Application of Electron Spin Resonance Spectroscopy to Problems of Structure and Conformation. VII. Radical Anions Derived from Cyclohexanones and Decalones. Assignment of Structure to 19-Nor-3-keto Steroids and 18-Nor-D-homo-17-keto Steroids[1]

Erach R. Talaty and Glen A. Russell

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50010. Received July 20, 1965

Treatment of a variety of alicyclic ketones having α-methylene groups with potassium t-butoxide and oxygen in dimethyl sulfoxide produces radical anions (semidiones) or mixtures of radical anions derived from α-diketones. An analysis of the electron spin resonance (e.s.r.) spectra of these radical anions provides a means of assigning structures to the starting ketones and conformations to the semidiones. Positional isomers of alkylcyclohexanones or decalones are readily distinguished, while cis or trans configurations can be assigned to decalones and related steroidal ketones without the use of model compounds. Furthermore, 5α,10α-19-nor-3-keto steroids can be distinguished empirically from the corresponding 5β,10β-steroids and the same method can be utilized to differentiate between 13α,14α-18-nor-D-homo-17-keto steroids and the corresponding 13β,14β-steroids.

Stable radical anions derived from aromatic α-diketones (**1**, R, R′ = Ar) have been recognized for some time.[2] However, the corresponding radicals

with R = Ar, R′ = aliphatic[3a] or R = R′ = aliphatic[3-5] or the analogous alicyclic radical anions (**2**)[3a] have been detected and identified only recently. The aliphatic acylyls[6] are often stable for hours in dimethyl sulfoxide (DMSO) at 25–30° in the absence of oxygen. In fact, the acylyls with R = H and R′ = C_6H_5 or CH_3 have an appreciable stability under these conditions.[7]

Aliphatic acylyls are readily prepared by the oxygenation of monoketones,[3a,8] albeit in low yields (see

(1) Reactions of Resonance Stabilized Anions. XIX. This work was supported by a grant from the National Science Foundation and the National Institute of General Medical Sciences.

(2) L. Michaelis and E. S. Fetcher, Jr., *J. Am. Chem. Soc.*, **59**, 1246 (1937).

(3) (a) G. A. Russell and E. T. Strom, *ibid.*, **86**, 744 (1964); (b) E. T. Strom, G. A. Russell, and R. D. Stephens, *J. Phys. Chem.*, **69**, 2131 (1965).

(4) G. R. Luckhurst and L. E. Orgel, *Mol. Phys.*, **7**, 297 (1964).

(5) H. C. Heller, *J. Am. Chem. Soc.*, **86**, 5346 (1964).

(6) We suggest the use of the trivial term "acylyl" for the group of radical anions derived from α or conjugated diketones. The relationship between "ketone–ketyl" and "acylil–acylyl" is obvious. For systematic nomenclature, the term "semidione" (analogous to "semiquinone") is more adaptable; e.g., the acylyl of cyclohexane-1,2-dione can be referred to as cyclohexane-1,2-semidione.

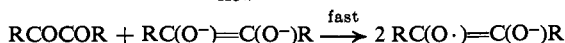(7) G. A. Russell, R. D. Stephens, and E. R. Talaty, *Tetrahedron Letters*, 1139 (1965).

the Experimental Section), and, in higher yields, by the oxygenation of α-hydroxy ketones,[3a] by the reduction of α-diketones,[3a] or from α-bromo ketones.[7,9]
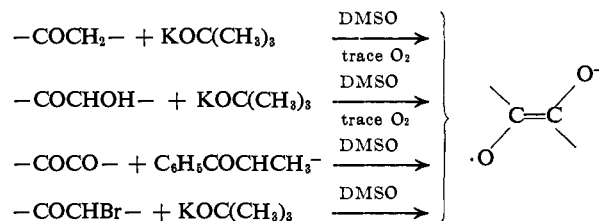

In a preliminary report we have illustrated the application of e.s.r. techniques in conjunction with base-catalyzed oxidation of 3-keto steroids to determination of the configuration of C-5 in 10β-methyl compounds.[8] These results were consistent with prior studies of the oxidation products of steroidal ketones in basic solu-

(8) G. A. Russell and E. R. Talaty, *J. Am. Chem. Soc.*, **86**, 5345 (1964).
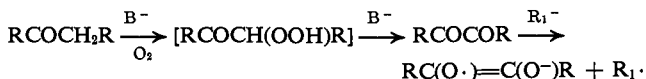
(9) Many α-hydroxy ketones, or α-diketones with an ionizable α-hydrogen atom,[7] spontaneously form acylyls in DMSO containing potassium t-butoxide in the absence of oxygen. Typical yields of acylyls are in the range of 5%. Formation of acylyls from α-bromo ketones apparently involves the formation of intermediate α-hydroxy ketones by reaction with traces of moisture. Thus, both phenacyl bromide[7] and α-hydroxyacetophenone form the phenylglyoxal semidione in the DMSO–potassium t-butoxide system in the absence of oxygen. On the other hand, phenylglyoxal itself under the reaction conditions forms the semidione of 1-phenylpropane-1,2-dione.[7] The formation of acylyls from α-hydroxy ketones may involve the slow formation of α-diketones in the presence of a large excess of the dianion of the enediol.

$$2RCOCH(OH)R \xrightarrow[\text{slow}]{B^-} RCOCOR + RCH(OH)CH(OH)R$$

$$RCOCOR + RC(O^-)\!\!=\!\!C(O^-)R \xrightarrow{\text{fast}} 2\,RC(O\cdot)\!\!=\!\!C(O^-)R$$

Oxidation of the α-hydroxy ketone to the α-dicarbonyl compound by DMSO in the presence of base may also be involved as well as the direct

$$RCOCH(OH)R + DMSO \xrightarrow{B^-} RCOCOR + DMS + H_2O$$
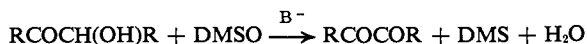
conversion (N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957)) of the α-bromo ketone to the α-dicarbonyl compound. Additional evidence on this point is the observation that 3-bromo-2-butanone and 3-hydroxy-2-butanone spontaneously form butane-2,3-semidione under the reaction conditions whereas biacetyl gives rise to the 2,5-dimethyl-p-benzosemiquinone.[3b] Autoxidation of 2-butanone in basic solution also forms this p-benzosemiquinone. Thus, we feel that the major route to semidiones in the oxidation of monoketones involves the α-diketone as an intermediate. The intermediacy of α-dike-

$$RCOCH_2R \xrightarrow[O_2]{B^-} [RCOCH(OOH)R] \xrightarrow{B^-} RCOCOR \xrightarrow{} $$
$$RC(O\cdot)\!\!=\!\!C(O^-)R + R_1\cdot$$

tones is consistent with epimerization at α-carbon atoms in the semidiones, exchange of α-hydrogen atoms with deuterium when the oxidations are conducted in d_6-DMSO, and the yellow or orange colors produced immediately after the exposure of the basic solutions to oxygen.

tion.[10-15] In the present work we illustrate how this technique can be applied, without reference to model compounds, to assign structures to substituted cyclohexanones (positional isomers) or to assign configurations to ring junctures in β-decalones (*cis–trans* isomers) and related steroids lacking angular methyl groups. In addition, an analysis of the e.s.r. spectra of the semidiones is a delicate probe of the conformations of these cyclohexene derivatives.

Results and Discussion

Cyclohexanones. It was shown previously that when solutions of cyclohexanone and potassium *t*-butoxide in DMSO(80%)–*t*-butyl alcohol(20%) are exposed to a trace of air, **3a** is produced.[3a] We have found that

3a, R = H
b, R = (CH₃)₃C
c, R = (CH₃)₂CH
d, R = CH₃
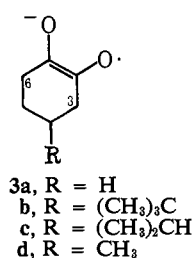
not only is **3a** formed by oxygenation in pure DMSO as solvent, but that treatment of cyclohexane-1,2-dione with potassium *t*-butoxide in DMSO in the absence of air also generates **3a**, presumably by electron transfer.[16] The e.s.r. spectrum of **3a** is similar
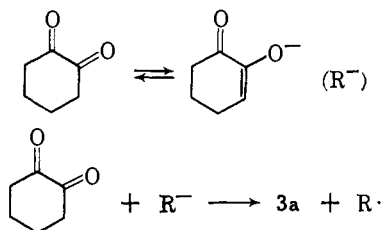
in pure DMSO (a^H = 9.83 gauss) and in the mixed solvent (a^H = 9.82 gauss). At 25° there is no evidence of conformational stability of the cyclohexene ring and all four hydrogen atoms α to the diketone system are magnetically equivalent. Hyperfine splitting by hydrogen atoms β to the dicarbonyl system must be <0.05 gauss.

