



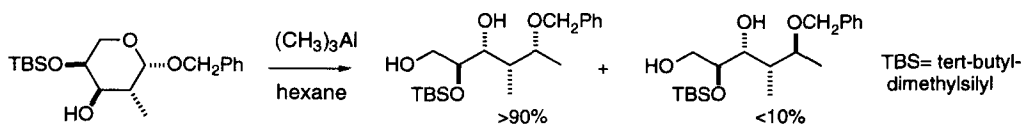
Is a Hydrogen-Bonded Carbene an Intermediate in the Organoaluminum-Induced Ring Opening of Pyranosides?¹

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Abstract Semiempirical and *ab initio* quantum chemical computations indicate that the intermediate formed prior to the selectivity-determining methyl transfer step in the reaction between glycosides and trimethylaluminum is a strongly hydrogen-bonded equilibrium $O\cdots H-C \rightleftharpoons O-H\cdots C$, which is proposed to be an important selectivity promoting factor in the alkyl transfer reaction.
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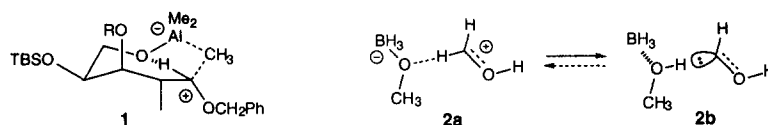
Ring-opening reactions of glycosides offer access to open chain molecules with several stereogenic centra of well-defined stereochemistry. One such example is the organoaluminum-induced reaction shown in Scheme 1, which proceeds with good diastereoselectivity.²



Semiempirical PM3 computations, performed to shed light on the selectivity of the reaction in Scheme 1, indicate that the initial product after ring opening in this reaction is an intermediate **1**, which *via* methyl transfer leads to the products. We report here that, according to *ab initio* calculations on a model system, the intermediate may exist as hydrogen-bonded complexes **2a** and **2b** (Scheme 2). Recently, Corey *et al.* reported that the enantioselectivity in boron Lewis acid catalysed reactions can be rationalized in terms of a C—H \cdots O hydrogen bond in the transition state.³

Hydrogen bonds of the type O—H \cdots C are rare, and for non-anionic C-moieties only “ π -hydrogen bonds” to electron-rich C-atoms in alkynes, alkenes and aromatics have been described, to our knowledge.⁴ The C—H \cdots O hydrogen bond is well established.⁵ We have characterized complex **2** by *ab initio*

calculations.^{6,7} The O—H...C hydrogen bonded complex **2b** is a stable species in the gas phase, whereas attempts to localize **2a** as a minimum on the potential energy surface failed. Some structural data are given in Fig. 1, together with results from a vibrational frequency analysis,⁸ and calculated dissociation energies of the complex.⁹ As is apparent from these data, **2b** is a strongly hydrogen-bonded complex between a carbene as acceptor and a Lewis acid-activated alcohol as donor. The C...H distance (1.989 Å), the shift in O-H frequency (ca. -350 cm⁻¹), the dissociation energy (≥10 kcal/mol), and the participation of the carbene lone pair together with orbitals of the CH₃OH·BH₃ unit in the two highest occupied MO's are clear indicators. The tetrahedral structure of the oxygen and the non-linear O-H...C angle (169°) seem to allow for both σ- and π-type interactions. The carbene is a singlet (S₀) in the ground state stabilized by the hydrogen bond. The LUMO is totally localized to the carbon and oxygen p-orbitals.



Scheme 2

These computations pertain to gas phase properties. Recently, Scheiner and Kar carried out calculations of a similarly hydrogen-bonded system, formic acid and methyleneimine,¹⁰ in dielectric media varying between ϵ 1 and 50 using the same basis sets. For small dielectric constants ($\epsilon = 1$ to 4) the neutral complex, HCOOH...NHCH₂, was favoured, but in more polar media the ion pair HCOO⁻...⁺HNHCH₂ became gradually more stable and totally dominating in higher dielectrics. According to single point calculations at different dielectric constants **2** behaves similarly and the neutral complex **2b** is more stable in dielectrics below at least $\epsilon = 5$. Notable is also that the strength of the hydrogen bond in **2b**, measured as dissociation energy, is much stronger than that in HCOOH...NHCH₂ ($\Delta H \approx 10$ and 2 kcal/mol, respectively). The fact that the reaction in Scheme 1 is performed in hexane as solvent ($\epsilon = 2$) suggests that the carbene might be an intermediate in this reaction.¹¹ The proton transfer from carbon to oxygen giving a carbene in this reaction bears obvious resemblance to the formation of carbenes by intermolecular deprotonation of oxo- or thiocarbenium ions by bases such as tertiary amines.¹²

