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TRAPPING OF RADICAL INTERMEDIATE IN REACTION OF SULPHONATES WITH SODIUM IODIDE/ ZINC/ DME. TOTAL FRONTIER ORBITAL CONTROL OF STEREOSELECTIVITY IN RING CLOSURE.

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Abstract: Reductive cyclization has been shown to accompany reduction on NaI/Zn/DME treatment of sulphonates of γ,δ- unsaturated alcohols. Stereoselectivity is due to FMO control with axial extension of SOMO of cyclohexyl radical playing a crucial role.

The facile conversion of primary and secondary sulphonates of general formula $C_nH_{m+1}SO_2OR$ to the corresponding hydrocarbon C_nH_{m+2} by refluxing in dimethoxy ethane (DME) with NaI and zinc was discovered by Fujimoto[1]. Besides reduction, elimination was also observed. Sulphonates prone to elimination or rearrangement could be expected to give compounds analysing for C_nH_m as main or side products. What has apparently escaped notice is the possible formation of C_nH_{m+2} compounds having structures differing from that of the normal product. The normal reduction product can be presumed to lie at the end of the following sequence:-

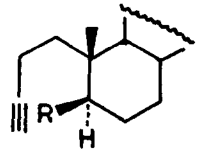
$$R\text{-}OSO_2R' \longrightarrow R\text{-}I \longrightarrow R^{\cdot} \longrightarrow R^{-} \longrightarrow R\text{-}H.$$

Modified sequences wherein $R^{\cdot}$ is by-passed by a rapid two-electron reduction of R-I by zinc <u>or</u> wherein R^{-} is excluded by hydrogen atom abstraction by $R^{\cdot}$ are also probable. R-Zn-I may also have a finite existence and may behave not only as R^{-} but also as $R^{\cdot}$.

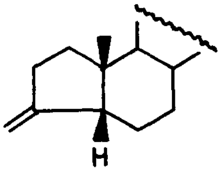
We anticipated that one or the other of the intermediates capable of functioning as $R^{\cdot}$ or R^{-} would have sufficient "half-life" to attack a triple bond located at the γ position to give a reductively cyclized product.

The methane sulphonates of the epimeric 4,5-secocholest-3-yn-5α and 5β-ols had earlier failed to yield[2a] iodo compounds on treatment with NaI in acetone. The 5α-ol mesylate gave the elimination product (M^+ 368) whereas its epimer gave a complex mixture. It was of interest to see if either of these would give products having M^+ 370 on using NaI/Zn/DME. The 5α-ol mesylate did not. The only products having M^+ 370 were obtained from the 5β-ol mesylate (I)[2b]. Besides the normal reduction product, 4,5-secocholest-3-yne (II), obtained in 72 % yield, a reductively cyclized product was isolated in 22%

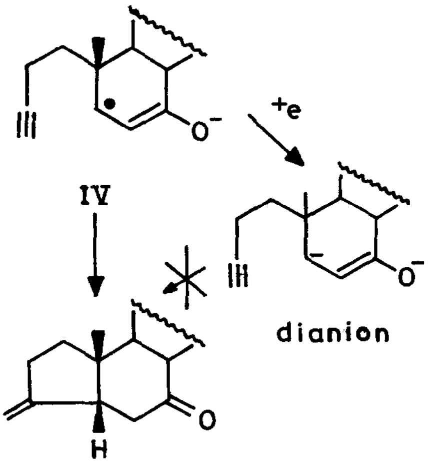
yield. This was shown to be 3-methylene-A-nor-5β-cholestane (III). This compound had been prepared earlier[3] but the stereochemistry was assigned recently[4]. The ring closure was totally stereoselective. The formation of an A:B cis compound could be a result of radical attack. Similar stereoselectivity has been observed[4] in the ring closure of the radical anion IV to V. The corresponding dianion failed to cyclize.

