Acc. Chem. Res. **1989**, *22*, 8–14

Table V
Relative Reactivities toward *tert*-Butyl Radical at 35–40 °C

substrate	final product	rel react
CH_2=C(Cl)CN	t-BuCH_2CH(Cl)CN[a]	160
PhSO_2Cl	t-BuCl	11
CH_2=CHSO_2Ph	t-BuCH_2CH(HgCl)SO_2Ph	7.4
PhSSPh	t-BuSPh	4.3
CH_2=CHCO_2Et	t-BuCH_2CH(HgCl)CO_2Et	3.0
CH_2=CHP(O)$(OEt)_2$	t-BuCH_2CH(HgCl)P(O)$(OEt)_2$	1.0[b]
HC≡CCO_2Et	t-BuCH=C(HgCl)CO_2Et	0.6
CH_2=CPh_2	t-BuCH_2CHPh_2 + t-BuCH=CPh_2	0.4
MeSSMe	t-BuSMe	0.3
CH_2=CHSOPh	t-BuCH_2CH(HgCl)SOPh	0.2
CH_2=CHSPh	t-BuCH_2CH_2SPh[a]	0.1
Ph_2C=CHI	t-BuCH=CPh_2	0.1
(*E*)-PhCH=CHI	(*E*)-t-BuCH=CHPh	0.28
(*Z*)-PhCH=CHI	(*Z*)-t-BuCH=CHPh	0.18
(*E*)-PhCH=CHBr	(*E*)-t-BuCH=CHPh	0.35
(*E*)-PhCH=CHCl	(*E*)-t-BuCH=CHPh	0.22
(*Z*)-PhCH=CHCl	(*E*)-t-BuCH=CHPh	0.03
PhC≡CH	t-BuCH=C(HgCl)Ph	0.04
Me_2C=NO_2Li	t-BuCMe_2NO_2	0.02
i-PrSPr-i	t-BuSPr-i	4×10^{-3}
t-BuSSBu-t	$(t\text{-Bu})_2S$	5×10^{-4}

[a] Observed with $NaBH_4/CH_2Cl_2$. [b] Data of ref 45 with E_a = 4 kcal/mol yields 4.8×10^5 M^{-1} s^{-1} for the rate of attack of t-Bu$^\bullet$ at 35 °C.

0.3:1.8:1.0.[26] Evidence for t-Bu$^\bullet$ attack is also provided in a comparison of the reactivity of 2-cyclopentenone and 2-cyclohexanone with t-BuHgI/I^- ($h\nu$/40 °C, Me_2SO), $(t\text{-Bu})_2CuLi$ (−30 °C, Et_2O), and $(t\text{-Bu})_3ZnLi$/TMEDA (0 °C, Et_2O). The C_5/C_6 relative reactivities are 3.8 for t-Bu$^\bullet$, 4.2 for $(t\text{-Bu})_2CuLi$, and 3.9 for $(t\text{-Bu})_3ZnLi$.[26] Reaction with n-Bu$^\bullet$ gives C_5/C_6 = 2.4 but now the n-butylcuprate or -zincate reacts preferentially with 2-cyclohexenone ($C_5/C_6 \sim 0.2$) by a mechanism obviously not involving attack by the butyl radical. Table V lists some additional relative reactivities toward t-Bu$^\bullet$ from which the absolute rate constants can be calculated from the known rate constant for addition of t-Bu$^\bullet$ to CH_2=CHP(O)$(OEt)_2$.[45] Relative reactivities and regioselectivities of attack of c-$C_6H_{11}^\bullet$ and PhS$^\bullet$ upon 1,2-disubstituted alkenes or alkynes are reported elsewhere.[24,25]

Conclusions

Alkylmercurials are excellent sources of alkyl radicals that can be utilized in a variety of alkylation reactions proceeding by a chain process. *tert*-Butylmercury halides are more reactive than primary alkylmercurials in many of these processes not only in chain initiation but also in the chain propagation reactions 1–3 with a variety of donor or acceptor radicals formed by addition, addition–elimination, or S_H2 reactions of the *tert*-butyl radical.

It is a pleasure to acknowledge the contributions, many of which are unpublished, of my collaborators, J. Hershberger, H. Tashtoush, P. Ngoviwatchi, W. Jiang, S. Hu, R. K. Khanna, S. Herron, D. Guo, Y.-W. Wu, and A. Pla Dalmau. Financial support has been provided by the National Science Foundation and the Petroleum Research Fund.

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Probing Ring Conformations with EPR Spectroscopy[1]

K. U. INGOLD[2a] and J. C. WALTON*,[2b]

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6, and Department of Chemistry, University of St. Andrews, St. Andrews, Scotland KY16 9ST

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The conformational options open to alicyclic molecules have far-reaching chemical consequences. NMR spectroscopy has proved to be an extremely valuable tool for studying ring conformations. The equatorial preferences of substituents and, particularly, the dynamic stereochemistry of cyclohexanes and of medium-ring compounds have been investigated in this way.[3-5] The analogous technique of EPR spectroscopy has been used to study the conformations of some persistent radicals such as mono- and bicyclic semidiones[6] and nitroxides.[7] This technique has also been used to study ring inversions for a few transient cyclic radicals such as cyclohexyl and other radicals in which the unpaired electron is localized on one or more ring carbon atoms.[8-13] Unfortunately, such radicals contain the planar radical center in the ring, which drastically alters the ring's conformation in comparison with that of the

Keith U. Ingold received his B.Sc. degree from University College London and his D.Phil. from Oxford. He is Associate Director of the Division of Chemistry of the National Research Council of Canada, and his research has concentrated on the chemistry of free radicals in solution.

