Acetolysis of Cyclic Acetals: Regioselective Acylative Cleavage of Cyclic Formals

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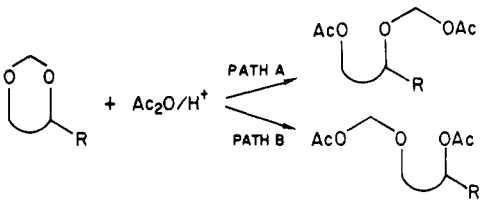
The acid-catalyzed reaction of cyclic acetals with acetic anhydride has been investigated. Acylative cleavage of cyclic formals has been found to be a clean, high-yield reaction involving rupture of the C(2)–O bond with loss of stereochemical integrity at the C(2)-position to give hemiacetal acetate products. Ring cleavage of unsymmetrically substituted cyclic formals with either acetic anhydride or acetyl chloride occurs via preferential rupture of the less congested C(2)–O bond (Scheme I, path A). Such cleavage is totally regiospecific for 1,3-dioxanes and displays high (75–85%) regioselectivity for smaller and larger ring systems. Acetolysis of cyclic acetals other than formals is a slow process that leads to loss of the aldehyde derived fragment and formation of simple diacetates. These results are rationalized in terms of rate-limiting electrophilic attack that is acutely sensitive to steric effects engendered by substituents located at positions adjacent to ring oxygens.

Acylative cleavage of acetals with acetic anhydride to give hemiacetal acetates [RCH(OR')OAc] was first reported by Claisen nearly a century ago.[2] This acid-catalyzed acetolysis[3] has been used to prepare a variety of simple hemiacetal esters[4] whose novel chemistry has attracted recent attention.[5] When the reaction is applied to unsymmetrically substituted cyclic acetals, such as the 4-substituted formal depicted in Scheme I, two modes of C–O bond cleavage may be distinguished.

The regiochemistry of the acylative cleavage of cyclic acetals was first addressed in pioneering studies of the acetolysis of carbohydrate acetals.[6] Early work by Hudson's group revealed[7] that methylene acetals linking primary and secondary hydroxyls in a carbohydrate are preferentially cleaved via path A (Scheme I) to afford products having an acetate at the primary site and an acetoxymethyl ether moiety at the secondary position. This preference for cleavage of the C–O bond remote from the substituent was subsequently observed in the acetolysis of a limited number of noncarbohydrate formals including several 4-substituted-1,3-dioxolanes[8] and Prins reaction products such as 4-(chloromethyl)-1,3-dioxane,[9] 4-phenyl-1,3-dioxane,[10–12] and 4,4-dimethyl-1,3-dioxane.[13] In contrast of this facile cleavage of cyclic formals, acetolysis of cyclic acetals prepared from other aldehydes has been reported to be a sluggish reaction[8] leading to loss of the aldehyde derived fragment and formation of simple diacetates of the precursor diols.[14]

The apparently high regioselectivity observed in the acetolysis of cyclic formals is mechanistically intriguing and potentially useful as a method for the differential functionalization of α,ω-diols.[15] Unfortunately, the regiochemistry of the acylative cleavage has, for the most part, been inferred from the results of degradation studies[7,11,13] or assumed by analogy with earlier work[6,8–10] and it is difficult to estimate the actual regioselectivity of the reactions from the reported yields of the major products. We have, therefore, reexplored the acylative cleavage of simple cyclic acetals. As we shall show in the sequel, acetolysis of cyclic formals is a clean, high-yield reaction occurring via path A of Scheme I with essentially total regiospecificity for 1,3-dioxanes and high (75–85%) regioselectivity for larger and smaller rings by a process that leads to loss of stereochemical integrity at the C(2)-formal carbon.

Scheme I



Results and Discussion

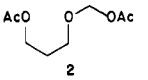
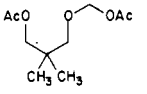
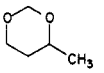
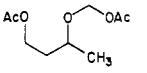
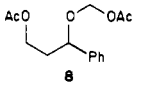
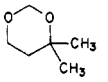
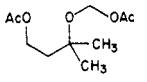
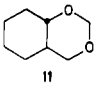
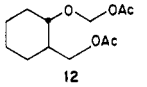
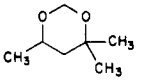
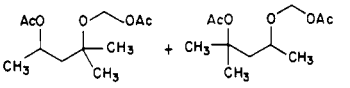
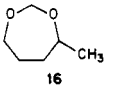
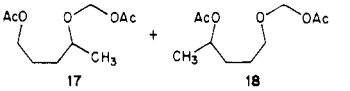
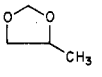
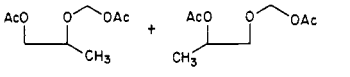
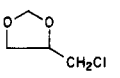
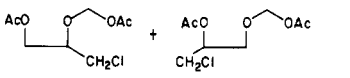
Treatment of cyclic formals at room temperature with 1.0–1.5 equiv of acetic anhydride (Ac_2O) containing a catalytic quantity of sulfuric acid results in acylative cleavage of the C(2)–O bond in good to excellent yield (Table I). The reactions are clean and are easily monitored by ^1H NMR. Such analyses reveal that cleavage of all but the highly substituted **13** is a virtually quantitative process. The lower yields reported in Table I for isolated, purified material undoubtedly reflect the sensitivity of the hemiacetal acetate products to hydrolysis in the presence of adventitious acid or base.[5]

The results (Table I) demonstrate that the cleavage of 4-substituted, 4,4-disubstituted or 4,5-disubstituted 1,3-dioxanes (Table I, entries 3–6) is totally regiospecific within the limits of detection by GLC and ^1H NMR of the crude reaction mixture. The exclusive product of these reactions results from cleavage of the C(2)–O bond that is remote from C(4)-substituent (Scheme I, path A).

