Conformational effects on the mechanism of acid-catalyzed dehydration of hexitols

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ABSTRACT: The Monte Carlo search of the low-energy regions of D-mannitol (**4**) and D-glucitol (**5**) conformational space was undertaken in order to investigate conformational effects on the stereochemistry of the acid-catalyzed dehydrative cyclization reaction of **4** and **5** to the corresponding 1,4:3,6-dianhydrohexitols. It was found that although dominant conformations in water resemble closely the crystal state conformations of **4** and **5**, the same is not true in solvents of low polarity. The magnitudes of the calculated energies of the reactive conformations for the dehydrative cyclization reaction suggest an S_N2 mechanism with a late transition state. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: D-glucitol; D-mannitol; conformation; dehydration reaction; molecular mechanics

INTRODUCTION

The mechanism of the dehydration of secondary 1,4-diols to tetrahydrofurans, under acidic conditions, proceeds stereoselectively by an S_N2-type mechanism with inversion of configuration at either of the chiral carbon atoms.[1] In the cyclization of primary–secondary (a) or secondary–tertiary (b) 1,4-diols, dehydration takes place with inversion of configuration at the more substituted carbon atom and with retention of the stereochemistry of the less substituted chiral carbinol carbon atom[2] (Scheme 1).
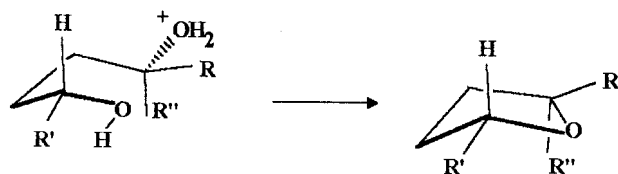
a.   R = alkyl,   R' = R" = H
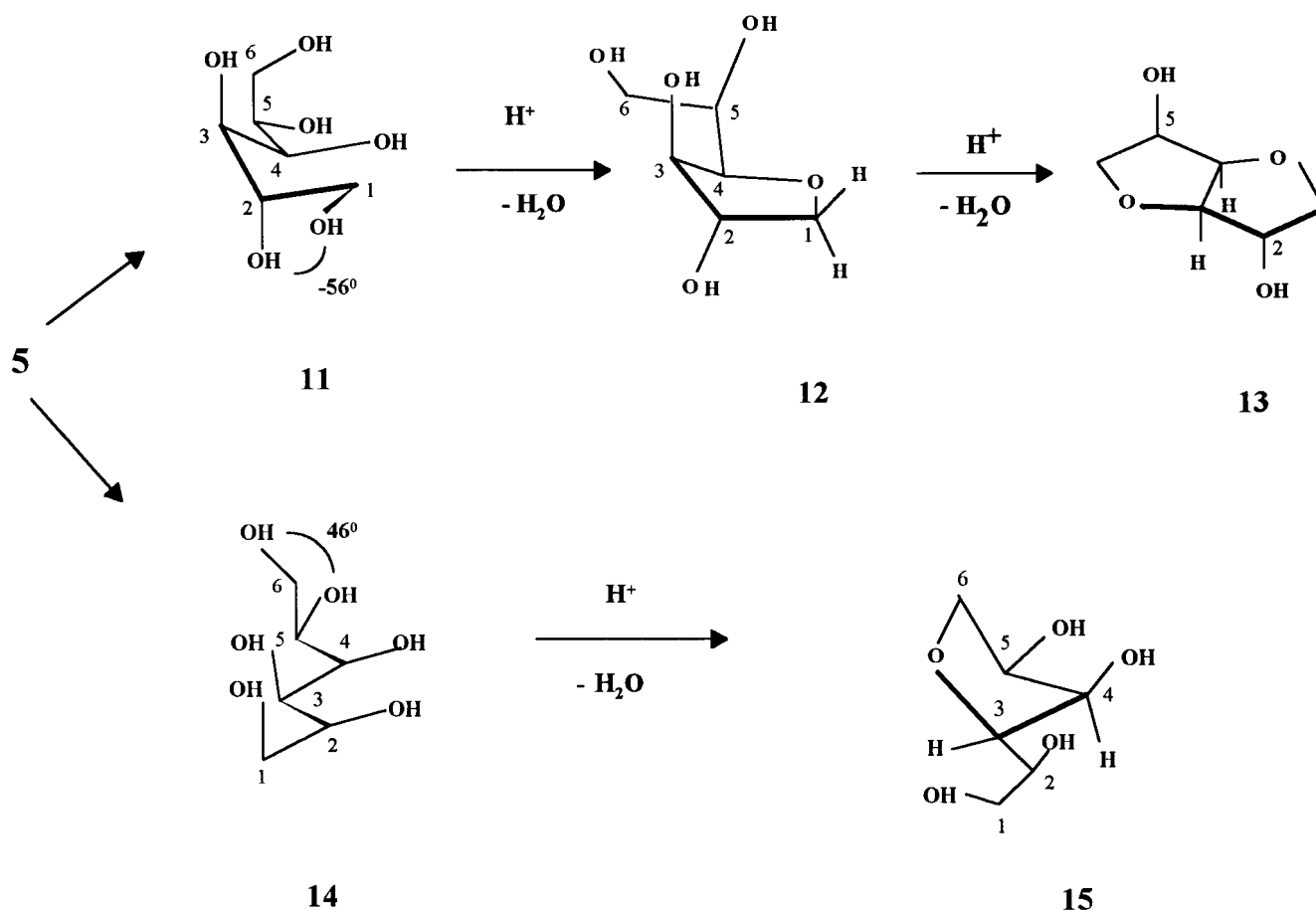
b.   R = R' = R" = alkyl

