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NMR Motional Averaging in the Isotopically Perturbed Cope Rearrangement

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Abstract: The effect of deuterium substitution on the positional equilibrium and rate of the Cope rearrangement in barbaralone-d_1 has been investigated by ^{1}H and ^{13}C dynamic NMR spectroscopy. Deuterium favors the allylic position over the cyclopropyl position. Skewing of the equilibrium requires that the Cope rearrangement be considered as a nonmutual exchange process that transports ^{13}C−^{1}H spin pairs between unequally populated molecular configurations. The NMR fast-exchange results are critically interpreted in light of a recently proposed alternative averaging theory (Jones, D. H.; Kurur, N. D.; Weitekamp, D. P. *Bull. Magn. Reson.* **1992**, *14*, 214). Our experimental results are consistent with the traditional theory but do not agree with the prediction of the alternative theory. The use of ^{1}H−^{13}C inverse detection is demonstrated for the observation of very broad ^{13}C resonances in the coalescence region via their directly attached exchange-narrowed ^{1}H signals, and the contribution of rapid chemical exchange to the decay of heteronuclear zero- and double-quantum coherence is discussed.

Introduction

The precession frequency in nuclear magnetic resonance depends on the nature of the nuclear environment and results in chemical shifts and multiplet splittings in NMR spectra. When the environment changes rapidly as a result of a chemical exchange process the spectral features of the individual environments associated with each state or conformation are motionally narrowed into a single line at some average frequency. This effect has been known since the earliest days of NMR,[1] and the theory of dynamic nuclear magnetic resonance has long been applied to the study of rate processes in molecular systems.

Recently Jones, Kurur, and Weitekamp (JKW) have proposed an alternative[2] to the usual method of calculating the line positions of motionally narrowed lines. They suggest that the nuclear spin energies need to be explicitly taken into account in the calculation of the motionally averaged frequency. This is in direct contrast to the assumption of the traditional theory,[3] which considers the average resonance frequency to be independent of spin energy and dependent only upon conformational energy. Although the two theories are in agreement for mutual exchange between two equally populated states or conformations, the JKW theory differs from the traditional theory in its prediction for nonmutual exchange[4] between states of unequal energy. In view of the significance of this disagreement for the dynamic NMR literature, several authors have contrasted the traditional and proposed motional averaging predictions in the context of earlier published work. Anet and Freedberg[5] reexamined a ^{13}C line shape analysis of ring inversion in methylcyclohexane[6] and concluded that the traditional theory gives a better fit to the data. O'Hara and Slichter[7] have reviewed experimental data on the contact shift of the central transition of ^{63}Cu atoms induced by paramagnetic manganese impurities[8] and have likewise concluded that the experimental result is consistent with the traditional theory but inconsistent with the JKW prediction. Apparently no molecular system that meets certain experimental criteria (vide infra) has yet been designed for specifically contrasting the two theories for the case of a nearly degenerate equilibrium, i.e., an important regime as the traditional and JKW theories converge for a degenerate equilibrium. We have chosen to reinvestigate such a molecule, namely, barbaralone-d_1, for the purpose of studying via ^{1}H and ^{13}C NMR spectroscopy the isotopically perturbed Cope rearrangement that it undergoes. As has been previously reported,[11] deuterium favors the allylic position over the cyclopropyl position, thus skewing the equilibrium and requiring that the Cope rearrangement be considered as a nonmutual exchange process that transports ^{13}C−^{1}H spin pairs between unequally populated molecular configurations. Our experimental results are consistent with the traditional theory but do not agree with the prediction of the alternative theory. We briefly discuss several reasons for the inapplicability of the alternative theory to the resonant observation of nuclear spin systems. Finally, we demonstrate the use of ^{1}H−^{13}C inverse detection for the observation of very broad ^{13}C resonances in the coalescence region via their directly attached exchange-narrowed ^{1}H signals

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[11] Barborak, J. C.; Chari, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 5275. The reported equilibrium constant of 0.802 is incorrectly calculated from the experimental data.