(1) Taken in part from the Ph.D. Dissertation of Alberto D. Rivera, University of Connecticut, Storrs, CT, 1983.
(2) Claisen, L. *Chem. Ber.* **1898**, *31*, 1018.
(3) Hughes, W. B.; Kleene, R. D. *J. Am. Chem. Soc.* **1954**, *76*, 5161.
(4) (a) Akiyoshi, S.; Okuno, K. *J. Am. Chem. Soc.* **1954**, *76*, 693. (b) Keith, D. D.; Tortora, J. A.; Yang, R. *J. Org. Chem.* **1978**, *43*, 3711. (c) Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778. (d) Petrakis, K. S.; Fried, J. *Synthesis* **1983**, 891.
(5) Gallucci, R. R.; Going, R. C. *J. Org. Chem.* **1982**, *47*, 3517.
(6) For reviews on the acetolysis of carbohydrate acetals see: (a) Guthrie, R. D.; McCarthy, J. F. *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 11. (b) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 13.
(7) Ness, A. T.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1943**, *65*, 2215.
(8) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 734.
(9) Price, C. C.; Krishnamurti, I. V. *J. Am. Chem. Soc.* **1950**, *72*, 5335.
(10) Heslinga, A. *Recl. Trav. Chim. Pays-Bas*, **1959**, *78*, 473.
(11) Moe, H.; Corson, B. B. *J. Org. Chem.* **1959**, *24*, 1768.
(12) It has been reported that the acid-catalyzed acetolysis of 4-phenyl-1,3-dioxane affords 1-phenyl-1,3-propanediol diacetate [Shorygina, N. V. *J. Gen. Chem. USSR* **1956**, *26*, 1643] but this result has been questioned by others: cf. ref 10 and 11.
(13) Maguet, L.; Lerer, M. *Bull. Soc. Chim. Fr.* **1967**, *4172*.
(14) Haskins, W. T.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1942**, *64*, 132.
(15) Synthetic methods for the selective and differential functionalization of hydroxyl groups in diols have been recently reviewed: Wilkinson, S. G. In "Comprehensive Organic Chemistry"; Vol. 1; Pergamon Press: New York, 1979; p 681ff.

0022-3263/84/1949-4958$01.50/0

Table I. Acylative Cleavage of Cyclic Formals[a]

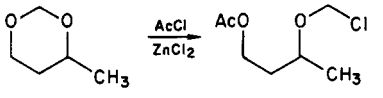
entry	acetal	reactn time, h	product	yield,[b] % (product ratio)[c]
1	 1	3	 2	81
2	 3	10	 4	96
3	 5	8	 6	90
4	 7	12	 8	85
5	 9	6	 10	88
6	 11	12	 12	77
7	 13	8	 14 15	17 (3.0:1)
8	13	168	14 + 15	50 (3.0:1)
9	 16	10	 17 18	64 (5.8:1)
10	 19	10	 20 21	67 (3.3:1)
11	 22	10	 23 24	71 (3.0:1)

[a] Reactions performed at room temperature by stirring appropriate formal with 1.0–1.5 mol equiv Ac_2O containing a catalytic quality of concentrated H_2SO_4. [b] Isolated yield, not optimized, of purified product. [c] When no ratio is given only one product was detected by GLC, ^1H NMR, and ^{13}C NMR.

In sharp contrast to the behavior of mono- and disubstituted 1,3-dioxanes, acylation of 4,4,6-trimethyl-1,3-dioxane (**13**) is a slow reaction that leads to a mixture of **14** and **15** in a ratio of 3:1. The reaction period for the room temperature cleavage of **13** had to be extended to 1 week (Table I, entries 7 and 8) in order to obtain even moderate (50%) conversion to product. However, even this rather sluggish reaction is a moderately regioselective process that involves preferential cleavage of the C(2)–O bond adjacent to the less congested C(6)-position.

Acylative cleavage of five- and seven-membered cyclic formals also leads to preferential cleavage of the C(2)–O bond that is remote from the 4-substituent (Table I, entries 9–11). The regioselectivity displayed in the reactions of these systems, while high (75–85% of the product is one regioisomer), is significantly lower than that observed in the cleavage of 1,3-dioxanes. It is of some interest (vide infra) to note that the acylative cleavage of the seven-membered 4-methyl-1,3-dioxepane (**16**), although less selective than that of the corresponding 1,3-dioxane (**5**), is more regioselective than the ring opening of 4-methyl- (**19**) or 4-(chloromethyl)-1,3-dioxolane (**22**).

Acylative cleavage of cyclic formals may also be accomplished using acetyl chloride containing a catalytic amount of anhydrous zinc chloride.[1] Such reactions produce chloromethyl ether acetates in good yield with a regiospecificity that is comparable to that of the acylations reported in Table I. Thus, for example, 4-methyl-1,3-dioxane, **5**, is converted to a single product (**25**) in 86% yield



5 **25**

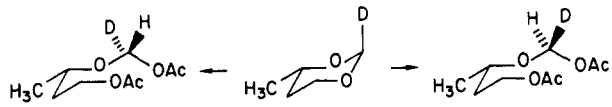
by rupture of the C(2)–O bond remote from the 4-methyl group. The high regioselectivity of these ring cleavages, coupled with the inherent reactivity of a chloromethyl ether moiety, suggests that the reaction might find use in the selective, differential functionalization of α,ω-diols via reaction of cyclic formals with acetyl chloride.

As suggested by the earlier work of Senkus[8] and Hudson,[14] acetolysis of cyclic acetals other than formals is an exceedingly slow process that does not result in the formation of hemiacetal acetates. For example, treatment of 2-methyl-1,3-dioxane with Ac_2O containing a catalytic quantity of sulfuric acid for 36 h at room temperature results in very little consumption of the acetal: 85% of the starting materials were recovered from the reaction mixture and the only product detected was the diacetate of 1,3-propanediol. The failure of 2-methyl and other 2-substituted 1,3-dioxanes to undergo facile ring cleavage[1]

indicates that carbocation stability is apparently not a major factor in determining the ease of acylative cleavage since alkyl substitution at C(2) would be expected to stabilize a cation generated at this center by rupture of the C(2)–O bond. This observation, and the high regioselectivity noted above (Table I) for cleavage of unsymmetrically substituted cyclic formals, suggests that attack of an electrophilic acylating species in the rate-limiting step of the reaction is acutely sensitive to steric effects engendered by substituents located at positions adjacent to the ring oxygens (i.e., positions C(2), C(4), and C(6) of a 1,3-dioxane).

The stereochemistry of the C(2)–O bond cleavage was investigated by examination of the acid-catalyzed acylation of a diastereoisomerically pure 2-deuterio-4-methyl-1,3-dioxane. This study was prompted by the favorable ^1H NMR spectroscopic properties of the hemiacetal diacetate, **6**, formed upon ring opening of 4-methyl-1,3-dioxane (**5**). The methylene protons in the OCH_2OAc group of **6** are diastereotopic and appear as a tightly coupled AB pattern (δ_A 5.29, δ_B 5.25, J_{AB} = 6.42 Hz). Although these resonances can not be unambiguously assigned to the diastereotopic protons of **6**, the fact that they are resolvable implies that the stereochemical course of the C–O bond cleavage may be probed by ^1H NMR if the prochiral C(2)-position of **5** can be rendered chiral by appropriate substitution with deuterium. To this end, *trans*-2-deuterio-4-methyl-1,3-dioxane (**26**) was prepared by $LiAlD_4/AlCl_3$ reduction of *trans*-2-methoxy-4-methyl-1,3-dioxane following the method Eliel and Nader.[16] The actual material used in the study was 90% pure **26** containing 10% of the cis epimer.

