The Oxidation of Acetals by Ozone[1]

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Ozone reacts very smoothly with acetals to give the corresponding esters. There are six *gauche* conformations that are theoretically possible for an acetal function. It is shown that only three of them are reactive toward ozone. It is proposed that a reactive acetal function must take a conformation in which each oxygen must have an electron pair orbital oriented antiperiplanar to the C—H bond. The mechanism of this reaction is also discussed.

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Les acétals se transforment facilement en esters correspondants sous l'action de l'ozone. Il y a six conformations *gauches* pour une fonction acétal dont trois seulement sont réactives avec l'ozone. Il est de plus proposé que chaque atome d'oxygene de la fonction acétal doit posséder une orbitale d'électrons libres orientée de manière antipériplanaire par rapport au lien C—H pour qu'elle soit réactive avec l'ozone. Le mécanisme de réaction est aussi discuté.

We reported in 1971 (1) in preliminary form that ozone reacts in essentially quantitative yield and in a completely specific fashion with the acetal function of an aldehyde to give the corresponding ester.

$$\underset{\displaystyle H}{\overset{\displaystyle |}{R—C(OR')_2}} + O_3 \rightarrow R—COOR' + R'—OH + O_2$$

In 1972, we also published in a preliminary communication (2) the relationship between the precise conformation of the acetal function and its reactivity toward ozone. We have now completed this work and wish to report in detail the result of our entire investigation.

Table 1 describes the results of the oxidation of different types of simple acetals. It clearly indicates that this new oxidation reaction is a general one; the nature of the alkyl groups (R and R′) of the acetal function does not influence the final result. Each example shows that this reaction proceeds in essentially quantitative yield.

However, there exists a tremendous difference in the rate of reaction as particularly shown by examples 1–5 (Table 1): the cyclic acetals react much faster than the acyclic ones. For instance, 10 mmol of dimethoxy acetal was completely oxidized after 15 h, while the same molar quantity of the five-membered ring dioxolane acetal required only 10 min. In fact, this last reaction is practically instantaneous since the ozone was generated at a rate of 1 mmol per minute and the ozone generator was stopped after 10 min, just when the blue color of ozone appeared in the reaction mixture. This result suggests that a completely new method for the titration of ozone at −78° can in principle be developed by utilizing this remarkably fast and specific reaction between ozone and dioxolane acetals. We took advantage of this instantaneous reaction to establish the stoichiometry of the reaction. A saturated solution of ozone in ethyl acetate was prepared at −78°. A solution (0.01 *M*) of a dioxolane acetal in ethyl acetate was slowly added at −78°. The blue color of ozone disappeared rapidly. During the addition, there was a constant formation of a gas which was measured. The molar quantity of oxygen produced was found identical to the amount of acetal used. This indicated that 1 mol of ozone

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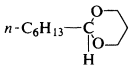
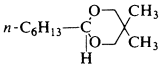
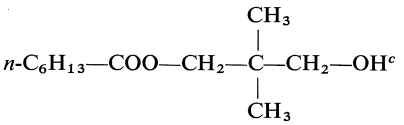
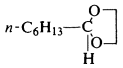
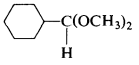
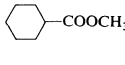
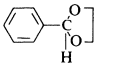
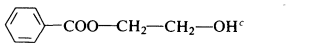
TABLE 1. Oxidation of various types of acetals[a]

Reaction No.	Acetal	Product	Reaction time	Yield (%)[d]
1	n-C_6H_{13}—$CH(OCH_3)_2$	n-C_6H_{13}—$COOCH_3$[b]	15 h	91
2	n-C_6H_{13}—$CH(OC_2H_5)_2$	n-C_6H_{13}—$COOC_2H_5$[b]	8 h	94
3		n-C_6H_{13}—COO—CH_2—CH_2—OH[c]	2 h	97
4			1 h	98
5		n-C_6H_{13}—COO—CH_2—CH_2—OH[c]	10 min	98
6			13 h	98
7			10 min	100

[a]Reaction was carried out at −78° in ethyl acetate using 10 mmol of acetal; rate of ozone: 1 mmol/min.
[b]Spectroscopic (i.r., n.m.r.) data was obtained for this compound which was also compared with an authentic sample.
[c]This product was isolated as the corresponding acetate derivative (Ac_2O–pyridine). Spectroscopic (i.r., n.m.r.) and satisfactory analytical data have been obtained for this derivative.
[d]Yield of isolated material.

reacts at −78° with 1 mol of acetal yielding 1 mol of ester and 1 mol of oxygen.

Table 2 shows that the oxidation of open-chain acetals (dialkoxy acetal) can be achieved more conveniently if the reaction is simply carried out at room temperature. This large difference in rates between cyclic and acyclic acetals is easily explained when the preferred conformation of each acetal is taken into consideration (*vide infra*).

This new reaction constitutes a novel method for converting an aldehyde into an ester.[5] It is likely that it proceeds via the insertion of ozone into the C—H bond of the acetal (**1**) forming an intermediate[6] such as **2** or **3** which then breaks down to give the reaction products, the ester **4** and the alcohol **5**. Such an insertion reaction has been shown to be operative in the reaction of ozone with simple ethers, silanes, hydrocarbons (anthrone), and aldehydes (6). Based on our study of the oxidation of various complex acetals by ozone (2), the results obtained on the hydrolysis of complex orthoesters (4), and the work of King and Allbutt (7) on the stereoselective hydrolysis of dioxolenium ions and of orthoesters, we conclude that the ozonolysis of acetals doubtless proceeds via the formation of an intermediate analogous to a hemiorthoester.

TABLE 2. Effect of temperature on the rate of oxidation of n-C_6H_5—$CH(OCH_3)_2$ in ethyl acetate

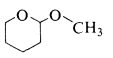
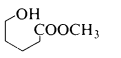
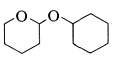
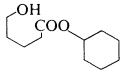
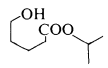
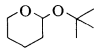
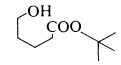
Acetyl (mmol)	Reaction temperature (°C)	Reaction time (h)
13.6	−78	15
13.5	0	1.5
23.2	25	1.5

All the acetals studied so far were symmetrical, since the OR groups were identical. It was of interest to examine the oxidation of unsymmetrical acetals. If a tetrahedral intermediate is formed during the oxidation of an acetal function, a substrate such as **6** should lead to an

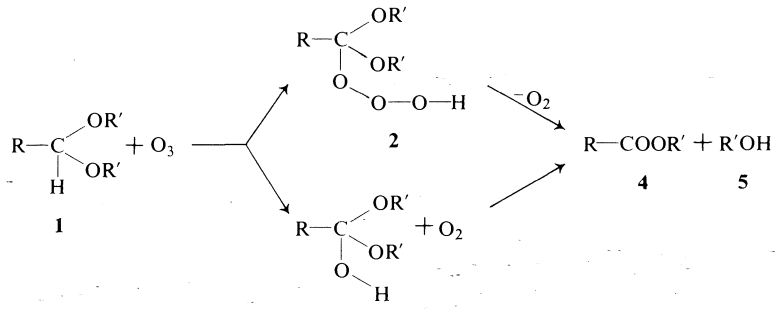
[5]For a practical example of the conversion of a dimethoxy acetal into a methyl ester, see ref. 3.

[6]We have recognized very early during our work that the intermediate which is formed during the oxidation of acetals is either identical or equivalent to a hemiorthoester which is the tetrahedral intermediate formed during the transesterification of esters. This finding has led us to the development of a new stereoelectronic theory for the hydrolysis of esters (4), and later, of amides (5).

