5. Formation of Cyclic Ketals from Hydroxyalkyl Enol Ethers, a Stereoelectronically Controlled *endo-trig*-Cyclization Process

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Dedicated to *Albert Eschenmoser* on the occasion of his 70th birthday

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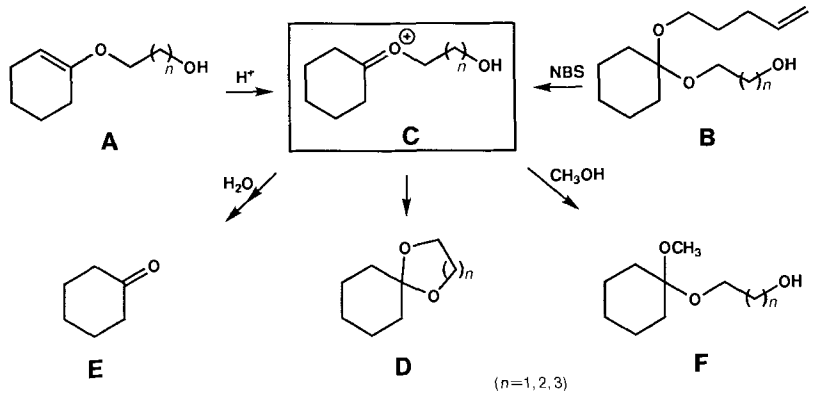
Acid-catalyzed cyclic ketal formation *vs.* hydrolysis of a series of hydroxyalkyl cyclic enol ethers in the presence of 1 equiv. of H_2O, and acid-catalyzed cyclic-ketal formation (same ketals as above) *vs.* methanolysis of a series of mixed pent-4-enyl hydroxyalkyl ketals with *N*-bromosuccinimide in the presence of 4 equiv. of MeOH led to the same result: the intramolecular cyclization processes occur at similar rates as the intermolecular H_2O or MeOH attacks independently of the size of the rings formed (five-, six-, or seven-membered), by cyclizations. These results can be explained by the facts that, due to stereoelectronic effects which impose a torsional strain to the sp^2 hybridized O-atom, the cyclization activation enthalpy decreases, as the length of the hydroxyalkyl chain increase (ease of cyclization: 7 > 6 > 5), whereas the entropy factor favors the cyclization in the reverse fashion (ease of cyclization: 5 > 6 > 7). The various reaction pathways have been examined using the semi-empirical *Hamiltonian* AM1, and the results obtained confirm that large-ring formation is enthalpically much favored over the cyclization processes leading to small rings (ease of cyclization: 7 > 6 > 5).

Introduction. – Using the semi-empirical *Hamiltonian* AM1 in order to define the reaction pathway in the hydrolysis of some bicyclic acetals (models for α- and β-glycosides) and spiro-ketals, we have recently obtained theoretical confirmation that the hydrolysis of these compounds is controlled by powerful stereoelectronic effects [1]. In that study, the formation (or hydrolysis) of acetals and spiro-ketals were the result of either intermolecular or *exo-trig* [2] cyclization processes which can take place without severe conformational restraint at the transition-state level.

As pointed out by *Kirby* [3], the formation of five-membered-ring acetals (1,3-dioxolanes) presents an intriguing problem, because it is an *endo-trig*-cyclization process where stereoelectronic effects should render the approach of the incoming OH group geometrically difficult. This problem and also the formation of larger-ring acetals can be studied experimentally by generating cyclic oxocarbenium ions in the presence of an external nucleophile such as H_2O (or MeOH) while varying the length of the hydroxyalkyl side chain. As shown in *Scheme 1*, cyclic oxocarbenium ion **C** can be generated in the presence of H_2O from the corresponding cyclic enol ether **A** under mild acid conditions, or, under essentially neutral conditions, by a method recently discovered by *Fraser-Reid* and coworkers [4], *i.e.*, from the reaction of mixed pentenyl ketal **B** with *N*-bromosuccinimide (NBS) in the presence of MeOH in MeCN. In the first case, ion **C** can either cyclize to the corresponding ketal **D** or react with H_2O to give a hemiketal which can then produce ketone **E**. In the second case, **C** can either give ketal **D** or the mixed ketal **F** by reaction with MeOH.

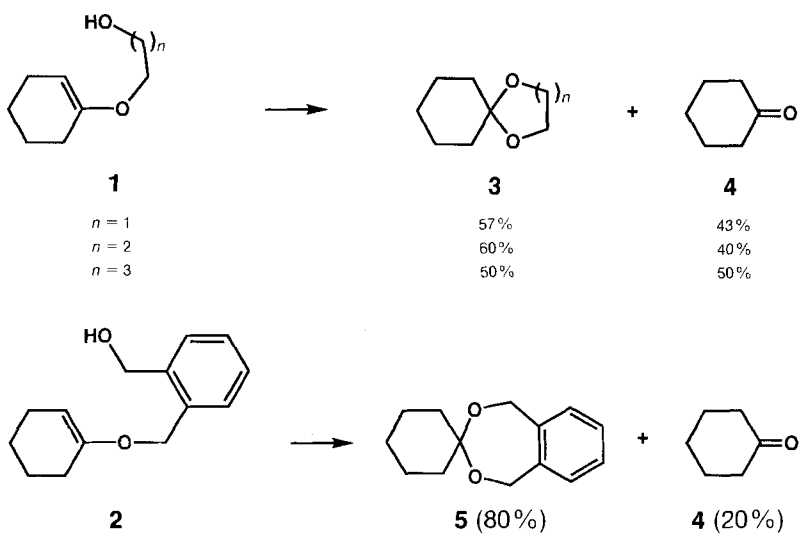
Scheme 1



We have studied the *endo-trig* acid cyclization of hydroxyalkyl enol ethers **1** (n = 1–3) and **2** in the presence of H_2O (*Scheme 2*). We have also studied the reactivity of mixed pent-4-enyl ketals **6** (n = 1–3) and **7** with NBS in the presence of MeOH (*Scheme 3*). For comparison, the *exo-trig*-cyclization behavior of mixed pent-4-enyl ketal **11** (*Scheme 4*) was also carried out. We wish to report this work.

