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MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS—XCII[1]

FURTHER STUDIES ON THE McLAFFERTY REARRANGEMENT OF ALIPHATIC KETONES

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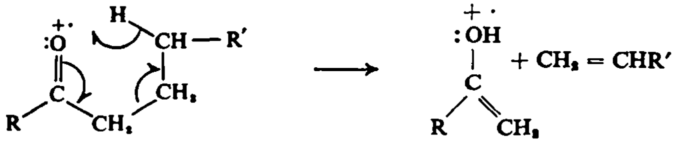
Abstract—Energetic factors governing the McLafferty rearrangement of ketones are discussed. Through the use of deuterium labeled n-butyl-isobutyl ketones it is shown that when two competing alternatives for the transfer of a hydrogen atom from a γ-position are available abstraction of a secondary hydrogen will be highly favored over a primary one. Other effects, such as the stability of the final products and preferred conformations must also be taken into account.

The itinerant hydrogen atoms in the double McLafferty rearrangement of aliphatic ketones, which hitherto have not been investigated, are shown to be principally the γ- and γ'-hydrogen atoms.

IT IS now widely known that the fragmentation of organic molecules upon electron impact is frequently accompanied by the transfer of hydrogen atoms,[3] whose origin can often be elucidated by judicious labeling with deuterium. However, not too much is known about the energetic factors governing such migrations and especially which of two competing reactions may be expected to prevail. Since these questions are of outstanding importance for the prediction of fragmentation processes of organic compounds it seemed to us best to study in depth a few well-defined reactions in which hydrogen migrations are intimately involved. Especially pertinent for this purpose is the so-called McLafferty rearrangement of aliphatic ketones,[4] i.e. the elimination of a neutral olefin molecule with transfer of a γ-hydrogen atom and production of a charged enol (*a*).

Evidence for the mechanism of this rearrangement and especially for the fact that it is the γ-hydrogen that is transferred has been compiled recently[5] and it seems that this reaction is the best defined hydrogen transfer process known. By choosing



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[1] Part XCI, J. Karliner, H. Budzikiewicz and C. Djerassi, *J. Org. Chem.* in press.

[2] Present address: Institut für Organische Chemie, Technische Hochschule, Braunschweig, Germany.

[3] For a recent summary see H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds.* Holden-Day, San Francisco (1964).

[4] F. W. McLafferty, *Analyt. Chem.* 31, 82 (1959).

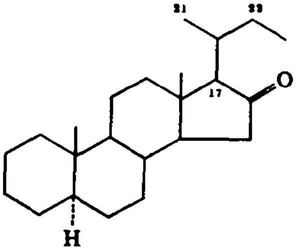
[5] S. Meyerson and J. D. McCollum in *Advances in Analytical Chemistry and Instrumentation* (Edited by C. N. Reilley) Vol. 2; pp. 184–199. New York (1963).

suitable pairs of competing reactions, it is thus possible to study various factors influencing hydrogen transfer processes, which in turn may shed some light on the sometimes puzzling observation that apparently closely related substances may exhibit quite different fragmentations. A short summary of past pertinent results will be presented together with new data on the McLafferty rearrangement.

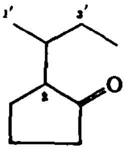
As studies of the type indicated necessitate the labeling of certain positions with deuterium, the extent of any isotope effect had to be established. By comparing the relative rate of transfer of hydrogen and deuterium in methyl butyrate with its γ-d_1-, and γ,γ-d_2-analogs a rate of 0·88 atoms D per atom H was found to be operative.[6] Whether this is a general value for the McLafferty rearrangement or whether it pertains only to this specific case still remains to be shown.

Next, the importance of interatomic distance between the departing hydrogen and the acceptor oxygen has been studied in various steroidal ketones[7] and a critical range of 1·5–1·8 Å determined.