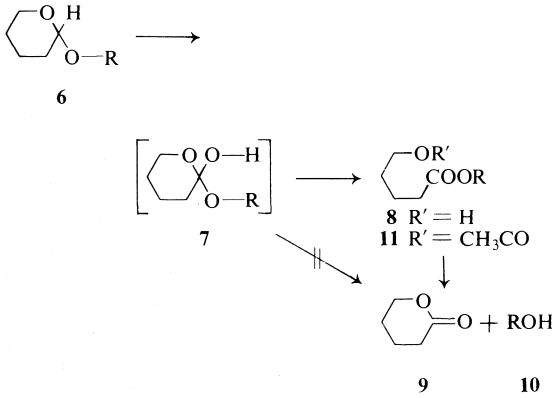
TABLE 3. Oxidation of tetrahydropyranyl ether[a]

Acetal	Amount (mmol)	Product[b]	Reaction time (h)	Yield[c] (%)
	40		2	99
	10		1	91
	30		2	95
	12.6		3	91

[a]Reaction carried out at −78° in ethyl acetate; rate of ozone: 1 mmol/min.
[b]This product was isolated as the corresponding acetate derivative (Ac_2O–pyridine). Spectroscopic (i.r., n.m.r.) and satisfactory analytical data have been obtained for this derivative.
[c]Yield of isolated material.

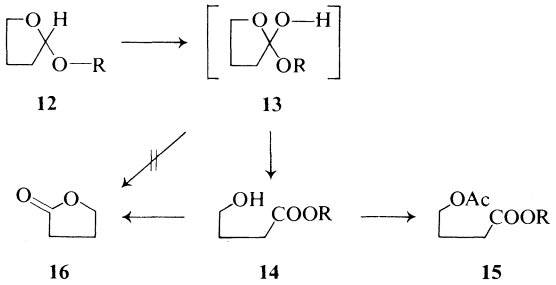


intermediate such as **7** which can in principle decompose in two different ways to give the hydroxy ester **8**, or the lactone **9** plus the alcohol **10**. We found experimentally, that ozone reacts very smoothly with tetrahydropyranyl ethers (an unsymmetrical acetal) in a completely specific manner, yielding the hydroxy ester **8** exclusively. No trace of lactone **9** could be detected. These results are summarized in Table 3. This reaction also constitutes a new highly efficient method for the cleavage of the tetrahydropyranyl ether protecting group under neutral conditions. Simple heating of the resulting hydroxy ester **8**, in a neutral solvent, produces δ-valerolactone (**9**) and liberates the alcohol **10**.[7]



[7]The hydroxy ester **8** can be esterified (Ac_2O–pyridine) to give the acetoxy ester **11**. Therefore, whenever an alcohol function needs to be protected by an acid sensitive blocking group and then by an ester type protecting group which is not as sensitive to acid, a tetrahydropyranol ether can be used, transformed by ozone into the hydroxy ester **8** which can then be acetylated to give the acetoxy ester **11**.

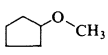
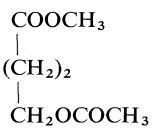
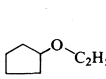
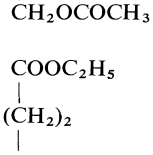
We have also demonstrated that tetrahydrofuranyl ethers (**12**) (8) were smoothly oxidized by ozone to the hydroxy ester **14** exclusively (Table 4), thus the specific opening of a tetra-



12 **13** **16** **14** **15**

hedral intermediate (**13** → **14**) was again observed. In these experiments, acetic anhydride and sodium acetate was used as solvent in order to trap the hydroxy ester **14** which was subsequently isolated as the corresponding acetoxy ester **15**. The use of this solvent system was found to be a very convenient means of preventing lactonization of the hydroxy ester (**14** → **16**). We have also found that it served another purpose when the ozonolysis reaction had to be carried out for long periods of time at room temperature with excess of ozone; it protected against further oxidation of the primary and secondary alcohols which are formed during the reaction. In cases where there is no need to trap an alcohol function, it was our experience that reagent grade ethyl acetate was the best solvent. However, other solvents which do not react with ozone can be used with success such as carbon tetrachloride, dichloromethane, and glacial acetic acid. When the reaction is carried out at room temperature and takes a few hours, large excesses of ozone–oxygen gas go through the solution, therefore a high boiling solvent is preferred to reduce the amount of solvent lost by evaporation.

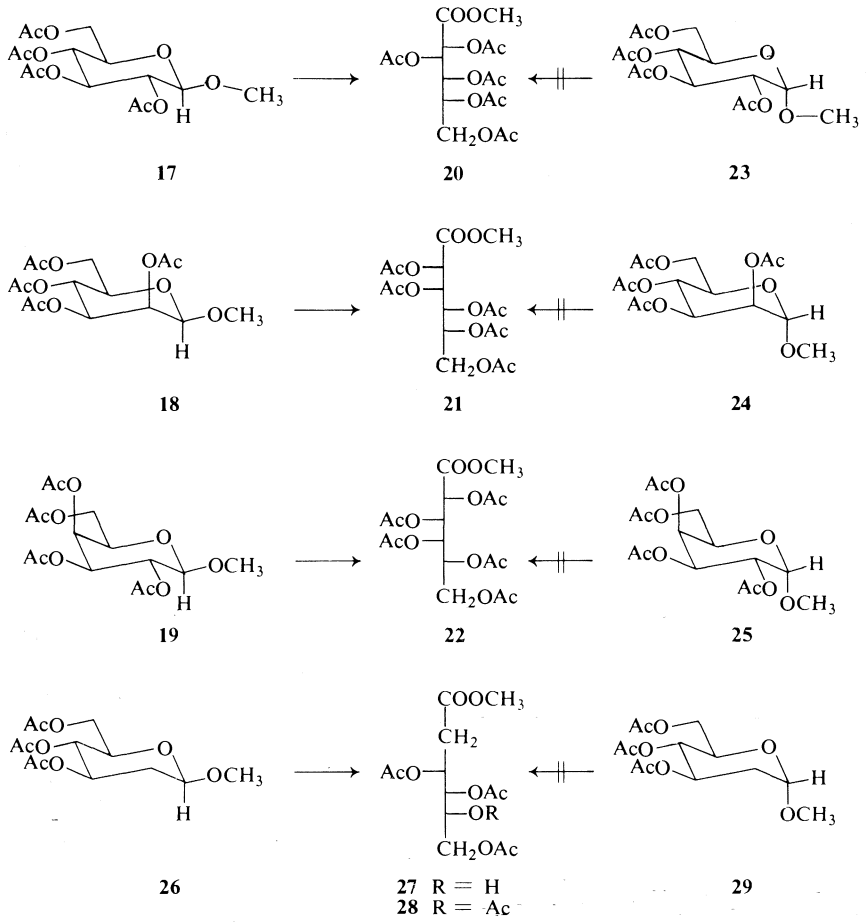
TABLE 4. Oxidation of tetrahydrofuranyl ether[a]

Acetal	Product[b]	Yield[c] (%)
		85
		87

[a]Reaction carried out with 10 mmol of acetal at room temperature for 6 h in acetic anhydride – sodium acetate; rate of ozone: 1 mmol/min.
[b]Spectroscopic (i.r., n.m.r.) and satisfactory analytical data (±0.3) have been obtained for this product.
[c]Yield of isolated material.