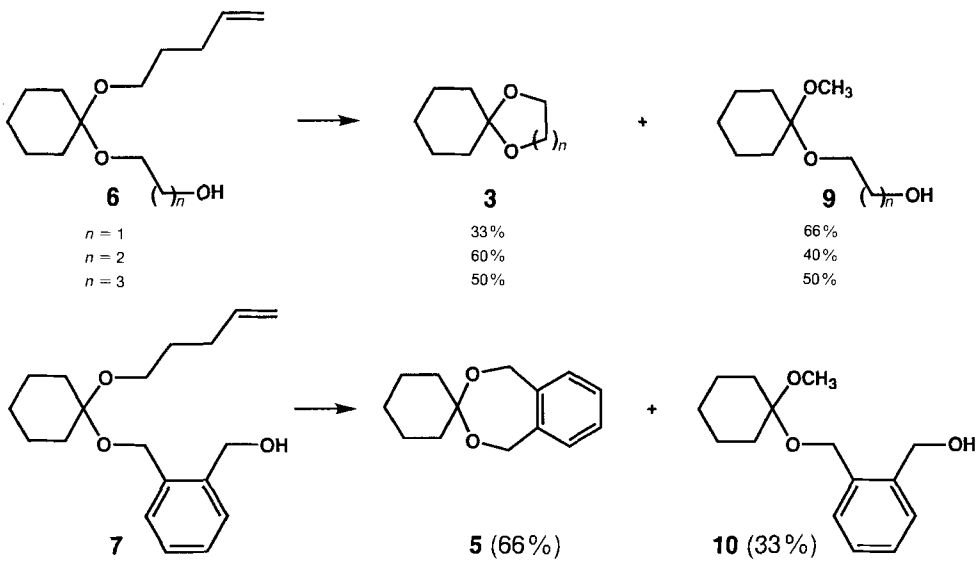
Chemistry. – The hydroxyalkyl enol ethers were prepared by ring opening of the corresponding cyclic ketals. Compound **1** (n = 1) was obtained from ketal **3** (n = 1) [5] (*Scheme 2*) using the method of *Gassman* and coworkers [6] (*a*) Me_3SiOTf, i-Pr_2NEt, CH_2Cl_2; *b*) Bu_4NF, THF). Compounds **1** (n = 2 [7], 3) and **2** were prepared from the corresponding ketals **3** (n = 2, 3) [5] [8] and **5** [9] using the procedure of *Naruse* and *Yamamoto* [10] (*a*) (i-Bu)$_3$Al, CH_2Cl_2; *b*) NaOH, H_2O).

Scheme 2



The mixed pentenyl ketals **6** (n = 1, 2) and **7** (*Scheme 3*) were prepared by the addition of pent-4-en-1-ol on the corresponding enol ethers **1** (n = 1, 2) and **2**. The mixed pent-4-enyl ketals **6** (n = 3) and **11** (*Scheme 4*) were obtained by a three-step procedure: the enol ethers **1** (n = 3) and **8** [11] were acetylated, (AcCl, Et_3N, THF), ketalyzed (pent-4-en-1-ol, Ph_3PHBr) [12], and hydrolyzed (NaOH, H_2O).

Scheme 3

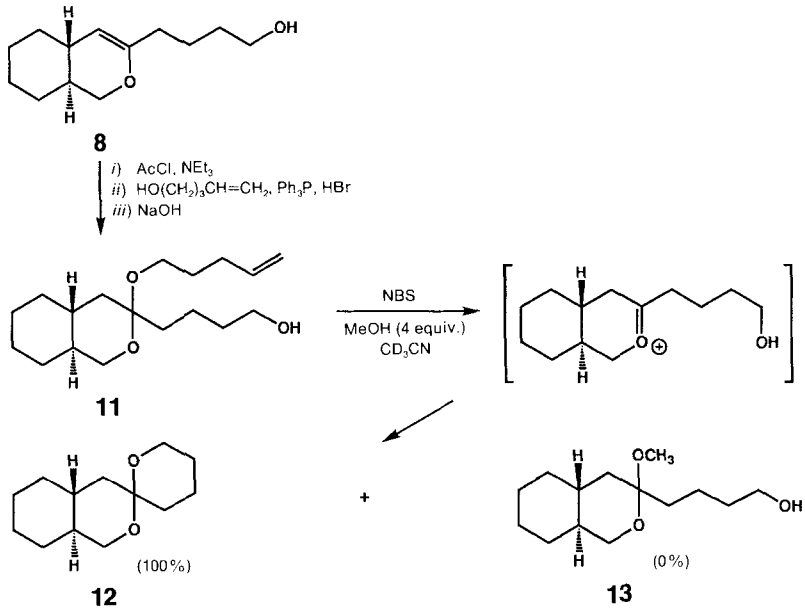


Results and Discussion. – The acid-catalyzed cyclizations of hydroxyalkyl enol ethers **1** (n = 1–3) and **2** were carried out in the presence of 1 equiv. of H_2O in CD_3CN. The NBS-catalyzed cyclization of mixed pent-4-enyl ketals **6** (n = 1–3), **7**, and **11** were done in CD_3CN in the presence of 4 equiv. of MeOH.