John C. Walton received his B.Sc. and D.Sc. degrees from Sheffield University and his Ph.D. from St. Andrews. He is now a Reader in organic chemistry at St. Andrews. His research interests are mainly in the area of organic free radicals.

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(2) (a) NRCC. (b) University of St. Andrews.

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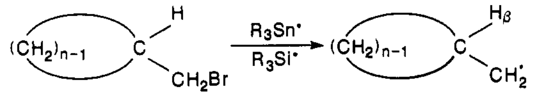
parent cyclic compound. The results are therefore specific to the radical itself and have little or no larger implications for the chemistry of stable alicyclic compounds.

In this Account we describe a new EPR approach to conformational problems that is of more general utility. It is based on our use of the $CH_2^•$ moiety as a "spin probe". That is, cycloalkylmethyl radicals, **1**, contain the small, nonpolar $CH_2^•$ group, which causes minimal perturbation of the adjacent ring. EPR studies on cycloalkylmethyl radicals therefore not only allow conformational analysis to be carried out on short-lived radicals but also give data that are of direct interest to all chemists working with alicyclic rings. A second reason for employing EPR spectroscopic methods is that the "time scale" for EPR is much shorter than for NMR so that dynamic processes with free energies of activation much lower than those generally measurable by NMR become accessible.

How Are Cycloalkylmethyl Radicals Made?

The preferred method for spectroscopic studies involves continuous UV photolysis in the cavity of an EPR spectrometer of an appropriate mixture of reagents in an inert solvent, which is frequently cyclopropane. Thus, bromine atom abstraction from cycloalkylmethyl bromides using tin- or silicon-centered radicals has been employed to generate small-,[14-16] medium-,[14,17-20] and large-ring[20] cycloalkylmethyl radicals. Diacyl peroxides have been used as the precursors of several **1**, e.g., cyclopentylmethyl,[21] a radical that has also been made by cyclization of hex-5-enyl.[21-23]



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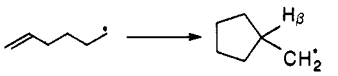
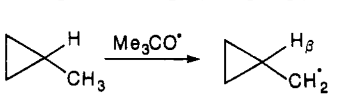
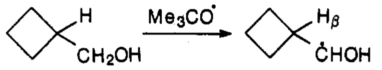
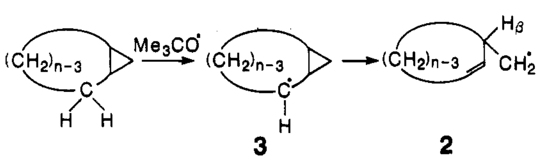


Hydrogen atom abstraction by *tert*-butoxyl radicals has proved useful for generating cyclopropylmethyl,[24,25] as well as various substituted cyclopropylcarbinyls[24,26-31] and certain cyclobutylcarbinyls, e.g.[32]



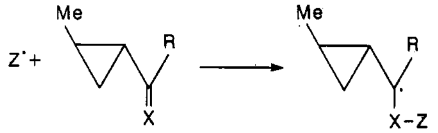


Cycloalk-2-enylmethyl radicals, **2**, can be generated by hydrogen abstraction from bicyclo[n.1.0]alkanes, a process that preferentially occurs adjacent to the C_3 ring. The intermediate bicyclo[n.1.0]alk-2-yl radical, **3**, then undergoes a rapid β-scission to produce an exocyclic radical center.[33-35]



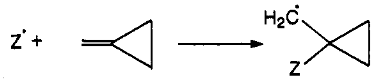
3 **2**

Cycloalkylmethyl radicals have also been made by radical addition to C═O[26,27,29] and C═C[38] double bonds, e.g.



X = O; Z = n-$Bu_3Sn^•$; R = H, Me, Bu
X = CH_2; Z = $(EtO)_2\dot{P}O$, $Me_3SiO^•$, t-$BuS^•$; R = H, Me

More interestingly, since radicals normally show a very strong preference for addition to the less substituted end of a C═C double bond,[39] it has been shown that a number of electrophilic radicals preferentially add to the more substituted end of the double bond in methylenecyclopropane.[40]



Z = $Me_3CO^•$, $Me_3SiO^•$, $(Me_3COH)^{•+}$

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(35) Note that the bicyclo[2.1.0]pent-2-yl radical (**3**, n = 5) undergoes a stereoelectronically forbidden β-scission of the central C(1)–C(4) bond to form cyclopent-3-en-1-yl.[34,36] Bicyclo[1.1.0]but-2-yl (**3**, n = 4) also undergoes the stereoelectronically forbidden β-scission of the central C(1)–C(3) bond to form the cyclobutenyl radical.[33,34,37]

