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Long-Range Intrinsic NMR Isotope Shifts as a Probe of Hyperconjugation. Demonstration of the Angular Dependence in Bicyclic Carbocations

David A. Forsyth,* James H. Botkin, and Virginia M. Osterman

Contribution from the Department of Chemistry, Northeastern University, Boston, Massachusetts 02115. *Received January 27, 1984*

Abstract: The long-range NMR isotope shift is demonstrated to be strongly angle dependent in the manner expected for a hyperconjugative origin in two benzylic cations with rigid bicyclic alkyl systems. The NMR isotope shifts produced at ^{19}F due to deuterium substitution in the 2-(*p*-fluorophenyl)-2-bicyclo[2.2.2]octyl cation are 0.143 ppm for each deuterium at C_3 and 0 ppm for deuterium at the bridgehead C_1 position. In the 2-(*p*-fluorophenyl)-2-bicyclo[2.2.1]heptyl cation, the isotope shifts at ^{19}F are 0.202 ppm for exo substitution at C_3 and 0 ppm for endo substitution. These results are consistent with other experimental and theoretical data, indicating that an *exo*-C–H is better aligned for hyperconjugation than an *endo*-C–H in classical norbornyl cations.

Downfield NMR isotope shifts due to deuterium substitution at a carbon atom adjacent to a π-electron system have been postulated to result from a perturbation of the hyperconjugative interaction.[1-7] In an effect fundamentally arising from vibrational differences, the C–D bond behaves as a poorer electron donor than a C–H bond in cationic hyperconjugation, as evident in long-range deshielding of nuclei in cations with charge delocalized in a π system.[1-3,7] This type of intrinsic NMR isotope shift could be a valuable new probe of hyperconjugation, because it differs from kinetic or equilibrium isotope effects in being a measured property of a single structure rather than reflecting a change in force constants between two states.

A consequence of the postulated hyperconjugative origin of the long-range NMR isotope shift in carbocations is that the isotope effect should exhibit a dependence on the dihedral angle between the C–H(D) bond and the electron-deficient p orbital of the cation center. The angular dependence of β-deuterium isotope effects has been clearly demonstrated experimentally for kinetic isotope effects[8] and is supported by theoretical studies.[9] We have previously assumed an angular dependence of the NMR isotope shift in accounting for the nonadditive behavior of such isotope shifts in conformationally mobile carbocations.[3,10]

In this paper, we demonstrate in two "rigid" bicyclic systems that the NMR isotope shift is strongly angle dependent in the manner expected for a hyperconjugative origin. Specifically, we report long-range isotope shifts due to deuteration at the C_3 and bridgehead C_1 positions of a 2-bicyclo[2.2.2]octyl cation and show also that the isotope shift provides a dramatic distinction between the C_3 exo and endo hydrogens of a classical 2-bicyclo[2.2.1]heptyl cation.

Results

The 2-(*p*-fluorophenyl)-2-bicyclo[2.2.1]heptyl cations (**1**) were prepared in 1:1 FSO_3H:SbF_5 and SO_2ClF as separate **1**-*exo-3-d*, **1**-*endo-3-d*, and **1**-*3,3-d*$_2$ species from the correspondingly labeled 2-(*p*-fluorophenyl)bicyclo[2.2.1]heptan-2-ols. The complete retention of deuterium in the cations was evident by the coupling of C_3 to deuterium in the ^{13}C NMR spectra of the labeled ions. The ^{13}C chemical shifts matched the spectral data reported in earlier studies which established **1** as a classical ion with use of the "tool of increasing electron demand".[11]

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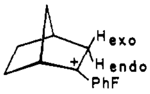

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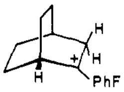

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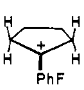

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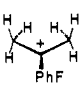

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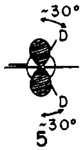
The long-range isotope shifts were measured in 56.2-MHz ^{19}F spectra of ion **1**, at −70 °C, from mixtures of the unlabeled ion with the labeled ions. A downfield isotope shift of 0.202 ± 0.005 ppm at ^{19}F was observed for both **1**-*3,3-d*$_2$ and **1**-*exo-3-d*. No isotope shift was observed, nor any line broadening due to an unresolved shift, for **1**-*endo-3-d*. Clearly, the entire isotope shift in the dilabeled ion is due to the exo deuterium. That the isotope shift is intrinsic rather than an equilibrium isotope shift is indicated by the very small temperature dependence.[12] For **1**-*exo*-**3**-*d*, the shift varied from 0.195 ppm at −36 °C to 0.205 ppm at −108 °C, which is comparable to the variations observed for other benzylic ions.[3]