Scheme 1.

However, hexitols (**1**) undergo the elimination of water, under acidic conditions, with retention of configuration at the more substituted carbon atom, secondary carbons C-3 and C-4, which means that the primary

hydroxyl groups at C-1 and C-6 are eliminated (Scheme 2), rather than the hydroxyl groups from secondary positions.[3–6] An S_N2 reaction mechanism beginning with protonation of primary hydroxyl followed by inversion at the primary carbon atom has been suggested,[6] and supported[5] by the reaction of acid-catalyzed dehydration of (1S)-[1-²H]-D-mannitol. The occurrence of 2,5-anhydrides, as minor products in this reaction, is most readily explained[6] on the basis of the intermediate formation of 1,2-epoxides. The possibility that 1,2-epoxides are intermediates in the formation of 1,4 anhydrides has been shown[6] to be unimportant in this type of reaction, possibly because of inability of the molecules to satisfy stereoelectronic demands[7] of the transition state. The detailed stereochemical pathway of the dehydration reaction of hexitols has been considered previously.[3]

In earlier work,[3] the mechanistic and stereochemical factors implicated in the unusual stereochemical course of this dehydration reaction (**1** → **2** → **3**) (Scheme 2) were considered qualitatively. It was suggested[3] that the preferred conformations of the starting hexitols, D-mannitol (**4**) and D-glucitol (**5**), play a major role in the course of the dehydration cyclization reaction. The idea is summarized in Schemes 3 and 4. The most stable conformations, **6** and **9** of D-mannitol (**4**) and **11** and **14** of D-glucitol (**5**), were suggested[3] to lead to the high-yield products. The conformational stability was estimated[3] qualitatively, based on the assumed tendency of hexitols to avoid 1,3-interactions of parallel C—O bonds. However, in the light of recent theoretical studies on the conformations of inositols,[8] it appears that intramolecular hydrogen bonds are dominant in determining conformations and conformation-related properties of polyfunc-

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Scheme 2.

Scheme 3.

tional alcohols in the gas phase and presumably in non-polar solvents. It has been calculated[8] that the order of conformational stability may be reversed in aqueous solution.

Comparing the relative energies of the *scyllo-*, *myo-*, *neo-*, *epi-* and *dl*-inositols, calculated by the *ab initio* MP2/6–31 + G* method[8] and also by the MM2 method, we were able to the estimate the significance of conformational stabilization introduced by one intramolecular hydrogen bond. The estimated value is 2.0 – 2.5 kcal mol^{-1}, depending on the type of hydroxyl group involved: eq–eq, eq–ax, ax–ax. The experimentally determined[9] value of the hydrogen bond strength is 1.9 kcal mol^{-1} for the eq–eq orientations and 2.2–2.5 kcal mol^{-1} for the ax–eq orientation of OH groups.

