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Molecular Mechanical Investigations of the Properties of Oxocarbenium Ions. 2. Application to Glycoside Hydrolysis

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Contribution from the Laboratory for Molecular Modeling, Divisi   f Medicinal Chemistry and Natural Products, School of Pharmacy, The University of North   lina at Chapel Hill, Chapel Hill, North Carolina 27599, and Burroughs Wellcome Cc   ny, 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709. *Received April   1991*

Abstract: The relative stabilities and heats of formation of cyclic oxocarbenium ions, of rele   e to glycoside hydrolysis, have been estimated by performing molecular mechanical (MM2(87)) calculations. Enhanced ele   atic interactions associated with hydroxyl substituents, as compared to methyl substituents, are reported. These interactio   .d to a preference for axial configurations, for hydroxyl groups at C-3 and C-4, in cyclic six-membered oxocarbenium   A rationalization for the rates of hydrolysis of pyranosides is presented and discussed in terms of the steric and elec   atic interactions associated with the relevant oxocarbenium ions.

Glycoside hydrolysis is one of the oldest and most studied reactions in carbohydrate chemistry. A wealth of data pertaining to variations on the rate of the reaction as a function of the sugar, the aglycon, and pH has been reported over the past century.[2] However, the transient nature of the cyclic oxocarbenium ions, believed to be intermediates in the acid-catalyzed hydrolysis of glycosides,[3] has prevented their direct observation. On the basis of kinetic studies,[4] some evidence for the existence of a cyclic intermediate in the hydrolysis of the *p*-nitrophenyl glycoside of the simplest pyranose analogue (1-hydroxytetrahydropyran) has been provided. Studies of the hydrolysis of glycosides derived from naturally occurring sugars are complicated by the presence of concomitant anomerization and ring-isomerization reactions. In the gas phase, cyclic oxocarbenium ions have been shown to be produced during the decomposition of protonated methyl 2,3,4,6-tetra-*O*-methyl-α- and β-D-galactopyranosides and permethylated deoxyhexopyranosides.[5]

Acid-catalyzed glycoside hydrolysis is believed to proceed via the fast protonation of the exocyclic anomeric oxygen atom, rather than the ring oxygen atom, followed by a slow cleavage of the C-1–O-1 bond, to generate a cyclic oxocarbenium ion.[3a,b] Attack by water then results in the formation of the free sugar as an anomeric mixture. The cleavage of the endocyclic C-1–O-6 bond (Chart I), to generate an acyclic oxocarbenium ion, has been suggested to occur during the mutarotation of aldopyranoses.[3a,6]

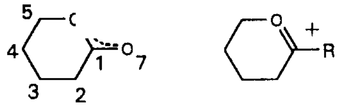
That the stability of the oxocarbenium ion might be relevant to the rate of hydrolysis was proposed over 30 years ago.[7] While such a simplistic correlation ignores the effects of solvation and ion pairing, and would be unlikely to explain the extreme enhancement of the reaction rates observed for 2-deoxypyranosides,[2] it was of interest to us to examine the extent to which such a hypothesis could be quantified.

Method

Molecular mechanical calculations were performed on several six-membered cyclic oxocarbenium ions employing MM2(87)[8] and a newly developed force field.[9] The results of these calculations have been compared to experimental data as well as to data generated from high-level ab initio molecular orbital calculations. The ab initio calculations were performed using the Gaussian90 series of software packages,[10] at both the restricted Hartree–Fock (RHF) and second-order Møller–Plesset (MP2) levels.[11] Geometry optimizations were performed with no constraints unless otherwise stated.

Discussion

Chart I



1

2: $R = CH_3$

3: $R = H$

Table I. Selected Structural Features for **1** and **2**

	1	**2**
Bond Lengths[a]		
C-1–C-2	1.483 (8)[b]	1.476
C-2–C-3	1.521 (10)	1.530
C-3–C-4	1.514 (9)	1.528
C-4–C-5	1.514 (9)	1.500
C-1–O-6	1.474 (7)	1.489
C-5–O-6	1.267 (7)	1.262
Bond Angles[c]		
C-1–C-2–C-3	112.3 (6)	113.6
C-2–C-3–C-4	108.6 (5)	107.5
C-3–C-4–C-5	110.5 (5)	109.4
C-4–C-5–O-6	111.6 (5)	110.9
C-5–O-6–C-1	122.4 (5)	124.0
O-6–C-1–C-2	125.2 (6)	123.5
Torsion Angles[c]		
C-1–C-2–C-3–C-4	43.5	42.8
C-2–C-3–C-4–C-5	−61.6	−63.3
C-3–C-4–C-5–O-6	49.6	50.9
C-4–C-5–O-6–C-1	−20.0	−18.2
C-5–O-6–C-1–C-2	2.99	−2.46
O-6–C-1–C-2–C-3	−15.3	−11.0

[a] Values in angstroms. [b] Values in parentheses are estimated standard deviations. [c] Values in degrees.

Ring Conformations. As a test of the transferability of the MM2(87) parameters, developed for acyclic oxocarbenium ions,[9] we sought to compare the results of MM2(87) calculations for a cyclic oxocarbenium ion to experimental structural data. We

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(1) (a) The University of North Carolina. (b) Burroughs Wellcome.

