Long-range Substituent Effects in Steroidal Systems

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THE work of Barton[1] provided extensive kinetic evidence that in the condensation of a number of triterpenoid and steroid 3-ketones with benzaldehyde the difference in rates arises principally from conformational distortion. It has recently been suggested[2] that "conformational transmission" is not a main contributing factor in the acetolyses of some steroid sapogenins, but that the dominant factor governing the rate effects is inductive. We present evidence that conformational factors are equally as important as inductive effects in the solvolytic reactions.

TABLE

Acetolysis of steroidal 3β-tosylates in acetic acid–sodium acetate

Compound	Rate (10^5k; sec.$^{-1}$) 75°	100°	$\Delta H\ddagger$	$\Delta S\ddagger$	Products
5α-Cholestan-3β-yl tosylate (I)	3·01	39·8	25·9	−5·18	5α-Cholestan-3α-yl acetate (70%) 5α-Cholest-2-ene (30%)
5α-Cholest-6-en-3β-yl tosylate (II)	2·14	33·3	27·6	−0·87	5α-Cholest-6-en-3α-yl acetate (50%) 5α-Cholesta-2,6-diene (50%)
6-Methylene-5α-cholestan-3β-yl tosylate (III)	1·17	18·9	28·0	−0·93	Mainly 6-methylene-5α-cholestan-3α-yl acetate
5α-Cholest-7-en-3β-yl tosylate (IV)	1·22	17·4	26·7	−4·57	5α-Cholest-7-en-3α-yl acetate (66%)
7-Methylene-5α-cholestan-3β-yl tosylate (V)	2·03	30·2	27·1	−2·44	5α-Cholest-7-en-3α-yl acetate (>95%)
5α-Cholest-8(14)-en-3β-yl tosylate (VI)	1·51	21·8	27·1	−7·04	—
5α-Cholest-8-en-3β-yl tosylate (VII)[a]	2·36 2·61[b]	27·75 30·7[b]	24·9	−8·45	—

[a] Mixture of Δ^8 (77%) and $\Delta^{8(14)}$ (23%) estimated by n.m.r.
[b] Corrected rates.

The results, summarised in the Table, show that whilst inductive effects are clearly operating over large distances, there is at least one other important factor affecting the rates of solvolysis. Conformational analysis[3] of the A- and B-rings of an A/B-*trans*-steroid indicates that the introduction of a double bond between C-7 and C-8 decreases the C-1–C-4 dihedral angle, whereas Δ^6, Δ^8 and $\Delta^{8(14)}$ double bonds increase the same angle. Exocyclic methylene groups at C-6 and C-7 increase the C-1–C-4 dihedral angle. However, the enlargement is smaller with exocyclic methylene groups than with the introduction of endocyclic double bonds. The net effect is a change in the shape of ring-A; an increase in the C-1–C-4 dihedral angle results in increased puckering and a decrease in flattening of the ring, thus changing the relative direction of the C-3 substituents.

It has been shown,[4] from a comparison of the rates of solvolysis of 5α-cholestan-3β-yl tosylate and *trans–cis*-2-decalyl tosylate, that the introduction of the C-10 angular methyl group increases the rate by 30%. This was rationalised by assuming that nonbonded repulsions between axial hydrogens and the methyl group result in a lowering of the C-3 carbon atom.† It would thus be expected that all double bonds that produce an increase in the C-1–C-4 dihedral angle result in an enhanced rate. Conversely, a decrease in the C-1–C-4 dihedral angle will produce retardation compared to the saturated analogue.

It is evident from the results that, qualitatively, the above predictions are substantiated. Assessment of the inductive effects from work on other systems where the double bond is three or four bonds distant from the reaction centre in solvolysis reactions is complicated by neighbouring-group participation.[5] Nevertheless, it can be concluded that the rate of acetolysis of (II) is twice as fast as could be predicted on inductive grounds[5a,c] and (IV)

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† Reasons for the change in rate with the C-3 movements are not fully understood but could be explained by nonbonded interactions and Schleyer's torsional effects (ref. 6).

is twice as slow. Similarly it is evident the distortion effects on the rates of solvolysis of (III) and (V) are small. Solvolysis of (VI) seems to be retarded relative to that of (I); this might be due to nonbonded interactions between the C-7 and C-14 methylene groups which nullify the distortion produced by the double bond.

The same considerations applied to the benzylidene condensations[1] lead to the conclusion that the introduction of a Δ^2 double bond into ring-A increases the C-1–C-4 dihedral angle. Thus, the introduction of double bonds that increase the same dihedral angle should result in an accelerated rate of condensation, and double bonds that decrease the same angle produce retardation. Once again the predictions are in line with the experimental fact.

The larger relative differences in the rates between the condensation and solvolysis reactions are probably the best demonstration that the transition state for the formation of an enolate anion resembles very closely a double bond with the negative charge residing on oxygen. In fact, the group rate factors defined for the condensation reactions, a measure of the free energy of formation of the Δ^2-enolate, are largely proportional to the torsional distortions produced by the substituents.

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[1] D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1960, 1297.

[2] K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, 1966, **31**, 734.

[3] R. Bucourt, *Bull. Soc. chim. France*, 1963, 1262.

[4] S. Nishida, *J. Amer. Chem. Soc.*, 1960, **82**, 4290.

[5] (a) C. F. Wilcox and S. S. Chibben, *J. Org. Chem.*, 1962, **27**, 2332; (b) J. P. Schaefer and J. Higgins, *ibid.*, 1967, **32**, 553; (c) P. D. Bartlett, W. S. Trahanovsky, D. A. Bolon, and O. H. Schmid, *J. Amer. Chem. Soc.*, 1965, **87**, 1314.

[6] P. Schleyer, *J. Amer. Chem. Soc.*, 1967, **89**, 701.