These experimentally determined values of the hydrogen bond strength are close to the calculated values. Therefore, in a non-polar solvent, any conformation may be considerably destabilized by the absence of only one intramolecular hydrogen bond. An ax–ax intramolecular hydrogen bond strength of 1.6 kcal mol^{-1} (in CCl_4) was measured[10] for *cis*-cyclohexane-1,3-diol. The amount of the internally hydrogen bonded conformer of *cis*-cyclohexane-1,3-diol decreased considerably[10] on going from non-polar CCl_4 to aqueous solution. The ability of the MM2 program to account properly for the 1,3-interactions of the C—O bonds in alditols has been demonstrated[11] by successful reproduction of the experimental values of the vicinal proton coupling constants of 25 peracetates of alditols, including peracetates of D-

Scheme 4.

mannitol (**4**) and D-glucitol (**5**). We believe that MM2 is a suitable method to be used to reinvestigate the suggestions in the earlier work.[3]

In this work, we investigated the earlier suggestions[3] more thoroughly. Using molecular mechanics calculations in combination with a Monte Carlo routine (for the automatic search of conformational space), the conformational space of the starting compounds **4** and **5** was calculated. This allowed probable transition states for the dehydrative cyclization reaction to be postulated which are consistent with the observed products and stereochemistry of this reaction.

EXPERIMENTAL

The calculational approach[12] used in this work was the Monte Carlo conformational search method in torsional angle space, in combination with Allinger's MM2 force field[13] used for geometry optimization. This method permits a conformational search in low-energy regions of the conformational space while the 'temperature shaking' procedure facilitates escape from deep local minima. To take into account the effect of solvation, the solvent dielectric constants were used in the electrostatic

interaction calculations. A dielectric constant of 1.5 was used for vapor-phase and non-polar solvents and a value of 80 was applied for water.

The heats of formation (HF) of the protonated species were calculated using the PM3 semiempirical quantum chemical method of the HyperChem 4.0 program package (Hypercube, Waterloo, ON, Canada), after PM3 optimization of the geometry.

The coupling constants were calculated by the option in the PCMODEL program (Serena Software, Bloomington, IN, USA), which is based on Haasnoot *et al.*'s method.[14]

RESULTS AND DISCUSSION

First we investigated the low-energy regions of the conformational space of the molecules D-mannitol (**4**) and D-glucitol (**5**) in a search for their global minimum conformations and the other low-energy conformations possessing orientation of the functional groups such as to assist a dehydrative cyclization reaction.

In the case of D-mannitol (**4**), a Monte Carlo run of 2500 steps was performed with a dielectric constant of 1.5 and 117 conformations were located within the
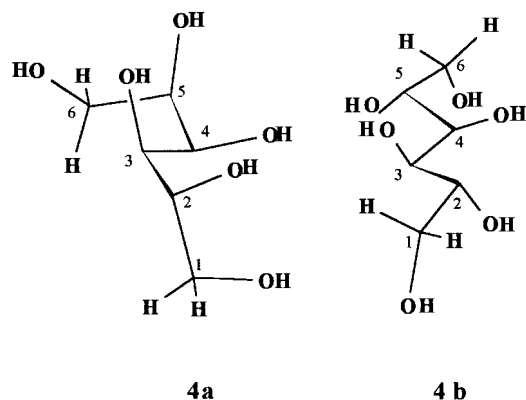
Figure 1. Global minimum conformation, **4a**, and the lowest energy extended carbon chain conformation, **4b**, of **4**

energy window of 8 kcal mol^{-1} above the local minimum. The global minimum conformation **4a** (Fig. 1) was found to have conformational energy $E = -4.47$ kcal mol^{-1}. This conformation is stabilized by two sets of hydrogen bonds: 1-OH, 2-OH, 4-OH and 3-OH, 5-OH, 6-OH. The lowest energy conformation with an extended planar, zig-zag arrangement of the carbon chain, **4b** (Fig. 1), was found at 6.81 kcal mol^{-1} above the global minimum conformation, and consequently contributes very little to the conformational mixture in non-polar solvents.