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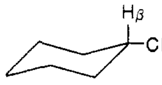
Cyclohexane Ring Conformations

The cyclohexylmethyl radical occupies a key place in the development of conformational analysis by EPR spectroscopy. At low temperatures (T < 180 K) only one radical species can be observed.[14] At 140 K this radical has two normal H_α hyperfine splittings (hfs) of 21.5 G and one H_β hfs of 30.4 G. It can be identified as the lowest energy chair conformer in which the $CH_2^\bullet$ group is in the equatorial position, **4** (equational conformer). At higher temperatures a second, minor, radical can be observed,[17,18] again with two normal H_α hfs but with a much larger H_β hfs of 41.2 G at 182 K. This minor radical was identified as the chair conformer in which the $CH_2^\bullet$ group is in the axial position, **5** (axial conformer), rather than the twist-boat conformer, **6**, in two ways. First, the radical derived from (*trans*-4-*tert*-butylcyclohexyl)methyl bromide, which must be diequatorial, **7**, had an H_β hfs very similar to that of **4**, whereas the radical derived from (*cis*-4-*tert*-butylcyclohexyl)methyl bromide, **8**, in which the *tert*-butyl group monopolizes the equatorial position, had an EPR spectrum very similar to that of the minor cyclohexylmethyl radical, including, in particular, a large H_β hfs of 41.9 G at 140 K.[17,18] Second, the 2-adamantylmethyl radical, **9**, in which the rigid structure ensures that the $CH_2^\bullet$ group is axial with respect to one chair cyclohexane ring and that H_β is equatorial in this same ring, had an H_β hfs of 41.1 G at 140 K.[41]



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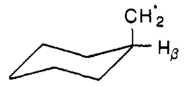

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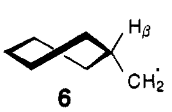

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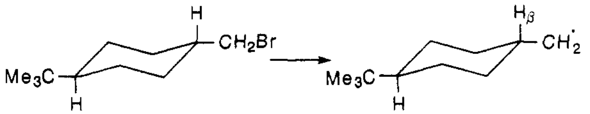

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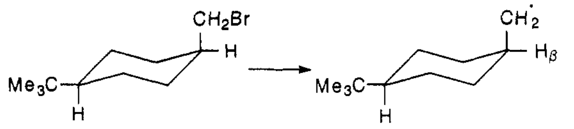

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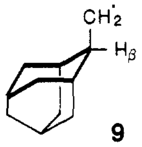
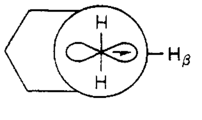


9

Both the axial (**5**) and equatorial (**4**) radicals prefer conformations in which the semioccupied $2p_z$ orbital on $C_\alpha^\bullet$ eclipses H_β, **10**, as can be deduced from the fact that for both radicals the H_β hfs decreases as the temperature increases and libration from the preferred eclipsed position becomes more and more pronounced. The surprisingly large difference in the H_β hfs of the axial (ca. 42–43 G at 140 K) and equatorial (ca. 30–31 G at 140 K) radicals is a consequence of the different potential energy functions governing rotation about their C_β–$C_\alpha^\bullet$ bonds.[17,18] The equatorial radicals have H_β hfs similar to those of analogues such as isobutyl (H_β hfs = 31.7 G at 140 K)[14] and probably have similar potential energy functions. The axial radicals have "abnormally" high H_β hfs, which result from much higher barriers to rotation due to steric hindrance by the syn-axial hydrogens, H^3_{ax} and H^5_{ax} in **11**.[17,18] This steric hindrance "holds" the axial radical rather "firmly" in the eclipsed position and produces unusually high H_β hfs. That axial substituents at C-1 experience steric repulsion from H^3_{ax} and H^5_{ax} is well-known. This phenomenon destabilizes axial conformers, inhibits approach by reagents in the axial mode, and has far-reaching chemical consequences.[42] Surprisingly, the effect on the rotation of the substituent at C-1 had not previously been discovered. In the present case, it has the useful consequence of making axial and equatorial cyclohexylmethyl radicals clearly distinguishable by EPR. Moreover, it also allows other quasi-axial and quasi-equatorial cycloalkylmethyl and cycloalkenylmethyl radicals to be distinguished and studied by EPR.



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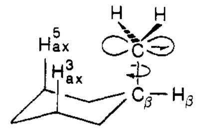

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The relative concentrations of the two cyclohexylmethyl radical conformers were measured over a range of temperatures, and the conformational free energy difference of the $CH_2^\bullet$ group ($-\Delta G^\circ_{300}$) was found to be 0.71 kcal/mol.[17,18] As might be expected, the $CH_2^\bullet$ group has a somewhat greater equatorial preference than OH ($-\Delta G^\circ_{300}$ = 0.52 kcal/mol in aprotic solvents)[43] and OCH_3 ($-\Delta G^\circ_{300}$ = 0.60 kcal/mol)[43] but a considerably lower equatorial preference than CH_3 ($-\Delta G^\circ_{300}$ = 1.74 kcal/mol)[44,45] and other alkyl groups.[45] By this measurement, therefore, the $CH_2^\bullet$ group is "smaller" than CH_3.