Guided by these computational data, we considered the design of a system that might permit trapping of the carbene. The reaction of a carbene with an alkene, may be described in frontier orbital terms as an interaction of the carbene LUMO with the alkene HOMO.¹³ Thus, a system such as **2b** could react as an electrophilic carbene without breaking the hydrogen bond prior to reaction.

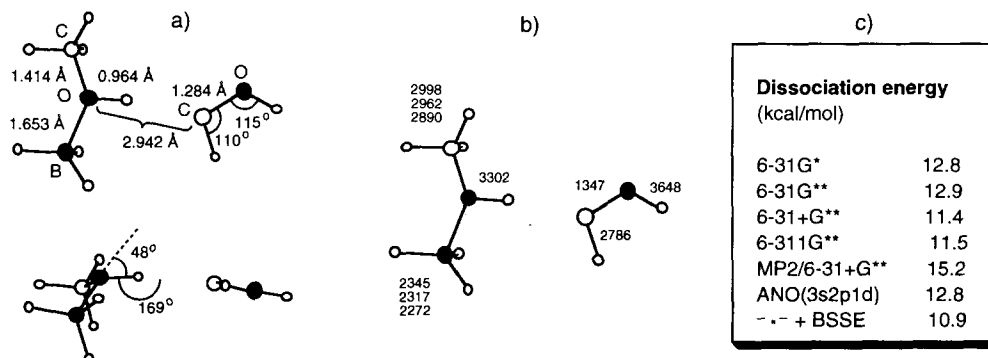


Figure 1. Selected results obtained from computations of **2b** by full geometry optimization at the *ab initio* 6-311G** level. a) Structural parameters. b) Vibrational frequencies (cm^{-1}), scaled by a factor 0.9. c) Dissociation energy with various basis sets.^{6,7}

We tried several approaches. In the reaction in Scheme 1, a seven-membered ring is formed, as shown for the intermediate **1**. Since six-membered rings are usually more stable, a furanoside, expanding to a six-membered hydrogen-bonded intermediate, was considered more auspicious. This prediction was experimentally confirmed.¹⁴ In order to further increase the electrophilicity of the carbene, an electron acceptor was introduced on the carbene carbon. Finally, Lewis acids of varying acidity and with low tendency to transfer their substituents to the carbene carbon were selected. These experiments gave at best traces of cyclopropane products. In retrospect, the LUMO is an anti-symmetric combination of the p_z -orbitals of carbon and oxygen, and thus less susceptible to interact with the symmetric alkene HOMO in a thermal reaction.

In summary, a model for the intermediate in the organoaluminum induced ring-opening reaction of glycosides has been identified as a strongly O-H...C hydrogen-bonded carbene in the gas phase and in solvents of low polarity by *ab initio* computations. The carbene is a singlet and is stabilized by the oxygen lone pair and the strong hydrogen bond. Trapping experiments with olefins such as cyclohexene were not successful. The hydrogen-bonded carbene might be an intermediate in the Lewis acid induced ring-opening reaction of glycosides and appears to be of importance for the selectivity in the subsequent alkyl transfer reaction. Preliminary computations give concurring results for alane adducts, also for ring-closed complexes.¹⁵

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Notes and References

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11. PM3 computations identify (CH₃)₃Al analogues to **2a** and **b** as two minima with the neutral carbene 13.2 kcal/mol more stable and separated by a barrier 1.1 kcal/mol above the ion pair, whereas *ab initio* calculations only identify the **2b** analogue as a minimum in gas phase.
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15. Transition states for the methyl transfer reaction in Scheme 1 have been identified by PM3 calculations and are in agreement with experimental selectivity. Furthermore, the methyl group is transferred with formal retention at the carbon (*syn* attack). These findings will be reported in a subsequent publication.

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