An *Ab initio* Study of Dimethoxymethane Protonation and its Relevance to Glycoside Hydrolysis

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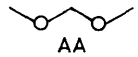
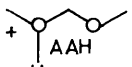
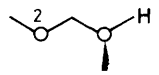
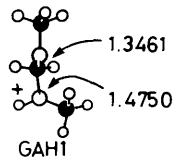
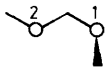
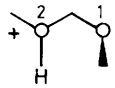
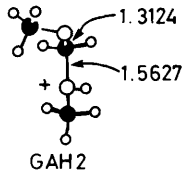
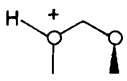
An *ab initio* study of the protonation of the various conformers of dimethoxymethane using Gaussian 82 and 86 and 6-31G* basis set shows that $n\sigma^*$ delocalization decreases the proton affinity of an acetal oxygen, and that *syn*-periplanar alignment of a lone pair with the leaving group lies on the pathway to the transition state and is indeed ~0.5 kcal mol^{-1} (1 kcal = 4.184 kJ) more favourable than the antiperiplanar arrangement.

An understanding of the mechanism of glycoside hydrolysis is of central importance for synthetic manipulations of sugars[1] and for elucidating the biochemical requirements by which glycosidases act on nature's oligosaccharides.[2] However, the stereo-[3,4] and regio-chemistry[4—7] of the process have not been established. Our interest in this area was triggered by the observation that the α- and β-pent-4-enyl glycosides (**1**)[8,9] react to give (**2**) at comparable rates[9] in spite of the fact that the restraining rings, particularly in the case of (**1b**), prevent the β anomers from adopting boat-like conformations, as

Table 1. 6-31G* Geometry optimized protonated forms of dimethoxymethane.

Ground state conformations [a]	Optimized protonated species [a]	Proton affinity [b]	Geometry optimized forms
 AA -267.94505 Zero nσ* interactions	 AAH	Unstable - converts spontaneously into GAH2	
 GAH1 -268.27164		201.6	 GAH1
 GA -267.95035 One nσ* interaction	 GAH2 -268.27464	203.5	 GAH2
 GG -267.95466 Two nσ* interactions	 GGH -268.27431	200.6	 GGH

[a] Energies in atomic units. [b] Energies in kcal mol^{-1}, obtained as described in ref. 14, p. 310.

required by the 'Antiperiplanar Lone Pair Hypothesis' (ALPH).[3] In these reactions, the activated oxygen is present as an oxolanium ion (**3**) and is comparable to the conjugate acid (**5**) formed in acidic hydrolyses of (**6**).[1b,10] We have therefore attempted to study the stereochemical requirements of glycoside hydrolysis by means of an *ab initio* study of the protonation of acetals.

Dimethoxymethane† was chosen for analysis, and geometry optimization using Gaussian 82 and 86 and the 6-31G* basis set[14] reproduced the well known order of conformational stability,[12,13] GG > GA > AA, with the associated energy values shown in column 1 of Table 1. We then protonated these conformers by initially placing the proton 1.0 Å from the oxygen of interest in the COC plane with a 120° C–O–H angle, and optimized at the 3-21G level. Four conjugate acids were generated, one each for GG and AA [since these two conformers have C(2) axes of symmetry], and two for GA, since both oxygens, labelled arbitrarily O(1) and O(2), are 'different'. These, described as GGH, AAH, GAH1, and GAH2, respectively, were then optimized at the 6-31G* level of theory, and their associated energies are shown in column 2 of Table 1. Notably, AAH was unstable at the 6-31G* level and converted spontaneously to GAH2. The proton affinities were then computed[14] for each conjugate acid, and the resulting values are shown in column 3 of Table 1.

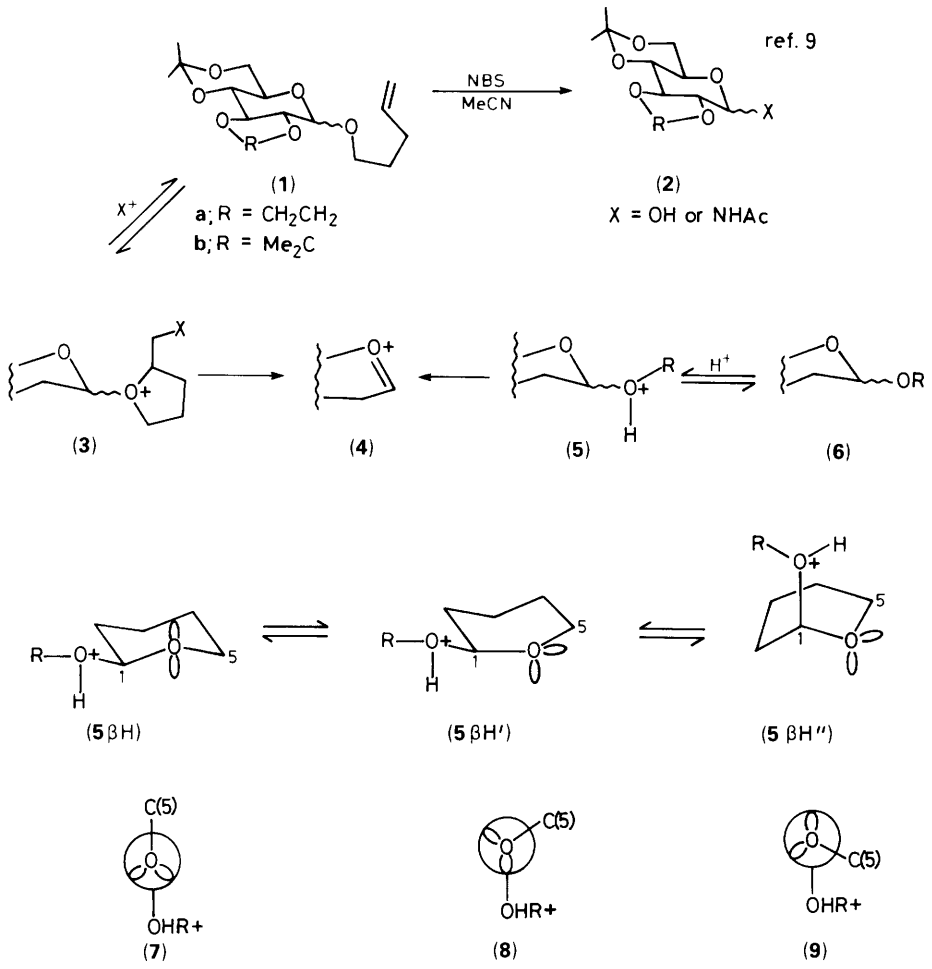
Our results fully support Deslongchamps' intuitive postulate[3] that an acetal oxygen which is not engaged in nσ* bonding[15] has a higher proton affinity than one which is so engaged. That this is indeed the case is exemplified by the proton affinities for the two oxygens in GA where O(2), which is not engaged in nσ* donation, forms the more stable conjugate acid (*i.e.*, GAH2). We also observed that GA should be protonated more readily than GG, since the proton affinity for GAH2 is greater than that for GGH by 2.9 kcal mol^{-1} (1 kcal = 4.184 kJ).‡