The results described in *Schemes 2* and *3* indicate clearly that the addition of H_2O (or MeOH) an intermolecular process[1]) can compete effectively with the *endo-trig*-cyclization process as shown by the important amounts of ketone **E** (or mixed ketal **F**) formed in the reactions. Furthermore and remarkably, the formations of six- and even seven-membered rings are as effective as that of five-membered ring in competing with the addition of H_2O (or MeOH). In the case of **2** and **7**, the formation of the seven-membered ketal is even favored. This trend is of course contrary to what is normally observed in relative rate of cyclization where five-membered rings are usually formed much faster ($\sim 10^2$) than six-membered rings which are in turn formed much faster ($\sim 10^2$) than seven-membered rings [13]. On the other hand, and contrary to the above results, the bicyclic mixed ketal

[1]) To avoid the possibility that these results might be the result of a pre-association (*via* H-bonding) of H_2O (or MeOH) with the hydroxyalkyl group, the cyclization of **1** (n = 1) was carried out with CF_3COOH (cat.) in DMSO containing H_2O (4 equiv.) during 2 h. This experiment gave a 54:46 ratio of ketal **3** (n = 1) and cyclohexanone.

Scheme 4



11 (*Scheme 4*) gave exclusively the corresponding ketal **12** [11], none of the corresponding mixed ketal **13** being observed[2]). In this case, formation of **12** is the result of an *exo-trig*-cyclization process, which as previously mentioned should take place with ease; therefore, the formation of **13** *via* an intermolecular process cannot compete.

Due to stereoelectronic effects which impose a conformational restriction, the activation enthalpy of the *endo-trig*-cyclization process should decrease as the length of the hydroxyalkyl side chain increases (ease of cyclization: 7 > 6 > 5). On the other hand, the entropy factor should favor the cyclization to small rings (ease of cyclization: 5 > 6 > 7). As these factors work in opposite directions, the relatively close ratio of cyclization and hydrolysis (or methanolysis) can, therefore, be explained qualitatively on that basis.

To gain a better understanding of the enthalpy contribution in these reactions, we have studied the reaction pathways for the acid hydrolyses of five-, six-, and seven-membered-ring ketals along with 1,1-dimethoxycyclohexane for comparison using the semi-empirical *Hamiltonian* AM1[3]). We have calculated the conformations of the starting neutral ketals, their protonated forms, and the corresponding oxocarbenium ions. Each ketal having two O-atoms can be in principle protonated at four positions. For simplicity, only the axially protonated positions are reported here, since protonation at the equatorial O-atom led quantitatively to similar results. We have also looked for cleavage

[2]) The mixed hydroxyalkyl methyl ketals **9** (n = 1–3), **10**, and **13** can be obtained in quantitative yield from the corresponding mixed ketals **6** (n = 1–3), **7**, and **11**, when the NBS reaction is carried out in MeOH as solvent.

[3]) Computational procedure: All the calculations were done at the RHF level. The first input files for MOPAC 6.00 were created by means of SYBYL 6.01 (*Tripos Associates, Inc.*: 16995 Hanley Rd, Suite 303, St. Louis, Missouri 63144-2913, USA) for *IBM RISC 6000* computers. The gradient norms of these draft structures were then fully optimized using EF or TS subroutines.

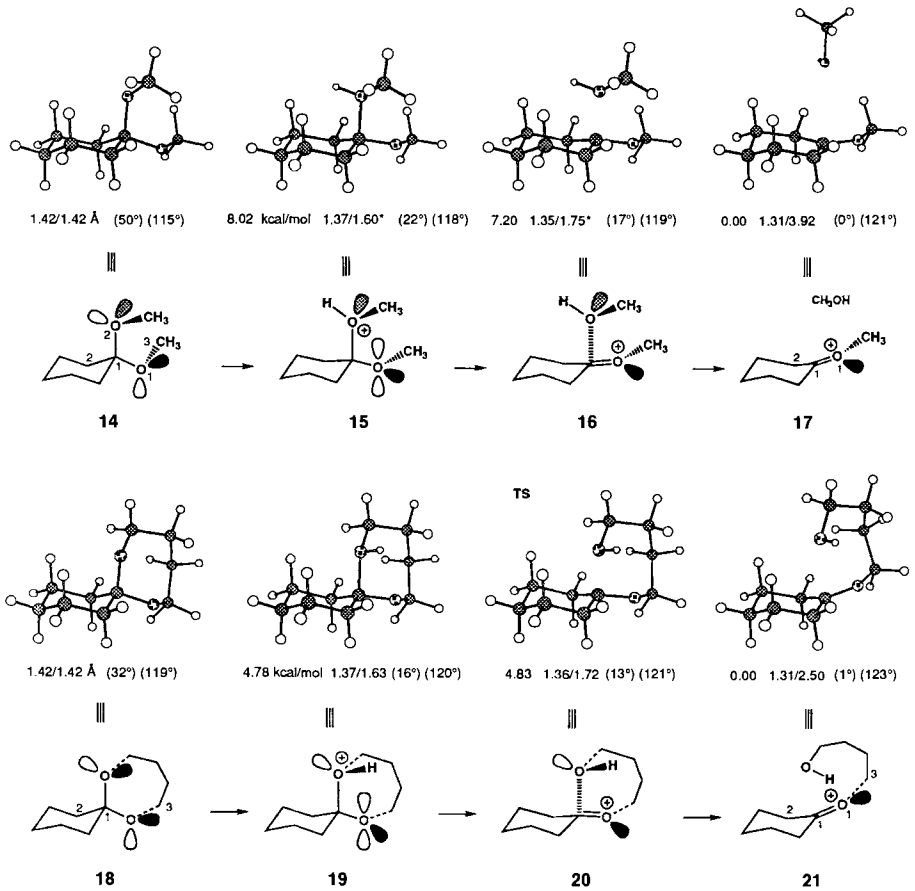


Fig. 1. *Relative heat of formation and* d(*C(1)–O(1)*)/d(*C(1)–O(2)*) *for* **14–21**. In parentheses: the angles C(2)–C(1)–O(1)–C(3) and C(1)–O(1)–C(3), resp. *: Fixed reaction coordinate.

transition structures [14]. These results are described in *Figs. 1* and *2* where various angles are specified.