In cyclohexane-1,2-semidione, and 3,3- or 4,4-dialkyl derivatives (see below), the time averaging between axial and equatorial positions at 25° must occur in significantly less time than the precession of the electron magnetic moment around the axis of the nuclear magnetic moment. This corresponds to a conformational lifetime much less than $1/\nu$ where ν = $2.8a^H$

(10) E. J. Bailey, J. Elks, and D. H. R. Barton, *Proc. Chem. Soc.*, 214, (1960); E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).
(11) R. Hanna and G. Ourisson, *Bull. soc. chim. France*, 1945 (1961).
(12) B. Camerino, B. Patelli, and R. Sciaky, *Tetrahedron Letters*, 554 (1961).
(13) W. G. Dauben, G. A. Boswell, and W. Templeton, *J. Org. Chem.*, 25, 1853 (1960).
(14) L. J. Chinn, *ibid.*, 29, 3304 (1964).
(15) S. Nakajima and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), 12, 1530 (1964).
(16) (a) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, 86, 1807 (1964); (b) G. A. Russell and E. G. Janzen, *ibid.*, 84, 4155 (1962).

in Mc.p.s. Using 9.8 gauss for a^H yields ν = 25 × 10⁶ c.p.s. and $1/\nu$ = 4 × 10⁻⁸ sec. At slower rates of interconversion of axial and equatorial positions a 1:2:1:2:4:2:1:2:1 (slow) or 1:4:1 (intermediate rate) spectrum is expected.[17] Recent estimates of ΔH^* for half-chair interconversions in cyclohexene,[18a] or 4-bromocyclohexene,[18b] are in the range of 5–6 kcal./mole. At 25° a cyclohexane chair conformation (ΔF^* = 10–11 kcal./mole) has an average lifetime 4000 times greater than a half-chair conformer of cyclohexene (ΔF^* = 5.3 kcal./mole).[18a]

A. gem-Disubstituted Cyclohexanones. 2,2-Dimethylcyclohexanone forms upon oxidation a single radical anion (**4a**) with a 1:2:1 triplet structure and with a^H = 9.74 gauss. The conformational interconversion

4a, R = R' = CH₃; R'' = R''' = H
b, R = R' = H; R'' = R''' = CH₃
c, R = CH₃; R' = R'' = R''' = H
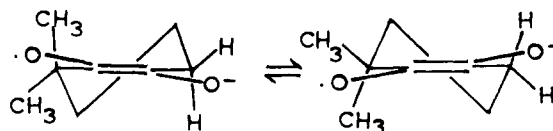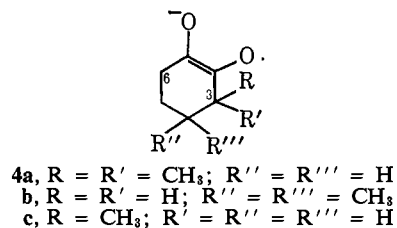
is so rapid that the α-hydrogen atoms spend equal time in quasi-axial and quasi-equatorial conformations. 4,4-Dimethylcyclohexanone also gives a single radical anion (five groups of lines) with two nearly equivalent pairs of α-hydrogen atoms, a^H = 9.74 and 9.41 gauss. By analogy to the 2,2-dimethyl isomer and the unsubstituted acylyl, the hydrogens at C-6 are assigned the 9.74-gauss splitting and the hydrogens at C-3 the 9.41-gauss splitting. The first, second, and third multiplets of the symmetrical spectrum are shown in Figure 1.

B. Monosubstituted Cyclohexanones. Oxidation of 2- or 4-monosubstituted cyclohexanones gives spectra consistent with a single radical anion (**4c, 3b–3d**). Because of the asymmetry at the substituted carbon atom both half-chair conformers are not expected to be present in equal concentrations and the conformer with a quasi-equatorial substituent should be preferred. As a result one pair of hydrogen atoms (at C-3 and C-6) should spend more time in the quasi-axial configuration while the other α-hydrogen atom or pair of α-hydrogen atoms should be predominantly in the quasi-equatorial configuration. We have no evidence that conformational interconversion of the two half-chair structures is prevented even with a 4-*t*-butyl group, although we will presently show that such interconversions are prevented in the corresponding Δ^2-semidiones of *cis*- and *trans*-decalins. Because the two α-methylene groups are not chemically equivalent, small differences between the splitting constants of the "equatorial" or of the "axial" hydrogen atoms at C-3 and C-6 might have been expected. However, for **3b–3d** we have not been able to resolve such differences.

(17) S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, 41, 994 (1964).
(18) (a) F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.*, 87, 3147 (1965); (b) F. R. Jensen and C. H. Bushmeller, *ibid.*, 87, 3285 (1965).
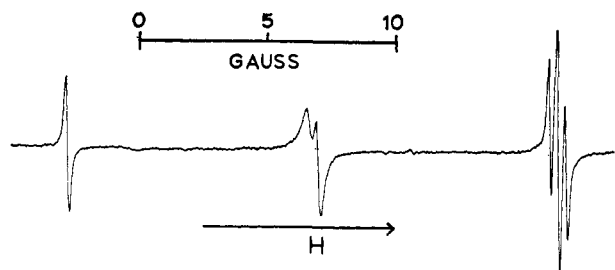
Figure 1. First-derivative e.s.r. spectrum showing the first three low-field multiplets of the symmetrical five-multiplet spectrum observed for the oxidation product of 4,4-dimethylcyclohexanone in dimethyl sulfoxide at 25°.
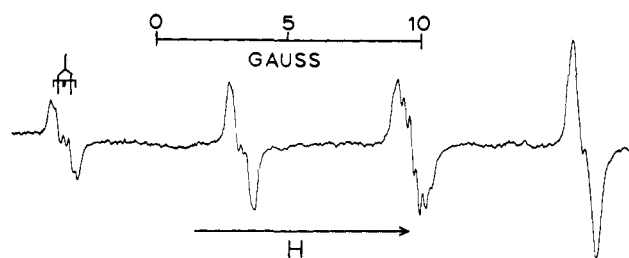

Figure 2. First-derivative e.s.r. spectrum showing the first four low-field multiplets of the symmetrical seven-multiplet spectrum observed for the oxidation product of 4-t-butylcyclohexanone in dimethyl sulfoxide at 25°.

The larger splitting constants have been assigned to the "axial" hydrogens from an elementary consideration of dihedral angles.[3a] Table I lists the observed values of the hyperfine splitting constants.

Table I. Hyperfine Splitting Constants for Substituted Cyclohexane-1,2-semidiones (gauss)

Substituent	a^H_{ax}	a^H_{eq}	$2(a^H_{av})$
4-t-Butyl (**3b**)	13.02	6.64	19.66
4-Isopropyl (**3c**)	12.63	7.02	19.65
4-Methyl (**3d**)	12.33	7.34	19.67
3-Methyl (**4c**)	11.15,[a] 10.29	8.56	19.71[a]
Unsubstituted (**3a**)		9.83	19.66
3,3-Dimethyl (**4a**)		9.74	19.48
4,4-Dimethyl (**4b**)		9.74,[a] 9.41	19.48[a]
trans-Δ^2-Decalin semidione (**10**)	13.18[b]	6.59[b]	19.77

[a] Assumed to be at C-6. [b] These and other h.f.s.c. are considered to be more accurate than those obtained previously[8] with a spectrometer having a 6-in. magnet.

Under high resolution the spectrum of **3b** shows a further hyperfine splitting. Figure 2 shows the first, second, third, and fourth multiplets of the symmetrical seven-peak spectrum observed for **3b**.[3a] Peaks 1, 2, 4, 6, and 7 show a quintet splitting, caused possibly by a partially overlapping doublet of 1:2:1 triplets, a^H = 0.19, 0.19, 0.45 gauss. Peaks 3 and 5 show considerable fine structure, in part due to the fact that a^H_{eq} is not exactly $1/2a^H_{ax}$. The splitting of these two peaks seems most consistent with a heptet splitting composed of overlapping quintets with an average distance between peaks of about 0.22 gauss. This hyperfine splitting into quintets may result from the three hydrogen atoms β to the dicarbonyl system, although no two of these atoms would have been expected to be magnetically exactly equivalent because of the conformational preference of the t-butyl group. Additional hyperfine splitting (that is, besides that produced by interaction with α-hydrogen atoms) is less pronounced in **3c** and has not been detected in **3d**.[19]

It is tempting to calculate the relative concentrations of the two conformers (quasi-axial substituent and quasi-equatorial substituent) from the data of Table I.

(19) The factors that control the magnitude of long-range splittings by hydrogens attached to carbon atoms β or γ to a carbon p_z orbital containing unpaired spin density will be discussed in future publications. Such splittings are very sensitive to geometry and are most pronounced in rigid systems (unpublished results with Drs. K. Y. Chang and R. D. Stephens).

However, this would require that the hyperfine splitting constants for purely quasi-axial and quasi-equatorial α-hydrogen atoms be known, that alkyl substituents do not have an appreciable effect upon these hyperfine splitting constants (or that at least a correction for the effect of an alkyl group can be made), and that only half-chair conformers are involved. That alkyl substituents at C-4 do create small differences in the magnetic environments of quasi-axial (or quasi-equatorial) hydrogens at C-3 and C-6 has already been shown from a consideration of the oxidation product of 4,4-dimethylcyclohexanone. However, a single alkyl substituent at C-4 does not seem to have a significant effect on the hyperfine splitting constants for hydrogens at C-3 as evidenced by the constancy of the sum of a^H_{ax} and a^H_{eq} in Table I. It is well known that trans-decalin shows a great preference for the double-chair conformation in which the hydrogen atoms at the ring junction are axial. Hence, we have selected the trans-Δ^2-decalin semidione as a model for assigning values to hyperfine splittings of purely quasi-axial and quasi-equatorial hydrogen atoms, namely, 13.18 and 6.59 gauss, respectively. Using these values as measures of the hyperfine splittings of frozen quasi-axial and quasi-equatorial hydrogen atoms in unsubstituted and in 3- and 4-monosubstituted cyclohexane-1,2-semidiones, the fraction (x) of semidione existing in the thermodynamically more stable conformation (quasi-equatorial alkyl substituent) can be calculated by the equations

$$\text{observed } a^H_{ax} = 13.18(x) + 6.59(1 - x)$$

$$\text{observed } a^H_{eq} = 6.59(x) + 13.18(1 - x)$$

The results of this simple calculation are summarized in Table II.

