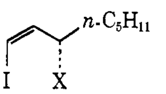
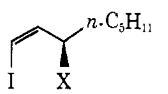
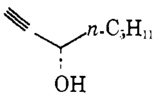
Enzymatic hydrolysis[2] of **16a** gave **16b**, mp 84.5–85.5°, $[\alpha]_D$ +90° (*c* 0.48, CH_3OH), $[\Phi]_{312}$ +6100°, $[\Phi]_{272}$ −5340°[16] Enzymatic hydrolysis[2] of **10a** gave **10b**, mp 84–85°, $[\alpha]_D$ −81° (*c* 0.41, CH_3OH), $[\Phi]_{312}$ −5630°, $[\Phi]_{272}$ +4880°.[16,17]



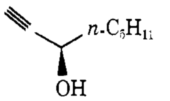
11a, X = OH
b, X = $OC(CH_3)_2OCH_3$



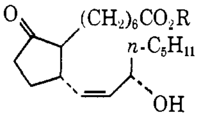
12a, X = OH
b, X = $OC(CH_3)_2OCH_3$



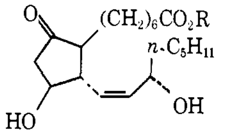
13



14



15 a, R = CH_3
b, R = H

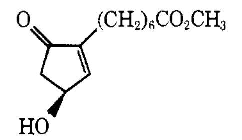


16a, R = CH_3
b, R = H

There are two points of striking contrast when comparing the conjugate additions of the two cuprates **1** and **2**. Firstly, the yields obtained with the cis reagent **2** are very much higher than those obtained with the trans reagent **1**. For example, a 27% yield of 1,4 addition was obtained from **7a**[2] with a threefold excess of reagent **1**, whereas equivalent quantities of **2** and **7a** gave a 60% yield of conjugate addition product.[18] Secondly and indeed the most interesting contrast is found in the high degree of stereoselectivity obtained with the cis reagent. While reaction of trans reagent **1** with **7a** gave a 45:55 mixture of 15α and 15β diastereomers,[2] the cis reagent **2** gave only the 15β diastereomer.[9] Obviously, one diastereomeric transition state (that for the 15β product) is specifically favored in the case of the cis reagent. The net effect of this remarkable result is that we have achieved an asymmetric induction in which the newly created asymmetric center is three carbons removed from the locus of the original asymmetry. We are continuing our investigations in order to elucidate the underlying reasons for this stereoselectivity; an attractive possibility is that coordination of the C-15 oxygen (prostaglandin numbering) with copper would produce a planar reagent with restricted rotation about the C-14–C-15 bond, thereby favoring regiospecific attack on the enone through a coordinated intermediate.

---

obtained by resolution of racemic i. We wish to thank Dr. Pappo for informing us of this result prior to publication.



i

(16) In the *E*-series prostaglandins the sign of the Cotton effect has been correlated with the configuration at C-8 (see O. Korver, ref 15). Thus, the natural series (8-*R*) exhibit negative Cotton effects and the retro series (8-*S*) exhibit positive Cotton effects. The Cotton effects observed with the 11-desoxy-13-cis compounds **8b** and **15b** are also consistent with this correlation. For compounds **10b** and **16b**, the absolute configuration at C-15 is determined by the asymmetric organocopper reagent and the configuration at C-8 is derived from the sign of the Cotton effect. The trans–trans configuration assigned to the two remaining asymmetric centers is predicted from the method of synthesis and is corroborated by the successful use of this method in the synthesis of (−)-PGE_1.[2]

(17) Combination of equimolar amounts of enantiomers **16b** and **10b** gave the racemate *dl*-**10b**, mp and mmp 87.0–87.5°.

(18) Others have observed slightly higher yields with cis reagents; see ref 7.

(19) Syntex Postdoctoral Fellow, 1971–1972.