In ketals **14**, **18**, and **22**, the C–O bond lengths at the anomeric center are all equal (1.42 Å) in agreement with the fact that each O-atom of the ketal function has one anomeric effect. In the case of 1,3-dioxolane **26**, these C–O bonds are also of equal length but longer (1.43 Å) due to the geometry of the strained five-membered ring which is of course quite different from all previous cases.

Upon axial protonation of all four ketals, major structural changes occur: the bond length defined by the anomeric C-atom and the protonated O-atom (C(1)–O(2)) increases, whilst that defined by the same anomeric C-atom and the other O-atom (C(1)–O(1)) diminishes; the dihedral angle C(2)–C(1)–O(1)–C(3) decreases, as the short C(1)–O(1) bond tends to assume a double-bond geometry; and the C(1)–O(1)–C(3) angle increases as the O-atom O(1) rehybridizes from sp^3 in the neutral ketal to sp^2 in the oxocarbenium ion.

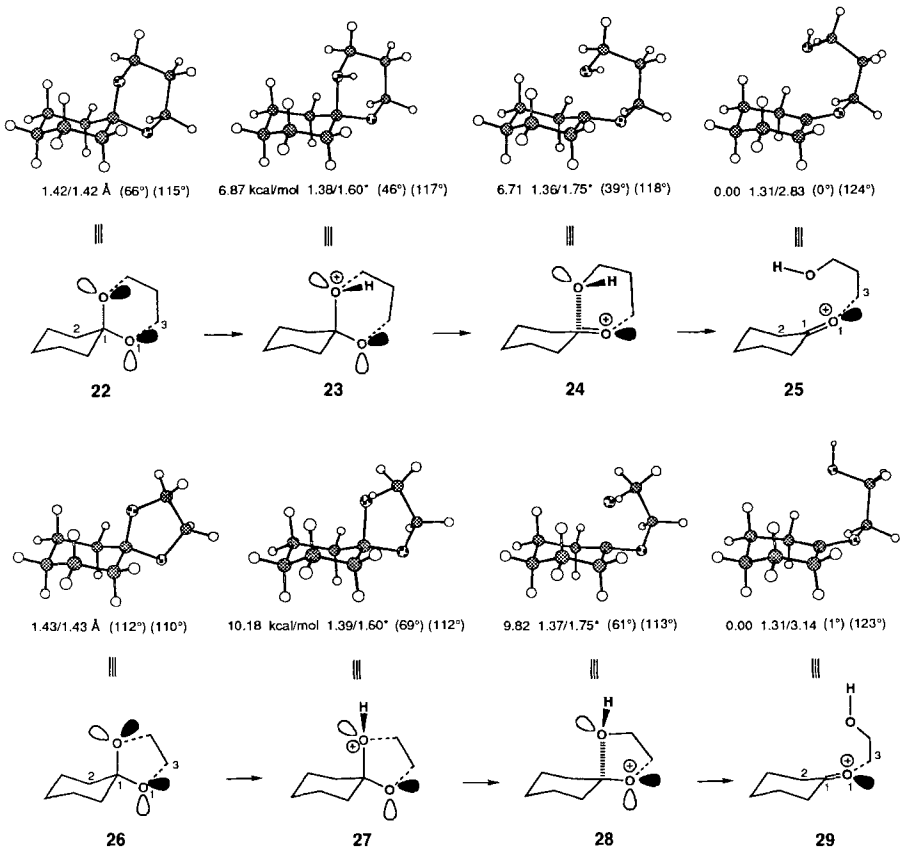


Fig. 2. *Relative heat of formation and* d(*C(1)–O(1)*)/d(*C(1)–O(2)*) *for* **22**–**29**. In parentheses: the angles C(2)–C(1)–O(1)–C(3) and C(1)–O(1)–C(3), resp. *: Fixed reaction coordinate.

In the dimethyl ketal **14**, upon protonation of the axial MeO group, the dihedral angle defined by C(2), C(1), O(1), and CH_3 diminishes from 50° to 22°, the pseudo-equatorial O-atom O(1) appears to be already sp^2-hybridized (angle C(1)–O(1)–C(3) 118°) in the protonated form **15**, and as the reaction proceeds the dihedral angle vanishes to 0°. The difference in energy between the protonated form **15** and the oxocarbenium ion **17** is 8.02 kcal/mol, and no energy barrier is found between these two structures. No energy barrier has also been found after protonation in the other ketals **18**, **22**, and **26**[4]); such results

[4]) A transition structure **20** (TS; *Fig. 1*) was actually found on the potential-energy surface for the seven-membered ring-protonated ketal. However, due to the very small energy gap between this transition structure **20** and **19** (0.05 kcal/mol), the corresponding energy barrier can be omitted in the discussion. The bond length between the anomeric C-atom and the protonated O-atom in the transition structure **20** is 1.72 Å. For comparison, the same bond-length reaction coordinate was constrained at 1.75 Å in **16**, **24**, and **28** (*Fig. 2*), although these structures are not stationary points on the potential-energy surface. The structures **15**, **23**, and **27** are not stationary points either, their C(1)–O(2) bond-length coordinate has been constrained at 1.6 Å in agreement with other theoretical calculations [1] [15].

have been previously observed in our AM1 calculations on spiroketals [1]. The case of the seven-membered ketal **18** is very similar to ketal **14**. The C(2)–C(1)–O(1)–C(3) dihedral angle for the protonated ketal **19**, which is 16°, and the C(1)–O(1)–C(3) angle of 120° indicate that the O-atom O(1) is also sp^2-hybridized; the difference in energy between **19** and the oxocarbenium ion **21**[5]) is notably low at 4.78 kcal/mol.

In the case of the six-membered ketal **22**, a large C(2)–C(1)–O(1)–C(3) dihedral angle (46°) is maintained in the protonated form **23** which vanishes fully only in the oxocarbenium ion **25**. The O-atom O(1) appears to become sp^2-hybridized only in the vicinity of the oxocarbenium ion, and the energy difference between **23** and **25** has now increased to 6.87 kcal/mol. This trend further increases in the five-membered ketal **26**. With a 69° dihedral angle, O(1) must be sp^3-hybridized in the protonated ketal **27**, and this is further confirmed in the C(1)–O(1)–C(3) angle of 112°. The difference in energy between **27** and the oxocarbenium ion **29** has now reached 10.18 kcal/mol.

