Supplementary Material Available: Detailed information concerning the synthesis and variable temperature spectroscopic data of compounds **1**, **1a**, and **1b** (10 pages). Ordering information is given on any current masthead page.

Acid-Catalyzed Dehydration of Diols. Kinetic and Stereochemical Ramifications of Spirotetrahydrofuran Synthesis

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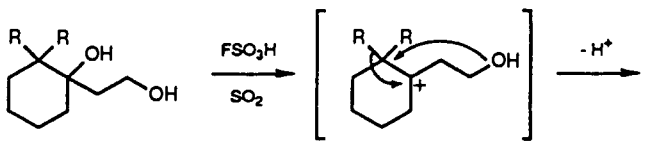
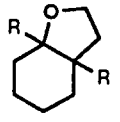
Carbocations play a major role in modern chemistry, and information linking structure to relative ease of ionization in the formation of these electrophilic species abounds.[1] Experiments showing the relative ease of carbocation generation to be tertiary > secondary > primary are detailed in all introductory texts.[2] At the next level, ditertiary diols are known to give rise to dications when dissolved in superacidic media.[3] Comparable treatment of 1-(2-hydroxyethyl)cyclohexanols, e.g., **1** (R = H, CH_3), results in kinetically controlled ionization to **2** and subsequent 1,2-hydride or -alkyl shift, setting the stage for ultimate cyclization to the perhydrobenzo[*b*]furan **3**.[4]





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We herein report the discovery that acid-catalyzed dehydration of the homologous 1,4-diols **4** and **5**[5,6] can proceed under the proper circumstances with *high levels of stereochemical retention*. Our findings establish further that formation of the spirocyclic tetrahydrofurans **6** or **7**, respectively, proceeds by *selective displacement of the primary hydroxyl functionality without wholesale concurrent heterolysis of the tertiary C–O bond*. This striking reversal in the reactivity norm surfaces because of the large rate accelerations that can accompany the intramolecular displacement of protonated *primary* hydroxyl by *tertiary* hydroxylic oxygen.[7] This previously unappreciated kinetic factor

Scheme I

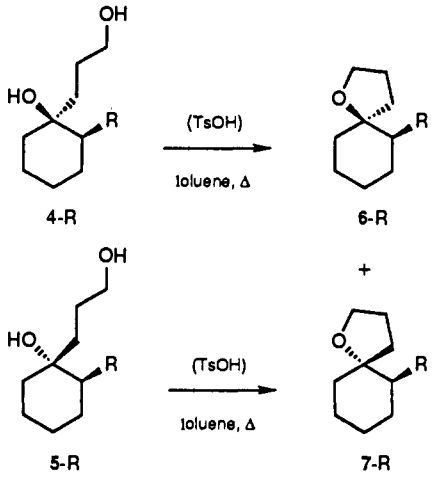

Table I. Stereochemical Consequences of Acid-Catalyzed Ring Closure Involving Diols **4** and **5**[a,b]

compd	6, %	7, %	compd	6, %	7, %
4-OCH_3	96	4	**5**-C_6H_5	55	45
5-OCH_3	8	92	**4**-CH_3	40	60
4-C_6H_5	67	33	**5**-CH_3	55	45

[a] Cat. TsOH, toluene, reflux. [b] Product analyses were determined by capillary GC analysis.

Table II. Extent of Retention of ^{18}O Following Acid-Promoted Cyclization of Specifically Labeled **4** and **5**[a]

starting diol	% ^{18}O at C-1	combined product yield, %	extent of isotopic label present, %	
			6	**7**
4-OCH_3	40	47[b]	40, 39	11[c]
5-OCH_3	39	52[b]	16[c]	38, 39
4-C_6H_5	45	84	20, 25	0, 0
5-C_6H_5	45	73	0, 0	19, 22
4-CH_3	39	68	9, 11	0, 0
5-CH_3	38	53	0, 0	6, 10

[a] Analyses performed by the ^{13}C NMR method described in the text. [b] Yields in these cases refer to major product only. [c] High-resolution mass spectral analysis made necessary because of limited quantities. Percentages obtained by analysis of *combined* minor products from duplicate runs.

can be attributed to the extensive operation of neighboring-group participation.[8] This cooperative pathway can become sufficiently preferred to permit useful stereoselectivities to be implemented.[9] Anionically driven intramolecular S_N' processes have recently been shown to hold substantial synthetic potential.[10]

We have analyzed the response of six diols to acid-catalyzed cyclization (Scheme I, Table I). The methoxyl derivatives **4**-OCH_3 and **5**-OCH_3 were examined first since (a) application of the Taft equation to limiting S_N1-type ionization of the proximate tertiary carbinol predicts that a 10^{-2} rate-retarding influence should be operative[11] and (b) the rate of ionization of *trans*-2-methoxycyclohexyl *p*-toluenesulfonate is known to be slowed approximately 100-fold.[12] Thus, electron-withdrawing electrostatic factors gain importance in these systems, while anchimeric as-

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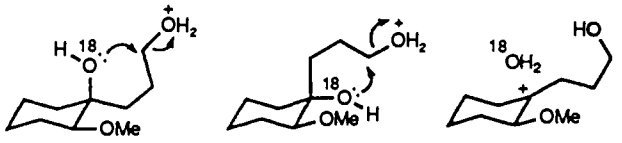
sistance is essentially ineffective, if operational at all. In fact, this pair of diols proved to be exemplary, displaying levels of stereochemical retention that exceed 90% *in opposite directions*.