Table II. Conformational Preferences of Substituted Cyclohexane-1,2-semidiones in DMSO at 25 ± 3°

| Substituent | Fraction of molecules in thermodynamically stable conformation (x) | | |
	Calcd. from a^H_{ax}	Calcd. from a^H_{eq}	"A"-value,[a] kcal./mole
4-t-Butyl	0.98	0.99	>2.3[b]
4-Isopropyl	0.92	0.93	1.5
4-Methyl	0.87	0.89	1.2
3-Methyl	0.69	0.70	0.49

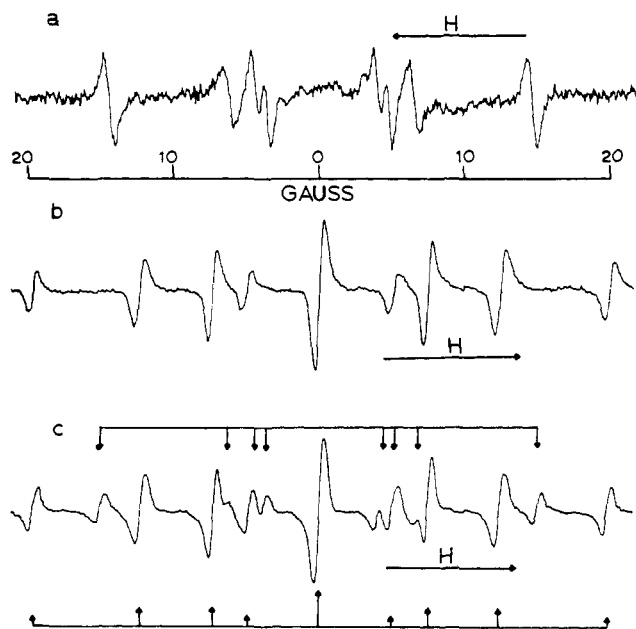[a] Calculated using the equation $A = RT \ln K$.[20] [b] Assuming x to be at least 0.98.

Figure 3. First-derivative e.s.r. spectra for the oxidation products of methylcyclohexanones in dimethyl sulfoxide at 25°: a, 2-methylcyclohexanone; b, 4-methylcyclohexanone; c, 3-methyl-cyclohexanone.

The "A"-values obtained from these data in our cyclohexene-type system are considerably less than the A-values calculated for the cyclohexane system.[20]

The position of conformational equilibrium of the 3-methylcyclohexane-1,2-semidione is somewhat surprising in view of the much greater stability of one conformation of the 4-methyl analog. Presumably in both cases the thermodynamically stable conformer is the one involving a quasi-equatorial alkyl substituent. For the 3-methyl compound this conformer is de-stabilized owing to eclipsing of the methyl group and the oxygen atom.[21] From the hyperfine splitting constants
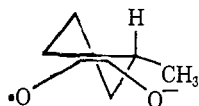

of Table I (two large, one small), it does appear certain that the hydrogen at C-3 must be mainly (69%) in the quasi-axial position and that the most stable conformer does involve a quasi-equatorial methyl group.[22]

(20) S. Winstein and N. J. Holness, J. Am. Chem. Soc., 77, 5562 (1955).
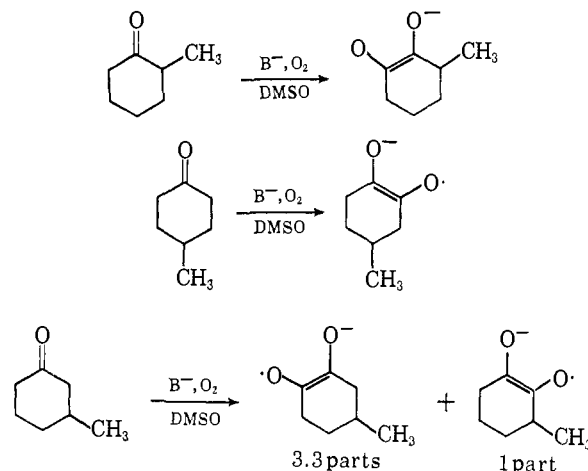
(21) Similar conclusions have been reached in conformational studies of 1,6-disubstituted cyclohexenes: E. W. Garbisch, Jr., J. Org. Chem., 27, 4249 (1962).

(22) All of the calculations on conformational preference in the present paper have been based on the assumption that boat conformers need not be considered. Some evidence can be presented to support this assumption. For cyclohexene itself the boat conformer has been shown not to represent an energy minimum: R. Bucourt and D. Hainaut, Compt. rend., 258, 3305 (1964). In the trans- Δ²-octalin derivative used as a model, a boat conformation cannot be achieved in the unsaturated ring.

The most likely chair-boat equilibrium for a monosubstituted cyclohexane semidione should have a pronounced effect on the hyperfine
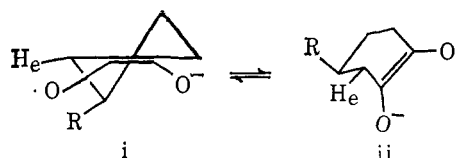
C. Analysis of Isomeric Cyclohexanones by E.s.r. Spectroscopy. Application of the results of the previous section provides a convenient method of analysis of a variety of substituted cycloalkanones. The semidiones derived from 2,2-dimethyl- and 4,4-dimethylcyclohexanones are readily distinguished (vide supra). The application of this technique to the three isomeric methylcyclohexanones is illustrated in Figure 3. Oxi-

dation of 2-methylcyclohexanone yields a single radical anion (4c)[23] (Figure 3a) whose e.s.r. spectrum consists of eight lines of nearly unit intensity. This spectrum requires a radical anion with three non-equivalent α-hydrogen atoms.[24] 4-Methylcyclohexanone gives the single radical anion (3d) shown in Figure 3b whose spectrum demands four α-hydrogen atoms of which two exist mainly in the axial conformation and two mainly in the equatorial conformation. 3-Methylcyclohexanone produces a mixture of 3d and 4c (Figure 3c). The fact that the spectrum of Figure 3c represents a mixture of radical anions is easily ascertained since the peaks due to 4c decay more rapidly than those due to 3d. Exposure to additional oxygen also causes the destruction of 4c in preference to 3d.[24a]

splitting constants (h.f.s.c.) of the α-hydrogen atoms. Since the h.f.s.c. is determined by the dihedral angle between the carbon–hydrogen bond and the p_z orbital of the carbonyl carbon,[3a] the h.f.s.c. of H_e in ii ($\theta \sim 90°$) would be much less than for H_e in i. However, the time averaged "equatorial" h.f.s.c. of α-hydrogens in 3b–3d or 4a–4c are never less than the pure equatorial h.f.s.c. observed for trans-Δ²-decalin semidione.

(23) Oxidation of ketones with a single α-substituent yields a lower concentration of acylyl radical anions than an unsubstituted or α,α-disubstituted ketone. This is apparently due to preferred ionization and oxygenation at the tertiary carbon atom to give nonradical products.

(24) The position of the hydrogen atoms can be checked by oxidation in d_6-DMSO wherein α-hydrogen atoms are replaced by α-deuterium atoms: G. A. Russell and K. Y. Chang, J. Am. Chem. Soc., 87, 4381 (1965).

(24a) NOTE ADDED IN PROOF. After this manuscript was submitted a pertinent publication appeared: J. W. Lown, Can. J. Chem., 43, 2571 (1965). Lown makes the startling conclusion that ketyls ($R_2CO\cdot^-$) of cyclohexanone and cyclopentanone can be prepared at room temperature or above by the reaction of potassium with the cycloalkanones in dimethoxyethane solution. The "ketyls" are apparently formed in low yield but are quite stable at room temperature once formed. The spectra reported for the "ketyls" of cyclopentanone, cyclohexanone, and 4-t-butylcyclohexanone are essentially identical with the spectra previously reported for the corresponding semidiones.[3a] Significantly different hyperfine splitting constants for a ketyl and an acylyl are not expected. Thus, the spin density of a carbonyl group is about 0.4 in both benzophenone ketyl and benzil semidione: P. H. Rieger and G. K. Fraenkel, J. Chem. Phys., 37, 2811 (1962); R. Dehl and G. K. Fraenkel, ibid., 39, 1793 (1963).

The spectra reported by Lown for 3- and 4-methylcyclohexanone "ketyls" are not highly resolved but appear consistent with a single

Presumably 3,3-dialkylcyclohexanones would also give a mixture of $\Delta^{1(2)}$- and $\Delta^{1(6)}$-acylyls. Since *gem*-dialkylcyclohexane-1,2-semidiones have magnetically equivalent quasi-axial and quasi-equatorial α-hydrogen atoms on a time average basis, there should be no problem in differentiating *gem*-dialkylcyclohexanones from other dialkylcyclohexanones.