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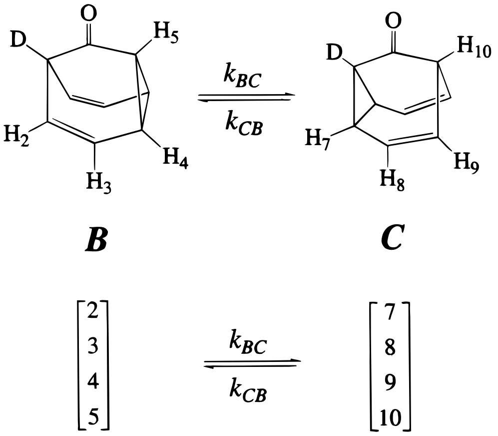
Scheme 1. The Cope Rearrangement of Barbaralone-d_1, with Numbering of Hydrogens (and their directly attached carbons) Used in the Text[a]



[a] Exchange Connectivities Are Indicated at Bottom.

and consider the effect of rapid chemical exchange upon the relaxation of heteronuclear multiple quantum transitions.

Results and Discussion

To provide a definitive distinction between the two theories, JKW have suggested a set of necessary experimental criteria for a molecule chemically exchanging between two conformations of unequal energy:

(1) The conformational interconversion barrier should be 10 kcal/mol or greater, so that measurements in both the slow and fast exchange limits are possible.

(2) Bonding in the reactant and product should be as similar as possible to minimize the temperature dependence of conformer parameters.

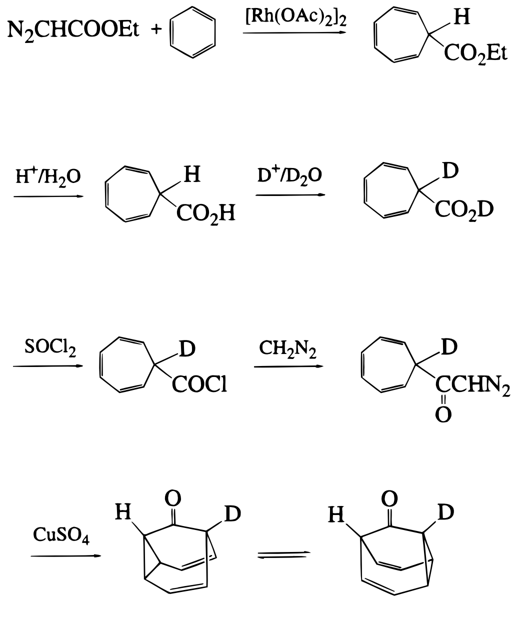
(3) Any temperature dependence of such parameters must be measurable over a large range to allow extrapolation through the fast exchange region.

(4) The conformational free energy difference should not exceed 1000 cal/mol to ensure observation of the slow exchange spectrum of the minor conformer and the accurate measurement of the conformational equilibrium constant.

We have chosen as such an example barbaralone-d_1,[11] which undergoes the Cope rearrangement depicted in Scheme 1. Owing to deuterium substitution the rearrangement is no longer degenerate, with deuterium preferring the allylic position over the cyclopropyl position.

Accordingly, conformer B predominates over conformer C (our notation is chosen to be consistent with that of Anet and Freedberg[5]) and $K_{\text{eq}} = [\text{C}]/[\text{B}]$ is less than one. A previous study[11] gives an estimate of $K_{\text{eq}} \approx 0.895$ "at room temperature" so that both conformers will be separately observable in the slow exchange limit. Fluxionality interconverts hydrogen pairs (and their directly attached carbons) with forward and reverse rate constants k_{BC} and k_{CB} as indicated at the bottom of Scheme 1. Thus H2 and H7 interconvert, as do H4 and H9. We will focus our attention on these interconverting spin pairs. Similarly H5 and H10 interconvert whereas H3 and H8 are expected to be invariant to the exchange owing to chemical shift degeneracy. The activation barrier for unlabeled barbaralone in acetone-d_6 has been estimated by Lambert from line shape analysis to be 9.8 kcal/mol at 300 K,[12] so that both slow and fast exchange regimes are experimentally accessible. Finally, deuterium substitution does not change the shape of the potential energy barrier itself, which remains a symmetric double well potential, but only alters the position of vibrational energy levels within each well. The greater mass of deuterium results in lower-lying levels and skews the conformational equilibrium. The deuterium isotope effect on the H2 and H7 resonance frequencies is an upfield shift of less than 0.6 Hz so that the similarity in bonding should result in a negligible or only very small temperature dependence of the hydrogen chemical shifts.