After completing our work on the simple tetrahydropyranyl ethers, the next logical step was to study this new reaction on tetrahydropyranyl ethers which possess a rigid chair conformation. Consequently, the oxidation of a series of conformationally rigid α- and β-methyl glycopyranosides was undertaken. We found that β-methyl glycopyranosides were converted smoothly into their corresponding 5-acetoxy aldonic acid methyl esters whereas the α-methyl glycopyranosides were recovered unchanged in quantitative yield. β-Anomers of methyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (**17**), -D-mannopyranoside (**18**)[8], and -D-galactopyranoside (**19**)[8] were converted into their corresponding penta-*O*-acetyl-D-aldonic acid methyl esters **20**, **21**, and **22**. However, their respective α-anomers **23**, **24**, and **25**[8] were found to be completely inert toward ozone. Poly-*O*-acetyl methyl β-glycosides were used because the oxidation of the anomeric center is a fairly slow reaction and the hydroxyl groups need protection against ozone. Acetic anhydride – sodium acetate was used as solvent to trap *in situ* the newly formed hydroxyl group at position 5 so that a good yield of poly-*O*-acetyl aldonic acid methyl ester could be isolated. When there is no substituent at position 2, as in methyl 2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (**26**), the oxidation of the anomeric center is sufficiently rapid that there is no need to protect the 5-hydroxyl group which is being formed. When glacial acetic acid is used as solvent, methyl 2-deoxy-3,4,6-tri-*O*-acetyl-5-hydroxy-D-gluconate (**27**) can be isolated in good yield. Acetylation of **27** gave methyl tetra-*O*-acetyl-2-deoxy-D-gluconate (**28**), which can also be obtained directly by carrying out the oxidation of **26** in acetic anhydride and sodium acetate. The nonreactivity of the α-glucosides suggests a new method for the separation and the purification of α-glycoside from a mixture of α and β. We have used this method successfully to purify methyl 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**29**). Triacetyl glucal was trans-

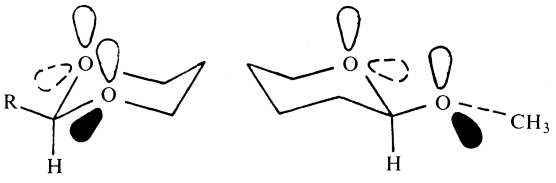
[8]We are grateful to Professor A. S. Perlin (McGill University) for his generous gift of this compound.



formed into a mixture of the two anomers of methyl 2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranoside (9). The pure β-anomer (**26**) was obtained by crystallization. The remaining mixture of α- and β-anomers in the mother liquor was then treated with ozone in ethyl acetate. This process converted the β-anomer into methyl 5-hydroxy-2-deoxy-3,4,6-tri-*O*-acetyl gluconate (**27**) which has a much lower R_f value on thin-layer chromatography than the unreacted α-anomer. The α-anomer **29** was easily obtained pure by a simple column chromatography.

So far we have shown that cyclic acetals react with ozone, dialkoxy acetals react but the rate is low, β-glycosides are reactive, and α-glycosides are inert. It was clear from these results that there was a relationship between the conformation of the acetal function and its reactivity toward ozone. This led us to propose that any reactive conformer must have on each oxygen atom a lone pair orbital oriented antiperiplanar to the C—H bond of the acetal function (1).

This requirement was met with dioxolane acetal (**30**) and the most stable rotamer of β-glycoside (**31**) (10). In an α-glycoside, which can be represented as its favored rotamer by structure **32**, the ring oxygen orbitals are not oriented antiperiplanar to the C—H bond; it is the ring carbon – oxygen bond which is antiperiplanar. The lone pair orbitals of the ring oxygen in an α-glycoside (regardless of the rotamer) are never available, indicating that the oxidation does not proceed if only one oxygen has the proper orbital orientation. Furthermore, dialkoxy acetals are known (11) to exist in one preferred conformation (**33**) which is identical to the favored rotamer of an α-glycoside (**32**). This is quite normal because this conformer is the only one which avoids the anomeric effect (10). This conformer is inert toward ozone. In order to react with ozone, the



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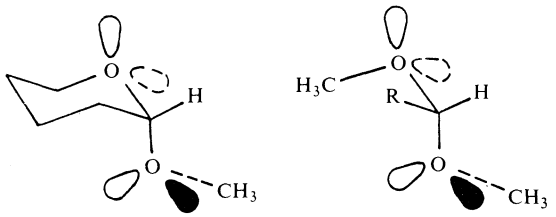


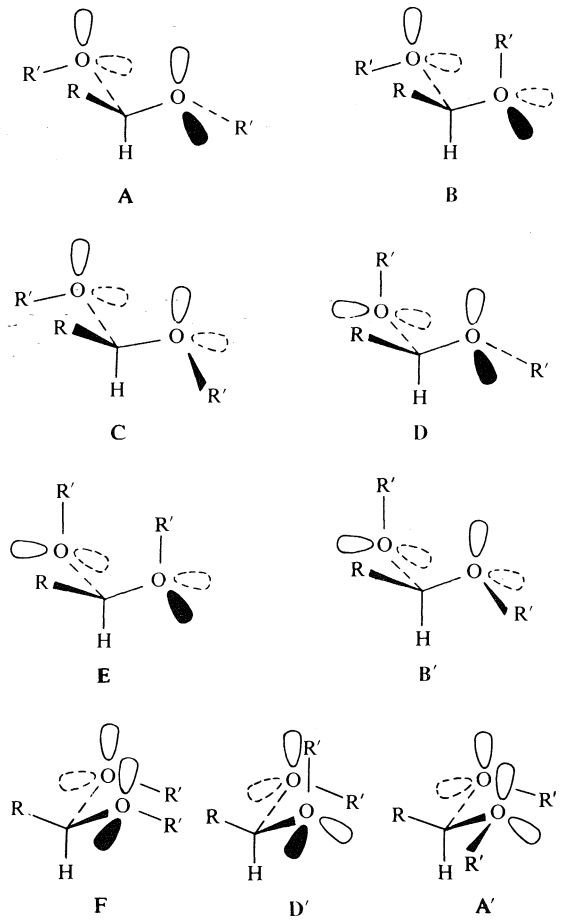
32 33

dialkoxy acetal must adopt another conformation which has proper orbital orientation. This is possible with the dialkoxy acetal but impossible with chair-rigid α-glycosides. However, any reactive conformer of the dialkoxy acetal will be present only in a very small amount at equilibrium because such a conformer has to overcome the anomeric effect which exists when two lone pair orbitals are in a 1,3-synperiplanar arrangement.[9] Consequently, the reaction rate which is dependent upon the concentration of the reactive conformer is going to be fairly low.

It was clear at this stage of our investigation that the postulate of the orientation of the lone pairs had to be verified in a more rigorous manner. Consequently, we had to consider all the possible *gauche* conformers that an acetal function can assume, make rigid chemical models of each of them if possible, and verify their respective reactivity with ozone.

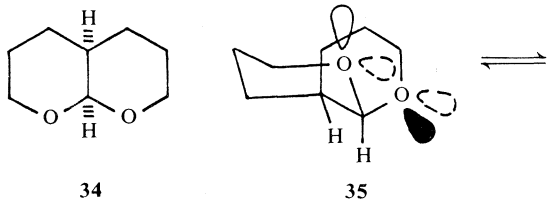
Scheme 1 shows the nine *gauche* conformers that are theoretically possible for an acetal function. Conformers A, B, and D have no plane of symmetry and in fact conformers A′, B′, and D′ are their respective mirror images, therefore chemically equivalent. The remaining conformers C, E, and F possess a plane of symmetry. Consequently, there are only six conformers (A, B, C, D, E, and F) which are chemically different for an acetal function. Of those, only conformers A, C, and F possess a lone pair orbital on each oxygen oriented antiperiplanar to the C—H bond. Conformers B and D have only one oxygen with a lone pair properly oriented, and conformer E has none. Consequently if our postulate is valid, conformers B, D, and E should be inert and conformers A, C, and F should be reactive toward ozone.

