

Isotope Effects in Kinetic Enolate Formation from 2-Pentanone and 2-Pentanone-1,1,1-d₃

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This paper is dedicated to Professor Jacob Bigeleisen on the occasion of his 70th birthday

2-Pentanone and 2-pentanone-1,1,1-d₃ were treated with three-fold excesses of lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF) with and without hexamethylphosphoric triamide (HMPA, 3 mol per mol of base) at temperatures ranging from 24 to –70 °C. The deuterium kinetic isotope effects calculated from the product ratios (measured by GLC as trimethylsilyl enol ethers) showed a range of temperature dependences: none (LDA in THF), attenuated with $A_H/A_D = 2.53$ (LHMDS in THF), and normal with $A_H/A_D \sim 0.6$ indicating moderate tunneling (LDA and LHMDS in THF-HMPA). The variation in temperature dependence is attributed to reaction via multiple base species in which HMPA affects the equilibria between the base species.

Key words: Isotope Effects, Kinetic Enolates, Temperature Dependence, Lithium Dialkylamide Bases

Introduction

It has long been recognized that the temperature dependence of an isotope effect gives more useful information than the magnitude of the effect at a single temperature. Application of the transition state theory of isotope effects [1] to hydrogen transfer reactions leads to the conclusion that most of the effect will normally reside in the exponential term of the Arrhenius equation [2]. The preexponential factor, A_H/A_D , will usually be close to unity. In the absence of tunneling, it must remain in the range 0.5–1.4. The lower limit results when bending vibrations of the A–H–B transition state approach a frequency of zero, an unlikely physical situation. The upper limit should be observed only at very high temperatures.

Model calculations confirm these general predictions. Stern and Weston found A_H/A_D to remain in the range 0.7–1.3 in the absence of tunneling [3]. Models for elimination reactions give still narrower limits, 0.8–1.2, with most of the values between 0.9–1.1 [4]. Tunneling can cause A_H/A_D values well below any of these lower limits [2–5], but values above 1.2–1.3 should never be observed for simple one-step hydrogen transfers at temperatures near ambient.

While abnormally large values that cannot be attributed to experimental uncertainty are not common, significant numbers of apparently reliable A_{aH}/A_{aD} [6] values greater than 1.4 are to be found in the literature. In some cases the isotope effects are even temperature independent over the range of temperatures studied; $k_H/k_D = A_{aH}/A_{aD}$. The late Harold Kwart reported a number of such cases and suggested that a temperature-independent k_H/k_D was diagnostic of nonlinear hydrogen transfer [7]. Others have pointed out that there is no theoretical justification for this proposal, and extensive calculations of deuterium isotope effects for different angles of hydrogen transfer failed to find any that were temperature independent [8].

There remains the problem of finding a cause or causes for the experimental observations. One possible cause is mechanistic complexity. If two or more steps affect the overall rate of reaction, or if two or more reactions lead to the same product, the Arrhenius parameters will be composite values, and no a priori limits can be set on their magnitudes. A possible example of the former effect is found in eliminations from certain fluorinated substrates, where A_{aH}/A_{aD} values of 1.5–4.8 are reported [9]. These reactions may involve a hydrogen-bonded carbanion which can return to substrate as well as go on to product (internal return) [10]. A model of two competing reactions

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giving the same product has been shown to be capable of generating abnormal Arrhenius parameters [11], but at the time no identifiable examples of the phenomenon were known.

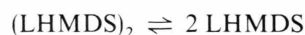
Recently $A_{\text{aH}}/A_{\text{aD}}$ values as high as 3.25 have been found for the deprotonation of 2-methyl-3-pentanone and its α -deuterated analogs by lithium diisopropylamide (LDA) in tetrahydrofuran (THF) [12]. When hexamethylphosphoric triamide (HMPA) is added, the $A_{\text{aH}}/A_{\text{aD}}$ values become normal (0.4–1.0). The base is known to exist as an equilibrium mixture of monomer and dimer in THF solution [13], and it was proposed that both species contributed in varying proportions to the overall reaction and with different isotope effects, thereby generating abnormal $A_{\text{aH}}/A_{\text{aD}}$ values.