Scheme 2. Synthesis of Barbaralone-d_1



We have employed a modification of a previously reported synthesis[10] of barbaralone-d_1, detailed in Scheme 2. The final step is a copper-mediated carbene insertion reaction to afford labeled barbaralone with greater than 99.2% isotopic purity as determined by NMR integration.

When the rate of the Cope rearrangement in barbaralone-d_1 substantially exceeds the chemical shift difference of interconverting hydrogen pairs, these collapse to single resonances at particular average frequencies. At 303 K H2 and H7 have collapsed to a first-order doublet (due to coupling with H3/H8) whereas H4 and H9 have collapsed to a first-order triplet (due to coupling with H3/H8 and H5/H10), as shown in Figure 1. These multiplets are virtually symmetrically distributed about the collapsed triplet of added unlabeled barbaralone referenced to 0 Hz so that the deuterium isotope effect on the H2/H7 chemical shift may be safely neglected. Increasing temperature sharpens the signals. In addition, the conformer equilibrium more nearly approaches one with increasing temperature, causing the center frequencies of these multiplets to approach each other. We now analyze this latter effect in detail with respect to the predictions of the traditional and JKW averaging theories.

Traditional averaging holds that the fast-exchange frequency is the population-weighted average of the individual frequencies. Therefore the average frequency of the H2/H7 spin pair measured in the fast exchange limit is given by $\nu_{2,7} = p_B\nu_{\text{vinyl}} + p_C\nu_{\text{cyclopropyl}}$ whereas the average frequency of the H4/H9 spin pair is given by $\nu_{4,9} = p_B\nu_{\text{cyclopropyl}} + p_C\nu_{\text{vinyl}}$. The measured frequency difference δ between these resonances is expressed by eq 1, with $\Delta = \nu_{\text{vinyl}} - \nu_{\text{cyclopropyl}}$.

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(12) Lambert, J. B. *Tetrahedron Lett.* **1963**, *27*, 1901. We have measured $\Delta G^{\ddagger}$ (300 K) = 10.2 kcal/mol for labeled barbaralone in toluene-d_8.

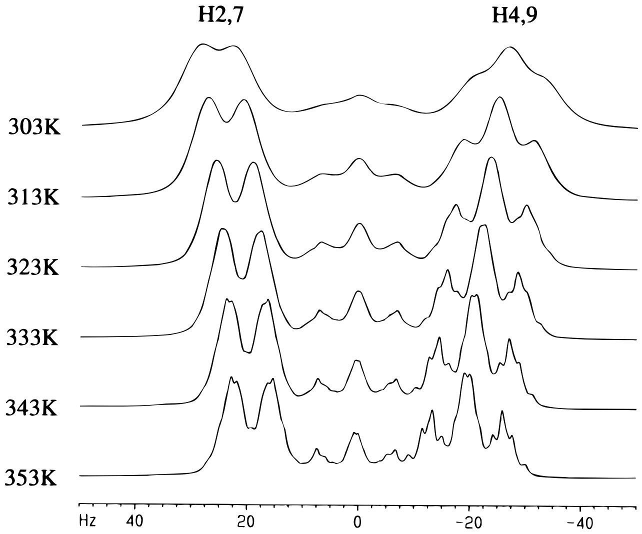

Figure 1. Decoalescence ^{1}H spectra of barbaralone-d_1 in the fast exchange limit in toluene-d_8 from 353 to 303 K, referenced to 8% unlabeled barbaralone at 0 Hz. The H2,7 and H4,9 averaged signals are indicated.

$$\delta \equiv (\nu_{2,7} - \nu_{4,9}) = (p_B - p_C)\Delta = \frac{(1 - K_{\mathrm{eq}})}{(1 + K_{\mathrm{eq}})}\Delta \qquad (1)$$

From this expression the conformer equilibrium constant can be calculated according to eq 2.

$$K_{\mathrm{eq}} = \frac{\Delta - \delta}{\Delta + \delta} \qquad (2)$$

Measurement of Δ at low temperature when exchange is slow and δ at high temperature in the motionally narrowed limit permits the calculation of the equilibrium constant as a function of temperature in the latter regime.

