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Is the McLafferty Rearrangement of Ketones Concerted or Stepwise? The Application of Kinetic Isotope Effects†

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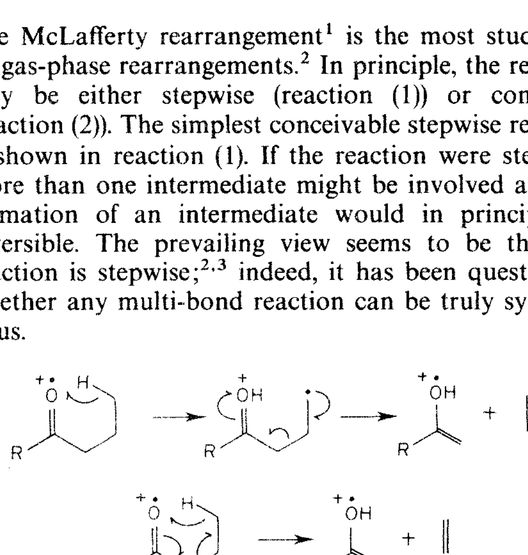
Intramolecular ^{13}C and ^{2}H isotope effects have been measured for unimolecular losses of ethene (the McLafferty rearrangement) from metastable molecular ions of 2-ethyl-1-phenylbutan-1-one, 3-ethylpentan-2-one and heptan-4-one. Primary and secondary deuterium isotope effects are observed at the γ-(terminal) and β-positions, respectively. Large primary ^{13}C isotope effects occur at β-positions and for the γ positions of 3-ethylpentan-2-one and heptan-4-one. The carbon isotope effects in the cases of the doubly isotopically labelled $CH_3COCH(C_2H_5)(^{13}CH_2CH_3)$ and $CD_3COCD(C_2D_5)(^{13}CD_2CD_3)$ are 1.17 (±0.01) and 1.04 (±0.01), respectively. All of these isotope effects are consistent with a stepwise mechanism in which more than one step is rate determining.

INTRODUCTION

The McLafferty rearrangement[1] is the most studied of all gas-phase rearrangements.[2] In principle, the reaction may be either stepwise (reaction (1)) or concerted (reaction (2)). The simplest conceivable stepwise reaction is shown in reaction (1). If the reaction were stepwise, more than one intermediate might be involved and the formation of an intermediate would in principle be reversible. The prevailing view seems to be that the reaction is stepwise;[2,3] indeed, it has been questioned[4] whether any multi-bond reaction can be truly synchronous.


(1)

(2)

The evidence in favour of stepwise mechanisms for McLafferty rearrangements in carbonyl systems is extensive. An early theoretical analysis favoured a stepwise mechanism;[5] more recent calculations have led to the same conclusion.[6,7] An early field ionization kinetics study showed that hydrogen scrambling occurred within tens of picoseconds in a ketone molecular ion with a tertiary carbon at the γ-position, compared with the more usual times of microseconds with a secondary γ-carbon.[8] This difference was explained in terms of the stabilities of what would now be called the distonic ion intermediates of a stepwise mechanism for the McLafferty rearrangement.

The observation[9] by field ionization kinetics that the McLafferty rearrangement of the hexanal molecular ion gave the oxygen-containing ion $[C_2H_4O]^{+\bullet}$ at times of tens of picoseconds but the hydrocarbon ion $[C_4H_8]^{+\bullet}$ at longer times has been rationalized in two different ways. One explanation is in terms of competing reactions of the distonic ion intermediate formed by γ-hydrogen transfer in a stepwise mechanism.[10] The other is that the fast formation of $[C_2H_4O]^{+\bullet}$ is concerted and the slow formation of $[C_4H_8]^{+\bullet}$ is stepwise.[9] Hydrogen equilibration occurring during the elimination of ethene from the *n*-butanoic molecular ion suggested a stepwise process,[11–14] but field ionization kinetic studies cast doubt on this proposal.[15–17] At ion lifetimes $< 10^{-10}$ s, γ-hydrogen transfer and β-bond cleavage are observed. At ion lifetimes $> 10^{-8}$ s, the rearrangement is preceded by hydrogen exchange between the hydroxylic hydrogen and the β- and γ-hydrogens.