A Monte Carlo run of 1700 steps was carried out using a solvent dielectric constant of 80. D-Mannitol (**4**) was found to be highly flexible in both polar and non-polar solvents. Ninety-six conformations were found in the low-energy region within the energy window of 6 kcal mol^{-1} above the global minimum. Sixteen conformations were found within only 1 kcal mol^{-1} above the global minimum. The conformations represented in Fig. 1 were found to be the global minimum conformation of $E = 5.61$ kcal mol^{-1} and the lowest energy conformation with an extended carbon chain of $E = 8.78$ kcal mol^{-1}, respectively. The energy gap be-

tween the global minimum conformation and the extended carbon chain conformation which has been found in the crystalline state[15,16] is reduced to 3.17 kcal mol^{-1} compared with 6.81 kcal mol^{-1} in non-polar solvents. The amount of extended carbon chain conformation in polar solvents is probably somewhat underestimated owing to the crude model of solvation. The MM2 method accounts for solvation effects attenuating electrostatic interactions within the solute molecule with increasing solvent dielectric constant. However, it does not take into account specific solute–solvent interactions such as solute–solvent hydrogen bonds. Nevertheless, the calculations demonstrate that the proportions of extended conformations decrease considerably on going from polar to non polar solvents.

In the case of D-glucitol (**5**), two Monte Carlo runs were performed with dielectric constants of 1.5 and 80 and with 3500 and 4000 steps, respectively. With a dielectric constant of 1.5, 61 conformations were located in the low-energy region, within the energy window of 8 kcal mol^{-1}. The global minimum conformation, **5a**, is bent (Fig. 2) and has a conformational energy $E = -4.68$ kcal mol^{-1}. The lowest energy conformation with the extended carbon chain, **5b**, is only 0.84 kcal mol^{-1} above it (Fig. 2). In polar solvents, with a dielectric constant of 80, D-glucitol is still highly flexible. Ninety conformations were found within the energy window of 8.5 kcal mol^{-1}. The global minimum conformation has a conformational energy $E = 5.0$ kcal mol^{-1} and, except for the orientation of some O—H bonds (2-OH, 4-OH, 6-OH), it is bent and identical with the global minimum conformation in a non-polar solvent. The lowest energy conformation with an extended carbon chain is only 0.37 kcal mol^{-1} above the global minimum.

These results are in general agreement with the results of MD simulations[17,18] where fixed-bond, fixed-angle models of **4** and **5** were studied in a vacuum, in an artificial non-polar solvent and in water. Both compounds were found in that study to be very flexible in vacuum and
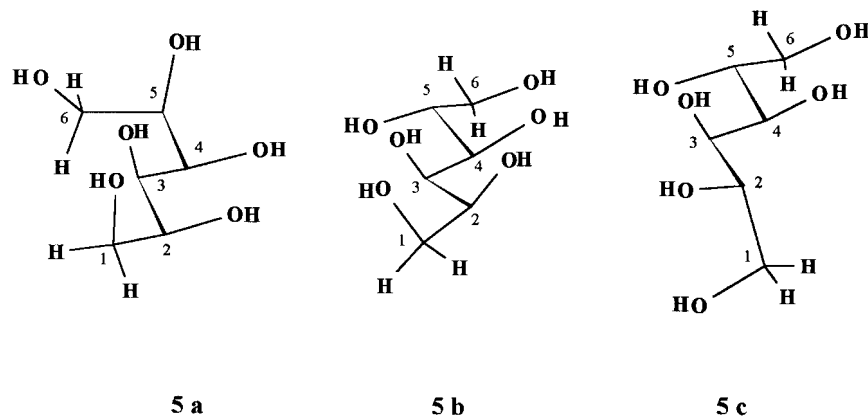

Figure 2. Global minimum conformation **5a** of **5**, the lowest energy extended carbon chain conformation, **5b**, and the conformation **5c** found in crystal

