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MOLECULAR ORBITAL CALCULATIONS RELATING TO THE MECHANISM OF THE REACTIONS OF SUGAR ORTHOESTERS

1,2,4-ORTHOACETYL-α-D-XYLOPYRANOSE

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Abstract—Quantum chemical studies of 1,2,4-orthoacetyl-α-D-xylopyranose and three protonated forms, four acyloxonium ions, and the glycosyl cation by means of the MINDO/2 method are reported. The protonated forms (oxonium ions) should not be considered as product-determining intermediates in acid-catalysed reactions of ortho-esters due to their fast rearrangement into isomeric acyloxonium ions. Of the latter, only 1,2- and 1,4-acyloxoniums, adopting a conformation close to that of starting orthoester (i.e. a distorted boat), were found to be relatively stable and reactive and so are considered to be the main product-determining intermediates. The distribution of the positive charge in these ions was interpreted as evidence of preferred nucleophilic attack on C-1 rather than on other centres of these ions. The isomerisation of the 1,2-acyloxonium ion into the glycosyl cation was found to be energetically very unlikely and so would be product determining only in fast, especially intramolecular, reactions. The results obtained were in good agreement with qualitative data on the chemistry of sugar orthoesters.

Semi-empirical quantum chemical calculations have proved to be a useful approach for the investigation of organic reaction mechanisms.[1] In the case of catalyzed reactions such calculations may be used to estimate the stability and reactivity of all supposed intermediates. These data indicate the most profitable pathway for the reaction from the energetic point of view. However, this procedure includes calculations of the geometry for all intermediates using the total energy minimisation and so requires much computer time.

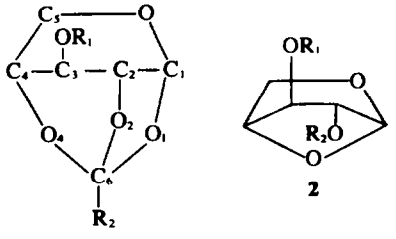
Earlier semi-empirical methods were used to study intermediates in acyl-transfer reactions in aqueous medium.[2] In that work the wave function obtained in the initial calculation was the zero approximation for all calculations but the first one. Such method appeared to be very effective and made possible the study of rather complex reactions.

As a further development of the approach we have studied the mechanism of acid-catalyzed reactions of cyclic sugar orthoesters described in this paper. Sugar orthoesters, which are used for the synthesis of glycosides, oligosaccharides and polysaccharides (for review see[3]), can undergo acid-catalyzed reactions with alcohols leading to the cleavage of ortho ester rings and formation of 1,2 - trans - glycosidic bond and acyloxy group at C-2. Much data on synthetic applications of this reaction are available,[3] but its mechanism has not been studied systematically as yet. However the following principal steps were proposed for the reaction.[3-6] The protonation of one oxygen of the orthoester ring system leads to a five-membered cyclic acyloxonium ion. The latter forms thermodynamically-controlled products by nucleophilic attack of alcohol on C-1, with the cleavage of the acyloxonium ring and formation of the glycosidic bond. The protonation of another oxygen atom leads to intermediates differing from the five-membered acyloxonium ion and giving rise to side products (see, e.g.[6-8]). The acid-catalyzed isomerisation of tricyclic orthoesters of D-xylopyranose **1** to 1,5 - anhydro - β - D - xylopyranose derivatives **2** were rationalized in terms of a fast reversible isomerisation of the intermediate 1,2-acyloxonium ion to the glycosyl cation followed by the cyclization of the latter.[6,8] Appreciable experimental difficulties for study of the mechanism, as well as the synthetic importance of the reaction, have stimulated us to choose it for a quantum chemical study. 1,2,4 - Orthoacetyl - α - D - xylopyranose **3** was used as a model compound.

RESULTS

Orthoester **3**, the products of its protonation at O–1 **4**, O–2 **5** and O–4 **6**, as well as the cyclic acyloxonium ions 2,4-**7**, 1,4- **8** and 1,2- (in two conformations **9** and **10**), and the glycosyl cation **11**, were the subjects of MO calculations. The geometry of the pyranose ring and the hydroxyl group at C-3 for orthoester **3** and ions **4–9** and **11** were taken from X-ray data,[9,10] and the geometry of the ion **10** from X-ray data for the similar bicyclic system 1,2 - ethylorthoacetyl - 3,4,6 - tri - O - acetyl - α - glucopyranose.[11] The coordinates of all other carbon and oxygen atoms were determined by total energy minimization. The standard values of bond length, bond and torsion angles were used for the determination of the hydrogen-atoms positions. All calculations were carried out by the MINDO/2 method[12] using a BESM-6 computer (Computer Centre of Academy of Sciences of USSR).