Scheme 2 describes the conformers of Scheme 1 in which a six-membered ring has been incorporated. One can observe that the first three conformers A, B, and C represent the three rotamers of a conformationally rigid β-glycoside. Conformers D, E, and B′ correspond to the three conformers of a rigid α-glycoside (10). We have found that α-glycosides are inert toward ozone; conformers D, E, and B′ are therefore not reactive. Conformer B′ is chemically equivalent to conformer B, they are mirror image in Scheme 1, B is therefore not reactive. These conformers were further eliminated by observing that *cis*-1,8-dioxaoctahydronaphthalene (**34**) does



SCHEME 1

[9]A 1,3-synperiplanar arrangement is equivalent to a 1,3-diaxial arrangement in a six-membered ring.



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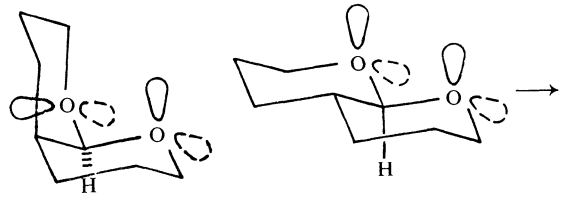

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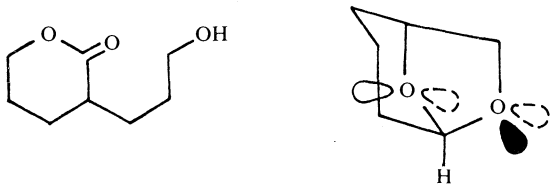
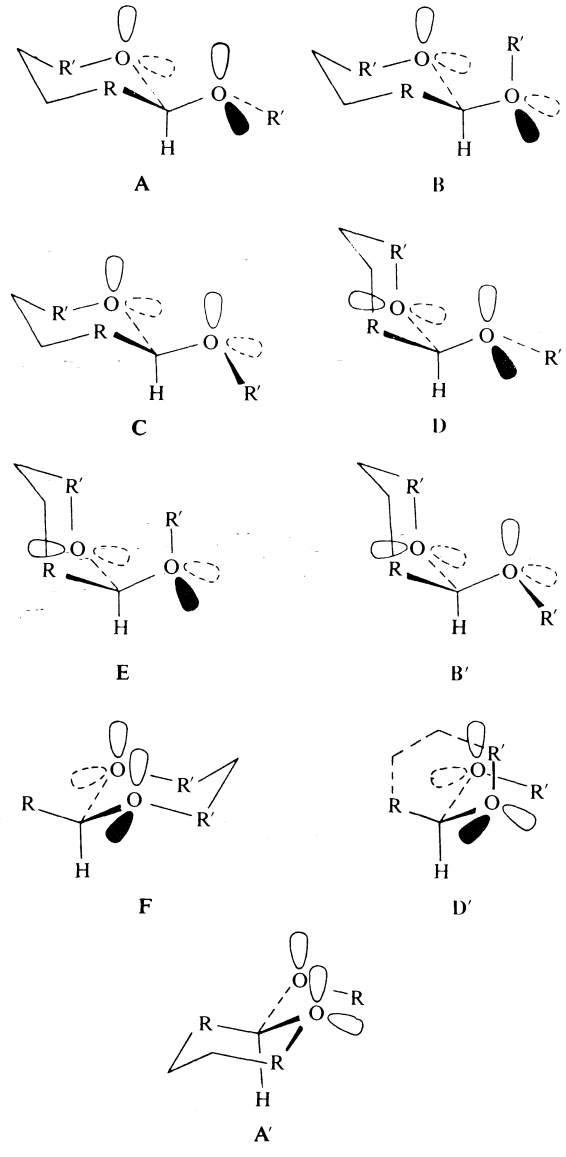


38 39

not react with ozone. Being a *cis* decalin, this compound (**34**) is conformationally mobile and exists in the two conformations, **35** and **36**, which are in perfect equilibrium since they are mirror images; they also correspond to conformers B and B′, respectively, and constitute ideal chemical models for these two conformers. *trans*-1,8-Dioxaoctahydronaphthalene (**37**) is an excellent rigid model for conformer C and it was readily oxidized by ozone to hydroxy lactone **38** in quantitative yield within 1.5 h at −78°. 6,8-Dioxabicyclo[3.2.1]octane (**39**)[10] is a rigid model for conformer E and it was found to be unreactive toward ozone. This result has to be taken with some reserve because this compound is not the most appropriate rigid model for E since the hydrogen of the acetal function is incorporated in a bridgehead. Conformer D is the most stable rotamer of an α-glycoside; since α-glycosides are inert to ozone, D is eliminated as a reactive conformer and there is no need to look for a more rigid chemical model for this one. Conformer A or its mirror image A′ represents the most stable rotamer for a β-glycoside and it is very likely that A is a reactive conformer. The best chemical model that we have studied for conformer A is the β-glycoside. It is very difficult to construct a rigid bicyclic model starting with the preferred rotamer (10) of a β-glycoside; the direction that the O—R′ bond is taking makes it difficult to reattach this side chain to the ring in a rigid manner. Finally, 1,3-dioxane acetals represent an ideal model for conformer F and such acetals have been shown to be reactive with ozone.

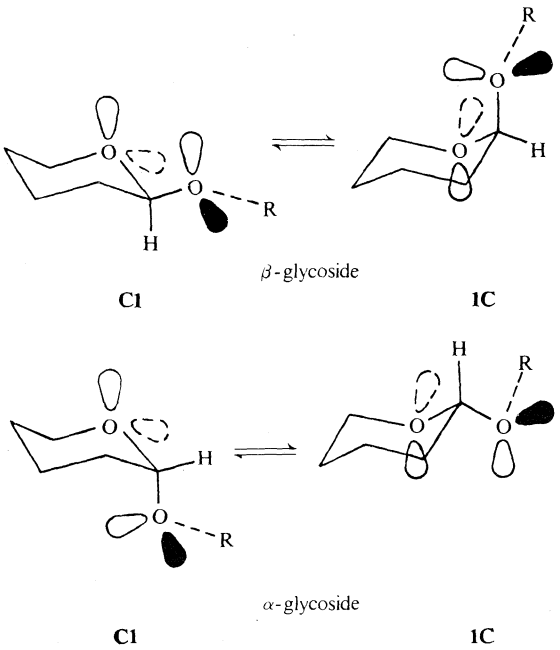
The relationship between the conformation of the acetal function and its reactivity toward ozone was further confirmed by a study of the



A B C D E B′ F D′ A′

SCHEME 2

[10]We are grateful to Professor R. K. Brown (University of Alberta) for his generous gift of this compound.



SCHEME 3

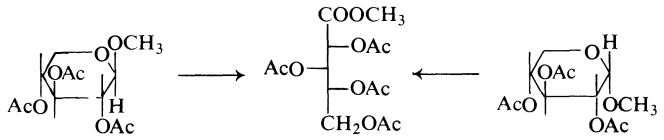
ozonolysis of some labile glycopyranosides as well as some glycofuranosides. Chair-rigid methyl α- and β-glycopyranosides are known to exist in their respective Cl conformations (Scheme 3). There are some α- and β-methyl glycopyranosides which are known to be conformationally labile; they exist as an equilibrium mixture of their Cl and 1C conformations (12). If our postulate is valid, both anomers should be reactive: the β-anomer through its Cl conformation and the α-anomer through its 1C conformation. Furthermore, their respective rates of reaction should depend mainly on the concentration of the Cl conformer for the β-anomer and the concentration of the 1C conformer for the α-anomer.

Methyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (**40**) exists mainly in conformation Cl (81%) (12); it is converted smoothly within 8 h into methyl 2,3,4,5-tetra-*O*-acetyl-D-xylonate (**41**). Methyl 2,3,4-tri-*O*-acetyl-α-D-xylopyranoside (**42**) exists in a small proportion (<2%) in conformation lC (12). Consequently, it should react with ozone but the rate of the reaction should be fairly low. This was found to be the case since the oxidation of this α-anomer was not complete (92% of conversion) after 71 h of reaction. It is the first example of a reactive α-anomer toward ozone. The methyl α- and β-arabinopyranosides represent an interesting pair of anomers. It is known (12) that the tri-*O*-acetyl β anomer **43** exists to a large extent in the abnormal lC conformation (≃97%). The tri-*O*-acetyl α-anomer **45** also exists preferentially in the lC conformation (83%). The α-anomer **45** in the arabinose series should therefore be oxidized at a much faster rate than the β-anomer **43** and this conclusion agrees with the experimental results. Methyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranoside (**45**)[11] was completely oxidized into methyl 2,3,4,5-tetra-*O*-acetyl-D-arabinonate (**44**) within 7 h. The β-anomer **43** was only partially oxidized (71% of conversion) after 80 h. This pair, **43** and **45**, represent the first examples of an α-anomer being more reactive than the corresponding β-anomer. No conformational rigidity can normally be expected from a five-membered ring. Consequently, in methyl glycofuranoside, each anomer should be able to take a conformation which would have proper orbital orientation. Thus, both anomers should react with ozone. Methyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside (**46**) as well as its α-anomer (**48**) are both converted into methyl 2,3,4,5-tetra-*O*-acetyl-D-ribonate (**47**) at approximately the same rate (≃16 h) at room temperature.

The preceding experimental results establish fairly rigorously that of the six possible *gauche* conformers for an acetal function, three (A, C, and F) are reactive and three (B, D, and E) are inert toward ozone. Consequently, the postulate that each reactive *gauche* conformer of an acetal function needs to have a lone pair orbital on each oxygen oriented antiperiplanar to the C—H bond has been verified. To obtain the real chemical significance of this postulate, a good knowledge of the mechanism of the ozonolysis reaction has to be gained so that we can understand the role of the orientation of the lone pair orbitals in the reaction.

A detailed study of the mechanism of the oxidation of acetals by ozone has not yet been achieved. However, we think that enough evidence has been obtained to propose a mechanism. As we have already mentioned, this reaction very likely proceeds through the formation of an intermediate which is either identical or equivalent to a hemiorthoester. No direct evidence has yet been obtained but indirect evidence strongly supports this proposal. There appears to be very little doubt that the hydrolysis of orthoesters

[11]We are grateful to Professor J. K. N. Jones (Queen's University) for his generous gift of this compound.



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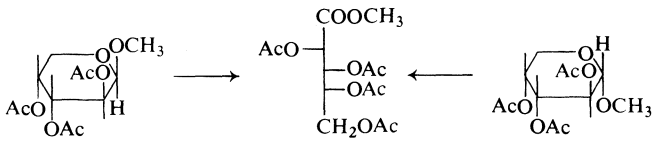

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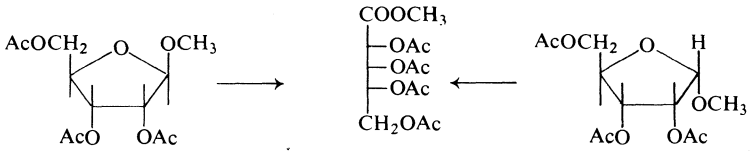
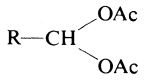


46 47 48

proceeds through the formation of a hemiorthoester (4, 7). We have shown that the ozonolysis of acetals gives the same products obtained from the acid hydrolysis of orthoesters. This observation strongly suggests that the same kind of intermediate is formed in the ozonolysis reaction (2).

Experiments have been carried out to get information on the mechanism by which the C—H bond of the acetal is oxidized, in order to get the proposed tetrahedral intermediate. Diacetoxy acetal (**49**) as well as α- and β-D-glucose pentaacetate (**50** and **51**) do not react with ozone. These results suggest that a positive charge must be developed at the carbon of the acetal function in the transition state of the reaction. Proper alignment of the lone pair orbitals of the ether oxygens can easily stabilize such a positive charge, but the acetoxy group cannot. Ethyl diethoxyacetate (**52**) was found to be completely inert, confirming this suggestion. At the same time this eliminated the possibility of a free radical mechanism, which would lead to the formation of an intermediate such as **53**. A carbethoxy group should facilitate the formation of such a radical intermediate. Finally, competitive oxidation experiments between *para*-substituted benzaldehyde acetals have been carried out. These experiments show that **54** (R = OCH_3) is twice as reactive as **54** (R = H) which in turn is also twice as reactive as **54** (R = NO_2). Thus, an electron-donating group enhances the rate of the reaction, while an electron-attracting group retards the rate. The effect of the methoxy or the nitro group on the rate of the reaction is not very pronounced. We suggest that this is because of the two oxygens of the acetal function which are directly linked to the reacting carbon. These oxygens are in a much better position to stabilize the positive charge than a remote electronic group. Thus, groups in the *para*-position cannot have an important effect on the rate.[12] On the other hand, in compound **52** the carbethoxy group is directly attached to the



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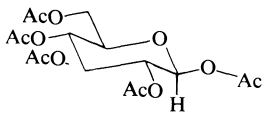

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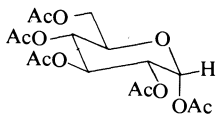

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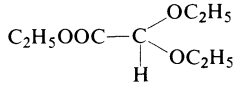

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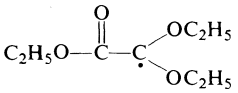

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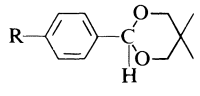


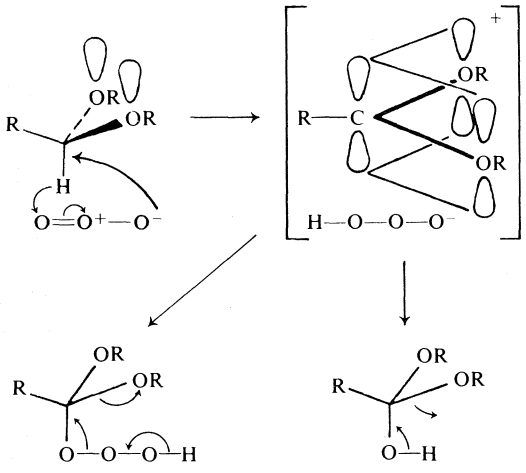
54

[12]Professor S. Fliszár (Université de Montréal, personal communication, results to be published) has made a kinetic investigation of this reaction. He has found that the rate correlates well with σ with a ρ value of −1.10, in agreement with the above discussion.

carbon which is going to become positively charged and its electron-withdrawing property will therefore play a major role. Its role must be predominant since **52** is inert toward ozone.

At present, we think that the most appealing mechanism which comes to mind is the following. Ozone would insert in a 1,3-fashion into the C—H bond of the acetal function (6) to form either a hemiorthoester and molecular oxygen or a hydrotrioxide hemiorthoester (Scheme 4). The latter would then break down to give the ester and alcohol products. We should emphasize that ozone would insert only when the acetal function has a conformation in which each oxygen has a lone pair orbital antiperiplanar to the C—H bond. The breakdown of the tetrahedral intermediate is also governed by the same type of stereoelectronic rule, specific cleavage of a carbon–oxygen bond taking place when the other oxygens of the tetrahedral intermediate each have a lone pair orbital oriented antiperiplanar to the departing *O*-alkyl group (4).

