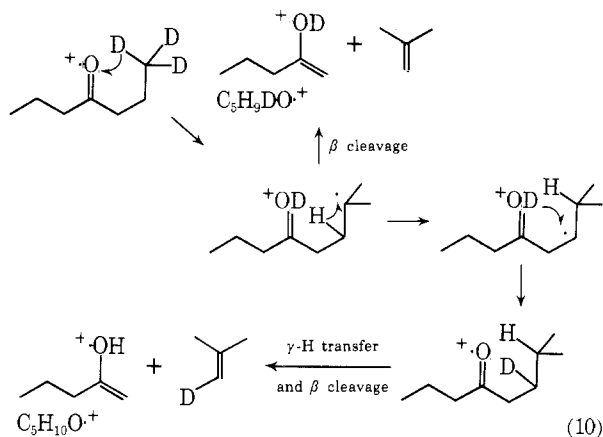


apparently random H-D rearrangement is thus able to compete successfully with the McLafferty rearrangement, even at times less than  $10^{-10}$  sec.

To explain these kinetic results we propose the following mechanism<sup>41</sup>



We are concerned primarily with reaction at times of  $10^{-10}$  sec and longer, at which times we consider the McLafferty rearrangement to be stepwise (*cf.* hexanal). The crucial question is: does the species formed by the initial  $\gamma$ -D transfer undergo hydrogen shifts in

(41) G. Eadon and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 3084 (1970).

the hydrocarbon chain or does it undergo  $\beta$  cleavage? We argue that the tertiary radical formed by  $\gamma$  transfer in a  $\gamma$ -branched molecule is significantly more stable than the secondary radical formed with a straight-chain or  $\alpha$ -branched molecule, and that the increased stability will favor hydrogen shifts over  $\beta$  cleavage.<sup>40</sup> Thus branching at the  $\gamma$  position enables H-D rearrangement to compete more effectively with McLafferty rearrangement. Support for the proposed mechanism (eq 10) can be derived from the relative rates of McLafferty rearrangement in straight-chain and  $\gamma$ -branched ketones.<sup>40</sup>

The point we wish to make is that the apparently random H-D rearrangements in aliphatic alkenes and ketones are explicable in terms of perfectly conventional chemical reactions. We suggest that this is generally true for aliphatic species.<sup>42</sup> The only probable exceptions are alkane ions.<sup>21</sup> Hydrogen and deuterium atoms in aliphatic ions containing unsaturation or functional groups arrive at a degree of isotopic randomization by a series of highly specific hydrogen (deuterium) shifts.

We gratefully acknowledge the financial support of the National Science Foundation Grant NSF GP 38389X, the National Aeronautics and Space Administration Grant NGL 05-003-003, and the Ramsay Memorial Fellowship Trust (Great Britain).

(42) See D. J. McAdoo, F. W. McLafferty, and T. E. Parks, *J. Amer. Chem. Soc.*, **94**, 1601 (1972).

## Long-Range Carbon-Proton and Carbon-Carbon Spin-Spin Coupling Constants

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During the 1960's a profusion of experimental proton nmr data, in conjunction with excellent theoretical work, allowed very satisfactory correlation of molecular structure with proton-proton spin-spin coupling constants.<sup>1</sup> This correlation has given the organic chemist a powerful tool for structure elucidation of even very complex molecules. Proton nmr work was so fruitful because of three inherent features: (1) the ubiquitousness of the proton in organic molecules, giving the nmr spectroscopist an almost unlimited number of systems to explore; (2) the high natural abundance of the <sup>1</sup>H isotope (99.98%), whose spin of  $\frac{1}{2}$  gives sharp signals, allowing precise measurements of high-resolution spectra; (3) the high sensitivity of the <sup>1</sup>H nucleus, and hence the large nmr signals.

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Arthur M. Ihrig, a graduate of the University of Kentucky, was a postdoctoral fellow at North Texas State University during 1970-1972. D. E. Müller, S. A. Conn, and R. Seiwel are graduate students with Dr. Marshall.

