

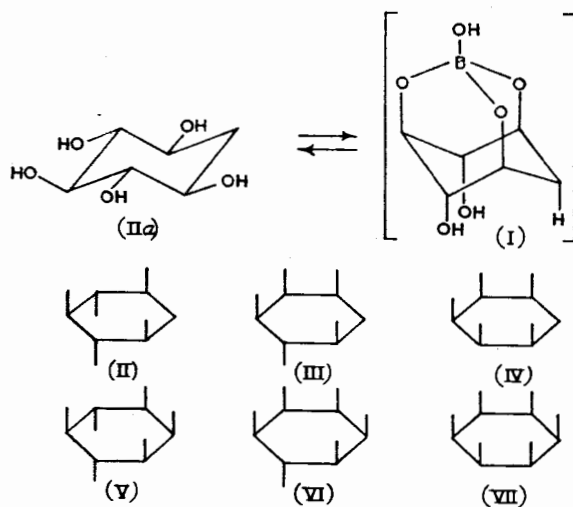
## INTERACTION ENERGIES OF AXIAL HYDROXYL GROUPS

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It is now generally recognized that the preferred chair conformation of cyclitols and sugar pyranosides is the one with the maximum number of equatorial groups. In particular, interaction of two or three axial hydroxyl groups on the same side of the ring is believed to increase the energy of the molecule by a considerable, but yet unknown, amount. The authors have now determined the values of these interaction energies.

It has been found that cyclitols which possess *cis*-hydroxyl groups in the 1 : 3 : 5-positions give complexes with sodium borate in aqueous solution even when *cis*-1 : 2-glycol groupings are absent. These complexes are formed from their components in a 1 : 1 ratio, in contrast to those of other cyclitols, of hexitols, and of simple glycols. Complex formation reduces the pH of a borate solution and, therefore, the complexes are anions of acids stronger than boric acid; from the changes in pH caused by the addition of varying amounts of cyclitols the equilibrium constants,  $K = [\text{complex}^-]/[\text{borate}^-] \times [\text{cyclitol}]$ , have been



determined. The tridentate structure, e.g., (I), first suggested to us by Dr. J. A. Mills, has been assigned to these complexes; *cis*-phloroglucitol has also been found to form such a complex. The following  $K$  values have been determined at 22°: *scylloquercitol* (II), 5.0; *epiquercitol* (III), 310; *cisquercitol*<sup>1</sup> (IV),  $7.9 \times 10^3$ ; *myoinositol* (V), 25; *epiinositol* (VI),  $7.0 \times 10^3$ ; and *cisinositol*<sup>1</sup> (VII),  $1.1 \times 10^6$ . The free energy changes of complex formation have been calculated from these equilibrium constants, employing the relationship:  $\Delta F = -RT \ln K$ .

The varying extent of complex formation is due to the different non-bonded interactions in the complexes and in the parent cyclitols; the energies of these interactions can be calculated from the free energy changes. The following terms were considered: the energy of interaction between two axial oxygen atoms, ( $O_a : O_a$ ); between an axial oxygen and an axial hydrogen atom, ( $O_a : H_a$ ); and between two oxygen atoms on adjacent carbon atoms, both being equatorial or one equatorial and the other axial, ( $O_1 : O_2$ ). Other non-bonded interactions, being much smaller, were neglected. In each case, on formation of the complex, the more stable chair form (*1e* : *3e* : *5e*) is converted into the *1a* : *3a* : *5a* conformation and then esterified with borate ion: the free energy change of this process is designated as  $\Delta F_b$ . For example, in the case of *scylloquercitol*, the relevant energy terms are:

In the cyclitol (IIa):  $4(O_1 : O_2)$

In the complex (I):  $\Delta F_b + 2(O_a : H_a) + (O_a : O_a)$   
The difference between these values is the free energy change of complex formation and is equated with the experimentally determined value:

$$\Delta F_{II} = \Delta F_b + 2(O_a : H_a) + (O_a : O_a) - 4(O_1 : O_2) = -0.95$$

The following equations are similarly obtained for the other cyclitols:

*epiquercitol* (III):

$$\Delta F_{III} = \Delta F_b - 2(O_1 : O_2) = -3.36$$

*cisquercitol* (IV):

$$\Delta F_{IV} = \Delta F_b - 2(O_a : H_a) - (O_a : O_a) = -5.26$$

*myoinositol* (V):

$$\Delta F_V = \Delta F_b - 4(O_1 : O_2) + (O_a : O_a) = -1.90$$

*epiinositol* (VI):

$$\Delta F_{VI} = \Delta F_b - 2(O_1 : O_2) - (O_a : O_a) = -5.20$$

*cisinositol* (VII):

$$\Delta F_{VII} = \Delta F_b - 3(O_a : O_a) = -8.15$$

Best values to satisfy these equations were found\* by the method of least squares; the fitted values, with 90% confidence limits, are:

$$\Delta F_b = -2.5 \pm 0.2 \text{ kg.-cal./mol.}$$

$$(O_1 : O_2) = 0.35 \pm 0.07$$

$$(O_a : H_a) = 0.45 \pm 0.05$$

$$(O_a : O_a) = 1.9 \pm 0.1$$

(Some other values, for comparison, are: ( $Me_1 : Me_2$ ) 0.8,<sup>2</sup> ( $Me_2 : H_2$ ) 0.9,<sup>3</sup> ( $Cl_1 : Cl_2$ ) 2.2, ( $Cl_a : H_a$ ) 1.0, ( $Cl_a : Cl_a$ ) 5.5, the last three being calculated from the heats of combustion of the isomeric hexachlorocyclohexanes.<sup>4</sup>)

One axial hydroxyl group—since it interacts with two axial hydrogen atoms—introduces, therefore, an additional energy of  $2(O_a : H_a) = 0.9$  kg.-cal./mol. (Winstein and Holness<sup>3</sup> found 0.8); two axial hydroxyl groups on the same side of the ring introduce  $(O_a : O_a) + 2(O_a : H_a) = 2.8$ , and three axial hydroxyls  $3(O_a : O_a) = 5.7$  kg.-cal./mol.

Although these values are only approximate, they

can also be used for energy calculations in hexose pyranosides. For example, existing figures on the equilibria of aldohexoses with their 1 : 6- $\beta$ -anhydrides allow the calculation of energy differences. In equilibrium, altrose<sup>5</sup> gives 57%, gulose<sup>6</sup> approx. 55%, and allose<sup>7</sup> 14% of the anhydride. In the first two compounds (which have equal interactions) there is no change in interactions on anhydride formation, whereas in allose two equatorial interactions disappear and an interaction between axial hydroxyl groups is introduced on formation of the anhydride. The difference between the free energy changes of altrose or gulose on the one hand, and allose on the other, calculated from the equilibrium constants, is 1.2 kg.-cal./mol.; calculated with the above values:  $(O_a : O_a) - 2(O_1 : O_2) = 1.2$  kg.-cal./mol., an agreement which is fortuitously better

than could be expected. It should be noted that the two axial oxygen atoms on C(2) and C(4) have no interactions with a third axial atom since the ring-oxygen carries no substituent.

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