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REMOTE DEUTERIUM ISOTOPE EFFECT IN THE NUCLEOPHILIC-ADDITION OF BH_4^- TO CIS 2,6-DIPHENYL 4-PIPERIDONE : ANISOTROPY OF THE STERIC ISOTOPE EFFECT.

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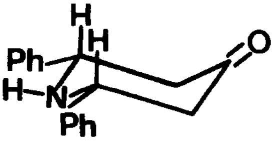
In previous papers[1] secondary deuterium isotope effects were reported for nucleophilic addition to a series of carbonyl compounds having deuterium atoms attached to the α-carbon atoms. More recently we investigated *remote* (β and γ) deuterium isotope effects, using as substrate 2-norbornane deuterated at the 5,6 endo positions[2]. A complete absence of isotope effect i.e.k_H/k_D=1.00 was observed in these studies, both for borohydride addition to the ketone and decomposition of the corresponding bisulphite complex-reactions which on steric grounds one might have anticipated otherwise. Thus in the sp^3 hybridised transition state for borohydride addition there is a possibility that steric interactions between the bonds being formed and the 5,6 endo C-H bonds will be generated, whereas on the contrary, with bisulphite decomposition, steric strain will be relieved on passing from a tetrahedral to a trigonally arranged transition state[1].

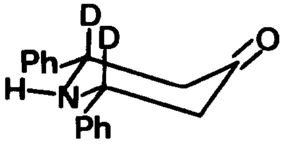
The absence of an isotope effect could imply that the non-bonding interactions are merely less severe than expected (softer potential functions). Alternatively however it could be a manifestation of the *anisotropic nature* of these interactions i.e. that non-bonded interactions are in reality orientation dependent[3]. We would like now to present evidence which lends support to the latter hypothesis.

It is well established that axial attack by a nucleophile on the carbonyl group in cyclohexanones is normally preferred, and that because the angle which the entering group makes with the carbonyl plane is of the order of 109°[4], the approach of the reactant is hindered by the β or syn axial 3,5 hydrogens. As a model for this type of interaction we chose to examine 2,6-diphenyl 4-piperidone, for its preparation by a Mannich reaction involving the mixing together of benzaldehyde (2 moles) *ketone* (1 mole) and ammonium chloride (1 mole) at room temperature, is facile[5]. That the product has a chair conformation[5,6], is additionally confirmed by its NMR spectrum ; the observed coupling constants for the ABC system of protons at positions 1 and 3 and 5 and 6 ($^2J_{AB}$=13.3Hz ; ($^3J_{AC}$=3.0Hz ; ($^3J_{BC}$=12.0Hz), being in very good agreement with that expected for a rigid chair form in which phenyl substituents are equatorial and cis to each other. The corresponding 2,6 axially dideuterated product is similarily prepared by commencing with deuterated benzaldehyde[7]. Its deuterium content has been checked by NMR spectroscopy and found ≃ 98% by mass spectroscopy.

Kinetic studies of the borohydride reduction of these two compounds were carried out under bimolecular conditions following the decrease in carbonyl absorption at 280nm (25°C) using a U.V. spectrometer as described in our earlier studies[1]. A product analysis by VPC using a 10 Ft OV 17 column at 165°C revealed that under the kinetic conditions (water-dioxane, 0,01M NaOH) 95% equatorial and 5% axial alcohol are formed.



1h



1d

The second order rate constants for 1h and 1d are k_H=0.74$_0$ l.mole^{-1} sec^{-1} and k_D= 0.76$_8$ l.mole^{-1} sec^{-1} respectively. Errors expressed as average deviations for six runs are less than 1%. *Thus a kinetic isotope effect of 0.96$_3$*(k_H/k_D < 1) is observed of the same order of magnitude than γ-deuterium kinetic isotope effects for solvolysis reactions in which deuterium is similarly situated in non hyperconjugative positions[9]. This value may indicate that in the transition state the constraints on the vibrational motions of the C-H bond are more severe than on that of the C-D bond i.e. that the proton requires more space than the deuterium atom. In other words non-bonding interactions in axial nucleophilic attack on cyclohexanone are more important for the H-product than for the D compound -observations which are in perfect accord with Bartell's[10] steric hypothesis recently reviewed by Carter and Melander[11].

We believe that the factor which *distinguishes* the behaviour of the *piperidone* from that of the *norbornyl compounds* is that whereas with the former the non bonding interactions act along the *vibrational stretching* motions, with the bicyclic compounds the non-bonding interactions act along the *bending motions*, whose energy is too weak to lead to an isotope effect.

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Corelation coefficient > 0.99.
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