Nuclear Spin–Spin Coupling via Nonbonded Interactions. 3. Importance of Bridgehead Interactions on Vicinal ^{13}C–^{1}H and ^{13}C–^{13}C Coupling Constants in Bicycloalkanes

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Abstract: To investigate the importance of nonbonded interactions between the bridgehead carbon atoms in bicycloalkanes, experimental and theoretical methods were used to investigate ^{13}C–^{1}H and ^{13}C–^{13}C nuclear spin–spin coupling constants. Compounds were synthesized with ^{2}H, ^{13}CO$_2$H, and ^{13}CH$_2$OH at the C1 bridgehead position and the NMR spectral parameters were measured; some of these were obtained by the "*J*-resolved" method of two-dimensional FT NMR spectroscopy. The calculated INDO-FPT molecular orbital results for the Fermi contact contributions to vicinal ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants are in good agreement with the experimental data for these compounds. The vicinal coupling constants increase in magnitude with the number of three-bond paths, but by an amount less than would be expected on the basis of simple additivity of coupling over equivalent three-bond paths. By means of a modified molecular orbital study it is shown that the nonbonded interactions between the bridgehead carbons give coupling-constant contributions of negative sign, and these become quite large in magnitude for the bicyclo[1.1.1]pentane compounds where the bridgehead carbon atoms are separated by only 1.84 Å.

Introduction

The importance of the nonbonded interactions between the bridgehead carbon atoms in the series of bicycloalkanes **1–4**

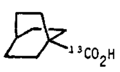
1a (X = ^{1}H)
1b (X = ^{2}H)

2a (X = ^{1}H)
2b (X = ^{2}H)

3 (X = ^{1}H)

4 (X = ^{1}H)

has been the subject of a number of theoretical discussions[2,3] and experimental studies which include ionization potentials[4] and hyperfine coupling constants from electron spin resonance spectra[5–7] of related organic radicals. It was suggested that the nonbonded ("through-space") interactions increase in the series of radicals related to **1–4** and parallel the decrease in the bridgehead C1···C4 distances in the series. In the present study experimental nuclear magnetic resonance (NMR) data and theoretical molecular orbital (MO) results are given for the ^{13}C–H and ^{13}C–^{13}C coupling constants between H and ^{13}C nuclei, which are bonded to the bridgehead C1, and the other bridgehead ^{13}C (C4) in compounds **1–12**. Both the experimental data and the molecular orbital results for these coupling constants indicate an increase in the magnitudes as the number of three-bond paths increases in the series. However, the increments are smaller than would be expected on the basis of additivity of the coupling contributions. By means of a modified MO procedure, which is described in the first paper in this series,[8] it is demonstrated that the apparent nonadditivity is partially due to interactions between the bridgehead carbons. These make negative contributions of increasingly greater magnitude as the C1···C4 distance decreases in the series **1–4**.



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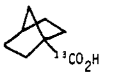

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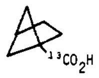

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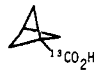

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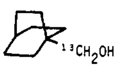

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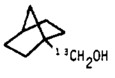

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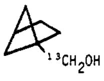

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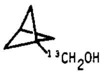

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Results and Discussion

The experimental NMR parameters for compounds **1b, 2b, 5–7,** and **9–11** are entered in Table I. In most cases the ^{13}C–^{13}C coupling constants were determined by direct measurement of the 95% ^{13}C-labeled compounds. A number of the coupling constants were determined by the two-dimensional NMR technique of "*J*-resolved" spectroscopy[9] described in the Experimental Section. Chemical-shift assignments follow from the literature data for these compounds,[10,11] intensities, and off-resonance decoupling experiments. Additional ambiguities would be removed by the magnitudes of the coupling constants in the labeled compounds. However, an interesting ambiguity occurred for the C2 and C3 resonances in **11** because the unlabeled material was not available to assign the chemical shifts. The four-line pattern obtained for the C2 and C3 resonances of **11** in Figure 1a could arise either for equal chemical shifts and coupling constants of 1.3 and 4.8 Hz or for two nearly equal coupling constants and a chemical-shift difference of 1.7 Hz. In the *J*-resolved spectrum in Figure 1b the coupling constants are measured along the F$_1$ axis and the chemical shift along the F$_2$ axis. Clearly, the C2 and C3 resonances are split by about the same amount (3 Hz) and shifted by 1.7 Hz.

