

Primary Kinetic Hydrogen Isotope Effects in Hydride Transfer: *ab initio* MO and Experimental Studies

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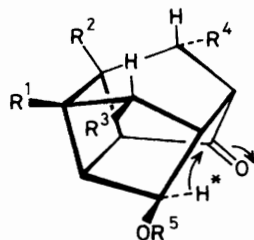
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Measurement of the primary kinetic hydrogen isotope effects for the intramolecular migration of hydride from alcohol methine to ketonic carbonyl in hydroxy-ketones and their interpretation using *ab initio* MO calculations show good agreement between theory and experiment.

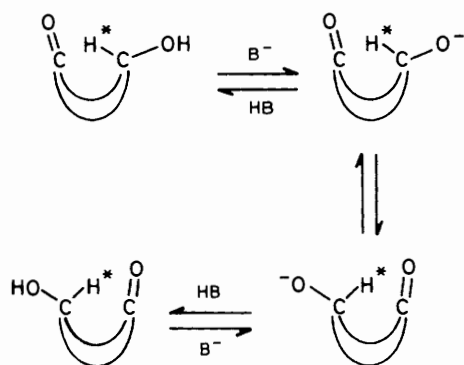
Hydride ion transfers between electron deficient carbon are important in areas of chemistry as diverse as enzymic redox processes involving the nicotamide co-factors,¹ and the industrial catalytic cracking where transfer occurs between cationic centres in hydrocarbons.² The potential of the primary kinetic isotope effect (k.i.e.) associated with the migrating hydrogen in characterising the transition state is acknowledged,³ with comparison being made between experimental values and those calculated with various

assumptions of transition state geometry and force constant behaviour.⁴ *Ab initio* MO calculations have also been carried out for some idealised model systems,⁵ and have led to the conclusion that non-linearity of the [C-H-C] array is not an intrinsic feature of the hydride transfer process.

In an attempt to bridge the gap between 'accurate' calculation on small models, and empirical calculations on observable systems, we here report experimental measurement of hydrogen k.i.e. for rearrangements of (**1a**) to give



- (1a) $R^1 = \text{Me}; R^2, R^3, R^4, R^5 = \text{H}$
 (1b) $R^2 = \text{Me}; R^1, R^3, R^4, R^5 = \text{H}$
 (2a) $R^3 = \text{Me}; R^1, R^2, R^4, R^5 = \text{H}$
 (2b) $R^4 = \text{Me}; R^1, R^2, R^3, R^5 = \text{H}$
 (3) $R^1, R^2 = \text{H}; R^3, R^4 = \text{Me}; R^5 = \text{Na}$
 (4) $R^1, R^2, R^3, R^4 = \text{H}; R^5 = - \text{ve charge}$



Scheme 1. Base-induced rearrangement of hydroxy-ketones by intramolecular hydride transfer.

(1b), (2a) to give (2b) under specific aqueous base catalysis,⁶ and for the degenerate rearrangement of the sodium salt of (3) in [²H₆]dimethyl sulphoxide (DMSO) solution.⁷ All involve long range migration of hydride, H*, between the oxygen-bearing carbons as outlined in Scheme 1.

The reactions of (1a) and (2a) were monitored by conventional sampling and analysis giving second order rate constants at 1.2×10^{-2} and $4.4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ respectively, in 50% v/v aqueous dioxane at 25 °C. For (2a), the reaction proceeds to completion, but (1a) yields an equilibrium mixture [$K = 1.84 (\pm 0.03)$ at 25 °C], whose composition is unaffected by replacement of the migrating hydrogen by deuterium. For the reaction of (3) (Na), the k.i.e. was determined by line shape analysis of the methyl signals of the proton n.m.r. spectra of mixtures of known composition (*ca.* 50 : 50) of the salts of the isotopomers. This method is only capable of providing rate ratios with any degree of reliability between coalescence points for the signals of the components of the solution.† The strong concentration dependence of the observed rates of these salts⁷ was used to obtain coalescence behaviour at a range of temperatures. The data are collected in Table 1.

Ab initio MO calculations were carried out on the demethylated anionic form, (4), of the experimental substrates. An

† Values of $k_{\text{H}}/k_{\text{D}}$ were obtained by non-linear least squares fit to the experimental spectra of summed contributions from the two components, using $k_{\text{H}}/k_{\text{D}}$ as an adjustable parameter, and confirmed by visual comparison of experimental and calculated spectra. See ref. 7 for details of the spectra of (3).

Table 1. Experimentally determined primary hydrogen k.i.e.s for rearrangement of (1a), (2a), and (3a).

Substrate	$T/^{\circ}\text{C}$	$k_{\text{H}}/k_{\text{D}}$
(1a)	17.2	$3.71(\pm 0.09)^{\text{a}}$
	27.3	$3.56(\pm 0.07)$
	40.0	$3.37(\pm 0.04)$
	54.9	$3.27(\pm 0.04)$
	69.7	$3.10(\pm 0.08)$
(2a)	14.8	$3.64(\pm 0.07)^{\text{a}}$
	25.0	$3.40(\pm 0.20)$
	40.0	$2.92(\pm 0.14)$
	49.9	$2.71(\pm 0.11)$
	69.7	$2.56(\pm 0.09)$
(3a)	32	$2.76(\pm 0.23)^{\text{b}}$
	63	$2.52(\pm 0.19)$
	86	$2.36(\pm 0.19)$

^a These are the means and standard deviations of three pairs of determinations. ^b These are the means and standard deviations of determinations from within 3 °C on either side of the reported temperature.