A recent study of ionized carboxylic acids has led to the suggestion that perhaps ion-dipole or hydrogen-bonded species are intermediates in McLafferty rearrangements.[18] One of the more compelling pieces of evidence for a stepwise McLafferty rearrangement has recently been provided by Osterheld and Brauman[19] in an infrared multiphoton dissociation of the butyrophenone radical cation. An unexpectedly lower yield of product ion for a shorter laser pulse (the yield would normally depend only on the number of photons and not on their rate of delivery) is consistent with a stepwise mechanism in which the molecular ion is formed

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† This paper is dedicated to Arthur Fry on the occasion of his retirement from the University of Arkansas at Fayetteville.

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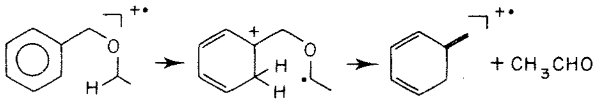
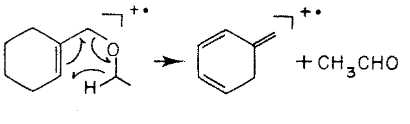
initially and then, when energized, isomerizes to the distonic ion.

The cognate γ-hydrogen rearrangement from ionized benzyl ether has been studied in depth. Again, the reaction can in principle be the stepwise (reaction (3)), concerted (reaction (4)) or still more complicated. Evidence based on heavy-atom and deuterium isotope effect data has been interpreted in terms of a concerted mechanism,[20] but this conclusion was questioned[12] primarily on the grounds that at very long reaction times (and hence low energies) hydrogen scrambling occurred.[21] The peak supposed to evidence scrambling was shown, however, to represent a new, and minor, fragmentation channel, as the same peak appeared with both the undeuterated and the deuterated benzyl ethyl ether.[22] A detailed kinetic analysis of deuterium, oxygen-18 and combined deuterium/oxygen-18 isotope effects using Rice–Ramsperger–Kassel–Marcus (RRKM) theory supported the conclusion that the McLafferty rearrangement in the bis(benzyl ethyl ether) ion is concerted.[22]



(3)



(4)

In the latest study[23] of the McLafferty rearrangement of the benzyl ethyl ether ion, a stable distonic ion with the structure of the expected intermediate has been formed by an ion–molecule reaction, and it has been shown that there is an energy barrier to the isomerization of this distonic ion to the benzyl ether ion. The existence of such an energy barrier provides a possible explanation for the absence of scrambling in the McLafferty rearrangement.[22] This picture[23] of the benzyl ethyl ether ion system does not, however, readily explain the isotope effects data,[20,22] because a small barrier to dissociation would be expected to give an inverse isotope effect (ratio <1) for $CH_3CH^{16}O/CH_3CH^{18}O$ loss, whereas a normal isotope effect was found experimentally.[20,22] The isotope effect data has been explained in this most recent study[23] on the basis of the intervention at low energies of an ion–molecule complex, within which the cyclohexadiene-type ion isomerizes to a toluene ion. Thus the suggestion[23] is that the measured $^{16}O/^{18}O$ isotope effects[20,22] do not arise purely in the McLafferty rearrangement, but reflect isotope effects arising in an unspecified manner from intervention of an ion–molecule complex at low energies.

Intramolecular isotope effects in unimolecular reactions of ions represent an effective means of elucidating transition-state properties, although detailed kinetic analysis using RRKM or comparable rate theory tends to be necessary in order to extract reliable information. Kinetic isotope effects for gaseous ions are more sensitive, and potentially more powerful, probes of reaction dynamics[24] than solution effects,[25] but their interpretation is less straightforward and more challenging. The magnitudes of these gaseous isotope effects span far greater ranges than comparable isotope effects on solution reactions, and the guidelines established in solution chemistry as to sizes of isotope effects for given types of reactions are in general not directly relevant for gaseous ions. In particular, the simple criteria proposed by Knowles and co-workers[26] for enzyme reaction in solution to distinguish between a concerted reaction and a stepwise reaction in which both steps are rate determining on the basis of double isotope labelling are not in general relevant to isotope effects on unimolecular reactions of gaseous ions. The BEBOVIB IV[27] program is similarly inappropriate for the study of isolated ions.