The directly bonded ^{13}C–^{13}C coupling constants increase regularly in the series **5–7** and **9–11**, whereas the geminal coupling constants exhibit substantial dependencies on both substituents and ring size. Since coupling to the C3 and C4 carbon atoms is of primary interest in this study, the data are reproduced in Table II. The J(^{13}C–^{1}H) values in Table II were obtained from the J(^{13}C–^{2}H) values in Table I by multiplication by the ratio of the magnetogyric ratios (γ_H/γ_D = 6.514). Vicinal ^{13}C–^{13}C coupling constants to the C3 carbon vary by less than 0.5 Hz in the two series of compounds with no apparent trends.

The most interesting trend occurs for coupling to the C4 or bridgehead carbon atom; in the bicyclo[2.2.2]octane compounds (**5** and **9**) there are no three-bond paths and the experimental coupling constants are less than 0.3 Hz. For the bicyclo[2.2.1]heptane compounds **2, 6,** and **10** the vicinal coupling constants to C4 are uniformly larger in magnitude than those to C3. In the bicyclo[2.1.1]hexane compounds **7** and **11** the number of three-bond paths is doubled (and the C1···C4 distance decreased) but the coupling increases by 57 and 88%,

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Table I. Carbon-13 Chemical Shifts,[a] ^{13}C–^{2}H Coupling Constants[b] in the Deuterated Compounds **1b** and **2b**, and ^{13}C–^{13}C Coupling Constants[b] in the ^{13}C-Labeled Compounds **5–7** and **9–11**

compd		C1	C2	C3	C4	C5	C6	C7	C8	C9
1b	δ^{c}	23.9	26.0	26.0	23.9	26.0	26.0	26.0	26.0	
	J	20.51	0.44[d]	1.08	≤0.5	1.08	≤0.5	≤0.5	1.08	
2b	δ^{e}	36.4	29.8	29.8	36.4	29.8	29.8	38.4		
	J	21.66	≤0.5	1.08	1.34	1.08	≤0.5	≤0.5		
				(1.04)[f]	(1.34)[f]	(1.04)[f]				
5	δ^{g}	38.4	28.7	26.0	24.6	26.0	28.7	28.7	26.0	180.2
	J	59.20	0.88	3.52	0.29	3.52	0.88	0.88	3.52	
6	δ^{g}	52.6	33.5	30.5	38.4	30.5	33.5	42.8	178.6	
	J	62.72	≤0.9	3.81	5.42	3.81	≤0.9	≤0.9		
7	δ^{g}	52.7	29.6	28.1	37.1	42.2	42.2	176.2		
	J	65.41[d]	1.87[d]	3.39	8.49	0.52[h]	0.52[h]			
9	δ^{i}	32.3	27.6	25.6	24.5	25.6	27.6	27.6	25.6	71.8
	J	40.40[d]	0.58[h]	3.39[d]	0.22[h]	3.39	0.58[h]	0.58[h]	3.39	
10	δ^{i}	50.1	31.8	30.5	37.3	30.5	31.8	40.6	66.9	
	J	42.22	1.71	3.51	4.15	3.51	1.71	1.02[d]		
11	δ^{i}	53.5	28.2[h,j]	28.2[h,j]	36.7	39.6	39.6	65.2		
	J	42.69[e]	3.03	3.09	7.81	≤0.12	≤0.12			
			(3.09)[k]	(3.03)[k]						

[a] In parts per million downfield from internal tetramethylsilane. [b] In hertz, ±0.05 Hz unless otherwise noted. [c] Literature values from ref 10. [d] Values are ±0.1 Hz. [e] Literature values from ref 11. [f] Ayadin, R.; Günther, H. A., private communication, 1979. [g] In acetone-d_6 solvent; the values are somewhat different than those measured in chloroform-d.[11] [h] These values were determined by the J-resolved technique as described in the Experimental Section. [i] Measured in chloroform-d solvent. [j] The C2 and C3 references were separated by 1.7 Hz and were not assigned. [k] Because of the ambiguity in the chemical shifts of C2 and C3, the coupling constants are either 3.03 or 3.09 Hz.

