THE ROLE OF LONE PAIR INTERACTIONS IN THE CHEMISTRY OF THE MONOSACCHARIDES. STEREO-ELECTRONIC EFFECTS IN UNSATURATED MONOSACCHARIDES

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Abstract - The X-ray crystallographic structural data for simple unsaturated monosaccharides do not support the participation of the electron density of a C2-C3 π bond in the modification ofthe geometry at the anomeric center, or the existence of a vinylogous anomeric effect in glycals. The delocalization phenomena (n-σ*, n-π* and π-σ*) are insignificant in the ground states of the simple sugars, and n-n repulsions are the dominant stereo-electronic effects in these molecules.

INTRODUCTION

Recently the anomeric effects were reviewed[1] and lone pair -lone pair (n-n) interactions were shown to be significantly more important influences, than n-σ* interactions, in these stereo-electronic effects and in the chemistry of the sugars. The practice of invoking small differences in the bond lengths and bond angles at the anomeric center as evidence of the presence of n-σ* interactions, while ignoring similar and larger variations in these parameters at stereo-electronically unperturbed centers in the same molecule, was shown to be misleading. The long-standing view that perturbations of bond lengths and bond angles are consequences of simple steric and electronegativity factors, rather than of n-σ* and related delocalization interactions, was strongly supported.

In order to provide more support for these concepts, the structural and chemical properties of some unsaturated monosaccharides are now reviewed. The unsaturated monosaccharide contains several functional groups that have been implicated in the anomeric and related effects. Their structural and chemical features are therefore uniquely valuable in the negation, or corroboration, of the concepts put forward for the origin of these anomeric effects. Further, this study promised to provide some useful insights into the mechanisms of the reactions of enol ethers.

DISCUSSION

The ball (atom) and vibrating spring (bond) physical model of the attachment of two atoms (bonding) has been extensively used for decades by physical scientists to generate models for the rationalization of phenomena such as infra-red spectroscopy[2] and kinetic isotope effects,[3] and in the development of molecular mechanics algorithms. The reliability of this model, having blended into it the concepts of quantum theory, allows us to glean further useful insights into the nature of a chemical bond and some transition state based theories.

A vibrating spring possesses a range of lengths over which it can be reversibly elongated, or compressed. While the spring is vibrating within the range of its elastic limits its structural integrity is unaltered and its strength remains nearly the same. Compressing the spring does not make it stronger, and elongating the spring, within its elastic limit, does not make it weaker. However, if the amplitude of vibration causes the spring to be elongated beyond its elastic limit, then the spring suffers irreversible structural changes, causing it to weaken, and it will eventually break.

If these ideas are extrapolated to a chemical bond, then one concludes that shortening a given bond requires the input of energy but does not make the bond stronger. Also, the lengthening of a bond within its "elastic limit" requires the input of energy but does not make it weaker. However, if the amplitude of the vibrating bond causes the bond to be lengthened beyond a critical limit, then the bond will be weakened and should the lengthening continue, the bond will eventually break. The "elastic limit" of a bond is the crucial dimension that one should seek to define in order to develop an appreciation of the processes of bond breaking and, ultimately, bond making. These intuitively acceptable concepts are opposite to the views of some theoretical chemists regarding the events leading up to the cleavage of a bond at the anomeric center of a monosaccharide.[4] They suggest that any lengthening of a bond at the anomeric center is evidence of the progression of the molecule to the transition state for the cleavage of that bond. Hence, any stereo-electronic effects that are present in the transition state and the reaction intermediate should be present, proportionately, in the molecule in its ground state.

When a bond at an acetallic center is broken in a unimolecular process, the intermediate onium ion is thought to be stabilized by the delocalization of the lone pair of electrons borne by the neighbouring heteroatom into the empty p orbital. This n-p delocalization, in essence a π bond, is regarded as the full manifestation of the n-σ* interaction which was present before, and developed during, the process of bond cleavage. Hence, it is suggested that a bond to the anomeric center which is "longer than it should be", must be weakened and hence be on the reaction path to cleavage. However, this view is the same as suggesting that a spring begins to be broken at the very instance that it begins to be elongated from its equilibrium dimension, a non-intuitive concept for which there is no physical support. Rather than acknowledging the existence of a range of lengths of a given stable bond, within which the bond strength remains almost unaltered, these theoreticians have polarized the concept into one in which there is only one bond length associated with a particular stable bond. All larger bond lengths must then represent some stage of cleavage of that bond and all smaller bond lengths must represent some stage of strengthening of the bond.