Equatorial (**4**) and axial (**5**) cyclohexylmethyl radicals can interconvert by ring inversion. At sufficiently high temperatures this process would become so rapid (on the EPR time scale) that only an averaged EPR spectrum would be observable. In practice, exchange broadening due to ring inversion occurs at temperatures above 400 K where signal intensities become too weak to measure. However, for (*cis*-4-methylcyclohexyl)methyl the dynamics of the axial, **13a**, and equatorial, **13e**, ring inversion could be examined, albeit not by line broadening.[18] Since the bromide precursor consists of an equilibrium mixture of the two conformers **12a** and **12e**, it yields a mixture of **13a** and **13e**. At temperatures above ca. 200 K, ring inversion is rapid relative to the radicals' lifetimes, and the ratio of the radicals' concentrations yields the equilibrium constant, i.e., $[\mathbf{13a}]/[\mathbf{13e}] = k_b/k_f = K$. The temperature dependence of K could be represented by $\log K = (1.35 \pm 0.05) -$

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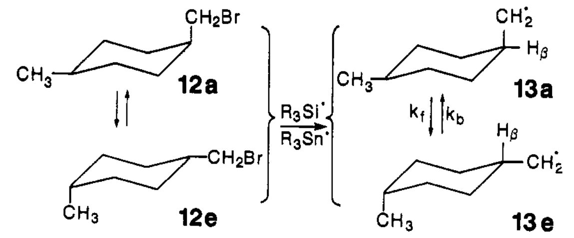
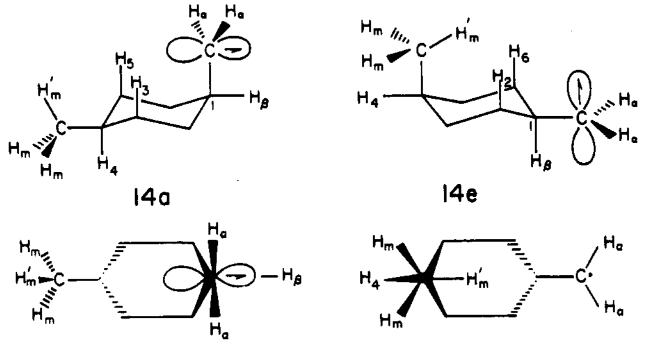


$(1.07 \pm 0.08)/\Theta$, where $\Theta = 2.3RT$ kcal/mol.[18] At temperatures below ca. 200 K radical–radical reactions occur more rapidly than ring inversion, and under these conditions, the ratio of the radicals' concentrations should be equal to the ratio of the concentrations of their starting bromides, i.e., [**13a**]/[**13e**] = [**12a**]/[**12e**], a result that was confirmed by an NMR study of **12**.[18] With these NMR data and the known rate constants for radical–radical reactions in solution, the measured [**13a**]/[**13e**] ratios over the entire temperature range (124–328 K) were employed to calculate Arrhenius expressions for the two interconversion processes, viz.[18]

$$\log (k_f/\text{s}^{-1}) = (13.30 \pm 1.0) - (9.0 \pm 1.0)/\Theta$$

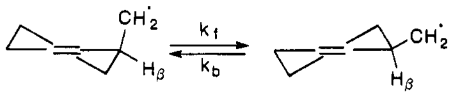
$$\log (k_b/\text{s}^{-1}) = (14.65 \pm 1.0) - (10.1 \pm 1.0)/\Theta$$

These enthalpic inversion barriers are similar to the inversion barriers obtained by dynamic NMR spectroscopy for various alkyl-substituted cyclohexanes.[3] Interestingly, under equilibrium conditions the equatorial radical, **12e**, would predominate at temperatures below 175 K despite the fact that this radical has the "larger" methyl group in the axial position. The reason for this totally unexpected result is that the axial *nonrotating* CH_3 group can adopt a staggered, minimum-energy conformation, **14e**, whereas the axial nonrotating $CH_2^•$ group cannot because of its planarity, **14a**. That is, the cyclohexane ring probe tells us that a rotating methyl group is "larger" than a rotating $CH_2^•$ group but that a nonrotating methyl is "smaller" than a nonrotating $CH_2^•$ group!



