MECHANISM OF CYCLIC ACETAL FORMATION

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Abstract—The mechanism of formation of 1,3-dioxolanes is considered in the light of Baldwin's rule for ring-closure.

The mechanism for the acid-catalyzed formation of acetals and ketals has been extensively studied and several good reviews are now available.[1] It has been shown to proceed through the following mechanism in which the removal of a water molecule is said to be the rate determining step (eqn 1).
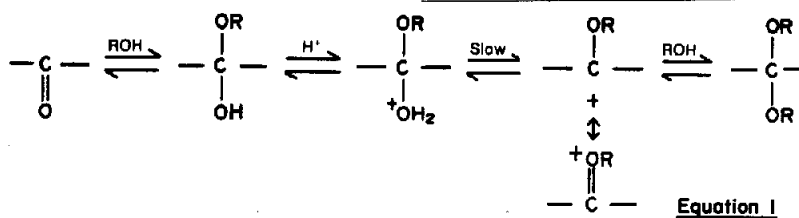
should not react under the usual conditions. However this cyclization proceeded in 60% yield[3] (eqn 2). Since Path II is not available and Path I is not "favourable" by Baldwin's rules,[2] the only available alternative is Path III. Baldwin *et al.* have clearly demonstrated that compounds 2 and 3 do not cyclize to give 4 and 5 respec-


Equation 1

When this mechanism is extended to the acid-catalyzed formation of dioxolanes, it presents some problems which are summarized in Scheme 1.

If the protonated hemiacetal *A* eliminates a mole of water through the participation of lone pair of electrons on the neighbouring oxygen, the resultant intermediate would have two resonance forms viz. *B* and *B'*. Therefore one would expect a double bond character between the carbon and oxygen. Cyclization of this intermediate via Path I would be a 5-Endo-Trig cyclization, which is "unfavourable" by Baldwin's rules for ring closure.[2] The intermediate *B* could loose an α-proton and become an enol ether *C* which could cyclize via a "favourable" 5-Exo-Trig cyclization (Path II). Alternatively the protonated hemiacetal *A* could directly cyclize via another "favourable" 5-Exo-Tet cyclization (Path III).

If the dioxolane ring formation were to proceed via an enol ether (Path II), an α,α disubstituted aldehyde like 1

tively under basic conditions[4] (eqn 3). This reaction is analogous to Path I in Scheme 1. They have shown that the lack of ring closure (or ring opening) is a result of a kinetic rather than a thermodynamic barrier.

It might be argued that the above conclusions on

Equation 2

Scheme 1.

2	R=H		4	R=H	
3	R=OMe		5	R=OMe	Equation 3

Table 1.

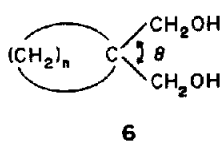| n	6	5	4	3
K	61	26	11	0.94
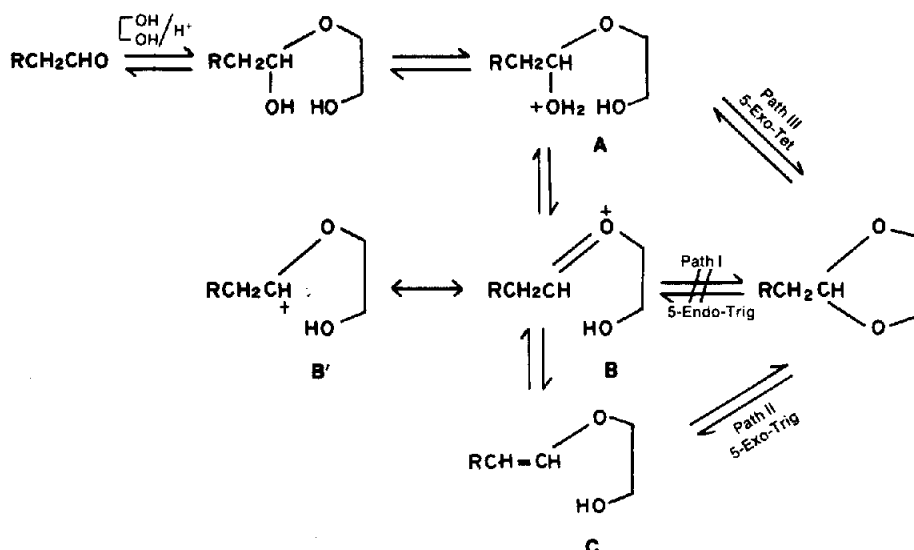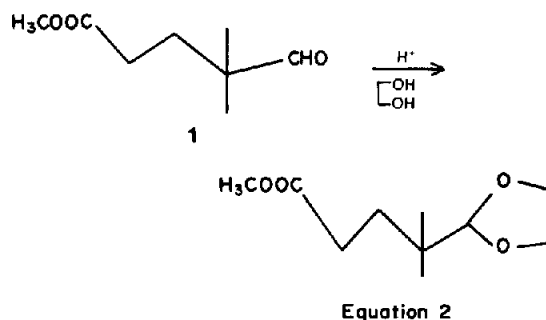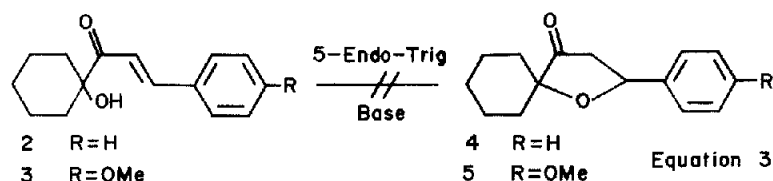
acid-catalyzed acetal formation reactions rely heavily on the assumption that Baldwin's rules for ring closure are applicable to transient species of the type B. While this question is difficult to answer at the present stage,[5] a few kinetic data available in the literature tend to support the above mechanisms. After the excellent review by Cordes[1c] (1967), a few papers have appeared which specially deal with the kinetics of acid-catalyzed formation/hydrolysis reactions of cyclic acetals and ketals. These have been reviewed by Hine.[6]