Arthur F. Kluge,[19] Karl G. Untch, John H. Fried*
Institute of Organic Chemistry, Syntex Research
Palo Alto, California 94304

Received August 21, 1972

Conformational Effects in the Electron Paramagnetic Resonance Spectra of Cyclohexanonyl Radicals in Adamantane

Sir:

Several authors have reported observation of conformational effects in the epr spectra of free radicals derived from cyclohexane. For example, Ogawa and Fessenden[1] studied the spectrum of the cyclohexyl radical in solid cyclohexane between 188 and 273°K and observed alternating line width effects[2] which were attributed to interconversions between the two chair forms of the radical with an activation energy of 4.9 kcal/mol. Similar effects have been noted in spectra of radicals derived from piperidine[3] and dioxane[3,4] and, more recently, in semidione[5] and cyclohexenone[6] radical anions. Consideration of these results reveals that the amount of information which can be obtained regarding structure and conformation of free radicals containing six-membered rings is in direct proportion to the temperature range over which they can be studied. For this reason, we wish to report here preliminary results on a series of cyclohexanonyl radicals trapped in adamantane which illustrate the versatility of this technique[7] for epr studies over a wide temperature range and provide valuable new information on the properties of β-carbonyl radicals.

Cyclohexanonyl radicals are produced by room temperature X-irradiation of a solid pellet of carefully purified adamantane containing a small amount of deliberately added ketone and are studied using a Varian E-4 spectrometer equipped with a variable temperature controller. The radicals are formally obtained by removal of a hydrogen atom from the C-2 position; for example, X-irradiation of cyclohexanone yields the radical I which undergoes conformational interconversions between the two half-chair forms A and B.

Selective line broadening is observed when the interacting β protons (H_a and H_b) experience different magnetic environments at a rate which is comparable to the difference in hyperfine splitting constants (hfsc) in the two sites (pseudoaxial and pseudoequatorial).[8] Figure 1a illustrates this phenomenon for the radical obtained from cyclohexanone in adamantane-d_{16}. At

---

(1) S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, **41**, 994 (1964).

(2) For a review, see P. D. Sullivan and J. R. Bolton, *Advan. Magn. Resonance*, **4**, 39 (1970).

(3) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4850 (1964).

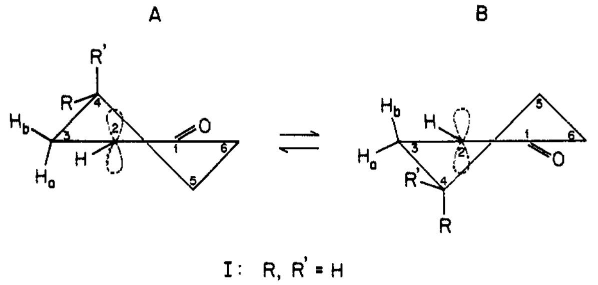
(4) H. Zeldes and R. Livingston, *J. Chem. Phys.*, **45**, 1946 (1966).

(5) G. A. Russell, G. R. Underwood, and D. C. Lini, *J. Amer. Chem. Soc.*, **89**, 6636 (1967).

(6) I. H. Elson, T. J. Kemp, and T. J. Stone, *ibid.*, **93**, 7091 (1971).

(7) D. E. Wood and R. V. Lloyd, *J. Chem. Phys.*, **52**, 3840 (1970); **53**, 3932 (1970).

(8) E. L. Eliel, *et al.*, "Conformational Analysis," Interscience, New York, N. Y., 1965, Chapter 2.



I: R, R' = H

II: R=CH_3, R'=H

93°K the interconversion IA $\rightleftharpoons$ IB is slow and the radical exhibits three inequivalent protons with hfsc of $a_\alpha = 18.1$, $a_{\beta_1} = 23.5$, and $a_{\beta_2} = 43.4$ G as determined from a computer fit of the observed spectrum. Increasing the temperature increases the rate of interconversion which results in the broadening and eventual loss of the central multiplet near 193°K. This multiplet then reappears as a doublet at still higher temperatures and narrows further as the spectrum approaches the high-temperature limit expected for a single α proton and two equivalent β protons with $a_\alpha = 18.0$ and $a_\beta = 33.0$ G at 313°K. Careful analysis of spectra obtained at low temperatures reveals that the 93°K values of the β-proton hfsc reported above are true limiting values for pseudoaxial and equatorial protons. As a result, rate constants (k) for the interconversion process in the cyclohexanonyl radical can be determined using the two-jump model of Russell, *et al.*,[5] independent of any assumptions about the structure of the radical in the low-temperature limit. For example, calculation of k from the excess width of one of the central lines at 273°K (where $\delta\nu 2\tau \ll 1$)[9] yields the value $k\ (=1/2\tau) = 4.4 \times 10^9\ \text{sec}^{-1}$ and a plot of ln (k/T) *vs.* $(1/T)$ from 213 to 333°K gives a straight line with $\Delta H^{\ddagger} = 2.9 \pm 0.3$ kcal/mol.