Table 1. Calculated and experimentally determined vicinal H–H coupling constants, J (Hz)

| | D-Mannitol (**4**) | | | | | D-Glucitol (**5**) | | | | | |
| | Calc.[a] **4a** | Calc.[a] **4b** | Calc. **4** | Exp.[b], H_2O | Exp.[b], pyridine | Calc.[a] **5a** | Calc.[a] **5b** | Calc.[a] **5c** | Calc. **5** | Exp.[b], H_2O | Exp.[b], pyridine |
J											
J_{12}	4.60	4.65	4.54	6.43	6.17	3.14	3.27	3.91	3.14	3.55	5.15
$J_{1'2}$	6.13	7.03	2.68	2.93	4.19	5.08	2.72	6.83	4.20	6.55	5.90
J_{23}	2.68	9.31	2.79	8.99	8.23	0.25	0.12	9.45	0.20	6.0	4.25
J_{34}	0.90	1.61	1.65	1.02	0.82	0.34	0.93	0.74	0.34	1.7	2.0
J_{45}						2.25	9.56	9.32	3.83	8.25	7.89
J_{56}						6.84	7.71	7.20	6.98	6.3	5.94
$J_{56'}$						4.23	6.18	6.23	3.64	2.95	4.07

[a] J_{12}, $J_{1'2}$, J_{56} and $J_{56'}$ are weighted averages (OH rotation around C1—C2, C5—C6) for the given carbon chain conformation.
[b] Ref. 18.

in solution. It was found that **4** adopts a bent conformation in a vacuum and non-polar solvents and an almost fully extended conformation in water, whereas **5** was found to have a bent conformation both in a vacuum and in water.

Both computational methods, MD simulations[17,18] and MM2, predict high flexibility of **4** and **5** in a vacuum and in aqueous solution. This is in accordance with experimental NMR results.[18] Other NMR results[18] suggest that in the aqueous solution and in the crystal state both molecules have an *anti* orientation around the central C3—C4 bond. This is perfectly reproduced by our calculations. All the low-energy conformations of **4** and **5** have torsional angle $\phi 2$ (C2—C3—C4—C5) close to 180°. The MD simulations[18] of **4** and **5**, in aqueous solution, afforded mean $\phi 2$ angles near 90° and 137°, respectively. The most probable values of the other two carbon chain torsional angles $\phi 1$ (C1—C2—C3—C4) and $\phi 3$ (C3—C4—C5—C6), determined by NMR,[18] molecular dynamics[18] and MM2, are as follows: for D-mannitol (**4**), $\phi 1 = 180°$ (NMR), 180° or 120° (MD), $-60°$ (MM2) and $\phi 3 = 180°$ (NMR), 180° or 120° (MD), $-60°$ (MM2); and for D-glucitol (**5**), $\phi 1 = 180°$ or 60° (NMR), 60° (MD), 180° (MM2) and $\phi 3 = 180°$ (NMR), 180° or 0° (MD), 180° or $-60°$ (MM2). The values determined experimentally were mainly reproduced by our calculations, the discrepancies being attributed to underestimated solvation effects, which are discussed below.

Analysis and comparison of the calculated and experimentally determined[18] vicinal H—H coupling constants of **4** and **5**, (Table 1) afford additional insight into the conformations of these compounds in solution. Statistically weighted averages of the J values calculated in this work for all the conformations of **4** and **5** within 1 kcal mol^{-1} above the global minimum are presented in Table 1. It was estimated that the remaining higher energy conformations will contribute less than 10% to the calculated coupling constants. The interior coupling constant J_{34} is remarkably stable in the set of conformations studied, for both **4** and **5**. Its low value, both calculated and determined experimentally, suggests an