Results and Discussion

The present research was undertaken in order to provide further evidence on the possible role of competing base species in reactions showing abnormal Arrhenius behavior. For this purpose we chose 2-pentanone (**1**) and its **1-d₃** analog as substrates. When these are treated with an excess of lithium dialkylamide base in THF, irreversible generation of a mixture of enolates results. The enolates can be trapped by trimethylsilyl chloride to yield a mixture of the enol ethers **2–4**, which can be analyzed by gas chromatography. The isotope effect is then given by the ratio of the **2**/(**3** + **4**) ratios for **1** and **1-d₃**, on the reasonable assumption that any isotope effect on the formation of

3 and **4** will be negligibly small. Sample product ratio data for LDA in THF between 0 and -60°C are shown in Table 1. Overall yields are excellent, and the product ratios are reproducible to a precision of a few percent.

The reaction was also run with lithium hexamethyldisilazide (LHMDS) as base. The equilibrium constant for



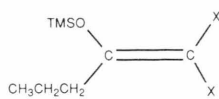
has been measured over a range of temperatures, and the proportion of the dimer found to increase with increasing temperature [14]. We hoped that this more thoroughly investigated base might give results that were easier to interpret. With both LHMDS and LDA, reactions were run with and without added hexamethylphosphoric triamide (HMPA). Literature data indicate that HMPA can break up ion-pair aggregates [15], so our purpose in adding it was to shift the equilibrium between the base species toward the monomer.

The resulting isotope effects are shown in Table 2. The temperature independence of $k_{\text{H}}/k_{\text{D}}$ in the reaction with LDA in THF is immediately obvious. Less obviously, the temperature dependence of $k_{\text{H}}/k_{\text{D}}$ in the reaction with LHMDS in THF is also abnormal, with $A_{\text{aH}}/A_{\text{aD}} = 2.53$ (Table 3). When HMPA is added to both reaction mixtures the temperature dependence of $k_{\text{H}}/k_{\text{D}}$ becomes normal, with $A_{\text{aH}}/A_{\text{aD}}$ near 0.6, a value that may indicate modest tunneling. The results thus

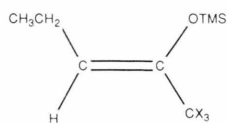


1, X=H

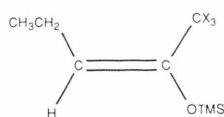
1-d₃, X=D



2



3



4

Table 1. Products from the enolization of 2-pentanone-1,1,1- X_3 by lithium diisopropylamide in tetrahydrofuran ^{a,b}

Temp. $^\circ\text{C}$	X	2 /(3 + 4) ^c	3/4 ^c	Yield, % ^c
0.0	H	7.85 ± 0.10	0.195 ± 0.005	92.4 ± 2.1
	D	2.76 ± 0.03	0.191 ± 0.004	87.7 ± 4.8
-16.0	H	7.84 ± 0.23	0.181 ± 0.005	88.3 ± 0.8
	D	2.72 ± 0.02	0.178 ± 0.005	89.3 ± 2.0
-30.0	H	7.62 ± 0.02	0.172 ± 0.002	91.0 ± 3.1
	D	2.65 ± 0.02	0.161 ± 0.001	88.2 ± 3.7
-45.0	H	7.35 ± 0.11	0.156 ± 0.003	89.1 ± 1.7
	D	2.56 ± 0.01	0.148 ± 0.001	95.5 ± 2.9
-60.0	H	7.07 ± 0.05	0.148 ± 0.001	92.4 ± 1.9
	D	2.47 ± 0.01	0.130 ± 0.004	87.4 ± 3.7

^a Base: ketone **3**: **1**.

^b Product determination by treatment of enolate mixture with trimethylsilyl chloride followed by GLC analysis. Yield by internal standard.

^c Each result is the average of 2–3 independent runs. Deviations are standard deviations.

Table 2. Isotope effects in the enolization of 2-pentanone-1,1,1-d₃ by strong bases.

Temp. °C	k_H/k_D under Conditions ^a			
	1 ^b	2 ^c	3 ^d	4 ^e
24.0	—	—	10.55 ± 0.04	—
0.0	2.84 ± 0.05	4.45 ± 0.09	12.27 ± 0.33	13.29 ± 0.12
−15.0	—	4.95 ± 0.20	—	15.70 ± 0.06
−16.0	2.88 ± 0.09	—	—	—
−30.0	2.87 ± 0.02	5.56 ± 0.01	15.50 ± 0.15	—
−33.5	—	—	—	19.37 ± 0.48
−45.0	2.88 ± 0.05	6.50 ± 0.10	16.11 ± 0.43	—
−45.5	—	—	—	22.34 ± 1.10
−60.0	2.87 ± 0.03	—	—	32.66 ± 0.43
−62.0	—	7.93 ± 0.14	—	—
−70.0	—	—	20.90 ± 0.65	—

^a All reaction carried out in tetrahydrofuran (THF) solutions ca. 0.05 M in ketone and 0.15 M in base. When hexamethylphosphoric triamide (HMPA) was used, it was ca. 0.45 M.