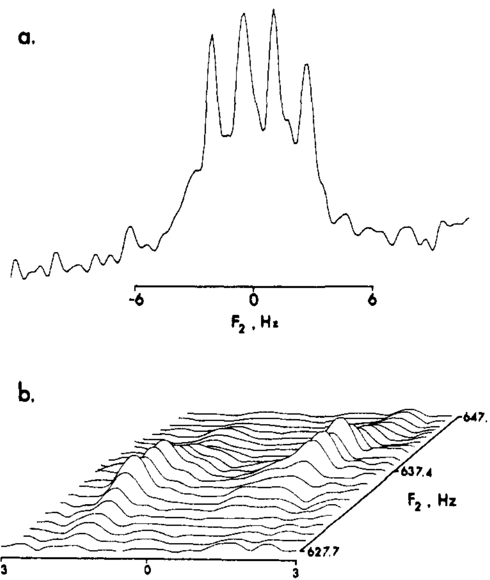


Figure 1. (a) The two doublets due to the C2 and C3 resonances in the ^{13}C NMR spectrum of **11**. The center of this pattern (0 Hz) is 637.4 Hz downfield from Me_4Si. The assignment of the two doublets is ambiguous. (b) The J-resolved ^{13}C NMR spectrum of the C2 and C3 resonances of **11**; the F_2 axis, which contains the same information as in (a), is measured in hertz downfield from Me_4Si. The F_1 axis, which contains the coupling-constant information, indicates that both coupling constants are about 3 Hz, and removes the ambiguity in the doublets.

respectively. Unfortunately, the bicyclo[1.1.1]pentane compounds were not available and it was necessary to rely on the calculated molecular orbital results.

Molecular orbital results for the Fermi contact contributions to the ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants to the C3 and C4 carbon atoms of compounds **1–12** are also entered in Table II. These calculations were based on the FPT (finite perturbation theory) method in the INDO (intermediate neglect of differential overlap) approximation of self-consistent-field MO theory.[12] Molecular geometries were based on the electron-diffraction results.[13] The bond lengths and bond angles for the hydroxymethyl group were based on a standard geometrical model,[14] whereas those for the carboxyl were taken from the compilation of Sutton.[15] All computations were performed on a Control Data Corp. CYBER 175 digital computer.

Because the calculated ^{13}C–^{13}C coupling constants depend on the orientation of the substituents, average values are entered in Table II. The $-CH_2OH$ group was assumed to be staggered with respect to the C–C bonds at the bridgehead carbon C1 in each of the bicycloalkanes. Because of the symmetry of **9** and **12**, a single calculation with simple averaging gave the values entered in Table II. In the other cases the average was weighted with respect to the total INDO energies:

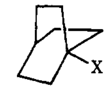
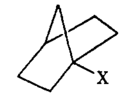
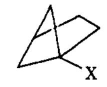
$$\langle J_{CC'}\rangle = \sum_i J_{CC'}(i)e^{-\Delta\epsilon_i/kT} \Big/ \sum_i e^{-\Delta\epsilon_i/kT} \qquad (1)$$

where $J_{CC'}(i)$ is the coupling constant calculated for the ith conformation with total energy $\Delta\epsilon_i$ relative to the lowest energy conformation. Weighted averages according to eq 1 were also used for the carboxylic acid compounds **5–8**; the $-CO_2H$ groups were assumed to be either cis or trans to each of the three C1–C bonds.