For example, a tetrahydropyranyl ether would react through its most stable rotamer giving specifically a tetrahedral intermediate. This intermediate has proper orbital orientation to break the ring oxygen–carbon bond, thus forming the hydroxy ester (Scheme 5). Loss of the OR group to generate the δ-lactone is not possible through an orbital-assisted mechanism simply because the lone pair orbitals of the ring oxygen cannot be used; they are not properly oriented. It is the C_6—O bond of the ring oxygen which is antiperiplanar to the OR group.



SCHEME 4

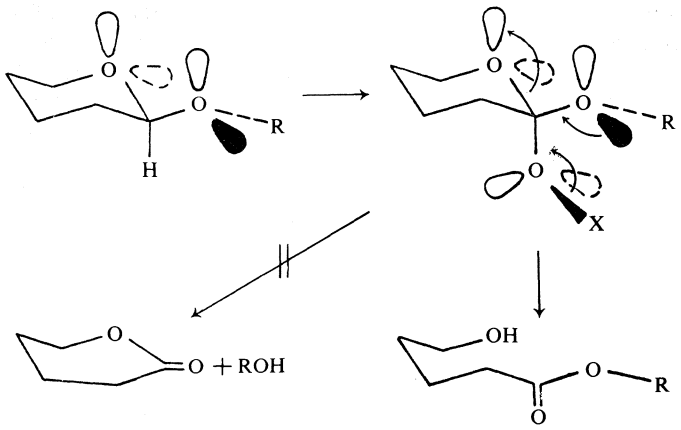
Various oxidations of aldehyde acetals into esters have been reported and we believe that these reactions proceed also through a hydride transfer (or its equivalent) from the acetal to the oxidizing agent. Different types of acetals (13) have been oxidized by *N*-bromosuccinimide and no evidence has yet been obtained against a hydride transfer from the acetal to a bromonium ion as one of the key steps. Oxidation of acetal by hydride transfer with triethyloxonium tetrafluoroborate (14, 15) and with triphenylmethane tetrafluoroborate (15) has also been described. Angyal and his co-workers have reported the oxidation of acetals by chromium trioxide in acetic acid (16). This last reaction is quite interesting since the same stereospecificity and outcome of the reaction has been observed with α- and β-glycoside.

We believe that the oxidation of acetals and the hydrolysis of hemiorthoesters (4) and of hemiorthoamides (5) are isolated examples of a general chemical process. The reactions described in Scheme 6 also belong to the same class: (*a*) the haloform reaction, (*b*) the basic fragmentation of α-diketone monothioketals (17), (*c*) the Grob fragmentation with two heteroatoms (18) and related reactions (19), (*d*) the retro-Claisen condensation, and (*e*) the benzilic rearrangement. The Cannizaro reaction, the facile opening of cyclopropanone (Favorski rearrangement), and the cleavage of nonenolizable ketone by sodium amide (Haller–Bauer reaction (20)) and by hydroxide ion (21) can also be added to the preceding list of reactions. The combination of two heteroatoms with proper orbital orientation is a very powerful driving force for expelling a leaving group. The reaction should be easier if one of the two heteroatoms is negatively charged; if both heteroatoms can bear a negative charge, it should proceed with even greater ease and work with an even poorer leaving group.

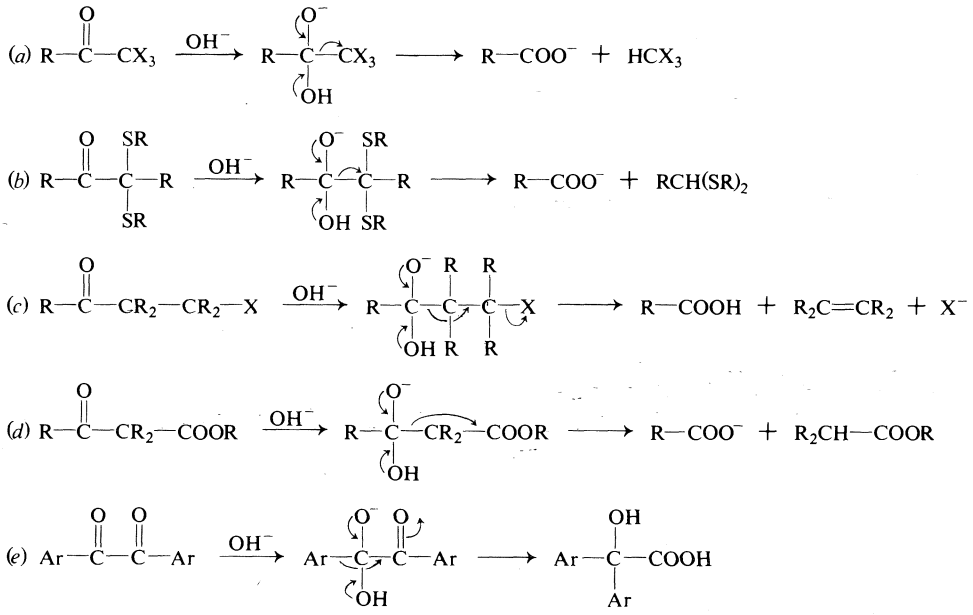
Thus, this general chemical process can take place whenever two heteroatoms (oxygen and/or nitrogen) and a leaving group are linked to the same carbon. The only requirement is a stereoelectronic one where each heteroatom should have a lone pair orbital oriented antiperiplanar to the leaving group.

Experimental

The i.r. spectra were taken on a Perkin-Elmer 257 Spectrophotometer; n.m.r. spectra (τ values) were recorded on a Varian A-60 spectrometer in the solvents



SCHEME 5



SCHEME 6

indicated and with TMS as standard. The v.p.c. analyses were done on a Varian Aerograph, model 90-P. The ozonolysis reactions were carried out with a Welsbach Ozonator, model T-816. Organic solution were dried over anhydrous magnesium sulfate and Silica gel was used in all the chromatography (columns and plates). Microanalysis were performed by Dr. C. Daesslé, Organic Microanalyses and by Mr. J. Tamas, Laboratoire de Microanalyse, Université de Sherbrooke.

Stoichiometry of the Reaction

A stream of ozone–oxygen gas was passed through cold (−78°) ethyl acetate (50 ml) for 1 h. A cold solution (−78°) of 2-phenyl-1,3-dioxolan (1.5 g, 10 mmol) in ethyl acetate (10 ml) was then added. The blue color of ozone disappeared after 20 s and the volume of gas formed was ≃60 ml (≃2.7 mmol). The solvent was then evaporated to dryness. The two compounds which were present in the reaction mixture were identified (n.m.r.) as 2-phenyl-1,3-dioxolan (≃7.2 mmol) and ethyl 2-hydroxybenzoate (≃2.8 mmol). This experiment was repeated twice.

The same experiment was also carried out with 2-*n*-hexyl-1,3-dioxolan and an analogous result was obtained. In this case, it took approximately 3 min for the blue color of ozone to disappear.

Typical Procedures for the Ozonolysis of Acetals

(a) 1,1-Dimethoxyheptane

1,1-Dimethoxyheptane (3.716 g, 23.22 mmol) in ethyl acetate (100 ml) was ozonized at room temperature (rate of ozone: 1 mmol/min). The reaction was followed by proton n.m.r. analysis of aliquots and was found to be complete after 1.5 h. Excess ozone was removed by

flushing the system with nitrogen. The solvent was removed by evaporation and the residue was dissolved in ether. This solution was washed with aqueous sodium carbonate and water. The dried ethereal solution was concentrated *in vacuo*; the resulting product was distilled to give pure methyl heptanoate (3.017 g, 91%), identified by comparison with an authentic sample. The same experiment was carried out at −78° but the reaction required a longer time to go to completion (Table 2).

