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SECONDARY DEUTERIUM ISOTOPE EFFECT IN ADDITION REACTIONS ON CARBONYL COMPOUNDS

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Secondary kinetic isotope effects have become, in the last few years, a particularly effective means for the study of the mechanisms of organic reactions (1). Nucleophilic substitution reactions on saturated carbon have been particularly explored and it has been hoped, from the measurement of k_H/k_D, to arrive at a differentiation between SN_1 and SN_2 mechanisms and even to provide evidence for the process of anchimeric assistance (2).

One problem remains still unsolved: it is that of the very origin of the isotope effect: the cause of the isotope effect is the object of a sharp controversy, some attributing it to a steric origin, others attributing it to an electronic origin. We have felt that the study of secondary isotope effect in nucleophilic addition reactions on carbonyl compounds would perhaps permit us to cast some light on this problem since it is known that, in this type of reaction, the steric hindrance caused by the Hydrogens α to the carbonyl play a dominant role (3).

Since the experience we have acquired in the utilization of HCN has shown to us that we could not expect a precision better than 3 to 5 % on the rate constants, we have used an other nucleophile, the Borohydride ion. The reduction of ketones by Sodium Borohydride has been made the object of many kinetic studies by BROWN and his collaborators (4); the reaction seemed to be simple, the precise determination of BH_4 seemed easy to achieve and the close parallelism observed among the rates of addition of CN^- and BH_4^- on cyclic ketones having 5 to 7 Carbon atoms seemed to indicate that the BH_4^- ion was closely comparable to the CN^- ion as a nucleophile.

Our results are summarized in the following table :

TABLE I

Compounds	k_H/k_D at 25ºC.	
ACETONE	0.97_1	$(0.98_1)^b$
DIETHYLKETONE	0.93_9	
ACETOPHENONE	0.99_0	
CYCLOPENTANONE	0.95_9	
CYCLOHEPTANONE	0.92_2	
NORCAMPHOR	0.98_1	$(0.96_2)^a$
CYCLOHEXANONE	$0.88_6{}^c$	
4-t-butyl-CYCLOHEXANONE	$0.88_0{}^c$	
cis 2-DECALONE	$0.94_8{}^c$	

a) To take into accont for the fact that there are only 2 H in the α position
b) To take into accont for the fact that there are 6 H in the α position
c) At 0ºC. We have verified that there is no significant temperature dependance on the isotope effect.
The reproducibility of the rates constants was better than ± 0.5%.

We can, <u>apriori</u>, list four factors responsible for this isotope effect :

a) Inductive effects which are different for D and for H,

b) Differences in basicity between deuterated and normal ketones,

c) Steric effects,

d) Hyperconjugation (or any other phenomena with conjugative character).

<u>a)</u> It is known that the C-D bond is more polar than the C-H bond; the stronger electron-donating effect in the deuterated ketone will lower the rates and we should observe $k_H/k_D > 1$ if this effect is the preponderant one.

b) The differences in basicity of deuterated ketones will play a role if we assume, as have certain other workers (5), that the reactive species in a hydroxylic solvent is not the ketone itself but a complex formed from one molecule of ketone and one molecule of solvent :

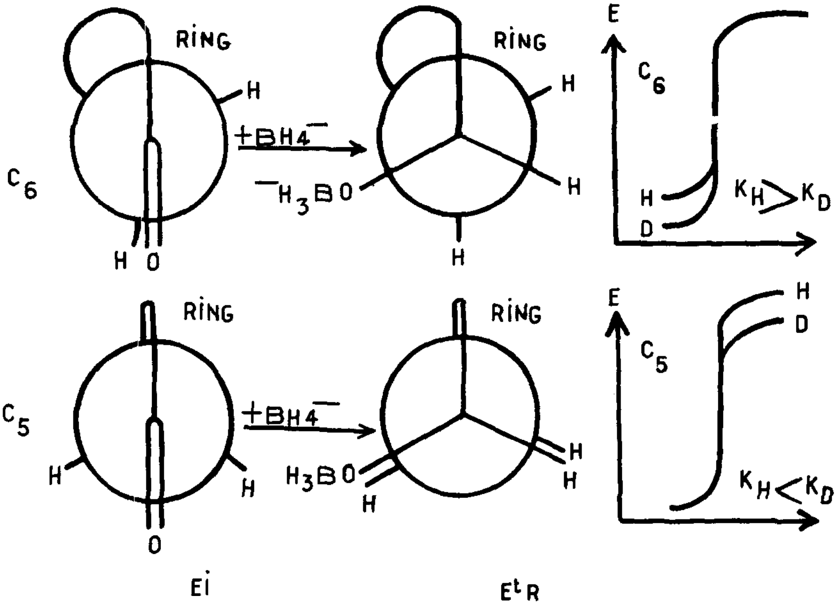
$$>C{=}O + R{-}OH \rightleftarrows >C{=}O{-}{-}{-}H{-}O{-}R \quad \text{(here } R = H\text{)}$$

The concentration of this complex in the reaction medium depending upon the basicity of the ketone and the deuterated compounds being weaker bases (6) than the normal ketones, we should observe again, if this effect was preponderant, $k_H/k_D > 1$.