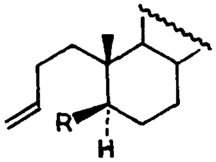


I, R = OSO_2CH_3
II, R = H

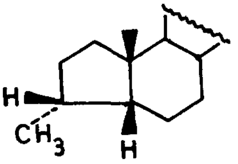


III





VI R = OSO_2CH_3
VII R = H



VIII

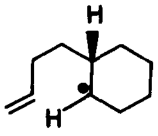
In order to obtain more definitive evidence of radical involvement, the corresponding ethylenic compound VI was subjected to NaI / Zn / DME treatment. The normal reduction product, VII, was obtained in only 10 % yield. The major product, also having M$^+$ 372, was 3α-methyl-A-nor-5β-cholestane, (VIII), (30 %). The remaining material contained five compounds[5] all having M$^+$ 370. The stereochemistry of VIII was confirmed[6] when catalytic hydrogenation of III gave VIII as the major product.

Not only is the cyclization highly stereoselective but the relative stereochemistry at 3,5 and 10 positions in VIII is identical with that observed for a radical cyclization of a closely related compound. Thus Beckwith[7] observed that the major product of ring closure of the cyclohexyl radical IX, formed by the action of Bu_3SnH on the corresponding chloro compound, picks up an hydrogen atom to give all cis 1-methyl hydrindane (X).

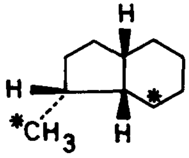
We turn now to an explanation of this stereoselectivity. On the basis of extensive work with acyclic analogues[8], these authors had expected the major product to be XI. But the yield of XI was less than 4 % whereas the all cis compound X was formed to the extent of 56 %. We had on the other hand, anticipated that a C-5 radical derived from VI would cyclize to the all cis compound VIII.

Our expectations were based on the considerations outlined below.

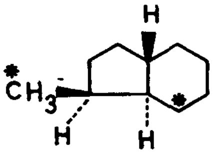
Frontier Molecular Orbital (FMO) control can be taken for granted since radical ring closures are highly exothermic[9] and yet non-ionic.



IX



X



XI

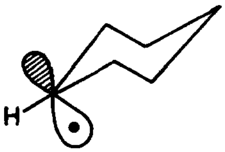
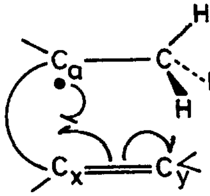


Fig. A

Following the work of Fukui[10], the cyclohexyl radical is pictured as shown in Fig.A i.e. the singly occupied Molecular Orbital (SOMO) is regarded as being extended in the axial direction. This causes a favourable interaction, between SOMO and the appropriate orbitals of the double bond, to set in at a longer distance in the axial direction than in the equatorial direction. Formation of a cis ring junction is thereby ensured. The present approach is a distinct departure from those which rely on differences in non-bonded "steric" interactions at equal distances in the axial and equatorial directions[7]. Inherent in the latter approach is the assumption that the two lobes of the "p" orbital are of equal dimensions on both sides of the nodal plane.

The stereochemistry at the 3 position in VIII is the outcome of the same interactions as those which cause the carbons marked with (*) to take up a cis disposition and also lead to the preferential formation of cis 1,2-dimethyl cyclopentane through ring closure of hept-6-ene-2-yl radical. For the latter Beckwith has given an explanation[11] involving secondary orbital interactions. The explanation depicted in Fig.B. involves the assumption that the radical SOMO interacts with the ethylene π^* orbital (LUMO). We have pointed out recently [12] that the assumption that only SOMO-LUMO come into play, is unjustified. The SOMO energy is in fact nearer the ethylenic HOMO energy in value[13]. In fact, according to Fukui all radical reactions involve a composite of both SOMO-HOMO and SOMO-LUMO interactions[14]. Taking this into consideration leads to the modified proposal given in Fig.C drawn to show that the secondary orbital interaction is equally favourable. The three carbon system $C_aC_xC_y$ seen in Fig.C represents ψ_2 in the orbital interaction diagram given[15] in Fig.D.

