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ELECTRONIC CONTROL OF THE STEREOCHEMISTRY OF ELECTROPHILIC AND NUCLEOPHILIC ATTACK ON DOUBLE BONDS IN 6-MEMBERED RINGS*

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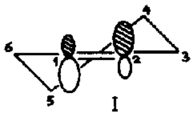
Abstract—CNDO and ab initio MO calculations reveal a deformation of the π^* and π orbitals of cyclohexene in the axial directions, thus providing a reasonable explanation for the axial attack on cyclohexene either by electrophiles or by nucleophiles. It is shown in the case of 1-butene by an ab initio calculation that this orbital deformation is a result of the mixing of the π and σ orbitals of the double bond under the influence of the allylic C–C bond.

A trigonal atom located in a 6-membered ring is attacked preferentially,[1,2] by nucleophiles from the axial and by electrophiles from the equatorial direction. The steric course of these reactions was attributed to the distortion of the LUMO and HOMO respectively.[1,2] Different electron densities have been found by ab initio calculations[3] on the diastereotopic faces of acyclic ketones.

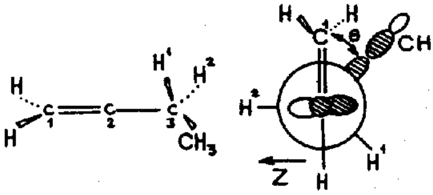
Our rule was stated for rings containing one but not two trigonal atoms,[1,2] since either electrophilic[4–6] or nucleophilic attack on cyclohexenes proceed from the axial direction. Halogenation and addition of hydrogen halides[5] to cyclohexenes[7] is axial as well as halogenation[8] and protonation of enols, enolates and enamines.[9] Thiophenolate,[10] cyanide,[11] methoxide[12] or chloride[13] attack on a cyclohexene activated by an exocyclic[10,11,13] or endocyclic group[12] is preferentially axial.

The axial attack of nucleophiles and electrophiles on enols and enones was recently rationalized[14] by orbital distortion of the double bond interacting with the oxygen-bearing function. We wish to report our results of CNDO and ab initio calculations, showing that the tetramethylene segment of the half-chair cyclohexne induces alone, without functional groups, orbital distortions that influence the axial course of electrophilic *and* nucleophilic attack in this molecule.

Electrophilic attack. Our working hypothesis was that the π orbital of the cyclohexene half-chair (I) is polarized by interactions with the C_3–C_4 and C_5–C_6 bonds at a skew angle to the double bond in such a way that their density is more pronounced in the axial direction. If this were correct then a similar polarization could be expected on the carbon 2 of butene-1 (II). In fact, an STO 3G *ab initio*[15] calculation showed that the contribution of the s-orbital of the olefinic carbon in butene to the π-bond (Table 1) (this is the measure of the unsymmetrical distortion of the π-orbital on the two sides of the plane) was appreciable and depended on the dihedral angle θ of ($C^1C^2C^3C^4$). A positive (negative) coefficient of s(2) means an extension of the π-orbital towards the positive (negative) z-axis. The π-HOMO extends more in the direction of the methyl group than in the opposite one. The orbital dissymmetry of C^2 only in butene-2 is considered in comparison with cyclohexene, since the twofold symmetry of the last compound imposes an orbital distortion on C^1 similar to that on C^2 due to interaction with the C^5–C^6 σ-bond.



I



II

The explanation for the polarization of the electron density was given by Hoffmann[16] in terms of the perturbation theory using second-order corrections to wave functions. Fukui[17,18] has shown in a similar manner by an orbital mixing analysis that the π-HOMO in norbornene is extended unsymmetrically in the endo and exo directions, thus explaining preferential exo electrophilic attack on norbornene.

The rehybridization of the HOMO in 1-butene originates from the mixing of the π- with the σ orbital (composed of s(1) and s(2)) of the double bond under the influence of the C–CH_3 (Σ) bond whose orbital mix simultaneously with π and σ. The new HOMO (π^1) has then the form (1)

$$\pi^1 = +\frac{h_{\pi\Sigma}h_{\sigma\Sigma}}{(E_\pi - E_\Sigma)(E_\pi - E_\sigma)}\sigma + \frac{h_{\pi\Sigma}}{E_\pi - E_\Sigma}\Sigma \tag{1}$$

where π, σ and Σ are the unperturbed orbitals, E_i represent the energies of the orbitals and h_{ij} the resonance integrals. The signs of the basis orbitals have been defined in phase (as in II) so as to have positive overlap representing bonding and hij < 0. Since $E_\pi > E_\sigma$ and $E_\pi > E_\Sigma$ and $h_{ij} < 0$, the negative coefficient of the Σ in (1) shows that it has an out of phase relation to the π *and* σ orbitals in π^1 (III). The π-¹HOMO is therefore extended in the direction of the C–CH_3 bond Σ (IV). The same result is obtained using directly the orbital mixing rules of Fukui.[18]

Nucleophilic attack. We assume by a reasoning analogous to that on electrophilic addition that the direction of the nucleophilic attack will be determined by the dis-

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*Dedicated to Sir Derek Barton on the occasion of his sixtieth birthday.