In similar fashion, isotope shifts were measured for the 2-(*p*-fluorophenyl)-2-bicyclo[2.2.2]octyl cation (**2**).[13] Precisely additive, downfield isotope shifts at ^{19}F of 0.143 and 0.286 ppm were observed at −60 °C for **2**-*3-d* and **2**-*3,3-d*$_2$, respectively. The bicyclo[2.2.2]octyl cation deuterated at the bridgehead C_1 position, **2**-*1-d*, exhibits no isotope shift measurable at 56.2 MHz, i.e., a shift of 0.00 ± 0.01 ppm.

Isotope shifts for two other *p*-fluorophenyl carbocations are relevant for purposes of comparison. The 1-(*p*-fluorophenyl)-cyclopentyl cation (**3**), when tetradeuterated as **3**-*2,2,5,5-d*$_4$, produced a total downfield isotope shift at ^{19}F of 0.603 ppm, or an average of 0.151 ppm per deuterium.[10] In the 2-(*p*-fluorophenyl)-2-propyl cation (**4**), complete deuteration of both methyl groups gave a downfield isotope shift of 0.461 ppm, or 0.230 ppm per methyl or 0.077 ppm per deuterium.[3]

Discussion

Relation of Isotope Shifts to Angular Dependence of Hyperconjugation. The bicyclo[2.2.2]octyl cation (**2**) provides an unambiguous demonstration of the angular dependence of the long-range NMR isotope shift. By symmetry, the C_3 methylene C–H(D) bonds are equivalent and must have equal, approximately 30°, angles with respect to the p orbital at C_2, as shown in **5**. These C–H(D) bonds are suitably aligned for hyperconjugative overlap, and the observed downfield isotope shift at ^{19}F of 0.143 ppm for each deuterium is consistent with a hyperconjugative origin of these shifts.[1-7] The cyclopentyl cation (**3**) must also have an average alignment as shown in **5**, and a very similar isotope effect is seen. On the other hand, the bridgehead C_1 hydrogen in **2** is constrained to a 90° angle with respect to the p orbital at C_2, as shown in **6**. No hyperconjugation with the C_1–H(D) bond is possible, and no isotope shift is observed at ^{19}F.



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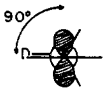

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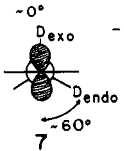

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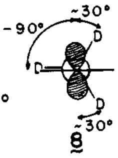

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A hyperconjugative origin of the long-range isotope shifts, when linked with the results for the bicyclo[2.2.1]heptyl cation (**1**), requires that the exo C–H bond at C_3 in this classical 2-norbornyl cation be strongly involved in hyperconjugation and that the endo C–H bond be particularly ineffective in hyperconjugation. The large exo isotope shift compared to the isotope shifts in **2** and **3** and the lack of an endo isotope shift suggest that the C_3 methylene is twisted to align the exo C–H bond with the electron-deficient orbital, as shown in **7**.

It has commonly been assumed[14-18] that classical 2-norbornyl cations have a bisected geometry along the C_2^+–C_3 bond, with the exo and endo hydrogens each at 30° from the vacant orbital. However, the preponderance of the evidence, with the exception of ^{13}C–^{1}H coupling constants, is qualitatively consistent with the exo C_3–H bond being better aligned for hyperconjugation than the endo C_3–H bond. Our results can be compared with six other sources of information, summarized below, which are pertinent to the questions of hyperconjugation and structure in classical 2-norbornyl cations.