Cyclohexene Ring Conformations

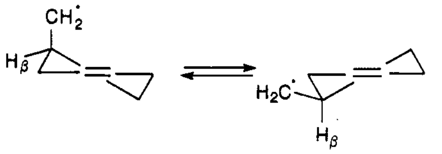
The cyclohexene ring has also been studied by using the $CH_2^•$ "spin probe".[19] The quasi-axial (**15a**) and quasi-equatorial (**15e**) cyclohex-2-enylmethyl radicals



15a **15e**

have overlapping EPR spectra but can be distinguished by the relative magnitudes of their H_β hfs, which are 32.6 and 30.6 G, respectively, at 140 K.[19] From measurements of the relative concentrations of these two radicals, the conformational free energy difference of the $CH_2^•$ group ($-\Delta G_{300}°$) was found to be 0.17 kcal/mol, an equatorial preference much less pronounced than in cyclohexylmethyl radicals, as would be expected. The spectra showed exchange broadening due to ring inversion, which is much more facile than in cyclohexane. Line-shape analysis over the temperature range 170–280 K yielded $\log (k_f/\text{s}^{-1}) = 12.3 - 5.7/\Theta$ and $\log (k_b/\text{s}^{-1}) = 12.0 - 5.5/\Theta$. These inversion barriers are of similar magnitude to the free energies of inversion measured by NMR for cyclohexene, viz.,[46,47] $\Delta G^\ddagger_{108} \approx 5.3 - 5.4$ kcal/mol, and for some 4-halogenocyclohexenes, viz.,[47] $\Delta G^\ddagger_{122} = 5.3 - 6.3$ kcal/mol.

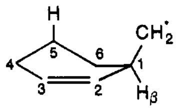
The more nearly truly axial (**16a**) and equatorial (**16e**) cyclohex-3-enylmethyl radicals have H_β hfs of 32.3 and 28.8 G, respectively, at 140 K.[19] In this pair of radicals



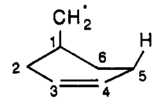
16a **16e**

the $CH_2^•$ group exhibits no conformational preference, and the equilibrium mixture has [**16a**] = [**16e**], i.e., $-\Delta G_{300}° \sim 0$ within experimental error.

In both **15a** and **16a** the $CH_2^•$ group experiences repulsion by only *one* axial hydrogen at C-5 (**17a** and **18a**, respectively), and for this reason the axial conformers



17a (≡**15a**)



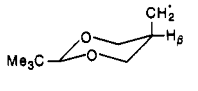
18a (≡**16a**)

are closer in energy to their equatorial counterparts and the $-\Delta G°_{300}$ values are much smaller than for the cyclohexane case. The lower H_β hfs for **15a** and **16a**, as compared with axial cyclohexylmethyl radicals, are due to the same factor.

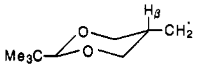
Despite the presence of only one axial H at C-5, the magnitudes of the H_β hfs and their decrease with increasing temperature for all four radicals, **15a**, **15e**, **16a**, and **16e**, indicate that they all adopt eclipsed conformations analogous to cyclohexylmethyl (**10** or **11**).

3,5-Dioxolanylmethyl Radicals

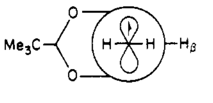
These radicals lack even a single axial H at positions 3 or 5, and this has a profound and unexpected effect on their conformation. Both axial (**19a**) and equatorial (**19e**) (2-*tert*-butyl-3,5-dioxolanyl)methyl radicals have



19a



19e



20

H_β hfs below the "free-rotation" limit of ca. 26.8 G,[48] viz.,[41] 19.8 and 16.5 G, respectively, at 140 K. This

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(46) Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147–3150.

(47) Jensen, F. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 5774–5782.

(48) This is the expected magnitude of the H_β hfs if there were no barrier to rotation about the $C_\alpha^•$–C_β bond; see: Kochi, J. K. *Adv. Free Radical Chem.* 1974, *5*, 189–317.

indicates that both radicals adopt a bisected conformation, **20**.[41] The absence of steric repulsion from axial H-3 and H-5 means that the difference in energy between eclipsed and bisected conformations will be very small, and the precise factors that control this "switch" in conformation (i.e., steric or electronic) are therefore extremely difficult to pinpoint.[41]

Cyclopropyl, Cyclobutyl, and Cyclopentyl Rings

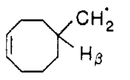
The cyclopropane ring is necessarily planar. Interest in the EPR spectroscopy of cyclopropylmethyl has centered largely on its ring opening to form the but-3-enyl radical at ca. 140 K.[24,25,49] More recently, the barrier to rotation about the C_β–$C_\alpha^\bullet$ bond has been obtained by analysis of the exchange broadening in its low-temperature EPR spectrum.[16] These data imply that the cyclopropylmethyl radical is stabilized to an extent similar to that of the $HOCH_2^\bullet$ radical.[16]

Cyclobutane and cyclopentane are both nonplanar but ring inversion of the former and ring pseudorotation of the latter are so rapid that only conformationally averaged EPR spectra of these two cycloalkylmethyl radicals can be observed.[14,21-23,32,50] However, cyclobutylmethyl radicals do have exceptionally well resolved long-range hfs, which has enabled the preferred conformations and rotation barriers of C-2 and C-3 methyl substituents to be determined.[51]

Seven- and Eight-Membered Rings

Cycloheptane undergoes a very rapid pseudorotation,[3] which explains why the cycloheptylmethyl radical shows no dynamic EPR effects even at very low temperatures.[52] The single radical observed is probably an average over all possible conformations. By way of contrast, the inversion barrier for cyclooctane is ca. 7–8 kcal/mol according to NMR measurements,[3,53] and therefore distinct EPR spectra would be expected for different conformers of the cyclooctylmethyl radical. Surprisingly, the EPR spectra show only a single radical,[14,20] which suggests that the concentrations of conformers other than the main one are too low for detection.