Thus it appears that in the ring closure described here conventional steric factors[16] have given way completely to frontier orbital control.[17,18]



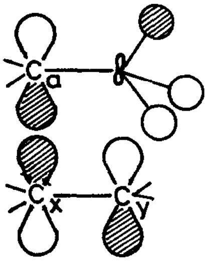


Fig. B

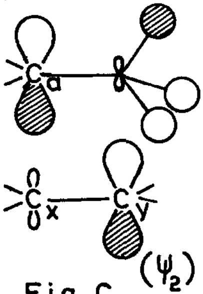


Fig. C

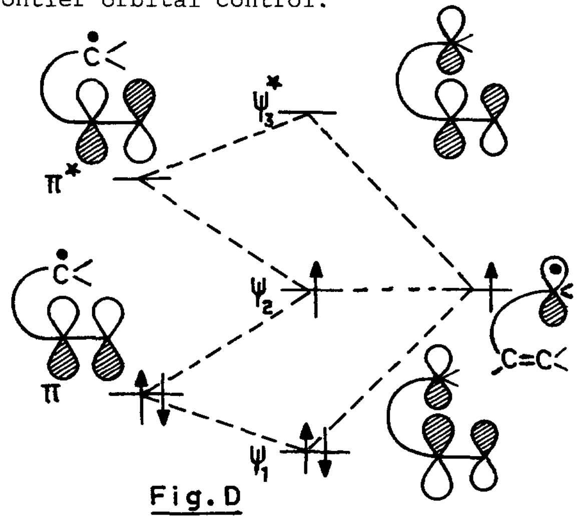


Fig. D

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5. *Mass spectra and proton NMR established that all the five compounds were unconjugated dienes. A minor compnent was the unrearranged 4,5-secocholesta-3, 5-diene. The rest were formed by migration of the 9:10 bond to 9:5 followed by a loss of a proton from the resulting carbonium ion.*
6. *The correct structure and stereochemistry was already indicated by ^1H and ^{13}C MMR and Mass Spectra. GC-MS revealed a 95:5 ratio of VIII:isomer [3β -methyl].*
7. *A.L.J. Beckwith, G. Phillipou and A.K. Serelis, Tetrahedron Lett., 1981, 2811.*
8. *A.L.J. Beckwith, C.J. Easton and A.K. Serelis, J. Chem.Soc., Chem. Commun., 1980, 482.*
9. *Exothermic because a carbon-carbon double bond is replaced by two single bonds. For discussion of FMO control of radical reactions see I.Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976. Chapter 5.*
10. *K. Fukui, "Theory of Orientation and Stereoselection", Springer Verlag, West Berlin, 1975, P.80.*
11. *A.L.J. Beckwith, I. Blair and G. Phillipou, J. Amer.Chem.Soc., 1974, 96, 1613.*
12. *See Ref.4. The figure given therein shows only ψ_1 and ψ_2 .*
13. *Ref.9, p.194 gives a value of -7.8 eV for the SOMO of the cyclohexyl radical.*
14. *Ref.10, p.37.*
15. *Analogy with allyl radical is readily discernible when it is realized that overlapping lobes at $C_aC_xC_y$ in ψ_1 above are in phase just as $C_1C_2C_3$ are in phase in ψ_1 of allyl radical[see p.20, Ref.9). ψ_2 here is the counterpart of the NBMO of allyl radical.*
16. *A.L.J. Beckwith, Tetrahedron., 1981, 37, 3073 has reviewed all such aspects.*
17. *The results of radical cyclization reported here are remarkably similar, in terms of stereoselectivity, to those of ketyl radical anion cyclization reported in Ref.4. Such similarity may be expected whenever models indicate that alkoxide repulsion cannot come into play.*
18. *We are grateful to Council of Scientific and Industrial Research and the University Grants Commission, New Delhi for awards of fellowship to JNK and JSM respectively.*

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