(2) See for example: Overend, W. G. In *The Carbohydrates, Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. IA, Chapter 9 and references therein.

(3) (a) Goto, K.; Chitani, T. *Bull. Chem. Soc. Jpn.* **1941**, *16*, 403. (b) BeMiller, J. A. *Adv. Carbohydr. Chem.* **1967**, *22*, 25–108. (c) Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond, Formation and Cleavage*; Pergamon: New York, 1979; pp 177–201.

(4) (a) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888–7900. (b) Craze, G.-A.; Kirby, A. J. *J. Chem. Perkin Trans. 2* **1978**, 357–368.

(5) (a) Solov'ev, A. A.; Kadentsev, E. I.; Chizhov, O. S. *Bull. Akad. Nauk SSSR, Div. Chem. Sci.* (*Engl. Transl.*) **1976**, *25*, 2105–2109; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, *25*, 2256–2260. (b) Solov'ev, A. A.; Kadentsev, V. I.; Chizhov, O. S. *Bull. Akad. Nauk SSSR, Div. Chem. Sci.* (*Engl. Transl.*) **1976**, *25*, 2110–2117; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, *25*, 2261–2268.

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Table II. Selected Structural Features for **3** Predicted by ab Initio Calculations and by MM2(87)

	HF/ 6-31G*	MP2/ 6-31G*	MP2/ 6-311G**	MM2(87)
	Bond Lengths[a]			
C-1–C-2	1.481	1.470	1.472	1.473
C-2–C-3	1.531	1.525	1.526	1.532
C-3–C-4	1.529	1.526	1.527	1.530
C-4–C-5	1.512	1.505	1.507	1.501
C-1–O-6	1.232	1.260	1.253	1.252
C-5–O-6	1.494	1.514	1.506	1.518
	Bond Angles[b]			
C-1–C-2–C-3	113.1	113.7	113.9	112.7
C-2–C-3–C-4	109.6	109.2	108.8	108.2
C-3–C-4–C-5	110.3	110.1	109.8	109.9
C-4–C-5–O-6	110.6	111.0	111.0	110.3
C-5–O-6–C-1	124.2	121.8	121.4	122.5
O-6–C-1–C-2	125.2	125.8	126.1	125.8
	Torsion Angles[b]			
C-1–C-2–C-3–C-4	38.5	38.3	37.1	41.4
C-2–C-3–C-4–C-5	−58.8	−60.2	−60.1	−63.1
C-3–C-4–C-5–O-6	49.2	51.3	52.9	51.2
C-4–C-5–O-6–C-1	−20.8	−21.4	−22.9	−19.0
C-5–O-6–C-1–C-2	0.7	−0.4	−0.5	−2.2
O-6–C-1–C-2–C-3	−10.1	−8.7	−7.4	−10.0

[a] Values in angstroms. [b] Values in degrees.

are grateful to Professor R. F. Childs, at McMaster University, for kindly supplying very recent data from a low-temperature X-ray crystallographic study of a series of tetrahydropyrilium hexachloroantimonate salts (**1**) (Chart I) generated from the corresponding lactones. While we lacked the necessary parameters to perform MM2(87) calculations on **1**, we have performed calculations on the closely related species 1-methyltetrahydropyrilium ion (**2**) in the $^4H_3$ conformation. Selected bond lengths and angles for both the calculated and experimental geometries are presented in Table I. It is noteworthy that in **2** the value of the C-5–O-6–C-1 angle was predicted to be larger, and that of the O-6–C-1–C-2 angle to be smaller, than observed in **1**, by approximately 1.6 and 1.8°, respectively. It is likely that the differences between the values for these angles in **1** and **2** arise from the greater charge delocalization associated with the O-6–C-1–O-1 linkage in **1**. The slight nonplanarity of the C-5–O-6–C-1–C-2 fragment, found in **1** to be approximately 3.0°, was also predicted for **2**; however, in the case of **2**, MM2(87) predicted a value of −2.5° for this angle. Furthermore, the value of the O-6–C-1–C-2–C-3 torsion angle in **1** (−15.3°) differs from that predicted for **2** (−11.0°). These torsional deviations may reflect the differences in the natures of the substituents at C-1 in **1** and **2**. While the overall agreement in the absolute values for the structural parameters for **1** and **2** was encouraging, the extent to which the differences arose from weaknesses in the MM2(87) force field, or from physical differences in the chemical structures, was uncertain.

Table III. Cremer and Pople Puckering Parameters for **1–3**

parameter	**1**[a]	**2**[b]	**3**[c]	**3**[d]	**3**[e]	**3**[b]
Q^f	0.491	0.520	0.480	0.493	0.499	0.514
q_2^f	0.362	0.406	0.364	0.379	0.385	0.400
q_3^f	0.332	0.325	0.313	0.314	0.316	0.323
Φ^g	47.5	51.3	49.3	50.4	50.6	51.0
ϕ_2^g	84.8	83.2	78.4	76.7	74.2	81.2

[a] Derived from the data provided by Prof. R. F. Childs. [b] Derived from the MM2(87) geometry. [c] Derived from the HF/6-31G* geometry. [d] Derived from the MP2/6-31G* geometry. [e] Derived from the MP2/6-311G** geometry. [f] Values in angstroms. [g] Values in degrees.