However, a dispassionate examination of the X-ray crystallographic structural data of sugars dispels this concept by demonstrating that the length of any given type of bond lies within a range of values and this range is determined only by the steric and electronegative environment of the bond.[1] Having discarded the fallacy of a single length for a particular stable bond, we can embrace the logical, physical similarity of a vibrating bond to a vibrating spring and the consequences of this similarity.

An understanding of the events leading up to the transition state of a unimolecular bond cleavage cannot be arrived at by a linear extrapolation from the stereo-electronic milieu of the reaction intermediate back to the transition state and thence back to the ground state. The reaction path from the ground state to the transition state need not be linear, and wrinkles and bumps along this path might be undetectable if they are small in comparison with the overall energy changes being observed. Similarly, the reaction path from the transition state to the reaction intermediate might not be linear. Indeed, the stereo-electronic features present in the transition state must be considerably modified by the time the complex is fully transformed into the reaction intermediate.

Stable molecules often possess structural features which will assist the molecule's passage to the transition state under the proper circumstances. These participating groups/orbitals can intervene only AFTER the reacting bond in the molecule has been deformed beyond its "elastic limit" and is weakened. Beyond that critical limit of deformation, as the bond strength decreases rapidly, the neighbouring group/orbital then intervenes and facilitates the rest of the process. If the neighbouring group/orbital can successfully intervene in the structural integrity of the bond before it was weakened by an external event, then the molecule would have undergone spontaneous reaction and would not have been stable/isolable.

The precise definition of the "elastic limit" of a bond will require the definition of the range of bond lengths which are encompassed by this "elastic limit". Within this range, the bond strength will be maximal and remain nearly the same regardless of the amplitude of its vibrations. Only after this limit has been ascertained, shall we be able to declare that a particular bond is indeed breaking and that the molecule is undergoing chemical change.

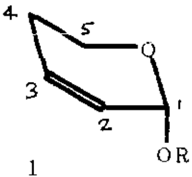
This concept of bond length ranges has been addressed, in the context of acetals and glycopyranosides.[1] Now, the X-ray crystallographically determined bond lengths and bond angles of glycals and glycohex-2-enopyranosides have been examined[5] in order to ascertain the nature of the dominant stereo-electronic effects which are present in these systems.

STEREO-ELECTRONIC EFFECTS IN GLYCOHEX-2-ENOPYRANOSIDES

The hex-2-enopyranosides (1) possess both structural features thought to be critical to the anomeric effect and the vinylogous anomeric effect. If one assumes that the delocalization hypotheses are viable, then those compounds in which the C1-O1 bond of the α-anomers will be favourably oriented for interaction with the C2-C3 π bond and the O5 n orbital. Thus, the C1-O1 bond should simultaneously experience a π-σ* interaction and a n-σ*. These congruent, combined, interactions should cause significant lengthening of the C1-O1 bond, and flattening at C1, as the C1-O1 bond acquires more p-character. These structural changes at C1 should be revealed by the X-ray crystallographic structural data for these molecules.

The X-ray structural data for the structures of hex-2-enopyranosides show no distortions at C1. For example, the X-ray data[6] for molecule (2) revealed bond lengths which were identical to those of simple saturated glycopyranosides. Further, there was no evidence of any flattening at C1, since the bond angles at C1 were all distinctly tetrahedral (C2-C1-O5 : 111.7°, C2-C1-O1 : 107.4°, and O1-C1-O5 : 111.7°). The X-ray data[7] for the molecule (3) also showed no evidence of any distortion at C1.

The absence of the structural distortions predicted by the delocalization phenomena forces us to conclude that these phenomena (n-σ* and π-σ*) are not important factors in determining the structural features of the α-hex-2-enopyranosides and make no significant contribution to the ground state stereo-electronic features of these molecules. The stereo-electronic requirements for efficient delocalization require that these delocalizations must be significantly stronger in the α-anomers than in the β-anomers. Thus, we must also conclude that these delocalization phenomena will be even more insignificant in the β-anomers. This result will be of great importance in the discussion of the vinylogous anomeric effect.