**Carbon-Proton Couplings.** It would seem desirable to extend structural correlations to carbon-proton couplings, since carbon exists in all organic compounds, by definition. However, the common isotope of carbon—<sup>12</sup>C, whose nuclear spin is 0—is nmr inactive, and carbon-proton couplings are not a significant feature in routine proton nmr spectra. Actually, the nmr inactivity of carbon-12 has been a blessing during the extensive proton-proton investigations of the past 15 years, because it removed the complication of carbon-proton couplings. Now that our understanding of proton-proton couplings is fairly complete, however, the attractiveness of additional nmr methods involving carbon increases. The isotope of carbon that is nmr active (<sup>13</sup>C, with a nuclear spin of  $\frac{1}{2}$ ) exists in nature to the extent of 1.1%. Hence, if one chooses a system wherein the main proton signals do not mask the much weaker signals arising from the carbon-proton couplings, one may obtain accurate measurements for these couplings. In practice, only large carbon-proton splittings may be observed,

(1) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

because the smaller splittings are not spread out sufficiently to emerge from under the intense center band of the normal proton signals. Generally, only those carbon-proton couplings which are directly bonded ( $^1J_{C-H}$ ) are large enough (120–250 Hz) to be directly observable. These patterns, attributable to the directly bonded carbon-proton couplings, flank the more intense center bands in a pattern known as "satellite spectra." Unfortunately, these satellite spectra can be quite complex and only the simplest molecules are amenable to satellite spectral analysis.

A different approach to obtaining carbon-proton couplings is to observe these splittings in the  $^{13}C$  nmr spectra. This approach suffers from two difficulties. First, for a compound with  $x$  different carbon atoms, there appear  $x$  different spectra, all appearing simultaneously and potentially overlapping in an indiscernible manner. Second, the sensitivity of the carbon nucleus is low, only 0.016 that of  $^1H$ . Hence, obtaining satisfactory spectra can be laborious and can suffer from lack of resolution. Nevertheless, some excellent carbon-proton coupling data have been obtained by this method in suitably chosen systems.

**Carbon-Carbon Couplings.** A further area of exploration involving carbon-13 is carbon-carbon couplings. An experimental benefit here is the possibility of using proton decoupling. Proton decoupling helps alleviate the two problems noted immediately above. First, since carbon-proton coupling is removed, simplified spectral patterns result; second, proton decoupling generally enhances carbon signals, owing to the nuclear Overhauser effect. Unfortunately, because of the low natural abundance of carbon-13, the chance of two carbon-13 nuclei existing simultaneously at two given positions in a molecule is quite small. Time-averaging can enhance these carbon-carbon satellite signals so that they are measurable if the values are sufficiently large to be apart from the large center band. With a few exceptions, only directly bonded carbon-carbon coupling constants ( $^1J_{C-C}$ ) can be obtained by this method.

**Carbon-13 Enriched Samples.** In view of these difficulties in studies involving natural abundance carbon-13, using enriched samples is an obvious advantage. Several research groups have adopted this approach with considerable success. In the past five years, carbon-13 precursors have become available at reasonable prices (about \$700 for 1 mol of >90%  $^{13}C$  carbon dioxide), allowing the economically reasonable synthesis of molecules with a specific carbon-13 label. Although carbon-13 precursors of lower isotopic purity are available at low prices, it is usually desirable to use isotopic purities sufficiently close to 100% so that the center-band problem will not obscure small couplings. The major difficulty with the approach is tedious synthetic sequences originating from the labeled precursor.

With a specific position labeled with carbon-13, the proton spectrum would involve exclusively the proton system coupled with the labeled carbon. Carbon-carbon couplings could be obtained from these specifically labeled systems by observing the naturally occurring carbons, each of which could potentially be coupling with the labeled carbon. Thus, the naturally occurring carbon signals would each be split into

a doublet, reflecting coupling with the labeled carbon.