If the factors a) and b) are present they cannot be very important since in all cases we have observed $k_H/k_D < 1$. In the absence of more precise information one can only hope that these factors act in the same fashion in all cases and shift the observed isotope effect by the same amount.

c) Steric effects. As already mentionned the nucleophilic addition reactions on C=O bonds are very sensitive to non-bonded interactions with the Hydrogens in the α position. The difference in reactivity between cyclopentanone and cyclohexanone is due in large part to the fact that the initial state, trigonal carbonyl carbon, is sterically hindered in cyclohexanone and is not in cyclopentanone, while the contrary is true in the tetragonal transition state. (See figure below). Replacing the H in the αposition by a smaller moiety, e.g. Deuterium, should therefore lower the energy of the initial state of cyclohexanone and that of the transition state of cyclopentanone.

Therefore if this explanation for the difference in reactivity is correct, if the transition state for the addition of BH_4^- is indeed tetragonal and if the isotope effect has an essentially steric origin, one should obtain $k_H/k_D > 1$ for cyclohexanone and $k_H/k_D < 1$ for cyclopentanone, or at least $(k_H/k_D)_{C6} > (k_H/k_D)_{C5}$.



The results of Table I show that such is not the case and therefore one at least of the above assumptions is false; the only thing which is certain is that the steric effects on the isotope effect are not preponderant, if they exist at all, in the case of BH_4^- addition.

d) Hyperconjugation. It is known that the C-D bond is less polarizable than the C-H bond and will, therefore, be less apt to hyperconjugate with the π electrons of the C=O bond of the ketone, resulting in an augmentation of the energy of the initial state and $k_H/k_D < 1$. One can predict furthermore a conformational dependance on the isotope effect; all of the H in the α position are not equivalent : those whose orientation is optimum for maximum overlap of σ electrons of C-H (or C-D) bonds will produce a maximum isotope effect.

Examination of the results shows that this factor indeed seems to be preponderant; the maximum isotope effect, of about 12 %, is obtained precisely by the compounds in which there exist Hydrogens (axial) whose position is favorable for maximum hyperconjugation such as cyclohexanone or 4-t-butyl Cyclohexanone. Acyclic compounds which are a mixture of conformation isomers and alicyclic compounds of 5 and 7 carbons in which the Hydrogens are less favorably situated lead to a considerably diminished isotope effect, 4 to 6%. A supplementary indication of the preponderance of the conjugative effect is shown by the study of partially deuterated 4-t-butyl Cyclohexanone which shows that the exchange of the first two Hydrogens provides 3/4 of the total isotope effect. It seems almost certain to us that in the reaction studied conjugative effects are, in major part if not completely, responsible for the observed isotope effect.

One must not however conclude that such would be the case for all carbonyl addition reactions. In another case of so-called "nucleophilic" addition, RAAEN and COLLINS have obtained results completely different from ours (7). The isotope effect which they have observed in the formation of phenylhydrazones is about 11% for acetophenone whereas for the addition of BH_4^- it is only 1%. The complexity of the reactions mechanisms is certainly the cause for such a discrepancy. We think, in fact, that the BH_4^- is not the "typical" nucleophile which we hoped to find : the researches carried on in differents laboratories after this work was already under way indicate that the mechanismof the action of BH_4^- is much less certain now that it was 4 years ago (8); furthermore the parallelism between the rates of addition of BH_4^- and CN^- has not been maintained for all the products studied, seeming to indicate that the steric requirements of the BH_4^- ion are less important than those of the CN^- ion. In our opinion the fact that we have not been able to find the steric influence in the addition of BH_4^- does not prevent us from expecting to find evidence for it in more simple nucleophilic addition reactions. such as CN^- or SO_3^{--} additions.

Work which is in progress in our laboratory can verify this hypothesis.

Finally we wish to single out the completely surprising result obtained with cis 2-Decalone; the observed isotope effect, 0.94_8, is of the same order of magnitude as that obtained with cyclopentanone and cycloheptanone; it can, by no means, be explained if we only assume that this molecule exists in the form of a rapid equilibrium between two double-chair conformations, the "steroid" and the "non-steroid". This one more example to be put on record of the "exceptional" behaviour of this compound.

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