Tetrahedron Letters No. 52, pp 5027 - 5030.
Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/1222-5027$02.00/0

SITE-SPECIFIC HYDROGEN ABSTRACTION IN THE ELECTROCHEMICAL OXIDATION OF KETONES

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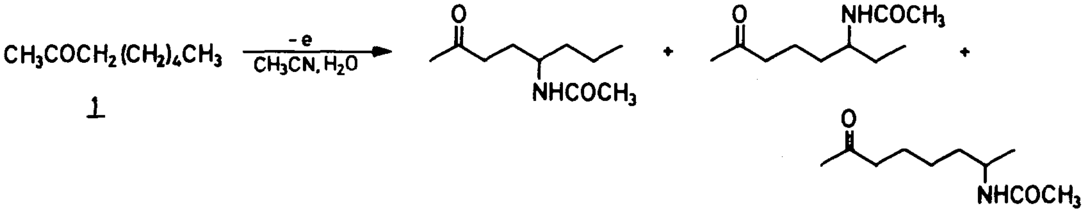
Summary: Electrochemical oxidation of saturated ketones involves specific abstraction of one γ hydrogen by the carbonyl oxygen in a six-membered ring cyclic transition state, reminiscent of the first chemical steps of the McLafferty rearrangement and Norrish type II photofragmentation.

Miller and coworkers[1] recently reported that anodic oxidation of saturated straight chain aliphatic ketones in acetonitrile gives rise to acetamidated products, e.g., oxidation of 2-octanone produces a mixture of 5-, 6-, and 7-acetamido-2-octanones:



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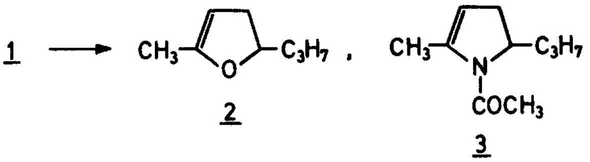
This behavior is at variance with that observed upon anodic oxidation of other aliphatic compounds,[2] inasmuch as substitution in ketones does not occur predominantly near the end of the aliphatic chain. Miller's observations[1] suggested that for ketones the hydrogen abstraction step preceding acetamidation is intramolecular, but he pointed out[1] that the results did not show whether the hydrogen abstraction would occur with positional specificity for long-chain ketones with several potential sites of attack.

We have therefore reinvestigated the electrochemical oxidation of aliphatic ketones,[3] to establish whether the hydrogen abstraction step is site-specific. Our initial results may be summarized as follows:

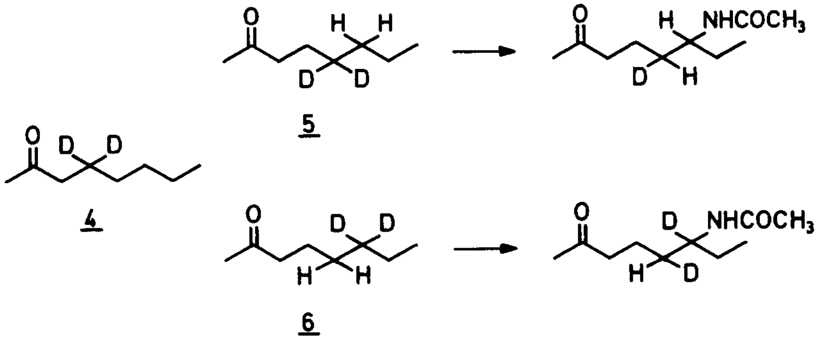
(i) The major product obtained by oxidation of long-chain ketones is the

γ-acetamidated ketone; lesser amounts of products substituted at positions further removed from the carbonyl group are also formed.[4] In addition, the reaction leads to substituted dihydrofuran and 2-pyrroline products, e.g., 2 and 3. The pyrroline (3) is presumably formed in an intramolecular condensation reaction of the 5-acetamidated ketone.

