Carbohydrate Research, 97 (1981) 257–262
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

THE ROLE OF OXYGEN SUBSTITUENTS IN THE ELIMINATION AND ENOLISATION REACTIONS OF 4,6-*O*-BENZYLIDENE-HEXOPYRANOSIDES AND -HEXOPYRANOSIDULOSES

VERNON G. S. BOX
Department of Chemistry, University of the West Indies, Kingston 7 (Jamaica, West Indies)

(Received May 20th, 1981; accepted for publication, July 1st, 1981)

ABSTRACT

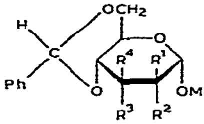
An attempt is made to rationalise the elimination and enolisation processes observed in 4,6-*O*-benzylidenehexopyranosides and hexopyranosiduloses. The roles of the oxygen substituents on the pyran ring are outlined, and it is suggested that these oxygen atoms control the paths of the reactions.

INTRODUCTION

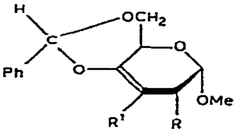
Many eliminations and enolisations have been observed in the course of carbohydrate research, but often the selective or specific reactions found have not been discussed with the aim of clarifying the guiding features involved. Were a model developed to rationalise the courses of these reactions, it would strengthen the armamentarium of researchers, particularly those engaged in synthetic endeavours, as this model would assist in the prediction of the outcome of these processes.

DISCUSSION

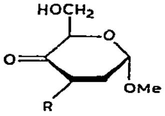
The preparation of the methyl 2-*O*-acetyl-3-*C*-alkyl-4,6-*O*-benzylidene-3,4-dideoxy-α-D-hex-3-enopyranosides (**3**) from the related derivatives (**1**) of the methyl 3-*C*-alkyl-α-D-allopyranosides by the action of thionyl chloride in pyridine at 0° has been reported[1,2]. These stereospecific reactions were pivotal in the preparation of the methyl 3-*C*-alkyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-uloses (**4**). The obvious importance of compounds **4**, coupled with the intention of preparing other analogues of **4**, required that the processes leading to compound **3** be thoroughly



1 R^1 = H, R^2 = OAc, R^3 = OH, R^4 = allyl, benzyl, or Me
2 R^1 = SPh, R^2 = R^4 = H, R^3 = OMs



3 R = OAc, R^1 = allyl, benzyl, or Me



4 R = allyl, benzyl, or

0008-6215/81/0000–0000/$ 02.50, © 1981 — Elsevier Scientific Publishing Company

studied, in order to enable prediction of the outcome of similar dehydrations, dehydrohalogenations, or dehydrosulphonyloxylations.

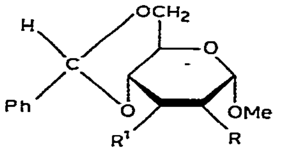
The dehydrations of **1** to **3** were fascinating, in that, of the possible alkenic products, namely, **3**, **5**, and **7**, only compounds **3** were formed. Even when the branch at C-3 was allyl or benzyl, no trace of compound **7** (R = vinyl or phenyl) was formed in the respective reaction-mixture.

There must, therefore, be an electronic or steric factor that biases the path of the eliminations towards the alkenes **3**, rather than to the alkenes **5**, or to the stable, π-conjugated alkenes **7**. Any mechanism proposed for rationalising the path of the reactions must, in particular, show why there was a selective loss of H-4, rather than of H-2, both of which were suitably oriented to participate in an E1 or E2 reaction. It is well known that similar dehydrations of cyclic tertiary alcohols occur endocyclically, rather than exocyclically[3], and this could be rationalised as being due to conformational factors which did not allow any of the hydrogen atoms on the branch to be suitably disposed, and so to participate in either the E1 or E2 process. Furthermore, if there was free rotation about the carbon–carbon bond between the ring-carbon atom and the substituent, the lifetimes of desirable conformations might be very small and so make these orientations inconsequential as compared to those of the ring-hydrogen atoms, which are suitably oriented permanently.

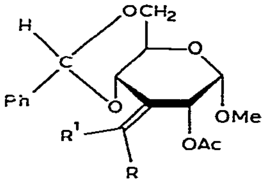
A comparison of the E1, or E2 process with the enolisation of 3-glyculoses would also be instructive, as these enolisations have been shown[4] to involve H-2 rather than H-4, unless H-2 was not properly oriented[5], *i.e.*, *axial*. The fact that an enolisation involved the formation of an *electron-rich* intermediate and product[6] (rich on the α-carbon atom and carbonyl oxygen atom), whereas the elimination process involved an *electron-deficient* intermediate[6] (as in the E1 reaction), or transition state (as in an E1-like E2 reaction), must be important in the rationalisations.

A thorough examination of models of compounds **1**, **3**, **5**, and **7** revealed no steric factors which might have influenced the path of the reaction. The electronic factors that might affect the relative stabilities of alkenes **3** and **5**, and the transition states leading to **3** and **5**, were therefore examined. Both **3** and **5** are derivatised enols, and so the factors affecting the stabilities of enols are important.