Thus, it appears clear that, throughout the process, an oxygen lone pair must be periplanar with the leaving group. However, when its O-atom (O(1)) has no choice but taking an sp^3 hybridization (case of **26**) or is part of a severely twisted π bond (case of **22**), the energy of the overall process is much higher than when this O-atom is geometrically free to become sp^2-hybridized (cases of **14** and **18**). This is in agreement with recent *ab initio* calculation of *Grein* which indicates a strong anomeric effect (> 6 kcal/mol) and a preference for sp^2-hybridized O-atom in protonated dihydroxymethane; the length of the C–O bonds (*ca.* 1.38 and 1.6 Å) also agree [1] [5].

The large energy difference of 8.0 kcal/mol calculated in the case of dimethyl ketal **14** comes from the fact that the process **15** → **17** is the reverse of an intermolecular reaction. In this case, the steric interaction due to the MeOH group in the protonated ketal **15** completely disappears on formation of the oxocarbenium ion **17** and MeOH.

Thus, the above AM1 results indicate that on the basis of $\Delta H^{\neq}$ only, the ease of cyclization would be 7 > 6 > 5, and this phenomenon is due to a severe conformational restriction imposed by stereoelectronic requirements. On the other hand, $\Delta S^{\neq}$ will be working in the opposite direction favoring the five-membered-ring cyclization process. The real energy barrier ($\Delta G^{\neq}$) will thus be the results of enthalpies which are opposing entropy effects, and which are different in the four types of ketals.

As a result, and as observed experimentally, the ratio of intermolecular *vs.* intramolecular processes do not vary a great deal in five-, six-, and seven-membered ring cases, because enthalpy and entropy terms must compensate giving similar free-energy reaction profiles for all three cases.

McClelland et al. [16] have recently reported that the acid-catalyzed hydrolysis of 2-hydroxyethyl and 3-hydroxypropyl enol ethers of acetophenone yields a mixture of acetophenone and the corresponding cyclic ketal. The rate constant for forming five-

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[5]) The oxocarbenium ions **21**, **25**, and **29** (*Figs. 1* and *2*) are geometrically related to the corresponding protonated ketals **19**, **23**, and **27** by continuous shortening of the C–O bond-length reaction coordinate. These folded structures are energetically close to the true global minima which are also folded. In such conformations, the alcohol O-atom remains close to the oxocarbenium cation to stabilize this positively charged centre, the calculations corresponding to gas-phase cases. Such stabilizing effects do not take place for rotamers having their side chain in a fully extended geometry, their energies are consequently much larger than the global minima. The relative energies of the extended conformers corresponding to **21**, **25**, and **29** are 4.09, 5.47, and 5.51 kcal/mol, respectively.

membered ketal is very similar to the value for forming the six-membered ketal. These results can also be explained by the above rationalization.

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Experimental Part

General. All the solvents used were dried and purified by the usual methods. The cyclic ketals were prepared according to the procedures described in [5] [8] [9] [11]. The flash chromatography (FC) purifications were carried out on silica gel *Merck 60*, 230–400 mesh. IR Spectra: on a *Perkin-Elmer 1600* series FTIR. NMR Spectra: on a *Bruker AC 300* instrument. MS: on a *ZAB-1F* spectrometer.

Synthesis of 2-[(Cyclohex-1-enyl)oxy]ethanol 1 ($n = 1$). A soln. of **3** ($n = 1$) (2.84 ml, 20 mmol) and $(i\text{-Pr})_2NEt$ (4.6 ml, 28 mmol) in CH_2Cl_2 (20 ml) was cooled in an ice-water bath, and Me_3SiOTf (5.0 ml, 26 mmol) was added dropwise. The soln. was warmed to r.t. and stirred overnight. Bu_4NF (1M in THF, 30 µl, 30 mmol) was added and the mixture stirred for 3 h. The solvent was evaporated *in vacuo* and the residue purified by FC (hexane/acetone/Et_3N 85:14:1) to give **1** ($n = 1$; 2.68 g, 94%). IR (film): 3359, 1660, 1190. ^{1}H-NMR (C_6D_6): 4.46 (*t*, $J = 3.5$, CH=CO); 3.52 (br., CH_2O); 3.45 (*t*, $J = 4.5$, CH_2O); 2.1–1.95 (*m*, 2 CH_2); 1.55–1.35 (*m*, CH_2). ^{13}C-NMR (C_6D_6): 154.70 (CH=*C*O); 94.11 (*C*H=CO); 67.91 (CH_2O); 61.27 (CH_2OH); 28.09; 23.82; 23.19; 23.09 (CH_2). MS: 142 (M^+). HR-MS: calc. for $C_8H_{14}O_2$: 142.0994; found: 142.0988.

Synthesis of 1 ($n = 2, 3$) and 2. *General Procedure: 3-[(Cyclohex-1-enyl)oxy]propan-1-ol* (**1**; $n = 2$). To a soln. of **3** ($n = 2$; 1.56 g, 10 mmol) in CH_2Cl_2 (10 ml) was added $(i\text{-Pr})_3Al$ (15.0 ml, 1M in toluene, 15 mmol) at −78°. The soln. was warmed gradually to r.t. and stirred for 12 h. The mixture was then poured into aq. NaOH (2N, 100 ml) and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FC (hexane/acetone/Et_3N 85:14:1) to yield **1** ($n = 2$; 1.28 g, 82%). IR (film): 3356, 1666, 1188. ^{1}H-NMR (C_6D_6): 4.53 (*t*, $J = 3.5$, CH=CO); 3.58 (*t*, $J = 6$, CH_2O); 3.51 (*m*, CH_2OH); 2.1–1.95 (*m*, 2 CH_2); 1.67 (*quint.*, $J = 6$, $OCH_2CH_2CH_2O$); 1.55–1.4 (*m*, 2 CH_2). ^{13}C-NMR (C_6D_6): 154.43 (CH=*C*O); 93.47 (*C*H=CO); 63.51 (CH_2O); 59.79 (CH_2OH); 32.09; 27.84; 23.48; 22.84; 22.77 (CH_2). MS: 156 (M^+). HR-MS: calc. for $C_9H_{16}O_2$: 156.1150; found: 156.1147.

