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Inversion Barrier of the Cycloheptyl Radical[1]

T. J. Burkey, D. Griller,* and R. Sutcliffe

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

C. J. Harding

Department of Chemistry, The Open University, Walton Hall, Milton Keynes, England

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Inversion barriers have been measured for a variety of cyclic radicals containing five or six ring atoms.[2] To our knowledge, there have been no measurements of inversion barriers for radicals based on seven-membered ring systems,[3] although there have been careful studies of molecules with this general structure.[5-8] Accordingly, we have measured the inversion barrier for cycloheptyl, the prototypical radical in this class, so as to compare the behavior of the seven-membered ring with smaller cyclic radicals and with molecules of this general type.

Experimental Section

Materials. Cycloheptyl iodide was prepared from the corresponding alcohol by a standard procedure.[9] All other materials were commercially available and with the two exceptions described below were used without further purification. Di-*tert*-butyl peroxide was washed with aqueous silver nitrate so as to remove olefinic impurities and then with water. It was dried over magnesium sulfate and was finally passed through a column of alumina so as to remove any residual hydroperoxide. Hexa-*n*-butyldistannane was purified by distillation.

Apparatus. Electron paramagnetic resonance (EPR) spectra were recorded on a Varian E104 spectrometer. Radicals were generated by continuous photolysis using a 1000-W mercury–xenon lamp. The heating effect of the lamp at the cavity was reduced to 1° by filtering the light through an aqueous solution of cobalt and nickel sulfates.

Results

The inversion barrier of a free radical can be measured by analysis of its EPR spectra, provided the spectra reflect rapid inversion at high temperatures and an effectively "frozen" conformation at low temperatures. This was found to be the case for the cycloheptyl radical.

Cycloheptyl was generated by two methods. At high temperatures (ca. 275 K) it was formed by photolysis, in the spectrometer cavity, of a mixture containing di-*tert*-butyl peroxide, hexa-*n*-butyldistannane, and cycloheptyl iodide each (15% v/v) in propane solvent, eq 1–3.[10] The spectrum showed splitting from an α-hydrogen, $a^{H_1} = 22$ G and four β-hydrogens $a^{H_{2,7}} = 29$ G.

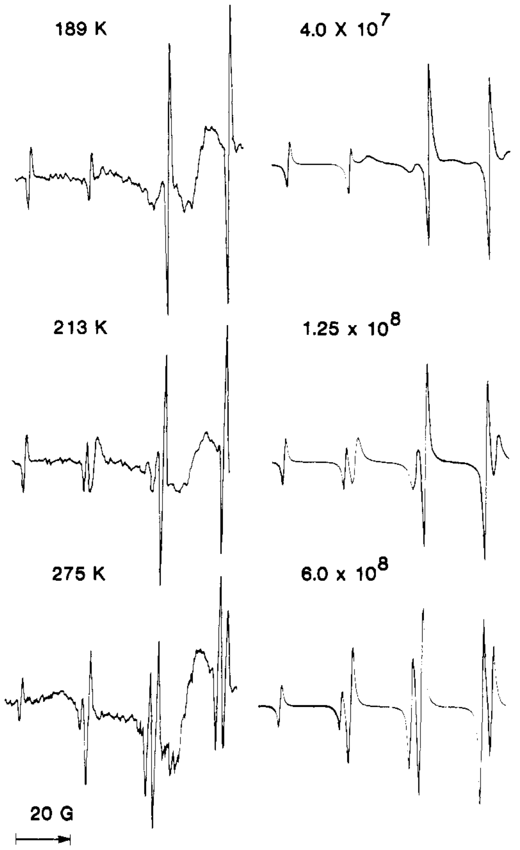

Figure 1. Some experimental EPR spectra (lower-field half) for the cycloheptyl radical at different temperatures (left) and simulated spectra (right). Rate constants for exchange are given in s^{-1} units. The broad line at the center of each experimental spectrum was due to a cavity background signal.