As discussed in detail by Anet and Freedberg,[5] the JKW prescription results in another expression for δ, given in eq 3.

$$\delta = \frac{-2K_{\mathrm{eq}} \ln K_{\mathrm{eq}}}{(1 + K_{\mathrm{eq}})^2}\Delta + \frac{(1 - K_{\mathrm{eq}})}{(1 + K_{\mathrm{eq}})}\Delta \qquad (3)$$

For a degenerate equilibrium eqs 1 and 3 are in agreement but clearly differ for $K_{\mathrm{eq}} \neq 1$, as here or for any nonmutual exchange process with a skewed equilibrium. Thus the traditional and JKW prescriptions yield different values for K_{eq} in the fast exchange limit from the measurement of δ. This difference forms the experimental basis for our test of the two theories. For $K_{\mathrm{eq}} \geq 0.9$ the two terms of eq 3 are virtually equal so that to an excellent approximation K_{eq} will be given by eq 4, in contrast to eq 2 obtained from the traditional theory. We will use the exact expression of eq 3 to calculate K_{eq} with the JKW formalism.

$$K_{\mathrm{eq}} = \frac{\Delta - \delta/2}{\Delta + \delta/2} \qquad (4)$$

Table 1. Tabulation of δ and δ/Δ Measured from the Decoalescence ^{1}H Spectra of Figure 1[a]

T (K)	δ (Hz)	δ/Δ	$\Delta G^\circ_{\mathrm{trad}}$ (cal/mol)	$\Delta G^\circ_{\mathrm{JKW}}$ (cal/mol)
353	38.88	0.0370	51.95	25.98
343	40.87	0.0389	53.06	26.53
333	43.28	0.0412	54.57	27.28
323	46.25	0.0440	56.57	28.27
313	49.32	0.0470	58.48	29.22
303	52.40	0.0499	59.94	30.05

[a] Values of δ/Δ are used to calculate K_{eq} from eq 2 (traditional) or eq 3 (JKW) and the appropriate free energy difference from $\Delta G^\circ = -RT \ln K_{\mathrm{eq}}$.

Table 2. Thermodynamic Data Obtained by Least-squares Fitting of the Free Energy Values of Table 1[a]

	traditional	JKW
ΔH° (cal/mol)	108.37 ± 6.92	55.45 ± 3.31
ΔS° (eu)	0.161 ± 0.021	0.084 ± 0.010
$\Delta G^\circ_{198\ \mathrm{K}}$ (cal/mol)	76.57 ± 2.75	38.82 ± 1.33
K_{eq}(198 K)	0.823 ± 0.006	0.906 ± 0.003

[a] The free energy and equilibrium constant at 198 K calculated for each theory are also given. Errors listed correspond to one standard deviation.

The quantity δ has been measured from the decoalescence spectra of Figure 1 over the temperature range 353 to 303 K and is given in Table 1. The chemical shift difference $\Delta = \nu_{\mathrm{vinyl}} - \nu_{\mathrm{cyclopropyl}}$ was measured from the slow exchange spectrum at 198 K to be 1090 ± 1 Hz and was found to be independent of temperature over the range 198 to 228 K, above which point substantial exchange broadening of the vinylic and cyclopropyl signals occurs. From the ratio δ/Δ the equilibrium constant over the temperature range 353 to 303 K was calculated from the traditional and JKW prescriptions by using eqs 2 and 3, respectively, and the result converted to the free energy difference according to $\Delta G^\circ = -RT \ln K_{\mathrm{eq}}$.

The free energy difference calculated from the JKW prescription is half that calculated from the traditional averaging theory and temperature dependent in both cases, indicating a nonnegligible entropy contribution to the free energy. Plots of the free energy ΔG° vs temperature were linear ($r = 0.996$) and the intercept and slope yielded the thermodynamic enthalpy ΔH° and entropy ΔS° for the barbaralone-d_1 equilibrium obtained with each theory. These are given in Table 2.

