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Axial and Equatorial Cyclohexylacyl and Tetrahydropyranyl-2-acyl Radicals. An Experimental and Theoretical Study

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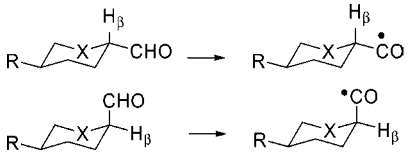
ABSTRACT



Axial and equatorial cyclohexylacyl and tetrahydropyranyl-2-acyl radicals gave distinct EPR spectra thanks to surprisingly large β-hydrogen atom hyperfine splittings that enabled them to be characterized and monitored. DFT computations indicated that the axial species ($X = CH_2$) had a higher barrier to rotation about the (O)C_α–C_β bond. The computed difference ΔH° for the axial and equatorial radicals ($R = H$, $X = CH_2$) was 0.8 kcal mol^{-1}.

The structures, reaction mechanisms and synthetic applications of acyl radicals have received much attention in recent years.[1] Alicyclic acyl radicals have been successfully used in preparations of acyl halides[2] and esters[3] and in numerous and varied routes to carbonyl compounds.[1,4,5a−d] Moreover, acyl generation by carbonylation of C-centered radicals, which is important from a synthetic standpoint,[5d] has been investigated for cyclohexylacyl radicals.[6] Cyclohexylacyl radicals are capable of existing in axial and equatorial conformations, but no attention has hitherto been given to this phenomenon, although cyclopropylacyl and cyclobutylacyl radicals have been shown by EPR spectroscopy to exist in both *s-cis* and *s-trans* conformations in which the plane of the acyl group bisects the ring.[7a−d] A spectroscopic method for distinguishing axial and equatorial cyclohexylcarbinyl radicals, which depended on their differing H_β hyperfine splittings (hfs), was established some time ago.[8] Acyl radicals are σ-radicals with small H_β hfs and low g-factors,[9a−c] unlike the π-type cycloalkylcarbinyl radicals. However, in the hope that axial and equatorial cyclohexylacyl radicals could be observed, we examined the EPR spectra of the radicals formed by hydrogen atom abstraction from alicyclic carbaldehydes.

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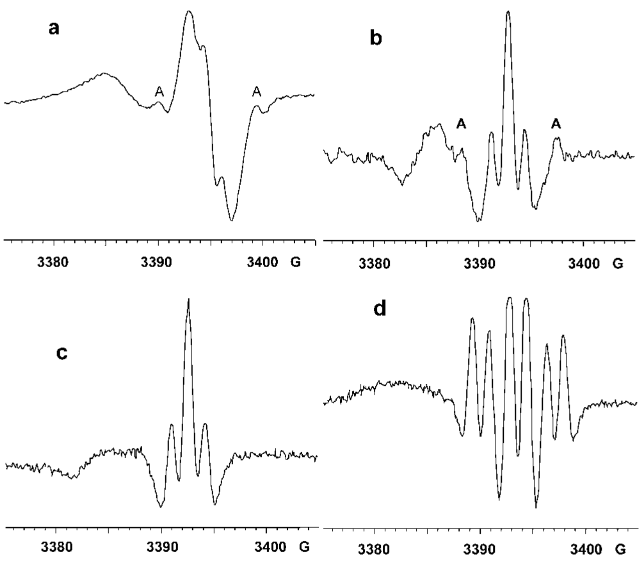

Figure 1. 9.5 GHz EPR spectra obtained from cyclohexane carbaldehydes in solution: (a) first-derivative spectrum from **1a** in *n*-propane at 120 K; (b) second-derivative spectrum from **1a** in cyclopropane at 140 K; (c) EPR spectrum (second derivative) from equatorial 4-*t*-Bu aldehyde **1e** in cyclopropane at 140 K; (d) EPR spectrum (second derivative) from axial 4-*t*-Bu aldehyde **1c** in cyclopropane at 140 K.

When a cyclopropane solution of cyclohexane carbaldehyde **1a** (0.14 M) containing di-*tert*-butyl peroxide (DTBP, 20 μL) was photolyzed at 140 K, the spectrum shown in Figure 1b was obtained. Similar spectra were obtained up to ca. 165 K and in the range 120−150 K in *n*-propane solvent (Figure 1a), but extensive broadening set in at higher temperatures. The expected mechanism is outlined in Scheme 1.

