Hydrogen–Deuterium Kinetic Isotope Effects for γ-Hydrogen Rearrangement in 2-Hexanone Following Photochemical Excitation, Electron Impact Ionization, and Anodic Oxidation

Sir:

Photochemical excitation, anodic oxidation, and electron impact ionization all lead 2-hexanone to a reactive state in which a hydrogen atom is transferred from C-5 to the carbonyl oxygen.[1] In the photochemical and mass spectrometric experiments this event leads to fragmentation of the rearranged molecule to produce propene and, respectively, the enol of acetone and the cation radical of the enol of acetone.[2] This famous example of parallelism in chemical behavior between molecules ionized by electron impact and molecules subject to photochemical excitation is sullied by the comparison of the hydrogen–deuterium kinetic isotope effects which is nearly 6[3] for the photochemically reactive triplet state and nearly 1 for the cation radical produced in the mass spectrometer.[4]

Because isotope effects may be reduced in magnitude by increasing the internal energy of the reacting molecules, as by raising the temperature,[5] the reduced isotope effect in the cation radical produced by electron impact could be assigned to a high internal energy residue left by the ionization process. Such a conclusion would be in conflict with the quasi-equilibrium theory of mass spectrometry[6] which can be shown to predict that a reaction with a slow preexponential factor and a low energy of activation should only occur from molecular cation radicals of low internal energy.[7] The electron impact induced rearrangement under discussion here is a process which is characterized by these kinetic parameters.[1c]

An alternative explanation would relate the low isotope effect to the earlier transition state demands of the cation radical compared with that of the triplet. Such reasoning would see the cation radical as inherently more reactive and would relate the difference between the photochemical triplet and the cation radical to the same reasons as the long-known difference in isotope effect between chlorine atom and bromine atom undergoing homolytic substitution at hydrogen or deuterium on the methyl group of toluene: the isotope effects are nearly 1 for chlorine atom and nearly 5 for bromine atom.[8] In further support of this notion the isotope effect for the γ-hydrogen abstraction of the primary amine cation radical intermediate of the Hofmann–Loeffler–Freitag reaction is 1.2, while the same reaction for the stabilized *N*-alkyl-substituted amino group cation radical is 3.2.[9]

If the low isotope effect for the γ-hydrogen rearrangement observed in the mass spectrometer derived from the reactive nature of the cation radical rather than its means of production, then one might expect a comparable isotope effect for a γ-hydrogen rearranging cation radical produced in solution. Anodic oxidation of 2-hexanone to 2-hexanone cation radical takes place in solution at near ambient temperatures[1b] and we therefore measured the hydrogen–deuterium isotope effect for the γ-hydrogen transfer in this species.

In addition to isolation of the previously described γ-acetamido-2-hexanone (**1**), we have also obtained a second new material 2,4,7-trimethyl-4,5-dihydro-1,3-oxazepine (**2**)[10] substituted at the γ position which is apparently the result of internal capture of the intermediate precursor to **1**. These transformations are shown in Scheme I.

Miller has presented evidence for the mechanism outlined in Scheme I.[1b] Such a process in which a chemical step (γ-hydrogen transfer) is both preceded and followed by electron-transfer steps is commonly encountered and is designated an ECE mechanism.[11] At potentials above the oxidation potential, as utilized in this work, the electron-transfer steps are expected to be much faster than the chemical step. This kinetic

Scheme I
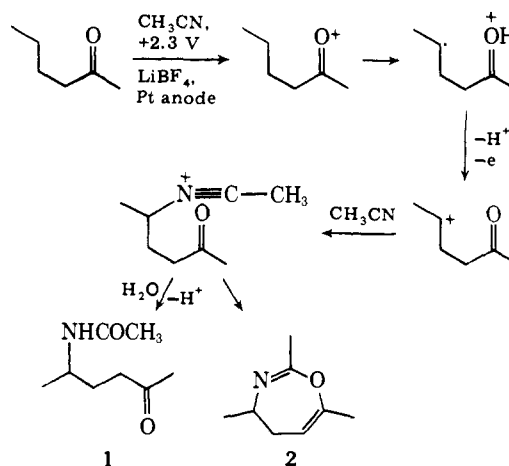
situation will both preclude reversal of the γ-hydrogen transfer and as well make this step rate determining. Electrolysis of 5-monodeuterio-2-hexanone (**3**)[9] in the electrochemical cell and measurement of the hydrogen–deuterium content of the products **1** and **2** would therefore yield the isotope effect for the γ-hydrogen transfer.

Table I presents the results of these electrochemical experiments. We have moreover subjected **3** to electron impact mass spectrometry at varied ionizing voltage and temperature and measured the deuterium to hydrogen ratio of the $[C_3H_6O]^{+\cdot}$ product of the rearrangement. These data are presented in Table II.

