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STERIC EFFECT OF α-HYDROGENS IN NUCLEOPHILIC ADDITION REACTIONS TO CARBONYL COMPOUNDS

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We have been using, since some time, the secondary kinetic deuterium isotope effect as a means to assess the relative importance of the reactivity factors in nucleophilic addition reactions to carbonyl compounds. We have previously shown that the ratio k_H/k_D depends both upon the structure of the ketones and the nature of the nucleophile [1-3]. We pointed out[1-2] with SO_3^{--} the importance of the hyperconjugative factor previously mentioned in BH_4^- addition[3] for which there is superimposed a steric effect due to a change in the internal rotation barrier.

The case of hydroxylamine addition is different. The transition state is "reactant-like" as for SO_3^{--} addition[4] but, - the incipient C-N bond being substantially shorter than the C-S bond - the nucleophile will be nearer the central carbon atom. Thus steric hindrance by α-H atoms can eventually come into play and bring about a decrease of reactivity ; the introduction of D atoms in α position will reduce this steric hindrance and enhance the kinetic isotope effect[5]. In some compounds, such as cycloheptanone and benzylmethylketone, we effectively observed a kinetic isotope effect of greater importance for addition of NH_2OH than for addition of SO_3^{--} ion. It has been postulate by JENCKS[6] that the NH_2OH molecule approaches the substrate preferentially along a line perpendicular to the plane of the carbonyl group. A closer look at the models shows that the compounds, for which a "high" isotope effect has been observed, are those in which this preferential direction of approach in impossible : an atom, or group of atoms, located somewhere else in the molecule - a pseudo-axial 3-H atom in cycloheptanone for example (fig.1) - pushes the nucleophile out of the regular way and makes it "bump" against the α-H atoms. If this interpretation is correct, such a steric hindrance will occur every time the direction of approach is not strictly perpendicular to the plane of the carbonyl group ; moreover, the bigger the repelling group, the more important the deviation, the higher the isotope effect. (fig. 2). To check this idea we have used methylalkylketones $RCOCH_3$ and $RCOCD_3$, with alkyl groups of increasing bulk and have measured the isotope effect of the methyl group. We have also measured the isotope effect in symmetrical ketones R-CO-R to estimate the contribution of a R group to the isotope effect ; so, the contribution of the methyl group alone is easy to appreciate. Our results are presented in table I.

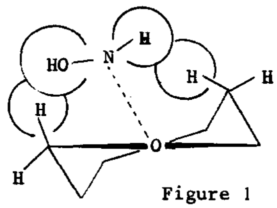

Figure 1

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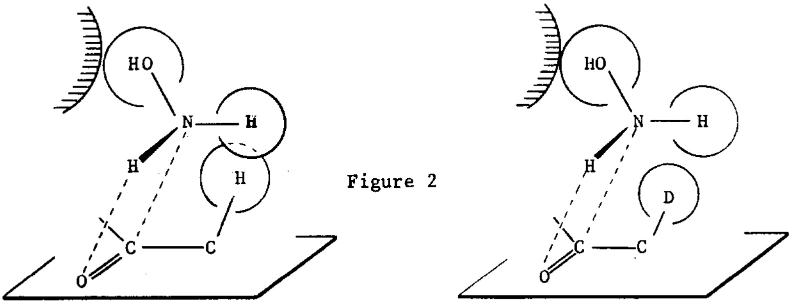

Figure 2

ketones	k^H / k^D	$(\Delta\Delta G^{\neq})_{-X}$ calories	10^{-3} k l.mole^{-1}.min^{-1}	R-CO-R	k^H / k^D	$\Delta\Delta G^{\neq}$ calories
Me-CO-Me	0.92	$-X=-CH_3$ 24	2.53	R = Me	0.92	48
Et-CO-Me	0.94	" 27	3.14	Et	0.97	16
Benz-CO-Me	0.83	" 36	1.23	Benzyl	0.80	136
i-Pr-CO-Me	0.90	" 48	1.22	i-Pr	0.95	28
t-But-CO-Me	0.87	" 81	0.111	-	-	-
Cyclopentanone	0.84	$-X=-CH_2$ 50	0.578			
Norcamphor	0.88	" 74	0.0837			
α-Indanone	0.86	" 84	0.00685			

We can see at once that when we go from acetone to pinacolone, the isotope effect of the methyl group is multiplied by a factor greater than 3 - from 24 to 81 cal/mole - although the hyperconjugative contribution is essentially the same. We find the same sort of situation in the cyclic compounds : cyclopentanone, norcamphor, and α-indanone. The dihedral angles around the C-C bonds adjacent to the carbonyl group are almost the same in all these compounds and the hyperconjugative contribution to the isotope effect is thence very similar ; however in cyclopentanone - an unhindered ketone - the normal way of approach is open to the nucleophile ; whereas the hydroxylamine molecule is pushed towards the α-hydrogen atoms by the syn-7-H atom in norcamphor and by the π electrons cloud of the benzene ring in α-indanone. The D-atoms being less "space demanding" than the H-atoms a substantial increase in the isotope effect is observed in these two compounds as shown in table.

The very marked trend observed all along the two series of compounds is consistent with the ideas developed above. Moreover it is worth noticing that this increase in magnitude of the isotope effect is accompanied, as expected by a sharp decrease of the absolute rate constant k_H.

REFERENCES

1) - G. LAMATY, J.P. ROQUE, Tetrahedron Letters, 5293 (1967)
2) - J.P. ROQUE, Doctorat ès-Sciences Physiques, Montpellier (1970)
3) - P. GENESTE, G. LAMATY, Bull. Soc. Chim. Fr., 669 (1968)
4) - Preceding papers
5) - L.S. BARTELL et H.K. HIGGINBOTHAM, J. Chem. Phys., 42, 851 (1965)
6) - W.P. JENCKS, in "Progress in Physical Organic Chemistry", Vol. 2, p. 63, N.Y. (1964)