Scheme 1. Mechanism of the Photochemical Reaction of Cyclohexane Carbaldehyde with DTBP

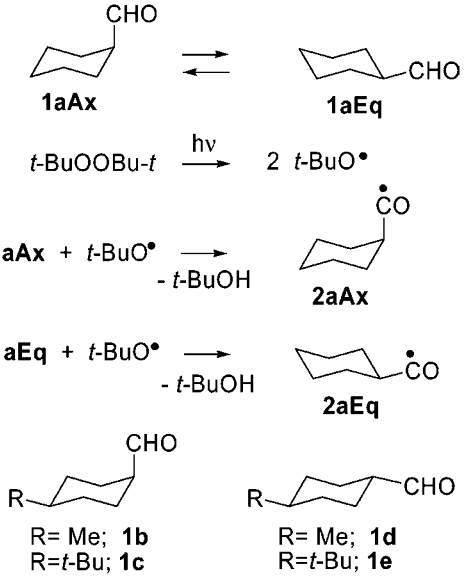

Table 1. EPR Parameters for Cyclohexylacyl and Related Radicals[a]

radical	T/K or comp method	g-factor	$a(H_\beta)$/G	a(2H)/G	w/G[c]
2aEq, R = H	120[b]	2.0001	<1.0	1.6	
2aEq, R = H	UB3LYP/ EPR-III		−1.6[d]	1.6 (H_δ)[d]	
2aAx, R = H	120[b]	2.0001			8.9
2aAx, R = H	UB3LYP/ EPR-III		−2.2[d]	3.7 (H_γ)[d]	9.6
2bAx, R = Me	140	2.0001	1.8	3.6	9.0
2cAx, R = Bu-*t*	140	2.0007	<1.0	1.6	
2eEq, R = Bu-*t*	145	2.0007	1.5	3.6	8.7
4Eq, R = H	140	2.0000	2.4	1.1[e]	
4Ax, R = H	140	2.0000	[7.0]	[0.7][e]	7.7

[a] Solvent: cyclopropane. [b] Solvent: *n*-propane. [c] w = separation of outer lines of multiplet. [d] Averaged over PES (see text). [e] a(1H).

The main feature of the spectrum was a triplet (see Figures 1a and b) with a low g-factor (2.0001) appropriate for a σ-acyl radical. The triplet multiplicity was unexpected for a cyclohexylacyl radical containing a single β-hydrogen.[10] The spectrum showed small additional features, marked A in Figure 1a,b, on either side of the triplet, which have a separation (w) of 8.9 G. A broad line at lower field (g = 2.0046) was also observed.[11,12]

The bulky *t*-Bu group always maintains an equatorial or pseudoequatorial orientation in cycloalkanes so that in *trans*-4-*tert*-butylcyclohexane carbaldehyde **1e** the formyl group must be equatorial whereas in the cis analogue **1c** it must be axial. EPR spectra from these two aldehydes, run under similar conditions, gave the spectra shown in Figure 1c,d. The triplet spectrum from **1e** was very similar to the central multiplet from **1a** (EPR parameters in Table 1), thus confirming that these signals are from radical **2aEq**. The triplet structure is due to long-range interactions. Since there is no doublet, it is evident that for radical **2aEq** (and **2eEq**) the $a(H_\beta)$ value is less than the line width (<1 G). The axial radical **2cAx** has a significantly larger $a(H_\beta)$ (1.6 G at 140 K) leading to a distinct *dt* pattern (Figure 1d). The separation of the outer lines (w) of this multiplet (8.7 G at 140 K) is very close to the measured w of the weak outer features marked A in Figure 1a,b. Thus, we assign the latter to the axial radical **2aAx**, the central portion of the multiplet being obscured by the stronger **2aEq** signal. These data show, for the first time, that axial and equatorial acyl radicals can be distinguished by EPR spectroscopy.

EPR spectra were also obtained from the *cis*-4-methyl aldehyde **1b** which showed predominantly axial radical **2bAx**

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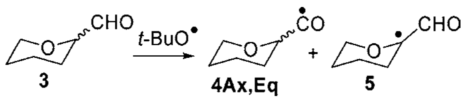
(10) The analogous acyclic acyl, i.e., $Me_2CHC(^\bullet)O$, had $a(H_\beta)$ < 1.5 G,[9b] i.e., within the line width, so that a singlet or doublet was anticipated.

(11) Redistilled aldehyde showed the same broad feature, as did spectra from all the other aldehydes of this study; therefore, these features are not due to impurities. Most likely they are due to the 1-formylcyclohexyl radicals generated by abstraction of the tertiary H-atoms adjacent to the formyl groups. The g-factor of the analogous $Me_2C(^\bullet)CHO$ radical is 2.0045, in close agreement.[12]

(12) Foster, T.; Klapstein, D.; West, P. R. *Can. J. Chem.* **1974**, *52*, 524.

(Supporting Information and Table 1) with parameters similar to those of **2aAx** and **2cAx**.

We also examined H-abstraction from tetrahydropyran-2-carbaldehyde **3** under similar conditions. The main acyl spectrum had a *dd* structure. It also showed satellite features from a second minor acyl radical. A tentative analysis of these signals in terms of axial and equatorial species **4Ax,Eq** is given in Table 1. The spectrum showed additional minor features ($g = 2.0042$) probably due to the 2-formyltetrahydropyran-2-yl radical **5** derived from abstraction of the tertiary H-atom adjacent to oxygen.