Intermolecular isotope effects in unimolecular reactions of gaseous ions cannot necessarily be interpreted with confidence because observed effects are influenced by and often dominated by internal energy deposition effects.[24]

In this paper, we describe the use of ^2H, ^{13}C and double $^2H/^{13}C$ isotope effects to probe the McLafferty rearrangements of the 3-ethylbutyrophenone, 3-ethylpentan-2-one and heptan-4-one molecular ions.

RESULTS AND DISCUSSION

The γ-hydrogen rearrangement of butyrophenone systems

The first study of deuterium isotope effects in the McLafferty rearrangement was reported by MacLeod and Djerassi.[28] Decompositions occurring in the ion source were measured and low values were found for the kinetic isotope effect for the transferring γ-hydrogen. The decomposing ions, in general, would have been expected to have energies well in excess of the threshold for reaction. In the work described here, the peak-area ratios of appropriate metastable (unimolecular) ions were measured and used to determine H/D and $^{12}C/^{13}C$ values. The first system studied was butyrophenone (**1**); labelled compounds **2**–**8** were prepared. Butyrophenone was chosen because it was believed that hydrogen scrambling reactions (which often accompany the MacLafferty rearrangement of aliphatic ketones) would be minimal in this system.

$C_6H_5COC_3H_7$ **1**

$C_6H_5COCD_2CH_2CH_3$ **2**

$C_6H_5COCH_2CD_2CH_3$ **3**

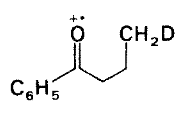
$C_6H_5CO(CH_2)_2CD_3$ **4**

$C_6H_5CO(CH_2)_2CH_2D$ **5**

$C_6D_5COC_3H_7$ **6**

$C_6H_5COCH_2{}^{13}CH_2CH_3$ **7**

$C_6H_5CO(CH_2)_2{}^{13}CH_3$ **8**



a

H/D = 1.81 ± 0.02

The unimolecular losses of variously labelled ethenes from the metastable molecular ions of **1**–**8** show the loss of ethene to be completely specific: no H or C scrambling accompanies the γ-hydrogen rearrangement. The deuterium isotope effect for **5**, measured using the unusually large research mass spectrometer (MMM), was 1.81. Measurement of intermolecular isotope effects, either deuterium or ^{13}C (e.g. comparing the metastable losses of C_2H_4 and $^{12}C^{13}CH_4$ from the molecular ions of **1** and **8**, respectively) gave, as expected,[24] results which could be interpreted either in terms of kinetics or in terms of internal energy deposition effects. In the condensed phase, measuring rate constants *k* (or some function of *k*) independently for the labelled and unlabelled compounds is the classical method.[25]

Intramolecular isotope effects needed to be measured in order to probe the kinetics of the McLafferty rearrangement free from the masking interference of internal energy differences, i.e. a symmetrical molecule with two side-chains must be built, one labelled and the other unlabelled, so that direct comparison of two metastable losses may be made from the same decomposing molecular ion.

In order to measure intramolecular isotope effects for loss of ethene from a butyrophenone system, compounds **9**–**17** were prepared. Metastable ratios for this system were measured using MMM. In one respect, this was a good system to study, since the spectra of **10**, **11**, **14** and **15** showed specific loss of the appropriate labelled ethene: no H or C scrambling accompanied the γ-hydrogen rearrangement.