Spectrum 3c illustrates the application of e.s.r. techniques to the question of the preferred direction of ionization of unsymmetrical ketones having two chemically different α-methylene groups. Probably the ratio of **3d** to **4c** formed from 3-methylcyclohexanone reflects the relative rates of ionization at C-6 and C-2 and/or the relative equilibrium concentrations of the $\Delta^{1(6)}$- and $\Delta^{1(2)}$-enolate anions. In support of this presumption, the bromination of 3-methylcyclohexanone in *t*-butyl alcohol containing potassium *t*-butoxide followed by treatment with DMSO yields the same ratio of **3d** to **4c** as formed in the oxygenation of the monoketone.[7]

1-Decalone and Related 19-Nor- and 18-Nor-D-homosteroidal Ketones. Oxidation of cis-1-decalone gives rise to a single radical anion (**5**), whose spectrum at low resolution is a 1:1:2:2:1:1 sextet from nearly

5
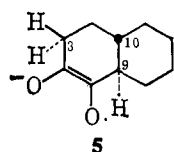
equivalent "axial" hydrogens ($a^H \sim 13$ gauss) at C-3 and C-9 and the "equatorial" hydrogen atom ($a^H = 7.09$ gauss) at C-3. Evidence for epimerization at C-9 in the formation of **5** is found in the fact that the same sextet is one of the oxidation products of both cis- and trans-2-decalone (see Figures 5 and 6). At higher resolution it becomes apparent that the axial hydrogen atoms in **5** are not exactly equivalent ($a^H = 12.66$, 13.17 gauss) and that a further splitting, presumably from certain hydrogen atoms β to the dicarbonyl system, is observed.[19] This splitting causes peaks 1, 2, 5, and 6 of the spectrum of **5** to be split into quintets (having intensities approximately equal to 1:4:6:4:1) ($a^H = 0.28$ gauss) and peaks 3 and 4 to be split into heptets (overlapping quintets) with intensities approximately equal to 1:4:7:8:7:4:1. Substitution of a methyl group at C-9 in cis-2-decalone gives rise upon oxidation to a mixture of radical anions (Δ^1 and Δ^2) of which the Δ^1 radical anion involves hyperfine splitting by two magnetically different α-hydrogen atoms, $a^H = 12.95$ and 7.11 gauss, assigned to "axial" and "equatorial" hydrogens, respectively. This result lends further support to our

radical anion from the 4-methyl compound and the same radical anion plus another from the 3-methyl compound (see Figure 3).

Dr. D. C. Lini in our laboratories had previously attempted to prepare the ketyls of cycloalkanones by the technique described by Lown. He found that an e.s.r. signal consistent with the *oxygenated semidione* was detectable under conditions of incomplete deoxygenation. With careful deoxygenation using helium passed through a ketyl trap, we cannot detect any e.s.r. signal from the reaction of potassium with cyclohexanone in dimethoxyethane solution. Exposure of such solutions to traces of air produces e.s.r. signals consistent with the semidiones including the formation of two radical anions from 3-methylcyclohexanone. We conclude that Lown actually observed the acylyls rather than ketyls and that reaction of a cycloalkanone with potassium or NaK in dimethoxyethane, tetrahydrofuran, or hexamethylphosphoramide in the presence of a trace of air is an alternative method of synthesis of acylyls.
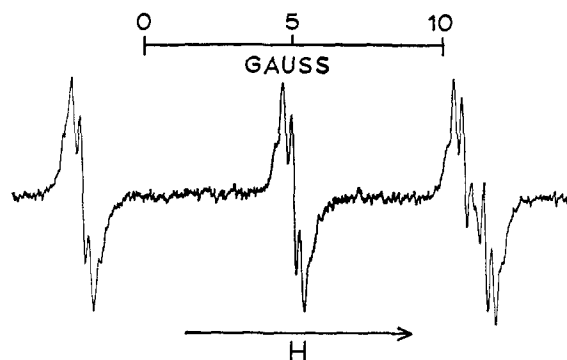

Figure 4. First-derivative e.s.r. spectrum (low-field half) of acylyl prepared from $3\beta,17\beta$-dihydroxy-17α-methyl-19-nor-5α-androstan-4-one in dimethyl sulfoxide at 25°, showing further resolution of the 1:1:2:2:1:1 sextet observed at low resolution.

contention that the two nearly equivalent pair of hydrogen atoms in **5** are the "axial" hydrogens at C-3 and C-9.

The formation of a single radical anion (*trans* form) from cis-1-decalone is interesting in view of the work of House and Trost[25] who showed that a significant amount of the cis-enolate accompanies the *trans*-enolate when 1-decalone is treated with lithium or potassium triphenylmethide in 1,2-dimethoxyethane under conditions favoring either kinetic or thermodynamic control of products. The difference between our results and those of House and Trost may be ascribed to the different conditions used, or to kinetic discrimination in the conversion of the two enolates to radical anions (either in the formation of diketone intermediates or in their subsequent one-electron reduction), or to different positions of equilibrium of enolates and acylyls.

By analogy with the results of oxidation of 1-decalone, one may expect oxidation of 1-, 4-, 15-, or 17a-ketones in the 19-nor- and 18-nor-D-homo series of steroids to produce a single radical anion, similar to **5**, with hyperfine splitting by three hydrogen atoms which are either magnetically nonequivalent or of which two are magnetically nearly equivalent. Treatment of 17α-methyl-19-nor-5α-androstane-$3\beta,17\beta$-diol-4-one (**6**) with potassium *t*-butoxide in DMSO in the absence of air produces a radical anion[9] which exhibits a sextet splitting (1:1:2:2:1:1) under low resolution and to which structure **6a** is assigned. Under higher resolu-
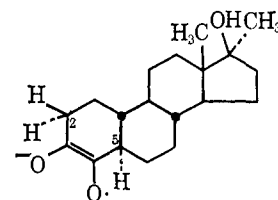
6a

$a^H = 13.66$, 12.89, 7.13 gauss

tion, peaks, 1, 2, 5, and 6 are split into quintets ($a^H = 0.29$ gauss), while peaks 3 and 4 are split into octets (two sets of overlapping quintets) (Figure 4). Oxidation of 18-nor-D-homo-5β-androstan-3α-ol-17α-one (**7**) gives a similar radical anion the spectrum of which is

(25) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965); however, we have found cis- and trans-Δ^2-semidiones for the 9-methyldecalins.
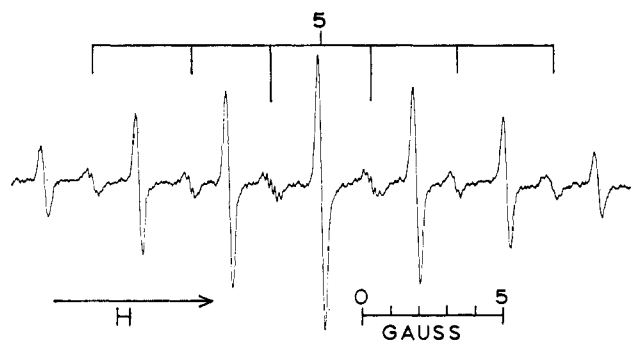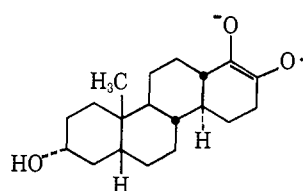
Figure 5. First-derivative e.s.r. spectrum of mixtures of acylyls formed in the oxidation of *trans*-2-decalone in dimethyl sulfoxide at 25°.

consistent with structure **7a**. Oxidation of 4β-methyl-19-nor-5α-androstan-17β-ol-1-one (**8**) affords an anion radical which contains three magnetically nonequivalent

7a
$a^H = 13.75, 12.87, 7.10$ gauss

α-hydrogen atoms and to which structure **8a** has been assigned. Presumably, the larger splittings in **8a** are due to
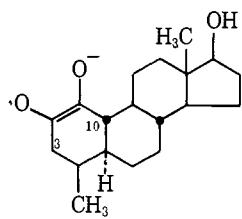

8a
$a^H = 13.08, 10.84, 5.95$ gauss

the quasi-axial hydrogen atoms at C-3 and C-10 and the smaller splitting due to the quasi-equatorial hydrogen at C-3.[26] Finer splittings were not resolved because of the low concentration of radicals.[23] At higher amplification a second radical anion, possibly the *cis* isomer (**10α**) of **8a**[25] can be detected.

2-Decalones. Oxidation of *cis*-2-decalone and *trans*-2-decalone gives rise to mixtures of **5** and **9**, and **5** and **10**, respectively. The hyperfine splittings observed for **5** and **10** demand preferred conformations for these

(26) The low value of a^H_{eq} suggests the presence of a boat conformation for the A-ring. Boat conformations are feasible for the unsaturated
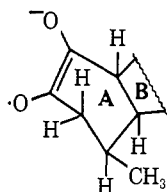
rings of Δ^{1(2)}-octalins and the corresponding steroids in which the adjacent saturated ring (ring B) maintains a chair conformation. With the exception of the 4β-methylsteroid derivative we do not see any evidence that such boat conformations are of importance based on a comparison of h.f.s.c. of *trans*-Δ^{1(2)}- and *trans*-Δ²-decalin semidiones.[22]
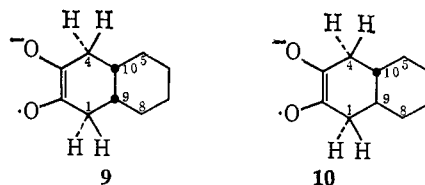
9   **10**
$a^H = 13.83, 12.72, 7.37, 6.55$ gauss $a^H = 13.18, 13.18, 6.59, 6.59$ gauss

trans-octalin derivatives at 25–30°. In the case of **9**, the data demand a frozen conformation in terms of e.s.r. frequency (approximately 9500 Mc.p.s.) since otherwise the hydrogen atoms of the methylene groups would be magnetically equivalent as is the case for cyclohexane-1,2-semidione and *gem*-dimethylcyclohexane-1,2-semidiones.[27] This result allows an immediate distinction to be made between the *cis* and *trans* structures by e.s.r. spectroscopy *without reference to model compounds.* The C-1 and C-4 hydrogen atoms in **9** are adjacent to carbon atoms (C-9 and C-10) which differ in that one has an equatorial and one an axial methylene group (C-5 and C-8) relative to the cyclo-

