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STEREOCHEMISTRY OF NUCLEOPHILIC AND ELECTROPHILIC REACTIONS BY THE ORBITAL DISTORTION TECHNIQUE.

ADDITION REACTIONS TO ENONE AND ENOL SYSTEMS

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An understanding of the fundamental factors which dictate the stereochemical course of nucle philic and electrophilic attack on organic substrates is of paramount importance in organic synthesis. Many workers have stressed the importance of steric factors in this regard.[1] Recently, it has been suggested that orbital factors may be partially responsible for the direction of reagent approach toward the substrate.[2,3] It has been shown by ab initio (STO-3G) calculations that an unsymmetrical distribution of a π-system about the nodal plane of a carbonyl group may be induced by an unsymmetrical distribution of substituents about this plane.[2] As a result, the reactivity of the two faces of the carbonyl group toward reagents will not be the same. Unfortunately, the amount of time and effort required to carry out such calculations for large molecules is formidable. Recently, Klein[3] has attempted to rationalize the stereochemistry of electrophilic and nucleophilic attack on rigid cyclohexanone from simple orbital considerations. Klein states, however, that his approach applies only "to compounds containing a single and not two neighboring trigonal atoms in the ring." This communication reports a general approach to predicting the stereochemistry of nucleophilic and electrophilic reactions not bound by these limitations. Some simple rules for predicting the stereochemical course of nucleophilic and electrophilic processes are presented and several simple examples are discussed.

The postulates and rules for the "orbital distortion technique" are as follows:

(1) An unsymmetrical distribution of atoms about a center or region of chemical interest produces an unsymmetrical distribution (or distortion) of electron density about that center or region.

(2) Distortion results from π-p, σ-p, π-π and/or σ-π interaction of the atoms responsible for

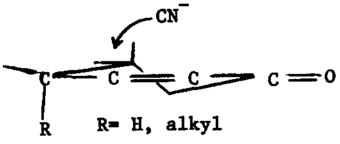
the asymmetry with the center or region of chemical interest.

(3) For electrophilic reactions, the direction of distortion is controlled by the nodal properties of the highest occupied molecular orbital (HOMO) of the pertinent π-p, π-p, π-π region of the substrate. For nucleophilic reactions, the lowest unfilled molecular orbital (LUMO) controls in the direction of distortion.

(4) The atomic orbitals (of the linear combination) in the pertinent region of the substrate are distorted in directions which minimize antibonding and maximize bonding.

(5) Reagent attack occurs at a particular site on the substrate in the direction of greatest atomic orbital probability.

The following observations have been made regarding addition reactions to enone systems: (1) The kinetically controlled addition of cyanide ion to a cyclohexenone or related derivative usually yields a mixture of products in which the product with an axial cyano group predominates (I).[4] (2) The stereochemical outcome of metal ammonia reductions of enones at the β-carbon is



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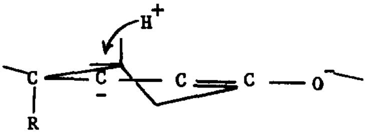

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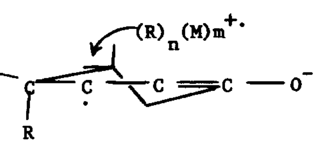
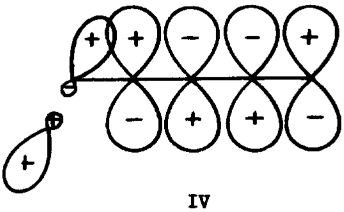


III

believed to be determined by the allylic anion (or perhaps its precursor, the allylic radical) adopting the conformation of lowest energy prior to protonation, axial protonation being the major direction of attack (II).[5] (3) Reactions of enones with reagents believed to proceed by single electron transfer followed by transfer of alkyl group, R, from the metal cluster of an oxidized $(R)_n(M)_m^{+\cdot}$ (lithium dialkyl cuprates) have been also found to occur with predominant axial attack (III)[6]. Arguments based upon well accepted stereochemical principles, i.e., maximum orbital overlap (stereoelectronic control)[7] and least motion principle[8], have been advanced by several authors to account for the above observations. This communication suggests that the preference for axial approach of each of these reagents is controlled by the direction of distortion of the LUMO of the enone substrate about the nodal plane of the π-system due to the unsymmetrical distribution of atoms about this plane. In the above examples, it is the pseudo axial C-R group in the 4-position which is primarily responsible for the distortion. Figure IV represents the nodal properties of the undistorted π-system and C-R sigma bond and Figure V



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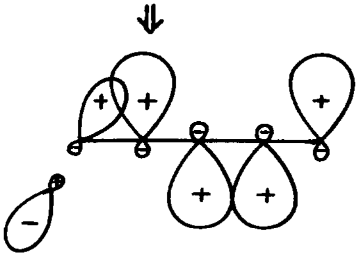
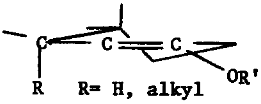


V

shows the distortion of the system about the nodal plane after minimizing antibonding and maximizing bonding.[9] Figure V. clearly illustrates that the most probably direction of attack is the axial direction which is consistent with experimental observations.[4,5,6]

It is well established that cyclohexanone enols, enol ethers and enol esters protonate and halogenate predominantly from the axial direction (VI).[10] Since these reactions involve electrophilic attack on the substrate the HOMO is the pertinent molecular orbital for predicting the direction of reagent attack. Examination of models indicate that it is the pseudo-axial C-R group in the 3-position which is primarily responsible for distortion of the π-system about the nodal plane.



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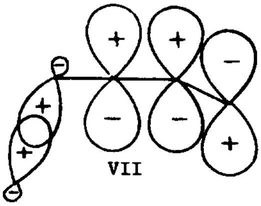

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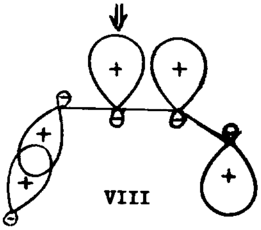

VIII

Figure VII represents the nodal properties of the undistorted π-system and the C-R sigma bond and Figure VIII shows the distortion about the nodal plane.[9] It should be emphasized that the pseudoaxial C-R in the 6-position is also favorably disposed to interact with the π-system, however, this would represent a cross conjugated system and thus should not be as important as the interaction of C-R in the 3-position with the π-system. Figure VIII indicates that the most probable direction of attack is axial, again reflecting experimental observations. It is interesting to note that the orbital distortion picture suggests that the geometry of the enol, enol ether and enol ester is biased in the direction of the chair conformation of the cyclohexane product.

In conclusion, it appears that the orbital distortion technique does predict the correct direction of attack of reagents toward enone and enol systems. Thus, while steric arguments may be effectively used to describe these reactions, it is believed that the orbital distortion approach is more fundamental. It is proposed that this procedure provides a basis for predicting the stereochemistry of a wide variety of synthetically important reactions(baring the presence of gross steric effects)and many other examples will be demonstrated in future publications.

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