Anteunis and Rommelaere have estimated the equilibrium constants for the formation of cyclic ketals from acetone and various diols at 25° using NMR.[7] They found that 1,2-ethanediol and 1,3-propanediol react at different rates (equilibrium constant $K = 0.14$ and 0.026 respectively). One would not expect any difference in the rate of the formation of hemiketals by a mere increase in the chain length, because Skrabal and Eger have shown that the velocity constants of acid-catalyzed hydrolysis of formals of ethanol, n-propanol and n-butanol were practically same[8] (0.013, 0.0144 and 0.0143 respectively). Protonation of the hemiketal leaves two paths open for cyclization. If the reaction were to proceed via the formation of carbonium ion as the rate determining step the subsequent cyclization step would be fast and therefore the two diols (1,2-ethanediol and 1,3-propanediol) should react with comparable velocities. However if cyclization were to be the rate determining step, a 6-membered ring formation should be slower on entropy considerations. The latter was indeed found to be the case. Introduction of alkyl substituents on the carbon chain of the diols would restrict the free rotation around the C–C bonds and thereby should increase the rate of the reactions. This was again found to be true: 1,2-ethanediol $(K = 0.14)$ vs 1,2-propanediol $(K = 0.48)$; 1,3-propanediol $(K = 0.026)$ vs 2,2-dimethyl-1,3-propanediol $(K = 0.27)$.

If the cyclization were to proceed via S_N2 displacement mechanism, the bond angle sustained between the entering and leaving groups should ideally be 180°. Factors that alter this angle of approach, should also effect the velocity of the reaction. In their studies on the acid-catalyzed hydrolysis of acetals of naphthaldehydes, Newman and Dickson changed the angle θ on the 1,3-propanediol moiety 6 by changing the ring size (n) from cyclohexane to cyclopentane, cyclobutane and cyclopropane.[9] The equilibrium constants varied progressively as the angle θ was changed. The values for the ring formation reactions are given in Table 1.[6]

The above results could be interpreted as follows on the basis of studies using molecular models. When the cyclization proceeds via an S_N2 displacement mechanism the transition state would be strain free when n = 6. As θ is progressively increased, the attainment of the (preferred) angle of attack would also be altered and result in a reduced rate of reaction. As expected the strain free 6-6 ring system is formed most easily.

From the above observations it could be suggested that *at least in the case of cyclic acetal/ketal formation reactions* the final cyclization step proceeds via S_N2 displacement mechanism[10] (Path III in Scheme I).

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[5]In their paper Baldwin et al.[4] have applied their theory for ring closure reactions to a transient species i. We thank the referee
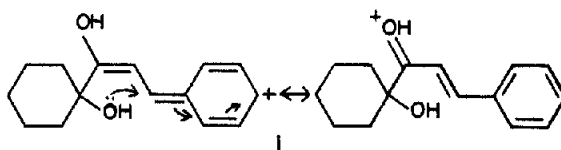
for pointing out that our species B is $>C=\overset{+}{O}\diagdown$ which is close to $>C=N\diagdown$. Though the experiments on $>C=N\diagdown$ rotation are inconclusive, the available evidence tends to indicate that the activation energy for this process should be high.[11] Calculations on protonated acetaldehyde suggest an activation energy of 27.9 kcal/mole for rotation and 18.0 kcal/mole for inversion.[11b] The values should be compared with the barrier for rotation for $>C=C<$ which is 36–60 kcal/mole. These values suggest a reduced double bond character in $>C=\overset{+}{O}\diagdown$ species and thereby question the applicability of Baldwin's concept of endo double bonds to intermediate B. It is of interest to point out here that α,β-unsaturated ketones yield β,γ-unsaturated ketals, obviously via Path II and not via Path I or Path III suggesting an inadmissible 5-Endo-Trig system to be still operative.
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[10]An example for intramolecular cyclization of an enol ether (Path II in Scheme I) is discussed in an earlier short communication (C. P. Reddy, S. M. Singh and R. Balaji Rao, *Tetrahedron Letters* 973–976 (1981)). We stand corrected on the structure 9 in the above communication and therefore the support we drew thereupon. However this does not alter the main thesis which is presented in detail in this paper.
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