$C_6H_5COCH(C_2H_5)_2$
9

$C_6D_5COCH(C_2H_5)_2$
14

$C_6H_5COCH(CD_2CH_3)_2$
10

$C_6H_5COCH(CH_2{}^{13}CCH_3)_2$
15

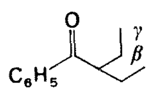
$C_6H_5COCH(CH_2CD_3)_2$
11

$C_6H_5COCH(C_2H_5)({}^{13}CH_2CH_3)$
16

$C_6H_5COCH(C_2H_5)(CD_2CH_3)$
12

$C_6H_5COCH(C_2H_5)(CH_2{}^{13}CH_3)$
17

$C_6H_5COCH(C_2H_5)(CH_2CD_3)$
13



b

γ:	H/D	1.75 ± 0.05
	$^{12}C/^{13}C$	1.01 ± 0.02
β:	H/D	1.16 ± 0.05
	$^{12}C/^{13}C$	1.04 ± 0.02

In other respects, the system was not so satisfactory. The kinetic energy release produced overlapping peaks which were difficult to measure accurately. Results are shown alongside formula *b*. There is a moderate deuterium kinetic isotope effect at the γ-position and a smaller deuterium isotope effect at the β-position. It was not possible to say whether there was a ^{13}C isotope effect at the γ-position, but there was a small ^{13}C effect at the β-position. There would have been a mass discrimination in transmission efficiency of about 1% so the measured isotope effect of 1.01 for the γ-position would be 1.00 after correction for this effect (see Experimental). It was clear that for double isotope labelling experiments it would be desirable to find another system, where the peaks were better separated and preferably one which showed larger isotope effects.

Pentanones and heptanones

With aliphatic ketones, hydrogen scrambling will compete with the γ-hydrogen rearrangement, but the carbon skeleton may remain intact making the ^{13}C isotope effects potentially meaningful. The methyl analogue **18** of **9** and the labelled compounds **19**–**28** were prepared. Results are summarized alongside formula *c*. Metastable ratios were measured using both MMM and the ZAB for this series.

$CH_3COCH(C_2H_5)_2$
18

$CH_3COCH(C_2H_5)(C_2D_5)$
24

$CD_3COCD(C_2H_5)_2$
19

$CH_3COCH({}^{13}CH_2CH_2)_2$
25

$CH_3COCH(CD_2CH_3)_2$
20

$CH_3COCH(CH_2{}^{13}CH_3)_2$
26

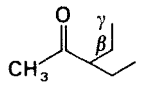
$CH_3COCH(CH_2CD_3)_2$
21

$CH_3COCH(C_2H_5)({}^{13}CH_2CH_3)$
27

$CH_3COCH(C_2H_5)(CD_2CH_3)$
22

$CH_3COCH(C_2H_5)(CH_2{}^{13}CH_3)$
28

$CH_3COCH(C_2H_5)(CH_2CD_3)$
23



c

		MMM	ZAB
β:	H/D	4.0 ± 0.5	2.8 ± 0.2
	$^{12}C/^{13}C$	1.17 ± 0.01	1.10 ± 0.01
γ:	H/D	2.9 ± 0.3	1.5 ± 0.2
	$^{12}C/^{13}C$	1.26 ± 0.01	1.17 ± 0.01

Hydrogen scrambling was indeed a problem with this system: analysis of all deuterated derivatives indicated ~30% of γ-hydrogen scrambling for measurements made using MMM and ~10% with the ZAB. Hydrogen scrambling in ketone molecular ions is manifested to greater degrees as longer reaction times are considered.[29] The larger scale (by a factor of 3) of MMM compared with the ZAB means that at the same accelerating potential the reaction times probed are longer (by a factor of $\sqrt{3}$) for any given ion. However, deutrium isotope effects for the various losses of ethene were very high: there appeared to be both a pronounced primary γ-effect and a large secondary deuterium effect at the β-position.