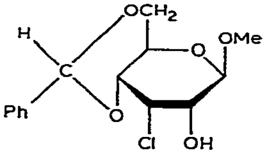
If an LCAO* model is used, and it is assumed that the oxygen atom of an enol



5 R = OAc, R^1 = allyl, benzyl, or Me
6 R = Sph, R^1 = H



7 R = phenyl, or vinyl, R^1 = H
R = H, R^1 = phenyl, or vinyl

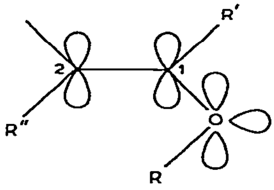


8

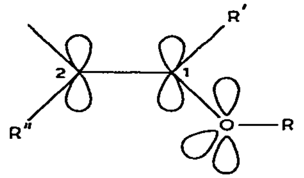
---

*Linear combination of atomic orbitals.

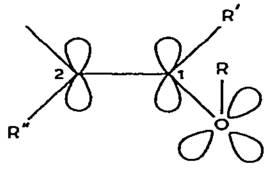
ether–ester moiety **9** is sp^2-hybridised, there are two electronically favourable conformations available to **9**, *i.e.*, **9a** and **9b**, in which there is maximum delocalisation of the "lone pair" over the π bond by virtue of the coplanarity of the oxygen atom's "p-orbital" with the "p-orbital" of C-1. Any conformation which does not allow this delocalisation to be achieved should be less stable than both **9a** and **9b**, *e.g.*, **9c**. The sizes of the groups R, R′, and R″ will be of importance to the relative stabilities of the two conformers, **9a** and **9b**, as these will decide the steric factors encountered.



9a

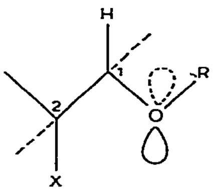


9b

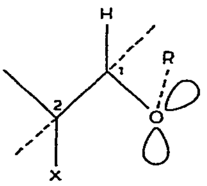


9c

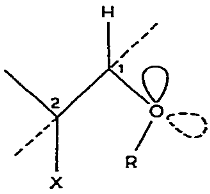
If R is fixed relative to the π bond, such that the relationship of the "p-orbitals" is always favourable, this system will be more stable than that in which there is free rotation about the RO–C-1 bond. Free, or partially restricted, rotation would mean that the "p-orbital" of the oxygen atom would not always be advantageously disposed. Furthermore, if R was required by steric factors to assume a position that would not allow favourable overlap, the relative instability of this conformation (*e.g.*, **9c**) would be exaggerated.



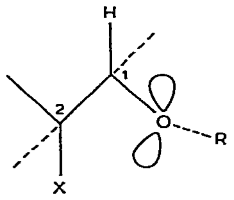
10a



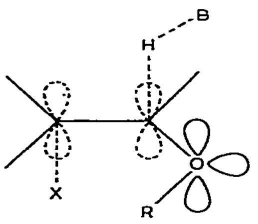
10b



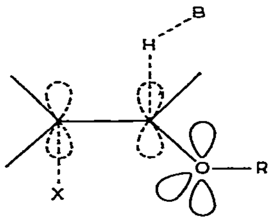
10c



10d



11a



11b

The elimination of H-X from such moieties as **10** would be significantly stabilised if the E1-like E2, or the E2, reaction attained a transition state such as is shown in **11**, as the incipient π bond would enjoy the developing resonance stabilisation due to the oxygen atom's "p-orbital", and the *electron-deficient* carbon system would benefit from the high, available electron-density.

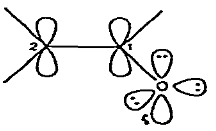
Thus if **10** had a geometry such that one of the oxygen atom's "sp^3/p-orbitals" was always coplanar with the C-1–H bond (*cis* or *trans*), so leading to a transition state such as **11a** or **11b**, elimination as shown would be very favourable.

Any factors which would not allow the "sp^3/p-orbital" of the oxygen atom to maintain the desirable orientation would also lower the stability of the transition state relative to that of the system first described, and hence, would require a less favourable elimination process.

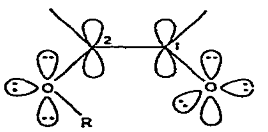
The molecules **1** and **8** (ref. 7) have precisely the geometry shown partially in **10a**; H-4 and H-2 are both anti-coplanar with the leaving group, but there is *free rotation* about the C-2–OR bond in both cases, whereas there is the *fixed*, anti-coplanar arrangement of the "sp^3-orbital" of O-4 relative to H-4. Thus, as the leaving groups depart, and molecules **1** and **8** attain their transition states, O-4 can more efficiently stabilise the loss of H-4, than can O-2 similarly stabilise the loss of H-2. All the molecules **1** and **8** undergo exclusive elimination involving H-4. Thus, when the elimination of an axial substituent at C-3 proceeds *via* the E1-like E2, or E2, process (*electron deficiency* on the carbon atom in the transition state) in such molecules as **1**, or **8**, O-4 will control the path of the reaction.