The entropy term, although small, is significant and positive, favoring conformer *C*. Also tabulated are the free energy difference ΔG° and equilibrium constant K_{eq} at 198 K calculated with each formalism.

The quality of the results given in Table 2 depends upon the assumed temperature independence of Δ and the accuracy with which δ can be measured. Although Δ is virtually independent of temperature from 198 to 228 K, we examine the effect of a variation of ± 1 Hz/K from 228 to 353 K, resulting in $\Delta(353\ \mathrm{K}) = 1090 \pm 125$ Hz. Calculation of ΔG° for both theories with this temperature variance included followed by least-squares extraction of ΔH° and ΔS° provides values of ΔG° and K_{eq} at 198 K virtually unchanged from those reported in Table 2. Thus the accuracy of these quantities is not seriously affected by our assumption that Δ remains temperature independent or largely so between 353 and 303 K. In addition, the assumption of a ± 3 Hz error in the measurement of δ results in new values for K_{eq} at 198 K within the error bars given for this quantity in Table 2. Moreover, as the errors in ΔH° and ΔS° are known to be highly correlated and compensatory, we conclude that the reported values for ΔG° and K_{eq} at 198 K in Table 2 are quite accurate.

The JKW and the traditional fast-exchange theories thus make different predictions about the value of the equilibrium constant in the slow exchange limit, providing the basis for a distinction between them. At 198 K the Cope rearrangement in barbaralone-d_1 is slow ($k \approx 12\ \mathrm{s}^{-1}$) and both conformers are separately observable, as shown in Figure 2.

The spectrum may be directly integrated, with the H2,9/H3,8 region set to 4.000. This results in a value for the integral of

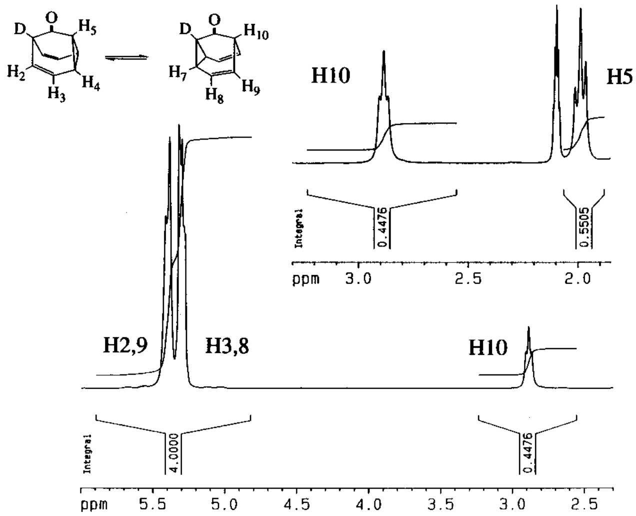

Figure 2. Slow exchange ^{1}H spectrum of barbaralone-d_1 in toluene-d_8 at 198 K. The H10/H5 ratio of integrals provides K_{eq} = [C]/[B] = 0.815 ± 0.015.

the allylic proton H10 in conformer *C* of 0.4476 and that of the cyclopropyl proton H5 in conformer *B* of 0.5505. Although the latter value is less accurate owing to overlap with the signal of toluene-d_7, it is correctly given by $1 - 0.4476 = 0.5524$. Subtracting 0.004 from each integral to account for up to 0.8% unlabeled barbaralone, the equilibrium constant at 198 K is determined to be $K_{eq} = 0.815 \pm 0.015$, where this value and the associated error reflect the result of multiple integrations. The measured equilibrium constant at 198 K is thus seen to agree with the prediction of the traditional averaging theory (K_{eq} (198 K) = 0.823 ± 0.006) but to differ substantially from that of the JKW theory, which predicts (K_{eq} (198 K) = 0.906 ± 0.003). We conclude that the traditional averaging theory is correct.