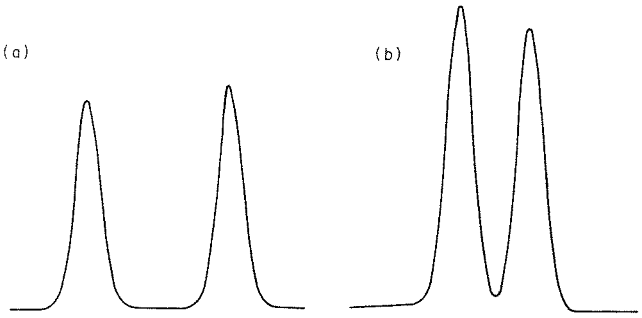


Figure 1. Metastable peaks for losses of C_2H_4 and $^{12}C^{13}CH_4$ from the molecular ions of (a) $CH_3COCH(C_2H_5)(CH_2{}^{13}CH_3)$ (measured on MMM; loss of $^{12}C^{13}CH_4$ is the left-hand peak) and (b) $C_3H_7COCH_2CH_2{}^{13}CH_3$ (measured on the ZAB; loss of $^{12}C^{13}CH_4$ is the right-hand peak). The transitions measured are *m/z* 115 → 86 and *m/z* 115 → 87 in both (a) and (b); resolution is higher in the case of MMM.

Measured peak ratios were consistently higher for MMM than those determined using the ZAB. This is a consequence of the longer flight times, which in turn mean that the decomposing ions have lower internal energy ranges, and hence higher isotope effects are observed.[24] The molecular ions of **25** and **26** specifically eliminated $^{12}C^{13}CH_4$: the carbon skeleton remains intact during loss of ethene. The metastable peaks were well resolved (see Fig. 1(a) for the peaks for **27** measured with MMM), and large primary ^{13}C isotope effects were observed at β- and γ-positions, with the γ-effect being the smaller (cf. data for *b*). A small loss of $C_2H_5^{\bullet}$ co-occurred with loss of C_2H_4 from $[CH_3COCH(C_2H_5)_2]^+$ $((-C_2H_4):(-C_2H_5) = 100:5$ (MMM) or $100:2$ (ZAB)). The loss of C_2H_5 must be subtracted from the overall loss of 29 u, consequently giving a slightly larger isotope effect than, for example, that visually apparent in Fig. 1(a).

Finally in this series, the symmetrical ketone **29** was studied together with its labelled derivatives **30**–**38**. Isotope effects for these compounds were measured only with the ZAB; results are listed alongside formula *d*.

$C_3H_7COC_3H_7$
29

$C_3H_7COCH_2CH_2CD_3$
34

$C_2H_5CD_2COCD_2C_2H_5$
30

$CH_3{}^{13}CH_2CH_2COCH_2{}^{13}CH_2CH_3$
35

$CH_3CD_2CH_2COCH_2CD_2CH_3$
31

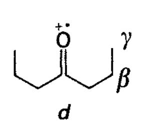
$^{13}CH_3CH_2CH_2COCH_2CH_2{}^{13}CH_3$
36

$CD_3CH_2CH_2COCH_2CH_2CD_3$
32

$C_3H_7COCH_2{}^{13}CH_2CH_3$
37

$C_3H_7COCH_2CD_2CH_3$
33

$C_3H_7COCH_2CH_2{}^{13}CH_3$
38



d

γ:	H/D	2.3 ± 0.4
	$^{12}C/^{13}C$	1.08 ± 0.01
β:	H/D	1.6 ± 0.2
	$^{12}C/^{13}C$	1.06 ± 0.01

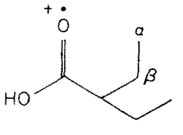
Again there was γ-hydrogen scrambling: careful examination of **30** to **34** indicated about 25% scrambling with estimated γ- and β-deuterium effects of 2.3 and 1.6, respectively. The spectra of **35** and **36** showed specific loss of $^{12}C^{13}CH_4$; again the carbon skeleton remained intact. Both γ- and β-^{13}C primary kinetic isotope effects were noted, and metastable peaks were reasonably well resolved with the ZAB (see, e.g., Fig. 1(b) for the losses of C_2H_4 and $^{12}C^{13}CH_4$ from the molecular ion of **38**).