The calculated INDO FPT MO results for coupling to the C1 and C4 carbon atoms in the series **1–12** are in good agreement with the experimental data in Table II. An exception is the four-bond coupling in **9**, where the predicted negative sign could be incorrect. In several cases the calculated results are within experimental error of the measured values despite uncertainties in the structural data and the averaging procedures. The most important point is that the experimental trends within the series are reproduced. In particular, it is noted that the vicinal coupling constants to the C4 carbon are larger than to the C3 carbon in **2**, **6**, and **10**, and that the increases in the coupling constants with increase in the number of three-bond paths are 63 and 52% in **7** and **11**, respectively, and 41 and 49% in **8** and **12**, respectively. These are all substantially less than would be expected on the basis of equal contributions along equivalent paths.

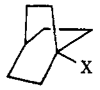
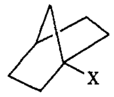
To determine the importance of the nonbonded interactions between the bridgehead carbon atoms on the coupling constants in these series of molecules, a modified INDO-FPT MO procedure was adopted. Elements of the Fock matrices associated with orbitals centered on C1 and C4 were set equal to zero in each SCF cycle, thereby eliminating the transmission

Table II. Comparison of Calculated INDO-FPT Results for Vicinal ^{13}C-^{13}C and ^{13}C-^{1}H Coupling Constants in Compounds **1-12** with the Experimental Data[a]

compd	coupling of X to carbon	X = ^{1}H calcd	X = ^{1}H exptl[b]	X = ^{13}COOH calcd	X = ^{13}COOH exptl	X = ^{13}CH$_2$OH calcd	X = ^{13}CH$_2$OH exptl
	C4	0.36		0.20[c]	0.29	−0.04	0.22
	C3	7.72	7.0	4.81[d]	3.52	3.98[e]	3.39
	C4	8.56	8.7 (8.75)[f]	5.17[g]	5.42	4.25[h]	4.15
	C3	7.19	7.0 (6.76)[f]	4.44[g]	3.81	3.42[h]	3.51
	C4	13.75		8.42[g]	8.49	6.46[h]	7.81
	C3	5.90		3.44[g]	3.39	3.23[h]	3.09[i] (3.03)
	C3	17.55		11.87[c]		9.62	

[a] All values in hertz. [b] Converted from the $J(^{13}C-H)$ data in Table I by multiplication by $\gamma_H/\gamma_D = 6.514$. [c] A weighted average according to eq 1 in which the CO$_2$H group is cis and trans to the bonds at the bridgehead. [d] Averaged according to eq 1 with six possible orientations of C3 with respect to the carboxyl. [e] A simple average of coupling constants in three orientations in which the C-O bond is trans or gauche to C1-C2. [f] Ayadin, R.; Günther, H. A., private communication, 1979. [g] Averaged according to eq 1 with six possible orientations. [h] Averaged according to eq 1 with three possible orientations. [i] The experimental value is either 3.09 or 3.03 Hz as noted in the text.

Table III. ΔJ Changes in the Calculated ^{13}C-^{1}H and ^{13}C-^{13}C Coupling Constants Due to Elimination of the Interactions between the Bridgehead Carbon Atoms, Which Are Separated by a Distance R[a]

compd	X = ^{1}H ΔJ_{CH}, Hz	X = ^{13}COOH $\Delta J_{CC'}$, Hz	X = ^{13}CH$_2$OH $\Delta J_{CC'}$, Hz	R, Å	θ, deg
	−0.47 (**1**)	−0.12 (**5**)	0.06 (**9**)	2.567	180
	−3.46 (**2**)	−1.63 (**6**)	−1.19 (**10**)	2.317	151.5
	−7.53 (**3**)	−3.91 (**7**)	−2.77 (**11**)	2.172	174.6
	−30.12 (**4**)	−17.31 (**8**)	−12.39 (**12**)	1.844	180

[a] The angle θ is measured between C1-H and C1···C4 in the parent compound.