Our two-site conformational equilibrium is a particular case of nonmutual intramolecular exchange in which spins move about but do not physically interchange,[4] as with mutual exchange. The Hamiltonian of the system switches from H_i to H_j as a result of an exchange event transforming the molecule from configuration *i* to configuration *j*. Such exchange is described by a composite Liouville space involving a sum of individual simple Liouville spaces. The density matrix elements σ_{12} for each simple Liouville space which represent single quantum coherence induced by the radio frequency pulse are coupled by exchange[4] and decay according to

$$\frac{d}{dt}\begin{pmatrix}\sigma_{12}^{B}\\ \sigma_{12}^{C}\end{pmatrix} = \begin{pmatrix} -R - i\omega_B - k_{BC} & k_{CB} \\ k_{BC} & -R - i\omega_C - k_{CB}\end{pmatrix}\begin{pmatrix}\sigma_{12}^{B}\\ \sigma_{12}^{C}\end{pmatrix} \qquad (5)$$

where *R* is the transverse relaxation rate and other quantities have been previously defined. For rapid exchange the decay is governed by a single eigenvalue λ_- obtained by diagonalization of the rate matrix of eq 5.

$$\lambda_- = R + \frac{(\omega_B - \omega_C)^2}{4(k_{BC} - k_{CB})^2} + \mathrm{i}(\omega_B p_B + \omega_C p_C) \qquad (6)$$

The real and imaginary components of eq 6 determine the line width and line position, respectively. The latter is seen to be the population-weighted average of the individual site frequencies. Conformer populations are determined entirely by the conformational free energy difference and spin energies have negligible effect. Moreover, eq 5 is valid over the entire range of exchange rates.

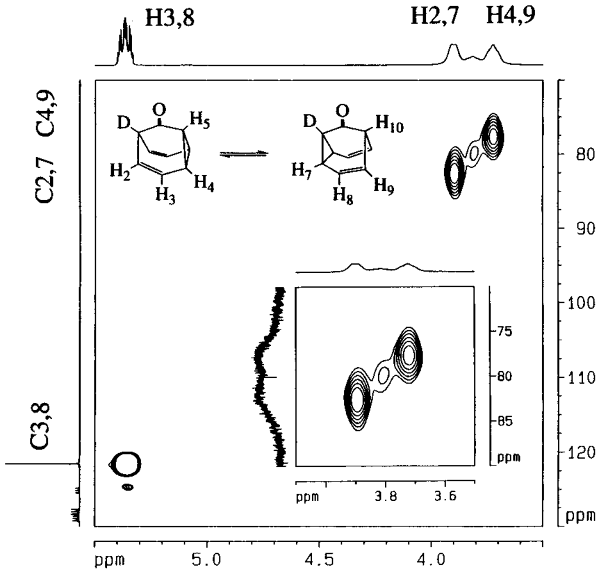

Figure 3. Proton-detected ^{1}H/^{13}C HMQC chemical shift correlation experiment of the sample of Figure 1 at 300 K. The ^{13}C F$_1$ projection is a proton-decoupled ^{13}C spectrum. The C2,7 and C4,9 exchange-broadened signals plotted at increased amplitude (×64) are apparent in the inset.

Chemical Exchange of Multiple Quantum Coherence

In the course of our ^{13}C investigations of the Cope rearrangement in barbaralone-d_1 we have observed that whereas the C3,8 resonance remains sharp at all temperatures the C2,7 and C4,9 signal pairs broaden beyond detectability at 300 K, as illustrated in the ^{13}C projection of Figure 3. The directly attached hydrogen pairs of these carbons have already attained the fast exchange limit at this temperature, however, owing to their smaller frequency separation (1090 Hz for ^{1}H vs 7250 Hz for ^{13}C). As the one-bond scalar coupling J_{CH} is neither broken nor substantially modulated by exchange it should prove possible to exploit this coupling in a chemical shift correlation experiment[17,18] that utilizes the relative sharpness of the ^{1}H signals to indirectly detect the exchange-broadened ^{13}C signals. The result of an experiment utilizing heteronuclear multiple quantum coherence (HMQC) to correlate chemical shifts[14] is illustrated in Figure 3, clearly revealing the exchange-averaged chemical shifts of the very broad carbon resonances. Although the line widths in the ^{1}H dimension are narrow (ca.15 Hz) those in the ^{13}C dimension are ca.350 Hz. The line positions and widths in the ^{13}C dimension are governed by the chemical exchange process that couples the multiple quantum transitions of the ^{13}C−^{1}H spin pairs.

