Relative Positions of the Transition States in the Protonation of Enamines and Enol Ethers. Orbital Bias

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Summary Contrary to previous reports the stereoselectivity of the deuteriation of enamines is low and is indicative of a reactant-like transition state; enol ethers show a greater preference for axial deuterium incorporation.

APPLICATION of the concept of $A^{1,3}$ strain[1] leads to the conclusion that electrophilic attack, on a 2-substituted cyclohexanone enamine, in which the substituent is in a quasi-axial orientation, occurs from the axial or β-direction rather than from the equatorial or α-direction. The latter process would be expected to be less favourable since it leads to a boat or twist conformation of the resulting iminium salt, destabilised by severe $A^{1,3}$ interactions between the substituent and the α-methylene of the amine group of the enamine (Scheme). In agreement with this the deuteriolysis of the pyrrolidine enamine (I) of 2-methylcyclohexanone is reported[2] to give 6-*e*-deuterio-2-methylcyclohexanone as the major product. If the methyl substituent is assumed to be in the quasi-axial orientation in the enamine, and in an equatorial orientation in the ketone, this indicates that deuteriation occurred from the β-(axial) side of the enamine. Similarly Schaefer and Weinberg[3] have reported that the deuteriolysis of the morpholine enamine (II) of 4-t-butylcyclohexanone gives 2-β-deuterio-4-t-butylcyclohexanone, and House *et al.*[4] have reported that the corresponding enol ether (III) and the pyrrolidine enamine (IV) give greater than 90% axial deuterium incorporation.

However the analytical methods upon which these conclusions are based are not absolutely convincing. Malhotra and Johnson[2] used the relative intensities of the peaks at 2190 cm^{-1} and 2120—2150 cm^{-1} in the i.r. spectrum and assumed these to be due to the equatorial and axial C–D stretching absorptions respectively. However their conclusions are invalid if (a) both isomers absorb at 2190 cm^{-1}, (b) the extinction coefficients of the two isomers differ appreciably, or (c) one isomer gives one strong absorption and the other several weak absorptions. In the absence of pure standards these possible sources of error cannot be ruled out. House[4] has also criticised this method and in his work used the fact that equatorial protons are deshielded relative to the axial protons in benzene solution and therefore give signals to lower field in the ^1H n.m.r. spectrum.[5] He therefore assumed that the signals at τ 7·6—8·02 were due to the equatorial protons and those at τ 8·02—8·53 were due to the axial protons and the C-4 methine proton.† However, as the right hand side of the spectra (Figure) shows there is considerable overlap of these signals and this method is therefore also unreliable.

Schaefer and Weinberg[3] do not report any experimental verification of their results, and conclude that axial deuteriation would be expected from stereoelectronic considerations. This means that for maximum overlap of interacting orbitals the transition state for axial approach goes through a chair conformation of the cyclohexyl system whereas for equatorial approach a higher energy boat or twist conformation would be involved. However these thermodynamic considerations are only relevant if the transition state for

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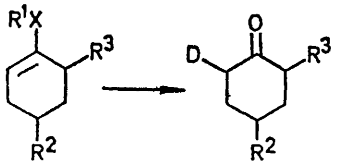
† In fact this proton gives a signal to higher field and is overlaid by those due to the C-3 and C-5 axial protons. Praseodymium induced shifts clearly demonstrated that the signals at τ 8·02—8·53 in the 60 MHz ^1H n.m.r. spectrum of 4-t-butyl-2,2,6,6-tetradeuteriocyclohexanone (in C_6D_6) are due to the two C-3 and C-5 equatorial protons.

protonation is product-like. If the transition state is reactant-like, as has been reported for the alkylation and of the enol ether. The signals due to the α-equatorial protons at low field and the α-axial protons at slightly higher field are clearly separated and the extent of deuterium incorporation at each position can be unambiguously determined. Our results using this technique are summarised in the Table. We confirm that the enol ether undergoes mainly axial deuterium incorporation, although the stereoselectivity is not as great as previously supposed,[4] but deuteriolysis of the enamines shows low stereoselectivity. Very little deuterium incorporation into the ketones occurs