of coupling along the path provided by these nonbonded interactions.[8] Entered in Table III are the differences ΔJ_{CH} and $\Delta J_{CC'}$ obtained on subtracting the recalculated values from the previous ones. These quantities provide a qualitative measure of the importance of the nonbonded paths to the coupling constants of interest.[8,16] Also given in Table III are the C1···C4 internuclear separations and the angle θ which the H-C1 bond makes with the C1···C4 internuclear line in the parent compounds.[13]

Except for the small positive contribution of 0.06 Hz to the four-bond ^{13}C-^{13}C coupling constant in the bicyclo[2.2.2]octane compound **9**, all of the other nonbonded contributions are of negative sign and increase in magnitude with internuclear separations, R. The more negative values of $\Delta J_{CC'}$ for the bicyclo[2.1.1]hexane derivatives **7** and **11** would account for the lack of additivity of the calculated and experimental ^{13}C-^{13}C coupling constants in Table II. However, the very large magnitudes of the nonbonded contributions calculated for the bicyclo[1.1.1]pentanes in Table III clearly show the importance of the proximity of the bridgehead carbons on this type of coupling. One consequence of this result is that the coupling constants are predicted to be only slightly larger than those for the bicyclo[2.1.1]hexanes in Table II. An experimental criterion for the importance of the nonbonded interactions on coupling in the bicyclo[1.1.1]pentane is found in the measurement of 18 Hz for the long-range coupling between hydrogens bonded to the bridgehead carbon atoms,[17] whereas in other situations long-range H-H coupling over four saturated bonds is seldom greater than 3 Hz.[18,19] The calculated value of 28.3 Hz for $^{4}J_{HH'}$ decreases to 3.5 Hz on eliminating the nonbonded interactions between the C1 and C3 carbon atoms.[20] Thus, the interactions between the "rear lobes" of carbon hybrid orbitals of the bridgehead carbon atoms provide the dominant mechanisms for long-range H-H coupling.[18,21] A dependence of $^{4}J_{HH'}$ on internal angle θ and C-C internuclear separation of the form $\cos^2 \theta/R$ has been proposed;[19] however, the calculated results for the nonbonded contributions to vicinal ^{13}C-H and ^{13}C-^{13}C coupling constants correspond to an exponential dependence on R. Such an exponential dependence is found in the overlap integrals,[22] which are the most important terms entering the off-diagonal elements of the Fock matrices.[8,12]

The assumption of additivity of coupling constants over multiple paths has been implicit in many studies,[23] and with a few exceptions this appears to be a reasonable approximation. Exceptions are found in those cases in which the effects of substituents are large,[18,24] or from the importance of nonbonded interactions as noted in this study. In fact, rigorous additivity of coupling contributions would not be expected because of the changes in the contributions of the many nonbonded interactions[8,16] arising from the molecular changes which are required to increase the number of equivalent paths; cf. the series **1–4**. A suggestion[25] that the presence of two equivalent paths would increase the coupling by a factor of 4 times that for a single path is contradicted by the experimental results (i.e., **6** and **7** or **10** and **11**) reported here.

Experimental Section

All ^{13}C NMR spectra were recorded on a Bruker Instruments Fourier transform NMR spectrometer operating at a frequency of 22.63 MHz. Spectra of **1b**, **2b**, and **9–11** were obtained in chloroform-*d* solvent, and **5–7** in acetone-d_6 solvent, which served as internal ^{2}H lock. Chemical shifts, referenced downfield from tetramethylsilane, were routinely assigned by intensities of signals and off-resonance decoupling. Resolution of $J_{CC'}$ values was usually possible if they were >0.5 Hz with an accuracy of ±0.05 Hz. However, depending on computer settings and computer resolution higher and lower resolution and precision were obtained as noted in Table I.

A number of ^{13}C NMR spectra were obtained by the two-dimensional NMR technique of *J*-resolved spectroscopy.[9] This was performed with NTCFT software[26] on a NIC-80/WH-90 spectrometer with a NIC-293 pulse programmer. An assembly language computer program was written to perform the transposition of the spectra. The $90°-\tau-180°$ spin-echo pulse sequence was used; typical spectra were obtained with 16 τ values ranging from 0.0 to 3.75 s. The resolution depends on the individual carbon T_2 values, but was at least 0.12 Hz with an accuracy of at least ±0.05 Hz.