Although the EPR spectrum of the cyclooct-4-enylmethyl radical, **21**, showed only a single species, that of the cyclohept-4-enylmethyl radical, **22**, showed the presence of two conformers, the major one (ca. 80%) and the minor one (ca. 20%) having H_β hfs of 33.7 and 42.9 G, respectively, at 200 K.[54] The major conformer can be identified with the equatorial chair form, **22ec**, which will be lowest in energy. The H_β hfs of the minor radical suggests that it is an axial conformer for which there are three main candidates: an axial chair form **22ac** (the counterpart to **22ec**), an axial boat form **22ab**, and a twist form **22tb**. With regard to **22ab**, we note that the boat form of cycloheptene is believed to be a stable conformation not greatly above the chair form in energy,[55,56] while models suggest that steric repulsion in **22ab** may be quite small. Chair conformers interconvert via boat conformers, and NMR measurements on cycloheptene have shown that this process has a free energy of activation of only 5.0 kcal/mol.[57] Whether the minor conformer is **22ac**, **22ab**, or **22tb**, the fast equilibrium between all the cyclohept-4-enylmethyl radical conformers (**22ec**, **22ac**, **22ab**, an equatorial boat, and **22tb**) ensures that this radical has access to conformer **22ab**. This is important because the radical center in **22ab** is immediately above the double bond, which puts it in a nearly ideal position for a transannular cyclization. Indeed, reaction of the bromide precursor of **22** with n-Bu$_3$SnH gave excellent yields of bicyclo[3.2.1]octane, particularly at higher temperatures.[54] Reaction of the bromide precursor of **21** with n-Bu$_3$SnH also gave transannular cyclized products.[54]



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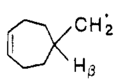

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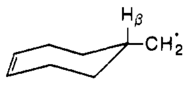
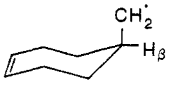
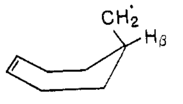


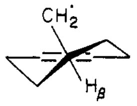
22 ec



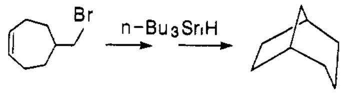
22 ac



22 ab



22tb



Nine- to Fifteen-Membered Rings

Conformational options become more numerous and the problems of conformational identification and assignment become more difficult as the ring size increases. For these large rings three main methods of study have been employed heretofore: (1) NMR spectroscopy, but both ^{1}H and ^{13}C spectra become very complex, and, in some cases such as cyclodecane,[58] the slow inversion limit spectra cannot be obtained; (2) X-ray diffraction with crystalline derivatives, but the potential influence of crystal forces on conformational preference cannot be ignored; (3) force field calculations. Obviously, new methods, such as our $CH_2^\bullet$ "spin probe", that can help to clarify our understanding of large rings are very desirable.

Remarkably, cycloalkylmethyl radicals having nine- or fifteen-membered rings (excluding only cyclotetradecylmethyl, which we have not examined) show just two readily distinguishable conformers (although with both cyclodecylmethyl and cyclopentadecylmethyl there may be an additional conformer that does not give a

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(49) Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 1734–1736.

(50) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970–974.

(51) Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 443–450.

(52) Walton, J. C., unpublished results.

(53) Anet, F. A. L.; Hartman, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1204–1205. Anet, F. A. L.; St. Jacques, M. *Ibid.* **1966**, *88*, 2585–2586, 2586–2587.

(54) MacCorquodale, F.; Walton, J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 1456–1457.

(55) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1977**, *94*, 5734–5747.

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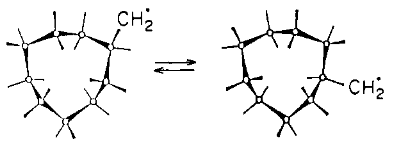
Table I
Conformational Preferences of Medium- and Large-Ring Cycloalkylmethyl Radicals

ring size (*n*)	conf and structures	[corner]^a / [outer edge]	[QA]/[QE] (temp)^b
9	[333], **23c**, **23oe**	1.0	0.79–1.33 (97–139)
10	[2323], **24–26**	1.33	0.85–1.63 (128–184)
11	[335], **27**	0.75	0.68–0.83 (94–172)
12	[3333], 28	1.0	0.54–0.67 (139–211)
13	[346],^{c} **29**	0.6	0.35–0.50 (141–195)
15	[33333]^d	1.0	2.37–1.12 (141–221)

^{a} Statistical ratio for the indicated conformation. ^{b} Range of experimentally measured [QA]/[QE] ratios and, in parentheses, range of temperatures (K). The first [QA]/[QE] ratio refers to the lowest and the second to the highest temperature measurement. Good van't Hoff plots were obtained in all cases (see ref 20). ^{c} Conformation determined in this work (see text). ^{d} And other quinquangular structures (see text).

clearly resolved EPR spectrum).[20] We designate as quasi-equatorial (QE) the conformer with the smaller H_β hfs and as quasi-axial (QA) the conformer with the larger H_β hfs.