trans-octalin, H_1, H_4 magnetically equivalent   *cis*-octalin, H_1, H_4 magnetically not equivalent

hexene ring. In **10** the methylene substituents (C-5 and C-8) at both C-9 and C-10 are equatorial relative to the cyclohexene ring. Thus, *trans*-2-decalone produces a Δ²-semidione that contains two pairs of magnetically equivalent hydrogen atoms α to the dicarbonyl system (quasi-equatorial hydrogen atoms at C-1 and C-4, and quasi-axial hydrogen atoms at C-1 and C-4), whereas *cis*-2-decalone produces a Δ²-semidione containing four magnetically different α-hydrogen atoms. The resulting e.s.r. spectra are immediately distinguishable. Two pairs of magnetically equivalent hydrogen atoms will produce a triplet of triplets or by fortuitous overlap a 1:2:3:4:3:2:1 spectrum, *i.e.,* 9 or 7 lines. Four magnetically different hydrogen atoms can give spectra that contain 11–16 lines. The 16-line spectrum would contain lines of equal intensity whereas the other intensity patterns occurring because of fortuitous overlap are (15-line) 1:1:1:1:1:1:1:2: 1:1:1:1:1:1:1; (14-line) 1:1:1:1:1:2:1:1:2:1:1: 1:1:1, 1:1:1:1:2:1:1:1:1:2:1:1:1:1, and 1:1:1:2: 1:1:1:1:1:1:2:1:1:1; (13-line) 1:1:1:1:1:2:2:2:1: 1:1:1:1, 1:1:1:1:2:1:2:1:2:1:1:1:1, and 1:1:1: 2:1:1:2:1:1:2:1:1:1; (12-line) 1:1:1:2:2:1:1:2:2: 1:1:1; and (11-line) 1:1:1:2:2:2:2:2:1:1:1 (a_1^H: a_2^H:a_3^H:a_4^H = 1:2:3:4).

All of the *trans*-2-decalones that we have studied give the 7-line pattern (Figure 5) for the Δ²-acylyl.

(27) A boat conformation for the unsaturated ring is possible in a *cis*-Δ²-octalin (provided the saturated ring simultaneously assumes a boat conformation). Comparison of the h.f.s.c. of **10** (boat conformation impossible for unsaturated ring) and **9** suggests that **9** does not exist in a boat conformer to any appreciable extent.[22] The same conclusion is reached when the Δ²-acylyls of steroids with a *cis*-A/B ring fusion are considered. In the steroids with a *cis*-A/B ring fusion a boat conformation for ring A of a Δ²-semidione is prevented due to ring B being locked in a chair conformation. It is of interest that *cis*-decalin may exist in a double twist conformation: P. Geneste and G. Lamaty, *Bull. soc. chim. France*, 2439 (1964); see, however, F. G. Riddell and M. J. T. Robinson, *Chem. Commun.* (London), 1, 227 (1965).

The cis-Δ^2-acylyl in the unsubstituted decalone system gives the second of the 13-line patterns listed in Figure 6. Hyperfine splittings due to hydrogen atoms β to the dicarbonyl system in 9 and 10 have not been resolved.
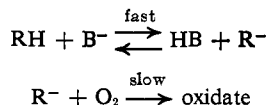
Initially, trans-2-decalone produces approximately three parts of the Δ^2-acylyl (10) to one of the Δ^1-acylyl (5) while cis-2-decalone produces approximately 1.5 parts of the Δ^1-acylyl (5) to one of 9. Upon standing 5 decays more rapidly than 9 or 10. Thus, 8 hr. after oxygenation of trans-2-decalone, only 10 can be detected.

Epimerization at C-9 in the formation of the Δ^1-acylyl from cis- or trans-2-decalone may involve the 1,2-diketone as an intermediate.[9] Consistent with this view is the fact that when the oxygenation is
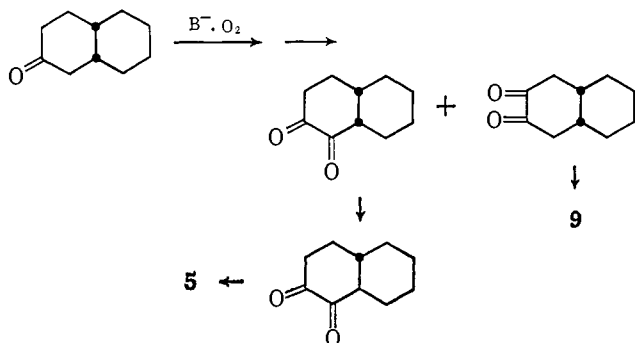
conducted in d_6-DMSO all hydrogen atoms of the α-methylene groups or of the α-methine group are exchanged.

At present we are not completely certain whether the observed products of oxygenation represent kinetically or thermodynamically controlled ionizations. We have seen no significant difference in the ratio of products formed when trans-2-decalone is allowed to ionize for 10 min. before oxygenation and when ketone, base, and oxygen are mixed simultaneously with either ketone or base in excess of a 1:1 molar ratio. Moreover, we will report in the future that in the oxygenation of acetophenone or fluorene in basic solution under similar conditions the kinetic processes involved are[28]

$$\text{RH} + \text{B}^- \underset{\text{}}{\overset{\text{fast}}{\rightleftharpoons}} \text{HB} + \text{R}^-$$

$$\text{R}^- + \text{O}_2 \xrightarrow{\text{slow}} \text{oxidate}$$

It thus appears most likely that we have measured the thermodynamic equilibrium of Δ^1- and Δ^2-enolate anions in our oxygenation studies of the 2-decalones.[29] By infrared spectroscopy it was estimated that approximately 75% of trans-2-decalone is enolized 3 min. after treatment with base under the usual conditions of our experiments (see the Experimental Section for details).

It is of interest to compare our results with the alkylation studies of Stork, et al,[30] who have re-

(28) A. G. Bemis, unpublished results; see also G. A. Russell and A. G. Bemis, Chem. Ind. (London), 1262 (1965).

(29) Under the reaction conditions, the rate of oxidation of ketones such as propiophenone is independent of the concentration of base.[28] This result indicates that the acid-base equilibrium is extensively on the side of the enolate anion.

(30) G. Stork, P. Rosen, and N. L. Goldman, J. Am. Chem. Soc., 83, 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, ibid., 87, 275 (1965).
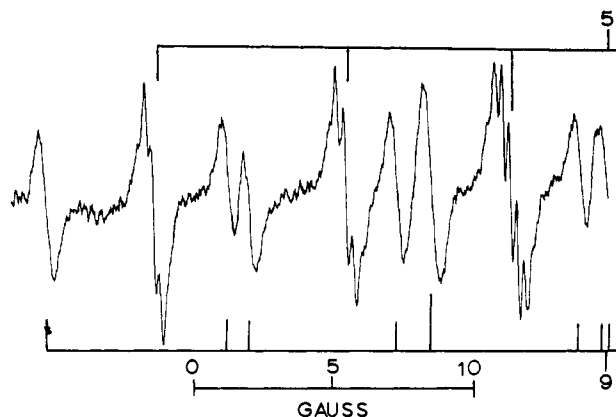
Figure 6. First-derivative e.s.r. spectrum (low-field half) of a mixture of acylyls formed by oxidation of cis-2-decalone in dimethyl sulfoxide at 25°. The central peak in the 13-line spectrum of the minor radical (9) has a tendency to split into a doublet.

ported that alkylation of the lithium–ammonia reduction products of $\Delta^{1(9)}$-2-octalones yields the 1-alkyl-trans-2-decalones in liquid ammonia, but when the ammonia is replaced by DMSO (after reduction) only the 3-alkyl-trans-2-decalones are formed. This result was explained in terms of the thermodynamic stability of the enolate anions and the slow interconversion of enolate anions. Our experiments with
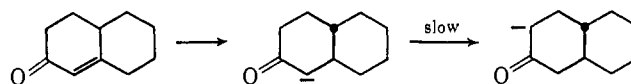
trans-2-decalone suggest that considerable amounts of the Δ^1-enolate (25%) should be present at equilibrium in DMSO at 25–30°. The absence of the 1-alkyl-2-decalone in the alkylation experiments in DMSO may involve isolation techniques or kinetic discrimination between the Δ^1- and Δ^2-enolates in the alkylation, or possibly oxidation, reactions.

The proportions of the radical anions obtained in the oxidation of the decalones generally do not agree with the proportions of the enolates produced in the ionization of the same decalones under conditions of either kinetic or thermodynamic control in 1,2-dimethoxyethane as reported recently by House and Trost.[25] Appropriate data are summarized in Table III. Our values are closest to the kinetically controlled values

Table III. Composition of Mixtures of Enolates and Acylyls from Decalones

Decalone	cis-$\Delta^{1(2)}$	trans-$\Delta^{1(2)}$	cis-Δ^2	trans-Δ^2
1-Decalone	22[a]	68[a]		
	13[b]	21[b]		
		100[c]		
trans-2-Decalone		13[a]		87[a]
		53[b]		47[b]
		25[c,d]		75[c,d]
cis-2-Decalone	68[a]		32[a]	
	68[b]		32[b]	
	60[c]		40[c]	

[a] Enolates, kinetic control, triphenylmethyllithium, 1,2-dimethoxyethane.[25] [b] Enolates, equilibrium control, triphenylmethyllithium, 1,2-dimethoxyethane.[25] [c] Acylyls, dimethyl sulfoxide, potassium t-butoxide, 25 ± 3°. [d] Same ratio when oxygen present during ionization or when ionization precedes oxygenation.
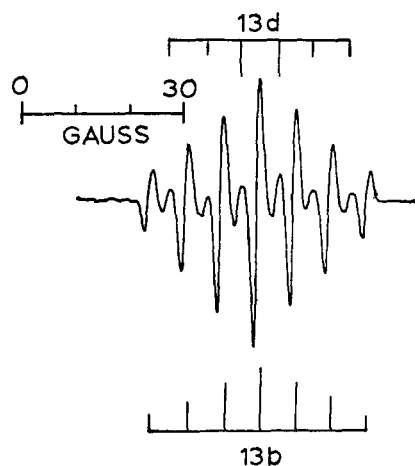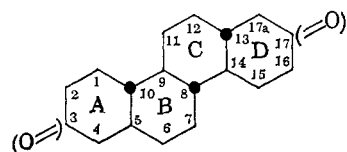
Figure 7. Low-resolution, first-derivative e.s.r. spectrum formed in the oxidation of 3-methoxy-D-homo-18,19-bisnorandrosta-1,3,5(10)-trien-17-one in dimethyl sulfoxide at 25°.