**Synthesis of Labeled Compounds.** In our group, the synthesis of the labeled compounds has almost exclusively involved initially reacting a Grignard reagent with labeled carbon dioxide to form the  $^{13}C$ -carboxyl carboxylic acid.<sup>2</sup> Vacuum-line techniques had previously been worked out for carbon-14 labeled compounds which were immediately adaptable to our carbon-13 systems;<sup>3</sup> however, the technique of washing out a synthesized labeled compound with natural compound, which is routine in carbon-14 syntheses where dilution of the radioactivity is not a serious concern, in our systems would immediately destroy the (virtually) pure label. Only small adjustments in the published procedures, however, were necessary for satisfactory syntheses. Because carboxyl-labeled carboxylic acids were immediately available *via* these procedures, it was natural to concentrate on carboxylic acids in our carbon-proton and carbon-carbon coupling studies. However, these carboxylic acids have sometimes been converted to different functionalities.

### Long-Range Carbon-Proton Coupling

A major question pursued by several investigators in the past several years has been: is carbon-proton coupling analogous to proton-proton coupling? With no nonbonding valence electrons, carbon is like proton, and perhaps carbon couplings would differ from proton couplings only in that the magnetogyric ratio would predict the former couplings would be smaller. Specifically, with a magnetogyric ratio *ca.* one-fourth that of proton, carbon-proton couplings should be one-fourth those of geometrically equivalent proton-proton couplings. In some initial calculations taking into consideration mean excitation energies and electron densities, a slightly higher figure was suggested (*ca.* 20% higher).<sup>4,5</sup>

In testing the idea that proton-proton systems will reflect geometrically equivalent carbon-proton systems, one should choose a labeled carbon atom which is similar to a proton. By this "similarity" one would suggest a carbon which is singly bonded to the organic molecule, rather than a multiply bonded carbon. The natural direction to test this hypothesis, therefore, is to isolate the labeled carbon as a substituent rather than as a nucleus inherent in a  $\pi$  system. The choice of labeled carboxyl carbons, which was pointed out above to be desirable synthetically, therefore seemed natural, and a major portion of our work has accordingly involved such systems.

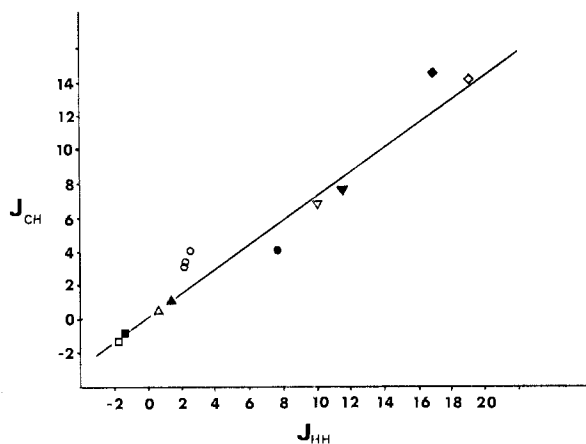
**$^{13}C$ -Carboxyl-Labeled Carboxylic Acids.** A good method of determining coupling constants *including* signs is that of "spin tickling." In spin-tickling studies, appropriate nmr signals are irradiated ("tickled"), whereupon certain other signals are split into doublets in a manner consistent with a certain choice of signs for the coupling constants. In spin-tic-

(2) J. L. Marshall and D. E. Müller, *J. Amer. Chem. Soc.*, **95**, 8305 (1973).

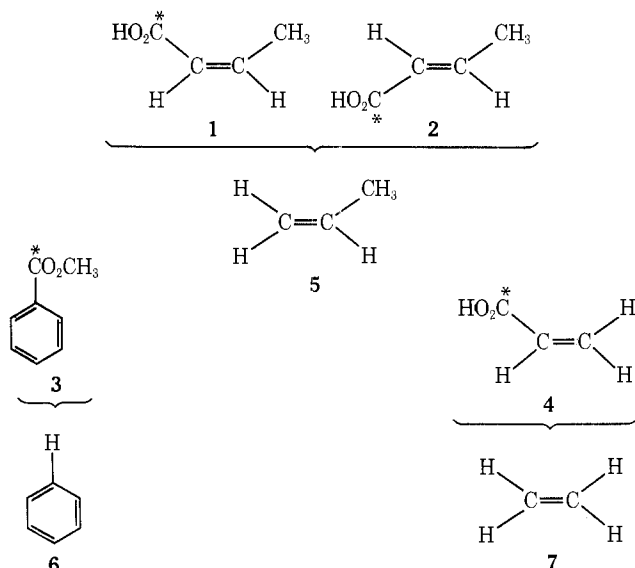
(3) A. Murray, III, and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958.

