AN ELECTRONIC INTERPRETATION OF THE STEREOCHEMISTRY

OF THE REDUCTION OF CYCLOHEXANONES

J. Klein

Department of Organic Chemistry, The Hebrew University,
Jerusalem, Israel.

An empirical rule for the stereochemistry of the reduction of cyclohexanones by complex hydrides was first pronounced by Barton[1]. This rule stated that reduction of unhindered cyclohexanones gave predominantly equatorial, and that of hindered ones - axial alcohols. Since it was known that the equatorial cyclohexanols were the more stable isomers, the preceding rule was recast by Dauben and Noyce[2] in another form which said that the steric course of the reduction of unhindered cyclohexanones was determined by product development control and that of hindered ketones by steric approach control. It was clear, however, that the equatorial cyclohexanols were not formed by equilibration of the isomeric alcohols, but were kinetically formed products. The reason for their preferential formation was given in terms of steric hindrance[3,4] to approach from the equatorial side by the axial hydrogens at the 2 and 6 positions of the ketones. This explanation was later found to be incorrect[5]. Another explanation for the inhibition of equatorial attack of cyclohexanones was formulated by Felkin[6] in terms of eclipsing effects[7] between the axial C-H bonds at the 2 and 6 positions and the bond being formed between the attacking hydride ion and the carbon of the carbonyl group. This explanation was first favored by us on the ground of kinetic results.[5] Later work on hydroboration of methylenecyclohexanes[8] has led us to a different explanation for the same phenomenon which involved eclipsing, in the transition state of the attack from the equatorial side, of the C-O and the equatorial C-H bonds at the 2 and 6 positions.

Recent results[9] have thrown a doubt in our mind on the last explanation and we would like to propose a new electronic interpretation of the steric course of these reductions. This interpretation is based

on the difference, already stressed by Felkin, between the steric course of reduction of cyclo-

hexanones and that of acyclic ketones.   The reduction of unhindered cyclohexanones is expected

to proceed from the equatorial side, when steric interactions alone (valid for acyclic ones)

are considered.   However, the opposite is observed.   In our view, this difference resides in

the non-equivalence of the two faces of the carbonyl group, which is inherent to substituted

cyclohexanones but not to the acyclic ketones.   In the substituted cyclohexanones all the atoms

and bonds are on one side of the carbonyl group and particularly important are the β C-C bonds

which enter into a hyperconjugation interaction with the π-electrons of the carbonyl (see Scheme).

The symmetrical bonding σ orbital of these bonds interacts with the π bond forming two orbitals

of different energies.   A similar interaction exists between the antibonding symmetrical σ^*

orbital of the β C-C bonds and the anti-bonding π^*-orbital, again forming two orbitals of different

energy.   The bonding orbital of highest energy has an antibonding interaction of the carbonyl

with the orbitals of the C-C bonds and the electron density at the carbonyl on the side containing

these bonds is diminished, but the density on the other face would be therefore larger.   This

is the frontier orbital (HOMO) that will be attacked by electrophiles such as borane[8] or also

a proton[10] in the case of an enol since a similar scheme can be established for an exocyclic

C=C double bond.   The attack will therefore be equatorial as observed.

     Nucleophiles, on the other hand, will attack the lowest unoccupied orbital (LUMO) (frontier

orbital also).   Here the situation is reversed, since the interaction with the symmetrical C-C

σ^* bond orbital makes the lobe of the orbital on the carbon of the carbonyl of the HOMO, smaller

on the face containing the C-C bonds thus avoiding electron repulsion, and therefore the orbitals

of the LUMO are larger on the side of the β C-C bonds.   The attack of nucleophiles such as

hydride ion by interaction with the LUMO will be therefore easier from the axial direction in

the absence of steric effects.   This is what is observed in the reduction of cyclohexanones.

     The interesting results of Levisalles[11], explained by him in terms of a product-like

transition state, could also be interpreted using the electronic considerations of our Scheme.

     Another approach to the same problem is to take into consideration the interactions between

the occupied and the corresponding vacant orbitals.   Electrophilic attack involves the occupied

π exocyclic orbital.   This interacts (I) with the antibonding C-C orbitals in the β-position.

In order to secure better overlap, the lobes of the π orbital are larger on the equatorial side

and the electrophilic reaction occurs predominantly there.   Nucleophilic attack, on the other

side, involves the vacant antibonding π^* orbital which is stabilised (II) by interaction with