$$t\text{-BuOOBu-}t \xrightarrow{h\nu} 2t\text{-BuO}\cdot \qquad (1)$$

$$t\text{-BuO}\cdot + n\text{-Bu}_3\text{SnSn-}n\text{-Bu}_3 \rightarrow t\text{-BuOSn-}n\text{-Bu}_3 + n\text{-Bu}_3\text{Sn}\cdot \qquad (2)$$

$$n\text{-Bu}_3\text{Sn}\cdot + \text{c-C}_7\text{H}_{13}\text{I} \rightarrow n\text{-Bu}_3\text{SnI} + \text{c-C}_7\text{H}_{13}\cdot \qquad (3)$$

The method of radical generation described above was unsatisfactory at low temperatures since some of the reagents crystallized. In fact, photolysis of di-*tert*-butyl peroxide in the presence of cycloheptane (each 5% v/v) in cyclopropane or ethane as solvents provided the best systems for low-temperature work and spectra of cycloheptyl were obtained between 117 and 275 K. However, in the lower part of the temperature range, there was some interference from the ethyl radical which was derived by hydrogen abstraction at the solvent, eq 1 and 4–5.

$$t\text{-BuO}\cdot + \text{c-C}_7\text{H}_{14} \rightarrow t\text{-BuOH} + \text{c-C}_7\text{H}_{13}\cdot \qquad (4)$$

$$t\text{-BuO}\cdot + \text{CH}_3\text{CH}_3 \rightarrow t\text{-BuOH} + \text{CH}_3\dot{\text{C}}\text{H}_2 \qquad (5)$$

The spectra of the cycloheptyl radical, obtained over the temperature range 117–275 K, showed the classical alternating line-width effect expected for a motion in which magnetically nonequivalent β-hydrogens exchange positions. At 275 K the exchange was rapid on the EPR time scale so that the spectrum reflected the average hyperfine splitting due to the four β-hydrogens, Figure 1. By contrast, the spectrum approached the slow-exchange limit

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I II

Figure 2. Two of the possible puckered conformations of cyclopentane.

at low temperatures so that the β-hydrogens no longer appeared to be equivalent.

The spectral parameters for the "frozen" conformation of the radical were $a^{H_1} = 21.0 \pm 0.3$ G, $a^{H_{2,7}} = 31.4 \pm 0.1$ G, and $a^{H_{2',7'}} = 21.0 \pm 0.3$ G. The individual hyperfine splittings for H_1 and $H_{2',7'}$ could not be more accurately defined because of overlap in the spectral lines. However, this imprecision introduced an error of only ca. 100 cal mol^{-1} in the barrier measured for the exchange motion. The change in solvent from cyclopropane to ethane had no effect on the hyperfine splittings in the overlapping temperature range. Finally, no γ hyperfine splitting could be resolved at any of the accessible temperatures, nor were there contributions to the spectrum from other conformers of the radical.

The spectra were accurately simulated at a number of temperatures by using the standard treatment for such an exchange process,[11] Figure 1. These analyses led to individual rate constants for the ring inversion process which are described by the Arrhenius expression given in eq 6, where the stated errors represent 1 standard deviation and where $\theta = 2.30RT$ (kcal mol^{-1}).

$$\log (k/\mathrm{s}^{-1}) = (11.6 \pm 0.3 - 3.4 \pm 0.3)/\theta \qquad (6)$$

Discussion

Barriers for the ring motions of cycloalkyl radicals in the series C_5 to C_7 bear strong resemblances to the behavior of the parent hydrocarbons and these have been investigated in great detail.

Cyclopentane adopts a puckered conformation,[12,13] I which has 4.3 kcal mol^{-1} more ring strain than the planar alternative but which alleviates interactions between the methylene groups, thus reducing the eclipsing strain by 7.8 kcal mol^{-1},[5] Figure 2. Interconversion of I to II does not require motion through the less stable, planar form but can be achieved by a low-energy pseudorotation pathway involving minor displacements of the ring atoms that preserve the puckered structure. The barrier for this process is less than 600 cal mol^{-1}.[5]

The EPR spectrum of the cyclopentyl radical has been investigated at low temperatures in matrices.[14-17] Early work in matrices of cyclopentyl bromide,[14] cyclopentane-,[15,16] or tetrahydrofuran[16] gave spectra with broad lines (line width ca. 250) which showed that there were two pairs of magnetically nonequivalent β-hydrogens which began to undergo exchange on the EPR time scale between 77 and 100 K. A barrier of 2.7 kcal mol^{-1} was calculated for this motion.[16] By contrast, sharp, isotropic spectra of cyclopentyl were later obtained in adamantane matrices and allowed a more accurate analysis of the exchange motion.[17] It was concluded[17] that the barrier for exchange was 1.3 kcal mol^{-1} and that the earlier measurements[16] had been influenced by a matrix effect. Thus, the barrier for the ring motion of the radical is similar to that of the parent hydrocarbon. Again, the pseudorotation mechanism is capable of providing a low-energy pathway for the exchange I–II.