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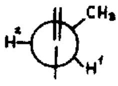
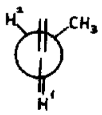
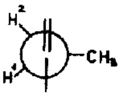
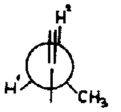
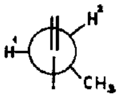
Table 1. Coefficients of s(2) in the π^1 and π^{*1} orbitals of butene-1

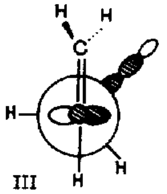
θ	 30°	 60°	 90°	 120°	 150°
s(2) in π^1	-8.2×10^{-3}	-9.24×10^{-3}	-6.83×10^{-3}	-6.75×10^{-3}	-5.77×10^{-3}
s(2) in π^{*1}	-3.43×10^{-3}	1.06×10^{-3}	3.04×10^{-3}	-1.24×10^{-3}	-4.2×10^{-3}

tortion of π^* brought about by its mixing with σ^* through Σ^*.

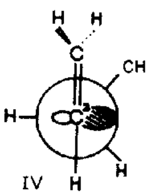
The perturbation of the LUMO (π^*) leads in a similar manner to π^{*1} (2).

$$\pi^{*1} = \pi^* + \frac{h_{\pi^*\Sigma^*} h_{\sigma^*\Sigma^*}}{(E\pi - E_{\Sigma^*})(E_{\pi^*} - E_{\sigma^*})}\sigma^* + \frac{h_{\pi^*\Sigma^*}}{\Sigma_{\pi^*} - E_{\Sigma^*}}\Sigma^* \tag{2}$$

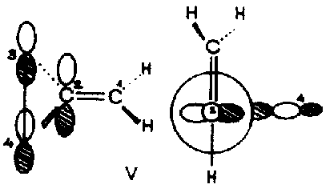
Since $E_{\pi^*} < E_{\sigma^*}$, $E_{\pi^*} < E_{\Sigma^*}$ and $h_{ij} < 0$ it follows that both mixing coefficients are positive and all the orbitals are in an in phase relation (V) if the C–CH_3 is parallel to the axis of the bond ($\theta = 90°$). The orbital distortion will in this case be in the direction away from CH_3. When the C^3–H is parallel to the axis ($\theta = 30°$), the distortion will be away from C–H and in the direction of CH_3 (Table 1). It is possible that the interaction of π^* and σ^* with Σ contributes also the extension of the LUMO in the direction of CH_3 (rule 2 of Fukui[17]) although the large energy difference between the orbitals will make this effect small.



III



IV



V

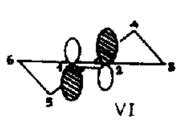
The HOMO of 1-butene is therefore extended towards the methyl in all conformations of this group, but the direction of the deformation of the LUMO depends on the dihedral angle θ. This effect illustrates the dependence of orbital distortions on stereoelectronic factors.[19] This distortion depends not only on the interaction between orbitals with similar energies, but the interaction between orbitals with a good overlap and a larger gap of energies sometimes takes precedence over the effect of interaction between orbitals with a smaller energy gap and less overlap. The overlap between Σ and π depends less on θ than the overlap between Σ^* and π^*, since in the first case both p(z1) and p(z2) have the same phase, but their phases are different in π^*. When dissecting these overlaps it is sufficient to look on the C^4 part of Σ^* ($\Sigma^*_{CH_3}$) and of Σ (Σ_{CH_3}) with the p orbitals in π^*. When this overlap is the smallest ($\theta = 30°$), the overlap of π^* with the H^2 part of the antibonding C^3–H ($\Sigma^*_{H^2}$) is the largest one and although not quite equal to the overlap ($\Sigma^*_{CH_3}/\pi^*$), it is rather close to it. The dissymmetry of π^* is then determined to a large extent by its interaction with the antibonding orbital of C^3–H^2. The values of the overlaps were determined by ab initio and ETH calculations.[20]

Cyclohexene. The chair-like cyclohexene should be considered as composed of two skew systems ($C^1C^2C^3C^4$) and ($C^2C^1C^6C^5$) with $\theta = 20°$. Each of the two Σ bonds (C^3C^4) and (C^5C^6) influences the olefinic carbon that is nearest to it and the HOMO has essentially the orbital polarized as in I. Ab initio calculations show that the π-HOMO and π^*-LUMO of cyclohexene have the expressions (3) and (4) respectively. The extension of the orbitals is therefore as in I for the π^1 and as VI for the

