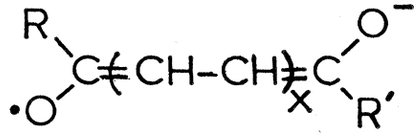
Electron Spin Resonance Spectroscopy: Application to Proof of Structure of Organic Ketones

Abstract. *Many ketones containing an α-methylene group can be converted to α-diketone radical anions in dimethyl sulfoxide solution. The resulting radical anions can usually be unambiguously identified by electron spin resonance spectroscopy, and the structure of the starting ketone may be deduced, often without reference to model compounds. The technique is also applicable to α-diketones, α-bromoketones, and α-hydroxyketones.*

Aliphatic "semiquinones" (I) are readily formed in dimethyl sulfoxide solution from cycloalkanones (*1*), acyclic ketones (*2*), and decalones (*3*) by reactions 1 to 4 wherein B^- is potassium *t*-butoxide (*4*).



I

$$RCOCH_2R' + B^- \xrightarrow{O_2} \mathbf{I},\ x = 0 \quad (1)$$

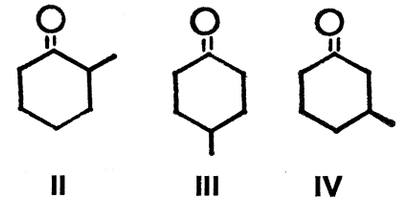
$$RCOCHOHR' + B^- \xrightarrow{O_2} \mathbf{I},\ x = 0 \quad (2)$$

$$RCOCOR' + B^- \longrightarrow \mathbf{I},\ x = 0 \quad (3)$$

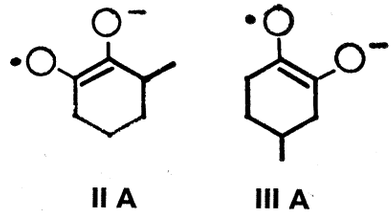
$$RCOCHBrR' + B^- \xrightarrow{DMSO} \mathbf{I},\ x = 0 \quad (4)$$

α-Diketone radical anions (**I**, $x = 0$) wherein R or R′ is methyl or hydrogen are best prepared by way of reaction 4 (*5*).

Figure 1 illustrates the application of these findings to the proof of structure of the three isomeric methylcyclohexanones (II-IV). Reaction 1



II III IV



II A III A

can yield only the radicals II*A* from II, and III*A* from III. Since an alkyl group confers conformational stability on a cyclohexene ring in terms of electron spin resonance (ESR) frequencies (about 9 Gc/sec), II*A* would be expected to have three magnetically nonequivalent α-hydrogen atoms. This leads to the experimental spectrum of Fig. 1*a* which contains 2^3 peaks of unit intensity (*6*). The radical III*A* might have been expected to have four magnetically different α-hydrogen atoms or two almost equivalent pairs of hydrogen atoms (a pair of axial and a pair of equatorial atoms). The spectrum (Fig. 1*b*) indicates pairs of magnetically equivalent hydrogen atoms with 3^2 peaks with the proper intensities for an overlapping triplet of triplets. From IV a mixture of approximately three parts of III*A* to one part of II*A* is formed in reaction 1 (Fig. 1*c*). Figure 1*c* illustrates the application of ESR techniques to the question of the preferred direction of ionization of an unsymmetrical ketone containing two α-methylene groups.

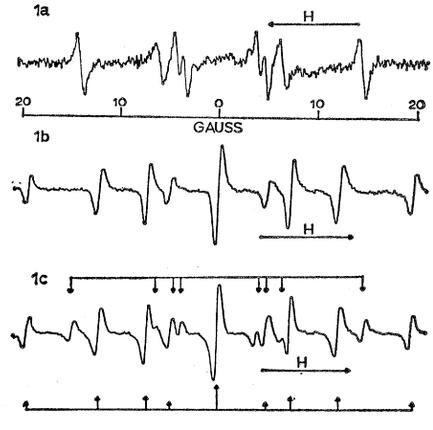
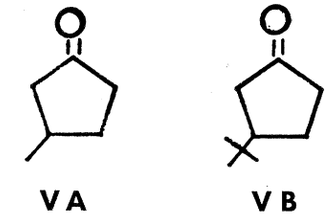
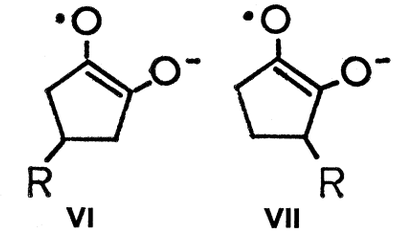