The local minimums on the potential energy surfaces



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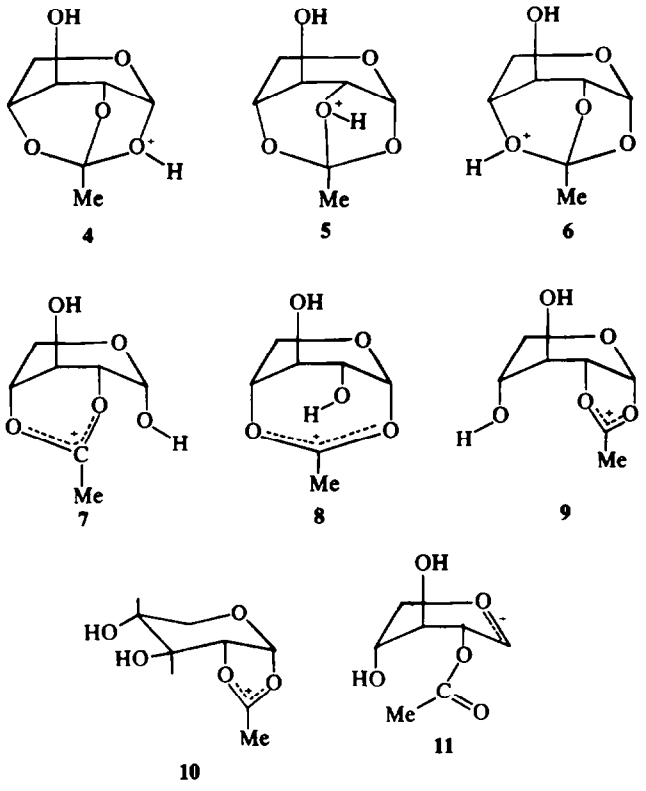
1: R_1 = Ac, Bz, R_2 = Me, Ph
3: R_1 = H, R_2 = Me



were found to exist for all the compounds under investigation. The results of our calculations are summarized in Tables 1–4.

Table 1. Total energies (E)

Compound	E(ev)	Relative energies (kcal/mol)
4	−2681·43	47
5	−2681·59	44
6	−2681·33	50
7	−2682·47	23
8	−2682·65	19
9	−2682·67	19
10	−2683·49	0
11	−2679·83	84

Table 2. Lengths of valence bonds (Å)

	Compound							
Bond	3	4	5	6	7	8	9	10
C1–O1	1·36	1·41	1·36	1·37	1·36	1·36	1·37	1·39
O1–C6	1·39	1·51	1·36	1·35	2·30	1·31	1·28	1·29
C2–O2	1·36	1·36	1·40	1·36	1·37	1·37	1·37	1·37
O2–C6	1·37	1·35	1·48	1·34	1·30	1·99	1·31	1·29
C4–O4	1·36	1·37	1·37	1·41	1·36	1·34	1·36	1·35
O4–C6	1·36	1·33	1·33	1·48	1·25	1·32	2·10	—

DISCUSSION

The results obtained being coupled with data on the mechanism of proton transfer in acid-base catalyzed reactions[13] lead to the following conclusions.

(1) The proton transfer from the acid catalyst (BH^+) to orthoester 3 is expected to proceed smoothly, although the presence of two methyl groups in the proton donor (2,6-dimethylpyridinium perchlorate was used in earlier work[5–7]) can result in elongation of the hydrogen bond $BH^+\cdots O$ and hence in the appearance of some potential barrier.

(2) The protonation of the orthoester results in significant elongation of the bonds of the orthoester carbon atom (C-6) with protonated oxygen atom (about 0·12 Å, see Table 2). Appreciable decrease in the electron density on these bonds takes place simultaneously (Table 3), indicating a very significant weakening of these bonds. Comparison of the total energies (see Table 1) shows that the stability of these oxonium ions falls in the series: **5** > **4** > **6**.

(3) The conversion of oxonium ions **4**, **5** and **6** into the corresponding acyloxonium ions **7**, **8** and **9**, respectively, proceeds with an energy gain of about 25 kcal/mol (Table 1). The calculation, however, does not take into account the interaction of these compounds with the conjugated base of the catalyst (the hydrogen bond formation with B:). For acyloxoniums **7**, **8** and **9** the energy of such interaction should be much less than for isomeric oxonium ions **4**, **5** and **6**. Hence the real energy gain should be less than 25 kcal/mol, but isomerisations **4** → **7**, **5** → **8** and **6** → **9** are expected to remain energetically favourable. The shifts of atomic nuclei in the course of these reactions are relatively small (the greatest change in interatomic distances is about 0·5 Å for the bonds cleaved, see Table 2). Therefore, such isomerisation is expected to proceed smoothly with low activation energy. As one can see from the comparison of the total energies (Table 1), the stability of the acyloxonium ions falls in the series: **9** ≥ **8** > **7**.