Conformational effects have also been observed in the epr spectra of several substituted cyclohexanonyl radicals. However, as in the case of analogous semidione radical anions,[5] the temperature dependence of the epr spectra of unsymmetrical radicals is qualitatively different because the two conformations A and B are of unequal energy and hence unequally populated. For example, Figure 1b shows a series of spectra obtained from an X-irradiated sample of adamantane-d_{16} containing 4-methylcyclohexanone. The spectrum at 143°K can be fit by assuming three inequivalent protons with $a_\alpha = 18.2$, $a_{\beta_1} = 20.4$, and $a_{\beta_2} = 44.1$ G. As the temperature is increased, significant line broadening is *not* observed but the β-proton hfsc becomes more nearly equal (*e.g.*, $a_{\beta_1} = 23.2$ and $a_{\beta_2} = 40.9$ G at 333°K). These results are consistent with assignment of the spectra to two conformations of the 4-methylcyclohexanonyl radical which exist in rapid equilibrium, *i.e.*, IIA $\rightleftharpoons$ IIB. If we assume that conformer A with the methyl group in the equatorial position is the more stable form, then observed values of the β-proton hfsc can be used to calculate equilibrium constants (K) for the interconversion process since the hfsc are the time average of limiting values observed in the low-temperature limit (∼140°K).[5] For example, from the hfsc quoted above, we obtain a fractional population $f_A = 0.874$ and $K[=(1 - f_A)/f_A] = 1.44 \times 10^{-1}$ at 333°K. Values of K obtained in this way over the temperature range 213–393°K were then used to determine the standard enthalpy difference ($\Delta H = H_B - H_A$) between the two conformers which is 3.2 ± 0.3 kcal/mol for the 4-methylcyclohexanonyl radical.

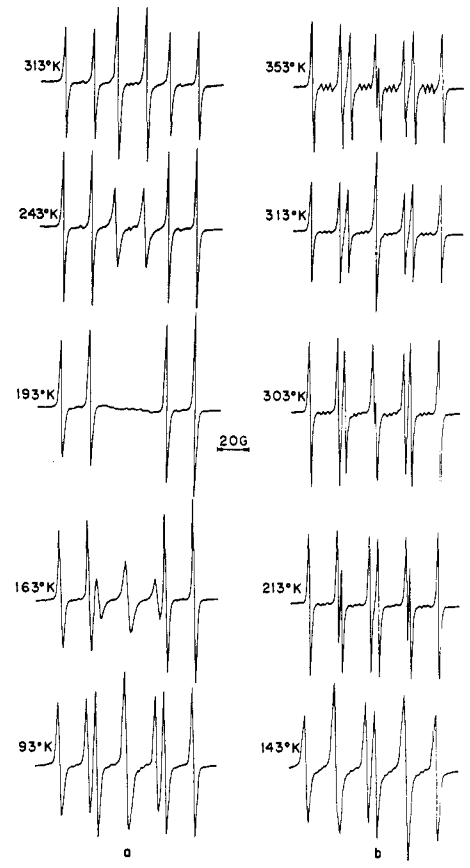


Figure 1. First-derivative epr spectra of (a) cyclohexanonyl and (b) 4-methylcyclohexanonyl radicals in adamantane-d_{16} as a function of temperature. Weak lines in the spectra are caused by partial deuteration of the parent radical resulting from exchange with the matrix.