(4) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Amer. Chem. Soc.*, **84**, 37 (1962).

(5) The presence of six additional bonding electrons for the carbon atom will further complicate the picture. Thus, the proton-proton system may be a working model, but this additional complicating factor should be kept in mind.



**Figure 1.**  $J_{C-H}$  of olefinic and aromatic carboxylic acids vs.  $J_{H-H}$  of geometrically equivalent hydrocarbons. The respective data points are derived from:  ${}^2J$  (○);  ${}^3J$  of 1 (●);  ${}^3J$  of 2 (▼);  ${}^3J$  of 3 (◆);  ${}^3J_{cis}$  of 4 (▲);  ${}^3J_{trans}$  of 4 (◊);  ${}^4J$  of 1 (▲);  ${}^4J$  of 2 (■);  ${}^4J$  of 3 (□);  ${}^5J$  of 1 (△). The line is that obtained by the method of averages not including the  ${}^2J$  values (○).



klung studies involving the proton nmr spectra of  ${}^{13}C$ -carboxyl crotonic acids (1, 2) and methyl benzoate (3), all long-range  $J_{C-H}$  values, including signs, were determined.<sup>6,7</sup> These  $J_{C-H}$  values, along with the values from acrylic acid (4),<sup>8</sup> found excellent correlation with the  $J_{H-H}$  values of geometrically equivalent systems (5, 6, and 7).<sup>6</sup> Figure 1 shows this correlation and includes  ${}^2J_{CH}$ ,  ${}^3J_{CH}$ ,  ${}^4J_{CH}$ , and  ${}^5J_{CH}$  values. Interestingly, the  ${}^2J_{CH}$  values (○ symbols) diverge from the general linearity of the plot, suggesting an additional mechanism is operating for  ${}^2J_{CH}$ , possibly *via* indirect coupling through the carboxyl oxygen atom. The slope of the plot of Figure 1 shows  $J_{CH} \approx 0.7J_{HH}$ , larger than anticipated from some theoretical calculations (*vide supra*), where it was suggested that  $J_{CH} \approx 0.4J_{HH}$ .<sup>4</sup> This  $J_{CH} \approx 0.7J_{HH}$  relationship also applies to  ${}^3J$  values for aliphatic carboxylic acids.<sup>9,10</sup>

The speculation that the  ${}^2J_{C-H}$  values experience

- (6) J. L. Marshall and R. Seiwel, *J. Magn. Resonance*, **15**, 150 (1974).  
 (7) A. M. Ihrig and J. L. Marshall, *J. Amer. Chem. Soc.*, **94**, 3268 (1972).  
 (8) K. M. Creceley, R. W. Creceley, and J. H. Goldstein, *J. Mol. Spectrosc.*, **37**, 252 (1971).  
 (9) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **83**, 1230 (1961).  
 (10) G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Amer. Chem. Soc.*, **83**, 2778 (1961).

**Table I**  
Geminal Carbon-Proton Couplings of Aliphatic Carboxylic Acids Compared with Geminal Proton-Proton Couplings of Geometrically Equivalent Hydrocarbons

Carbon-Proton Compound	${}^2J_{C-H}{}^{a,b}$	Proton-Proton Compound	${}^2J_{H-H}{}^a$
	(-)6.17		(-)12.6 <sup>c</sup>
	(-)7.56		
	(-)6.89		-12.5 <sup>d</sup>
	(-)4.61		-10.2 <sup>d</sup>