By comparing the spectra of labeled 20-ethyl-5α-pregnan-16-ones (I)[8] and 2-(sec-butyl)cyclopentanone (II)[9] it could be confirmed that restricted rotation of the C-17 side chain played an important role in the steroid (I). Noteworthy is the virtually exclusive transfer from C-22 (97%) as compared to the other γ-position (C-21).



I

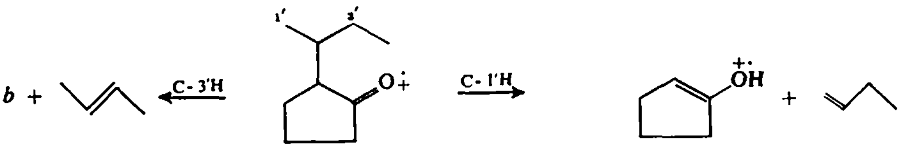


II

The sec-butylcyclopentanone (II) showed[9] a reduced but still preferential transfer from the secondary (3') position (84% *vs* 16% from C-1' including a correction for the 2:3 statistical factor and the above established[6] isotope effect of 0·88). Three factors, which could not be separated in the case of II could account for this phenomenon:

(1) energetically more favored removal of hydrogen (and deuterium) from a secondary as compared to a primary site;

(2) formation of the more stable 2-butene rather than 1-butene as the expelled particle



II b

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[6] D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, 284 (1964).

[7] C. Djerassi, *Pure Appl. Chem.* **9**, 159 (1964); C. Djerassi, G. v. Mutzenbecher, J. Fajkos D. H. Williams and H. Budzikiewicz, *J. Amer. Chem. Soc.* **87**, 817 (1965).

[8] C. Beard, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **86**, 269 (1964).

[9] H. Fritz, H. Budzikiewicz and C. Djerassi, *Chem. Ber.* in press.

(3) a preferred conformation which favors the proximity of the C-3′ hydrogens to the acceptor oxygen.

The first effect will influence the activation energy and the order of magnitude may be judged from the difference in bond energy between a primary and a secondary hydrogen (about 5 kcal).[10] The energy gained concomitantly by forming an O—H bond is the same in both cases and so is the energy necessary for the rupture of the C—C linkage (identical daughter ion *b* in both cases).

The second effect (stability of the butenes formed) will be reflected in the energy content of the final products (ΔF_0^{500} 29·55 kcal for butene-1 *vs.* 27·83 kcal for *trans*-butene-2)[11] and if the transition state resembles the products rather than the reactants, it should be noted also in the activation energy.[12]

The third factor (preferred conformation) will cause deviations from the theoretical 3:2 statistical ratio (three primary *vs* two secondary hydrogens), but its quantitative evaluation is difficult. The first two effects are working in the same direction (Fig. 1) while the third one may favor either one of the competing reactions.

Fig.1

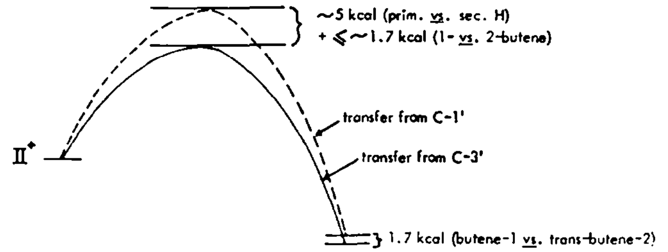

FIG. 1. Energy diagram for alternate modes of McLafferty rearrangement in 2-(sec-butyl)-cyclopentanone (II).

The energetic influence of the neutral particle expelled (factor 2) can be excluded by using a different model compound, namely n-butyl isobutyl ketone (III). Again, McLafferty rearrangement can occur either by transfer of a primary or of a secondary hydrogen atom, but in this case the neutral particle formed (propene) is the same in either instance. However, no data are available to evaluate the role of some preferred conformation. It is conceivable that in the case of the n-butyl chain the two γ-hydrogen atoms may approach the acceptor oxygen more frequently than the statistical value of twice as often as the δ-methyl group (either for steric reasons or because of hydrogen bonding). Similarly in the case of the isobutyl chain the statistical values may be disturbed for the same reasons.