Ring opening of (racemic) **26** can, in principle, give two diastereoisomeric products, **27** and **28**. Product **27** is



28 **26** **27**

formed upon cleavage of the C(2)–O bond with retention of configuration at C(2) while **28** is formed via cleavage with inversion. The proton in the OCHDOAc moiety of **27** will have a different chemical shift than that of **28** and, neglecting a small isotope effect due to the geminal ^2H, they should be centered at δ 5.29 and 5.25 as found for the methylene protons in the OCH_2OAc group of **6**. Although each of these protons is coupled to a geminal ^2H, the magnitude of the expected splitting ($^2J_{H-D} = {}^2J_{AB}$ (**6**)/6.51 = 6.24 Hz/6.51 ≈ 0.96 Hz) is such that the resonance would appear as a broad singlet.

In the event, acetolysis of 90% diastereoisomerically pure **26** afforded a 1:1 mixture of **27** and **28**. Moreover, as shown in Table II, the ratio of **27**/**28** remained essentially constant at unity over the entire course of the reaction to well beyond 95% completion. The ^1H NMR spectrum of the reaction mixture shows individual broad singlets for the downfield protons of **27** and **28** (Figure 1, supplementary material). Since the cleavage proved to be nonselective, the assignment of the ^1H resonances is of no consequence and no attempt was made to accomplish such an assignment.

The possibility that rapid trans ⇌ cis epimerization of **26** was responsible for the observed nonselectivity of the C(2)–O(6) bond cleavage was considered but excluded by the observation (Table II) that the acid-catalyzed isomerization of **26** occurs at an appreciably slower rate than

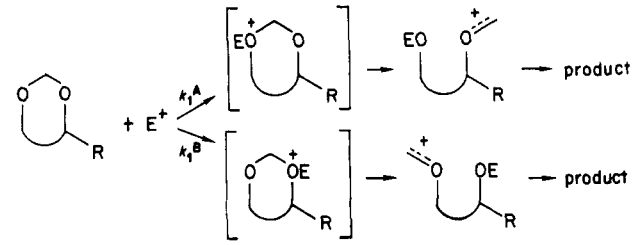
(16) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 3045.

Table II. Acylative Cleavage of *trans*-2-Deuterio-4-methyl-1,3-dioxane[a] (26)

reactn time, min	*trans*-**26**/cis epimer	yield,[b] %	**27**/**28**[c]
0	9.0		
2	4.5	67	1.2
4	3.3	75	1.1
6	2.9	80	1.1
8	2.7	84	1.1
10	2.4	87	1.1
12	2.2	88	1.0
14	1.8	90	1.2
16	1.4	90	1.0
21	1.3	92	1.2
30		95	1.0

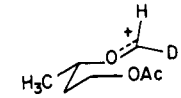
[a] Reaction performed by adding 1.05 equiv of Ac_2O containing a catalytic amount of H_2SO_4 to a solution of **26** in $CHCl_3$. [b] Total yield of **27** + **28**. [c] Determined by ^1H NMR; considered accurate to ±0.1.

Scheme II



the rate at which products are formed.

The formation of equal amounts of **27** and **28** in the cleavage reaction is attributable to rupture of the C(2)–O bond with total loss of stereochemical integrity at C(2) and this observation is most simply rationalized in terms of the intermediacy of an oxygen stabilized carbocation intermediate such as **29**. The result is, of course, also consistent



29

with a stereoselective cleavage, either with retention or inversion at C(2), provided that the initial product is rapidly isomerized via **29** to a mixture composed of equal amounts of **27** and **28**. The fact that the product ratio remains constant at unity from the earliest stages of the reaction to its completion requires that any such isomerization be such a rapid process that it would be indistinguishable in the present experiment from a nonselective cleavage.

A mechanism for the acetolysis of cyclic formals, which is consistent with the observations noted above, is proposed in Scheme II. The active electrophile is represented as E(+) in Scheme II since several reactive species are known to be present at equilibrium in a solution of Ac_2O and strong acid (i.e., protonated Ac_2O, mixed anhydride, and acylium ion)[17] and there is no evidence that allows for identification of the entity responsible for initiating the cleavage.

The slow step in the acylative cleavage presumably involves attack of the electrophile, E(+), on a ring oxygen since carbocation stability plays little role in determining the ease of reaction. The existence of a discrete oxocarbocation following rupture of the C(2)–O bond follows

(17) (a) Germain, A.; Commegras, A.; Casadevall, A. *Bull. Soc. Chim. Fr.* **1973**, 2527 and 2537. (b) Germain, A.; Commegras, A. *Bull. Soc. Chim. Fr.* **1973**, 2532.

from the observed loss of stereochemical integrity at C(2). Obviously, an oxonium ion need not necessarily be an intermediate since the reaction may well proceed by attack of E(+) on a ring oxygen with concerted, if not synchronous, cleavage of the C(2)–O bond.

Regardless of the intermediacy of oxonium ions, the regioselectivity of the acetolysis is due to the difference in transition state energies for approach of the electrophile via path A or B ($\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{A} - \Delta G^{\ddagger}_{B}$). On the basis of the assumption (implicit in Scheme II) that the ring opening is irreversible, the $\Delta\Delta G^{\ddagger}$ values for the two cleavage modes may be evaluated from the product ratios listed in Table I. The totally regiospecific acetolysis of 4-substituted 1,3-dioxanes (>99% via path A) indicates that $\Delta\Delta G^{\ddagger}$ is ≥2.7 kcal/mol. The lower selectivity observed in reactions of 4-substituted 1,3-dioxolanes (ca. 75% cleavage via path A) and 4-methyl-1,3-dioxepane (85% via path A) are consistent with smaller differences in transition state energies of ca. 0.7 and 1.1 kcal/mol, respectively.

The effect of ring size on the regioselectivity of the cleavage reaction is understandable in terms of the well-known conformational behavior of cyclic acetals. The 1,3-dioxane system adopts a well-defined chair conformation in which a C(4)-substituent preferentially occupies the equatorial position.[18] The lowest energy pathway for electrophilic attack on such a system would undoubtedly involve equatorial approach via path A of Scheme II so as to avoid the sterically unfavorable interaction engendered by the equatorial substituent at C(4). In contrast to these rather rigid constraints to electrophilic attack imposed by the 1,3-dioxane system, 4-substituted 1,3-dioxolanes and 4-substituted 1,3-dioxepanes adopt less well defined conformational minima.[19,20] The lower regioselectivity observed in acylative cleavage of five- and seven-membered cyclic formals is presumably a reflection of the ability of such rings to distort so as to minimize the steric interaction between a C(4)-substituent and an electrophilic species approaching the adjacent oxygen.