(b) 2-n-Hexyl-1,3-dioxolan

2-*n*-Hexyl-1,3-dioxolan (1.589 g, 10.05 mmol) was ozonized in ethyl acetate (100 ml) at −78° (rate of ozone: 1 mmol/min). After 10 min, the blue color of ozone appeared in the solution and the ozone generator was stopped. Excess ozone was removed by flushing the system with nitrogen. The solvent was removed by evaporation and the residue was dissolved in ether (200 ml); this solution was washed once with brine then dried. Removal of solvent *in vacuo* gave ethyl 2-hydroxyheptanoate (1.772 g, 100%); i.r.: ν_{max} (film) 3500 and 1740 cm^{-1}; n.m.r.: δ ($CDCl_3$) 4.30 (2H, multiplet, CH_2OCO) and 3.90 (2H, multiplet, CH_2O).

This crude material was then treated with a mixture of pyridine (5 ml) and acetic anhydride (5 ml). After 15 h, this solution was taken to dryness *in vacuo*. The residue thus obtained was dissolved in ether and then washed with aqueous sodium carbonate and water. The dried ethereal solution was evaporated *in vacuo* to give ethyl 2-acetoxyheptanoate (2.120 g, 98%). An analytical sample was prepared by microdistillation; i.r.: ν_{max} ($CHCl_3$) 1740 cm^{-1}; n.m.r.: δ ($CDCl_3$) 4.32 (4H, singlet, OCH_2CH_2O) and 2.10 (3H, singlet, CH_3COO).

Anal. Calcd. for $C_{11}H_{22}O_4$: C, 61.09; H, 9.32. Found: C, 61.18; H, 9.58.

(c) 2-Methoxytetrahydropyran

2-Methoxytetrahydropyran (5.588 g, 48.17 mmol) was ozonized in ethyl acetate (100 ml) at −78° (rate of ozone: 1 mmol/min). The reaction was followed by proton n.m.r. analysis of aliquots and was found to be complete after 2 h. Residual ozone was removed by flushing the system with nitrogen, then the solvent was removed *in vacuo*. The crude material was treated with a mixture of pyridine (10 ml) and acetic anhydride (10 ml). After 15 h, this solution was evaporated to dryness; the residue obtained was dissolved in ether. This solution was washed with aqueous sodium carbonate and brine. The dried ethereal solution was evaporated *in vacuo* to give methyl 5-acetoxypentanoate (6.380 g, 94%). An analytical sample was prepared by microdistillation; i.r.: ν_{max} (film) 1740 cm^{-1}; n.m.r.: (δ) 4.05 (2H, diffuse triplet, CH_2OAc), 3.63 (3H, singlet, $COOCH_3$), 2.34 (2H, multiplet), 2.00 (3H, singlet, $OCOCH_3$), and 1.70 (2H, multiplet).

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.06; H, 8.05.

(d) 2-Methoxytetrahydrofuran (8)

Sodium acetate (4 g) was added to a solution of 2-methoxytetrahydrofuran (1.02 g, 10 mmol) in acetic anhydride (100 ml). This mixture was ozonized (rate of ozone: 1 mmol/min) at room temperature. The reaction was followed by proton n.m.r. analysis of aliquots and was complete after 6 h. Residual ozone was removed by flushing the system with nitrogen. The mixture was heated (oil bath temperature 100°) for 2 h, then taken to dryness *in vacuo*. Water was added and the aqueous phase was extracted with chloroform. The extract was treated with activated charcoal, then filtered through celite. The filtrate was evaporated and the resulting residue was dissolved in ether. This was washed with aqueous sodium carbonate and brine. The ethereal solution was dried and evaporated *in vacuo*. The material thus obtained was distilled to give methyl 4-acetoxybutyrate (1.36 g, 85%); i.r.: ν_{max} (film) 1740 cm^{-1}; n.m.r.: δ ($CDCl_3$) 4.06 (2H, diffuse triplet, CH_2O), 3.63 (3H, singlet, OCH_3), and 2.0 (3H, singlet, CH_3COO).

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.76; H, 7.65.

Ozonolysis of Glycosides

*(a) Methyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (**17**) (22)*

Sodium acetate (4 g) was added to a solution of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (602 mg, 1.66 mmol) in acetic anhydride (100 ml). This mixture was ozonized (rate of ozone: 0.3 mmol/min) at room temperature; the reaction was complete after 16 h. Excess ozone was removed by flushing the system with nitrogen. The mixture was evaporated *in vacuo* and water was added. The aqueous phase was extracted with ether. The extract was washed with aqueous sodium carbonate and brine, then dried. Evaporation to dryness gave a residue which was purified by column chromatography (chloroform–ether, 4:1). This gave methyl penta-*O*-acetyl-D-gluconate (**20**, 667 mg, 92%) which was crystallized from ethanol – petroleum ether, m.p. 120–121°, $[\alpha]_{578}$ ($CHCl_3$) 9.4° (lit. (23) m.p. 124°, $[\alpha]_D$ ($CHCl_3$) 9.2°); n.m.r.: δ ($CDCl_3$) 3.78 (3H, singlet, OCH_3), 2.22 (3H, singlet, CH_3COO), and 2.1–2.13 (12 H, two signals corresponding to four acetate groups). This compound was found identical to an authentic sample (23).

The corresponding α-anomer **23** (22) was recovered unchanged after being subjected to the reaction conditions described above.

The following methyl glycosides were submitted to the same experimental conditions. The reactions were followed by proton n.m.r. analysis.

*(b) Methyl 2,3,4,6-Tetra-O-acetyl-β-D-mannopyranoside (**18**) (24)*

Compound **18** (155 mg, 0.43 mmol) gave (reaction time, 10 h) methyl penta-*O*-acetyl-D-mannonate (**21**, 132 mg, 74%) after preparative t.l.c. This product was crystallized from ether – petroleum ether, m.p. 80–81°, $[\alpha]_{578}$ ($CHCl_3$) +22°; n.m.r.: δ ($CDCl_3$) 3.68 (3H, singlet, OCH_3), 2.11 (3H, singlet, CH_3COO), 2.08 (3H, singlet, CH_3COO), 2.04 (3H, singlet, CH_3COO), and 2.02 (6H, singlet, two CH_3COO).

Anal. Calcd. for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.75. Found: C, 48.56; H, 5.80.

The corresponding α-anomer **24** (24) was recovered unchanged after the same treatment.

*(c) Methyl 2,3,4,6-Tetra-O-acetyl-β-D-galatopyranoside (**19**) (25)*

Compound **19** (225 mg, 0.62 mmol) gave (reaction time, 6 h) methyl penta-*O*-acetyl-D-galactonate (**22**, 241 mg, 92%) after preparative t.l.c. This product was crystallized with ether – petroleum ether, m.p. 125–126°, (lit. (23) m.p. 126–127°); n.m.r.: δ ($CDCl_3$) 3.68 (3H, singlet, OCH_3), 2.14, 2.09, 2.06, 2.01, and 1.99 (15 H, five singlets corresponding to five acetate groups).

The corresponding α-anomer **25** (25) was recovered unchanged after the same treatment.

*(d) Methyl 3,4,6-Tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**26**) (9)*

Method 1. Compound **26** (912 mg, 3 mmol) was treated with ozone under the conditions described above to give (reaction time, 1 h) methyl tetra-*O*-acetyl-2-deoxy-D-gluconate (**28**, 1.03 g, 81%) which was crystallized from ether – petroleum ether, m.p. 55–57°, $[\alpha]_{578}$ ($CHCl_3$) + 33°; n.m.r.: δ ($CDCl_3$) 3.67 (3H, singlet, OCH_3), 2.14 (3H, singlet, CH_3COO), and 2.04–2.07 (9H, two signals corresponding to three acetate groups).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.79; H, 6.09.