The epr spectra of other unsymmetrically substituted cyclohexanonyl radicals show both alternating line width and time-averaging effects with changes in temperature. For example, X-irradiation of 2-methylcyclohexanone yields primarily the 6-methyl radical which has hfsc of $a_\alpha = 18.0$, $a_{\beta_1} = 23.2$, and $a_{\beta_2} = 43.8$ G at 143°K. Increasing the temperature causes the center lines of this spectrum to first broaden and then sharpen as the high-temperature limit is approached; at the same time, the lines shift rapidly with temperature because of changes in the fractional populations. At 333°K, the β-proton hfsc of the 6-methyl radical are 30.7 and 35.4 G. Comparison of these results with those for the 4-methyl derivative suggests that both $\Delta H^{\ddagger}$ and ΔH are considerably smaller in the case of the 6-methylcyclohexanonyl radical. Computer analysis of the epr spectra of these and other substituted cyclohexanonyl radicals should provide valuable information on the effect of substituents on the kinetic and thermodynamic parameters governing the interconversion process.

The cyclohexanonyl radicals described above, which

---

[9] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).

have $a_\alpha \sim 18$, $a_\beta \sim 33$, $a_\gamma < 0.3$ G,[10] and $g = 2.0043$–2.0050, are homologs of the acetonyl radical previously studied by several workers[4,11,12] and found to have $a_\alpha = 19.7$ and $a_\gamma = 0.27$ G and $g = 2.0044$. Comparison of these parameters with those of the isoelectronic allyl radicals[13] appears to confirm recent conclusions[14] that β-carbonyl radicals are essentially alkyl-like with very little resonance stabilization of the type observed for allylic systems. Further experimental results bearing on this interesting question will be reported in due course.

Acknowledgments. This work was supported in part by AEC Contract No. AT(11-1)-3435 and by NSF Science Development Grant No. GU-3184. D. W. P. thanks the Merck Foundation for a Faculty Development Award, Dr. T. Cohen for valuable discussions, and Mr. M. O. Luke of Merck, Sharp & Dohme of Canada, Ltd., for the gift of adamantane-d_{16}.

(10) Determined from a comparison of the epr spectra of the cyclohexanonyl and cyclohexanonyl-2,6,6-d_3 radicals in adamantane-d_{16}.

(11) W. T. Dixon, R. O. C. Norman, and A. L. Buley, *J. Chem. Soc.*, 3625 (1964).

(12) G. Golde, K. Möbius, and W. Kaminski, *Z. Naturforsch., A*, **24**, 1214 (1969).

(13) See, for example, J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968); D. W. Pratt, D. M. Camaioni, and D. E. Wood, unpublished results.

(14) G. A. Russell and J. Lokensgard, *J. Amer. Chem. Soc.*, **89**, 5059 (1967); K. D. King, D. M. Golden, and S. W. Benson, *ibid.*, **92**, 5541 (1970).

(15) Undergraduate Research Participant.

Donald M. Camaioni,[15] David W. Pratt*
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15213

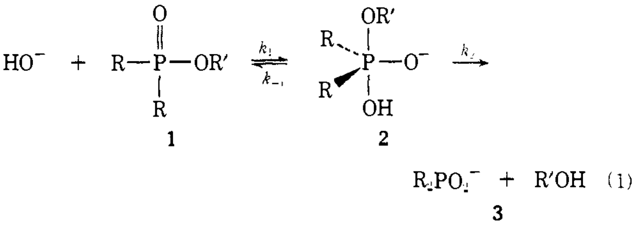
Received July 20, 1972

Pentacoordinate Intermediates and the Rate-Determining Step in Displacement at Phosphorus

Sir:

There has been great interest recently in pentacoordinate intermediates in nucleophilic displacement reactions at tetracoordinate phosphorus.[1] Although stable pentacoordinate phosphorus compounds are known,[2] there has been little experimental evidence for pentacoordinate intermediates along reaction pathways.[3] Although we previously found[4] that the effects of ring strain indicate an intermediate 2 in the alkaline hydrolysis of phosphinate esters (eq 1), we can now present direct kinetic evidence for a pentacoordinate intermediate 2 and for rate-determining breakdown of the intermediate to products.