<sup>a</sup> In hertz. <sup>b</sup> Reference 11. Signs are most probably negative.<sup>12</sup>  
<sup>c</sup> Reference 13. <sup>d</sup> Reference 14.

an additional mechanism in olefinic systems may be supported by geminal couplings in aliphatic carboxylic acids.<sup>11</sup> Various aliphatic carboxylic acids (8–11) show a  $|{}^2J_{CH}|$  value considerably less than analogous  $|{}^2J_{HH}|$  values of 12–14 (see Table I), whereas the reverse was the case for 1–7. The data of Table I<sup>11–14</sup> show a rough relationship,  ${}^2J_{CH} \approx 0.5{}^2J_{HH}$ . It is known that the orientation of the carboxyl group with respect to the geminal proton is not the same in these aliphatic systems as it was in the olefinic systems,<sup>15</sup> and this may explain why these aliphatic  ${}^2J_{CH}$  values are more nearly “normal.” That  ${}^2J_{CH}/{}^2J_{HH}$  for the aliphatic carboxylic acids ( $\sim 0.5$ ) is smaller than the general  $J_{CH}/J_{HH}$  relationship of Figure 1 ( $\sim 0.7$ ) may be due to a steric flaring of the  $HO_2C-C-H$  angle<sup>16</sup> (in  ${}^2J_{HH}$  systems, an increase of the involved angle decreases the  $|{}^2J_{HH}|$  value<sup>1</sup>). Consistent with the idea that the  $|{}^2J_{CH}|$  value of the  $HO_2C-C-H$  system decreases as the involved angle increases, this  $|{}^2J_{CH}|$  value is substantially lower in 11.

**The Dihedral Dependence of Three-Bonded Carbon-Proton Coupling.** Attempts to use proton-proton systems as models for carbon-proton systems have led to investigations concerning the angular dependence of three-bonded carbon-proton couplings.

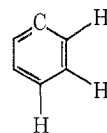
- (11) D. E. Miiller, Ph.D. Thesis, North Texas State University, 1974.  
 (12) E. Sackmann and H. Dreeskamp, *Spectrochim. Acta*, **21**, 2005 (1965).  
 (13) N. Muller and P. J. Schultz, *J. Phys. Chem.*, **68**, 2026 (1964).  
 (14) J. L. Marshall and S. R. Walter, *J. Amer. Chem. Soc.*, **96**, 6358 (1974).  
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 (16) In olefinic systems, a substituent does not flare the geminal proton as in aliphatic systems [M. A. Cooper and S. L. Manatt, *Org. Magn. Resonance*, **2**, 511 (1970)].

Although a thorough investigation has not been conducted, several studies strongly suggest a similar dependence does exist for aliphatic  ${}^3J_{C-H}$  values. Calculations for propane<sup>17</sup> suggest that, just as for Karplus proton-proton systems,<sup>18</sup> a minimum for  ${}^3J_{CH}$  occurs with a dihedral angle of  $90^\circ$ , a maximum at  $0^\circ$ , and a larger maximum at  $180^\circ$ . A conformational study of propionaldehyde and its *O*-methyloxime shows the angular dependence of  ${}^3J_{C-H}$  behaves as that of  ${}^3J_{H-H}$  in these systems.<sup>19</sup>

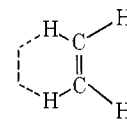
In another interesting system wherein  ${}^3J_{H-H}$  values are not helpful in establishing relative conformer populations—2-phenylsuccinic acid—the  ${}^3J_{C-H}$  values are quite helpful.<sup>20</sup> In this study, a  $J_{C-H}$  (trans) value of 11 Hz and a  $J_{C-H}$  (gauche) value of 2 Hz are suggested. The angular dependence of  ${}^3J_{C-H}$  has also been used to help establish the conformations of carbohydrates<sup>21</sup> and bases and nucleosides.<sup>22-24</sup>