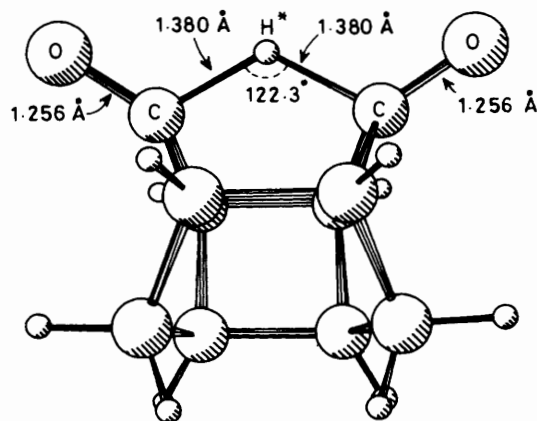


Figure 1. Details of the STO-3G computed transition state for the rearrangement of (4).

STO-3G basis set⁸ was employed, with complete geometry optimization of both reactant and transition state using analytic energy gradients.⁹ The transition state was characterised as such by determination of harmonic frequencies using analytic second derivatives¹⁰ when a single imaginary frequency was found. It exhibited C_s symmetry and details of its geometry are shown in Figure 1. The calculated frequencies were scaled by 0.83 and the semi-classical k.i.e. was computed at a number of temperatures, within the ideal gas, rigid rotor, harmonic oscillator approximation, with corrections for quantum mechanical tunnelling using Bell's model approximation.¹¹ The results are summarised in Table 2.

The correspondence between theory and experiment is encouraging in view of the minimal basis set gas phase calculations performed. The calculated barrier height, $18.5 \text{ kcal mol}^{-1}$ ($1 \text{ kcal} = 4.184 \text{ kJ}$), compares very well with the Arrhenius activation energy of $20.5 (\pm 0.2) \text{ kcal mol}^{-1}$ for the rearrangement of (1a), especially after adjustment is made for the acid-base equilibrium preceding anionic hydride transfer. For (2a), the experimental value, $14.9 (\pm 0.6) \text{ kcal mol}^{-1}$, is rather low and possibly accounted for by relief of the ground

Table 2. Calculated reaction parameters for rearrangements of (4).^a

Barrier height	18.5 kcal mol ⁻¹ ^b
Imaginary frequencies (ν_H and ν_D)	933 and 788 cm ⁻¹
$T/^\circ\text{C}$	k_H/k_D
0	4.76(2.90 × 1.64)
25	3.84(2.67 × 1.44)
50	3.31(2.49 × 1.33)
75	2.95(2.34 × 1.26)

^a The quantities in parentheses are the semi-classical k.i.e.s, and the calculated tunnel correction. ^b 1 kcal = 4.184 kJ.

state steric compression between the hydroxy group function and the pendant methyl group. Rearrangement of (3) in DMSO, in the presence of metal complexing agents is the closest approach we have to the 'gas phase' data of the calculation.¹² The experimental estimate is then 12.0 kcal mol⁻¹, and again, this low barrier can be attributed to the presence of the pendant methyl groups in the experimental substrate.

The calculated primary hydrogen isotope effects are small for a symmetrical transition state, reflecting the qualitative tightness of the hydride transfer process. A relatively large (40% at 25 °C) contribution is expected from quantum mechanical tunnelling. In this, it seems that the inter- and intra-molecular processes are similar.⁵ For the degenerate rearrangement of (3), experimental k.i.e.s are rather less than those calculated, but agreement between theory and experiment is quite good if the tunnelling correction is removed. As noted above, this experiment is the closest approach we have to the 'gas phase' of the calculation, and it is possible that tunnelling is reduced under solution conditions. Certainly, the activation parameter ratios ($A_H/A_D = 0.98$, and $[\Delta E]_D^H = 0.63$ kcal mol⁻¹) are not consistent with extensive tunnelling.

The k.i.e.s in the rearrangements of (1a) and (2a) are not directly comparable with the calculations, since they contain a secondary isotope effect on the acid-base equilibrium preceding anionic hydride transfer. A value of $K_{\beta H}/K_{\beta D} = 1.22$ at 25 °C has been reported for the deprotonation of methanol at the scaled STO-3G level¹³ and if this is combined

with our calculated k_H/k_D value, k.i.e.s of 4.68, or 3.26 without tunnelling correction, are obtained for rearrangement of the alcohol of (4). Again, there is better agreement between experiment and theory without application of tunnelling correction. The Arrhenius parameters for (1a) ($A_H/A_D = 1.18$, and $[\Delta E]_D^H = 0.66$ kcal mol⁻¹) show no unusual features, but interestingly, the data for (2a) yield values ($A_H/A_D = 0.37$ and $[\Delta E]_D^H = 1.34$ kcal mol⁻¹) in the range associated with the intervention of tunnelling, when found in single step reactions. Clearly there is a point of interest here, and experiments continue.

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