Figure 8. First-derivative e.s.r. spectrum of a mixture of acylyls formed in oxidation of 3-methoxy-D-homo-18,19-bisnor-13α,14α-androsta-1,3,5(10)-trien-17-one in dimethyl sulfoxide at 25°.

reported by House and Trost. In the case of cis-2-decalone where kinetic and thermodynamic control give the same ratios of $\Delta^{1(2)}$- and Δ^2-enolates, we find excellent agreement between our work and that of House and Trost.

19-Nor-3-keto Steroids and 18-Nor-D-homo-17-keto Steroids. The principles used to differentiate *cis*- and *trans*-2-decalones can be applied directly to steroids of the 19-nor-3-keto and 18-nor-D-homo-17-keto series. Formation of an acylyl with either the 1:2: 3:4:3:2:1 or the triplet of triplets spectrum will be characteristic of a *trans*-A/B or -C/D ring juncture in the 19-nor and 18-nor-D-homo series, respectively, whereas a 11–16 line spectrum will be characteristic of a *cis*-A/B or -C/D ring juncture. Since 3-keto-19-nor and 17-keto-18-nor-D-homo steroids can be enantiomers and can give identical oxidates, we have examined as many such pairs of 3- and 17-ketones as possible.

19-Nor-5α,10β-androstan-17β-ol-3-one **(11)**, 17β-acetoxy-19-nor-5α,10β-androstan-3-one **(11a)**, 3-methoxy-D-homo-18,19-bisnorandrosta-1,3,5(10)-trien-17-one **(12)**,[31] 3α,11α-diacetoxy-D-homo-18-nor-5β-androstan-17-one **(12a)**,[32] and 3α-hydroxy-D-homo-18-nor-5β-androstane-11,17-dione **(12b)**[32] are enantiomers as far as the partial structures shown are concerned and give rise to identical oxidates (Figure 7) in which the Δ^2- **(13a)** or Δ^{16}-acylyl **(13b)** predominates over the Δ^3- **(13c)** or Δ^{17}-acylyl **(13d)** by about seven parts to one part. Upon standing for 3 hr. the spectrum due to the Δ^3- or Δ^{17}-acylyl decays to leave a pure 1:2:3:4:3:2:1 heptet due to the Δ^2- **(13a)** or Δ^{16}-acylyl **(13b)** with a *trans* ring fusion. Hence, the preferred point of ionization in **11** and **12** is the same as in *trans*-2-decalone and 10β-methyl-5α-3-keto ster-

oids,[8] but the ratio of the two radical anions is intermediate between that from the decalone (attack at C-3:C-1 = 3:1) and from the 10β-methyl-5α-3-keto steroids (attack at C-2:C-4 = 95:5).
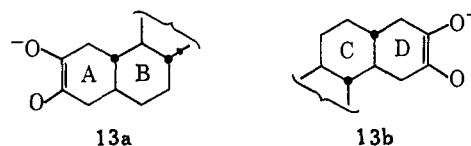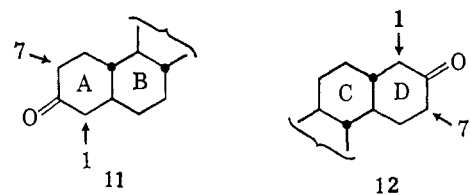
$a^H = 13.44, 13.44, 6.72, 6.76\,\text{gauss}$
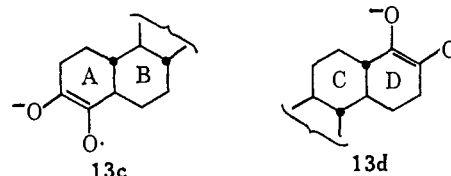
$a^H = 13.70, 12.88, 7.12\,\text{gauss}$

$a^H = 13.44, 13.44, 6.72, 6.72\,\text{gauss}$ $a^H = 13.70, 12.88, 7.12\,\text{gauss}$

17β-Acetoxy-19-nor-5β,10β-androstan-3-one **(14)**,[33,34] 17α-ethyl-19-nor-5β,10β-androstan-17β-ol-3-one **(14a)**, and 3-methoxy-D-homo-18,19-bisnor-13α-androsta-1,3,5(10)trien-17-one **(15)** are also enantiomers as far as the partial structures shown are concerned and give identical oxidates (Figure 8) consisting mainly of the Δ^3- **(13c)** or Δ^{17}-acylyl **(13d)** but having a minor amount of the Δ^2- or Δ^{16}-acylyl. The initial ratio of Δ^3 to Δ^2 (or Δ^{17} to Δ^{16}) is about 1.5:1. The minor radical **(16a or 16b)** is present in sufficient quantity to identify **16** as an acylyl with a *cis* ring fusion due to the presence of 13–16 lines (in several cases, all 16 lines were resolved). The preferred point of ionization in **14**

(31) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958); *J. Org. Chem.*, **28**, 1856 (1963).

(32) L. Velluz, G. Amiard, R. Heymes, and B. Goffinet, *Bull. soc. chim. France*, 2166 (1961).
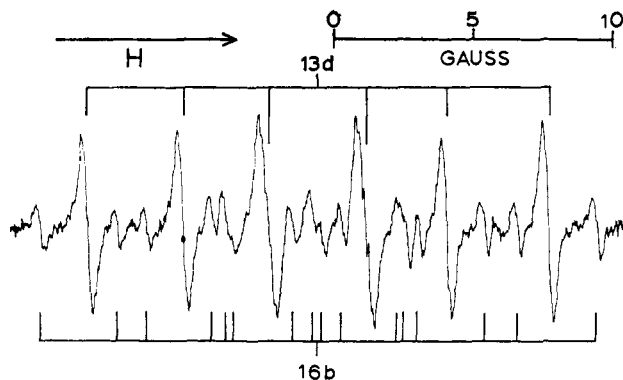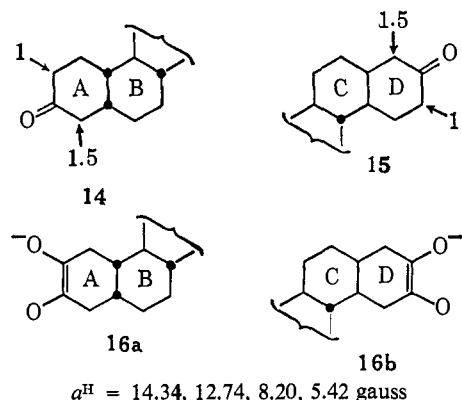
(33) C. Chen, *Tetrahedron*, **3**, 43 (1958); the configuration of **14** was originally assigned as 5α,10β. However, in view of the data of ref. 34 the configuration has been reassigned as 5β,10β: C. Chen, private communication. The 5β,10β-configuration is supported by the present work. On the same basis the compound originally assigned the 5β,-10β-configuration by Chen actually has the 5α,10β-configuration.

(34) A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957).

a^H = 14.34, 12.74, 8.20, 5.42 gauss

Figure 9. First-derivative e.s.r. spectrum (low-field half) of oxidation product of 17β-acetoxy-19-nor-5α,10α-androstan-3-one in dimethyl sulfoxide at 25°. The fifth peak (broadened) from each end of the 13-line spectrum has a tendency to split into a doublet.

and **15** is the same as that in *cis*-2-decalone (attack at C-1:C-3 = 1.5:1) and in 10β-methyl-5β-3-keto steroids (attack at C-4:C-2 = 4:1),[8] but there is a change in the ratio of the two acylyls formed in going from *cis*-2-decalone or **14** and **15** to 10β-methyl-5β-3-keto steroids, the 10β-methyl steroids again exhibiting greatest selectivity.

The oxidation of D-homo-18-nor-5β,13α-androstane-3α,11β-diol-17-one (**15a**)[32] yields a mixture of the same two radical anions as **15**, but the ratio of the radicals is markedly different ($\Delta^{17}:\Delta^{16}$ is initially about 1:3.5). Hence, the 11β-hydroxyl group is apparently destabilizing the Δ^{17}-acylyl for reasons not yet clear. In line with this presumption, we observed that the oxidation of a corresponding compound in which the hydroxyl group at C-11 was converted to a carbonyl function, namely, 3α-hydroxy-D-homo-18-nor-5β,13α-androstane-11,17-dione (**15b**),[32] yields a more normal ratio of the two radical anions ($\Delta^{17}:\Delta^{16}$ = 1:2). Therefore, the presence of these two acylyls is characteristic of 13α,14α-18-nor-D-homo-17-keto steroids (or 5β,10β-19-nor-3-keto steroids) (see following paragraph), but the relative amounts of the two radicals may depend upon the presence or absence of a substituent in the ring adjacent to that bearing the carbonyl group.