Presented in Table II are the results of ab initio (HF/6-31G*, MP2/6-31G*, and MP2/6-311G**) molecular orbital and MM2(87) geometry optimizations performed on the simplest six-membered cyclic oxocarbenium ion, tetrahydropyrilium ion (**3**). As reported previously,[9] the inclusion of corrections for electron correlation (MP2) led to more acute C-5–O-6–C-1 angles and longer C-1–O-6 bonds than predicted at the HF level. Only minor differences were observed between the structures predicted at the MP2/6-31G* and MP2/6-311G** levels, with the exception of a modest shortening of the C-1–O-6 and C-5–O-6 bonds, in the latter case. The values for the bond lengths and angles, predicted by MM2(87), were in close agreement with those predicted at the MP2 levels. A comparison of the values predicted by MM2(87) for the C-5–O-6–C-1 and O-6–C-1–C-2 angles in **3** (122.5° and 125.8°, respectively) with those reported for the corresponding angles in *cis-O*-methylacetaldehydium ion (122.6° and 127.5°, respectively)[9] indicated that incorporation of these angles into a six-membered ring introduced no distortion of the former angle and only a slight distortion of the latter. An examination of the corresponding ab initio values indicated that, in the cyclic system, a slight contraction of both angles occurred, of approximately 1° for each angle.

The values for the torsion angles for **3** indicated that, regardless of the basis set, the ab initio calculations predicted a flatter half-chair than was predicted by MM2(87). A quantitative measure of the conformation of a cyclic system may be obtained from the Cremer and Pople "puckering parameters",[12] in which the geometry of a six-membered ring may described by puckering amplitudes (Q, q_1, and q_2) and phase angles (θ and ϕ_2). An ideal half-chair conformation for **1–3**, that is, one in which atoms C-5, O-6, C-1, and C-2 are coplanar, would be characterized by θ and ϕ_2 values of 50.8° and 90°, respectively.[13] An examination of the puckering amplitudes for **1** and **2** indicated that MM2(87) predicted the ring in **2** to be more puckered than that found for **1**, by approximately 0.03 Å (see Table III). Furthermore, while the MM2(87) geometries for **3** also exhibited slightly higher puckering amplitudes than predicted by the ab initio calculations, improvements in the ab initio levels also led to increases in the values of the puckering amplitudes. Both of the MM2(87) geometries for **2** and **3** indicated values for θ that were closer to the ideal values for a half-chair than were found in the case of **1**. However, in **1**, substituent effects and interionic interactions in the solid state may be responsible for the deviations from the ideal puckering phase angles, as well as for the depression of the puckering amplitude, relative to the corresponding values for the gas-phase structures. On the basis of comparisons among structures **1–3**, albeit limited in number, we concluded that the MM2(87) force field for acyclic oxocarbenium ions could be extended to cyclic systems with reasonable success.

Ring Strain. The identical heats of hydrogenation of butene and cyclohexene (28.6 kcal/mol) have been cited in support of the hypothesis that a C=C bond may be incorporated into a six-membered ring without increasing the strain associated with that bond.[14] Furthermore, it has been proposed that the same may be true for the C=O bond in oxocarbenium ions.[14] In order to quantify this hypothesis, we have employed MM2(87) calculations to estimate the total steric energies (E_s)[15] and heats of

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(6) Isbell, H. S.; Pigman, W. *Adv. Carbohydr. Chem.* **1969**, *24*, 13–65.

(7) Edward, J. T. *Chem. Ind.* **1955**, 1102–1104.

(8) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134 and subsequent papers. The program MM2(87), which is an extended, but otherwise unchanged, version of MM2, is available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, IN 47401, and from Tripos Associates, 1699 Hanley Rd, Suite 303, St. Louis, MO 63144.

(9) Woods, R. J.; Bowen, J. P.; Andrews, C. W. *J. Am. Chem. Soc.*, preceding paper in this issue.

(10) 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. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90*; Gaussian, Inc.: Pittsburgh, PA, 1990.

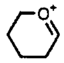
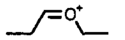
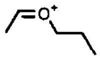
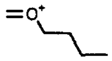
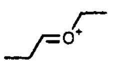
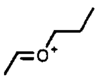
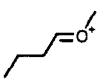
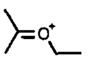
(11) (a) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem., Symp.* **1976**, *10*, 1–19. (c) Krishnan, K.; Pople, J. A. *Int. J. Quantum Chem.* **1978**, *14*, 91–100.

(12) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.

(13) The ideal value for θ (θ = arctan $[(3/2)^{1/2}]$) was derived for a regular hexagon with a small puckering amplitude (Q); see ref 12.

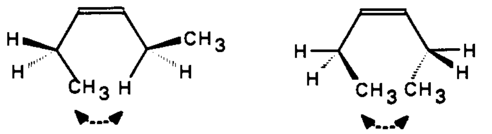
(14) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888–7900.

