Stereoelectronic Effects in Radical Fragmentation: Rearrangement of 3β,5-Cyclocholestan-6-yl Radical

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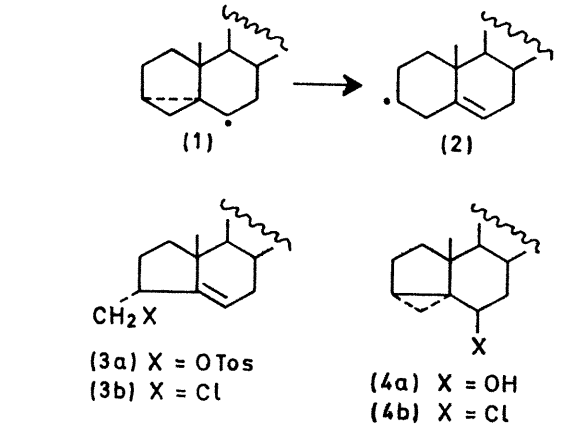
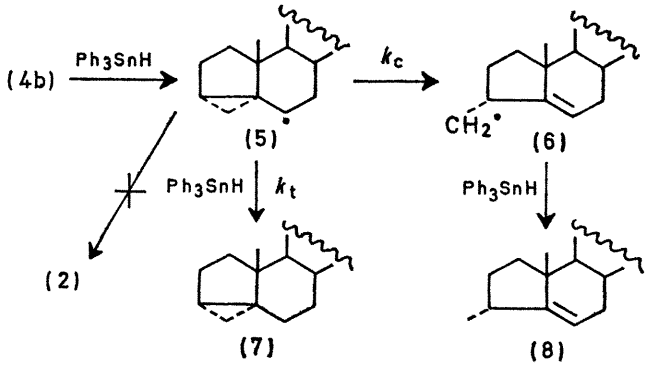
Summary A stereoelectronic requirement in a radical fragmentation reaction is demonstrated by the specific fission of the 4,5-bond in the 3β,5-cyclocholestan-6-yl radical.

UNLIKE their intermolecular counterparts, many intramolecular radical addition reactions specifically follow the less exothermic pathway. For example, the hex-5-enyl radical cyclizes preferentially to cyclopentylmethyl,[1] and generally in related systems five-membered ring formation takes precedence over six.[2] Such observations have led to the suggestion that radical addition to an olefinic bond involves initial interaction of the free-spin with the unoccupied π^* orbital, and the process is thus under stereoelectronic control.[2,3]





Extension of this mechanistic concept requires that ring fragmentation processes, being the reverse of cyclization, should also be subject to stereoelectronic control and should exhibit specificity in the mode of fission when the reaction occurs within an appropriately constituted molecule. There is some evidence[4] in support of this but it is generally less clear cut than is the case for cyclization. Clear definition of specificity in ring fragmentation reactions requires examination of two rigid systems which differ in the disposition of the orbital bearing free spin with regard to βγ-bonds, but which are otherwise closely related. The cyclocholestanyl radicals, (**1**) and (**5**), fulfil these requirements, since they are structurally similar, but in the former the plane of the *p*-orbital at C-6 lies close ($\theta \approx 30°$) to that of the 3,5-bond, whereas in the latter it lies close to that of the 4,5-bond. It has been shown[5] that (**1**) undergoes specific fragmentation to the more stable radical product (**2**).

The alcohol (**4a**),† prepared by solvolysis of the A-nor tosylate (**3a**), was converted by treatment with thionyl chloride at −78° for 4 min into a 3:1 mixture of the required chloride (**4b**) and its A-nor isomer (**3b**). The mixture was analysed by integration of the well defined n.m.r. signals at δ 3·9 (6α-H in **4b**) and 5·3 (6-H in **3b**) p.p.m. Because of its lability under chromatographic conditions it was not possible to separate the chloride (**4b**) in a pure state. Separate experiments using polarimetry showed that in benzene at 25° it underwent slow isomerization to (**3b**) by a first-order process ($k \approx 6 \times 10^{-6}$ s^{-1}). In pentane at 25° there was no detectable rearrangement during 24 h. The stereochemistry of the chloro-group in (**4b**) has not been confirmed. The 6β-configuration has been assigned on the assumption that the reaction of the alcohol with thionyl chloride proceeds, as in the 3α,5-cycloseries,[7] with retention. However, neither the presence of the isomeric chloride (**3b**) in the starting material nor the ambiguity concerning configuration at C-6 affects the validity of the free-radical investigations.