^b Base was lithium diisopropylamide (LDA).

^c Base was LDA, HMPA added.

^d Base was lithium hexamethyldisilazide (LHMDS).

^e Base was LHMDS, HMPA added.

reinforce the pattern previously observed with 2-methyl-3-pentanone and LDA [12].

It is interesting that the isotope effects vary widely in magnitude, particularly at the lower temperatures. The difference between LDA and LHMDS can be accounted for by the difference in pK_a values of their conjugate acids, 35.7 for LDA and 25.8 for LHMDS [16, 17]. Thus LDA is a much stronger base, and is consequently expected to react via a more reactant-like transition state than is LHMDS. The pK_a of the conjugate acid of LHMDS is close to the pK_a 's of aliphatic ketones [18], so a central transition state with a large k_H/k_D is to be expected. It must be kept in mind, however, that neither the reaction with LDA nor that with LHMDS involves a single, simple base species. Some part of the difference in k_H/k_D values may well arise from different proportions of reaction via the different base species under the two sets of conditions.

Evidence that this is probably the case is afforded by the increase in k_H/k_D observed for both the LDA and LHMDS reactions when HMPA is added. If HMPA increases the proportion of monomeric base [15], this result would suggest that the monomer reacts with a larger isotope effect than the dimer. It should be kept in mind, however, that the proportion of reaction via different paths will depend on the relative concentrations of the different reactant species

Table 3. Arrhenius parameters for isotope effects in the enolization of 2-pentanone-1,1,1-d₃ by strong bases.

Conditions ^a	A_{aH}/A_{aD}	$E_{aD} - E_{aH}$
1	2.78 ± 0.080	0.015 ± 0.014
2	0.614 ± 0.029	1.070 ± 0.022
3	2.53 ± 0.29	0.852 ± 0.055
4	0.605 ± 0.178	1.663 ± 0.140

^a See footnotes a–e of Table 2.

Table 4. Tunnel corrections to the isotope effects for the enolization of 2-pentanone-1,1,1-d₃ by strong bases^a.

Conditions ^b	k_H/k_D ^c	Q_{tH}/Q_{tD}	$(k_H/k_D)_s$ ^d
2	4.41	1.32 ± 0.04	3.37
4	12.95	1.33 ± 0.22	9.81

^a Calculated at 0 °C by fitting the first term of the Bell equation to the observed Arrhenius parameters (Table 3). See Refs. [20, 21].

^b See Table 2, footnotes a, c, and e.

^c Calculated from the Arrhenius parameters (Table 3).

^d The semiclassical (without tunneling) isotope effect.

only when the reactant species are not equilibrating rapidly relative to the rate of reaction. Otherwise, the proportions will depend only on the relative free energies of the respective transition states [19]. We do not know the relative rates of equilibration and reaction in these reactions.

To return to the A_{aH}/A_{aD} values of Table 3, the absence or the attenuation of the temperature dependence observed without HMPA can be explained if the proportion of reaction via the base species that gives the larger k_H/k_D increases with increasing temperature. The normal tendency of k_H/k_D to decrease with increasing temperature will then be partially or wholly counteracted. It is tempting to say that the reactions in the presence of HMPA involve a single base species and a small contribution from tunneling. Whether such a simple situation really obtains is not at all clear.

If the results with HMPA are taken at face value, the observed Arrhenius parameters can be used to estimate tunnel corrections by fitting the first term of the Bell equation to them [20, 21]. The results of such fits are given in Table 4. The tunnel corrections are the same for both bases, even though the k_H/k_D values differ by a factor of ca. 3. The semiclassical (without tunneling) k_H/k_D for the reaction with LHMDS is still rather large, though not unreasonably so. It corresponds, assuming exponential temperature dependence, to a k_H/k_D of 7.8 at 30 °C. Such a value can be

accounted for by zero-point energy effects alone. Even so, it would be wise to reserve judgment in the absence of hard evidence on the number and kinds of base species taking part in the reaction. The isotope effects in the presence of HMPA may still be composite values. Some details of our results, to be discussed in a later publication, suggest that the reactions are complex both with and without HMPA.