4-[(Cyclohex-1-enyl)oxy]butan-1-ol (**1**; $n = 3$): Yield 78%. IR (film): 3354, 1668, 1193. ^{1}H-NMR (C_6D_6): 4.54 (*t*, $J = 3.5$, CH=CO); 3.50 (*t*, $J = 6$, CH_2O); 3.37 (*t*, $J = 6.5$, CH_2OH); 2.15–2.0 (*m*, 2 CH_2); 1.65–1.4 (*m*, 4 CH_2). ^{13}C-NMR (CD_3CN): 154.88 (CH=*C*O); 93.92 (*C*H=CO); 66.31 (CH_2O); 61.79 (CH_2OH); 29.76; 28.02; 26.01; 23.66; 23.17; 23.03 (CH_2). MS: 170 (M^+). HR-MS: calc. for $C_{10}H_{18}O_2$: 170.1307; found: 170.1302.

2-{[(Cyclohex-1-enyl)oxy]methyl}benzenemethanol (**2**): Yield 94%. IR (film): 3399, 1666, 1449, 1187. ^{1}H-NMR (C_6D_6): 7.3–7.2 (*m*, 2 arom. H); 7.15–7.05 (*m*, 2 arom. H); 4.66 (*t*, $J = 3.5$, CH=CO); 4.62 (*s*, CH_2O); 4.47 (*d*, $J = 5$, CH_2OH); 2.1–1.95 (*m*, 2 CH_2); 1.5–1.35 (*m*, 2 CH_2). ^{13}C-NMR (CD_3CN): 154.75 (CH=*C*O); 140.66; 135.68; 129.03; 128.42; 128.12; 127.66; 94.96 (*C*H=CO); 66.49 (CH_2O); 61.74 (CH_2OH); 27.95; 23.71; 23.16; 22.97 (CH_2). MS: 218 (M^+), 200 ($[M - H_2O]^+$). HR-MS: calc. for $C_{14}H_{18}O_2$: 218.1307; found: 218.1305.

Synthesis of Mixed Pent-4-enyl Ketals 6 ($n = 1, 2$) and 7. – *General Procedure: 2-{{1-[(Pent-4-enyl)oxy]-cyclohexyl}oxy}ethanol* (**6**; $n = 1$). A mixture of **1** ($n = 1$; 0.43 g, 3 mmol), pent-4-en-1-ol (1.25 ml, 12 mmol), and AcOH (0.36 ml, 6 mmol) in benzene (5 ml) was stirred for 34 h at r.t., then Et_3N (1 ml) was added and the mixture evaporated *in vacuo*. The residue was purified by FC (hexane/acetone/Et_3N 85:14:1) to yield **6** ($n = 1$; 0.24 g, 36%). IR (film): 3433, 1639, 1450, 1105. ^{1}H-NMR (C_6D_6): 5.77 (*m*, *C*H=CH_2); 5.1–4.95 (*m*, CH=*C*H_2); 3.54 (*t*, $J = 5$, CH_2O); 3.4–3.25 (*m*, OCH_2, *C*H_2OH); 2.15–2.05 (*m*, 2 CH_2); 1.7–1.2 (*m*, 6 CH_2). ^{13}C-NMR (C_6D_6): 138.73 (*C*H=CH_2); 114.78 (CH=*C*H_2); 99.93 (OCO); 62.25 (CH_2O); 61.34 (CH_2OH); 58.93 (CH_2O); 33.93; 31.00; 29.62; 25.93; 23.23 (CH_2). MS: 228 (M^+). HR-MS: calc. for $C_{11}H_{19}O$ ($[M - C_2H_5O_2]^+$): 167.1436; found: 167.1431; calc. for $C_8H_{15}O_2$ ($[M - C_5H_9O]^+$): 143.1072; found: 143.1069.

3-{{1-[(Pent-4-enyl)oxy]cyclohexyl}oxy}propan-1-ol (**6**; $n = 2$). Yield 36%. IR (film): 3418, 1641, 1443, 1059. ^{1}H-NMR (C_6D_6): 5.80 (*m*, *C*H=CH_2); 5.1–4.95 (*m*, CH=*C*H_2); 3.64 (br., *C*H_2OH); 3.44 (*t*, $J = 6.0$, CH_2O); 3.32 (*t*, $J = 6.5$, CH_2O); 2.12 (*m*, *C*H_2CH=CH_2); 1.9–1.5 (*m*, 4 CH_2); 1.5–1.35 (*m*, 4 CH_2); 1.3–1.2 (*m*, CH_2). ^{13}C-NMR (C_6D_6): 138.74 (*C*H=CH_2); 114.77 (CH=*C*H_2); 100.02 (OCO); 61.71; 58.96 (CH_2O); 58.52 (CH_2OH); 33.88; 32.85; 31.02; 29.69; 25.92; 23.26 (CH_2). MS: 242 (M^+). HR-MS: calc. for $C_{11}H_{19}O$ ($[M - C_3H_7O_2]^+$): 167.1436; found: 167.1433; calc. for $C_9H_{17}O_2$ ($[M - C_5H_9O]^+$): 157.1228; found: 157.1226.

