial orientation of remote electronegative substituents in rings possessing electron-deficient carbon atoms seems to be a general phenomenon. In neutral systems, such as δ-lactones,[21,22] δ-lactams,[23] cyclohexanones,[24,25] and even 3-acetoxy tetrahydropyran,[19] remote heteroatom substituents prefer axial orientations. The axial preference is normally small, but the stability gained by positioning the substituent closer to the electron-deficient carbon atom overwhelms any steric penalty that this spatial arrangement may incur.[2]

In conclusion, we have proven that a C-4 alkoxy substituent adopts a pseudoaxial orientation in the ground-state structure of dioxocarbenium ion **5** in solution and in the solid state. This result supports our earlier hypothesis that conformer **2** is the ground-state structure of the intermediate leading to highly trans-selective reactions of C-4 alkoxy-substituted tetrahydropyran acetates.[2,4] The origin of this preference likely derives from through-space electrostatic effects as evidenced by computational, spectroscopic, and crystallographic data.

Acknowledgment. This research was supported by the National Institutes of Health, National Institute of General Medical Sciences (GM-61066). K.A.W. thanks Johnson & Johnson and Merck Research Laboratories for awards to support research. Dr. John Greaves and Dr. John Mudd are acknowledged for mass spectrometric data.

Supporting Information Available: Experimental procedures, characterization data for new compounds, spectral data for selected compounds (PDF), and X-ray diffraction data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419−3421 and references therein.
(2) (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.
(3) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916.
(4) (a) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604. (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864 and references therein.
(5) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247−1253.
(6) (a) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244−10245. (b) Prakash, G. K. S.; Rasul, G.; Liang, G.; Olah, G. A. *J. Phys. Chem.* **1996**, *100*, 15805−15809. (c) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900. (d) Olah, G. A.; Dunne, K.; Mo, Y. K.; Szilagyi, P. *J. Am. Chem. Soc.* **1972**, *94*, 4200−4205.
(7) (a) McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 5860−5866. (b) Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, *16*, 75−87.
(8) Details of calculations are provided within the Supporting Information.
(9) Deslongchamps, P.; Chênevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 1601−1615.
(10) Attempts were made to compare the allylation of dioxocarbenium ion **5** with data reported for similar reactions of acetates (ref 2). Consistent with our inability to observe alkylation at C-1, soft nucleophiles are known to attack 1-alkoxytetrahydropyrylium ions preferentially at C-5, with ring opening, or at C-8 by dealkylation: Beaulieu, N.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 164−167.
(11) The observed multiplicity derives from coupling to four vicinal protons and remote coupling to the C-2 equatorial proton. Computational and spectroscopic data for a C-4 methoxy analogue of **5**, which exhibits a similar conformational preference, appear in the Supporting Information.
(12) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017−3019.
(13) The X-ray structure of dioxocarbenium ion **9** is disordered, and only one of the two forms is shown for clarity. Data and a plot of the composite structure with a rationale for its formation (ref 10) appear in the Supporting Information.
(14) Childs, R. F.; Kostyk, M. D.; Lock, C. J. L.; Mahendran, M. *Can. J. Chem.* **1991**, *69*, 2024−2032.
(15) Anchimeric assistance can control the stereoselectivity of reactions: (a) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875−1878 and references therein. (b) Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765−774.
(16) Watkins, M. I.; Ip, W. M.; Olah, G. A.; Bau, R. *J. Am. Chem. Soc.* **1982**, *104*, 2365−2372.
(17) Jaffe, R. L.; Smith, G. D.; Yoon, D. Y. *J. Phys. Chem.* **1993**, *97*, 12745−12751.
(18) Briggs, C. R. S.; Allen, M. J.; O'Hagan, D.; Tozer, D. J.; Slawin, A. M. Z.; Goeta, A. E.; Howard, J. A. K. *Org. Biomol. Chem.* **2004**, *2*, 732−740 and references therein.
(19) Bernet, B.; Piantini, U.; Vasella, A. *Carbohydr. Res.* **1990**, *204*, 11−25.
(20) Chamberland, S.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 4739−4741.
(21) Brandänge, S.; Färnbäck, M.; Leijonmarck, H.; Sundin, A. *J. Am. Chem. Soc.* **2003**, *125*, 11942−11955.
(22) Morimoto, Y.; Shirahama, H. *Tetrahedron* **1997**, *53*, 2013−2024.
(23) Boudreault, N.; Ball, R. G.; Bayly, C.; Bernstein, M. A.; Leblanc, Y. *Tetrahedron* **1994**, *50*, 7947−7956.
(24) Baldry, K. W.; Gordon, M. H.; Hafter, R.; Robinson, M. J. T. *Tetrahedron* **1976**, *32*, 2589−2594.
(25) Nagao, Y.; Goto, M.; Ochiai, M.; Shiro, M. *Chem. Lett.* **1990**, 1503−1506.

JA050830I