(i) A strong preference exists for *exo*-3,2-hydride and alkyl migrations in rearrangements of 2-norbornyl cations. Indeed, *endo*-3,2-alkyl shifts are unknown in the Nametkin rearrangement, even when the endo shift would provide the shortest pathway to rearranged products.[19,20] In the parent 2-norbornyl cation, the *exo*-3,2-hydride shift has a barrier of 10.8 kcal/mol,[21] while the endo shift barrier is estimated to be >16 kcal/mol.[20,22]

(ii) The greater stability of the 2,3-*endo*-dimethyl-2-norbornyl cation over the 2,3-*exo*-dimethyl-2-norbornyl cation has been attributed to preferential overlap of the empty C_2 p orbital with the exo substituent, where a proton is favored over a methyl group.[20]

(iii) Kelly et al. have described a relation between one-bond ^{13}C–^{1}H coupling constants and hyperconjugative interactions.[17,18] These authors reported a triplet signal for C_3 with J_{CH} = 133 Hz for the 2-methyl-2-norbornyl cation and several 2-aryl-2-norbornyl cations, whereas two different coupling constants and a doublet-of-doublets pattern would have been expected if the suggested relationship is correct and if the C_3 hydrogens differ in alignment with the p orbital at C_2.

(iv) Kinetic deuterium isotope effects have been determined in the solvolysis of *exo*- and *endo*-2-norbornyl brosylates.[15,16] The authors concluded that the endo brosylate solvolyzes with initial formation of a classical cation, while the exo brosylate follows a nonclassical mechanism. The endo brosylate gave k_H/k_D values of 1.19 for the exo-*3-d* compound and 1.12 for the endo-*3-d* compound,[15] which are consistent with greater exo hyperconjugation.

(v) Fully optimized theoretical geometries have been determined for the classical and nonclassical structures of the 2-norbornyl cation through use of a split-valence 4-21G basis set in ab initio calculations.[23] The two forms are predicted very close in energy, with the classical cation resembling an unsymmetrically bridged species in geometry. This geometry includes a significant difference in C–H bond lengths at C_3, with an ordinary 1.079 Å endo bond and a long exo bond of 1.090 Å, which is attributed to hyperconjugation by the exo C–H. Semiempirical MINDO/3 calculations show only a slight difference in C_3–H bond lengths; however, they also fail to predict the large difference in barriers to 3,2-hydride shifts and predict a classical structure with no distortion toward bridging.[22]

(vi) Other experimental data for noncationic species also suggest a better alignment of an exo than endo group with the p orbital

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of an sp^2-hybridized C_2. An x-ray crystal structure of camphene-8-carboxylic acid shows a slightly better alignment of an *exo*-methyl than an *endo*-methyl.[24] We find that norbornan-2-one-*exo-3-d* has a weaker C–D stretch (2159 cm^{-1}) than the endo-*d* compound (2182 cm^{-1}) in IR spectra (CCl_4, thin film). This difference in C–D stretching frequencies should be compared with the smaller difference between norbornane-*exo-2-d* (2170 cm^{-1}) and norbornane-*endo-2-d* (2185 cm^{-1}).[25]

Inverse Isotope Shifts from In-plane C–H(D) Bonds? From the preceding discussion, and earlier work,[1-7] it is clear that the magnitude of a long-range downfield isotope shift of the type observed in benzylic cations is related to the extent of hyperconjugation of the C–H(D) bond. The hyperconjugative origin suggests that there should be a close analogy between these NMR isotope shifts and kinetic β-deuterium isotope effects for reactions involving carbocations. However, the correspondence between the two types of isotope effects need not be precise. In contrast to a kinetic isotope effect which results from changes in vibrational force constants between a ground state and transition state, an NMR isotope shift is intrinsic to a carbocation and its particular set of force constants. Also, kinetic or equilibrium isotope effects arise from the effect of deuterium substitution on energy content, whereas NMR isotope shifts must arise from the effects that the different vibrational characteristics of C–D bonds have on the vibrationally averaged electron distribution. One of the features of β-deuterium isotope effects is that the normal isotope effect ($k_H/k_D > 1$) is at a maximum for $\theta = 0°$, where θ is the dihedral angle of the C–H(D) bond with respect to the developing p orbital, and it actually becomes inverse ($k_H/k_D < 1$) when $\theta = 90°$.[8] Do the analogous NMR isotope shifts also decline from a maximum downfield shift at $\theta = 0°$ to reach a value of zero before $\theta = 90°$ and become upfield ("inverse") as θ approaches 90°?