Proton spectra were obtained on a Perkin-Elmer PE-24B NMR spectrometer using samples dissolved in chloroform-*d* and referenced to internal tetramethylsilane. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E double-focusing mass spectrometer. Melting points were taken on a Thomas-Hoover apparatus.

1,5-Hexadien-3-ol.[27] To an initiated Grignard reaction (prepared by adding 1.21 g (0.010 mol) of allyl bromide in 50 mL of ether to 35.3 g (1.45 g-atoms) of magnesium under nitrogen) was added a solution of 145.6 g (1.203 mol) of allyl bromide and 56 g (1.0 mol) of acrolein in 300 mL of ether dropwise. The resulting mixture was heated under reflux for 1.75 h and then cooled. With cooling 250 mL of saturated aqueous ammonium chloride solution was added, and the ethereal layer was removed. The aqueous phase was extracted with 3 × 100 mL of ether. The combined ethereal extracts were washed with brine, dried (anhydrous magnesium sulfate), concentrated in vacuo, and distilled to give 61.7 g (0.63 mol, 63% based on acrolein): 60–70 °C (50 mm); ^{1}H NMR δ (CDCl$_3$) 5.90 (m, 3 H), 5.24 (m, 3 H), 4.21 (m, 1 H), 3.80 (d, 1 H), 2.36 (t, 2 H); IR (neat) 3350, 3070, 1640 cm^{-1}.

1,5-Hexadien-3-one. To a solution of 32 g (0.327 mol) of 1,5-hexadien-3-ol dissolved in 837 mL of purified acetone, held below 5 °C, was added 96 mL of Jones reagent (prepared with 65 g of CrO$_3$, 58 mL of H$_2$SO$_4$, and 250 mL of water) dropwise. The cold mixture was stirred for an additional 1 h. Then 3.20 g of sodium bisulfite was added followed by an excess of sodium bicarbonate. The top layer was decanted and the precipitate was washed with pentane (4 × 200 mL). The combined organic layers were filtered (cotton), washed with brine and 5% aqueous sodium bicarbonate until clear, dried (anhydrous calcium chloride), and stored in the refrigerator under nitrogen: ^{1}H NMR δ (CDCl$_3$) 6.30 (m, 2 H), 5.80 (m, 2 H), 5.25 (m, 1 H), 5.00 (m, 1 H), 3.34 (d, 2 H); IR (neat) 3080, 1700 cm^{-1}.

Bicyclo[2.1.1]hexan-2-one. A solution of 20 g of 1,5-hexadien-3-one in 700 mL of purified pentane was photolyzed in a 1.0-L photolysis flask purged with nitrogen with a 450-W Hanovia mercury vapor lamp for 18 h. Several runs were made and combined. The solvent was removed by distillation under reduced pressure and the crude product was distilled to give 26.9 g (28%) of colorless liquid: 45–50 °C (20 mm); ^{1}H NMR δ (CDCl$_3$) 2.80 (m, 2 H), 2.15 (m, 4 H), 1.60 (m, 2 H); IR (neat) 2900–3000, 1750 cm^{-1}.

2,2-Dibromobicyclo[2.1.1]hexane. Under nitrogen 10.84 mL (0.208 mol) of bromine was added by syringe to 65 mL of phosphorus tribromide at a rate to keep the solution mobile. The resulting thick yellow slurry was allowed to stir for an additional 18 h, and then was cooled in an ice bath as 15.0 g (0.156 mol) of bicyclo[2.1.1]hexan-2-one was added dropwise. After an additional 24 h of stirring at room temperature, the reaction mixture was poured into an ice–pentane mixture and potassium carbonate was added cautiously until the evolution of carbon dioxide ceased. The pentane layer was decanted and the aqueous phase was extracted with pentane (4 × 100 mL). The combined pentane layers were washed with aqueous sodium bicarbonate, water, and brine, dried (anhydrous magnesium sulfate), concentrated in vacuo, eluted with pentane on alumina, and distilled to give 31.7 g (85%) of colorless liquid: 40–42 °C (1 mm); ^{1}H NMR δ (CDCl$_3$) 3.25 (m, 1 H), 2.95 (m, 2 H), 2.65 (m, 1 H), 1.80 (m, 4 H).[27]