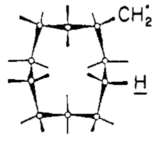
The stable conformers of medium- and large-ring cycloalkanes are believed to have triangular, quadrangular, or quinquangular structures made up with "edge" and "corner" methylene groups.[59] Fortunately, the introduction of a single substituent, such as a CH_3 or $CH_2^{\bullet}$ group, into medium- and large-ring cycloalkanes is not expected to change the stability order of the possible ring conformations, since there will always be on each of these a number of unhindered positions for the substituent.[60] The lowest enthalpy conformer of cyclononane, for example, is probably of the triangular type with D_3 symmetry, designated as [333],[61–64] and in this conformation there are just three possible sites for the $CH_2^{\bullet}$ "spin probe", a corner site, **23c**; an "outer-edge" site, **23oe**; and an "inner-edge" site. The last named site will be strongly disfavored because of steric crowding. In [333]-cyclononane and, in fact, in all triangular and quadrangular conformers, there is only one type of corner site because the "axial" and "equatorial" hydrogen atoms are identical; i.e., the corner H-atoms are homotopic. Therefore, just two conformers of the cyclononylmethyl radical are expected and just two were observed. We identify the QA conformer as **23c** and the QE conformer as **23oe** (H_β hfs = 37.2 and ~35.0 G, respectively, at 140 K) because models suggest that there will be slightly more hindrance to rotation of the $CH_2^{\bullet}$ group in a corner site than in an edge site. There are six corner and six outer-edge sites, so the statistical ratio of conformers, [**23c**]/[**23oe**], would be expected to be 1.0, a value that is in reasonable agreement with the measured [QA]/[QE] ratio[20] (see Table I).



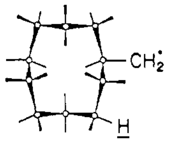
23c, [333] 23oe, [333]

Cycloalkylmethyl radicals having $n \geqslant 10$ have QA and QE conformers with H_β hfs in the range 38.3–40.4 and 27.7–32.0 G, respectively, at 140 K, values that are comparable to those of axial and equatorial cyclohexylmethyl radicals (e.g., 42.4 and 30.7 G for **13a** and **13b**, respectively, at 140 K).[18,20]

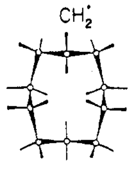
The predominant cyclodecane conformer has the quadrangular [2323] structure[5] so there are three possible sites for the $CH_2^{\bullet}$ "spin probe", **24–26**. Rotation of the $CH_2^{\bullet}$ group will be most strongly impeded at the corner (again by a 1,3-interaction with the syn H atom on C-3) so we assign structure **24** to the QA radical. There will be much less hindrance to $CH_2^{\bullet}$ rotation by the syn H at C-3 in **25** and negligible hindrance in **26** (in which the H atoms on C-3 are "round the corner"). Both **25** and **26** are therefore expected to give EPR spectra of the QE type, and there is, in fact, an indication in the spectrum that there may be two different QE radicals.[20] The statistical ratio [**24**]/([**25**] + [**26**]) agrees reasonably well with the experimental [QA]/[QE] ratio (Table I).



24, [2323]

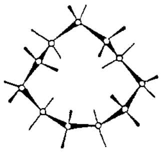


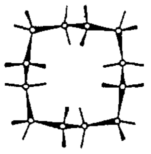
25,[2323]



26, [2323]

The preferred conformations of cycloundecane[58,65] and cyclododecane[58,66,67] are probably triangular, [335] (**27**), and quadrangular, [3333] (**28**), respectively. Both **27** and **28** should possess, just two distinct types of cycloalkylmethyl radicals and, indeed, as Table I shows, the statistical ratios of corner to outer-edge types in these two structures are in reasonable agreement with the experimental [QA]/[QE] ratios.


27, [335]


28, [3333]

The situation becomes even more interesting with cyclotridecane, for which there are five low-enthalpy conformations[59,65,68] with two quinquangular structures, [13333] and [12433], and a triangular structure, [346], being of the lowest calculated energy.[68] The ^{13}C NMR spectrum of cyclotridecane defied analysis,[68] but an X-ray structure of a 13-membered ring containing nitrogen showed that the main conformer had the [13333] structure.[68] However, both quinquangular conformers have ten corner and eight outer-edge sites, a statistical ratio of 1.25, which is very different from the experi-

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(59) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115–1129.

(60) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1149–1158.

(61) Dales's[59] shorthand notation describes cycloalkane conformations by means of numbers within brackets that give the number of bonds within one "edge" (side) starting with the shortest and proceeding around the ring so that the next number is the smallest possible.

(62) Also referred to as a "twist-boat-chair" conformation.

(63) Anet, F. A. L.; Krane, J. *Isr. J. Chem.* **1980**, *20*, 72–83.

(64) Anet, F. A. L.; Wagner, J. J. *J. Am. Chem Soc.* **1971**, *93*, 5266–5268.

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(67) Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7166–7171.