Two points may be drawn from inspection of Table I. The magnitude of the isotope effects[12] is consistent with a low primary effect and therefore in line with the ECE mechanism proposed[1b] and discussed above.[11] The mechanistic demand

Table I.[a,b] Isotope Effect (k_H/k_D)

temp, °C	1	2
0	1.27 ± 0.14	1.24 ± 0.10
20	1.47 ± 0.10	
40	1.38 ± 0.19	1.28 ± 0.12

[a] The deviations are the precision of various runs taken over some months. [b] The oxidations were conducted in an H cell at +2.3 V following Miller[1b] except that LiBF$_4$ was the supporting electrolyte. The products were separated and collected by extraction followed by GC on SE-30.[10]

Table II.[a] Isotope Effect (k_H/k_D)

eV	50 °C	75 °C	125 °C
10	1.4 ± 0.2	1.4 ± 0.2	1.5 ± 0.2
70	1.6 ± 0.1		1.6 ± 0.1

[a] Ratios of *m/e* 58 to 59 as shown corrected for ^{13}C contribution. Electron voltages are uncalibrated (electronvolts); temperatures are of the ion source; the inlet was at room temperature. Measured on a Du Pont 21-490 mass spectrometer.

(Scheme I) that the isotope effects be the same for production of **1** and **2** is met.

The key observation that the isotope effects in the two experimental systems (Tables I and II)[13] are nearly identical fits the hypothesis that the low isotope effect in the mass spectrometer derives from the nature of the cation radical independent of its formative history. The correspondence draws one to the conclusion that 2-hexanone cation radical demands the same transition state for γ-hydrogen abstraction under vacuum as in the complex solvent medium of an electrochemical cell. The molecular cation radicals undergoing rearrangement in the mass spectrometer cannot be distinguished from thermal molecules in their discrimination for hydrogen over deuterium.[14,15]

References and Notes

(1) (a) P. J. Wagner, *Acc. Chem. Res.*, **4**, 168 (1971), discusses the nature of this photochemical process and gives leading references to the earlier literature. (b) J. Y. Becker, L. R. Byrd, L. L. Miller, and Y.-H. So, *J. Am. Chem. Soc.*, **97**, 853 (1975). (c) D. G. I. Kingston, J. T. Bursey, and M. M. Bursey, *Chem. Rev.*, **74**, 215 (1974), is a review of these observations.
(2) See ref 1a above and S. Meyerson and J. D. McCollum *Adv. Anal. Chem. Instrum.*, **2**, 184 (1963), and ref 1c above.
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(4) See ref 1c above and J. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 5182 (1967).
(5) For a general treatment of these effects, see (a) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955); (b) L. Melander, "Isotope Effects on Reaction Rates", Ronald Press, New York, 1960; (c) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961); (d) R. P. Bell, *Chem. Soc. Rev.*, **3**(4), 513 (1974); (e) C. J. Collins and N. S. Bowman, *ACS Monogr.*, No. **167** (1970).
(6) H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig, and H. Eyring, *Proc. Natl. Acad. Sci. U.S.A.*, **38**, 667 (1952).
(7) D. H. Williams and I. Howe, "Principles of Organic Mass Spectrometry", McGraw-Hill, New York, 1972, Chapter 4; K. Levsen, "Fundamental Aspects of Organic Mass Spectrometry", Verlag Chemie, Weinheim/Bergstr., Germany, 1978.
(8) See K. B. Wiberg, in ref 5a herein.
(9) M. M. Green, J. M. Moldowan, M. W. Armstrong, T. L. Thompson, K. J. Sprague, A. J. Hass, and J. J. Artus, *J. Am. Chem. Soc.*, **98**, 849 (1976), and references therein.
(10) The NMR and mass spectra (MS) of **1** matched those of earlier report.[1b] **2** was isolated by extraction and GC collection on 20% SE-30 on Chrom W, flow 10 cm³/15 s, column temperature 175 °C, retention time 8 min (colorless liquid). Yield was ~3:1 **1:2** under typical conditions.[1b] By high resolution the MS molecular weight of **2** corresponds to $C_8H_{13}NO$ with major fragments at *m/e* 97, 96, 82 (base peak). ¹H NMR on an FX-60Q spectrometer at 59.75 Hz: δ 1.22 (d, 3 H, *J* = 7 Hz, C_4 CH_3, irradiation of C-4 H at 4.35 collapses 1.22 to a singlet), 2.17 (s, 3 H, C_2 CH_3), 2.2 (br, overlapping 2.17, 3 H, C_7 CH_3), 2.6 (v br, 2 H, CH_2), 4.35 (br, 1 H, C_4 H), 4.9 (br, 1 H, C_6 H). ¹³C NMR on a JEOL FX-60Q at 15.0 Hz including multiplicity from off-resonance data: δ 17.6 (q, 4-CH_3), 22.1 (q, 2-CH_3), 24.2 (q, 7-CH_3), 36.2 (t, C_5), 56.9 (d, C_4), 108.4 (d, C_6), 141 (v w, C_7), 167.4 (s, C_2).
(11) Z. Galus, "Fundamentals of Electrochemical Analysis", Ellis Horwood Ltd., Chichester, England, 1976, Chapter 15; "Organic Electrochemistry", M. M. Baizer, Ed., Marcel Dekker, New York, 1973, pp 99, 449; L. Meites in "Techniques of Chemistry", Vol. I, Part IIA, Wiley-Interscience, New York, 1971, Chapter IX.
(12) The k_H/k_D values in Table I are reasonable for a low primary isotope effect and would be remarkable for secondary isotope effects for monodeuterio substitution in varied classes of reactions. See D. E. Sunko and S. Borčić (Chapter 3) of ref 5e.
(13) We cannot account for the higher k_H/k_D values for 2-hexanone (Table II) compared with the values ranging from 1.0 to 1.2 for related molecules (2-hexanone was not measured) previously reported.[4] The invariance here within experimental error, of the results at 70 and 10 eV, argue against the scrambling mechanism which affected the earlier finding.[4] Moreover such scrambling processes[4] caused deviations in the opposite direction (k_H/k_D too low) from the results herein.
(14) The independence of temperature for k_H/k_D in both systems (Table I and II) is expected for low isotope effects and is consistent with recent results and predictions for bent transition states. See H. Kwart and T. J. George, *J. Org. Chem.* **44**, 162 (1979); H. Kwart, D. A. Benko, and M. E. Bromberg, *J. Am. Chem. Soc.*, **100**, 7093 (1978); H. Kwart, T. J. George, R. Louw, and W. Ultee, *ibid.*, **100**, 3927 (1978); M. E. Schneider and M. J. Stern, *ibid.*, **94**, 1517 (1972), and references therein. See also, S. B. Kaldor and W. H. Saunders, Jr., *ibid.*, **101**, 7594 (1979). A referee has suggested that the possibility that the k_H/k_D values reside substantially in a temperature-independent preexponential term would make the isotope effect a poor probe of the internal energy of the cation radical. Thus the present results, although demonstrating that electron impact is not prerequisite to the low isotope effects and that the transition states are comparable in the two systems (Tables I and II), could nevertheless allow that the cation radical in the mass spectrometer is vibrationally excited compared with its solution counterpart.
(15) See M. M. Green, T. J. Mangner, S. P. Turner, and F. J. Brown, *J. Am. Chem. Soc.*, **98**, 7082 (1976); M. M. Green, R. J. Giguere, and J. R. P. Nicholson, *ibid.*, **100**, 8020 (1978), and references therein to earlier papers in the

