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ELECTROSTATIC EFFECTS IN THE EQUILIBRATION OF 6-KETO STEROIDS

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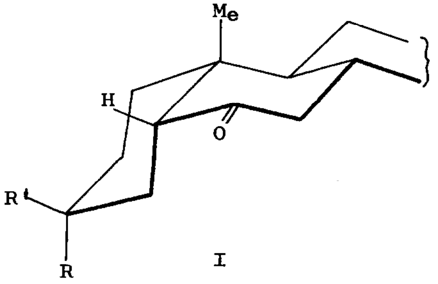
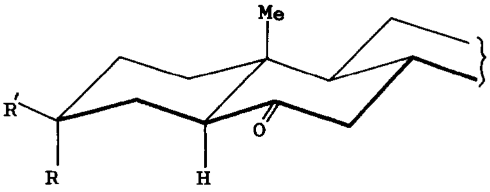
The position of equilibrium between 5β- and 5α-steroidal 6-ketones depends upon the position and orientation of substituents in ring A (1,2) and the phenomenon has usually been rationalised in terms of steric factors. However, electrostatic interactions between the 3α-chlorine and 6-keto group influenced the equilibrium between the chloro-ketones ($I \rightleftharpoons II$; R = Cl; R' = H) (3) and we now report that similar interactions are important in the equilibria between 3α-hydroxy-, 3α-methoxy-, and 3α-acetoxy-5β-cholestan-6-ones (I; R = OH, OMe, OAc; R' = H) and their 5α-isomers (II; R = OH, OMe, OAc; R' = H). It was recently suggested (4) that transannular electrostatic interactions between the hydroxy- and keto-group may affect the equilibrium between *cis*- and *trans*-2-t-butyl-4-hydroxycyclohexanone. The compounds were equilibrated in media chosen to ensure the absence of side reactions, and equilibrium was approached from both sides. Equilibrium constants were determined by the o.r.d. method (1,3) and the probable errors in the derived free-energy differences were ± 0.06 kcal/mole. From the equilibrium constants K_H (for $I \rightleftharpoons II$; R = R' = H) and K_X (for $I \rightleftharpoons II$; R = X; R' = H) the free-energy



I



II

differences $-\Delta G^o_H$ and $-\Delta G^o_X$ were derived, and $-\Delta G^o_H - (-\Delta G^o_X) = -\Delta\Delta G^o_X$ was compared with the known conformational preferences ($-\Delta G^o_A$) of the relevant substituents. Conformational analysis indicates that $-\Delta\Delta G^o_X$ and $-\Delta G^o_A$ should be the same if steric effects only are operating, and if ring A has the same conformation as that in the relevant monosubstituted cyclohexane. Conformational similarity of these cyclohexane rings was indicated by infrared and n.m.r. studies, and this was substantiated by the close similarity between $-\Delta\Delta G^o_X$ and $-\Delta G^o_A$ for the methyl group (3). For the hydroxy-, methoxy-, and acetoxy-groups $-\Delta\Delta G^o_X$ was smaller than $-\Delta G^o_A$ (Table), the three 3α-substituted 5α-cholestan-6-ones (II; R = OH, OMe, OAc; R' = H) being more stable relative to their 5β-isomers (I; R = OH, OMe, OAc; R' = H) than expected by analogy with the conformational equilibria in the corresponding monosubstituted cyclohexanes.

Table

Equilibration Data for I $\rightleftharpoons$ II*

R	R'	Medium†	$-\Delta G^o_X$	$-\Delta\Delta G^o_X$	$-\Delta G^o_A$		$[-\Delta G^o_A - (-\Delta\Delta G^o_X)]$ observed	calc.
OH	H	*A*	0.579	0.59	0.88 to 0.95	(5)	0.29 to 0.36	0.57
H	OH	*C*	1.98	0.86			0.02 to 0.09	0.07
OMe	H	*A*	1.170	0	0.60 to 0.74	(6)	0.60 to 0.74	0.44
H	OMe	*C*	1.58	0.46			0.1 to 0.28	0.14
OAc	H	*B*	1.029	0.22	0.41 to 0.70	(7)	0.19 to 0.48	-
			$-\Delta G^o_H$					
H	H	*A*	1.169					
H	H	*B*	1.246					
H	H	*C*	1.12					

* Free-energy differences in kcal/mole.

† *A*, 0.05 M ethanolic potassium hydroxide at 25°; *B*, dioxan (66.66%) containing acetic acid, acetic anhydride, and concentrated hydrochloric acid (20:5:1) (33.33%) at 25°; *C*, 3M-hydrochloric acid in 25% aqueous ethanol at 80°.