anti orientation and relative rigidity around the central C3—C4 bond in both **4** and **5**. The calculated values of J_{12}, $J_{1'2}$ and J_{56}, $J_{56'}$ cover a large range of magnitudes but their statistically weighted values are in relatively good agreement with the experimentally determined values. The only significant discrepancies, presumably a consequence of the crude model of solvation used, appear for J_{23} and J_{45} and suggest that the conformations **4b, 5c** and perhaps **5b** are present in solvents of high dielectric constant, and are underestimated in our calculations. Indeed, the water accessible surface areas of **4a** and **4b**, as calculated by PCMODEL, and the related octanol–water free energies of transfer, ΔG, equal to -12.5 and -14.0 kcal mol^{-1}, respectively, indicate further stabilization (around 1.5 kcal mol^{-1}) of **4b** in water. This additional stabilization of **4b** is not accounted for in MM2 calculations. The corresponding ΔG values for **5a, 5b** and **5c** are -12.3, -12.3 and -13.9 kcal mol^{-1}, respectively, predicting relative stabilization of **5c** in a polar solvent. Apparently, relative to a non-polar solvent, water stabilizes an extended conformation of **4** and the bent conformation **5c** of **5**. With this hydration effect taken into account, the agreement between our calculated and the experimentally determined coupling constants would be improved. A comparison of the experimental values of J_{23} and J_{45} in water and in the less polar pyridine suggests in addition that the relative proportions of conformations **4b** and **5c** decrease in solvents of lower polarity. It is therefore reasonable to assume that in non-polar and aprotic solvents the conformational distribution of **4** and **5** will be represented better by good-quality calculations in the gas phase (dielectric constant = 1.5 in MM2) than by the experimentally determined distribution in a polar solvent.

In an earlier paper[3], we suggested that the reaction of dehydrative cyclization of D-mannitol (**4**) and D-glucitol (**5**) with retention of configuration at the more substituted carbon atom to the corresponding five-membered cyclic ethers occurs through an early, reactant-like transition state. The proportions and type of products depend on the stability of the reactant conformations leading to the corresponding product. We endeavored here to identify
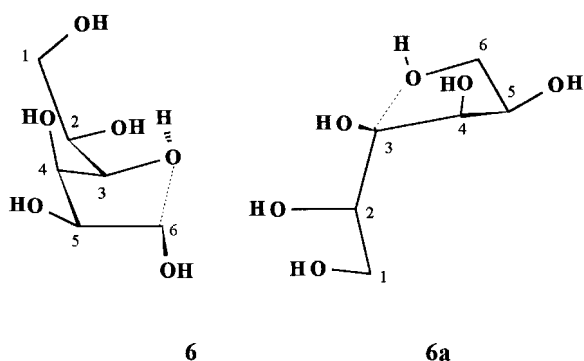
Figure 3. The lowest energy conformations, **6** and **6a**, of **4** leading to **7** and to the hypothetical 1,4-anhydrohexitol obtained by inversion of configuration at more substituted carbon

Figure 4. The lowest energy conformations **11** and **14**, leading to **12** and to hypothetical **15**, respectively

the low-energy conformations which could possibly give (i) reaction products with retained configuration at more substituted carbon atom and (ii) reaction products with inverted configuration at more substituted carbon atom.

Since the acidic dehydration of D-mannitol (**4**) and D-glucitol (**5**) has been most often carried out in non-polar solvents[19] such as benzene, toluene and xylene, in which they were almost insoluble, and the water formed was removed by azeotropic distillation, we adopted a dielectric constant of 1.5 as suitable for all the present calculations.

In the case of D-mannitol (**4**), the lowest energy conformation, **6** (Scheme 3), leading to the intermediate 1,4-monoanhydromannitol **7**, is found at the energy $E = 1.92\,\text{kcal mol}^{-1}$ (Fig. 3), only $2.55\,\text{kcal mol}^{-1}$ above the global minimum conformation, which implies that with small energy costs, the compound is brought to the conformation suitable for the reaction to occur. On conformational grounds, the reaction leading to **7** should be easy and fast. On the other hand, the lowest energy conformation, **6a**, leading to 1,4 cyclodehydration with inversion of configuration at the more substituted carbon atom, is found at the energy $E = 1.86\,\text{kcal mol}^{-1}$ (Fig. 3), i.e. $6.33\,\text{kcal mol}^{-1}$ above the global minimum. Although the protonation of the secondary hydroxyl, compared with the protonation of the primary hydroxyl group of **4**, is calculated to be favored by $2.2\,\text{kcal mol}^{-1}$, the transition state with this conformation would still be high enough, relative to **6**, to prevent formation of the product.