2-{{{1-[(Pent-4-enyl)oxy]cyclohexyl}oxy}methyl}benzenemethanol (7). Yield 34%. IR (film): 3430, 1450, 1046. ^{1}H-NMR (C_6D_6): 7.3–7.1 (*m*, 4 arom. H); 5.77 (*m*, C*H*=CH$_2$); 5.05–4.95 (*m*, CH=C*H*$_2$); 4.61 (br. C*H*$_2$OH); 4.48 (*s*, CH$_2$O); 3.27 (*t*, *J* = 5.5, CH$_2$O); 2.10 (*m*, C*H*$_2$CH=CH$_2$); 1.7–1.15 (*m*, 6 CH$_2$). ^{13}C-NMR (CD_3CN): 140.71; 137.26; 129.13; 128.27; 127.75 (arom. C); 139.19 (*C*H=CH$_2$); 114.60 (CH=*C*H$_2$); 100.92 (OCO); 62.20 (CH$_2$O); 60.05 (CH$_2$OH); 59.41 (CH$_2$O); 40.00; 30.83; 29.58; 25.78; 23.31 (CH$_2$). MS: 304 (M^+). HR-MS: calc. for $C_{19}H_{28}O_3$: 304.2038; found: 304.2036.

Synthesis of Mixed Pent-4-enyl Ketals 6 (*n* = 3) and 8. – *General Procedure: 4-{{1-[(Pent-4-enyl)oxy]cyclohexyl}oxy}butan-1-ol* (**6**; *n* = 3). To a soln. of **1** (*n* = 3; 0.51 g, 3 mmol) and Et_3N (0.5 ml) in THF (3 ml) was added AcCl (0.47 ml, 6 mmol) at 0°, and the mixture was stirred for 20 min at r.t. The mixture was diluted by adding Et_2O (40 ml), washed with H_2O (2 × 15 ml), dried ($MgSO_4$) and the resulting org. extract concentrated *in vacuo* to dryness. The crude product and pent-4-en-1-ol (0.39 ml, 4.5 mmol) in CH_2Cl_2 (2 ml) was mixed with $Ph_3P \cdot HBr$ (56 mg, 0.15 mmol) and stirred for 20 min at r.t.; then, hexane (40 ml) and Et_3N (60 µl) were added, and the resulting soln. was washed with H_2O (2 × 10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (hexane/acetone/Et_3N 90:9:1). The resulting acetate was hydrolyzed with a mixture of aq. NaOH (2N, 3 ml) and MeOH (6 ml) for 50 min at r.t. The soln. was diluted by adding H_2O (20 ml) and extracted with Et_2O (3 × 30 ml). The Et_2O phase was dried (Na_2SO_4) and concentrated *in vacuo* to dryness. The residue was purified by FC (hexane/acetone/Et_2O 84:15:1) to yield **6** (*n* = 3; 0.45 g, 58%). IR (film): 3385, 1448, 1441, 1101. ^{1}H-NMR (C_6D_6): 5.80 (*m*, C*H*=CH$_2$); 5.1–4.9 (*m*, CH=C*H*$_2$); 3.46 (br., C*H*$_2$O); 3.4–3.35 (*m*, 2 CH$_2$O); 2.15 (*m*, C*H*$_2$CH=CH$_2$); 1.7–1.25 (*m*, 8 CH$_2$). ^{13}C-NMR (CD_3CN): 139.27 (*C*H=CH$_2$); 117.81 (CH=*C*H$_2$); 114.53 (OCO); 62.04 (OCH$_2$); 59.53 (CH$_2$OH); 58.97 (OCH$_2$); 34.00; 30.86; 30.24; 29.68; 26.96; 25.88; 23.30 (CH$_2$). MS: 256 (M^+). HR-MS: calc. for $C_{11}H_{19}O$ ([$M - C_4H_9O_2$]$^+$): 167.1436; found: 167.1431; calc. for $C_{10}H_{19}O_2$ ([$M - C_5H_9O$]$^+$): 171.1385; found: 171.1382.

trans-*3-[(4-Hydroxybutyl)-3-[(pent-4-enyl)oxy]perhydroisochromene* (**11**): Yield 60%. IR (film): 3385, 1461, 1447, 1057. ^{1}H-NMR (C_6D_6): 5.80 (*m*, C*H*=CH$_2$), 5.1–4.9 (*m*, CH=C*H*$_2$); 3.55–3.45 (*m*, C*H*$_2$O); 3.4–3.3 (*m*, 2 CH$_2$O); 2.15 (*m*, C*H*$_2$CH=CH$_2$); 1.85–0.7 (*m*, 9 CH$_2$, 2 CH). ^{13}C-NMR (CD_3CN): 139.31 (*C*H=CH$_2$); 117.81 (CH=*C*H$_2$); 100.13 (OCO); 66.28; 61.96 (CH$_2$O); 58.79 (CH$_2$OH); 42.01; 40.64; 37.11; 35.90; 33.33; 31.00; 29.62; 28.00; 26.56; 26.30; 20.21 (CH$_2$, CH). MS: 223 ([$M - C_4H_9O$]$^+$), 211 ([$M - C_5H_9O$]$^+$). HR-MS: calc. for $C_{14}H_{23}O_2$ ([$M - C_4H_9O$]$^+$): 223.1698; found: 223.1693; calc. for $C_{13}H_{23}O_2$ ([$M - C_5H_9O$]$^+$): 211.1698; found: 211.1694.

Acid-Catalyzed Cyclization *vs.* Hydrolysis of Hydroxyalkyl Enol Ethers 1 (*n* = 1, 2, 3) and 2. – *General Procedure*: To a soln. of **1** (*n* = 1; 14.5 mg, 0.1 mmol) and H_2O (1.8 µl, 0.1 mmol) in CD_3CN (0.5 ml) in a NMR tube was added AcOH (12.0 µl, 0.2 mmol). The reaction course was followed by ^{1}H-NMR and the products ratio determined by integration of appropriate proton peaks (C*H*$_2$OR and C*H*$_2$OH).

All the cyclic ketals formed were found to be stable unter the reaction conditions. The results are shown in *Scheme 2*.