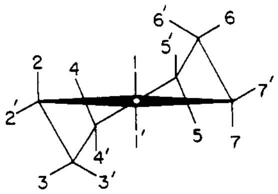

Figure 3. Chair conformation of cycloheptane, ref 23.

For cyclohexane, the most stable conformer is the chair form. However, chair to chair interconversion must proceed via the twisted-boat structure, there being no pseudorotation pathway accessible to the molecule. Crossing from the chair to the boat forms requires that the hydrogens on three methylene units become effectively eclisped. As a consequence the barrier is high (10 kcal mol^{-1}).[5]

The inversion of cyclohexyl radical has been studied both by experiment[15,18,19] and theory.[20] Analysis of the EPR data gives an inversion barrier of 4.9 ± 0.5 kcal mol^{-1}.[18] Theory suggests[20] that the radical center is nonplanar and that the chair to chair interconversion proceeds via a twisted-boat form as in the parent hydrocarbon. However, it was concluded that the motion of the carbon atoms was accompanied by an inversion at the radical center. Inspection of models shows that this is a very reasonable conclusion since the combined ring motion and inversion at the radical center minimize eclipsing interactions between the hydrogens. Accordingly, the barrier is much lower than the inversion barrier for the alkane.

It should be noted that the theoretical treatment calculates the minimum energy pathway for the molecular motion and does not take account of vibrational effects. In fact, the ^{13}C hyperfine splitting for cyclohexyl is similar to that for other simple alkyls even when the ring inversion is effectively frozen ($a^{^{13}C} = 41.3$ G at 193 K).[2] This implies that the motion of the α-hydrogen which inverts the radical center is much faster than the ring inversion and is not constrained by the latter. The ^{13}C hyperfine splitting therefore represents a vibrational average.[21] If this were not the case, the value for this splitting would be substantially greater than that observed. Thus, the α-hydrogen will, in general, be freely vibrating but may move in concert with the ring on the relatively infrequent occasions when ring inversion occurs.

For cycloheptane, the most stable conformer is a twisted-chair structure,[8] Figure 3, which again can interconvert to its mirror image via a low-energy pseudorotation process.[6-9] The energy required for this interconversion is only 1–2 kcal mol^{-1}.[8,22] By contrast, interconversion via

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the twisted-boat structure has a barrier of ca. 9 kcal mol^{-1}.[8]

If we assume that the hybridization for the cycloheptyl radical is somewhere between sp^2 and sp^3 at the radical center, then the center should, by comparison with cycloheptanone,[5] be at the 1, 2, or 7 positions, cf. Figure 3. We therefore presume that the motion which interconverts the magnetically inequivalent β-hydrogens is a pseudorotation just as in the parent hydrocarbon. As in the case of the cyclohexyl radical, such a molecular motion should be made easier by the inversion at the radical center. The barrier for inversion of the radical is greater than that of the parent hydrocarbon. However, the difference is relatively small and is difficult to associate with any molecular motion.

Summary

Analysis of the inversion barriers of cyclopentyl, cyclohexyl, and cycloheptyl radicals suggest that they are closely related to those of their parent hydrocarbons. In the five- and seven-membered rings the β-hydrogens are magnetically inequivalent in pairs but can be "exchanged" by a mechanism which probably involves pseudorotation. Like its parent hydrocarbon, the six-membered ring can only achieve such an exchange by a true inversion of the ring.

Registry No. Cycloheptyl radical, 4566-80-7.