Table IV. Calculated Heats of Formation[a] and Steric Energies[a] for **3** and $[C_5H_{11}O]^+$ Isomers

				backbone torsion angles[b,c]				
ion	structure	ΔH_f	E_s	φ	ψ	χ	ξ	γ
3		145.1	4.92	−63	−10	−19	51	41
4		139.3	7.08	179	98			
5		138.0	7.26		100	100		
6		138.4	6.09			97	62	
7		139.4	3.22			120	63	178
8		135.1	4.32		1	125		
9		135.9	3.68			119	63	
10		136.5	4.21	180	0			
11		134.4	6.01			106		

[a] Energies are in kilocalories per mole. [b] Angles are in degrees. [c] The labels refer to the following torsion angles: φ, C—C—C—C(=O); ψ, C—C—C=O; χ, C=O—C—C; ξ, O—C—C—C; γ, (O—)C—C—C—C.

Chart II



formation (ΔH_f) for a series of acyclic $[C_5H_{11}O]^+$ isomers. For each isomer the lowest energy conformer was located through the application of a grid search of the backbone torsion angles using 15° increments. The lowest energy conformer was then fully optimized with no torsional constraints. The results from these calculations are presented in Table IV. As expected, the trans isomers were predicted to be more stable than the corresponding cis isomers, by approximately 2.5 kcal/mol. An examination of the individual components of the steric energies for these configurational isomers indicated that the bending energies were higher in the cis isomers than in the trans isomers, by approximately 1.4 kcal/mol. In the cis isomers the higher bending energies were associated with increases in the values of the C—C—O and O=C—C angles. A second contribution to the instability of the cis isomers appeared to be related to reductions in the stabilization energies associated with the C—C—O=C and C—C—C=O torsion angles, of approximately 0.5 and 0.9 kcal/mol, respectively, relative to the corresponding values for the trans isomers. As discussed previously,[9] and as found for the trans isomers, the C—C—O=C linkage preferred eclipsed or anticlinal (±120°) conformations, whereas an eclipsed conformation was preferred by the C—C—C=O linkage. In the case of the cis isomers the optimum orientations for these torsion angles could not be adopted without introducing unfavorable van der Waals interactions (see Chart II). It is noteworthy that the steric energy for **3** was predicted to be larger than the corresponding values for acyclic trans isomers **8** and **10**, and smaller than the corresponding values for cis isomers **4**–**6**. The reduction in the steric energy of **3**, relative to that of **4**–**6**, reflected both the presence in **3** of favorable orientations for the C—C—O=C and C—C—C=O torsion angles, as well as a reduction in the van der Waals repulsions. While a discussion of the total steric energy in terms of the individual component energies provides insight into the nature of the interactions responsible for the instabilities of the ions, it should be noted that such an analysis does not imply that the interactions are the cause of the instabilities.[16] Regardless of the exact nature of the effects responsible for the steric energies of the isomers, incorporation of the C=O bond into a six-membered ring was not predicted to lead to higher steric energies than present in comparable acyclic oxocarbenium ions.

The two stable half-chair conformations of unsaturated six-membered rings ($^3H_4$ and $^4H_3$) may be interconverted via a pseudorotational pathway, along which a boat conformation ($^{2,5}B$) is a transition state.[17] By "driving"[18] the C-2–C-3–C-4–C-5 torsion angle from its equilibrium value (approximately ±60°) in either of the half-chair conformers, to a value of 0°, an estimate of the relative energy for the $^{2,5}B$ transition state may be obtained. While this value does not include entropic contributions, the entropy of mixing for the two chiral half-chair conformers, and the entropy associated with reaction pathway multiplicity, should be equal and opposite in magnitude.[19] On the basis of **3**, the barrier to ring interconversion of six-membered oxocarbenium ions was predicted to be approximately 6.4 kcal/mol. A comparable experimental value of 5.3 kcal/mol has been reported for the barrier to half-chair interconversion in cyclohexene.[20] Although great emphasis should not be placed on the slightly higher value predicted for **3** than for cyclohexene, it may reflect the unfavorable conformation adopted by the C-4–C-5–O-6–C-1 torsion angle (−46°) in the $^{2,5}B$ boat modification.[9]

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(15) Within the MM2 formalism the total steric energy is defined as the sum of contributions from bonded interactions, including bond stretching, angle bending, coupled stretch–bending, and out-of-plane bending, and from nonbonded interactions, such as torsional, van der Waals, and dipole interactions. For a complete discussion, see ref 8.

(16) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982; pp 184–189.

(17) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734–5747.

(18) The dihedral driver option in MM2(87) was employed to rotate the C-2–C-3–C-4–C-5 torsion angle from approximately 60° (chair conformation) to 0° (boat conformation), in 2° steps, optimizing all other geometrical variables at each step.

(19) Anet, F. A. L.; Yavari, I. *Tetrahedron* **1978**, *34*, 2879–2886.

(20) (a) Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147–3150. (b) Jensen, F. R.; Bushweller, C. H. *Ibid.* **1969**, *91*, 5774–5782. (c) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. B. *J. Am. Chem. Soc.* **1991**, *113*, 8293–8298.