A tendency toward upfield isotope shifts as θ goes to 90° may be indicated by the following, though a C–D at a bridgehead position in **2** did not cause a measurable upfield shift. First, the endo C–D bond in **1** also gave no isotope shift, although it is more likely that θ is closer to 60° than to 90°. Second, the effect of a CD_3 group in **4** is smaller than the effect of a CD_2 group in **2** or **3**, while one would expect it to be equal if there were no "inverse" effect. The CD_3 isotope shift of 0.230 ppm in **4** could be accounted for by structure **8**, if each hyperconjugating C–D bond were to cause a downfield shift of about 0.145 ppm, as for **2** and **3**, and the in-plane C–D were to cause an upfield shift of about −0.06 ppm.

The results described in this paper are consistent with a model in which downfield isotope shifts occur when an alkyl C–H(D) bond interacts hyperconjugatively with a cation center, which weakens the C–H(D) bond. Upfield isotope shifts may occur when the alkyl-cation interaction strengthens an in-plane bond, as is predicted by molecular orbital calculations for in-plane C–H bonds.[9c] Within this model, the reason that a larger upfield shift is suggested for an in-plane C–D of a methyl group in **4** than is observed for the bridgehead C–D in **1** is that the methyl group is free to respond to the electron demand by structural deformation, or rehybridization, while the bridgehead methine is more structurally constrained. MINDO/3 calculations show that the in-plane C–H bond is shortened more and the $^+$CCH bond angle is altered more for a methyl group interacting with the cation center in the *tert*-butyl cation than the bridgehead C–H bond length and angle are altered in the 2-methylbicyclo[2.2.2]octyl cation.[26]

Experimental Section

NMR Spectroscopy. A JEOL FX-60Q NMR equipped with a 5-mm ^{19}F probe was used to obtain ^1H decoupled ^{19}F NMR spectra at 56.2 MHz. Isotope shifts were determined by using a 500-Hz spectral width, with a digital resolution of 0.12 Hz, and 4 to 30 pulses of 60° flip angle. A dual, 10-mm C/H probe was used for ^{13}C and ^1H spectra. Some routine ^1H spectra were run on a Varian EM-360.

Preparation of Ions. A precooled solution of about 1 mmol of the appropriate alcohol precursor in SO_2ClF (0.5 mL) was added dropwise to a vigorously stirred (vortex mixer) solution of about 5 mmol of 1:1 FSO_3H–SbF_5 in SO_2ClF (1 mL) at −78 °C. The solutions were transferred to precooled NMR tubes via precooled pipets. Various ratios of labeled and unlabeled precursors were used so that the identity of ^{19}F NMR peaks could be established with certainty.

Ion Precursors. The ion precursors were tertiary alcohols prepared by the usual Grignard reaction of *p*-fluorophenylmagnesium bromide with either bicyclo[2.2.1]heptan-2-one (Aldrich) to give 2-(*p*-fluorophenyl)bicyclo[2.2.1]heptan-2-ol (mixture of exo and endo alcohols), or bicyclo[2.2.2]octan-2-one to give 2-(*p*-fluorophenyl)bicyclo[2.2.2]octan-2-ol. Bicyclo[2.2.2]octan-2-one was prepared by hydrogenation[27] of bicyclo[2.2.2]oct-5-en-2-one.[28]

The labeled alcohols were synthesized in the same manner from appropriately labeled ketones. Bicyclo[2.2.1]heptan-2-one-*exo-3-d* was prepared by NaOD-catalyzed exchange of the parent ketone in refluxing dioxane–D_2O and bicyclo[2.2.1]heptan-2-one-*3,3-d$_2$* by three repetitions of the exchange with a 5-day reflux for each repetition.[29,30] Bicyclo[2.2.1]heptan-2-one-*endo-3-d* was prepared from the dideuterated ketone by exchange in dioxane–H_2O.[31] The dioxane–D_2O exchange was also used to obtain a mixture of bicyclo[2.2.2]octan-2-one-*3-d* and *-3,3-d$_2$*. The bridgehead-deuterated ketone, bicyclo[2.2.2]octan-2-one-*1-d*, was prepared through the sequence below.