TABLE

Reduction of 6β-chloro-3β-5-cyclocholestane with triphenylstannane in pentane at 25°

$[Ph_3SnH]$/M	Total yield (**7**) + (**8**), (%)	Relative yield (**8**)/(**7**)
0·21	61	36·5
0·23	40	32·0
0·62	45	12·4
0·75	50	10·5
1·10	75	6·5
1·17	65	6·2
4·0	75	1·8

The reaction of the chloride (**4b**) with triphenylstannane in pentane at 25°, initiated by azoisobutyronitrile and irradiation with a tungsten lamp, proceeded smoothly and afforded only 3β,5-cyclocholestane (**7**) and 3α-methyl-A-norcholest-5-ene (**8**). The relative yields of (**7**) and (**8**), determined by g.l.c., varied with stannane concentration (see Table) in a linear manner.‡ This observation is

† All compounds had spectroscopic properties (n.m.r., i.r., and mass spectra) consistent with the proposed structures. New compounds gave satisfactory microanalytical data.

‡ In determining yields of products allowance was made for (**8**) arising by direct reduction of (**7b**) present in the starting material. A separate experiment indicated that cationic rearrangement of (**8b**) to (**7b**) was negligible under the reaction conditions.

compatible with the mechanistic scheme proposed and precludes the possibility of prior cationic rearrangement of the substrate, or of direct reduction of the non-classical cyclocholestanyl ion. If the rate constant (k_t) for hydrogen atom transfer from the stannane[8] is assumed to be approximately 5×10^6 M^{-1} s^{-1} it can be calculated that k_c, the rate constant for fragmentation of (**5**), is about $3{\cdot}7 \times 10^7$ s^{-1}, a value of the same order of magnitude as that estimated for fragmentation of (**1**).[8]

The absence of cholest-5-ene from the products of reduction of (**4b**) was confirmed by various chromatographic techniques. Clearly, fragmentation of the **3,5**-bond to give the cholesteryl radical (**2**) did not occur. Thus it appears that each of the isomeric radicals, (**1**) and (**5**), undergoes fragmentation in a highly specific manner. In each case the bond which suffers fission is that which lies closest to the plane of the *p*-orbital at C-6 bearing free spin.§ These results support the view that radical fragmentation reactions are under stereoelectronic control, and have a requirement for maximum overlap between the free electron and the bond to be broken (or its σ^* orbital).[2] Hence in rigid systems, or systems showing a strong conformational preference, the nature and relative yields of products will be determined primarily by the stereochemistry of the molecule, and not by the relative stabilities of possible intermediate radicals.

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§ We assume that ring B takes up the pseudo-chair conformation.

[1] See C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Amer. Chem. Soc.*, 1966, **88**, 5361; R. C. Lamb, P. W. Ayers, M. K. Toney, and J. F. Garst, *ibid.*, p. 4261; J. F. Garst, P. W. Ayers, and R. C. Lamb, *ibid.*, p. 4260.
[2] For a recent review of radical cyclization and fragmentation reactions, and a discussion of stereoelectronic effects see A. L. J. Beckwith, *Chem. Soc. Special Publ.*, 1970, No. 24, p. 239.
[3] D. L. Struble, A. L. J. Beckwith, and G. E. Gream, *Tetrahedron Letters*, 1968, 3701.
[4] See E. C. Friedrich, *J. Org. Chem.*, 1969, **34**, 528; W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, 1969, **34**, 2512.
[5] S. J. Cristol and R. V. Barbour, *J. Amer. Chem. Soc.*, 1968, **90**, 2832.
[6] G. Bauslaugh, G. Just, and E. Lee-Ruff, *Canad. J. Chem.*, 1966, **44**, 2837; G. H. Witham and J. A. F. Wickramasinghe, *J. Chem. Soc.*, 1964, 1655.
[7] E. M. Kosower and S. Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4347.
[8] D. J. Carlsson and K. U. Ingold, *J. Amer. Chem. Soc.*, 1968, **90**, 7047.