Structural Assignments. The structures reported in Table I for the acetoxymethyl ether acetates produced upon acetolysis of cyclic formals were, for the most part, established on the basis of their NMR spectroscopic properties. In particular, the ^{13}C splitting pattern observed for the acetoxymethoxy carbon of the products, OCH_2OAc, was diagnostic of the mode of ring opening.

The pattern exhibited by the methylene ^{13}C of the OCH_2OAc group is the result of a large, one-bond ^{13}C–^{1}H coupling of ca. 165 Hz and a smaller, three-bond ^{13}C–^{1}H coupling of 2–5 Hz (Table III). Thus, simple inspection of the splitting pattern for $O^{13}CH_2OAc$ gives the number of γ-hydrogens to which the ^{13}C is coupled and this serves to unambiguously establish the degree of substitution at the carbon attached to the oxygen of the hemiacetal acetate moiety: i.e., $RCOCH_2OAc$.

Proton and ^{13}C chemical shifts may also be used, albeit with less confidence, to assign structures of isomeric ring opened products. Such assignments rely on the fact that introduction of a substituent three bonds removed from a ^{13}C nucleus results in an upfield shift in the resonance of that nucleus.[21] This well-known γ-effect, which has been attributed to polarization of the C–H bond in a sterically perturbed group resulting in an increase in electron density about the carbon nucleus and a concomitant decrease in the electron density about the attached proton,[21] is evident upon examination of the ^{13}C and ^{1}H shifts of the isomeric products formed upon acetolysis of compounds **13**, **16**, **19**, and **22**. As shown in Table III, the methylene group of the OCH_2OAc moiety invariably resonates to higher field in the ^{13}C spectrum and lower field in the ^{1}H spectrum for that regioisomer having the larger number of γ-substituents (i.e., **14**, **17**, **20**, and **23**).

The structure of the single chlormethyl ether acetate (**25**) produced upon treatment of 4-methyl-1,3-dioxane with AcCl was confirmed, as described in the Experimental Section, by reduction of this material to 3-methoxy-1-butanol.

Table III. NMR Spectroscopic Data for OCH_2OAc Portion of Acetoxymethyl Ether Acetate Products[a]

compd	chemical shifts,[b] δ ^{1}H	chemical shifts,[b] δ ^{13}C	^{13}C NMR splitting pattern	$^{3}J_{^{13}C-^{1}H}$, Hz
2	5.24	89.12	triplet of triplets	2.89
4	5.22	89.38	triplet of triplets	2.65
6	AB 5.29, 5.25	87.65	triplet of doublets	4.52
8	AB 5.29, 5.02	86.94	doublet of a doublet of doublets[c]	4.11
10	5.28	83.65	triplet	0
12	AB 5.31, 5.24	87.68	triplet of doublets	4.98
14	5.28[d]	83.75	triplet	0
15	5.23[d]	87.38	triplet of doublets	3.05
17	5.29[d]	87.71	triplet of doublets	4.07
18	5.25[d]	89.18	triplet of triplets	2.60
20	5.18[d]	87.95	triplet of doublets	4.07
21	5.15[d]	89.12	triplet of triplets	3.39
23	AB 5.38, 5.34	88.16	triplet of doublets	4.30
24	5.27[d]	88.85	triplet of triplets	3.22

[a] Complete ^{1}H and ^{13}C NMR data is given in the Experimental Section. [b] In parts per million from internal Me_4Si in $CDCl_3$ solution. [c] $^{1}J_{^{13}C-^{1}H}$ = 167.85 Hz and $^{1}J_{^{13}C-^{1}H}$ = 169.90 Hz. [d] Apparent singlet at 60 MHz.

Experimental Section

Melting points and boiling points are uncorrected. Proton magnetic resonance spectra were recorded with 0.5 M solutions in $CDCl_3$ on a Varian EM-360 instrument or, where indicated, on a Bruker WH-90 or Bruker HX-270 spectrometer. Carbon-13 magnetic resonance spectra were obtained in $CDCl_3$ solution with a Bruker WH-90 spectrometer in the FT-mode and chemical shifts were assigned on the basis of multiplicities in the off-resonance proton-decoupled spectra (reported below) or completely coupled spectra (Table III) as well as from low power, single-frequency selective proton decoupling (spin-tickling, see procedure under 2) experiments. Both ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. Analytical gas-liquid chromatography (GLC) was effected with a Perkin-Elmer Model 3920-B instrument equipped with flame-ionization detectors and matched, stainless steel columns. Preparative GLC was accomplished on a Varian A-90P chromatograph fitted with one of the following 0.25-in. aluminum columns: (A) 5 ft, 5% FFAP on Chromosorb W (60/80 mesh); (B) 10 ft, 5% FFAP on Chromosorb W (60/80 mesh); (C) 6 ft, 10% SE-30 on Anakrom AB (60/80 mesh); (D) 10 ft, 10% SE-30 on Anakrom AB (60/80 mesh). Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Acetic anhydride and acetyl chloride used in the ring-opening reactions were freshly distilled at atmospheric pressure in an apparatus protected from moisture. Literature procedures were followed for the preparation of 4-phenyl-1,3-dioxane[22] (**7**) and *trans*-1,3-dioxadecalin[21] (**11**). The remaining acetals used in this

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study were prepared as described below.

Preparation of Cyclic Formals. This procedure a modification of that described by Aftalion.[23] An appropriately sized round-bottomed flask equipped with a magnetic stirrer, condenser for downward distillation, and a heating mantle was charged with the appropriate diol, 1.1 equiv of formaldehyde (as paraformaldehyde), water (ca. 75 mL for a 1-mol scale reaction), and concentrated H_2SO_4 (ca. 14 mL for a 1-mol scale reaction). The mixture was heated with stirring and the distillate (often heterogeneous) was collected until the still head temperature reached 100 °C. The distillate, which contains cyclic formal and water, was saturated with K_2CO_3, the organic phase separated, and the aqueous layer extracted with diethyl ether (ca. two 25-mL portions for a 1-mol scale reaction). The combined organic phases were dried (K_2CO_3), the diethyl ether removed by distillation through a short Vigreux column (the solid paraformaldehyde that invariably collected in the still head was discarded), and the residue was distilled. The following cyclic formals were prepared in this way (compound, % yield, boiling point and literature boiling point are given in parentheses): 1,3-dioxane (**1**, 71%, bp 105–107 °C, lit.[24] bp 105 °C (755 mm)); 5,5-dimethyl-1,3-dioxane (**3**, 84% bp 122–126 °C, lit.[23] bp 124–126 °C); 4-methyl-1,3-dioxane (**5**, 81%, bp 110–115 °C, lit.[25] bp 113–115 °C); 4,4,6-trimethyl-1,3-dioxane (**13**, 76%, bp 51–56 °C (31 mm), lit.[26] bp 56 °C (31 mm)); 4-methyl-1,3-dioxolane (**19**, 80%, bp 80–85 °C, lit.[24] bp 88–89 °C (755 mm)); 4-(chloromethyl)-1,3-dioxolane (**22**, 49%, bp 146–149 °C, lit.[27] bp 146–147 °C (745 mm)). This general procedure was also employed to prepare 4-methyl-1,3-dioxepane (**16**) in 59% yield: bp 126–131 °C (lit.[20] bp 105–107 °C). Since the boiling point of **16** did not agree well with the literature value, an elemental analysis was obtained. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.41; H, 10.19.