From the results for systems *b*, *c* and *d*, it can be concluded that there are (i) primary deuterium isotope effects operating at the γ-positions and smaller secondary deuterium isotope effects operating at the β-positions and (ii) primary ^{13}C isotope effects at the γ-positions (with the exception that there is no γ-effect in *b*) and larger primary ^{13}C isotope effects at the β-positions. All of these effects are normal, i.e. the reaction involving the lighter isotope is the more probable in all cases.

These isotope effects are consistent both with a concerted mechanism and with a stepwise mechanism in which more than one step is kinetically significant. With a concerted mechanism, weakened bonding in the transition state for the γ-H (or D) and weakened bonding in the transition state for the β-C could be expected to give rise to a normal deuterium isotope effect at the γ-position and a normal ^{13}C isotope effect at the β-position. The implication in the case of the γ-H (or D) would be that the loss of bonding with the γ-C outweighs any gain in bonding with the O atom. Similarly with the β-C, loss of bonding to the α-C would outweigh any gain from development of a double bond with the γ-C. The normal deuterium isotope effect at the β-position would be explained by the changes in bonding as the hybridization at that position moves from sp^3 to sp^2. The normal ^{13}C isotope effect at the γ-position would be attributed to weakened bonding in the transition state due to the partial C—H cleavage, offset but not cancelled (in most cases) by stronger bonding with the β-C. Such changes in bonding can be translated into changes in frequencies of normal modes of vibration, hence changes in zero-point energies and hence changes in critical energies for reactions giving rise to the isotope effects.

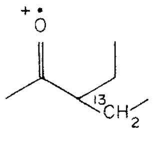
Essentially the same explanation can be applied in the case of a stepwise mechanism with more than one kinetically significant step. Considering the simple stepwise mechanism (reaction (1)), weakened bonding for the γ-H (or D) in the first step would lead to the deuterium isotope effect at the γ-position. Weakened bonding for the β-C in the second step would lead to the ^{13}C isotope effect at the β-position. The deuterium isotope effect at the β-position would arise in the second step. The ^{13}C isotope effect at the γ-position would be the sum of two contributions, one from the first step and the other from the second step. One approach to distinguishing the concerted mechanism from the so-called 'twin hump' stepwise mechanism, which we have used previously,[20,22] is to study the effects of deuteration on a heavy atom isotope effect, i.e. double isotope effects.

Detailed experimental investigations of a variety of ^{2}H- and ^{13}C-labelled derivatives of 2-ethylbutanoic acid have established that equilibrium of γ- and carboxyl hydrogens precedes (or accompanies) the loss of ethene from the butanoic acid molecular ion.[11–14] If equilibration of the two designated hydrogens in *e* occurred and there were ^{2}H and ^{13}C isotope effects, the mechanism for ethene loss would presumably be stepwise with two kinetically significant steps. Perversely, the molecular ion of *e* eliminates C_2H_5 to a much larger extent than ethene, making the measurement of the appropriate peak areas inaccurate and unreliable. The loss of $C_2H_5^{\bullet}$ is a rearrangement reaction.[28]