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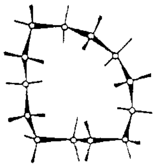
Table II
Arrhenius Activation Energies[a] for Ring-Atom Site Exchange in Cycloalkylmethyl Radicals[b]

ring size (n)	E_f (EPR)[c]	E_b (EPR)[c]	ΔG^* (NMR)[d]	E_Δ (FF)[e]
9	5.4	5.7	~6	7.7, 7.0
10	~6[f]	~6[f]	~6 (5.7)[g]	6.6
11	5.6	5.7	~6[h]	4.2
12	7.3	7.5	7.3	7.9
13	6.4	6.7		6.9
15	7.0	6.4		

[a] Log (A/s^{-1}) values ranged from 11.8 (n = 9) to 13.6 (n = 15). [b] All values in kcal/mol. [c] This work. Subscripts f and b refer to the processes QA → QE and QE → QA, respectively. [d] Free energy barrier for site exchange of the corresponding cycloalkane as measured by line broadening; from ref 3 unless otherwise noted. [e] Force field calculation of the strain energy difference between the transition state and the most stable cycloalkane conformer (see text and ref 20 for original sources). [f] Based on a coalescence temperature of ca. 230 K since simulation proved impossible (see footnote 69). [g] Value for 1,1-difluorocycloundecane: Noe, E. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 2020–2026. [h] Reference 65.

mental [QA]/[QE] ratio, the latter being in better agreement with the triangular structure (see Table I). Furthermore, the corner sites next to the one-bond edge in the quinquangular structures are not homotopic so that the $CH_2^\bullet$ group at these two corners can be pseudoaxial or pseudoequatorial. The pseudoaxial position would produce significantly greater steric hindrance to $CH_2^\bullet$ rotation than the pseudoequatorial position and so distinct EPR spectra would be expected for these two radicals. However, no "extra" lines could be detected and line widths were normal. Thus, our EPR "spin probe" indicates that the cyclotridecylmethyl radical, and hence cyclotridecane, **29**, preferentially adopts the triangular [346] conformation in solution.



29, [346]

Cyclopentadecane probably exists as a mixture of about five conformations, all of the quinquangular type[59,65] and all with a corner/outer edge ratio of 1.0, which is not too different from the experimental [QA]/[QE] ratio (Table I). The one-bond corner sites should give rise to novel corner radicals (vide supra), and the EPR spectrum of this radical did indeed show unusually broad lines for the QE radical.

The EPR spectra of all the medium- and large-ring cycloalkylmethyl radicals showed exchange broadening due to interconversion of the QA and QE radicals, and, at high temperatures, only the averaged spectrum was observable. The Arrhenius activation energies for the forward and reverse processes were obtained by line-shape analysis.[69] These activation energies, E_f and E_b

$$QA \underset{k_b}{\overset{k_f}{\rightleftarrows}} QE$$

(Table II), differ because the corner and outer-edge radicals differ in enthalpy. However, their mean value should be close to the activation energy for ring-atom exchange in the unsubstituted cycloalkanes because a single, small substituent will have little or no effect on these barriers.[3,60] Dale[70] has shown that interconversion of large-ring cycloalkane conformers takes place by a process of "corner migration", one completed cycle of which will have caused all the carbons to have moved one step around the ring. The transition state for corner migration of the $CH_2^\bullet$ group resembles the syn barrier for the n-butane internal rotation about the central C–C bond, which has a value of ca. 6 or 7 kcal/mol.[59] The values of E_f and E_b are of this general magnitude. Since the entropies of activation will probably be small, the mean of E_f and E_b would be expected to be similar to the free energies of activation, ΔG^*, estimated from the ^{13}C NMR coalescence temperatures of the cycloalkanes. Table II shows that this is the case and, moreover, that our measurements agree reasonably well with available barriers calculated by force field methods.

Concluding Remarks

We have discovered, as an unexpected consequence of steric repulsion between syn-axial hydrogens and an axial $CH_2^\bullet$ substituent in cycloalkane rings, that the barrier to rotation of this substituent is increased substantially. As a consequence, axial and quasi-axial cycloalkylmethyl radicals have much greater H_β hfs than equatorial and quasi-equatorial cycloalkylmethyls. The EPR spectra of these two types of radicals can therefore be easily distinguished, and this opens the way for the more general use of the $CH_2^\bullet$ "spin probe" for ring conformational analysis. When a greater range of conformational types has been studied, it may be possible to deduce preferred ring conformations from the EPR data but at present the spectra are most useful for (i) checking the conformational predictions of force field and other calculations, (ii) measuring rates of inversion and other dynamic ring processes having relatively low potential energy barriers, and (iii) determining the equatorial/axial preference not only of the "spin probe" but also of other substituents in different size rings. This method will certainly prove useful in exploring the conformational behavior of heteroatom-containing ring systems and can be extended to provide further valuable insights by using "spin probes" of different size, shape, and polarity (such as $CF_2^\bullet$).

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(69) Except for the cyclodecylmethyl radical where the exchange broadening could not be simulated with a simple two-jump, QA → QE model, probably because three conformers, **24–26**, are involved.

(70) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1130–1148.