The demesylation of compound **2** (ref. 8) proceeded *via* a carbanion, or E1cb-like transition-state, and was controlled by the phenylthio group, thus leading to **6**. This kind of reaction can, therefore be readily distinguished from the E2 processes described.

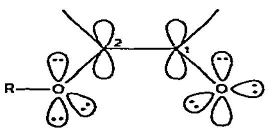
If the anti-coplanar orientation of the "sp^3/p-orbital" of O-4 relative to H-4 enhanced its loss in an elimination reaction which involved an *electron-deficient* transition-state, the same orientation might be expected to retard, or restrain, the loss of H-4 in a reaction which involved an *electron-rich* transition-state. This type of electron-rich transition-state would be encountered in the enolisation of ketone **15**. Both H-2 and H-4 are properly oriented, *i.e.*, *axial*, for efficient removal by a base, but it was found experimentally[4] that there was no evidence of any enolisation involving H-4.



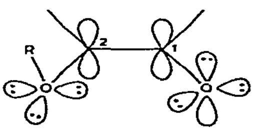
12



13a



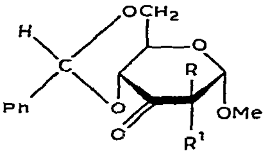
13b



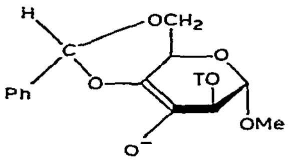
14

The LCAO model of an enolate anion would be as shown in **12**. If C-2 was attached to a properly oriented source of high electron-density (*e.g.*, an OR group, as in **13**) this interacting electron-density would produce an instability. If, however, the orientation of the -OR group was varied, to lessen, or remove, the π overlap, the stability of the entity should be increased, as C-2 would now largely experience the stabilising, negative inductive-effect of the -OR group.

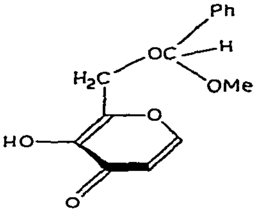
This situation is well portrayed in **15**, as enolisation involving H-4 will generate an unfavourable enolate, such as **13**, involving O-4, but enolisation with the loss of H-2 will be advantageous, as the -OAc group is freely rotating and can assume an orientation similar to that desired, *e.g.*, **14**.



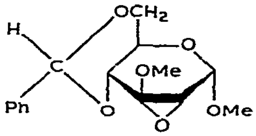
15 R = H, R^1 = OAc
16 R = H, R^1 = OTs
17 R = OTs, R^1 = H



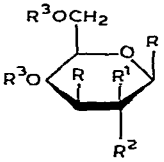
18



19



20



21 R^1, R^2 = O (R and R^3 = any group)
22 R^1 = leaving group (R, R^2, and R^3 = any group)

In congruence with the foregoing, the tosylate **16**, in methanol containing triethylamine, enolised, first with the loss of H-2, and so produced the epimeric ketone **17**. The ketone **17**, which now had only one hydrogen atom, H-4, properly oriented for efficient enolisation, was *then* converted into the enolate **18**, which rapidly fragmented, finally yielding **19**. Evidence for the configuration of the ketone **17** was found in the formation of the acetal-epoxide **20**.

This unified model of alkene formation in monosaccharides would suggest[9,10] that compounds **21**, in which both H-1 and H-3 are axially oriented, will only be enolised towards C-3, and furthermore, that compounds **22** will undergo exclusive elimination, in an E1-like E2, or E2, reaction, towards C-1.

REFERENCES

1 V. G. S. Box, L. L. Box, and E. V. E. Roberts, *Heterocycles*, 14 (1980) 1269–1271.
2 V. G. S. Box, L. L. Box, and E. V. E. Roberts, *Carbohydr. Res.*, 96 (1981) 215–222.
3 T. D. Inch, G. J. Lewis, and N. E. Williams, *Carbohydr. Res.*, 19 (1971) 17–27.
4 D. Baker, J. Defaye, A. Gadelle, and D. Horton, *J. Org. Chem.*, 41 (1976) 3834–3840.
5 A. Dmytraezenko, J. K. N. Jones, and W. A. Szarek, *Chem. Commun.*, (1971) 1220–1222.
6 T. J. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper and Row, New York, 1976, and references cited therein.
7 J. K. N. Jones, B. T. Lawton, and W. A. Szarek, *Chem. Commun.*, (1969) 787–788.
8 S. Hanessian and N. R. Plessas, *Chem. Commun.*, (1968) 706–708.
9 F. W. Lichtenthaler, J. Sakakibara, and E. Oeser, *Carbohydr. Res.*, 59 (1977) 47–61.
10 M. Černý, J. Kocourek, J. Pacák, and J. Staněk, *The Monosaccharides*, Academic Press, New York, 1963, pp. 392–395, and references cited therein.