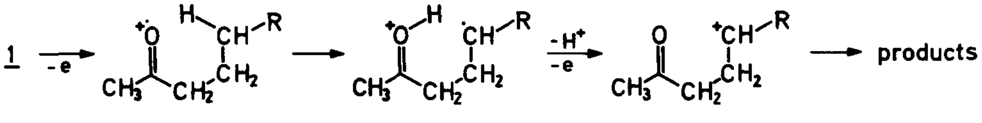


(ii) Oxidation of the deuterium labeled ketones[5] 4, 5 and 6 establish that the hydrogen atom abstracted in the oxidation process is always derived from the γ-position, regardless of the position of the acetamido substituent in the final product:

Oxidation of 5,5-dideuterio-2-octanone (5) yields exclusively monodeuterated acetamido-octanones, whereas oxidation of the 4,4- and 6,6-dideuterio-2-octanones (4 and 6) yield acetamidated products which all retain both deuterium atoms. In acetamidated 4 these remain at C-4; likewise, the one D retained by the three acetamidated ketones obtained in the oxidation of 5 remain at C-5. The two deuterium atoms present in all three acetamidated ketones derived from 6 remain in the 5-acetamido product at C-6, whereas the 6- and 7-acetamido products both appear to have one D at C-5 and one at C-6.



The firm experimental evidence for site-specific abstraction of one γ-hydrogen implies that the hydrogen abstraction step is intramolecular, for only thus can the specificity of reaction at the γ-carbon be understood. Hence, oxidation leads (possibly indirectly[6]) to the carbonyl cation-radical, which abstracts a γ hydrogen atom from the aliphatic chain, closely resembling the McLafferty rearrangement and the Norrish type II photofragmentation. However, rather than reacting by C-C bond cleavage, the product is deprotonated and further oxidized to the cation, which subsequently suffers nucleophilic attack by solvent or carbonyl group, or undergoes carbonium-ion rearrangements (here: 1,2-hydride shifts).



These results call attention to the possibility that there may be extensive parallels between electrochemical oxidation and mass spectrometric decomposition, both of which proceed via cation-radicals. Only a few examples of analogies between these two branches of chemistry have been reported.[1,7,8] Furthermore, the present results confirm the suggestion[1] that electrochemical oxidation is one of the reactions where an intermediate with radical character may undergo specific hydrogen transfer via cyclic six-membered ring transition states.[9]

References and Notes

1. J. Y. Becker, L. R. Byrd, L. L. Miller and Y-H. So, J. Am. Chem. Soc., 97, 853 (1975).

2. L. L. Miller and V. Ramachandran, J. Org. Chem., 39, 369 (1974).

3. Ketone (8 mmol) dissolved in acetonitrile containing lithium perchlorate (100 ml, 0.1 M) was oxidized at constant current (200 mA) at a platinum anode in a divided cell until 2F/mol had passed; the conversion of substrate was ca. 60 %. After removal of solvent (evaporation) and supporting electrolyte (washing with water), the product mixtures were analyzed by GC-MS using a Finnigan 1015 instrument. Products were identified from their mass spectra; the label distribution was inferred from an analysis of the mass spectral fragmentation reactions of labeled and unlabeled species.

4. Our relative yields are slightly different from those reported by Miller.[1] We consistently observe that the relative yield of acetamidated ketone is less the further the point of substitution is from the carbonyl group. A representative example is the oxidation of 2-undecanone where the 5-, 6-, 7-, 8-, and 9-acetamidated products constitute roughly 45:25:15:10:5 percent of the acetamido ketone product mixture (the true relative yield of the 5-acetamidated product may be even higher, cf. the formation of pyrroline products). The presence of 10-acetamido-2-undecanone (the ω-1 product) could not be reliably demonstrated.

5. The deuterium labeled octanones were prepared from ethyl acetoacetate and suitably labeled pentyl bromides.

6. L. L. Miller and K. Katz, J. Electroanal. Chem., 72, 329 (1976).

7. J. Y. Becker, L. L. Miller and T. M. Siegel, J. Am. Chem. Soc., 97, 849 (1975).

8. F. Sundholm, G. Sundholm and K. Suontama, Suom. Kemistil., B45, 339 (1972).

9. Name reactions of this kind include the Barton and Hofmann-Löffler-Freytag reactions, the Norrish type II photofragmentation and the McLafferty rearrangement.

(Received in UK 14 September 1979)