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A STERIC ISOTOPE EFFECT RECONSIDERED

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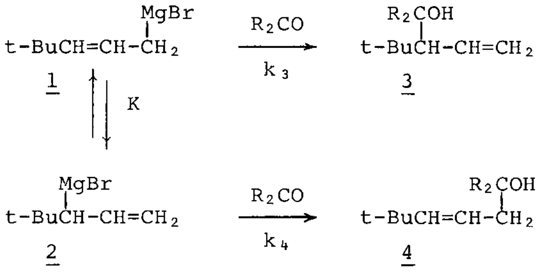
It was recently reported in this journal that the reaction of ketones with t-butylallylmagnesium bromide (eq 1), which exists in



$$\begin{tikzcd}
\text{t-BuCH=CH-}\overset{\text{MgBr}}{\text{CH}_2} \; \underline{1} \arrow[r, "R_2CO", "k_3"'] \arrow[d, shift left, "K"] & \text{t-Bu}\overset{R_2COH}{\text{CH}}\text{-CH=CH}_2 \; \underline{3} \\
\text{t-Bu}\overset{\text{MgBr}}{\text{CH}}\text{-CH=CH}_2 \; \underline{2} \arrow[r, "R_2CO", "k_4"'] \arrow[u, shift left] & \text{t-BuCH=CH-}\overset{R_2COH}{\text{CH}_2} \; \underline{4}
\end{tikzcd}$$

(1)

solution as a rapidly equilibrating mixture of the isomers 1 and 2, is remarkably sensitive to steric effects, and that the proportion of less crowded (4) to more crowded (3) product formed, [4]/[3], can in fact be used as a delicate measure of the effective bulk of substituent groups.[1] This criterion was then applied to normal and deuterated acetone, and CH_3COCH_3 was found to give less of the more hindered product than CD_3COCD_3: [4]/[3] = 3.4 and 3.1 respectively. It was therefore concluded that CD_3 is less bulky than CH_3 and that this isotope effect is steric in origin.

Since true steric isotope effects have proved to be both elusive and rare,[2] this is a significant result. It is of some consequence, moreover, that the effect observed here is also consistent with a non-steric explanation.

The carbonyl group is known to be polarized in a direction which puts positive charge on carbon, and, since this carbon atom is trigonal, the charge can be delocalized by hyperconjugative interaction with an adjacent methyl group. During the course of a reaction which converts this trigonal carbon into a saturated carbon atom, the delocalization is eliminated, and this change in hyperconjugation can be expected to give rise to secondary isotope effects. The effects $k_H/k_D = 0.78$ observed in hemiacetal formation from acetone and acetone-d_6 and $k_H/k_D = 0.69$ for the same reaction of cyclopentanone and cyclopentanone-d_4, as well as $k_H/k_D = 0.90$ found in the saponification of ethyl acetate and ethyl acetate-d_3, have in fact been justified in just this way;[3] it is also probable that the isotope effects observed in 2,4-dinitrophenylhydrazone formation from acetophenone and acetophenone-α,α,α-d_3 ($k_H/k_D = 0.89$) and propiophenone and propiophenone-α,α-d_2 ($k_H/k_D = 0.89$) and the absence of an isotope effect in the case of propiophenone and propiophenone-β,β,β-d_3 ($k_H/k_D = 1.00$) have a similar explanation.[4]

Similar hyperconjugative isotope effects can be expected in the reaction of acetone with Grignard reagents. In the case of ambident reagents such as t-butylallylmagnesium bromide, isotope effects on the two different reactions will not in general be of the same magnitude, and application of the Hammond postulate[5] leads to the prediction that the slower process with the later transition state will show the stronger effect. The present reaction gives less <u>3</u> than <u>4</u>, and it also seems likely that the equilibrium between 1 and 2 lies strongly on the side of 1; these factors combine to make $k_3 << k_4$. Thus, $(k_3)_H/(k_3)_D < (k_4)_H/(k_4)_D$, since both isotope effects are inverse. Rearrangement of this inequality gives $(k_4/k_3)_D < (k_4/k_3)_H$, and multiplication of both sides by K (K = [2]/[3]) leads to $K(k_4/k_3)_D < K(k_4/k_3)_H$ which, since $K(k_4/k_3)$ = [4]/[3], is equivalent to $([4]/[3])_D < ([4]/[3])_H$. This, of course, is consistent with the fact that $([4]/[3])_D = 3.1$ and $([4]/[3])_H = 3.4$

These considerations make it unlikely that the isotope effect observed in this reaction is wholly steric in origin. There may, of course, be a steric contribution to the overall effect, and in this regard it is of interest to note that steric and hyperconjugative isotope effects might be distinguished with a less crowded ambident Grignard reagent, perhaps i-propylallylmagnesium bromide, for which k_3 would be greater than k_4.[6] With such a reagent, steric isotope effects would still lead to more reaction of deuterated than undeuterated substrate at the more hindered site, and $([4]/[3])_D$ would remain less than $([4]/[3])_H$. The formation of 3, however, would now be the faster reaction, and, for a hyperconjugative isotope effect operating in accord with the Hammond postulate, $(k_3)_H/(k_3)_D > (k_4)_H/(k_4)_D$, or $K(k_4/k_3)_D > K(k_4/k_3)_H$ and $([4]/[3])_D > ([4]/[3])_H$, which is opposite to the result predicted for a purely steric isotope effect.

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6) In order to show that $k_3 > k_4$, K, as well as [4]/[3], would have to be determined.