(4) The interconversions of acyloxonium ions **7**, **8** and **9**

Table 3. Overlap populations

	Compound							
Bond	3	4	5	6	7	8	9	10
C1–O1	0·548	0·510	0·586	0·579	0·615	0·579	0·562	0·535
O1–C6	0·598	0·386	0·596	0·612	0·027	0·698	0·729	0·724
C2–O2	0·578	0·776	0·512	0·572	0·556	0·571	0·560	0·553
O2–C6	0·571	0·613	0·414	0·618	0·709	0·096	0·695	0·724
C4–O4	0·584	0·771	0·570	0·510	0·551	0·588	0·580	0·611
O4–C6	0·598	0·652	0·652	0·420	0·776	0·692	0·062	—

Table 4. Atomic charges

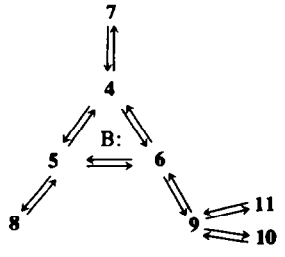
	Compound							
Atom	3	4	5	6	7	8	9	10
O–1	−0·46	−0·23	−0·42	−0·41	−0·44	−0·33	−0·30	−0·30
O–2	−0·44	−0·39	−0·20	−0·38	−0·30	−0·40	−0·28	−0·27
O–4	−0·45	−0·40	−0·41	−0·20	−0·27	−0·31	−0·43	−0·42
C–1	0·43	0·34	0·46	0·42	0·45	0·43	0·40	0·41
C–2	0·19	0·19	0·07	0·15	0·15	0·15	0·14	0·11
C-4	0·25	0·21	0·23	0·12	0·17	0·18	0·21	0·23
C–6	0·76	0·71	0·73	0·70	0·67	0·71	0·68	0·65

can proceed only *via* their oxonium isomers **4**, **5** and **6**, the latter being interconverted only with the assistance of proton-transfer agent B:, because these reactions require proton transfer for a distance more than 2 Å.

(5) The chair conformation of 1,2-acyloxonium **10** is the most stable (Table 1). However the conversion **9** → **10** is associated with significant (for a few Å) shifts of some oxygen and carbon atoms, and therefore is expected to require appreciable activation energy.

(6) The highest positive charge on the ions **4**–**9** is located at C-6 (Table 4). Hence, nucleophilic attack at this centre seems most probable. However such a reaction with an alcohol leads to a new orthoester, which in turn can be protonated and give the acyloxonium ion again. So this reaction does not seem a product determining one. After C-6, the most positively charged atom in all the above-mentioned ions is C-1 (Table 4). Nucleophilic attack at this centre is irreversible and so can be a product-determining step (compare[3–5]).

(7) Therefore, in acid-catalyzed reactions of orthoester **3** the cationic intermediates, which are included in the following system of equilibria, are expected to operate:



Of these intermediates, only **8**, **9** and **11** can be considered as product determining. Acyloxonium ion **7** should be rejected due to decreased reactivity (low concentration of positive charge on carbon atoms C-2 and C-4 as compared with C-1 in **8** and **9**; see Table 4) and its lower stability as compared with its isomers **8** and **9** (Table 1). It can be predicted that the reactions studied would give products from ions **8** and **9** by nucleophilic attack at C-1 in a ratio unaffected by temperature, due to the low energy difference between **8** and **9**, only 0·5 kcal/mol.

(8) The cleavage of the C-1–O-1 bond in acyloxonium **9** leading to glycosyl cation **11** requires about 65 kcal/mol, as calculated (Table 1). Even if a two-fold overestimation is supposed, this value remains too high for this reaction to be significant. However the interaction of **11** with a counter ion in the solution and its solvation should provide the requisite energy, higher than such interaction with acyloxonium ion **9** due to the comparative delocalisation of the charge in the latter. Only by taking this interaction into account can the conversion **9** to **11** be considered as leading to product. It should be noted in addition that the conversion **9** → **11** is accompanied by an increase of entropy. Hence elevated temperatures can be expected to favour this reaction. Therefore the products from the ion **11** should be expected to be formed by a very fast, preferably intermolecular, reaction. The high stereospecificity of glycosylation by sugar orthoesters, leading to 1,2 - trans - glycosides,[4,5] on the one hand, and isomerisation of orthoesters **1** to anhydrides **2** (intamolecular reaction), for which ions of type **11** are postulated, on the other hand, are in good agreement with the conclusions drawn here.

The results of our study show that the most probable mechanism of acid-catalysed reactions of orthoesters of type **3** involves at the initial stage the protonation of one of the oxygen atoms, leading to an equilibrium mixture of the oxonium ions **4**, **5** and **6**. The fast cleavage of the C-6-protonated oxygen atom bond of these ions gives rise at the second step to the mixture of acyloxoniums, where ions **8** and **9** predominate. These ions are attacked by the nucleophilic agent (alcohol) in the product-determining step on glycosidic centre (C-1), leading to compounds with acyloxy group either at C-4 or at C-2, respectively. The products of the type **2** (anhydrides) are formed *via* intramolecular reaction of the very unstable and reactive glycosyl cation **11** arising by isomerisation of acyloxonium **9** intermediate.

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