17β-Acetoxy-19-nor-5α,10α-androstan-3-one (**17**)[33] gives exclusively the Δ^2-acylyl (**19a**). The e.s.r. spectrum of Figure 9 (13 lines) demands that the A/B ring junction is *cis* in the starting ketone. A similar spectrum was observed from 17α-ethyl-19-nor-5α,10α-

a^H = 13.90, 12.65, 7.75, 6.56 gauss
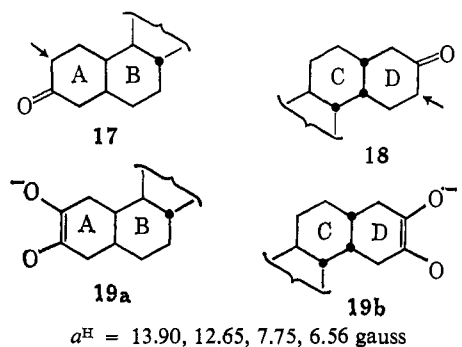
androstan-17β-ol-3-one (**17a**),[35] although in the sample examined another unidentified radical anion, presumably due to some impurity (detected by vapor phase chromatography), was also produced in a small amount. Examples of 18-nor-D-homo-13β,14β-17-keto steroids (**18**) are not reported in the literature. These compounds are expected to behave similarly, that is, afford

only a single radical anion (**19b**) whose spectrum should be the same as that of **19a**.

17β-Hydroxy-5α,9β,10α-19-norandrostan-3-one (partial structure **20**) is an interesting compound since **20** is a C-9 epimer of **17** and also a C-8 epimer of the
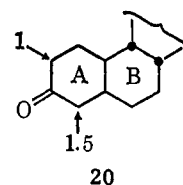
enantiomer of **14** (*i.e.*, **15**). Oxidation of **20** gives a mixture of the Δ^3- and Δ^2-acylyls, and the spectrum is essentially the same as that observed for **14** or **15** (see Figure 8). Thus, epimerization at C-8 in **14** (or C-9 in **15**) does not affect the extent of attack at C-2 and C-4 (or C-16 and C-17a). However, the oxygenation of **20** gives products quite different (60% oxygenation at C-4) from the C-9 epimer **17** (100% oxygenation at C-2). Thus, changes in configurations more remote than C-9 in a 19-nor-3-keto steroid (or C-8 in a 18-nor-D-homo-17-keto steroid) can be expected to have little effect on the acylyl radical anions formed. A change in configuration at C-5, C-9, or C-10 will have a pronounced effect upon the oxygenation of 19-nor 3-ketones, while a change in configuration at C-8, C-13, or C-14 will have a pronounced effect on the oxygenation products of 18-nor-D-homo 17-ketones.[36]

The h.f.s.c. observed for **16a** and **16b** (*cis*-5β,10β and *cis*-13α,14α) suggest that these cyclohexene derivatives have highly distorted half-chair structures for the A- and D-rings, respectively. On the other hand, the *cis*-5α,10α analog (**19a**) appears to have a fairly normal half-chair conformation of the A-ring.

The acylyls formed by oxidation in basic solution of a ketone having two α-methylene groups are a good measure of the products that can be formed in other substitution reactions of the enolate anion, such as alkylation (A), bromination (Br), or formation of enol acetates (EA). Table IV[37-40] summarizes pertinent

(35) R. T. Rapala and E. Farkas, *J. Org. Chem.*, **23**, 1404 (1958).

(36) We might expect that the C-9 epimer of **14** (or C-8 epimer of **15**) would give the same oxygenation products as **17** (or **18**), *i.e.*, 100% oxygenation at C-2 (or C-16).
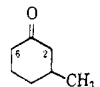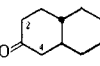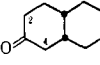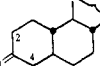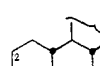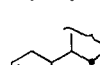
(37) R. Cornubert and R. Humeau, *Bull. soc. chim. France*, **49**, 1238 (1931).

(38) J.-M. Conia, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.) **24**, 42 (1963).

(39) R. Villotti, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5693 (1960).

(40) R. T. Rapala and E. Farkas, *ibid.*, **80**, 1008 (1958).

Table IV. Comparison of Oxidation (O) and Other Substitution Reactions (A, Br, EA) of Ketones in Basic Solution

Ketone	Percentage of attack at			Conditions	Ref.
	C-2	C-4	C-6		
(structure: 2-methylcyclohexanone)	23 (O)		100 (A) / 77 (O)	$NaNH_2$, $(CH_3)_2SO_4$	37
(structure: 2-decalone)	100 (A) / 100 (A) / 87 (EA) / 75 (O)	13 (EA) / 25 (O)		Li enolate, n-BuI, DMSO, $(C_6H_5)_3Li$, 1,2-dimethoxy-ethane	38 / 30 / 25
(structure: 2-decalone)	Minor (A) / 32 (EA) / 40 (O)	Major (A) / 68 (EA) / 60 (O)		$(C_6H_5)_3Li$, 1,2-dimethoxy-ethane	38 / 25
(structure: steroid)	67 (EA) / 63 (Br) / 88 (O)	33 (EA) / 37 (Br) / 12 (O)		Isopropenyl acetate, acid catalyzed[a] / BrCl in acetic acid, sodium acetate[a]	39 / 39
(structure: steroid)	40 (O)	100 (Br) / 60 (O)		Bromine in acetic acid[a]	40
(structure: steroid)	100 (O)				

[a] Data in basic solution not available.

information and predicts that the alkylation of a cis-5α,10α-19-nor-3-keto steroid should occur exclusively at C-2.

From the results presented it is clear that e.s.r. spectroscopy in conjunction with oxidation in basic solution, and without reference to model compounds, is an important and unambiguous method of assigning cis or trans configurations to A/B or C/D ring junctions in steroids that are derivatives of 5,6-substituted 2-decalones. Presumably this technique can be directly extended to the corresponding 7,8-substituted derivatives, i.e., the 2- and 16-keto steroids. In addition, positional isomers in the cyclohexanones or decalones, such as 1- and 2-decalones, and the 3- and 4-ketosteroids (or the 17- and 17a-keto steroids), can be readily distinguished. Furthermore, cis-β ring junctures can be empirically distinguished from cis-α ring junctures for the A/B or C/D rings on the basis of the presence or absence of oxygenation at C-4 in 19-nor-3-keto steroids or at C-17a in 18-nor-D-homo-17-keto steroids.

This e.s.r. technique is an attractive alternative to optical rotatory dispersion for configurational assignments in the 2-decalones and derivatives. Optical activity is not required, and the presence of other compounds which are optically active but which do not produce stable radicals does not interfere with our measurements. Usually only 2-5 mg. of a steroidal ketone is destroyed to obtain a spectrum, and in favorable cases good spectra have been obtained even with less than 1 mg. of ketone. By the use of a computer of average transients, a structure determination could be easily and routinely performed with less than 1 mg. of a steroidal ketone.

Experimental Section[41]

Materials. Dimethyl sulfoxide (Crown Zellerbach Corp.) was fractionally distilled under reduced pressure over calcium hydride after being dried with the same reagent. Potassium t-butoxide used was obtained from Mine Safety Appliance Research Corp. Other materials obtained from either commercial sources or other groups of workers were checked for purity by gas–liquid partition chromatography (g.l.p.c.). Analysis of steroids by g.l.p.c. was performed with a Chromalab instrument (Glowall Corp., Glenside, Pa.) having a radium foil–argon ionization detector and equipped with a 12-ft. column of 1% SE-30 on Chromosorb P, operating at 220° and a pressure of 30 p.s.i. of argon.

2,2-Dimethylcyclohexanone. To a stirred suspension of 16 g. (0.41 mole) of sodium amide in 200 ml. of refluxing ether (protected from moisture by tubes of Drierite and silica gel) was added gradually 38 g. (0.34 mole) of 2-methylcyclohexanone over a period of 20 min. The reaction mixture was refluxed for 19 hr., but ammonia was still being evolved. The ether was removed by distillation, 150 ml. of dry benzene was added to the residue, and the reaction mixture was refluxed for an additional period of 22 hr., then cooled in ice; 69 g. (0.49 mole) of methyl iodide was added gradually over a period of 25 min. The mixture was refluxed for 5 hr., left at room temperature for 2 days, and treated with 150 ml. of water. The aqueous layer was separated and extracted with ether, and the combined ether–benzene layers were washed twice with a saturated solution of sodium thiosulfate, then with water, and dried. Removal of ether and benzene under reduced pressure yielded a liquid in which 2,2-dimethylcyclohexanone was expected to be the major component.[42] Analysis of the crude reaction product by g.l.p.c. (2-m. column of 15% UCON LB-550-X on Chromosorb W, 128°) indicated the presence of four compounds, the major component constituting about 60% and 2-methylcyclohexanone about 5% of the total amount (second and first components, re-

spectively, to be eluted). Although the crude product was suitable for e.s.r. experiments, a small amount of virtually pure 2,2-dimethylcyclohexanone was collected by preparative-scale g.l.p.c. (the third compound to be eluted appeared as a shoulder on the major peak). The 60-Mc.p.s. n.m.r. spectrum (CDCl$_3$) showed a multiplet centered at about 2.41 (methylene group α to the carbonyl function), a broad peak at 1.70 (the remaining three methylene groups), and a sharp singlet at 1.11 p.p.m. (two methyl groups) downfield from tetramethylsilane used as an internal standard (integral ratio 1:3:3).