The energies of acyls **2aEq** and **2aAx** were computed using the UB3LYP method with the EPR-III basis set (structures at B3LYP/6-31G*)[13] implemented in the Gaussian 98 suite of programs.[14] Both species showed two minimum energy structures with the •C=O group practically eclipsing one or other of the $C_\beta-C_\gamma$ bonds of the cyclohexane ring. In **2aEq**, the $O=C_\alpha C_\beta H_\beta$ angle was computed to be 116.8° and in **2aAx** it was 103.0°. The total energy, plotted as a function of the rotation angle about the $C_\alpha(O)-C_\beta$ bond, was essentially an unsymmetrical double minimum for both species.[15] The main difference between the two was the height of the barrier to rotation which was 0.4 kcal mol^{-1} for **2aEq** but twice as large (0.8 kcal mol^{-1}) for **2aAx**, due to interaction of the CO group with the axial H-atoms attached to C(3) and C(5) (axial H_δ). Assuming several rotational states exist in each minimum, average $a(H_\beta)$ values of −1.6 and −2.2 G were derived for **2aEq** and **2aAx**, respectively.[16] The computations suggested the triplet long-range hfs of **2Eq**s were due to equatorial H_δ's, whereas the long-range hfs of **2Ax**s were associated with the axial H_γs.[17]

The concentrations of **2aAx** and **2aEq** were determined from double integration of their EPR signals in the two solvents by the usual method.[18] The error limits were large because of the limited resolution of the two species (Figure 2 and Supporting Information).

At these low temperatures, six-membered ring inversion is slow compared to the disappearance of radicals in bimolecular termination processes so that the concentration ratio measured by EPR spectroscopy does not correspond to their *equilibrium* ratio at the temperature of the measurements. The [**1aAx**]/[**1aEq**] aldehyde ratio was also determined by integrating the separate formyl signals from the axial and equatorial aldehydes in their low-temperature ^1H NMR spectra in CD_2Cl_2 (Figure 2). Coalescence of the formyl signals was observed at 213 K, and therefore, ring inversion will be very slow at lower temperatures. The EPR experiments were conducted at 120−165 K so the measured [**2aAx**]/[**2aEq**] ratios probably reflect the ratio of the concentrations of the two aldehydes that was "frozen" in as the sample was cooled. Examination of Figure 2 supports this conclusion. The log{[**2aAx**]/[**2aEq**]} ratio is practically independent of temperature, as is the log{[**1aAx**]/[**1aEq**]} ratio. The latter, measured in the polar solvent CD_2Cl_2, appear slightly lower than the log{[**2aAx**]/[**2aEq**]} ratios in the nonpolar *n*-propane and cyclopropane (Figure 2). This might be due to a small solvent dependence of the axial/equatorial ratios.

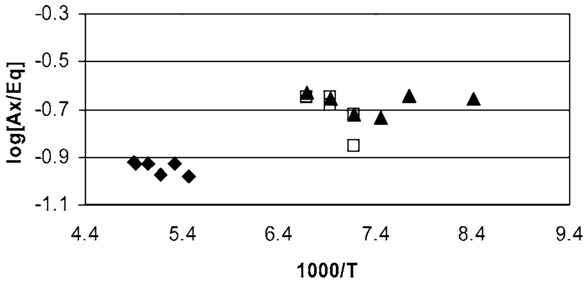
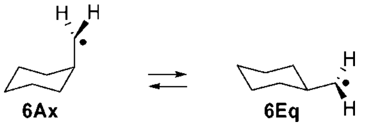


Figure 2. Plot of log[axial]/[equatorial] ratios vs $10^3/T$. Triangles: EPR data for [**2aAx**]/[**2aEq**] in *n*-propane. Squares: EPR data for [**2aAx**]/[**2aEq**] in cyclopropane. Diamonds: NMR data for [**1aAx**]/[**1aEq**] in dichloromethane.

The enthalpies of **2aAx** and **2aEq** were also computed giving $\Delta H°(\mathbf{2aAx})-(\mathbf{2aEq}) = 0.72$ (0.80 at 140 K) kcal mol^{-1}. This enthalpy difference is of the same order of magnitude as that determined experimentally for the analogous cyclohexylmethyl radicals **6Ax** and **6Eq** (0.71 kcal mol^{-1}).[8b] DFT computations (B3LYP/EPRIII//B3LYP/6-31G*) for **6Ax** and **6Eq** gave $\Delta H° = 1.2$ kcal mol^{-1} for their equilibrium, in reasonable agreement with the experimental value.