When recourse was made to 4-C_6H_5 and 5-C_6H_5, similar high degrees of stereocontrol were no longer evident. However, as for the methoxyl pair, greater stereochemical preservation occurred with the axial alcohol 4-C_6H_5. Our results suggest that 5-C_6H_5 may represent a crossover point where ionization to give the tertiary carbocation begins to override the totally retentive mechanism.

The 2-methyl substituent exerts little stereochemical influence. Both 4-CH_3 and 5-CH_3 reproducibly provided a similar product distribution, slightly richer in the inverted ethers. Control experiments established that the product distribution in every instance is entirely kinetic and not thermodynamic.[13] The configurations of tetrahydrofurans **6** and **7** were independently corroborated by direct cyclization of **4** and **5** with *p*-toluenesulfonyl chloride in triethylamine.

We next probed the source of the resident ethereal oxygen in **6** and **7** by ^{18}O labeling of the tertiary hydroxyl substituent in each substrate. Incorporation of the isotope was achieved by hydrolysis[14] of the cyclohexanone dimethyl ketals in water enriched to the extent of 50% with ^{18}O. The levels of isotopic incorporation in the three ketones were determined by relative integration of the well-separated ^{13}C–^{16}O and ^{13}C–^{18}O signals in their 75-MHz natural-abundance carbon spectra.[15] Comparable measurements performed subsequently on the six diols revealed that no dilution of the isotopic concentrations had occurred.[16] In a series of duplicate experiments, the specifically C-1/^{18}O-labeled diols were dehydrated under acidic conditions as before. The results are compiled in Table II.

Although cyclization can occur through initial protonation and loss of either hydroxyl group, the 100% retention of ^{18}O observed during the 4-OCH_3 → **6**-OCH_3 and 5-OCH_3 → **7**-OCH_3 transformations establishes that the associative S_N processes depicted in **8** and **9** are decidedly dominant. Although we have no in-



8 9 10

formation regarding the reacting conformation(s) of these diols, neighboring-group participation can operate from either chair arrangement. The higher percent of stereochemical retention achieved by 4-OCH_3 (and 4-C_6H_5) does suggest that an axial tertiary OH is perhaps better disposed to implement the S_N displacement than is its equatorial counterpart. The levels of residual ^{18}O that persist through the stereochemical inversion manifold of the methoxyl series are quite respectable. These data may reflect the tightness of the solvation shell in **10**[17] which prevents isotopically labeled water from escaping the vicinity of the carbocation as a consequence of its appreciable destabilization by electrostatic factors.

The gradual diminution in stereochemical control and isotopic retention as one progresses through the phenyl to the methyl analogues is best explained by a progressive attenuation of electron-withdrawing capacity at C-2, such that tertiary cyclohexyl carbocation formation becomes increasingly more competitive with operation of the associative S_N process. However, increased incursion of the classical S_N1 process is not accompanied by full equilibration of the cations prior to hydration. This phenomenon, which is most evident in the matched methyl diastereomers, requires that these intermediates be unsymmetrically hydrated or captured at a rate faster than conformational ring inversion.

The remarkable departure from traditional chemical behavior made clear in this study prompts the advocacy of α-heteroatomic substitution as a useful tool for effecting highly stereocontrolled intramolecular reactions under seemingly improbable circumstances. One of the many conceivable applications of this strategy is illustrated in the ensuing report.[9]

Acknowledgment. We gratefully acknowledge the National Science Foundation (Grant CHE-8703091) for support of this research effort and the Fulbright Commission for a travel grant (to J.T.N.).

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Belted Spirocyclic Tetrahydrofurans: A New Class of Preorganized Ionophoric Polyethers. Molecular Structure, Conformation, and Binding to Alkali-Metal Atoms

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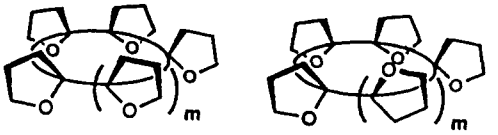
Nonmacrocyclic host molecules exhibit weaker cation-binding properties than coronands and cryptands unless their ligating oxygens are suitably preorganized for effective coordination.[2] These features can be found in select polyether antibiotics, e.g., monensin[3] and nonactin,[4] and in several totally synthetic tetrahydropyranoid podands.[5] Although interest in tetrahydrofuranyl building blocks has been high,[6] no attention has yet been accorded to poly(spiro ethers) of the type generalized by structures **1** and **2**. The effective binding capabilities of such host molecules are



1 2

expected to be linked to the limiting conformational restrictions offered by the central belt and to the energy required to cluster the oxygens properly about the guest ion during complexation. Knowledge of the extent to which **2** and more extensively epim-

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