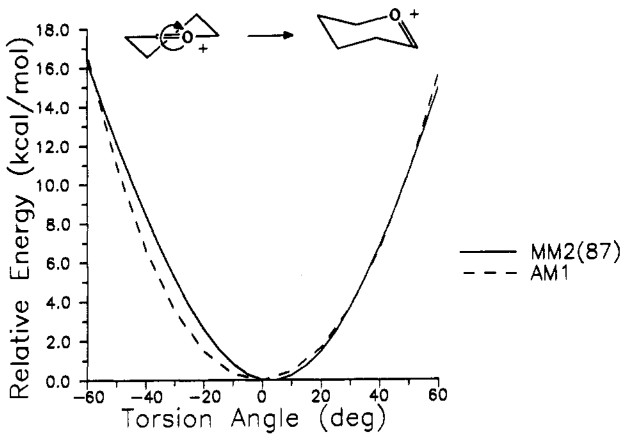

Figure 1. Relative energy versus rotation about the C═O bond in 3 predicted by AM1 and MM2(87).

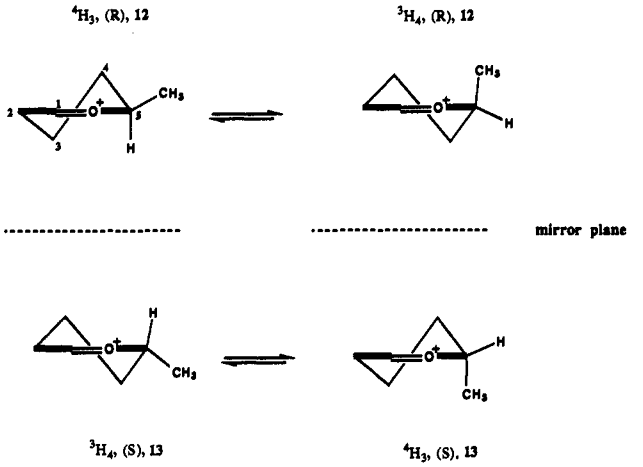

Figure 2. Stereochemical relationships between the $^4H_3$ and $^3H_4$ forms of 12 and 13.

As observed above, the C-5–O-6–C-1–C-2 torsion angle may assume slightly nonplanar orientations in the half-chair conformers, and the importance of the flexibility of this torsion angle, as concerns the rates of glycoside hydrolysis, has been recently discussed.[21] The ease with which this torsion angle may be distorted from planarity was estimated by driving it from 0° to 60° (the appropriate value for a $^4C_1$ chair conformation) in 2° increments. The results of these calculations are presented in Figure 1, in which +60° represents a $^4C_1$, 0° represents $^4H_3$, and −60° represents a $^{1,4}B$-like boat. Included for comparison are the results for corresponding calculations performed at the semiempirical molecular orbital level, employing AM1.[22] The similarity of the MM2(87) and AM1 results is notable. Moreover, the data in Figure 1 indicated that a distortion of the C-5–O-6–C-1–C-2 torsion angle, by as much as 35–40°, could be obtained for approximately the same energy as that required for half-chair to half-chair interconversion.

Substituent Effects. The relative energies for the $^3H_4$ conformations of cyclic oxocarbenium ions containing methyl and hydroxyl substituents at C-2, C-3, and C-4 were evaluated for ions 2 and 3 using MM2(87), and the results are presented in Table V. Included for comparison are the results for derivatives of 5(*R*)- and 5(*S*)-methyltetrahydropyrilium ions (12 and 13, respectively). Ions 2 and 3 serve as models for the ring systems in oxocarbenium ions derived from hexulopyranosides (in which the hydroxymethyl group at C-1 has been replaced by a methyl group) and pentopyranosides, respectively. Ions 12 and 13 provide models for intermediates derived from D- and L-hexopyranosides (in which the hydroxymethyl group at C-5 has been replaced by a methyl group), respectively (Figure 2). Due to the chiral relationship between the $^3H_4$ and $^4H_3$ conformations, the $^3H_4$ conformation of 12 is equivalent to the $^4H_3$ conformation of 13. D-Hexopyranosides generally adopt a $^4C_1$ conformation (in which the substituent at C-5 is equatorial), and hydrolysis of these glycosides would be expected to generate cyclic oxocarbenium ions in the $^4H_3$ conformation (in which the substituent at C-5 is pseudoequatorial).[23] The reverse would be expected to be the case for the L isomers; that is, in order to maintain a pseudoequatorial orientation of the substituent at C-5, the half-chair would adopt a $^3H_4$ conformation.

Table V. Steric Energies[a] of Substituted Cyclic Oxocarbenium Ions in the $^3H_4$ Conformation

ion	substituent	E_s axial	E_s equatorial	energy difference
2	2-CH_3[b]	8.29	7.61	0.68
	3-CH_3	6.88	5.37	1.51
	4-CH_3	6.14	5.44	0.70
3	2-CH_3[b]	7.08	6.24	0.84
	3-CH_3	6.24	4.97	1.27
	4-CH_3	5.76	5.03	0.73
12	2-CH_3[b]	9.01	8.15	0.86
	3-CH_3	10.31	6.94	3.37
	4-CH_3	7.80	7.93	−0.13
13	2-CH_3[b]	7.99	7.17	0.82
	3-CH_3	7.50	5.90	1.60
	4-CH_3	7.77	6.85	0.92
2	2-OH[b]	11.10	9.42	1.68
	3-OH	2.58	5.99	−3.41
	4-OH	1.76	6.34	−4.58
3	2-OH[b]	10.50	9.01	1.49
	3-OH	2.28	5.64	−3.36
	4-OH	1.28	5.97	−4.69
4	2-OH[b]	12.44	10.88	1.56
	3-OH	5.26	7.56	−2.30
	4-OH	3.25	8.29	−5.04
5	2-OH[b]	11.43	10.00	1.43
	3-OH	3.29	6.58	−3.28
	4-OH	2.73	7.17	−4.42

[a] Energies in kilocalories per mole. [b] Substituents at C-2 should be described as adopting pseudoaxial or pseudoequatorial configurations.