The effect was particularly pronounced in the methoxy-ketones ($I \rightleftharpoons II$; R = OMe; R' = H), where the introduction of the methoxy-group did not affect the position of equilibrium relative to that in the unsubstituted ketones ($I \rightleftharpoons II$; R = R' = H). Since these disparities are apparently not due to distortion of ring A, we consider that they are due mainly to electrostatic interactions between the 3α-substituents and the 6-keto group.

The magnitude of the differences in the calculated electrostatic interactions (8a) were at least in qualitative agreement with the observed effects for the hydroxy- and methoxy-groups, assuming an effective dielectric constant of unity for the medium separating the dipoles. The required angles and distances were derived from the relative co-ordinates of the atoms (8b) and the calculations were performed by a computer. Rotation of the dipoles about the C3 — O bond was taken into consideration, the interactions for each conformation (at 1° intervals) being calculated. The effect of torsional strains E_t upon conformer population was allowed for by weighting each conformation with a Boltzman factor taken from the potential function $E_t = V(1 + 3 \cos \omega)/2$, where V = 1.1 and 2.7 kcal/mole for the hydroxy-group and methoxy-group respectively (8c). Syn-diaxial interactions in the axial hydroxy- and methoxy-compounds (II; R = OH, OMe; R' = H) were assumed to be strong enough (cf. 9) to preclude conformers having ω between 100° and 260° (for the hydroxy-group) and between 70° and 290° (for the methoxy-group), where ω is zero when the O — R bond (R = H or Me) and the geminal C — H bond are eclipsed. Calculations showed that the neglected conformations were also destabilised by repulsive electrostatic interactions with the 6-keto group whereas the majority of the accepted conformations were not. Stabilisation of 3α-acetoxy-5α-cholestan-6-one (II; R = OAc; R' = H) relative to its 5β-isomer (I; R = OAc; R' = H) is also probably due to electrostatic effects, but they were not calculated because of the difficulty in locating with confidence the acetoxy dipole.

The disparities between $-\Delta\Delta G^o_X$ and $-\Delta G^o_A$ are probably not due to solvent effects. For the hydroxy-group they were both determined in hydroxylic solvents, whilst for the acetoxy-group the disparity is appreciably greater than expected for a change of solvent (7a); it is very unlikely that a change from water (6a) to basic ethanol will cause $-\Delta\Delta G^o_X$ and $-\Delta G^o_A$ for the methoxy-group to differ by 0.60 kcal/mole. Entropy effects large enough to cause these discrepancies are also very unlikely (cf. 5b, 7a).

Calculations revealed that electrostatic interactions affected the equilibria appreciably only if the C-3 substituents were α-orientated, since they differed little in 3β-substituted 5α- and 5β-cholestan-6-ones. Consonantly, the equilibrations $I \rightleftharpoons II$ (R = H; R' = OH, OMe, OAc) gave values for the conformational preferences of the 3β-substituents in reasonable agreement with those measured in monocyclic systems (1).

REFERENCES

1. D. Neville Jones and D.E. Kime, *J. Chem. Soc.* (C), 846 (1966).
2. R. Weichert, V. Kerb, P. Hocks, A. Furlenmeier, H. Furst, A. Langemann, and G. Waldvogel, *Helv. Chim. Acta*, **49**, 1581 (1966); J. B. Siddall, J.P. Marshall, A. Bowers, A.D. Cross, J.A. Edwards, and J.H. Fried, *J. Amer. Chem. Soc.*, **88**, 379 (1966); B. Rezabova, J. Hora, V. Landa, V. Cerny, and F. Sorm, *Steroids*, **11**, 475 (1968).
3. D. Neville Jones, R. Grayshan, and D.E. Kime, J. Chem. Soc. (C), in press.
4. R.D. Stolow and T. Groom, *Tetrahedron Letters*, 4069 (1968).
5. (a) E.L. Eliel and S.H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965). (b) E.L. Eliel, D.G. Neilson, and E.C. Gilbert, *Chem. Comm.*, 360 (1968).
6. D.S. Noyce and L.J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961); E.L. Eliel and M.H. Gianni, *Tetrahedron Letters*, 97 (1962).
7. (a) J.C. Celotti, J. Reisse, and G. Chiurdoglu, *Tetrahedron*, **22**, 2249 (1966); (b) F.A.L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962); (c) E.A. Allan, E. Premuzic, and C.W. Reeves, *Can. J. Chem.*, **41**, 204 (1963).
8. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, *Conformational Analysis*, (a) p. 461, (b) p.454, (c) p.140, Interscience, New York (1965).
9. H.S. Aaron, C.P. Ferguson, and C.P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967).