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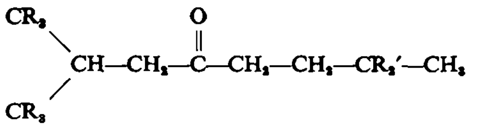
[10] T. L. Cottrell, *The Strength of Chemical Bonds* (2nd Edition) Academic Press, New York (1958).

[11] F. D. Rossini *et al. Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds.* Carnegie Press, Pittsburgh, Pa. (1953).

[12] That these energy differences can influence considerably the rate of competing reactions has been demonstrated in connection with the electron-impact induced retro-Diels-Alder reaction (H. Budzikiewicz, J. I. Brauman and C. Djerassi, *Tetrahedron* **21**, 1855 (1965)).



III R = R′ = H
IVa R = H, R′ = D
IVb R = D, R′ = H

The values calculated from the mass spectra (Figs. 2a–c) by assuming a statistical ratio of primary *vs* secondary hydrogens of 6:2 and an isotope effect[6] of 0·88 discriminating against deuterium, are listed in Table 1.

The most important conclusion that can be drawn from the above data is the predominance of transfer of a secondary hydrogen atom as compared to that of a primary one, which seems to be of the order of 10:1 to 20:1.* Since this effect is governed only by the bond energy of the C—H bond (Fig. 1), similar orders of magnitude should be expected in other hydrogen transfer processes if two or more such processes compete. This seems to be about the limit of general applicability that we are able to reach in this problem at present because the additional effects discussed below will differ with each compound and with the operating conditions and can, therefore, at best be estimated.

The values observed for the two labeled analogs (IVa and IVb) of III, are sufficiently close for a generally correct answer but a discrepancy (91 *vs* 95%) nevertheless exists. Furthermore, the differences between these values (91–95% *vs* 9–5%) and those observed with II (84 *vs* 16%) should be considered.

The different values observed with IVa (91:9) and IVb (95:5) are explainable in at least two ways. One may assume that an isotope effect operates here with a higher discrimination against deuterium than observed[6] with methyl butyrate (0·88). The resulting isotope effect (0·61) still falls within an acceptable range,[13] but if this is the correct and only explanation for the observed discrepancies than a rather wide range of isotope effects should operate in the McLafferty rearrangement.

Another factor which may have to be taken into consideration is the alteration of a given preferred conformation due to the smaller radius of deuterium.

Turning now to the second quantitative discrepancy—the transfer values in II as compared to III—everything being equal, a higher degree of transfer from the secondary site would be expected in II as compared to III, because in addition to the more favorable abstraction of a secondary hydrogen the formation of the more stable butene-2 must be added (Fig. 1). This is, however, clearly not the case, since the observed values (84% in II *vs* 91–95% in III) go in the opposite direction. It seems, therefore, that conformational effects must be involved, which operate in different directions in II and III. As mentioned above, these effects are difficult to

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* The same order of magnitude for preference of a secondary over a primary hydrogen atom has been observed in the photolysis of 4-methyl-2-hexanone (P. Ausloos, *J. Phys. Chem.* **65**, 1616 (1961)). Several investigators (for leading Refs. see N. J. Turro, D. C. Neckers, P. A. Leermakers, D. Seldner and P. D'Angelgo, *J. Amer. Chem. Soc.* **87**, 4097 (1965)) have already called attention to the similarity of the electron-impact-induced McLafferty rearrangement and the type II photochemical decomposition of ketones (P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.* **87**, 4009 (1965)).

[13] F. H. Field, J. L. Franklin, *Electron Impact Phenomena* Chap. 5. Academic Press, New York (1957).