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Reduction of Cyclic Compounds Having an N-O Linkage by Dihydrolipoamide-Iron(II)

Masashi Kijima, Yoko Nambu, and Takeshi Endo*

Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

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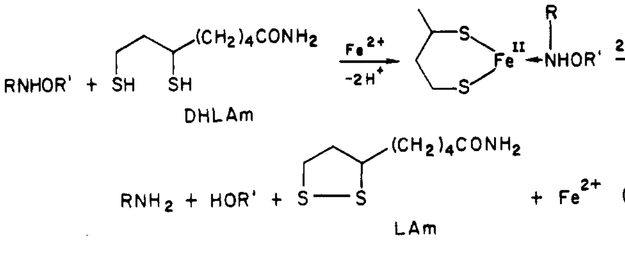
Lipoamide (LAm) is a coenzyme in acyl transfer and redox reactions in living systems, undergoing the redox reaction LAm $\rightleftharpoons$ dihydrolipoamide (DHLAm).

In the study of application of this redox function for organic synthesis, we have recently reported[1] that hydroxylamine derivatives were reduced by DHLAm-Fe(II) through coordination of substrates to a complex of DHLAm-Fe(II) under weakly basic conditions as shown in eq 1. We have also reported the reduction of azo- and azoxybenzene,[2] and selective reduction of monosubstituted nitrobenzenes with ester, ketone, nitrile, or other functional groups to corresponding anilines.[3] Further, we have found[4] that LAm and hydrophilic polymers having lipoamide structure in the presence of a catalytic amount of ferrous ammonium sulfate worked catalytically in the reduction of *O*-benzylhydroxylamine with sodium borohydride.

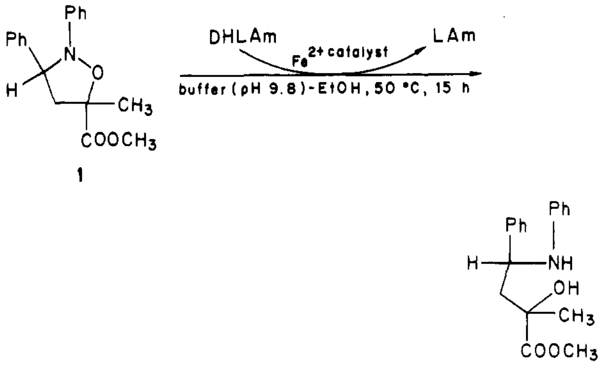


(1)

In this paper, we describe the reductive ring-opening reaction of isoxazolidines and isoxazoles by DHLAm-Fe(II).

Results and Discussion

Reduction of Isoxazolidines. The reduction of methyl 5-methyl-2,3-diphenylisoxazolidine-5-carboxylate (1) was carried out by DHLAm in the presence of a catalytic amount of ferrous ion under a slightly basic condition to give amino alcohol 2 in 81% yield (eq 2). Additionally, isoxazolidine 1 was not reduced by DHLAm or ferrous ion alone.

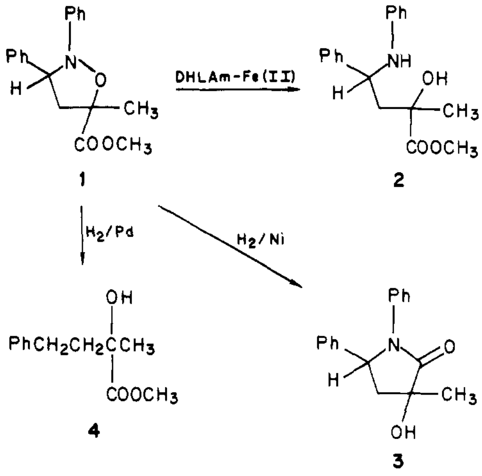


1

2

(2)

The reduction of isoxazolidines was widely studied by catalytic hydrogenation,[5] Zn-acetic acid,[6] LiAlH$_4$.[7] However, it was reported[8] that 1 was reduced by H$_2$/Ni and cyclized to give hydroxy lactam 3 and reduced by H$_2$/Pd to give 4 by the elimination of aniline (eq 3). In contrast, Amino alcohol 2 was obtained in the case of reduction by DHLAm-Fe(II), which proceeded under mild conditions to obtain 2 without elimination, cyclization, or



(3)

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