All the conformations leading to the 2,5-monoanhydride of mannitol **10** (Scheme 3), where the secondary hydroxyl displaces a secondary hydroxyl, are very high in energy, 10–$15\,\text{kcal mol}^{-1}$ above the global minimum, indicating that product **10** will not be formed in the reaction. However, **10** is obtained[5] experimentally from D-mannitol and in a relatively high yield. This suggests that another reaction mechanism operates in this case, involving epoxide intermediate formation with inversion of configuration at C-2 (C-5) as proposed earlier[6] for the formation of **10**.
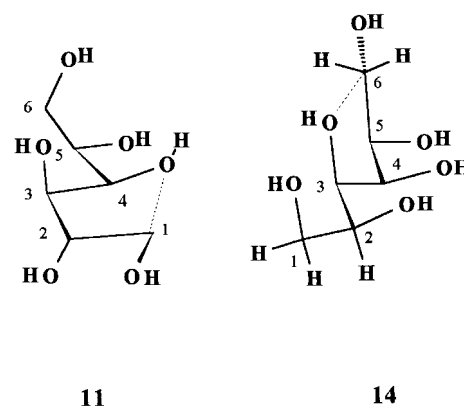
In the case of D-glucitol (**5**), the experimental results (Scheme 4) reveal the formation of only one 1,4-monoanhydro product, **12**, leading further to **13**. However, the conformation **11** of **5** (Scheme 4, Fig. 4), leading to the product **12**, has an energy of $E = 1.52\,\text{kcal mol}^{-1}$, and is $6.2\,\text{kcal mol}^{-1}$ above the global minimum. On the other hand the conformation **14** (Scheme 4, Fig. 4), leading to the other 3,6-monoanhydro product **15**, which has not been obtained experimentally, is calculated to be only $1.63\,\text{kcal mol}^{-1}$ ($E = -3.05\,\text{kcal mol}^{-1}$) above the global minimum. The formation of **12** from **5** has been rationalized earlier[6] on the basis of C-2 hydroxyl group orientation relative to the C-1 leaving group and on its inductive effect consequences. However, we believe that this is not the only explanation since the O—C1—C2—O (O—C5—C6—O) torsional angles in the two reactive conformations, **11** and **14**, differ by only $10°$, their values being $-56°$ and $46°$, respectively (Scheme 4).

This discrepancy in the prediction of the D-glucitol (**5**) product distribution prompted us to investigate the alternative possibility, that of a late transition state similar to the reaction product. The late transition state was built using the corresponding reactive conformations of **4** and **5** discussed above. The ring was made by the formation of a C—O bond and the molecule was allowed to relax. An MC search was done to find the optimum conformation of each substituent and the ring torsional angles closest to the corresponding angles in the reactive conformation of the starting compound. The reactive conformation is the lowest energy conformation satisfying stereoelectronic conditions for the S_N2 reaction leading to desired product.

In the case of D-mannitol (**4**), the cyclic transition state models **TS7** and **TS7a**, leading, respectively, to product **7**, and to the hypothetical product possible in the 1,4-cyclodehydration reaction with elimination of the secondary hydroxyl, are given in Fig. 5. Their energies are $E = 8.98$ and $12.45\,\text{kcal mol}^{-1}$, respectively. The considerably lower energy of the former transition state model suggests exclusive formation of **7**, as found
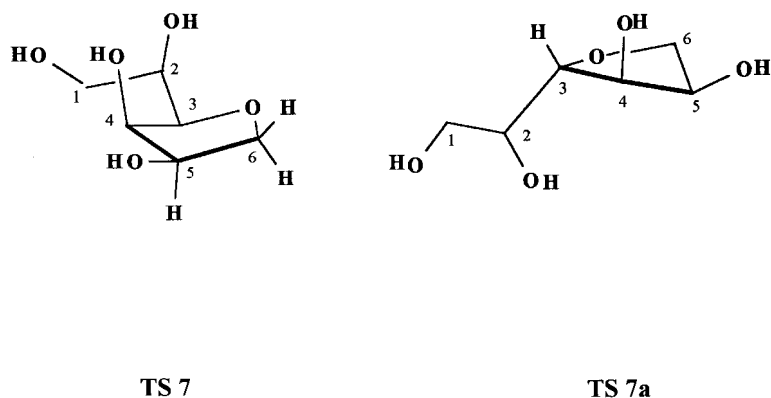
Figure 5. The cyclic models of transition states, **TS7** and **TS7a**, leading to **7** and to the hypothetical product obtained by inversion of configuration at the more substitute carbon atom, respectively