Fig. 1. First derivative electron spin resonance spectra of radical anions detected by the exposure to air, for 15 to 25 seconds, of 0.5 ml of a dimethyl sulfoxide solution containing 0.1*M* potassium *t*-butoxide; *a*, 0.05*M* 2-methylcyclohexanone; *b*, 0.05*M* 4-methylcyclohexanone; *c*, 0.05*M* 3-methylcyclohexanone. Spectra recorded immediately after oxygenation.

Although 3-methylcyclopentanone (V*A*) also underwent oxygenation to yield about three parts of VI*A* to one part of VII*A*, 3-*t*-butylcyclopentanone (V*B*) gave nearly exclusively VII*B*, presumably because of relief in eclipsing strain in forming the $\Delta^{1(2)}$-enolate anion during ionization (*7*). A com-



V A V B

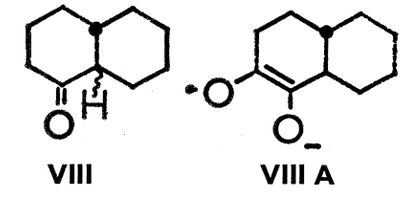


VI VII

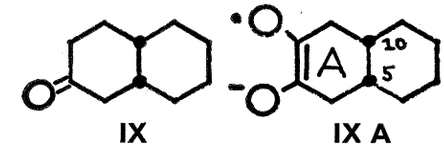
A, R = CH_3

B, R = $(CH_3)_3C$

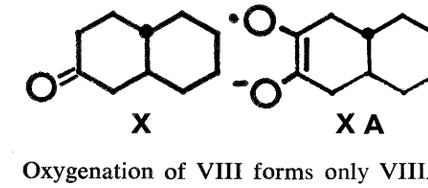
bination of oxidation in basic solution and ESR spectroscopy of the resulting oxidation product readily affords a means of distinguishing between 1-decalones (VIII), *cis*-2-decalones (IX), and *trans*-2-decalones (X) (*3*).



VIII VIII A



IX IX A

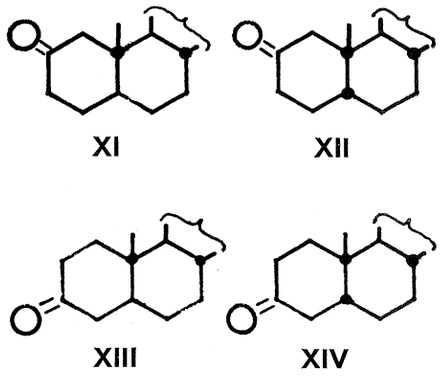


X X A

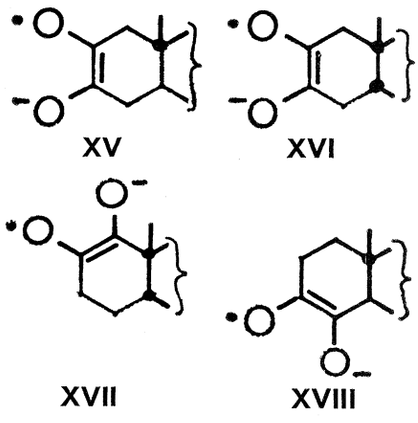
Oxygenation of VIII forms only VIII*A* whereas oxidation of IX forms a mixture of IX*A* and VIII*A*, and X forms a mixture of X*A* and VIII*A*. The spectrum of VIII*A*, a 1:1:2:2:1:1 sextet, results from the presence of

