A Relationship between Reactivity and Conformational Distortion in Aldol Condensation

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SEVERAL years ago, Foote[1] and Schleyer[2] succeeded in correlating the vast amount of kinetic data on the solvolysis of secondary toluene-*p*-sulphonates with the infrared frequency of the corresponding ketones. They have shown that to the first degree of approximation the rate of solvolysis is proportional to the frequency of the carbonyl band and that an even better relationship is obtained if a correction is allowed for eclipsing (torsional effects) and the strains in the ground and transition states. We now demonstrate that a similar relationship exists between the rate of benzylidene condensation[3] at C-2 of a steroidal 3-ketone and a physicochemical measurement, a change in the chemical shift of the protons on the C-19 methyl group.

In our recent Communication[4] we have qualitatively analysed the conformational changes of ring A on the introduction of a double bond in rings B or C; the introduction of a double bond produces either flattening or increased puckering, that is raising or lowering of C-3 atom. Furthermore, we

TABLE

Compound	Ketone at C-3		Hydrocarbon		$(\Delta K-\Delta H/c)$		
	C-19 (c./sec.)	ΔK (c./sec.)	C-19 (c./sec.)	$\Delta H/c$ (c./sec.)	c./sec.	Rel. rate	Ref.
Cholestane	60·9	0·0	47·0	0·0	0·0	1·00	3
Cholest-6-ene	57·7	−3·2	45·4	−1·6	−1·6	3·54	3
Cholest-7-ene	61·4	+0·5	46·8	−0·2	+0·7	0·27	
Cholest-8-ene	68·8	+7·9	55·6	+8·6	−0·7	1·60	
Cholest-8(14)-ene	54·8	−6·1	40·2	−6·8	+0·7	0·59	
6-Methylenecholestane	54·0	−6·9	40·3	−6·7	−0·2	1·17	
7-Methylenecholestane	68·3	+7·4	54·9	+7·9	−0·5	2·00	3
5α,25D-Spirostan	62·1	0·0	47·9	0·0	0·0	1·00	3
5α,25D-Spirost-9(11)-ene	69·6	+7·5	55·6	+7·7	−0·2	1·27	
11-Methyl-5α,25D-spirost-9(11)-ene	75·8	+13·7	62·6	+14·7	−1·0	2·38	
5α,25D-Spirost-11-ene	58·7	−3·4	45·4	−2·5	−0·9	2·28	3
11-Methylene-5α,25D-spirostan	75·6	+13·5	61·7	+13·8	−0·3	1·35	
12-Methylene-5α,25D-spirostan	64·0	+1·9	50·2	+2·3	−0·4	1·25	3
Androst-6-ene	58·5	—	—	—	−2·0[a]	4·28	
6,19-Oxidocholestane	238·1	—	223·3	—	+0·7	0·67	

[a] Calculated from Tables quoted in ref. 5. Rate relative to cholestane.

The n.m.r. measurements were done on Varian-A60, 100 c./sec. full scale expansion. $CDCl_3$ was used as a solvent with Me_4Si as an internal reference and external sideband technique was used for calibration. The concentration of the samples was between 8—15% and the frequencies quoted are a mean of 4—7 scans. We have shown in an independent experiment that the frequency of the signal due to the C-19 methyl group is independent of the concentration.

suggested that the group rate factors, being a measure of the free energy of formation of the Δ^2-enolate, should be proportional to the amount of distortion produced by the double bond. Thus if a carbonyl group is placed at C-3, the C-19 methyl group should be either more or less shielded (relative to the saturated parent ketone[†]) depending on the amount of distortion. As can be seen from Figure 1, the plot of the logarithm of the relative rate (corresponding parent ketone taken as unity) against the net change in shielding $[(\Delta K-\Delta H/c)]$ appears to be a straight line, thus bearing out our assumptions. The plot also shows that inductive effects are unimportant in these base-catalysed condensations compared to solvolyses of the toluene-*p*-sulphonates in the same system.[4] The only exception is cholest-7-en-3-one, which appears to have a more shielded C-19 methyl group than the relationship would predict. As the C-3 atom is lowered (Figure 2) a position is reached when the deshielding is minimal (θ = 0) and further lowering will result in increased shielding of the C-19 methyl group. It is possible that this situation has been

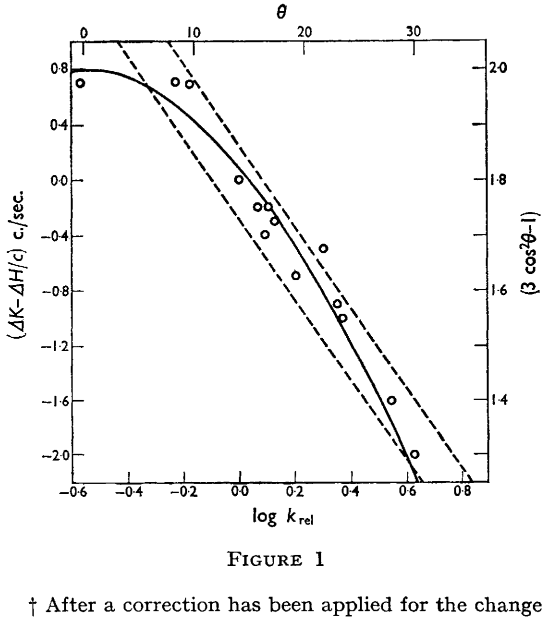

FIGURE 1

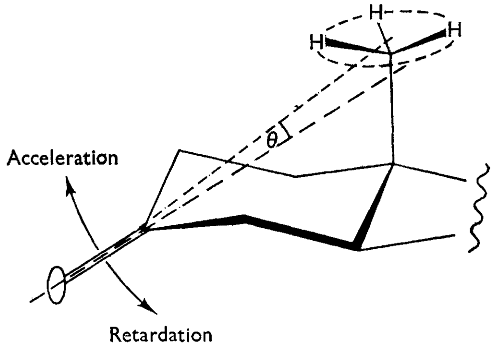

FIGURE 2

[†] After a correction has been applied for the change in the anisotropy on introduction of the double bond in the compound.

reached in cholest-7-en-3-one. In fact, this agrees with the theoretically derived equation of McConnell[6] which shows that the change in the anisotropy of the carbonyl bond is proportional to the $(3 \cos^2\theta - 1)$ function.

The above relationship supports completely Barton's original suggestion[7] that torsional strains introduced into a molecule on substitution are transmitted over the whole molecule by bond deformations and angle distortions. Malhotra *et al.*,[8] have recently discussed the application of nonbonded interactions [$A^{(1,2)}$ strain] to the isomer distribution in cyclohexene systems. We suggest that torsional energies must also be considered in their calculations.

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