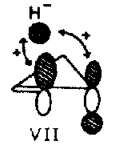
$$\text{HOMO: } 0.61p(z1) + 0.61p(z2) - 3.68\times10^{-3}s(1) + 3.68\times10^{-3}s(2) \tag{3}$$

$$\text{LUMO: } -0.78p(zl) + 0.78p(z2) + 5.6\times10^{-4}s(1) + 5.6\times10^{-4}s(2) \tag{4}$$

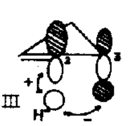
π^{*1} orbital, both in the axial directions. CNDO calculations[21] give similar values.



VI



VII



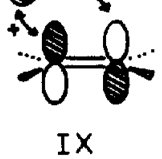
VIII

There is also a contribution from the σ bonds of the tetramethylene segment. In p(z1) and p(z6), p(z2) and p(z3) the π^1-HOMO have negative overlaps but in the π^{*1}-LUMO this overlap is positive as expected.

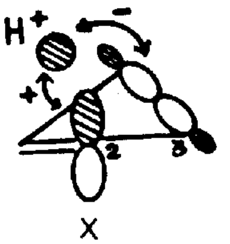
Transition states. A model for the evaluation of the direction of preferential attack was made by calculating pseudo-transition states in which a proton or hydride ion was located at distance of 2 Å along the p(z2) axis above or below the plane of the double bond (axial or equatorial approach respectively to I). Such a direction of the attack by an electrophile is justified by the calculations of Clark[22] who has shown that a proton approaching ethylene along the axis perpendicular to the plane of the molecule reaches a point that is a transition state for the rearrangement of Et cation into its positional isomer. Moreover, Lehn's calculation[23] supports the view that the energetics for the approach of a proton to ethylene along this axis or parallel to it and directly to the carbon are similar. In our case, where no plane of symmetry but an axis of symmetry in the place of the double bond is present, a direct attack on the carbons by the proton is even more plausible. The line of approach of a hydride ion is certainly not between the two C atoms, where the overlap with the antibonding π^* orbital is nil and can be assumed to be approximately along the axis of the p-orbitals on each of the carbons of the double bond. The hydride will approach (IX) to the double bond probably as to the carbonyl[24] at an angle larger than 90° to the C–C axis in order to diminish the antibonding overlap with p(z1). However such an approach will not change our result.

The two arrangements for a nucleophilic attack by a hydride VII and VIII (half of the formulas are drawn) have by CNDO calculations energies of −1401.13 eV and −1401.05 eV respectively, favoring approach from the axial direction VII that leads to a chair-like transition state. There is also a favorable "through space" interaction in VII between the attacking nucleophile and the p(z3) orbital whereas in VIII there is a "through space" repulsion between the reagent and the axial hydrogen on C^3. This result was confirmed by an *ab initio* calculation, which gave for the supermolecules VII and VIII the energies −230.395 a.u. and −230.387 a.u. respectively. The HOMO of the supersystem consists of the lone pair of the hydride and the LUMO of cyclohexene. There is a transfer of electrons into the antibonding orbital of the axial C^3–H bond. The bond order of C^3–H in cyclohexene is 0.385 in cyclohexene but only 0.376 in the supermolecule VII.

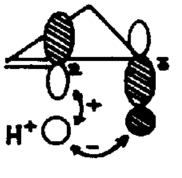
CNDO calculations of similar pseudo-transition states for the axial X and equatorial XI electrophilic attack of a proton on cyclohexene showed a lower energy for the axial than for the equatorial attack, i.e. −1391.45 eV *vs* −1391.38 eV respectively, −230.406 a.u and −230.401 a.u respectively, by the ab initio method. There is also a repulsion in XI between the proton and the C^3–C^4 bond but in XI the repulsion is even larger since it involves the p(z3) and axial hydrogen on C^3. A larger stabilizing interaction is also found between the C^4–C^5 antibonding orbital and the π-orbital in X relative to XI, apparently due to an overlap favorable to an axial polarization of X. The diminution of the C^4-C^5 bond order is larger in X than in XI.