The effect of slow chemical exchange on the relaxation of two-spin order $2I_zS_z$[19] and multiple quantum coherence $2I_xS_y$[20] in heteronuclear spin systems has previously been considered.[21] In the present case $k \approx 2.3 \times 10^5$ s^{-1} at 300 K and averages

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the ^{1}H and ^{13}C frequency differences. During the evolution period t_1 of the HMQC experiment the zero quantum coherence (ZQC) and double quantum coherence (DQC) of C2/H2 in conformer *B*ZQC and DQC of C7/H7 in conformer *C*. The average frequency for the ZQC pair is $\bar{\nu}_H - \bar{\nu}_C$ and that for the DQC pair is $(\bar{\nu}_H + \bar{\nu}_C)$, with $\bar{\nu}_H = (p_B\nu_H^{\text{vinyl}} + p_C\nu_H^{\text{cyclopropyl}})$ and $\bar{\nu}_C = (p_B\nu_C^{\text{vinyl}} + p_C\nu_C^{\text{cyclopropyl}})$. As the chemical shift evolution under the influence of $\bar{\nu}_H$ is refocused by a proton π pulse at the midpoint of the evolution period the final ^{1}H signal is modulated during detection by $\cos(\bar{\nu}_C t_1)$, producing a signal at $\bar{\nu}_C$ in the ^{13}C dimension of the HMQC spectrum (an analogous signal appears at $\bar{\nu}_C = (p_C\nu_C^{\text{vinyl}} + p_B\nu_C^{\text{cyclopropyl}})$ for the interconverting of C4/H4 and C9/H9 spin pairs).

For fast chemical exchange occurring at rate k between two equally populated conformations the exchange contribution to the relaxation rate[13] during the evolution time t_1 of the HMQC experiment is $\exp(-\Delta^2 t_1/8k)$, where Δ is some frequency difference being modulated by exchange. For the ZQC and DQC pairs these differences are $(\Delta_H - \Delta_C)$ and $(\Delta_H + \Delta_C)$, with $\Delta_H = (\omega_H^{\text{vinyl}} - \omega_H^{\text{cyclopropyl}})$ and $\Delta_C = (\omega_C^{\text{vinyl}} - \omega_C^{\text{cyclopropyl}})$ expressed in angular frequency units of rad/s. A product operator analysis indicates that the term $2I_xS_y$ generated at the beginning of the evolution period of the HMQC experiment decays during t_1 according to

$$2I_xS_y(t_1) = \frac{1}{2}[e^{-xt_1} + \mathrm{e}^{-yt_1}]2I_xS_y(t_1 = 0) \qquad (7)$$

with $x = (\Delta_H - \Delta_C)^2/8k$ and $y = (\Delta_H + \Delta_C)^2/8k$. This biexponential decay results in two Lorentzian lines of equal amplitude but unequal line widths x and y in the ^{13}C dimension of the HMQC spectrum, in contrast to the previous assertion of a single line of average width $(x + y)/2$.[18] For barbaralone-d_1 at 300 K the line widths x and y are calculated from the ^{1}H and ^{13}C frequency differences to be 260 and 475 Hz. The effective line width of 320 Hz calculated from the superposition of these Lorentzian lines is in reasonable agreement with the measured (coarsely digitized) ^{13}C 2D line width of 350 Hz. For individual line widths x and y which differ by less than a factor of 2 (as here) the average expression $(x + y)/2$ will also agree to within 15% of the calculated line width. However, for two lines of very different width the superposition of two Lorentzians will have a line width given effectively by the narrower of the two line widths and not the average.

Experimental Section

Ethyl 1,3,5-Cycloheptatrien-7-carboxylate. Ethyl diazoacetate (50.0 g) was dissolved in 5 L of dry benzene (Fisher Certified A.C.S., used as obtained from the supplier), and 50.0 mg of rhodium acetate $\{[Rh(OAc)_2]_2\}$ was added. The solution was warmed to 45 °C, and held at that temperature until the evolution of N_2 had ceased (about 8−10 h). Benzene was removed at reduced pressure. The procedure was repeated four additional times, reusing benzene from previous runs. Residues from evaporation of the benzene were combined for purification. Distillation of these residues resulted in 165 g of a mixture of ethyl 1,3,5-cycloheptatrien-7-carboxylate, diethyl maleate, and diethyl fumarate, collected over the temperature range 80−90 °C (3.5 mmHg). Careful analysis by ^{1}H NMR spectroscopy showed the mixture to be made up of 40% of the desired ester and 60% of maleate and fumarate.