1,2-Dibromobicyclo[2.1.1]hexane. A solution of 1.2 M (freshly sublimed) aluminum tribromide in carbon disulfide (5 mL) was added slowly to a solution of 16.0 g (0.067 mol) of 2,2-dibromobicyclo[2.1.1]hexane in 150 mL of purified carbon disulfide cooled to −5 °C. After an additional 1 h of stirring, the reaction mixture was filtered through Celite and eluted with pentane through neutral alumina. The pentane fraction was then concentrated in vacuo and distilled to give 9.17 g (0.0382 mol, 57%): 44–50 °C (1 mm); ^{1}H NMR δ (CDCl$_3$) 4.50 (m, 1 H), 2.75 (m, 2 H), 2.20 (m, 4 H), 1.85 (m, 1 H).[27]

1-Bromobicyclo[2.1.1]hexane (13). To 2.20 g (0.009 16 mol) of 1,2-dibromobicyclo[2.1.1]hexane under nitrogen was added 2.68 g (0.0092 mol) of tri-*n*-butyltin hydride dropwise. The resulting mixture was stirred for 18 h and distilled to give 1.32 g (0.008 25 mol, 90%): 44–55 °C (40 mm); ^{1}H NMR δ (CDCl$_3$) 2.55 (b, 1 H), 1.82 (b, 6 H), 1.55 (m, 2 H);[27] mass spectrum *m/e* M 160, 162 B 81 (M − Br), 145, 147 (M − 15), 132, 134 (M − 28), 119, 121 (M − 41).

1-Chlorobicyclo[2.2.2]octane (14) was synthesized using previously published procedures.[28]

1-Chlorobicyclo[2.2.1]heptane (15) was synthesized using the procedure of Bixler and Niemann.[29]

Syntheses of Activated Magnesium, Bridgehead Grignard Compounds, and ^{13}C-Labeled Carboxylic Acids. A modified procedure of Rieke and Bales[30] was used to synthesize activated magnesium, which was then reacted with the bridgehead halides to form the corresponding carboxylic acids. The following procedure to make the bicyclo[2.2.1]heptane derivative **6** is representative. In an argon tent, an oven-dried 100-mL two-neck round-bottom flask, equipped with a stirring bar, a reflux condenser with inlet tube, and a rubber septum, was charged with 2.01 g (0.002 11 mol) of anhydrous magnesium chloride (Aldrich), 3.55 g (0.002 14 mol) of oven-dried potassium iodide (Baker), and 1.5 g (0.003 84 g-atom) of potassium metal (MCB). The flask was removed from the argon atmosphere, placed in a hood, and flushed with argon. With stirring the flask was then injected with 50 mL of tetrahydrofuran (dried over sodium–potassium and distilled). The contents were heated to reflux, the potassium melted, and an exothermic reaction commenced that was moderated by removal of the heating mantle. The mixture was then heated under reflux for 3 h. Then 1.25 g (0.0096 mol) of 1-chlorobicyclo[2.2.1]heptane (**15**) was injected neat, and the mixture was stirred under reflux for 12 h. The flask was cooled, transferred to a vacuum line,[31] and cooled in a liquid nitrogen bath; 0.75 g of carbon-^{13}C dioxide (Prochem) was sublimed into the flask. Crushed dry ice was added to the liquid nitrogen bath, the magnetic stirrer was turned on so that the mixture would stir upon thawing, and the assembly was left alone for 24 h. The mixture was then poured into 15% aqueous ammonium chloride solution, washed with 3 × 100 mL of ether, acidified with concentrated hydrochloric acid (a milky precipitate ensued), and extracted with 3 × 100 mL of ether. The ethereal extracts were then extracted with 3 × 100 mL of 10% aqueous sodium hydroxide solution. The basic aqueous extract was then reacidified with concentrated hydrochloric acid and reextracted with 3 × 100 mL of ether. This ethereal extract was washed with aqueous sodium bisulfite solution to remove the iodine, dried (anhydrous magnesium sulfate), and concentrated in vacuo to give the crude product.