two equivalent axial hydrogens and one equatorial hydrogen. The 13-line spectrum of IX*A* results from four magnetically nonequivalent protons at C No. 1 and C No. 4 owing to the presence of axial and equatorial substituents to ring A at C No. 5 and C No. 10. In X*A* the substituents at C No. 5 and C No. 10 are both equatorial with respect to ring A and pairs of magnetically equivalent axial and magnetically equivalent equatorial hydrogen atoms at C No. 1 and C No. 4 give a 1:2:3:4:3:2:1 septet with $a_{\text{axial}}{}^{H}$ equal to 2 ($a_{\text{equatorial}}{}^{H}$), where a^{H} is the hydrogen hyperfine splitting constant.

A more challenging problem is the analysis of ketones in ring A of steroids with partial structures XI to XIV. Exposure of solutions of compounds XI to XIV to traces of air



in dimethyl sulfoxide containing potassium *t*-butoxide produces radical anions XV to XVIII (Fig. 2).



The analysis of a large number of steroidal ketones in the pregnane, androstane, cholestane, and spirostane series has shown that compound XI forms only a single product, the Δ^2-semiquinone XV (Fig. 2*a*). However, the 5β-2-ketone (XII) forms initially about equal parts of XVI (14 lines) and XVII (4 lines), two of whose lines overlap two of the 14 lines from XVI (Fig. 2*b*). The spectrum of XVII disappears more rapidly than that of XVI so the spectrum should be recorded immediately for proof of structure. The *trans*-3-ketone gives about 90- to 95-percent oxygenation at C No. 2 to yield XV and about 5- to 10-percent oxygenation at C No. 4 to form XVIII whose ESR spectrum is a 1:1:2:2:1:1 sextet (Fig. 2*c*) (*3*). Again, XVIII disappears more rapidly than XV, and the spectrum should be recorded immediately after oxygenation. An 11-keto substituent can increase the attack at C No. 4 to as much as 25 percent (*8*). The *cis*-3-ketone (XIV) gives predominant oxygenation at C No. 4 to form XVIII. Analysis of the spectrum of an analog of XIV and XVIII methylated at C No. 5 demonstrated that epimerization at C No. 5 had occurred in the oxygenation of XIV. Some attack also occurs at C No. 2 to form XVI but because the spectrum of XVI contains 14 lines whereas XVIII contains only six, the peaks due to XVI in Fig. 2*d* are hard to distinguish. A careful analysis of the spectrum indicates about 10 to 25 percent of XVI is formed from most 5β-3-ketones and that this percentage is rather independent of other substituents in the steroid nucleus, for example, an 11-keto group.