A destabilization energy of 1 kcal/mol has been reported for axial methyl groups, relative to equatorial substituents, in cyclohexene derivatives.[24] This value is lower than that reported for the same substituents in cyclohexane derivatives (1.75 kcal/mol),[25] due to the absence of 1,3-diaxial interactions in the half-chair conformation of cyclohexene. Similarly, on the basis of the results for 3, an average value of 1 kcal/mol was predicted for destabilization energy associated with axial methyl groups (see Table V). Moreover, in agreement with the case of cyclohexene,[23] methyl groups at the 3-position exhibited stronger preferences for the equatorial configurations than did methyl groups at the 4-position. An examination of the total steric energies for 2 and 3 indicated that substituents at C-2 introduced more strain than did substituents at C-3 or C-4. It is noteworthy that, in the case of the $^3H_4$ conformation of 12, an axial methyl group at C-3 led to a high value for the total steric energy (10.31 kcal/mol). In this conformation a 1–3 interaction is present between the axial methyl group at C-3 and the pseudoaxial methyl group at C-5. A destabilizing 1–2 interaction was also predicted to be present in the $^3H_4$ conformation of 12, between equatorial substituents at C-4 and the pseudoaxial methyl group at C-5, and was predicted to lead to nearly identical steric energies for epimers at C-4 in this species.

The total steric energies associated with hydroxyl substituents were found to exhibit markedly different trends than were found

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Table VI. Nonbonded Distances[a] between Hydroxyl Substituents and the Atoms of the $[\mathrm{C{-}O{=}C}]^+$ Fragments in the $^3H_4$ Conformation of **3**

		distances for nonbonded interactions					
		O···C-1		O···O-6		O···C-5	
ion	substituent	axial	equatorial	axial	equatorial	axial	equatorial
3	2-OH[b]	2.30	2.33	3.25	3.46	3.90	4.14
	3-OH	3.04	3.70	3.23	4.17	2.87	3.73
	4-OH	3.11	4.14	2.98	3.72	2.40	2.38

[a] Values in angstroms. [b] Substituents at C-2 should be described as adopting pseudoaxial or pseudoequatorial configurations.

for the methyl substituents. Species containing axial hydroxyl groups at C-3 or C-4 were predicted to be more stable than the corresponding equatorial epimers by 2.3–5.0 kcal/mol. This feature appeared to be independent of either ring conformation or configuration at C-5. Moreover, in all of the ions, axial hydroxyl groups at C-4 were found to be more stable than those at C-3, by approximately 1.5 kcal/mol. In contrast to these results, hydroxyl substituents at C-2 showed similar preferences for pseudoequatorial configurations as exhibited by methyl substituents. These rather remarkable features may be interpreted in terms of the presence of strong electrostatic interactions between the hydroxyl oxygen atoms and the atoms in the ion carrying partial positive charges.[9] In the case of hydroxyl groups at C-3 and C-4, axial configurations gave rise to shorter distances between the oxygen atoms of the hydroxyl groups and the atoms of the $[\mathrm{C{-}O{=}C}]^+$ fragment than were found in the corresponding equatorial configurations, and would be expected to give rise to higher stabilization energies (see Table VI).[9] In contrast, epimerization at C-2 resulted in little change in the nonbonded distances, and the differences in the energies of the C-2 epimers may be attributed to nonelectrostatic, or steric, effects. As in the case of methyl substituents, ions containing hydroxyl groups at C-2 exhibited higher total steric energies than did those containing hydroxyl groups at either C-3 or C-4.

Table VII. Hydrogen Bond Geometries for **14** and **15**

	distances and angles for hydrogen-bonding patterns					
	clockwise		counter-clockwise		bifurcated	
hydrogen bond parameter	**14**	**15**	**14**	**15**	**14**	**15**
	Distances[a]					
O-2···O-3	2.94	2.98	2.74	2.75	2.96	2.96
O-3···O-4	2.75	2.74	2.95	2.96	2.77	2.78
HO-2···O-3	2.56	2.61			2.56	2.64
HO-3···O-4	2.31	2.21				
HO-3···O-2			2.66	2.61		
HO-4···O-3			2.25	2.30	2.26	2.32
	Angles[b]					
O-2-HO-2···O-3	104.9	104.2			106.0	100.2
O-3-HO-3···O-2			98.5	102.5		
O-3-HO-3···O-4	108.2	114.6				
O-4-HO-4···O-3			111.7	109.5	111.3	109.3

[a] Values in angstroms. [b] Values in degrees.