The relative stability of the conjugate acids is one issue; the advancement of bond reorganization is another. With respect to the non-protonated oxygen, an nσ* interaction causes torsional changes leading towards a planar oxocarbonium ion. This is illustrated in column 4 of Table 1, where GGH and GAH2 both have virtually the same extent of bond lengthening, bond shortening, and leaving group orthogonality. By contrast, these parameters are much less mature in GAH1.

From the structures of GGH and GAH2 in Table 1 (column 4), it is obvious that bond shortening to give the oxocarbonium ion, and bond lengthening to give MeOH, are very well advanced. Therefore, these structures are relatively close to the transition state.

† Dihydroxymethane,[11] methoxymethanol, and dimethoxymethane[12,13] have been used as models for *ab initio* studies relating to the anomeric effect. The only study on protonation of rotamers was carried out on dihydroxymethane, and did not fully optimize the rotamers.[11]

‡ This result indicates that the ring oxygen of equatorial (βD) glycosides has a higher proton affinity than the glycosidic oxygen. The relevance of this to *endo- vs. exo*-cyclic cleavage[5–7] is currently under investigation.



NBS = *N*-bromosuccinimide

Scheme 1

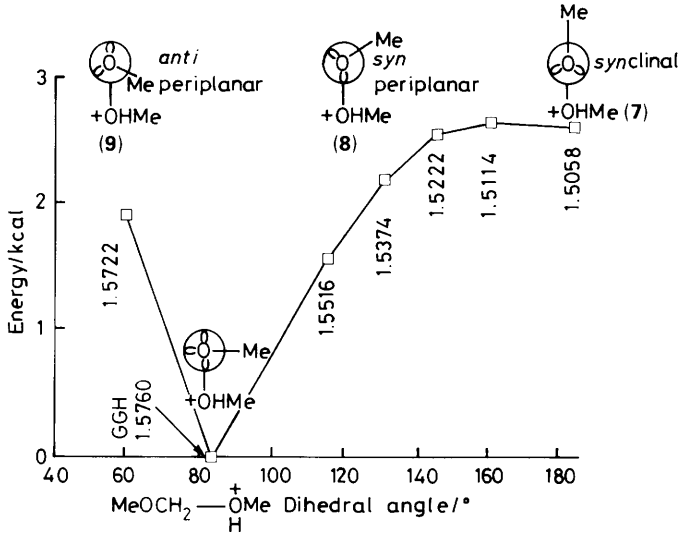


Figure 1. Antiperiplanar and synclinal approaches to reactive intermediate GGH. This study is confined to the protonated rotamers of GG (**9**) and GA (**7**), as shown, and the thermodynamically favoured geometry optimized species GGH. Bond lengths (Å) to the protonated leaving groups are shown. The developing C=O$^+$ is manifested by concomitant bond shortening.

As advanced by Deslongchamps,[3b] ALPH advocates that the protonated β pyranosides (**5**βH) (Scheme 1) would react through a boat [*e.g.*, (**5**βH'')] in which a lone pair of electrons is presented to the leaving group. Such conformational changes are tantamount to rotating the Newman projection, (**7**) → (**9**), which passes through half-chair structures (**5**βH') corresponding to (**8**) in which the leaving group and a lone pair are *syn*-periplanar.

It was therefore of interest to study the energy surface for bond rotation that links protonated rotamers (**7**), (**8**), and (**9**) with the most stable, geometry optimized, species GGH. The results in Figure 1 show that after rotation from (**7**) to (**8**), the system plunges into the reaction co-ordinate. This indicates that the *syn*-periplanar arrangement (**8**) is as favourable (indeed, it is favoured by approximately 0.5 kcal mol^{-1}) for bond reorganization as the antiperiplanar arrangement (**9**).

The foregoing theoretical predictions are in perfect agreement with the reactivities found in this laboratory for the conformationally restrained pent-4-enyl glycosides.[9] However, we are aware that our results, as with all other involving *ab initio* calculations on dimethoxymethane, are *in vacuo* data and may therefore be modified by solvation, as well as ring-strain effects. Therefore, further theoretical and experimental investigations of this problem are underway and will be reported in due course.

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