σ^*_A
σ^*_S
π^*

σ_A
σ_S
$s\pi$
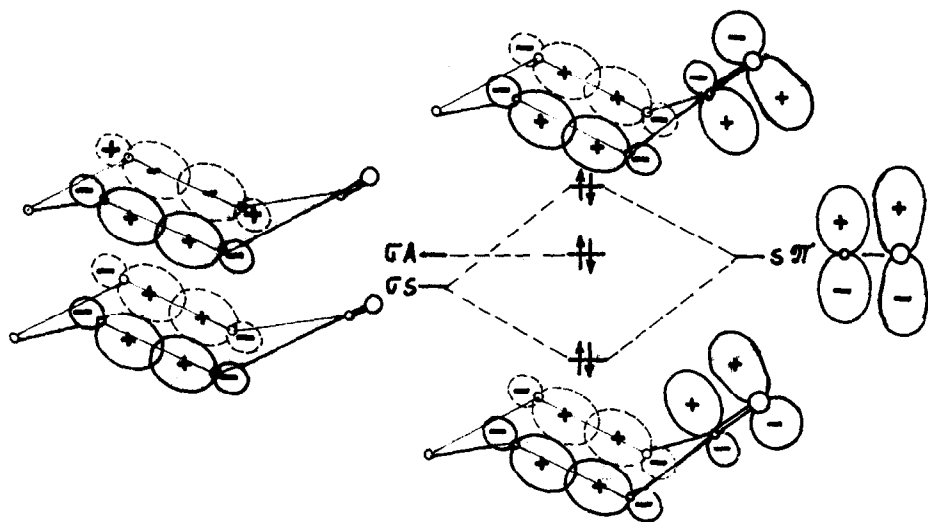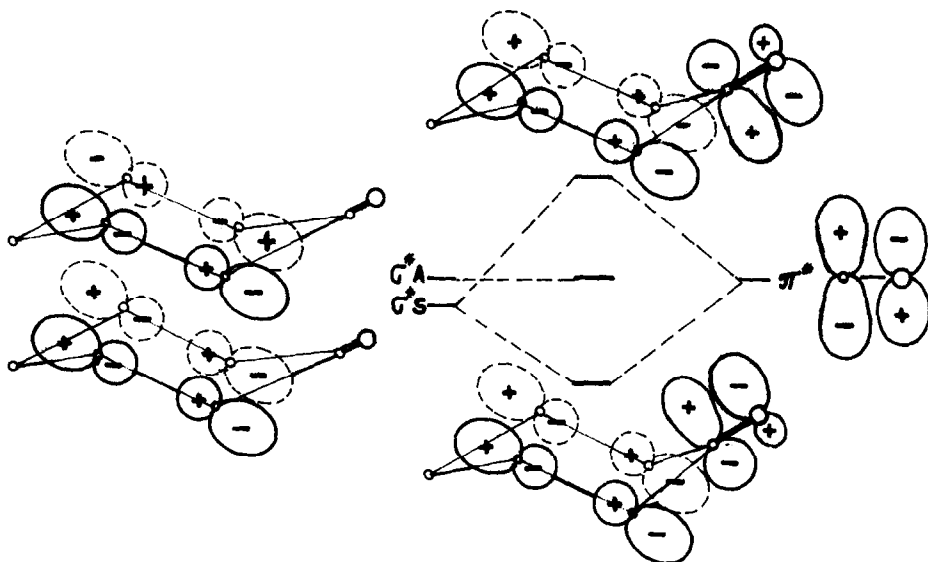
o ≡ Carbon

O ≡ Oxygen

the symmetrical occupied σ orbital.   Here, overlap is the best when the π^* orbital lobes are

larger on the axial side, where in fact nucleophilic attack by complex hydrides occurs.

I   II
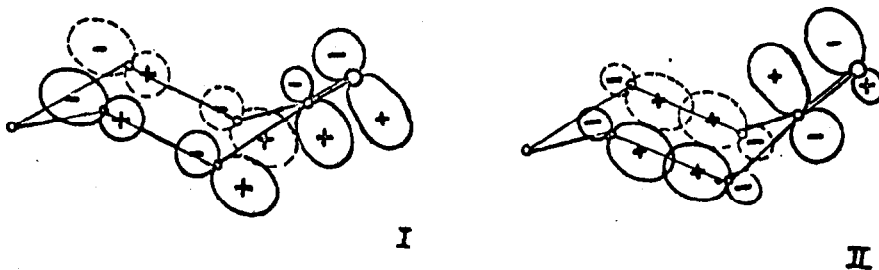
In summary, we propose that for electronic reasons electrophiles attack exocyclic double

bonds from the equatorial but nucleophiles from a similar reason attack those bonds from the

axial direction, when additional steric or polar interactions are absent.[12]

I would like to thank Professor Sir Ewart Jones for his kind hospitality

at The Dyson Perrins Laboratory, Oxford, where this paper was written.

References

1)   D. H. R. Barton, J. Chem. Soc., 1927 (1953).

2)   W. G. Dauben, G. J. Fonken and D. S. Noyce, J. Amer. Chem. Soc., 78, 2573 (1956).

3)   J. C. Richer, J. Org. Chem., 30, 324 (1965).

4)   J. A. Marshall and R. D. Caroll, ibid., 30, 2748 (1965).

5)   J. Klein, E. Dunkelblum, E. L. Eliel and Y. Senda, Tetrahedron Letters, 6127 (1968).

6)   M. Cherest and H. Felkin, ibid., 2208 (1968).

7)   P. von R. Schleyer, J. Amer. Chem. Soc., 89, 699, 701 (1967).

8)   J. Klein and D. Lichtenberg, J. Org. Chem., 35, 2654 (1970).

9)   J. Klein and E. Dunkelblum, to be published.

10) H. E. Zimmerman and P. S. Mariano, J. Amer. Chem. Soc., 90, 6091 (1968).

11) A. Calvet and J. Levisalles, Tetrahedron Letters, 2157 (1972).

12) After completion of this manuscript we have been informed (personal communication by Dr. H.
     Felkin) that an ab initio (STO-3G) calculation (Nguyen Trong Anh, O. Eisenstein, J. M. Lefour
     and M. E. Tran Huu Dau, J. Amer. Chem. Soc., submitted for publication) has shown that
     diastereotopic faces of open-chain carbonyl compounds of fixed conformation have a dissymetric
     π-electron cloud, due to σ-π mixing.   The direction of attack of nucleophiles was explained
     by the electron density being higher on one face than on the other.