2-Cyclohexen-1-one-*6,6-d$_2$*. A modification of the procedure of Rosenblum[32] was used. A mixture of 2-cyclohexen-1-one (8.0 g, 0.083 mol), concentrated sulfuric acid (0.4 mL), and D_2O (30 mL) was stirred at 55 °C under nitrogen for 38 h. After being cooled, the mixture was extracted four times with methylene chloride. The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was distilled (bp 88–90 °C at ca. 100 mm), giving 5.7 g (70%) of distilled product. ^1H NMR ($CDCl_3$) 1.8–2.6 (m, 4), 5.9 (d of t, J = 1.5, 10 Hz, 0.4), 7.0 ppm (m, 1); ^{13}C NMR ($CDCl_3$) 199.5, 150.7, 129.7, 129.4 (t, J_{CD} = 25 Hz), 37.7 (t, J_{CD} = 19.5 Hz), 37.4 (5 lines, J_{CD} = 19.5 Hz), 25.6, 22.6 ppm. ^1H NMR analysis using Eu(fod)$_3$ as a shift reagent showed the product to be ca. 60% deuterated at C_2 and 90% deuterated at C_6.

2-((Trimethylsilyl)oxy)-1,3-cyclohexadiene-*1-d*. A modification of the procedure of Girard and Conia[33] was used. To a cooled (salt–ice bath) solution of diisopropylamine (10 mL, 7.2 g, 0.072 mol) in 150 mL of diethyl ether was added a 1.6 M solution of *n*-butyllithium in hexane (45 mL, 0.072 mol). After 15 min, a solution of 2-cyclohexen-1-one-*6,6-d$_2$* (4.9 g, 0.050 mol) in 25 mL of diethyl ether was added dropwise and the solution stirred for 30 min. Chlorotrimethylsilane (7.3 g, 0.067 mol) was then added dropwise. The cooling bath was removed and the resulting mixture stirred for 1 h. The reaction mixture was poured into 100 mL of cold saturated $NaHCO_3$ solution and extracted once with 100 mL of hexane. The hexane extract was dried (Na_2SO_4), filtered, and evaporated. Distillation (bp 46–48 °C (3 mm)) gave 5.8 g (68%) of product. ^1H NMR ($CDCl_3$) 0.20 (s, 9), 2.10 (m, 4), 5.75 ppm (m, >1); ^{13}C NMR ($CDCl_3$) 148.0, 128.6, 126.4 (s on t), 102.2 (t, J_{CD} = 24 Hz), 22.6, 21.6 ppm.

Bicyclo[2.2.2]octan-2-one-*1-d*. A stirred solution of phenyl vinyl sulfone (5.3 g, 0.032 mol),[34] 2-((trimethylsilyl)oxy)-1,3-cyclohexadiene-*1-d* (5.0 g, 0.029 mol), toluene (5 mL), and a pinch of hydroquinone was heated to 130 °C under nitrogen for 38 h. The reaction mixture was evaporated, and the Diels–Alder adduct was taken up in methanol/chloroform and stirred for 2 days to effect methanolysis of the silyl enol ether. The solution was evaporated, and the crude keto sulfone was treated with 6% sodium amalgam (80 g) and potassium hydrogen phosphate (25 g) in methanol/methyl acetate for 24 h. This mixture was filtered, poured into water, and extracted four times with ether. The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated. ^{13}C NMR analysis showed that some reduction of the ketone had occurred, so the crude mixture was oxidized by activated manganese dioxide

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(25 g)[27] in methylene chloride for 18 h. The mixture was filtered and evaporated. The residue was triturated with pentane, filtration and evaporation of which gave 1.0 g (28%) of product as a white solid. ^{13}C NMR ($CDCl_3$) 217.4, 44.5, 42.1, 41.7 (t, $J_{CD} = 22$ Hz), 27.7, 24.4, 23.0 ppm. ^1H NMR analysis using $Eu(fod)_3$ as a shift reagent showed the product to be ca. 90% deuterated at C_1 and 15% deuterated at C_3.

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Registry No. 1, 51823-56-4; **1**-*exo-3-d*, 92720-86-0; **1**-*endo-3-d*, 92720-87-1; **1**-*3,3-d_2*, 92720-88-2; **2**, 51804-52-5; **2**-*3-d*, 92720-89-3; **2**-*3,3-d_2*, 92720-90-6; **2**-*1-d*, 92720-91-7; **3**, 51804-49-0; **3**-*2,2,5,5-d_4*, 91158-20-2; **4**, 25807-60-7; **4**-*d_6*, 79663-74-4; bicyclo[2.2.1]heptan-2-one-*exo-3-d*, 18139-04-3; bicyclo[2.2.1]heptan-2-one-*endo-3-d*, 18139-05-4; bicyclo[2.2.2]octan-2-one-*3-d*, 92720-92-8; bicyclo[2.2.2]octan-2-one-*3,3-d_2*, 92720-93-9; bicyclo[2.2.2]octan-2-one-*1-d*, 92720-94-0; 2-cyclohexen-1-one-*6,6-d_2*, 83350-38-3; 2-((trimethylsilyl)oxy)-1,3-cyclohexadiene-*1-d*, 92720-95-1; D_2, 7782-39-0; 2-cyclohexen-1-one, 930-68-7; chlorotrimethylsilane, 75-77-4; phenyl vinyl sulfone, 5535-48-8.