4,4-Dimethylcyclohexanone. A solution of 5.1 g. (0.041 mole) of 4,4-dimethyl-2-cyclohexen-1-one in 15 ml. of glacial acetic acid was shaken with 0.5 g. of platinum oxide (Adams catalyst) and hydrogen under an initial pressure of 16 p.s.i. for 50 min. The reaction mixture was filtered, and the filtrate was mixed with 85 ml. of water and extracted thoroughly with ether. The ether extracts were washed with a saturated solution of sodium bicarbonate, then with water, and dried over anhydrous sodium sulfate. By removal of the solvent under reduced pressure, 4.8 g. (91%) of 4,4-dimethylcyclohexanol was obtained.

A solution of 0.7 g. (0.0055 mole) of the crude 4,4-dimethylcyclohexanol in 14 ml. of reagent grade acetone was treated dropwise with Jones reagent[43] at room temperature until the solution acquired a distinct orange color for at least 5 min. The mixture was stirred with 45 ml. of water and thoroughly extracted with ether. The ether extracts were washed and dried as described above. After evaporation of the ether under reduced pressure, 0.55 g. (80%) of 4,4-dimethylcyclohexanone, m.p. 38.5–44.2°, was obtained. Recrystallization from methanol–water afforded white crystals, m.p. 40.5–43.5° (lit. m.p. 43–44.5°,[44] 38–41°,[45] 38–40°[46]).

cis-1-Decalone. 1-Naphthol (13.1 g.) in 40 ml. of glacial acetic acid in the presence of 2.1 g. of platinum oxide (Adams catalyst) absorbed 5 equiv. of hydrogen in a Parr hydrogenation apparatus at room temperature at 30 p.s.i. during 5 hr. The reaction mixture was filtered and evaporated to dryness under reduced pressure at 100°, and the residue was dissolved in ether. The ethereal solution was washed with a 5% solution of sodium hydroxide, then with water, and was dried (anhydrous sodium sulfate). Evaporation of the ether afforded a caramel-colored residue (13.0 g.) from which *cis,cis*-1-decalol was obtained as white needles, 3.2 g. (23%), m.p. 89–91° (lit. m.p. 89–91.5°,[47] 88–89°[48]), by crystallization from benzene.

cis,cis-1-Decalol (0.62 g.) in 8 ml. of acetone was oxidized with Jones reagent. The *cis*-1-decalone thus obtained (0.60 g., 98%) was used for the majority of the e.s.r. experiments. The e.s.r. signal was unchanged when material that had been subjected to bulb-to-bulb distillation under a pressure of 11 mm. was used. The

distilled sample was found to be free of any *trans*-1-decalone by infrared spectroscopy.[48]

cis-2-Decalone and trans-2-Decalone. "Decahydro-β-naphthol" (mainly *trans*) (L. Light and Co.) was dissolved in chloroform and the solution was resolved into its components by g.l.p.c. on a 2-m. column of UCON LB-550-X (15%) on Chromosorb W at 159°. Three fractions[49] were collected, the retention times being approximately 26, 31, and 37 min. The first two fractions overlapped, but consisted mainly of *trans,trans*- (21%) and *trans,cis*-2-decalol (59%), respectively. The third fraction was composed of *cis,cis*-2-decalol (20%). Fractions 1 and 2 from several runs were combined and oxidized with Jones reagent to obtain *trans*-2-decalone. Fraction 3 was similarly oxidized and furnished *cis*-2-decalone. Each decalone was found to be free from the other isomer by g.l.p.c. (10-ft. UCON column at 150°). The e.s.r. spectra obtained with these materials were identical with those from authentic samples of *cis*- and *trans*-2-decalones.

Formation and Detection of Radical Anions. Freshly prepared solutions of the ketone (0.05 M) and potassium *t*-butoxide (0.1 M; higher concentrations used if other base-sensitive groups were present) in DMSO were degassed separately in a U-type inverted mixing cell[16a] by a stream of prepurified nitrogen for 15–20 min., mixed, and exposed to air where necessary with gentle swirling for measured periods of time (usually about 10 sec. for a total volume of 0.2–0.3 ml.); the solution was shaken into the flat portion of a fused silica e.s.r. cell (Varian "aqueous sample cell"). The e.s.r. spectra were recorded immediately at 25 ± 3° with a Varian V-4500 spectrometer having a 9-in. magnet with 100-kc.p.s. field modulation. The *p*-benzosemiquinone radical, generated from 0.04 M hydroquinone and 0.08 M potassium hydroxide in 85% ethanol in the presence of a trace of air, was used as a standard ($a^H = 2.368$ gauss)[50] for calibration of all e.s.r. spectra.

Measurements of Concentrations of Radicals. The concentrations of radical anions produced in a few typical experiments were measured by recording their e.s.r. spectra and the spectrum of a standard solution of 1,1-diphenyl-2-picrylhydrazyl in DMSO at identical settings. Overmodulated spectra were used and the ratios of the areas under the peaks computed by a planimeter.

When 1.67 ml. of a degassed solution containing 0.05 M *cis*-1-decalone and 0.1 M potassium *t*-butoxide in DMSO was treated with 1 ml. of oxygen (2.5 × 10^{-2} M), the concentration of radicals was 1 × 10^{-5} M (conversion = 0.04%, based on the oxygen added). Essentially the same concentration of radicals was observed when 0.25 ml. of an identical solution was exposed to air for 12 sec. Since competitive attack of oxygen at the α-methine group can occur in 1-decalone,[28] this value represents approximately the lower limit of the concentration of radicals in our experiments. Exposure to air for 12 sec. of a solution containing 0.1 M cyclohexanone and 0.2 M potassium *t*-butoxide in DMSO (0.60 ml.) gave rise to approximately

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3×10^{-5} M concentration of radicals, while similar treatment of a solution of cis-2-decalone produced 2×10^{-5} M concentration of radicals.

Study of Enolization and Oxidation of Ketones by Infrared Spectroscopy. A study of the changes occurring during a typical oxidation reaction by infrared spectroscopy was undertaken to obtain some idea of the extent and speed of enolization and the subsequent oxidation of the enolate.

A thoroughly degassed solution of 0.05 M trans-2-decalone in DMSO was placed in an IRTRAN-II cell, and the change in the spectrum with time upon the addition of 0.1 M potassium t-butoxide in the absence of air was followed (only the region between about 1800 and 1600 cm.$^{-1}$ was scanned). The strong absorption of the carbonyl group at 1717 cm.$^{-1}$ decreased rapidly and a new broader band at 1597 cm.$^{-1}$ appeared. Three minutes after the addition of the base, about 77% of the ketone was calculated to have ionized, while after 20 min., there was barely any absorption at 1717 cm.$^{-1}$. At this stage, the basic solution was exposed to air for a short time (14 sec.)

whereupon a new, strong band appeared immediately at 1665 cm.$^{-1}$ (shoulders at 1677 and 1654 cm.$^{-1}$) along with a weaker band at 1577 cm.$^{-1}$ (shoulders at 1588 and 1566 cm.$^{-1}$). When air was admitted for a longer period (2 min.), these two bands became stronger (increase of about 30% in absorbance), but some absorption in the region of 1597 cm.$^{-1}$ persisted.

Nuclear Magnetic Resonance Spectroscopy. The Configurational Stability of Primary Grignard Reagents. Structure and Medium Effects[1]

George M. Whitesides and John D. Roberts

Contribution No. 3172 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. Received January 9, 1965

Qualitative and semiquantitative examination of the temperature dependence of the RCH_2-Mg proton n.m.r. spectra of several Grignard reagents indicates that the rate of inversion at this center is relatively insensitive to the structure of the group R. Secondary Grignard reagents invert much more slowly, if at all. The dependence of the inversion rate of the primary organometallic compounds on solvent character and on added salts suggests that inversion proceeds by means of a mechanism having kinetic order greater than one.

Introduction

The preceding paper[2] presented n.m.r. spectral evidence demonstrating that 3,3-dimethylbutylmagnesium chloride[3] in diethyl ether solution undergoes rapid inversion of configuration at the CH_2-Mg center.
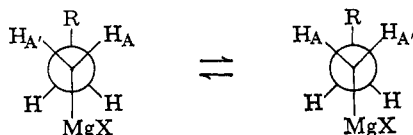
(1) Supported in part by the Office of Naval Research and the National Science Foundation.
(2) G. M. Whitesides, M. Witanowski, and J. D. Roberts, *J. Am. Chem. Soc.,* 87, 2854 (1965).
(3) For convenience, the organometallic compound formed by reaction of an alkyl halide with magnesium in an ethereal solvent will again be called an alkylmagnesium halide.

This observation suggests that careful examination of the spectrum of this and related compounds in different solvents and at different concentrations might provide data pertinent to the mechanism of this inversion and to the nature of Grignard reagents in solution.

Much of the modern work concerned with the structure of Grignard reagents has centered around attempts to evaluate the importance of the so-called Schlenk equilibrium in describing the Grignard reagent. In several well-known experiments, Dessy and co-workers examined the exchange reaction between labeled magnesium bromide and diethyl-[4] and diphenyl-

$$2RMgX \rightleftharpoons R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2$$

magnesium,[5] and concluded from these experiments that the equilibrium

$$2RMgBr \rightleftharpoons R_2Mg + MgBr_2$$

was not important in the Grignard reagents studied. In addition, conductometric measurements were reported to give identical[5] values for the dielectric constant of a 1:1 mixture of diethylmagnesium and magnesium bromide and of an equivalent concentration of "ethylmagnesium bromide."[6] It was therefore con-

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