4,4-Dimethyl-1,3-dioxane (9). Four 250-mL low-pressure bottles equipped with magnetic stirring bars were each charged with 100 mL of 37% formalin solution and 5.0 mL of concentrated sulfuric acid. The bottles were cooled to ca. −8 °C and 40.0 g (0.72 mol) of isobutylene was condensed into each of the four bottles by using a dry ice/acetone condenser. The bottles were capped, allowed to warm slowly to room temperature and stirred vigorously at ambient temperature for 24 h. The bottles, containing a homogeneous solution, were recooled in an ice bath and opened and the contents combined. Solid sodium chloride (ca. 40 g) was added and the mixture was extracted with three 100-mL portions of diethyl ether. The combined extracts were washed successively with 100 mL of 10% aqueous sodium bicarbonate, two 50-mL portions of 20% aqueous sodium bisulfite, and 100 mL of water. After drying ($MgSO_4$), volatile components were removed by rotary evaporation and the residue was distilled through a 6-in. Vigreux column to give 173 g (52%) of product: bp 125–140 °C (lit.[28] bp 132 °C); ^{1}H NMR ($CDCl_3$) δ 4.83 (s, 2 H), 3.88 (t, J = 5.5 Hz, 2 H), 1.65 (t, J = 5.5 Hz, 2 H), 1.28 (s, 6 H).

General Procedure for Acylative Cleavage of Cyclic Acetals with Acetic Anhydride. An appropriately sized round-bottomed flask fitted with a magnetic stirrer, gas inlet, and reflux condenser was flushed with dry argon and charged with the cyclic acetal and 1.0–1.5 mol-equiv of freshly distilled acetic anhydride. This solution was stirred and a catalytic quantity of concentrated sulfuric acid (ca. 1 drop for a 0.1-mol scale reaction) was added. Addition of the acid catalyst results in an exothermic reaction and discoloration of the solution. A cooling bath should be kept nearby in case moderation of the exotherm becomes necessary and, when reactions are conducted on a 1-mol or larger scale, the reaction flask should be immersed in an ice–water bath prior to the addition of the acid catalyst. Tha pale yellow-to-black solution was stirred at room temperature, typically for 6–12 h (see Table I), under an atmosphere of dry argon. Solid, anhydrous sodium acetate (ca. 0.5–1.0 g for a 0.1-mol scale reaction) was added to neutralize the sulfuric acid catalyst and the mixture was stirred for 1 h. Solids were removed by filtration, the filtrate concentrated at reduced pressure, and the residue distilled to give product.

1-Acetoxy-3-(acetoxymethoxy)propane (2). Treatment of 5.0 g (57 mmol) of 1,3-dioxane (**1**) with 11.6 g (114 mmol) of acetic anhydride and a trace of H_2SO_4 for 3 h gave 8.8 g (81%) of product, bp 88–91 °C (2.2 mm). An analytical sample was obtained by preparative GLC on column A at 180 °C: IR (neat) 1740, 1365, 1240, 1165, 1135, 1040 and 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 2 H), 4.13 (t, J = 6.4 Hz, 2 H), 3.70 (t, J = 6.2 Hz, 2 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.90 (5-line pattern, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.56 (s, C=O), 170.17 (s, C=O), 89.12 (t, OCH_2OAc), 66.90 (t, C(3)), 61.22 (t, C(1)), 29.02 (t, C(2)), 20.85 (q, $COCH_3$), 20.74 (q, $COCH_3$). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.56; H, 7.41.

The ^{1}H and ^{13}C chemical shifts of **2** were correlated and the assignments made on the basis of spin-tickling experiments. Irradiation in the ^{1}H region at δ 4.13 resulted in pertubation of a ^{13}C carbonyl signal at δ 170. This result indicates that the δ 4.13 triplet is due to a ^{1}H coupled to one of the acetate carbonyl carbons via a small $^3J_{^{13}C\text{-}^1H}$ and requires that the triplet be assigned to H(1) since the ^{1}H singlet at δ 5.24 must be due to OCH_2OAc. In a similar manner the ^{1}H triplet at δ 3.70 was assigned to H(3) since irradiation at the low-field line of this triplet produced pertubation in the ^{13}C signal of OCH_2OAc at δ 89.12 indicating that H(3) is coupled to the ^{13}C of OCH_2OAc (i.e., $^3J_{^{13}C\text{-}^1H}$ = 2.89 Hz, Table III). In order to confirm the assignment of the ^{13}C triplet at δ 61.22 to C(1) it was necessary to establish that this carbon was attached to the ^{1}H resonating at δ 4.13 (i.e., H(1)). This was accomplished by observation of a pertubation in the ^{13}C signal for C(1) upon irradiation at the low-field wing of the ^{13}C satellite of the ^{1}H absorption centered at δ 4.13 (i.e., irradiation at δ 4.93, corresponding to the low-field line of the H(1) resonance + $^1/_2{}^1J_{^{13}C\text{-}^1H}$). Analogous experiments served to confirm the assignments of ^{13}C and ^{1}H signals in the products described below.

1-Acetoxy-3-(acetoxymethoxy)-2,2-dimethylpropane (4). Reaction of 5.0 g (43 mmol) of 5,5-dimethyl-1,3-dioxane (**3**) with 5.1 g (50 mmol) of acetic anhydride for 10 h afforded 9.0 g (96%) of product, bp 78–86 °C (1.0 mm). An analytical sample was prepared by GLC on column B at 190 °C: IR (neat) 1750, 1370, 1240, 1160, 1120, 1040, 1010 and 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 2 H), 3.87 (s, 2 H), 3.40 (s, 2 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 0.93 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.53 (s, C=O), 170.18 (s, C=O), 89.38 (t, OCH_2OAc), 75.90 (t, C(3)), 75.58 (t, C(1)), 35.24 (s, C(2)), 21.71 (q, 2-CH_3), 20.89 (q, $COCH_3$), 20.71 (q, $COCH_3$). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.07; H, 8.26.