NBS-Catalyzed Cyclization *vs.* MeOH Addition of Mixed Pent-4-enyl Ketals 6 (*n* = 1, 2, 3), 7, and 11. – *General Procedure*. To a soln. of **6** (*n* = 1; 22.9 mg, 0.1 mmol) and MeOH (16 µl, 0.4 mmol) in CD_3CN (0.5 ml) in a NMR tube was added NBS (35.8 mg, 0.2 mmol). The reaction was monitored by ^{1}H-NMR, and, when the substrate had completely disappeared (~ 10 min), Et_3N (28.0 µl, 0.2 mmol) was added. The product compositions were determined according to the integrations of appropriate proton peaks by ^{1}H-NMR (C*H*$_2$OR and C*H*$_2$OH).

The results are shown in *Scheme 3*. When MeOH (or CD_3OD) was used as solvent, the cyclization could not compete with the addition of MeOH, and only the mixed ketals **9** (*n* = 1, 2, 3), **10**, and **13** were obtained.

2-[(1-Methoxycyclohexyl)oxy]ethanol (**9**; *n* = 1): IR (film): 3430, 1104. ^{1}H-NMR (C_6D_6): 3.53 (*m*, CH$_2$O); 3.30 (*t*, *J* = 4.5, CH$_2$O); 3.02 (*s*, MeO); 1.71 (br., OH); 1.65–1.2 (*m*, 5 CH$_2$). ^{13}C-NMR (C_6D_6): 100.10 (OCO); 62.21 (CH$_2$O); 61.49 (CH$_2$O); 47.20 (MeO); 33.47; 25.92; 23.16 (CH$_2$). MS: 174 (M^+), 157 ([M – OH]$^+$), 143 ([M – MeO]$^+$). HR-MS: calc. for $C_9H_{18}O_3$: 174.1256; found: 174.1247.

3-[(1-Methoxycyclohexyl)oxy]propan-1-ol (**9**; *n* = 2): IR (film): 3407, 1102. ^{1}H-NMR (C_6D_6): 3.72 (br., CH$_2$O); 3.47 (*t*, *J* = 6.5, CH$_2$O); 3.10 (*s*, MeO); 2.69 (br., OH); 1.75 (*m*, C*H*$_2$CH$_2$O); 1.65–1.55 (*m*, 2 CH$_2$); 1.5–1.45 (*m*, 2 CH$_2$); 1.4–1.25 (*m*, 2 CH$_2$). ^{13}C-NMR (C_6D_6): 100.14 (OCO); 61.33; 58.13 (CH$_2$O); 47.21 (MeO); 33.43; 32.97; 25.93; 23.20 (CH$_2$). MS: 188 (M^+), 171 ([M – OH]$^+$). HR-MS: calc. for $C_{10}H_{20}O_3$: 188.1412; found: 188.1406.

4-[(1-Methoxycyclohexyl)oxy]butan-1-ol (**9**; *n* = 3): IR (film): 3418, 1101. ^{1}H-NMR (C_6D_6): 3.45 (br., CH$_2$O); 3.32 (*t*, *J* = 5.5, CH$_2$O); 3.06 (*s*, MeO); 1.65–1.55 (*m*, 2 CH$_2$); 1.6–1.4 (*m*, 4 CH$_2$); 1.3–1.2 (*m*, 2 CH$_2$). ^{13}C-NMR (C_6D_6): 100.09 (OCO); 62.59, 59.53 (CH$_2$O); 47.23 (MeO); 33.56; 30.62; 27.20; 26.00; 23.13 (CH$_2$). MS: 202 (M^+), 171 ([M – MeO]$^+$). HR-MS: calc. for $C_{11}H_{22}O_3$: 202.1569; found: 202.1563.

2-{[(1-Methoxycyclohexyl)oxy]methyl}benzenemethanol (**10**): IR (film): 3430, 1089. ^{1}H-NMR (C_6D_6): 7.3–7.2 (*m*, 2 arom. H); 7.15–7.05 (*m*, 2 arom. H); 4.60 (*s*, CH_2O); 4.44 (*s*, CH_2O); 2.99 (*s*, MeO); 1.65–1.5 (*m*, 2 CH_2); 1.45–1.35 (*m*, 2 CH_2); 1.25–1.15 (*m*, CH_2). ^{13}C-NMR (CD_3CN): 140.75; 137.19; 129.23; 128.28; 128.11; 127.79 (arom. C); 101.03 (OCO); 62.19; 59.97 (CH_2O); 47.52 (MeO); 33.50; 25.75; 23.28 (CH_2). MS: 250 (M^+), 232 ($[M - H_2O]^+$). HR-MS: calc. for $C_{15}H_{20}O_2$ ($[M - H_2O]^+$): 232.1463; found: 232.1458; calc. for $C_{14}H_{19}O_2$ ($[M - MeO]^+$): 219.1385; found: 219.1376.

trans-*3-(4-Hydroxybutyl)-3-methoxyperhydroisochromene* (**13**): IR (film): 3385, 1183, 1057. ^{1}H-NMR (C_6D_6): 3.45 (*dd*, J = 11, 4.5, 1 H, CH_2O); 3.4–3.25 (*m*, CH_2OH, 1 H of CH_2O); 3.13 (*s*, MeO); 1.8–0.65 (*m*, 8 CH_2, 2 CH). ^{13}C-NMR (C_6D_6): 100.11 (OCO); 66.31; 62.45 (CH_2O); 47.09 (MeO); 41.85; 40.48; 36.45; 35.67; 33.34; 33.20; 27.94; 26.61; 26.32; 20.28 (CH, CH_2). MS: 211 ($[M - MeO]^+$), 169 ($[M - C_4H_9O]^+$). HR-MS: calc. for $C_{13}H_{23}O_2$ ($[M - MeO]^+$): 211.1698; found: 211.1694; calc. for $C_{10}H_{17}O_2$ ($[M - C_4H_9O]^+$): 169.1228; found: 169.1227.

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