Method 2. Compound **26** (580 mg, 1.9 mmol) was ozonized in glacial acetic acid (100 ml) during 1.5 h at room temperature. The solvent was removed *in vacuo* and purification of the residue by preparative t.l.c. gave pure methyl 3,4,6-tri-*O*-acetyl-2-deoxygluconate (**27**, 486 mg, 80%) which was crystallized from chloroform – petroleum ether, m.p. 106–107°, $[\alpha]_{578}$ ($CHCl_3$) +64°; n.m.r.: δ ($CDCl_3$) 3.68 (3H, singlet, OCH_3), and 2.05–2.10 (9H, two signals corresponding to three acetate groups).

Compound **27** (208 mg) was then treated with a mixture of pyridine (5 ml) and acetic anhydride (5 ml) for 17 h at room temperature. After evaporation of the solvent, the residue was dissolved in chloroform and the organic solution was washed with aqueous sodium bicarbonate and brine. The dried chloroform solution was evaporated to dryness and the residue was purified by preparative t.l.c. to give pure methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-gluconate (**28**, 178 mg).

The α-anomer **29** (9) was treated by ozone in acetic anhydride – sodium acetate and it was recovered unchanged.

*(e) Methyl 2,3,4-Tri-O-acetyl-β-D-xylopyranoside (**40**) (26)*

Compound **40** (645 mg, 2.20 mmol) gave (reaction time, 8 h) methyl tetra-*O*-acetyl-D-xylonate (**41**, 602 mg, 78%) after purification by preparative t.l.c. An analytical sample was prepared by microdistillation; $[\alpha]_{578}$ ($CHCl_3$) −6°; n.m.r.: δ ($CDCl_3$) 3.75 (3H, singlet, OCH_3), 2.19, 2.09, 2.06, and 2.04 (12 H, four singlets corresponding to four acetate groups).

Anal. Calcd. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.10; H, 5.66.

The corresponding α-anomer **42** (689 mg, 240 mmol (26)) was ozonized for 71 h and gave unreacted **42** (8%) and methyl tetra-*O*-acetyl-D-xylonate (**41**, 92%) which were separated by preparative t.l.c.

*(f) Methyl 2,3,4-Tri-O-acetyl-α-D-arabinopyranoside (**45**) (12)*

Compound **45** (2.0 g, 6.8 mmol) gave (reaction time, 7 h) methyl tetra-*O*-acetyl-D-arabonate (**44**, 2.28 g, 95%) after purification by preparative t.l.c. This material was crystallized from ethanol; m.p. 128–129° (lit. (27) m.p. 116°); n.m.r.: δ ($CDCl_3$) 3.74 (3H, singlet, OCH_3), 2.17 (3H, singlet, CH_3COO), and 2.06 (9H, two signals corresponding to three acetate groups).

Anal. Calcd. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.75. Found: C, 48.11; H, 5.82.

The corresponding β-anomer **43** (242 mg, 0.8 mmol (12)) was ozonized for 80 h and gave unreacted **43** (39%) and methyl tetra-*O*-acetyl-D-arabonate (**44**, 71%) which were separated by preparative t.l.c.

*(g) Methyl 3,4,5-Tri-O-acetyl-β-D-ribofuranoside (**46**) (28)*

Compound **46** (0.3 g, 1.18 mmol) gave (reaction time, 16 h) methyl tetra-*O*-acetyl-D-ribonate (**47**, 0.32 g, 90%); m.p. 89–90°, $[\alpha]_D$ ($CHCl_3$) −12.7° (lit. (29) m.p. 90°, $[\alpha]_D$ ($CHCl_3$) −13°); n.m.r.: δ ($CDCl_3$) 3.77 (3H, singlet, OCH_3), and 2.03–2.13 (12 H, signals corresponding to four acetate groups).

The corresponding α-anomer **48** (28) also gave compound **47** (reaction time, 18 h).

Ozonolysis of Model Compounds

*(a) trans-1,8-Dioxaoctahydronaphtalene (**37**) (30)*

Compound **37** (926 mg, 6.52 mmol) was ozonized in ethyl acetate (75 ml) at −78° (rate of ozone: 1 mmol/min). The reaction was found to be complete after 1.5 h. Residual ozone was removed by flushing the system with nitrogen, then, the solvent was removed *in vacuo* to yield crude hydroxy lactone **38** (1.140 g, ≃100%), i.r.: ν_{max} (film) 3450 and 1740 cm^{-1}; n.m.r.: δ ($CDCl_3$) 4.35 (3H, multiplet, CH_2OCO), and 3.75 (2H, multiplet, CH_2OH).

Crude hydroxy lactone **38** was then treated with a mixture of pyridine (5 ml) and acetic anhydride (5 ml). After 15 h, the solution was taken to dryness *in vacuo* to give compound **38** (H = CH_3CO) which was purified by column chromatography (1.025 g, 80%). An analytical sample was prepared by microdistillation; i.r.: ν_{max} (film) 1740 cm^{-1}; n.m.r.: δ ($CDCl_3$) 4.38 (2H, diffuse triplet, J = 6 Hz, CH_2—OCO), 4.15 (2H, diffuse triplet, J = 6 Hz, CH_2OAc), and 2.06 (3H, singlet, CH_3COO).

Anal. Calcd. for $C_7H_{12}O_4$: C, 59.98; H, 8.05. Found: C, 59.79; H, 7.96.

*(b) cis-1,8-Dioxaoctahydronaphtalene (**34**) (30)*

Compound **34** (865 mg, 6.52 mmol) was recovered unchanged after being subjected to the reaction conditions described above.

(*c*) The following compounds were found to be inert toward ozone (room temperature, ethyl acetate): ethyl diethoxy acetate (**52**, 3 h), β-D-glucosepentaacetate (**50**, 6 h), α-D-glucosepentaacetate (**51**, 6 h), 6,8-dioxabicyclo-[3.2.1]octane (**39**, (31), 6 h), and 1,1-diacetoxyheptane (**49**, (32), 2 h in glacial acetic acid).

*Ozonolysis of Para-substituted Benzaldehyde Acetal (**54**)*

(*a*) A mixture of phenyl 2,2-dimethyl-1,3-dioxan (0.01 *M*) and *p*-methoxyphenyl 2,2-dimethyl-1,3-dioxan (0.01 *M*) in ethyl acetate was ozonized at −78° during 10 min. The resulting mixture was analyzed by vapor phase chromatography (SE-30, temperature 135°). This experiment was repeated three times. Phenyl 2,2-dimethyl-1,3-dioxan was converted into 3-hydroxy-2,2-dimethylpropyl benzoate to the extent of 28%; *p*-methoxyphenyl 2,2-dimethyl-1,3-dioxan was transformed into 3-hydroxy-2,2-dimethylpropyl *p*-methoxybenzoate to the extent of 60%.

(*b*) Using the technique described above, an equimolar mixture (0.01 *M*) of *p*-methoxyphenyl 2,2-dimethyl-1,3-dioxan and *p*-nitrophenyl 2,2-dimethyl-1,3-dioxan was ozonized. The first compound was converted into 3-hydroxy-2,2-dimethylpropyl *p*-methoxybenzoate to the extent of 70% while the second compound was transformed into 3-hydroxy-2,2-dimethylpropyl *p*-nitrobenzoate to the extent of 20%.

Similarly, an equimolar mixture (0.01 *M*) of phenyl 2,2-dimethyl-1,3-dioxan and *p*-nitrophenyl 2,2-dimethyl-1,3-dioxan gave 3-hydroxy-2,2-dimethylpropyl benzoate (86%) and 3-hydroxy-2,2-dimethylpropyl *p*-nitrobenzoate (40%).

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