**The  $J_{C-H}/J_{H-H}$  Ratio.** The Fermi contact term is generally agreed to be the dominant contribution in  $J_{H-H}$  and  ${}^1J_{C-H}$ .<sup>4,25</sup> Dominance of the Fermi contact term would lead one to expect a strong dependence of  $J_{C-H}$  on the hybridization of the carbon atom. A singular lack of such dependence for  ${}^3J_{CH}$  in certain aliphatic systems<sup>4,10,25</sup> has been noted, and it was suggested that perhaps other mechanisms (*i.e.*, spin-dipole and/or electron-orbital contributions) may be operative. It was further calculated<sup>4</sup> that a purely Fermi contact mechanism would predict:  $J_{C-H} = J_{H-H} \times 0.30$  (for  $sp^3$ -hybridized  ${}^{13}C$ );  $J_{C-H} = J_{H-H} \times 0.40$  (for  $sp^2$ -hybridized  ${}^{13}C$ ); and  $J_{C-H} = J_{H-H} \times 0.61$  (for  $sp$ -hybridized  ${}^{13}C$ ). As noted above, the observed  $J_{C-H}$  values are consistently greater, suggesting additional coupling mechanisms may be operative and/or these calculations are not completely satisfactory. The excellent correlation of  $J_{C-H}$  with  $J_{H-H}$  (Figure 1) suggests the latter possibility is the correct one. Subsequent calculations<sup>26</sup> have indeed supported the contention that with carbon noncontact mechanisms are expected to be quite small. No doubt part of the large  $J_{C-H}/J_{H-H}$  ratio for carboxylic acids is partially due to the electronegative substituent ( $-OH$ ) on the carboxyl group, but even for ketones (diethyl ketone<sup>10</sup>) and for hydrocarbons (neopentane<sup>27</sup>) the ratio is still large ( $\sim 0.6$ ).

**Carbon-Proton Coupling in  $\pi$  Systems.** It is more difficult to envision a proton-proton model for carbon-proton systems where the carbon is olefinic-aromatic than where the carbon is a substituent. Nevertheless, surprising success has been experi-



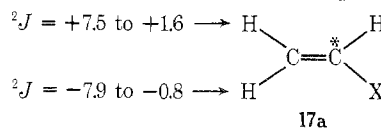
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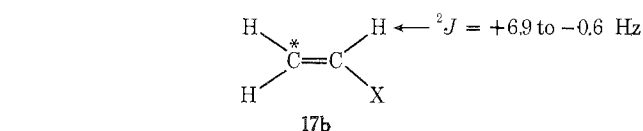
16

enced with benzene (15),<sup>28</sup> where  ${}^2J_{C-H}$ ,  ${}^3J_{C-H}$ , and  ${}^4J_{C-H}$  values were compared with  ${}^2J_{H-H}$  and  ${}^3J_{H-H}$  of ethylene (16) and an adjusted  ${}^4J_{H-H}$  value of allene. Here the  $J_{C-H}/J_{H-H}$  ratio was 0.4, just as predicted.<sup>4</sup> Choice of the correct proton-proton model was critical, however; if propylene is chosen as the model for the  ${}^4J_{C-H}$  value of benzene, agreement is poor. Using this  $J_{C-H}/J_{H-H} = 0.4$  ratio, reasonable agreement is also found in nitrogen heterocycles<sup>29</sup> and in olefins.<sup>30</sup>

Departure from the success of using proton-proton models is seen in  ${}^2J$  values in monosubstituted vinyl compounds (17). For these compounds a remarkable difference exists in the  ${}^2J_{CH}$  couplings of the  $\alpha$  carbon with the cis and the trans protons (see 17a).<sup>8</sup> Clearly no proton-proton model can be chosen here, although an oxime model (using a  $H-C-N$  model system) can give qualitative explanation.<sup>31</sup>



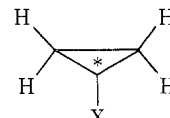
17a



17b

Long-range  $J_{C-H}$  values have also been determined for five-membered heterocycles<sup>32-34</sup> for which proton-proton models are difficult to choose.