experimentally. The cyclic transition state leading to **10** (Scheme 3) is 2 kcal mol^{-1} higher in strain energy than **TS7**, suggesting again the intermediate formation of a 1,2-(5,6)-epoxide which can rearrange to form a 2,5-anhydride with inversion of configuration at C-2 (C-5).

In the case of D-glucitol (**5**), the energies of the two cyclic transition-state models, **TS12** and **TS15**, leading to the 1,4-monoanhydro product **12**, and to the 3,6-monoanhydro product **15**, respectively (Fig. 6), are comparable, $E = 10.1$ and 9.7 kcal mol^{-1}, respectively. Compared with the corresponding reactant conformations discussed above, this implies a significant increase in the energy of the transition state model leading to the 3,6-monoanhydroglucitol **15**, and consequently predicts a smaller proportion of product **15**, which is in agreement with the experimental data. Therefore, although the product distribution is not reflected quantitatively, the calculated values suggest that the transition states are most likely product-like and that steric hindrance in the transition state leading to product **15** accounts for the negligible amount formed experimentally. Moreover, the lowest energy conformation of **5** leading to the 1,4-cyclodehydration reaction with elimination of a second-

ary C-4 hydroxyl by C-1 hydroxyl has relatively low energy, $E = 3.09$ kcal mol^{-1}. On the other hand, the cyclic model of the transition state for this reaction has an energy of 11.5 kcal mol^{-1}, 1.5 kcal mol^{-1} above the cyclic transition state leading to **12** (and **15**). This high value of the transition-state energy predicts a negligible amount of the product formed by the elimination of a secondary C-4 hydroxyl. This is in agreement with experimental results.[5]

Although empirical force field calculations without consideration of quantum effects do not allow a reaction mechanism to be studied quantitatively, we believe that the similarity of the reactants chosen here allows important qualitative predictions to be made. We are actually comparing transition states of the closely related isomers in one type of a chemical reaction. The quantum effects associated with bond breaking and bond formation are expected to be very similar. It has already been underlined that 'for most reactions leading to diastereomeric products, the reaction trajectories are so similar that, by cancellation of errors inherent in the force field method, one can qualitatively, and often times quantitatively, determine the preferred pathway.'[20] Hence we can conclude that the acid-catalyzed cyclodehydration reaction of hexitols with retention of configuration at the more substituted carbon atom follows an S_N2 mechanism involving a late, product-like transition state. The formation of the 2,5-anhydropentinol from D-mannitol does not adopt this mechanism, and probably involves the opening of an epoxide intermediate with inversion of configuration at the C-2 (C-5) atom.
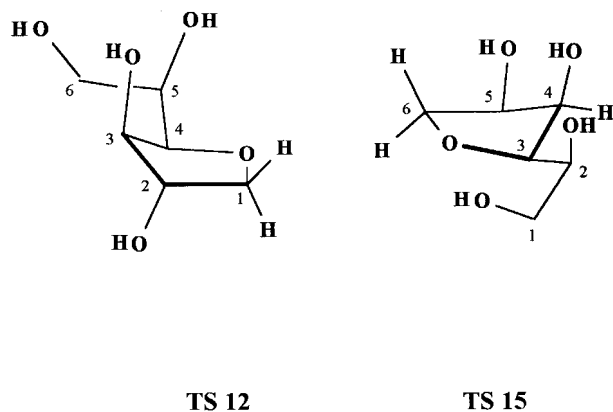

TS 12   **TS 15**

Figure 6. Cyclic models of the transition states, **TS12** and **TS15**, leading to **12** and **15**, respectively

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