Maleate and fumarate esters were removed via the following procedure. Addition of a 1.1 molar equiv of freshly prepared cyclopentadiene, relative to the amount of maleate and fumarate present in the carboxylate mixture, then stirring at about 40 °C for 4 h, converted the alkene esters to higher-boiling norbornene dicarboxylates, which were easily separated by subsequent distillation. In this way, pure ethyl 1,3,5-cycloheptatrien-7-carboxylate, in yields comparable to those previously reported,[9] was obtained.

7-Deuterio-1,3,5-cycloheptatrien-7-carboxylic Acid. Ethyl 1,3,5-cycloheptatrien-7-carboxylate was hydrolyzed, and the carboxylic acid product was purified, according to literature procedures.[9] To a mixture of 10 g of 1,3,5-cycloheptatrien-7-carboxylic acid in 20 g of D_2O (Aldrich Chemical Co., 99.9 atom % D), was added two drops of D_2SO_4 (Aldrich Chemical Co., 98 wt % solution in D_2O, 99.5+ atom % D), and the mixture was rapidly stirred under N_2 at 108 °C for 10 h. The stirring was stopped and the exchange mixture was allowed to cool. After careful removal of the supernatant aqueous portion with a Pasteur pipet, 20 g of fresh D_2O containing two drops of D_2SO_4 was added, and the heating sequence was repeated. A total of five exchanges, followed by removal of traces of water and distillation of the product, yielded 7-deuterio-1,3,5-cycloheptatrien-7-carboxylic acid containing >99% D.

The rest of the procedure (conversion of the cycloheptatriencarboxylic acid-d$_1$ to the acid chloride, reaction of the acid chloride with diazomethane to yield the diazoketone precursor to barbaralone-d_1, and decomposition of the diazoketone over anhydrous $CuSO_4$ to provide the target molecule) followed the literature descriptions precisely.[10] We have found that it is especially important that the thionyl chloride used in the preparation of 7-deuterio-1,3,5-cycloheptatrien-7-carbonyl chloride be carefully purified by distillation of 200 mL of the thionyl chloride from 50 mL of quinoline followed by redistillation from 100 mL of raw linseed oil.

NMR Spectroscopy. All NMR experiments were carried out on a Bruker DRX-300 NMR spectrometer operating at a ^{1}H frequency of 300.13 MHz and equipped with a BDTC variable temperature unit accurate to 0.1 °C. Barbaralone-d_1 was prepared at a concentration of 50 mM in toluene-d_8. ^{13}C spectra were acquired with a 5 mm broadband probe. A 5 mm inverse triple resonance probe was used to acquire ^{1}H spectra and the HMQC data. One-dimensional ^{1}H spectra utilized a 10 ppm spectral window, 64 K data points, and a 20 s interpulse delay to allow for complete relaxation, and were apodized with 0.1 Hz of line broadening. Spectra were baseline corrected by using Bruker Xwin-nmr 1.2 subroutines prior to integration and integration limits were chosen to include ^{13}C satellites. The ^{1}H-detected phase-sensitive HMQC spectrum was obtained at 300 K via the method of Bax and Subramanian[14] by using a BIRD pulse sequence[15] to minimize proton magnetization bound to ^{12}C with an empirically adjusted delay of 1.2 s. Spectral windows of 140 and 6 ppm were employed for ^{13}C and ^{1}H with a ^{1}H data block size of 1 K, 128 t_1 increments, and eight scans per increment, and zero-filled to 512 prior to Fourier transformation to afford digital resolution in the ^{13}C dimension of 20.5 Hz/point. Decoupling of ^{13}C during ^{1}H acquisition was accomplished with a GARP sequence.[16]

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(21) We use the product operator formalism from Sorensen, O. W.; Eich, G. W.; Levitt, M. H.; Bodenhausen, G.; Ernst, R. R. *Prog. NMR Spectrosc.* **1983**, *16*, 321.