Nuclear Magnetic Resonance Studies of Metalloporphyrin π-Cation Radicals as Models for Compound I of Peroxidases

Isao Morishima,* Yasuhiko Takamuki, and Yoshitsugu Shiro

Contribution from the Division of Molecular Engineering, Graduate School of Engineering, Kyoto University, Kyoto 606, Japan. *Received April 20, 1984*

Abstract: Hyperfine-shifted proton and deuterium NMR spectral studies are reported for ruthenium(II) and cobalt(III) octaethylporphyrin π-cation radicals, $[OEP{\cdot}Ru^{II}{\cdot}CO]^{+}{\cdot}Br^-$ (**1**), $[OEP{\cdot}Ru^{II}{\cdot}CO]^{+}{\cdot}ClO_4^-$ (**2**), $[OEP{\cdot}Co^{III}]^{2+}{\cdot}2Br^-$ (**3**), and $[OEP{\cdot}CO^{III}]^{2+}{\cdot}2ClO_4^-$ (**4**) and their meso-deuterated analogues. The meso proton (or deuterium) resonances were not seriously broadened for these radicals and exhibited upfield or downfield shifts depending on the counterions and the central metal. Non-Curie law behaviors for the meso proton shifts were interpreted in terms of a thermal equilibrium between $^2A_{1u}$ and $^2A_{2u}$ π-radical states which induce quite different electron spin distribution at the meso position. This thermal equilibrium was also confirmed by the variable-temperature UV spectral measurements. The thermodynamic parameters for this equilibrium were estimated and show that $^2A_{1u}$ and $^2A_{2u}$ states are energetically close and these two states are substantially mixed at room temperature. The downfield hyperfine shift of the meso proton for **2** was interpreted as arising from the π-cation radical in the predominant $^2A_{1u}$ state, and the substantial upfield shift for **1** was explained as due to mixing of the $^2A_{2u}$ state to the $2A_{1u}$ state. These assignments are in disagreement with the well-documented ones based on the UV-vis spectral studies. The effect of the axial ligand, imidazole, on the NMR spectra of **1** was also studied to mimic the electronic state of compounds I of peroxidases.

Peroxidases and catalase (CAT) are hemoprotein enzymes which catalyze a wide variety of organic or inorganic compounds by hydrogen or alkyl peroxides.[1,2] These enzymes react with peroxide to produce an oxidized enzyme intermediate referred to as compound I, which possesses two oxidizing equivalents above the resting ferric state.[3-5] Compound I has been assigned to a ferryl porphyrin π-cation radical in which one oxidizing equivalent is stored in the form of a tetravalent iron stabilized by oxygen ($Fe^{IV}{=}O$) and the second equivalent resides in a porphyrin π-cation.[6-13] The porphyrin π-cation radical species has also been implicated in the chlorophyll photochemical reaction for the primary products generated by the photooxidation of the chlorins in the photosystems I and II[14] and, possibly, in the intermediate of the cytochrome P-450 reaction cycle.[15,16]

With relevance to these biological implications, the porphyrin π-cation radical has been subjected to a great deal of physicochemical study in recent years.[6] Mauzerall first reported generation of a stable porphyrin π-cation radical of magnesium(II) octaethylporphyrin by chemical oxidation.[17] Dolphin and his co-workers were able to oxdize several synthetic metalloporphyrins to a stable π-cation radical state.[6] Depending on the particular combination of solvents, porphyrins, central metals, and counterions, they found two types ($^2A_{1u}$ and $^2A_{2u}$) of porphyrin π-cation radicals having characteristic UV–vis spectra.[6a] ESR spectra and molecular orbital calculations suggest that the highest filled π-orbitals, a_{1u} or a_{2u}, of porphyrin are comparable in energy and

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