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The Mechanism of Flavin 4a Substitution Which Accompanies Photolytic Decarboxylation of α-Substituted Acetic Acids. Carbanion vs. Radical Intermediates

Sir:

Flavin-mediated photodecarboxylation (PDC) of certain α-substituted acetic acids (eq 1) has been claimed to serve as a model for flavoenzyme-catalyzed dehydrogenations.[1,2] The reaction is facile only in cases in which a heteroatom (O, N, and S) is bonded directly or vinylogously to the methylene carbon of the substituted acetic acid (in eq 1, R is C_6H_5O- for **1a**, C_6H_5S- for **1b**, and 3-indolyl for **1c**). PDC of α-hydroxyl[2a] or α-amino acids[3] in the presence of Fl_{ox} yields α-keto or α-imino acids presumably by elimination from the 4a adduct.[4] It has been suggested that the mechanism of eq 1 involves
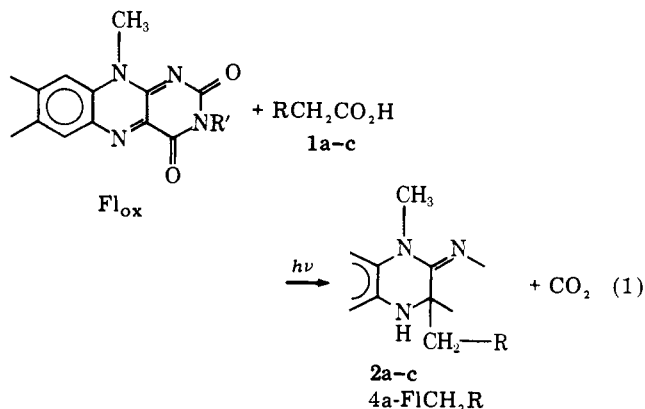
nucleophilic attack of a carbanion intermediate upon the 4a position of Fl_{ox} (eq 2).[1,2] However, PDC of the α-substituted
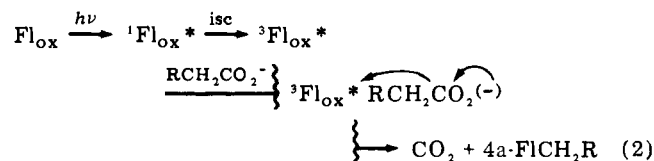
carboxylic acids **1a–c** by the triplet states of benzophenone, quinones and various quinoid dye molecules has been established (spin trapping, CIDNP, product analysis)[5] to be radical in nature. We are now able to show that a radical mechanism is involved in the $^3Fl_{ox}$*-mediated PDC reactions. This communication deals with the results of laser flash photolysis and