1-Bicyclo[2.2.2]octanecarboxylic acid-*carboxyl*-^{13}C (5) was synthesized in the manner described above to give 0.50 g (36%): mp 137.0–138.5 °C (lit.[32] mp 140.5–142 °C); ^{1}H NMR δ (CDCl$_3$) 10 (s, 1 H), 2.30 (b, 1 H), 1.30 (b, 12 H); IR (KBr) 1660 cm^{-1} (for *unlabeled* compound, 1740 cm^{-1}).

1-Bicyclo[2.2.1]heptanecarboxylic acid-*carboxyl*-^{13}C (6) was synthesized in the manner described above to give 0.54 g (37%): mp

109–110 °C (lit.[11] mp 109–110 °C); ^{1}H NMR δ ($CDCl_3$) 10 (s, 1 H), 2.27 (b, 1 H), 1.9–1.0 (complex, 10 H); IR (KBr) 1660 cm^{-1} (for *un*labeled compound 1740 cm^{-1}).

1-Bicyclo[2.1.1]hexanecarboxylic acid-*carboxyl*-^{13}C (7) was synthesized in the manner described above from the bromide **13** to give 0.80 g (66%): mp 40–45 °C (lit.[33] mp 50.7–52.4 °C); ^{1}H NMR δ ($CDCl_3$) 10 (s, 1 H), 2.37 (b, 1 H), 1.79 (s, 4 H), 1.28 (b, 4 H); IR (neat) 1660 cm^{-1}; mass spectrum *m/e* M 127, B 81 (M − ^{13}COOH), 112 (M − 15), 99 (M − 28), 98 (M − 29). Reaction of the activated magnesium with the bromide **13** was extremely vigorous, and the bromide had to be added dropwise. The crude product **7** retained water tightly, and in order to remove all of the water and ether a careful trap-to-trap distillation was done on the vacuum rack.

Reduction of carboxylic acids with lithium aluminum hydride was accomplished in the usual manner.[34]

1-Hydroxymethylbicyclo[2.2.2]octane-*9*-^{13}C (9) was made in 81% yield (0.191 g): mp 54–57 °C (lit.[32] mp 60–62 °C); ^{1}H NMR δ 3.02 (d, 2 H, J = 137 Hz) (for *un*labeled compound, s), 2.40 (s, 1 H), 2.34 (b, 1 H), 1.33 (b, 12 H); IR (KBr) 3400 cm^{-1}.

1-Hydroxymethylbicyclo[2.2.1]heptane-*8*-^{13}C (10) was made in 93% yield (0.30 g), semisolid:[29] ^{1}H NMR δ 3.53 (d, 2 H, J = 137 Hz) (for *un*labeled compound, s), 2.34 (s, 1 H), 2.20 (b, 1 H), 1.55–1.17 (complex, 10 H); IR (neat) 3400 cm^{-1}.

1-Hydroxymethylbicyclo[2.1.1]hexane-*7*-^{13}C (11) was synthesized in 95% yield (0.55 g), oil:[33] ^{1}H NMR δ 3.60 (d, 2 H, J = 136 Hz), 2.40 (s, 1 H), 2.35 (s, 1 H), 1.55 (b, 4 H), 1.25 (m, 2 H), 1.00 (m, 2 H); IR (neat) 3400 cm^{-1}.

1-Deuteriobicyclo[2.2.2]octane (1b) was synthesized by quenching 1-bicyclo[2.2.2]octanemagnesium chloride (prepared as described above with activated magnesium) with deuterium oxide to give 1.21 g (70%).

1-Deuteriobicyclo[2.2.1]heptane (2b) was synthesized in a manner analogous to **1b** to give 0.6 g (40%).

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