Experimental

General. All glassware was dried at 140°C and cooled under dry nitrogen. Syringes and needles were vacuum dried (0.5 torr) for at least 1 h. Low temperatures were achieved in a heavily-insulated 4.5 l bath filled with 99% ethanol and cooled by a Neslab CC-75W Cryocool unit. Ice water was used for 0°C. Product analysis by GLC was done as previously described for the products from 2-methyl-3-pentanone [12].

Solvents and Reagents. Solvents were purified as previously described [12]. 1,1,1,3,3,3-Hexamethyldisilazane (Aldrich) was dried over calcium hydride and distilled immediately prior to use (bp 125°C). Diisopropylamine was purified as before [12].

2-Pentanone-1,1,1- d_3 was prepared by the same general procedure as for the deuterated ketones in reference [12]. Deprotonation of 2-(1-propyl)-1,3-dithiane [22] followed by reaction with methyl- d_3 iodide (Aldrich 99.5% D) according to the procedure of Corey and Seebach [23] gave 2-(1-propyl)-2-methyl-1,1,1- d_3 -1,3-dithiane which was then hydrolyzed according to the procedure of Corey and Erickson [24] to give 2-pentanone-1,1,1- d_3 , purified by preparative GLC on a 10 ft \times 0.25 inch column packed with 30% SF-96 on Chromosorb N-AW; column and reference flow rates 30 and 60 ml min⁻¹, respectively; injector, detector, and column temperatures 150, 150, and 70°C, respectively. ¹H NMR (C₆D₆): δ 0.95 (3H, t),

1.62 (2H, h), 2.42 (2H, t). There was no detectable peak at δ 2.15 (1-CH₃ in the unlabeled ketone).

Trimethylsilyl enol ethers were prepared by the methods of House et al. [12, 25]. They were purified by preparative GLC (see conditions for 2-pentanone above) to give the following products: 1-penten-2-oxytrimethylsilane [26]. ¹H NMR (C₆D₆): δ 0.15 (9H, s), 0.85 (3H, t), 1.50 (2H, m), 2.01 (2H, t), 4.10 (1H, s), 4.17 (1H, s). Z-2-penten-2-oxytrimethylsilane [26]. ¹H NMR (C₆D₆): δ 0.10 (9H, s), 0.95 (3H, t), 1.65 (3H, s), 2.12 (2H, m), 4.42 (1H, t). E-2-penten-2-oxytrimethylsilane [27]. ¹H NMR (C₆D₆): δ 0.14 (9H, s), 0.88 (3H, t), 1.65 (3H, s), 1.87 (2H, m), 4.75 (1H, t).

Enolization of 2-Pentanone and 2-Pentanone-1,1,1- d_3 . The base solution was prepared by adding 8.25–8.70 \times 10⁻⁴ mol of amine to 7.5–8.7 \times 10⁻⁴ mol of *n*-butyllithium in 3.0 ml of THF. This was done at 0°C or below for diisopropylamine. For hexamethyldisilazane the solution was prepared at room temperature and after 5 min heated to 48°C and stirred for 15 min before cooling to the temperature of the reaction for 10 min (the prior warming improved yields and reproducibility). When HMPA was used, 3 mol of HMPA per mol of base was added. Then 2.5 \times 10⁻⁴ mol of ketone in 0.2 ml of THF was added dropwise with stirring (see [12] for details of the experimental procedure). After 10 min the enolates were quenched by adding 1.2 mol of trimethylsilyl chloride per mol of base. The products were analyzed by GLC. A J. & W. Scientific DB-1 (cross-linked silicone) 30 m \times 0.55 mm id fused silica capillary column was used. The column, injector, and detector temperatures were 40, 100, and 150°C, respectively. At 60 psi of He, 30 psi of H₂, and 26 psi of air, retention times were approximately 13 min for 1-penten-2-oxy-trimethylsilane, 15 min for Z-2-penten-2-oxy-trimethylsilane, and 16 min for E-2-penten-2-oxy-trimethylsilane. Toluene (retention time 6 min) was used as an internal standard, and the response factor was 2.101 by weight.

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