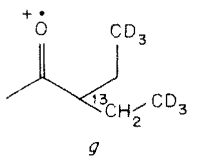
e

Ideally, the ^{12}C/^{13}C isotope effects for the losses of variously labelled ethenes from *f* and *g* would be compared. The loss of $C_2H_5^{\bullet}$ in the 3-ethylpentan-2-one system is negligible. The isotope effect for *f* is 1.17 (ZAB). In *g* there are two CD_3 groups. If the reaction were stepwise, the primary deuterium isotope effect should increase the kinetic significance of the first step for *g* (i.e. D transfer) and thereby decrease the kinetic significance of the second step (i.e. labelled ethene loss). Thus, for a stepwise process ^{12}C/^{13}C for *g* should be less than 1.17. For practical reasons, we synthesized the neutral ketone precursor **39** to *h*; the isotope effect ($-C_2D_4 : -{}^{12}C^{13}CD_4$) was measured as 1.06 (ZAB). Unfortunately, this value is inaccurate because of a small amount of H/D scrambling. To overcome this problem, we synthesized the ketone precursor **40** to *i*; the ^{13}C isotope effect for *i* was 1.04 ± 0.01 (ZAB). The fall from 1.17 ± 0.01 to 1.04 ± 0.01 on perdeuteration is dramatic and clear; cf. the change in the ^{16}O/^{18}O isotope effect on deuteration of the bis(benzyl ethyl ether) from 1.09 ± 0.07 to 1.06 ± 0.05.[22] These carbon isotope effects for the ketone are consistent with a stepwise mechanism, in which there is a kinetically significant barrier for more than one step. Qualitatively, however, this fall in the ^{13}C isotope effects is also consistent with a concerted mechanism. In a concerted process, replacing H by D (*i* compared with *f*) would be expected to raise the critical energy for a reaction. Consequently, those ions decomposing in the time window the experiment would have more internal energy and higher critical energies (in the case of the perdeuterated isotopomer), and hence the isotope effect would be smaller.[24]



f

(^{12}C / ^{13}C = 1.17 ± 0.01)



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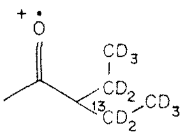

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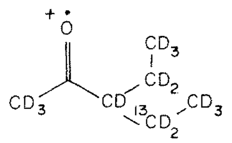

i

(^{12}C/^{13}C = 1.04 ± 0.01)

number of types of stepwise mechanism. A facile γ-hydrogen transfer to form the distonic ion followed by a kinetics-controlling β-bond dissociation is not supported by the isotope effects. If the barrier to the first step were much lower than that to the second step, it would be difficult to argue that perdeuteration had the effect of significantly shifting the rate constant ($k(E)$ *vs.* E) curves to higher internal energies. A high barrier to γ- hydrogen transfer followed by a facile β-bond dissociation is also not supported by the isotope effects, in that the magnitudes of the carbon isotope effects are too high. Indeed, an inverse isotope effect (< 1) might be expected for such a mechanism.[22]

CONCLUSION

The results presented here highlight how caution must be exercised in interpreting qualitatively kinetic isotope effects in the context of isolated organic ions. Consider how in one case (β-position H/D for *c*) values for the same isotope effect differed by a factor of about 2, depending upon whether MMM or ZAB was used for the measurement. The obstacle to a more detailed interpretation of the isotope effects reported here is the lack of information concerning critical energies of putative reaction pathways. Accurate critical energies would be essential for application of RRKM theory[24] to these ketone molecular ions. Where the McLafferty rearrangement in aliphatic ketone molecular ions differs from the analogous rearrangement of benzyl ethyl ether ions is that 'scrambling' occurs in the former but not in the latter. The occurrence of 'scrambling' and the weight of evidence in the literature[5–17,19,21,23,27] point to a stepwise mechanism; the ^{12}C/^{13}C and H/D isotope effects reported here are consistent with a stepwise mechanism. The isotope effects show unambiguously that more than one step in such a mechanism must be kinetically significant.

EXPERIMENTAL

The mass spectrometers used in this investigation were the unusually large reverse-geometry instrument MMM (University of N.S.W., now University of Warwick) and the VG ZAB 2HF (University of Adelaide). Isotope effects (H/D, ^{13}C/^{12}C) were measured as relative peak areas of metastable ions (unimolecular decompositions) formed in the field-free region preceding the electrostatic sector. Values are an average of a number of measurements; uncertainties are indicated in the text. Mass-analysed ion kinetic energy spectra were obtained by automatically scanning the electrostatic sector. Peak-area ratios were not corrected for mass discrimination in transmission efficiencies.[31] ^{13}C measurements on butyropheneone were carried out with MMM and ^{13}C isotope effects of pentanones and heptanones with the MMM and/or ZAB. The experimental conditions for MMM and ZAB were 70 eV electron ionization, accelerating voltage 8 kV and pressure reading outside second collision cell $<2 \times 10^{-8}$ mmHg.