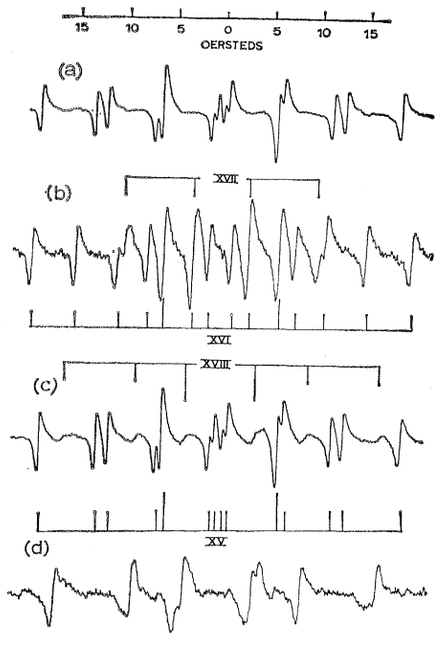


Fig. 2. Electron spin resonance spectra (1st derivative) for typical oxidation products of XI to XIV in dimethyl sulfoxide; *a*, XV formed from 5α-androstan-17β-ol-2-one; *b*, XVI and XVII formed from 5β,22a-spirostan-2-one; *c*, XV and XVIII formed from 5α-androstan-17β-ol-3-one; *d*, XVIII formed from 5β-androstan-17β-ol-3-one. Spectrum *d* shows the presence of about 15 to 25 percent of XVI but all peaks are not resolved (XVIII prepared from 4-keto-5α- or 4-keto-5β-steroids does not show this contamination). Spectra were obtained with a Varian Associates V-4500 spectrometer with 100 kc/sec field modulation. Spectra were recorded immediately after exposure to air for about 10 seconds, the solutions being approximately 0.05*M* in ketone and 0.10*M* in potassium *t*-butoxide, except in the case of spectrum *b* which was recorded a few minutes after oxygenation.

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References and Notes

1. G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.* **86**, 744 (1964).
2. E. T. Strom, G. A. Russell, R. D. Stephens, *J. Phys. Chem.*, in press.
3. G. A. Russell and E. R. Talaty, *J. Am. Chem. Soc.* **86**, 5345 (1964).
4. The general technique involves the preparation of 0.25- to 1-ml solutions of ketone (0.01 to 0.05*M*) and potassium *t*-butoxide in dimethyl sulfoxide. The solutions are deoxygenated by purified nitrogen in a U-type inverted mixing cell [G. A. Russell, E. G. Janzen, E. T. Strom, *J. Am. Chem. Soc.* **86**, 1807 (1964)], mixed, exposed to air, if necessary, and immediately introduced into a flat fused silica ESR cell ("aqueous sample cell").
5. G. A. Russell, R. D. Stephens, E. R. Talaty, *Tetrahedron Letters*, in press.
6. The oxidation of ketones having one tertiary hydrogen atom adjacent to the carbonyl group yields a low concentration of the radical formed by oxygenation at the methylene group, presumably owing to preferential ionization and oxygenation at the tertiary carbon atom to give nonradical products.
7. The ESR spectra of VII*A* and VII*B* are 1:1:2:2:1:1 patterns. VI*A* and VI*B* give resolved triplets of triplets.
8. The relative amounts of oxygenation observed at carbon Nos. 1, 2, 3, and 4 for XI–XIV agree well with studies of isolated products [E. J. Bailey, J. Elks, D. H. R. Barton, *Proc. Chem. Soc.* **1960**, 214 (1960); E. J. Bailey, D. H. R. Barton, J. Elks, J. F. Templeton, *J. Chem. Soc.* **1962**, 1578 (1962); S. Nakajima and K. Takeda, *Chem. Pharm. Bull. Tokyo* **12**, 1530 (1964)] and ultraviolet analysis [B. Camerino, B. Patelli, R. Sciaky, *Tetrahedron Letters* **1961**, 554 (1961)]. The isolated products from the oxidation in basic solution of 5β,22a-spirostan-2-one (XII) represent about one part of attack at C No. 1 to two parts of attack at C No. 3 (private communication, S. Nakajima and Dr. K. Takeda, Shionogi and Co., Ltd.).
9. We thank Professor C. H. DePuy and D. Rausch for samples of 2- and 3-*t*-butylcyclopentanones, Drs. R. Konaka, W. Nagata, K. Takeda, and Mr. S. Nakajima, Shionogi and Co., Ltd., for 17α-methyl-5α-androstan-17β-ol-2-one (XI), 5α,22a-spirostan-3-one (XIII), 5α,22a-spirostane-3,11-dione (XIII), 5β,22a-spirostan-2-one (XII), 17β-acetoxy-5β-androstan-3,11-dione (XIV), and 5β-methylcholestan-3-one; Dr. J. A. Edwards, Syntex Laboratories, Inc., for 5α-androstan-17β-ol-2-one (XI); and Dr. H. Slates, Merck and Company, Inc., for 5α,22a-spirostane-2,12-dione (XI). This paper is one of a series, *Application of Electron Spin Resonance Spectroscopy to Problems of Structure and Conformation. IV.* Supported by grants from NSF.

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