1-Acetoxy-3-(acetoxymethoxy)butane (6). Reaction of 5.0 g (49 mmol) of 4-methyl-1,3-dioxane (**5**) with 5.0 g (49 mmol) of acetic anhydride for 8 h gave 9.0 g (90%) of product, bp 73–77 °C (1.1 mm). An analytical sample was obtained by preparative GLC on column A at 188 °C: IR (neat) 1740, 1365, 1240, 1145 and 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.29 and 5.25 (AB pattern, J_{AB} = 6.42 Hz, 2 H), 4.13 (t, J = 6.41 Hz, 2 H), 3.83 (six-line pattern, 1 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 1.80–1.74 (m, 2 H), 1.21 (d, J = 6.24 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.52 (s, C=O), 170.19 (s, C=O), 87.65 (t, OCH_2OAc), 72.98 (d, C(3)), 61.06 (t, C(1)), 36.03 (t, C(2)), 20.93 (q, $COCh_3$), 20.75 (q, $COCH_3$), 20.63 (q, C(4)). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.77; H, 7.50.

1-(Acetoxymethoxy)-3-acetoxy-1-phenylpropane (8). Treatment of 164.0 g (1.0 mol) of 4-phenyl-1,3-dioxane (**7**) with 164.0 g (1.61 mol) of acetic anhydride for 12 h afforded 226.6 g (85%) of product: bp 132–142 °C (1.2 mm) [lit.[10] bp 162–163 °C (3.0 mm)]; IR (neat) 1740, 1370, 1230, 1160, 1120, 1040, 1010 and 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 5.29 and 5.02 (AB pattern, J_{AB} = 6.2 Hz, 2 H), 4.67 (dd, J = 5.0 Hz, J = 7.0 Hz, 1 H), 4.25–4.03 (m, 2 H), 2.2–1.8 (m, 2 H), 2.03 (s, 3 H), 1.92 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.49 (s, C=O), 170.13 (s, C=O), 141.18 (s, *ipso*-C), 128.55 (d, *m*-C), 127.98 (d, *o*-C), 126.55 (d, *p*-C), 86.94 (t, OCH_2OAc), 78.28 (d, C(1)), 60.99 (t, C(3)), 37.04 (t, C(2)), 20.74 (q, $COCH_3$), 20.65 (q, $COCH_3$).

1-Acetoxy-3-(acetoxymethoxy)-3-methylbutane (10). Reaction of 125.3 g (1.08 mol) of 4,4-dimethyl-1,3-dioxane (**9**) with 162.3 g (1.59 mol) of acetic anhydride for 6 h gave 207.2 g (88%) of product: bp 115–120 °C (8.0 mm) [lit.[13] bp 78–82 °C (0.1 mm)];

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IR (neat) 1745, 1385, 1230, 1150, 1110, 1030, 1010 and 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.28 (s, 2 H), 4.15 (t, J = 7.0 Hz, 2 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.87 (t, J = 7.0 Hz, 2 H), 1.27 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.66 (s, C=O), 170.11 (s, C=O), 83.65 (t, OCH_2OAc), 76.47 (s, C(3)), 60.69 (t, C(1)), 40.06 (t, C(2)), 26.38 (q, C(4)), 21.13 (q, $COCH_3$), 20.82 (q, $COCH_3$).

***trans*-2-(Acetoxymethyl)-1-(acetoxymethoxy)cyclohexane (12).** Treatment of 196.0 g (1.38 mol) of *trans*-1,3-dioxadecalin (**11**) with 260 mL (ca. 2.8 mol) of acetic anhydride for 12 h gave 237.4 g (77%) of product, bp 85–93 °C (3.0 mm). An analytical sample was obtained by preparative GLC on column C at 212 °C: IR (neat) 1745, 1370, 1245, 1150, 1110, 1010 and 940 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.31 and 5.24 (AB pattern, J_{AB} = 6.41 Hz, 2 H), 4.15–4.00 (m, 2 H), 3.60–3.10 (broad m, 1 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.0–1.15 (broad m, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.71 (s, C=O), 170.26 (s, C=O), 87.68 (t, OCH_2OAc), 79.14 (d, C(1)), 69.46 (t, CH_2OAc), 42.58 (d, C(2)), 32.34 (t, C(6)), 28.30 (t, C(3)), 25.00 (t, C(5)), 24.60 (t, C(4)), 20.99 (q, $COCH_3$) 20.76 (q, $COCH_3$). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.95; H, 8.20.

4-Acetoxy-2-(acetoxymethoxy)-2-methylpentane (14) and 4-(Acetoxymethoxy)-2-acetoxy-2-methylpentane (15). A mixture of the title compounds was prepared by treatment of 14.5 g (112 mmol) of 4,4,6-trimethyl-1,3-dioxane (**13**) with 22.8 g (224 mmol) of acetic anhydride for one week. Distillation afforded 12.8 g (50%) of product, bp 90–96 °C (1.6 mm), as a mixture of isomers consisting of 75% **14** and 25% **15**. The isomers were separated and analytical samples were obtained by preparative GLC on column B at 200 °C. The major component, having the longer GLC retention time, was found to be **14** on the basis of the following spectroscopic properties.

4-Acetoxy-2-(acetoxymethoxy)-2-methylpentane (14): IR (neat) 1740, 1370, 1250, 1150, 1100, 1040, 1010 and 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.28 (s, 2 H), 5.23–4.83 (m, 1 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.90–1.65 (m, 2 H), 1.1–1.3 [overlapping pattern, i.e., 1.23 (apparent s, 6 H), 1.22 (d, J = 6.0 Hz, 3 H)]; ^{13}C NMR ($CDCl_3$) δ 170.23 (s, C=O), 170.20 (s, C=O), 83.75 t, OCH_2OAc), 76.81 (s, C(2)), 67.70 (d, C(4)), 47.31 (t, C(3)), 26.95 (q, C(1)), 25.75 (q, 2 CH_3), 21.70 (q, C(5)), 21.39 (q, $COCH_3$), 21.27 (q, $COCH_3$). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 9.06. Found: C, 56.76; H, 8.79.