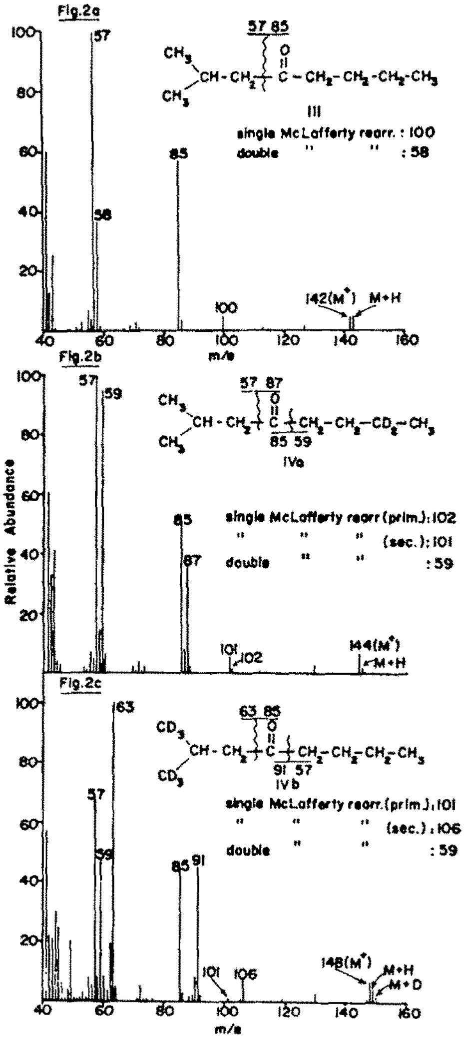


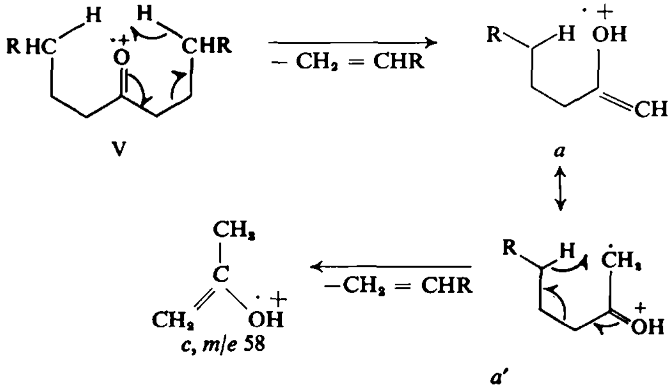
FIG. 2. Mass spectra of (a) n-butyl isobutyl ketone (III), (b) γ,γ-d_2-n-butyl isobutyl ketone (IVa) and (c) n-butyl γ,γ-d_6-isobutyl ketone (IVb) measured with a CEC model 21-103C mass spectrometer.

TABLE 1

Compound	Transfer from Primary carbon	Secondary carbon
IV*a*	9%	91%
IV*b*	5%	95%

predict in a quantitative manner since they will vary with the compound and very likely also with the operational conditions (ion source temperature, etc). They are not large enough to overshadow the general conclusion that in the McLafferty rearrangement a secondary hydrogen is abstracted predominantly as compared to a primary one.

Aliphatic ketones having in both side chains a γ-hydrogen atom (V) will show[14] a second McLafferty rearrangement and the sequence may be formulated[3] as follows:



As noted above, the simple McLafferty rearrangement has been studied intensively, but to our knowledge no attention has been paid to the double one in terms of isotope labeling. Since it has been demonstrated recently[15] in ethers and amines that hydrogen rearrangements of fragment ions, which were believed to be site-specific, actually occur in a random manner, it was of considerable interest to determine the origin of the migrating hydrogen in the second McLafferty rearrangement. Various labeled ketones were, therefore, prepared with the aim of clarifying this reaction. However, the quantitative examination of the data is in some cases difficult since the ion arising from double rearrangement has for α-unbranched ketones a mass of 58 which falls into a region where other peaks occur (e.g., $C_4H_9^+$, *m/e* 57, for dibutyl ketone, and below this value ions formed by its further decomposition) whose shifts upon deuteriation are not necessarily predictable.