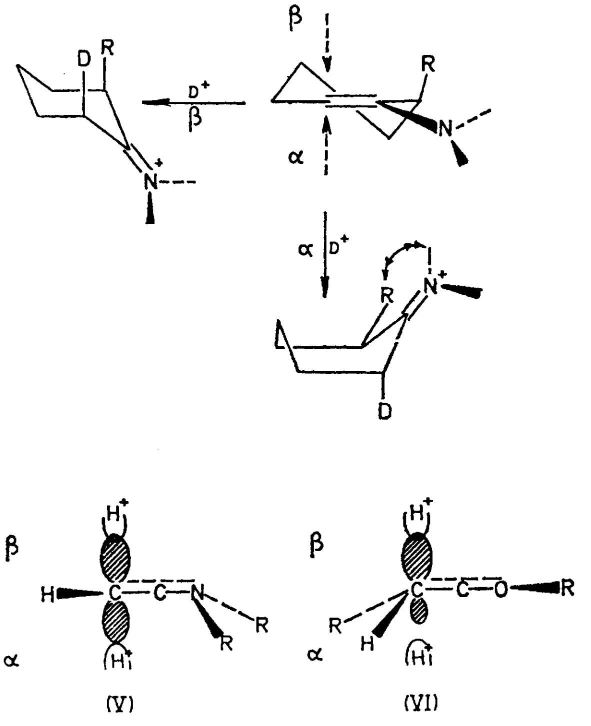
TABLE



R¹X	R²	R³	Conditions	Equat.	:	Axial	Deuterium incorporation D_0	D_1	D_2	D_3
EtO	Bu^t	H	DOAc–D_2O; 100°; 10 min[3]	30		70[a]	11	77	10	2
C_4H_8NO	Bu^t	H	DCl–D_2O; 20°; 20 min[2,3]	43		57[a]	6	78	15	1
C_4H_8N	Bu^t	H	(1) DCl–D_2O; 20°;20 min[3] (2) H_2O;20°; 15 h	47		53[a]	5·5	81	12	1·5
C_4H_8N	Bu^t	H	(1) DCl–D_2O; 20°; 20 min (2) D_2O–NaOD to pH 6·5	48		52	11	81	5	3
C_4H_8N	H	Me	DOAc–D_2O; 20°; 5 min[1]	50 (55)		50[a] (45)	22	48	29	1

[a] Average of six separate determinations.

protonation of enolate anions,[4,6] then high axial stereoselectivity in the protonation and deuteriation of enamines should not be observed. We have therefore reinvestigated the deuteriolysis of (I)[2] (II),[3] (III),[4] and (IV)[4] under the conditions reported in the literature. The resulting mixture of deuteriated ketones has been analysed by ^1H n.m.r. using Eu(fod)$_3$ to separate the signals.[7] The Figure shows the spectra obtained for 4-t-butylcyclohexanone and the partially deuteriated mixture obtained by deuteriolysis



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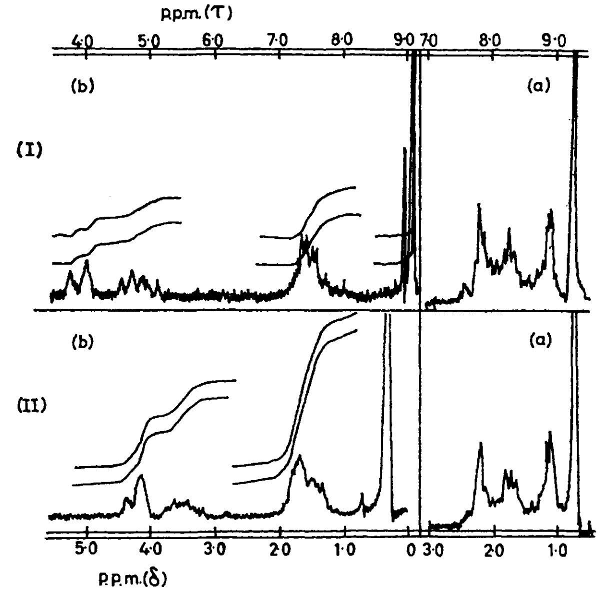
under the conditions used,[1,2,3] confirming that the products are not being isomerised *via* the enol form of the ketone.



FIGURE

(I) 60 MHz n.m.r. spectrum of 4-t-butylcyclohexanone; (a) in C_6D_6; (b) in C_6D_6 in the presence of Eu(fod)$_3$.

(II) 60 MHz n.m.r. spectrum of the partially deuteriated mixture obtained by deuteriolysis of the enol ether; (a) in C_6D_6; (b) in C_6D_6 in the presence of Eu(fod)$_3$.

The results can be explained in terms of the relative positions of the transition states on the reaction co-ordinate. Enol ethers are relatively unreactive and their transition states would be expected to be more product-like compared with those for enamines. In other words a greater degree of rehybridisation of the β-carbon, and of the oxygen, in enol ethers is required in order to achieve the necessary degree of bonding of the transition state. We suggest that as a consequence of the thermodynamic factors which favour a developing chair over a developing boat or twist transition state, an *orbital bias* develops (see VI) which favours bond formation with reagents approaching the β-face to a greater extent than with reagents approaching the α-face. The extent to which this oribtal bias develops in the transition state would be in the order: enol ethers $>$ morpholine enamines $>$ pyrrolidine enamines ($>$ enolate anions) and this accounts for the observed stereoselectivity. Clearly the transition state for the protonation and deuteriation of the enamines occurs earlier and the rehybridization of the β-carbon and the resulting orbital bias is less developed (see V). Since there is no obvious steric impediment to approach from either side of the double bond, the stereoselectivity is low. In the case of (I) if allowance‡ is made for the high proportion of D_2 relative to D_1 isomers in this product, the results (in parentheses) indicate a slight preference for equatorial attack, as would be expected if the quasi-axial methyl group is shielding the β-face of the enamine to some extent. In the reaction of enamines with less reactive electrophiles, such as alkylating agents, a greater degree of rehybridization of the β-carbon atom would be required in order to reach the transition state and hence a greater degree of stereoselectivity would be expected, and has been observed.[8]

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