Table VIII. Total Steric Energies[a] and Major Component Energies[b] for **14–17**

hydrogen bond pattern	component energies					total steric energy
	bending	van der Waals[c]	torsion	hydrogen bond	dipole–dipole	
			Clockwise			
14	4.12	4.43	0.38	−1.16	−0.76	7.33
15	4.23	4.51	−4.31	−1.31	−0.22	3.30
16	4.18	4.65	−3.65	−1.70	−0.39	3.54
17	3.31	5.15	2.71	−2.05	−1.90	7.64
			Counterclockwise			
14	4.18	4.30	−0.18	−1.18	0.48	8.02
15	4.32	4.41	−5.53	−1.15	1.00	3.49
16	4.32	4.35	−4.12	−1.51	1.18	4.68
17	3.30	5.22	2.66	−2.14	0.08	9.57
			Bifurcated			
14	4.04	4.26	1.29	−1.37	1.56	10.21
15	4.19	4.59	−4.99	−1.12	0.59	3.71
16	4.11	4.83	−3.32	−1.56	0.34	4.86
17[d]						

[a] Values in kilocalories per mole. [b] Compression and stretch–bend energies were less that 0.25 kcal/mol and have been omitted. [c] Includes all 1–4 and greater van der Waals interactions. [d] During optimization the bifurcated pattern spontaneously converted to a clockwise pattern.

While the energy differences between axial and equatorial hydroxyl configurations were predicted to be large, these energies were derived for ions containing a single hydroxyl substituent. Oxocarbenium ions derived from naturally occurring glycosides would be polyhydroxylated species with hydroxyl substituents located at C-2, C-3, and C-4. As any vicinal hydroxyl group may act as a proton acceptor or a proton donor in weak intramolecular hydrogen bonds with its neighbors, it was necessary to examine the effects of such interactions on the relative energies of configurational isomers. We chose to compare the energies of four polyhydroxylated species. The geometry and steric energy for the all-equatorial 2,3,4-trihydroxy derivative **14** (D-xylo configuration) was evaluated and compared to that of the monoaxial epimers **15** (L-arabino, axial at C-4), **16** (D-ribo, axial at C-3), and **17** (D-lyxo, axial at C-2). Gas-phase molecular orbital calculations have predicted that, in the case of monosaccharides, the lowest energy conformations were those in which the maximum number of intramolecular hydrogen bonds were present.[26] Furthermore, it is well known that, in the solid state, monosaccharides exhibit extensive hydrogen bonding.[27] On the basis of these observations, we chose to examine three hydrogen bond patterns for each of **14–17**, namely, a "clockwise"[28] pattern, in which hydrogen bonds were present between HO-2···O-3 and HO-3···O-4, a "counterclockwise"[28] pattern, in which hydrogen bonds were present between HO-3···O-2 and HO-4···O-3, and a bifurcated pattern, in which both HO-2 and HO-4 acted as proton donors in hydrogen bonds with O-3. For examples of the hydrogen bond geometries for each of these patterns in **14** and **15** see Table VII. The total steric and individual component energies predicted for each hydrogen bond arrangement for **14–17** are presented in Table VIII. Ions **15** and **16** were predicted to be more stable than **14**, by approximately 5 kcal/mol, in agreement with the results predicted for the monohydroxylated derivatives. An examination of the component energies indicated that each of **14–17** exhibited similar values for angle bending and van der Waals energies, whereas notable differences were found among the values for the torsional energies. A clear correlation between the torsional energies and the total steric energies was observed. As discussed in ref 9, the electrostatic interactions between the hydroxyl groups and the charged atoms within the ion were incorporated into the torsion potential energy terms of this force field. Consequently, large negative values for the torsional energies corresponded to stabilizing electrostatic interactions. Despite the variations in hydroxyl group orientations, the hydrogen bond energies, asso-

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(28) The terms "clockwise" and "counterclockwise" are used to describe the direction of proton donation between hydroxyl groups when the ring is viewed in the standard Haworth perspective formula; see: El Khadem, H. S. *Carbohydrate Chemistry. Monosaccharides and Their Oligomers*; Academic Press: New York, 1988; Chapter 2.

Table IX. Relative Rate Coefficients,[a] Activation Energies[a,b] and Entropies[a,c] for Pentopyranoside Hydrolysis and Total Steric Energies[b] of Relevant Half-Chair Intermediates

methyl glycoside configuration	k_{rel}	E_a	$\Delta S^{\ddagger}$	E_s[d] half-chair
		Axial Anomer		
α-D-*lyxo*	5.0	31.2	12.1	7.62
β-L-*arabino*	3.4	32.5	15.2	2.82
α-D-*xylo*	1.0[e]	33.5	15.7	7.16
		Equatorial Anomer		
α-L-*arabino*	2.4	30.6	10.2	2.82
β-D-*ribo*	1.5	31.4	11.8	3.40
β-D-*xylo*	1.0[e]	33.6	17.5	7.16

[a] Derived from the data in ref 30. [b] Values in kilocalories per mole. [c] Values in calories per degree per mole. [d] Derived from Boltzmann averaging, at 298 K, of the data in Table VIII. [e] The rate constants for the hydrolysis of α-D-xylopyranose and β-D-xylopyranose are 2.69 × 10^{-5} s^{-1} and 5.89 × $10^{-5}/s^{-1}$, respectively; see ref 30.

ciated with any given hydrogen bond pattern were similar for both **14** and **15**. Axial hydroxyl groups at C-3 or C-2 (**16** and **17**, respectively) were predicted to lead to slightly higher hydrogen bond energies than found for the corresponding equatorial epimers. However, when the energies for each hydrogen bond pattern for a given ion are compared, a more accurate estimate is provided by comparing the sums of the hydrogen bond, and dipole–dipole interaction, energies.[29] An examination of this type indicated that, for each ion, a clockwise orientation of hydroxyl groups was preferred over either a counterclockwise or a bifurcated pattern, by average values of 1.6 and 1.3 kcal/mol, respectively. While the extent to which the stabilization associated with the presence of an axial hydroxyl group would be attenuated in the solution phase is unknown, it would be unlikely that solvation would reverse the overall trends in stability.