The first set of compounds examined was dipropyl ketone (VI) and its α,α'-d_4-(VII) and γ,γ'-d_6-(VIII) analogs. Double rearrangement occurs (Fig. 3) only to a very minor extent (ion *c* at *m/e* 58 amounts to 2·4 % Σ_{40}) since two primary hydrogen atoms have to be transferred. Due to this low abundance of the ion *c*, calculations are of necessity of limited accuracy and it can only be stated that at least 85 % of the α-hydrogens are retained in *c* and at least 85 % of two γ-hydrogens are transferred from VII, in accordance with the depicted mechanism (V → *a* → *c*).

Better results are obtainable with dibutyl ketone (IX) where the appropriate rearrangement peaks are more intense (Fig. 4). All of the carbon atoms were labeled symmetrically with deuterium (X–XIII). Due to the fact that here secondary hydrogens are transferred, the final ion *c* (*m/e* 58) occurs with an ion yield of 16·6 % Σ_{40}. The observed shifts show that at least 95 % of the two hydrogen atoms transferred come from the two γ-positions in XI, while possibly up to 5 % stem from the δ sites in X. This latter figure however, is an unlikely maximum value computed on the premise that the entire ion yield at *m/e* 59 in the spectrum of the δ,δ'-d_6 analog X (after correction for C^{13}) is due to the double rearrangement ion *c* rather than to a hydrocarbon species stemming from decomposition of the d_3-butyl ion of mass 60. As an

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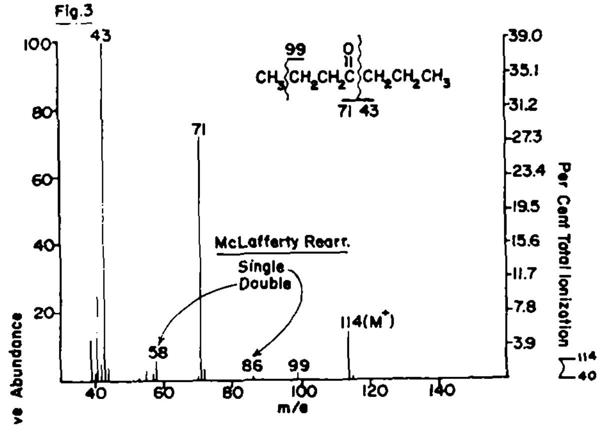
[14] A. G. Sharkey, Jr., J. L. Shultz, R. A. Friedel, *Analyt. Chem.* **28**, 934 (1956).

[15] C. Djerassi and C. Fenselau, *J. Amer. Chem. Soc.* **87**, 5747, 5752 (1965).



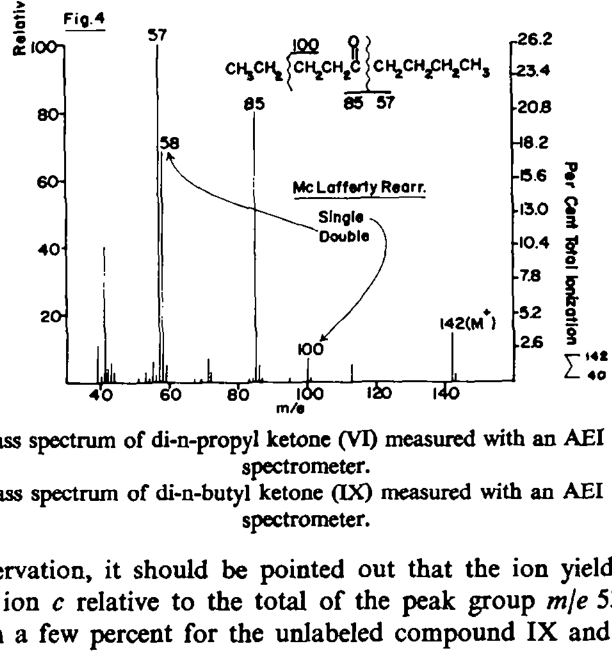


FIG. 3. Mass spectrum of di-n-propyl ketone (VI) measured with an AEI MS-9 mass spectrometer.