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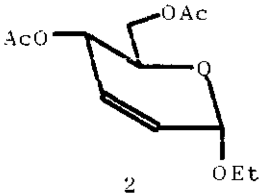

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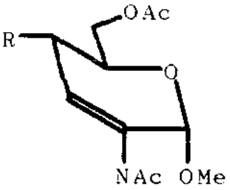

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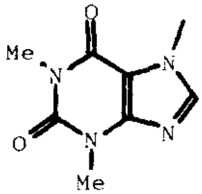

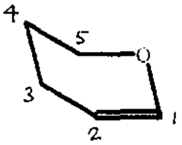

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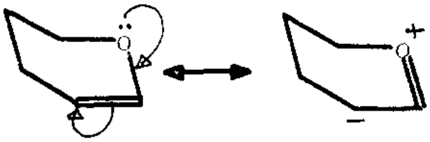

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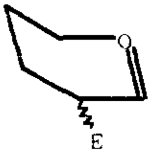

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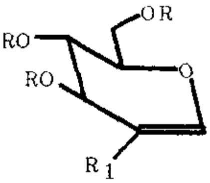

6 $R = Ac$, $R_1 = H$
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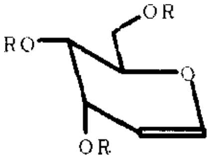


11 $R = Ac$

9A 10 9E

STEREO-ELECTRONIC EFFECTS IN GLYCALS

Glycals (4) ought to be ideal molecules in which to observe the presence, or absence, of the lone pair delocalization (5A) and (5B) thought to be present in the ground state of enol ethers. The ring minimizes the conformational/entropic factors and should allow maximal interaction of the particpating orbitals.

Enol ethers are much more reactive as nucleophiles than alkenes[5] and are transformed by a wide variety of electrophiles to intermediates such as (5C). This enhanced reactivity could be due either to the increased electron density in the carbon-carbon double bond (due to the n-π* delocalization), or to a lower activation energy for the formation of the intermediate onium ion (by the participation of the adjacent lone pair AFTER the attack on the π bond by the electrophile).

If the delocalization of the oxygen's lone pair into the π bond is a significant phenomenon, then the C-C π bond of glycals ought to be longer than an isolated C-C π bond because of the contribution of the cannonical form (5B) to the resonance hybrid.

Three independently performed X-ray crystallographic studies of triacetylglucal (6)[9] determined the length of the C-C π bond to be 131.1, 131.4 and 132.7 pm (a range of 1.6 pm), confirming that it was SHORTER than the 134 pm for simple, unhindered alkenes. n-π* Delocalization is therefore quite insignificant, and the noticeable shortening of this C-C π bond is due to the electronegativity of the oxygen atom. The X-ray study of tribenzylglucal (7)[6] showed the C1-C2 bond length to be 132 pm, consistent with the values above. Tetra-acetylglucal (8)[9b] showed a smaller C1-C2 bond length of 130.6 pm, due to the additive influence of the two electronegative oxygens attached to this π bond. All of these bond lengths for the C-C π bond were well within the normal (134 pm ±7%) range of values for all C-C π bonds.[1]

The lengths of the C1-O5 bonds of these molecules ranged from 136.4 to 137.5 pm, a smaller range (1.1 pm) of values than that observed for the C-C π bond in the studies of the glucal (6). These bond lengths are shorter than the lengths of the C-O bonds of simple ethers (141 pm) and reflect the effect of the increased electronegativity of the alkene's "sp^2 hybridized" carbon atoms over that of the "sp3 hybridized" carbon atom of simple ethers. The lengths of these C-O bonds are within the normal range of values for a C-O single bond.[1]

The interpretation given to the X-ray data given above was strongly corroborated by performing structure-energy minimization and VESCF minimization on a representative series of small molecules, iso-electronic with the enol ethers, in order to ascertain the electron density distribution in them.[5] The data is presented in the table below.