The computations (B3LYP/6-31G*) showed a double-minimum rotational PES for radical **6Ax** but a more complex surface for **6Eq.** The computed rotational barriers (B3LYP/EPR−III//B3LYP/6-31G*) were 1.1 and 0.3 kcal mol^{-1} for **6Ax** and **6Eq**, respectively, which agree rather well with experimental rotational barriers of 1.6 and 0.4 kcal mol^{-1} which were derived from the temperature dependence of the H_β hfs.[8b] Unfortunately, we later reported a much higher

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[13] The EPR-III basis set is of triple-ζ quality. See: Barone, V. In *Recent Advances in Density Functional Theory*; Chong, D. P., Ed.; World Scientific Publishing Co.: Singapore, 1996.

[14] Gaussian 98, Revision A.11. Frisch, M. J. et al. Gaussian, Inc., Pittsburgh, PA, 2001 (see the Supporting Information for the full citation).

[15] That is, the rotational potential about the dihedral angle $O=C_\alpha C_\beta C_\gamma$ for both plots showed some minor minima in the −200 to −300° range (see the Supporting Information).

[16] See the Supporting Information for the averaging method.

[17] In both cases these are the H-atoms with all-trans (W-plan) arrangements of bonds with respect to the radical centre, see: (a) Ellinger, Y.; Rassat, A.; Subra, R.; Berthier, G. *J. Am. Chem. Soc.* **1973**, *95*, 2372. (b) Ellinger, Y.; Subra, R.; Levy, B.; Millie, P.; Berthier, G. *J. Chem. Phys.* **1975**, *62*, 10. (c) Ingold, K. U.; Nonhebel, D. C.; Walton, J. C. *J. Phys. Chem.* **1986**, *90*, 2859.

[18] (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 193. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

rotation barrier (6 kcal mol^{-1}) derived (we now know on a false premise) from line-broadening effects in the EPR spectra of axial **6Ax**.[19] This very high barrier is incorrect, and the observed line broadening must be due to some as yet unidentified motion of the ring (not complete inversion) rather than to rotation of about the $-CH_2^{\bullet}$ bond.

Davies and Sutcliffe discovered a positive linear correlation between J(H,H) values in NMR spectra of the aldehydes and $a(H_\beta)$ values of the corresponding acyl radicals.[9b] The ^{1}H NMR spectra of both **1aAx** and **1aEq** at 183 K showed singlets for the formyl H-atoms; i.e., the J(H,H) values were too small to resolve. For the *t*-Bu analogues **1c(Ax)** and **1e(Eq)** the J(H,H) values were 0.8 and 1.8 Hz, respectively (see Supporting Information), which are of the opposite relative magnitudes expected from Davies and Sutcliffe's correlation since the $a(H_\beta)$ values of the acyl radicals gave 1.5 and < 1 G, respectively. Thus, Davies and Sutcliffe's linear correlation does not extend to axial and equatorial species. This is probably because of perturbations to the rotation barriers of axial species by steric interactions from the axial H-atoms attached to C(3) and C(5) (axial H_δ).

In summary, we have shown that cyclohexylacyl radicals exist in two conformations and that they can be characterized and their concentrations tracked by an EPR spectroscopic method. As with cycloalkylcarbinyl radicals, the key difference between axial and equatorial species lies in the larger H_β hfs of the former. Computational results indicate that this derives from the higher rotational barrier about the C_β-C_α(O) bond which results from 1,3-interactions of the CO group with the axial δ-H-atoms of the ring. The method also works for tetrahydropyranylacyl radicals and, judging by cycloalkylmethyl analogues,[20] it is probable that it can also be successfully applied for a variety of alicyclic rings including cyclohex-2-enyl-1-acyl, and cyclohept-4-enyl-1-acyl.

The conformational equilibria will lead to subtle chemical consequences. For example, it is likely that the rates of decarbonylations of the axial and equatorial radicals will differ since computations (B3LYP/EPR-III//B3LYP/6-31G*) give different enthalpies for these reactions:

$$\mathbf{2aEq} \rightarrow c\text{-}C_6H_{11}^{\bullet} + CO \qquad \Delta H^\circ = 7.4 \text{ kcal mol}^{-1}$$

$$\mathbf{2aAx} \rightarrow c\text{-}C_6H_{11}^{\bullet} + CO \qquad \Delta H^\circ = 6.6 \text{ kcal mol}^{-1}$$

Thermodynamically, loss of CO is predicted to be somewhat easier from the axial conformation and this is in accord with expectation.

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Supporting Information Available: General experimental and computational procedures, characterization for compounds **1a−c** and **3**, sample EPR spectra for radicals **2a−c**,**e** and **4**, tables of concentrations for **2aAx** and **2aEq** in both solvents, and plots of the rotation PESs for **2aAx**, **2aEq**, **6Ax**, and **6Eq**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Hughes, L.; Ingold, K. U.; Walton, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 7494.

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