FIG. 4. Mass spectrum of di-n-butyl ketone (IX) measured with an AEI MS-9 mass spectrometer.

additional observation, it should be pointed out that the ion yield of the double rearrangement ion *c* relative to the total of the peak group *m/e* 53–59 (Fig. 4) is constant within a few percent for the unlabeled compound IX and its α,α′-(XIII), β,β′-(XII) and δ,δ′-(X) analogs (i.e. for the cases where a *γ-hydrogen* is transferred), but that it drops to about four-fifths of its value in the γ,γ'-d_4 species (XI) where a *deuterium* is rearranged.

$(CR_3'{-}CH_2{-}CR_2)_2CO$

VI $R = R' = H$
VII $R = D, R' = H$
VIII $R = H, R' = D$

$(CR_3{-}CR_2'{-}CR_2''{-}CR_2''')_2CO$

IX $R = R' = R'' = R''' = H$
X $R = D, R' = R'' = R''' = H$
XI $R' = D, R = R'' = R''' = H$
XII $R'' = D, R = R' = R''' = H$
XIII $R''' = D, R = R' = R'' = H$

We may conclude, therefore, that the double McLafferty rearrangement ($a \rightarrow c$) is virtually as site-specific (γ-hydrogen transfer) as the single rearrangement ($V \rightarrow a$) even though a fragment ion (*a*) rather than the molecular ion (V) is involved. This is in marked contrast to the observation in ethers and amines,[15] the principal difference being that in the latter two series, the fragment ion is an even-electron species, while in the present instance an odd-electron intermediate (*a*) is involved. Whether this difference plays an important role in hydrogen transfer reactions is currently under investigation.

EXPERIMENTAL

All mass spectra were determined at least in duplicate (to assure reproducibility) either with a CEC model 21-103C or an AEI MS-9 mass spectrometer equipped with a heated (200°) glass inlet system and operating with an ionizing energy of 70 eV. We are indebted to Dr. D. Becher for some of the measurements.

Synthesis of labeled ketones. γ,γ'-d_6-Di-n-propyl ketone (VIII) was prepared from γ-d_3-n-propyl bromide[16] by conversion to the Grignard reagent, reaction with ethyl formate (2 hr reflux in ether) and oxidation of the resulting alcohol by the Jones procedure.[17] Purification of this and all other ketones was effected by gas phase chromatography with a Wilkens Aerograph instrument, using a column of 20% polybutylene glycol on chromosorb P, which had first been washed with 2% ethanolic KOH, followed by EtOH and then dried at 110°. The α,α'-d_4-di-n-propyl ketone was obtained by stirring at room temp for 1 week with a mixture of MeOD, D_2O and DCl,[18] isolating the ketone and repeating the process with fresh reagent for a second week.

The labeled di-n-butyl ketones X-XII were synthesized from the appropriately labeled butyl bromides[16, 19] by the Grignard reaction with ethyl formate and oxidation[17] of the resulting alcohol, while the α,α'-d_4 ketone XIII was prepared as described above for the lower homolog VII.

Compound IVb was obtained from d_6-acetone by LAH reduction, conversion to isopropyl bromide, carbonation of its Grignard reagent, LAH reduction of the resulting labeled isobutyric acid, transformation of the alcohol into the bromide, reaction of its Grignard reagent with valeraldehyde and finally oxidation with the Jones reagent.[17]

The compound IVa was synthesized in a similar fashion from the Grignard reagent of 3,3-d_2-butyl bromide[16, 19] and isovaleraldehyde followed by Jones oxidation.[17]

Acknowledgment—We are indebted to Dr. Peter Brown for supplying us with the two α,α'-d_4 ketones VII and XIII and to Dr. John I. Brauman for stimulating discussion. Financial assistance was provided by the National Institutes of Health (grants No. AM-04257 and CA-07195) of the U.S. Public Health Service.

[16] A. M. Duffield, H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 2913 (1965).

[17] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

[18] J. Seibl and T. Gäumann, *Helv. Chim. Acta* **46**, 2857 (1963).

[19] A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 805 (1965).