MOLECULE	π ELECTRON DENSITY DISTRIBUTION		
(1===2--3--4)	1	2	3
$CH_2{=}CH{-}CH{-}CH_3$	1.4736	1.1632	1.3605
$CH_2{=}CH{-}NH{-}CH_3$	1.1333	1.0450	1.8217
$CH_2{=}CH{-}O{-}CH_3$	0.9591	1.0529	1.9879
$O{=}CH{-}O{-}CH_3$	1.3376	0.7483	1.9141

These results indicate that there is no significant n-π* delocalization in simple enol ethers. Indeed, the vinylic methylene group is electron deficient in enol ethers, in contrast to the iso-electronic systems shown in the table above. Thus, the electronegativity of the oxygen plays the most significant role in determining the electron density distribution in the adjacent π bond, leading to the SHORTENING of the π bond of enol ethers, as is shown by the X-ray data.

Only 1.2% of the available electron density of the oxygen's lone pair has been delocalized into the π bond, in contrast to 17.8% for the enamine and 64.0% for the allylic anion. These calculations on methyl formate showed a 8.3% delocalization of the available lone pair electron density of the alkyl oxygen over the carbonyl group, consistent with the AM1 results reported.[1]

Therefore, the enhanced reactivity of enol ethers is indeed due to participation of the neighbouring oxygen's lone pair AFTER the attack of the electrophile on the π bond has begun and a more reactive species is being formed. This participation then reduces the activation energy for the formation of the intermediate onium ion. The enhanced reactivity of enol ethers is NOT due to a ground state feature of the isolated molecule. While the n-π* delocalization might be a feature of the proposed transition state, it was not present at the outset of the reaction.

THE VINYLOGOUS ANOMERIC EFFECT

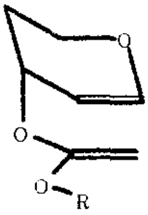
The conclusion arrived at above impinges directly on the validity of the concept of the vinylogous anomeric effect[10] which, like the anomeric effect, is suggested to be a ground state delocalization process. The vinylogous anomeric effect predicts that a properly oriented, axial bond to a leaving group at C3, as in compound (9A), can participate in a π-σ* interaction with the C1-C2 π bond and so cause the molecule to be more stable than the isomeric compound (9E). The application of the "bond - no bond" resonance concept to the molecules (9) would suggest that molecule (9A) should be more reactive than molecule (9E) because the orbital alignment in the ground state should ensure its easier passage to the intermediate oxonium ion (10).

The oxonium ion (10) is structurally identical to that which would be generated from the hex-2-enopyranosides discussed above, but the X-ray data clearly indicate that "bond - no bond" resonance is not important or meaningful in assessing the stability of the ground state of these hex-2-enopyranosides. We must conclude that the apparent stability of the transition state leading to the formation of the oxonium ion is irrelevant to the ground state features and properties of these molecules. This conclusion must also apply to the glycals (9A) and (9E). The use of the "bond - no bond" resonance concept might be useful for assessing the energy of the transition state leading to a particular intermediate, but it is of little value in assessing the stability of the ground state of the starting reactant molecule.

The π-σ^* interactions present in the molecules (9) must as unimportant as the n-π^* and π-σ^* interactions in the molecules (1) and (4), discussed above. Indeed, an examination of reports in which the vinylogous anomeric effect has been invoked reveals no physical evidence for the existence of this effect in the ground state of simply substituted glycals. Further, like acetals, glycals and other monosaccharidic enol ethers[11] are quite stable in the absence of high temperatures and acidic catalysts. Their lack of spontaneous reactivity and reluctance to undergo unassisted bond cleavage, as shown for (9A) to (10), provides us with experimental evidence for the absence of strong intramolecular bond weakening influences. The stabilities of the ground states of molecules like triacetylglucal (6) and triacetylallal (11) will therefore be largely determined by simple steric and dipolar intramolecular interactions. As usual, molecules having many of these unfavourable interactions will be less stable than those that have less.

The magnitude of the anomeric effect in glycopyranosyl derivatives depends on the characteristics of the exocyclic group attached to the anomeric center. According to the delocalization hypotheses, the energy of the σ^* orbital of a good leaving group attached to C1 will be low and so the n-σ^* interaction should be favourable. If the σ^* orbital is too high in energy, a poor leaving group, then a small anomeric effect is seen since the n-σ^* delocalization will be very unfavourable.

The ketene acetal group at C3 of compound (12) is a very poor "leaving group" since it would be transformed into a highly reactive (unstable) anion, and so the C3-O3 σ bond should be quite strong. Thus, if a



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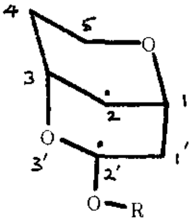

12A

vinylogous anomeric effect exists in this system it should be very weak and incapable of exerting significant control in the Ireland-Claisen rearrangements of glycals like (12).