All compounds listed in the text were prepared for this study, but the synthesis of many of these have by now been reported elsewhere, viz. butyrophenones[32] **1–9**, 3-ethylpentan-2-ones[33] **18–28** and heptan-4-ones[34] **29–38**. Deuterium incorporation for listed compounds was >99% and ^{13}C incorporation 91%. Labelled compounds whose syntheses have not been reported are indicated below.

Labelled ethylbutyrophenones 10–17

All compounds were prepared from the appropriately labelled 1-phenylbutan-1-one[32] by the reaction[35] with potassium hydride and the appropriate iodoethane. The products were colourless liquids which were purified by preparative thick-layer chromatography on silica gel eluting with diethyl ether–light petroleum (b.p. 40–50 °C) (3:17), followed by vacuum distillation (70–75 °C/0.05 mmHg). Products were checked for purity by gas chromatography. Yields were in the range 40–50%. Compounds **10–13** were prepared by alkylation of 1-phenyl[3,3-D$_2$]butan-1-one, 1-phenyl[4,4,4-D$_3$]butan-1-one, 1-phenyl[3,3-D$_2$]butan-1-one and 1-phenyl[4,4,4-D$_3$]butan-1-one with [1,1-D$_2$]iodoethene, [2,2,2-D$_3$]iodoethane and iodoethane, respectively. Compounds **14**, **16** and **17** were prepared from 1-([D$_5$]phenyl)butan-1-one, 1-phenyl[3-^{13}C$_1$]butan-1-one and 1-phenyl[4-^{13}C$_1$]butan-1-one with iodoethane. Compound **15** was prepared by the reaction of 1-phenyl[4-^{13}C$_1$]butan-1-one with [1-^{13}C$_1$]iodoethane. All labelled iodoethanes were available commercially.

Labelled pentanones

Products described below were distilled at 70–75 °C/10 mmHg using a small glass tube, then subjected to gas chromatographic separation on a 20% SE-30 Chromosorb AW (60-80 mesh) glass column, (6 mm × 3 mm i.d.), with nitrogen as the carrier gas at a flow rate of 40 cm^3 min^{-1} at 170 °C. The purity of the products was checked by ^{1}H or ^{13}C NMR mass spectroscopy (as appropriate).

3-([D$_5$]Ethyl)[4-^{13}C$_1$-4,4,5,5,5-D$_5$]pentan-2-one (39)

The reaction[33] of ethyl acetoacetate, [D$_5$]iodoethane and potassium gave ethyl α-([D$_5$]ethyl)acetoacetate (85% yield) which, on similar treatment with [1-^{13}C$_1$-D$_5$]iodoethane (D$_5$ > 99%, ^{13}C$_1$ = 91%; a commercial product) gave ethyl-α-([D$_5$]ethyl)-α-([1-^{13}C$_1$-D$_5$]ethyl)acetoacetate (82% yield). Hydrolysis of the ester with methanolic potassium hydroxide gave 3-([D$_5$]ethyl)[4-^{13}C$_1$-4,4,5,5,5-D$_5$]pentan-2-one as a colourless liquid (31% yield) (D$_1$ > 99%, ^{13}C$_1$ = 91%).

3-([D$_5$]Ethyl)[4-^{13}C$_1$-D$_9$]pentan-2-one (40)

3-([D$_5$]Ethyl)[4-^{13}C$_1$-4,4,5,5,5-D$_5$]pentan-2-one (30 mg) and NaOD–D$_2$O (2 M, 0.75 cm^3) were sealed in a glass ampoule and heated at 100 °C for 26 h. The mixture was cooled and extracted with anhydrous diethyl ether (4 × 1 cm^3). The organic extract was dried (MgSO$_4$) and fractioned in a T-tube (see above) to yield 3-([D$_5$]ethyl)[4-^{13}C$_1$-D$_9$]pentan-2-one as a colourless oil (22 mg) (D$_{14}$ > 99%, ^{13}C$_1$ = 91%).

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