**Cyclopropanes.** An interesting example where no proton-proton models are available is found with monosubstituted cyclopropanes (18),<sup>35</sup> where each long-range  $J_{C-H}$  value can be considered to be simultaneously a two-bonded coupling and a three-bonded coupling. These long-range values vary from  $-0.55$  to  $-5.5$  Hz.



18

### Long-Range Carbon-Carbon Coupling

The next question is: are  $J_{CC}$  values analogous to  $J_{HH}$  (and/or  $J_{CH}$ ) values? It will be increasingly difficult to find suitable proton-proton model systems, however, and carbon-proton model systems may sometimes be more useful.

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Table II  
Long-Range Carbon-Carbon Couplings of  
Aliphatic Derivatives Compared with Analogous  
Carbon-Proton Couplings

Compound	${}^2J_{CC}^a$	${}^3J_{CC}^a$	${}^2J_{CH}^a$	${}^3J_{CH}^a$
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOH 19*	1.8	3.6	6.4 <sup>b</sup>	5.5 <sup>c</sup>
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH 20*	<1	4.6	~4 <sup>d</sup>	6.4 <sup>d</sup>
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl 21*	<1	4.8	3.7 <sup>d</sup> 4.2 <sup>e</sup> 3.9 <sup>d</sup>	5.7 <sup>d</sup> 5.63 <sup>f</sup> 5.84 <sup>f</sup>
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br 22*	<1	5.2	4.0 <sup>e</sup>	5.84 <sup>f</sup>
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> I 23*	<1	4.9	-5.0 <sup>g</sup>	5.99 <sup>f</sup>
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> 24*	~0	1.9 (N) 4.8		
(CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> COH 25*	~0	5.0	3.8 <sup>b</sup>	4.5 <sup>h</sup>
(CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> CH 26*	0.8	3.8	-4.5 <sup>i</sup>	4.65 <sup>j</sup> ~4.8 <sup>c</sup>
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub> 27*	~0 <sup>k</sup>	4.0 <sup>k</sup>	-4.5 <sup>i</sup>	4.65 <sup>j</sup> ~4.8 <sup>c</sup>

<sup>a</sup> In hertz. <sup>b</sup> Reference 36. <sup>c</sup> Reference 9. <sup>d</sup> Reference 4. <sup>e</sup> Reference 37. <sup>f</sup> Reference 25. <sup>g</sup> Reference 12. <sup>h</sup> Reference 10. <sup>i</sup> Reference 31. <sup>j</sup> Reference 27. <sup>k</sup> Personal communication, G. J. Ray, Standard Oil Research Center, Naperville, Ill.

**Butane-1-<sup>13</sup>C Derivatives.** Aliphatic systems would appear *a priori* to be best for trying to correlate carbon-carbon couplings with proton-proton and/or carbon-proton couplings, since the involved nuclei are always substituents. Table II lists long-range carbon-carbon data (see ref 4, 9, 10, 12, 25, 27, 31, 36, and 37) compared with data from model carbon-proton systems for aliphatic compounds. These model systems were taken from aliphatic compounds whose functionality was the same, but unfortunately identical systems were not always available. Therefore, restraint must be exercised in making too close a comparison between  $J_{CC}$  and analogous  $J_{CH}$  values. However, a rough comparison of these  $J_{CC}$  and analogous  $J_{CH}$  values allows several interesting observations. (1) Again,  ${}^3J_{CC} > {}^2J_{CC}$ , just as  ${}^3J_{CH} > {}^2J_{CH}$ .<sup>9</sup> (2) Again, substituting a proton by a carbon produces a new  ${}^3J$  value about 0.7 the former value. That is, just as  ${}^3J_{CH} \approx 0.7{}^3J_{HH}$ , we find  ${}^3J_{CC} \approx 0.7{}^3J_{CH}$ . (3) Little, if any, correlation is possible between  ${}^3J_{CC}$  and the electronegativity of the substituent, as was observed for  ${}^3J_{CH}$ .<sup>10,38</sup> (4)  ${}^3J_{CC}$  does not appear to depend strongly on the hybridization of the carbon atom, just as was observed for  ${}^3J_{CH}$ .<sup>25</sup> (5)  ${}^2J_{CC}$  is *much* smaller than  ${}^2J_{CH}$ .