Glycoside Hydrolysis. It was noted by Edward[7] in 1955 that the relative rates of glycoside hydrolysis could be rationalized in terms of the ease with which the chair conformation of the glycoside could be converted to the half-chair conformation of the oxocarbenium ion in the transition state. He proposed that, because the 1,3-diaxial interactions in the chair conformation were attenuated in the half-chair form, the rates of hydrolysis would increase in proportion to the number of axial substituents at C-2, C-3, and C-4. On the basis of this hypothesis, the relative rates of hydrolysis (k_{rel}) for the $^4C_1$ forms of methyl α-hexopyranosides may be ranked as D-*ido*- (HO-2, HO-3, HO-4 axial) > D-*altro*- (HO-2, HO-3 axial, k_{rel} = 17.8),[30] D-*talo*- (HO-2, HO-4 axial), D-*gulo*- (HO-3, HO-4 axial) > D-*allo*-(HO-3 axial), D-*manno*- (HO-2 axial, k_{rel} = 3.0),[30] D-*galacto*- (HO-4 axial, k_{rel} = 5.0)[30] > D-*gluco*- (no axial substituents, k_{rel} = 1.0).[30,2] In the case of the methyl pentopyranosides, the relative rate constants are presented in Table IX. Included for comparison are the enthalpies and entropies of activation (E_a and $\Delta S^{\ddagger}$),[30] as well as the total steric energies (E_s) calculated by MM2(87) for the $^4H_3$ conformations of the relevant cyclic oxocarbenium ions. While an examination of the rate constant data indicated that axial configurations led to increased rates of hydrolysis, the rate enhancements were more significant in the case of the hydrolysis of the axial anomers than in the case of the equatorial anomers. If the properties of the transition states are similar to those of the cyclic oxocarbenium ions, then the presence of an axial hydroxyl group should lead to a stabilization of the transition state. Thus, the enhanced rates of hydrolysis, for oxocarbenium ions that contain axial hydroxyl groups, may be enthalpic in origin. However, it should be noted that these calculations inherently neglect the effects of solvation. The generally higher rates of hydrolysis of β-D-glycosides, as compared to those of the α-anomers, have been discussed in detail;[31] however, a strictly enthalpic interpretation is not sufficient to explain the differential rate enhancements observed for the hydrolysis of axial anomers that contain axial hydroxyl substituents. Nor can such arguments explain the rate enhancement in species containing an axial hydroxyl group at C-2 (lyxo), relative to that for species containing an axial hydroxyl group at C-4 (arabino). A more accurate interpretation may be provided by assuming that the transition state will resemble an intimate ion pair, in which the leaving group, derived from the protonated aglycon (methanol in the case of a methyl glycoside), would be coordinated to the cyclic oxocarbenium ion.[4a] The extent to which a solvent-separated ion pair could be formed might determine the extent to which internal return would be avoided, and hence, would lead to an increased rate of reaction. Hydroxyl substituents at C-2 may serve to either assist in the formation of a solvent-separated ion pair or assist in coordinating the attack of a water molecule. Our model does not address the nature of the interactions present in such ion pairs, nor have the effects of solvation on the free energies of the ions been investigated. Consequently, the extent to which a hydroxyl group at C-2 interacts with the leaving group may not be determined using this method, but will form the subject of future studies.

Conclusions

The effects of substituent configuration on the stability of cyclic oxocarbenium ions have been investigated by employing MM2(87) and a newly developed parameter set.[9] We have found that, contrary to the case of methyl substituents, hydroxyl substituents at C-3 and C-4 prefer axial configurations. Despite the presence of intramolecular interactions, the predicted trends in steric energies for polyhydroxylated species were found to agree with those determined for monohydroxy derivatives. An examination of the individual component energies indicated that the stability of the axial orientations arose from enhanced electrostatic effects. We have presented a novel interpretation for the observation that the rates of glycoside hydrolysis are proportional to the number of axial substituents in the glycoside. Exceptions to a simple enthalpy-based argument have been noted, and tentative explanations offered.

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(29) The hydrogen bond energy is derived from a simple distance-dependant function; see refs 8 and 9. For a given ion, differences in the dipole–dipole interaction energies arise nearly exclusively from differences in hydroxyl group orientations. Thus, a comparison of relative hydrogen bond energies requires the sum of these two components.

(30) The rates of hydrolysis were determined in 2 N HCl using polarimetric methods and are reported at 60 °C, and are relative to that of α-D-glucopyranose; see: Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429–3440.

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