4-(Acetoxymethoxy)-2-acetoxy-2-methylpentane (15): IR (neat) 1730, 1360, 1250, 1230, 1150, 1040, 1005 and 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.23 (apparent s, 2 H), 3.92 (six-line pattern, 1 H), 3.73 (s, 3 H) and 3.62 (s, 3 H) having a broad base containing a 2 H multiplet, 1.45 (apparent s, 6 H), 1.20 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.50 (s, C=O), 170.36 (s, C=O), 87.38 (t, OCH_2OAc), 81.34 (s, C(2)), 72.69 (d, C(4)), 46.95 (t, C(3)), 27.36 (q, C(1)), 26.36 (q, 2-CH_3), CH_3), 22.48 (q, C(5)), 21.56 (q, $COCH_3$) 21.10 (q, $COCH_3$). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 9.06. Found: C, 57.01; H, 8.90.

1-Acetoxy-4-(acetoxymethoxy)pentane (17) and 4-Acetoxy-1-(acetoxymethoxy)pentane (18). A mixture of the title compounds was obtained from the reaction of 5.0 g (43 mmol) of 4-methyl-1,3-dioxepane (**16**) with 4.4 g (43 mmol) of acetic anhydride for 10 h. Distillation gave 6.0 g (64%) of product, bp 90–105 °C (0.5 mm), consisting of 85% **17** and 15% **18** as adjudged by ^1H NMR analysis. Chromatographic separation of the isomers could not be effected by using any of a variety of GLC columns and an analytical sample of the mixture was obtained by GLC on column B at 180 °C. The major product was assigned structure **17** on the basis of the following spectroscopic data (particularly ^{13}C NMR listed in Table III) obtained from the product mixture. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found (mixture of **17** and **18**): C, 54.97; H, 8.37.

1-Acetoxy-4-(acetoxymethoxy)pentane (17): ^1H NMR ($CDCl_3$, 90 MHz) δ 5.29 (apparent s, 2 H), 4.07 (t, J = 6.2 Hz, 2 H), 3.75 (five-line pattern, 1 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 1.87–1.49 (m, 4 H), 1.20 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.64 (s, C=O), 170.25 (s, C=O), 87.71 (t, $^1J_{^{13}C\text{-}^1H}$ = 168.19 Hz, $^3J_{^{13}C\text{-}^1H}$ = 4.07 Hz, OCH_2OAc), 75.47 (d, C(4)), 64.21 (t, C(1)), 33.27 (t, C(3)), 24.74 (t, C(2)), 21.02 (q, $COCH_3$), 20.81 (q, $COCH_3$), 20.39 (q, C(5)).

4-Acetoxy-1-(acetoxymethoxy)pentane (18): ^1H NMR ($CDCl_3$, 90 MHz) δ 5.25 (s, 2 H), other signals are buried in patterns of major isomer; ^{13}C NMR ($CDCl_3$) δ 170.64 (s, C=O), 170.25 (s, C=O), 89.18 (t, $^1J_{^{13}C\text{-}^1H}$ = 168.53 Hz, $^3J_{^{13}C\text{-}^1H}$ = 2.70 Hz, OCH_2OAc), 70.37 (t, C(1)), 69.96 (d, C(4)), 32.49 (t, C(3)), 25.66 (t, C(2)), 21.02 (q, $COCH_3$), 20.81 (q, $COCH_3$), 20.00 (q, C(5)).

1-Acetoxy-2-(acetoxymethoxy)propane (20) and 2-Acetoxy-1-(acetoxymethoxy)propane (21). Treatment of 5.0 g (57 mmol) of 4-methyl-1,3-dioxolane (**19**) with 5.8 g (57 mmol) of acetic anhydride for 10 h gave 7.2 g (67%) of product, bp 65–76 °C (0.3 mm), as a mixture of isomers consisting of 77% **20** and 23% **21** as adjudged by ^1H NMR analysis. Chromatographic separation of the isomers could not be effected and an analytical sample of the mixture was obtained on column D at 200 °C. The major product was assigned structure **20** on the basis of the following spectroscopic data (particularly ^{13}C NMR listed in Table III) obtained from the product mixture. Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found (mixture of **20** and **21**): C, 50.37; H, 7.32.

1-Acetoxy-2-(acetoxymethoxy)propane (20): ^1H NMR ($CDCl_3$) δ 5.18 (s, 2 H), 3.97 (broad m, 1 H), 3.60 (d, J = 5.5 Hz, 2 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.21 (apparent d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 87.95 (t, $^1J_{^{13}C\text{-}^1H}$ = 168.86 Hz, $^3J_{^{13}C\text{-}^1H}$ = 4.07 Hz, OCH_2OAc), 73.88 (d, C(2)), 67.23 (t, C(1)), 17.37 (q, C(3)).

2-Acetoxy-1-(acetoxymethoxy)propane (21): ^1H NMR ($CDCl_3$) δ 5.15 (s, 2 H), other signals buried under patterns for major isomer; ^{13}C NMR ($CDCl_3$) δ 89.12 (t, $^1J_{^{13}C\text{-}^1H}$ = 168.90 Hz, $^3J_{^{13}C\text{-}^1H}$ = 3.39 Hz, OCH_2OAc), 72.50 (t, C(1)), 69.09 (d, C(2)), 16.47 (q, C(3)).

1-Acetoxy-2-(acetoxymethoxy)-3-chloropropane (23) and 2-Acetoxy-1-(acetoxymethoxy)-3-chloropropane (24). A mixture of the title compounds was prepared by reaction of 5.0 g (41 mmol) of 4-(chloromethyl)-1,3-dioxolane (**22**) with 4.4 g (43 mmol) of acetic anhydride for 10 h. Distillation afforded 6.5 g (71%) of product, bp 97–101 °C (0.4 mm), as a mixture of isomers. The isomers were separated by preparative GLC on column B at 185 °C and the major product, which had the longer retention time, was found to be **23** on the basis of the following spectroscopic data.

1-Acetoxy-2-(acetoxymethoxy)-3-chloropropane (23): IR (neat) 1745, 1370, 1235, 1160, 1120, 1045, 1015 and 950 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.38 and 5.34 (AB pattern, J_{AB} = 6.13 Hz, 2 H), 4.37–3.99 (m, 3 H), 3.66–3.57 (m, 2 H), 2.11 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.13 (s, C=O), 169.84 (s, C=O), 88.16 (t, OCH_2OAc), 77.44 (d, C(2)), 63.52 (t, C(1)), 43.48 (t, C(3)), 20.93 (q, $COCH_3$), 20.63 (q, $COCH_3$). Anal. Calcd for $C_8H_{13}ClO_5$: C, 42.77; H, 5.83; Cl, 16.02. Found: C, 42.64; H, 5.76; Cl, 16.02.