Undoubtedly, as in the reactions of enol ethers discussed above, participation of the C-C π bond in the unimolecular fragmentation reactions of enol ethers (9A) occurs only AFTER the flanking C-X bond has begun to break, AFTER the reacting molecule had begun to progress toward the transition state, and AFTER a reactive species (10) has begun to be formed. The rate differences encountered in these Ireland-Claisen rearrangements are best rationalized in terms of the "secondary orbital interactions" between the O5 lone pairs and the developing radical centers at C2 and C2' as the reaction progresses through the transition state to the diradicaloid intermediate (12A). These interactions would be examples of β-and τ-effects.[12] Note that the O5-C2 relationship is fixed, but the O5-C2' relationship will depend on the geometry of the transition state complex leading to, and hence the conformation of, the intermediate 6-membered diradicaloid ring. Models show that the boat-like transition states will have distinctly different O5-C2' interactions to chair-like transition states.

CONCLUSIONS

These results clearly reinforce the thesis that the n-σ*, n-π* and π-σ* delocalization phenomena are not ground state features of simple monosaccharide molecules. However, it is very likely that they play an important role in the chemistry of the bond cleavage reactions at, or vinylogously to, the anomeric center of the monosaccharides AFTER these molecules have begun to move towards the reaction transition state. Further, it is unrealistic to continue to assert that our ability to model some aspects these molecules, using algorithms based on the delocalization phenomena, validates the existence of the delocalization phenomena in the ground states of these molecules. Until the acquisition of indisputable physical evidence (preferably experimentally determined structural data, or definitive chemical reactivity, of these molecules in solution) supporting the existence of the delocalization phenomena in the ground states of these sugars has been achieved, we must be sceptical of their importance. To date, this data does not exist.

REFERENCES

1. V. G. S. Box, Heterocycles, **1990**, 31, 1157; and references cited therein.
2. R. M. Silverstein and G. C. Bassler, "*Spectrometric Identification of Organic Compounds*", John Wiley & Sons, New York, 1967.
3. B. K. Carpenter, "*Determination of Organic Reaction Mechanisms*", Wiley-Interscience, New York, 1984; and references cited therein.
4. An excellent review on the anomeric effect. I. Tvaroska and T. Bleha, Adv. Carbohydr. Chem. Biochem., **1989**, 47, 45; and references cited therein.
5. The X-ray crystallographically determined coordinate data was reviewed using the program STR3DI.EXE. This program is available from the author on request. Structure-energy and VESCF minimizations were performed using Serena Software's MMX.EXE, version 88.500. These programs were executed on MSDOS compatible computers.
6. M. Cesario, J. Guilhem, and J.-C. Martin, Carbohydr. Res., **1979**, 71, 1.
7. B. Kojic-Prodic, B. Danilov, and N. Pravdic, Carbohydr. Res., **1976**, 52, C7.

8a. E. Bienvenue-Goetz and J.-E. Dubois, J. Amer. Chem. Soc., **1981**, 103, 5388; and references cited therein.

8b. M. F. Ruasse, D. Poupard, and J.-E. Dubois, Int. J. Chem. Kinet., **1983**, 15, 855.

9a. J. W. Krajewski, Z. Urbanczyk-Lipkowska, P. Gluzinski, J. Bleidelis, and A. Kemme, Acta Cryst., **1979**, B35, 1248.

9b. K. Vangehr, P. Luger, and H. Paulsen, Carbohydr. Res., **1979**, 70, 1.

9c. W. Voelter, W. Fuchs, J. J. Stezowski, and P. Schott-Kollat, Angew.

Chem. Int. Edn. Eng., 1981, 20, 1042.

10. D. P. Curran and Y.-G. Suh, Carbohydr. Res., 1987, 171, 161; and references cited therein.

11a. V. G. S. Box, L. L. Box, and E. V. E. Roberts, Carbohydr. Res., 1981, 96, 215.

11b. V. G. S. Box, L. L. Box, and E. V. E. Roberts, Heterocycles, 1980, 14, 1269.

12. V. G. S. Box, Heterocycles, 1982, 19, 1939.

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