IX



X



XI

The stereochemistry of the reaction of electrophiles and nucleophiles with cyclohexene and olefins in general is determined by orbital distortion on one hand and interaction with bonds at allylic and homoallylic positions on the other hand. These interactions support generally the reaction from the same direction as orbital dissymmetry. Nucleophilic attack from the axial direction VII involves two favorable interactions (double-headed arrow with a minus sign). Electrophilic axial side VIII—one favorable and one unfavorable (double-headed arrow with a minus sign). Electrophilic axial attack X involves one favorable and one unfavorable interaction similar to the equatorial reaction XI. However, in the last case, eclipsing with the quasi-axial C–H bond is making the unfavorable interaction much stronger. It is therefore difficult to conclude, which of the two factors, orbital distortion or direct interaction of the reagent with the bonds neighboring to the π-orbital is determining the stereochemistry of the reaction. The last factor, that is first order should be more powerful than the second order orbital distortion, but it can be cancelled by the interaction of the reagent with other MO's. The repulsion of the proton with the orbital on C–H in the HOMO XI is counteracted by a stabilizing interaction between the corresponding atomic orbitals in a lower-lying MO. It seems therefore that the orbital extension determines the direction of the reaction at least in this case.

Our results show that the geometry of the tetramethylene segment in cyclohexene induces π and π^* orbital distortions that favor axial attack by nucleophilic as well as electrophilic reagents. These are presumably electronic and not steric-conformational effects, although they act in the same direction. Moreover, simultaneous addition[25] of a nucleophile and electrophile in a trimolecular Ad_{E^3} reaction is also diaxial for the same reason; the nucleophile attacks the π^* and the electrophile the π orbital from the direction of their larger orbital extension. However, secondary interactions with other orbitals have also to be taken in consideration.

REFERENCES

[1] J. Klein, *Tetrahedron Letters* 4307 (1973).
[2] J. Klein, *Tetrahedron* **30**, 3349 (1974).
[3] N. T. Anh, O. Eisenstein, J. M. Lefour and M. E. Tran Huu Dau, *J. Am. Chem. Soc.* **95**, 6146 (1973).
[4] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis.* Interscience, New York (1965).
[5] R. C. Fahey, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 3, p. 237. Interscience, New York (1968).
[6] H. O. House, *Modern Synthetic Reactions* p. 586. Benjamin (1972).
[7] D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.* **72**, 1066 (1950); D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.* 1048 (1951); G. A. Alt and D. H. R. Barton, *Ibid.* 4284 (1954).
[8] E. J. Corey, *J. Am. Chem. Soc.* **75**, 2301, 3297, 4832 (1952); **76**, 175 (1953).
[9] H. O. House, B. A. Jefertiller and H. D. Olmstead, *J. Org. Chem.* **33**, 935 (1968).
[10] R. A. Abramovitch, M. M. Rogic, S. S. Sieger and N. Venkateswaran, *Ibid.* **37**, 3577 (1972).
[11] C. W. Alexander, M. S. Hamdan and H. R. Jackson, *Chem. Commun.* 72 (1972); C. W. Alexander and W. R. Jackson, *J. Chem. Soc.* Perkin II, 1601 (1972).
[12] P. Chamberlain and G. H. Whitham, *Ibid.* Perkin II, 1601 (1972).
[13] W. R. Vaughan and R. Caple, *J. Am. Chem. Soc.* **86**, 4928 (1964); R. Caple and W. R. Vaughan, *Tetrahedron Letters* 4067 (1966).
[14] C. L. Liotta, *Ibid.* 519 (1975).
[15] W. J. Hehre, W. J. Lathan, R. Ditchfield, M. D. Newton and J. A. Pople, Gaussian 70, Q.C.P.E. No. 236; R. Ditchfield, W. J. Hehre and J. A. Pople, *J. Chem. Phys.* **54**, 724 (1971).
[16] R. Libit and R. Hoffmann, *J. Am. Chem. Soc.* **96**, 1370 (1974).

[17] S. Inagaki and K. Fukui, *Chem. Lett.* 509 (1974).

[18] S. Inagaki, H. Fujimoto and K. Fukui, *J. Am. Chem. Soc.* **98**, 4054 (1976).

[19] E. J. Corey, *Experientia* **9**, 329 (1953).

[20] R. Hoffmann, *J. Chem. Phys.* **39**, 1397 (1963).

[21] J. A. Pople, D. A. Santry and G. A. Segal, *Ibid.* **43S**, 129 (1965); J. A. Pople and G. A. Segal, *Ibid.* **435**, 136 (1965); **44**, 3289 (1966).

[22] D. T. Clark and D. M. J. Lilley, *Chem. Comm.* 549 (1970).

[23] J. M. Lehn and G. Wipff, *Ibid.* 747 (1973).

[24] H. B. Burgi, J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.* **96**, 1956 (1974); H. B. Burgi, J. D. Dunitz, J. M. Lehn and G. Wipff, *Tetrahedron* **30**, 1563 (1974); Nguyen Trong Anh and O. Eisenstein, *Nouveau J. Chim.* 1, 61 (1977).

[25] R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **93**, 2445 (1971).