2-Acetoxy-1-(acetoxymethoxy)-3-chloropropane (24): IR (neat) 1750, 1375, 1235, 1165, 1135, 1060, 1015 and 955 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.27 (apparent s, 2 H), 5.14 (five-line pattern, 1 H), 3.85 (d, J = 4.99 Hz, 2 H), 3.69 (dd, J = 5.28 Hz, J = 1.47 Hz, 2 H), 2.10 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.26 (s, C=O), 169.84 (s, C=O), 88.85 (t, OCH_2OAc), 71.30 (d, C(2)), 68.13 (t, C(1)), 42.34 (t, C(3)), 20.93 (q, $COCH_3$). Anal. Calcd for $C_8H_{13}ClO_5$: C, 42.77; H, 5.83; Cl, 16.02. Found: C, 42.63; H, 5.81; Cl, 15.63.

1-Acetoxy-3-(chloromethoxy)butane (25). A 50-mL round-bottomed flask fitted with a magnetic stirrer was dried under a stream of argon and charged with 5.8 g (57 mmol) of 4-methyl-1,3-dioxane (**5**), 25 mL of dry pentane and a few crystals of anhydrous zinc chloride. A solution of 4.6 g (59 mmol) of acetyl chloride in 5 mL of dry pentane was added dropwise to the stirred reaction mixture over a 15-min period and stirring was continued for 1 h following complete addition. The mixture was then concentrated by flash evaporation at reduced pressure and the residue distilled to give 8.8 g (86%) of product, bp 62–65 °C (0.7 mm). Attempts to prepare an analytical sample of this material failed to provide a satisfactory elemental analysis but its structure was established on the basis of the following spectroscopic data as well as by conversion to the known 3-methoxy-1-butanol (vide infra): IR (neat) 1740, 1380, 1370, 1250, 1150, 1110, 1050 and 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (apparent s, 2 H), 4.2–3.8 [overlapping patterns, 4 H, e.g., 4.07 (apparent t, J = 6.0 Hz, 2 H), ca. 3.95 (m, 1 H)], 2.0–1.6 [overlapping patterns, 8 H, e.g., 2.02 (s, 3 H), 1.80 (q, J = 6.0 Hz, 2 H), 1.27 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.64 (s, C=O), 81.18 (t, $^1J_{^{13}C\text{-}^1H}$ = 175.48 Hz, $^3J_{^{13}C\text{-}^1H}$ = 5.89 Hz, OCH_2Cl), 72.62 (d, C(3)), 60.76 (t, C(1)), 35.40 (t, C(2)), 20.84 (q, $COCH_3$), 19.50 (q, C(4)).

3-Methoxy-1-butanol from Reduction of 25. A solution of 8.7 g (48 mmol) of 1-acetoxy-3-(chloromethoxy)butane (**25**) in 150 mL of anhydrous diethyl ether was added dropwise to a stirred slurry of 4.1 g (110 mmol) of lithium aluminum hydride in 200 mL of anhydrous diethyl ether. After addition was completed the mixture was stirred for 2 h at room temperature and then hydrolyzed by sequential dropwise addition of 4.1 mL of water, 4.1 mL of 15% aqueous sodium hydroxide, and 12.4 mL of water. The mixture was filtered and the precipitate washed with five 20-mL portions of ether. The combined filtrate and washings were dried ($MgSO_4$), filtered, and then concentrated to give an oil which was distilled to give 4.0 g (80%) of 3-methoxy-1-butanol, bp 34–37 °C (17 mm) [lit.[29] bp 158–159 °C]. The IR and ^1H NMR spectra of the product were identical with those of an authentic sample (Aldrich Chemical Co.) of the title compound.

Acetolysis of *trans*-2-Deuterio-4-methyl-1,3-dioxane (26). A solution of 114 mg (1.1 mmol) of *trans*-**26** (containing 10% of the cis isomer) and 120 mg (1.2 mmol) of acetic anhydride in 1.5 mL of $CDCl_3$ containing 1% Me_4Si was placed in a 5-mm NMR tube. The reaction was initiated by the addition of 2.0 μL of concentrated sulfuric acid and the progress was monitored by ^1H NMR (Table II). The 270-MHz spectrum of the product mixture is shown in Figure 1 (supplementary material).

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Supplementary Material Available: ^1H NMR of **6** and a mixture of **27** and **28** (1 page). Ordering information is given on any current masthead page.

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Reaction of 9-(β-D-Ribofuranosyl)purine with Alkalies: Kinetics and Mechanism[1]

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The progress of the alkaline hydrolysis of 9-(β-D-ribofuranosyl)purine has been studied by LC analyses, NMR spectroscopy, and isotopic labeling techniques. Comparison of the results of different experimental approaches reveals that the hydrolysis consists of three consecutive reactions, viz., transformation of the starting material to 5-formamido-4-ribosylaminopyrimidine, its deformylation to 5-amino-4-ribosylaminopyrimidine, and the hydrolysis of the latter intermediate to free sugar and 4,5-diaminopyrimidine. Both of the intermediates involved have been shown to be equilibrium mixtures of anomeric furanoid and pyranoid derivatives. Pseudo-first-order rate constants have been determined for the consecutive reactions at different temperatures and hydroxide ion concentrations. The role that the glycosyl hydroxyl groups play in different stages of the hydrolysis reaction has been elucidated by comparing the kinetic data with those observed for 9-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)purine. The mechanisms for the consecutive reactions have been discussed.

Introduction

Several methods employed for the determination of nucleotide distribution in nucleic acids involve treatment of nucleic acids in alkali.[2-5] For this reason quantitative information about the degradation of the monomeric constituents, nucleosides, in basic solutions is desirable. Particularly purine nucleosides have been shown to be relatively susceptible to the action of hydroxide ion.[6-11] However, the data on the kinetics and mechanisms of their alkaline solvolyses are very limited.[11] One of the most labile nucleosides is unsubstituted 9-(β-D-ribofuranosyl)-purine.[6] Brown et al. have presented paper chromatographic and UV spectroscopic evidence for the appearance of 5-formamido-4-ribosylamino- and 5-amino-4-ribosylaminopyrimidine during the alkaline cleavage of 9-(β-D-ribofuranosyl)purine[6] and its 5′-monophosphate.[12] Presumably, nucleophilic attack of hydroxide ion at C8 of the starting material results in opening of the imidazole ring. Deformylation of the resulting 5-formamido derivative and rupture of the ribosyl–nitrogen bond would give 4,5-diaminopyrimidine as the final reaction product. The aim of the present study is to verify the suggested, partly tentative pathway by NMR, LC, and isotopic labeling studies. Kinetics of the consecutive partial reactions are determined as a function of temperature and hydroxide ion concentration. The role of the ribosyl hydroxyl groups is examined by comparing the kinetics of the hydrolysis of 9-(β-D-ribofuranosyl)purine and its 2′,3′-*O*-isopropylidene derivative. The factors affecting the accumulation of the intermediates are discussed on the bases

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