The rates of hydrolysis of a series of phosphinates **1** were evaluated titrimetrically by quenching an aliquot with acid and back-titrating with base. The reactions followed second-order kinetics, $v = k[\mathrm{HO^-}]\cdot[\mathrm{ester}]$. The rate constants were highly dependent on the substituents at phosphorus and oxygen (Tables I and II). Experiments in oxygen-18 enriched water have demonstrated that these esters hydrolyze by cleavage of the P–O bond.[5]



1 **2** **3** (1)

Table I. Rate Constants for the Alkaline Hydrolysis of $(C_6H_5)_2PO_2R$ at 50°

R	10^3k, M^{-1} sec^{-1} [a] 33% dioxane–water	50% dioxane–water	Rel k
CH_3	14.7		320
CH_2CH_3	1.21		27
$CH_2CH_2CH_3$		0.494	12
$CH(CH_3)_2$	0.0457	0.0428	1
$CH_2CH(CH_3)_2$		0.226	5
$CH_2C(CH_3)_3$		0.0397	0.9

[a] Most k values are the average of two–three separately determined constants.

Table II. Rate Constants for the Alkaline Hydrolysis of $R_2PO_2CH_3$ in 60% Dimethoxyethane–Water at 75°

R	10^3k, M^{-1} sec^{-1} [a]	Rel k
CH_3	500[b]	160
CH_2CH_3	10.9	4
$(CH_2)_3CH_3$	3.08	1
$CH_2C_6H_5$	11.5	4
$CH(CH_3)_2$	0.3[c]	0.1
C_6H_5	43	14

[a] Ionic strength constant at 0.1 *M*. [b] Extrapolated from data at 30 and 50° by log *k*. *vs.* $1/T$. [c] An induction period preceded this rate.

The hydrolysis of methyl diisopropylphosphinate (**1**, R = i-C_3H_7; R′ = CH_3) was unusual in that an induction period preceded second-order kinetics (Table II). The hydrolysis curve was analyzed by an analog computer with a circuit corresponding to eq 1. An excellent fit was observed corresponding to: $k_1 = 2.4 \times 10^{-3}\ M^{-1}\ \mathrm{sec}^{-1}$, $k_{-1} = 1.6 \times 10^{-2}\ \mathrm{sec}^{-1}$, $k_2 = 0.20 \times 10^{-2}\ \mathrm{sec}^{-1}$. Therefore, it appears that the induction period corresponds to initial *accumulation of the pentacoordinate intermediate*, **2**, and *rate-determining breakdown of* **2** *to products* (k_2 is an order of magnitude less than k_{-1}). Kinetic observation of an intermediate in this case probably can be attributed to the steric effect of the two isopropyl substituents.

Analysis of the relative rates in Tables I and II indicates generality of these hypotheses of an intermediate and rate-determining breakdown of **2** to products. The large rate effects in Table I contrast with the rates of alkaline hydrolysis of acetates where the rate ratio for R groups in CH_3CO_2R was isopropyl : ethyl : methyl

---

(1) (a) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); (b) K. Mislow, *ibid.*, **3**, 321 (1970); (c) I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *ibid.*, **4**, 288 (1971).

(2) (a) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966); (b) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

(3) Available evidence includes: (a) the kinetics of alkaline hydrolysis of phosphonium ions (M. Zanger, C. A. VanderWerf, and W. E. McEwen, *J. Amer. Chem. Soc.*, **81**, 3806 (1959)); (b) ring strain effects on rates of hydrolysis and ^{18}O exchange (P. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961)); (c) certain data (ref 1) indicate pseudorotation of a pentacoordinate species.

(4) P. Haake, R. D. Cook, T. Koizumi, P. S. Ossip, W. Schwartz, and D. A. Tyssee, *J. Amer. Chem. Soc.*, 92, 3828 (1970).

(5) P. Haake, C. E. Diebert, and R. S. Marmor, *Tetrahedron Lett.*, 5247 (1968). However, the *tert*-butyl ester reacts very rapidly, probably by a pathway involving C–O cleavage; see P. Haake and C. E. Diebert, *J. Amer. Chem. Soc.*, **93**, 6931 (1971).