The first four observations suggest a similar mechanism is operating for  ${}^3J_{CC}$  and for  ${}^3J_{CH}$ . The mean-

ing of the fifth observation is unclear: one may be tempted to reason that the flaring of the involved C-C-C linkage may be responsible for these small  ${}^2J_{CC}$  values, but in alicyclic compounds wherein the involved C-C-C linkage is constrained,<sup>2</sup> the  ${}^2J_{CC}$  value is only slightly larger (and  ${}^2J_{CC}/{}^2J_{CH} = 0.46$ ). However,  ${}^2J$  should be very sensitive to environment or angles,<sup>31</sup> and perhaps a theoretical treatment of  ${}^2J_{CC}$  would explain the anomalous behavior.

**The Angular Dependence of Three-Bonded Carbon-Carbon Coupling Constants.** As noted above, the angular dependence of  ${}^3J_{CH}$  has not been rigorously studied, but does appear to be dependable. For carbon-carbon couplings, two studies involving rigid systems have been conducted.<sup>2,39</sup> In our study<sup>2</sup> nine different carboxylic acids, all labeled in the carboxyl position, gave  ${}^3J_{CC}$  values for 16 different dihedral angles. The resulting plot ( $J_{CC}$  vs. dihedral angle) shows a maximum of 2.5 Hz at 0°, a minimum of (-)0.5 Hz at ~65°, another maximum of 5.6 Hz at ~164°, and a value of 3.6 Hz at ~180°. This plot is reminiscent of the  $J_{FF}$  relationship<sup>40</sup> where  $J_{min}$  and  $J_{max}$  are shifted to lower values of the dihedral angle, but the resemblance is probably coincidental, because with nonbonding valence electrons the fluorine-fluorine couplings should involve additional mechanisms.<sup>40</sup>

In the second  ${}^3J_{CC}$  study, five methylcarbinols, all labeled in the methyl position, give  ${}^3J_{CC}$  values for 12 different dihedral angles.<sup>39</sup> The resulting plot showed the largest maximum not at 180°, but at 0° (5.4 Hz), in contrast to the carboxylic acid study<sup>2</sup> and to the usual Karplus relationship.<sup>18</sup> The other maximum, at 180°, was 3.2 Hz. The minimum of ~0 Hz appeared near 90°.

Theoretical considerations<sup>39</sup> agree very well with the methylcarbinol data,<sup>39</sup> and in particular predict the larger maximum at 0°. These same theoretical studies agree relatively well with the carboxylic acid data,<sup>2</sup> and correctly predict the smaller maximum at 0°. However, these calculations predict a value too low for  $J_{0^\circ}$  (by 27%) and do not predict the shift of the maximum and minimum to lower dihedral angles. As was pointed out,<sup>39</sup> the orientation of the carboxyl group is not known, and different conformations of this group would change the  ${}^3J_{CC}$  values. That the observed  ${}^3J_{CC}$  for the carboxylic acids at 0° is larger than predicted has been surmised<sup>39</sup> to be due to indirect coupling.

**Carbon-Carbon Couplings One of Whose Involved Carbon Is Aromatic.** (1)  ${}^3J_{CC}$  Values. It was noted above that for equivalent geometries in aliphatic systems  ${}^3J_{CH} \approx 0.7{}^3J_{HH}$  and  ${}^3J_{CC} \approx 0.7{}^3J_{CH}$ , and in aromatic systems  ${}^3J_{CH}$  ( $J_{C_3-H_1}$  in 29)  $\approx 0.4{}^3J_{HH}$ .<sup>28</sup> It would be of interest to determine  ${}^3J_{CC}/{}^3J_{CH}$  for aromatic systems to see if the general trend continues. To answer this question, eight <sup>13</sup>C-7 labeled monosubstituted benzene derivatives of the general form 28 were studied;<sup>41</sup> their  ${}^3J_{C_7-C_3}$  values varied from 3.84 to 5.75 Hz, about 50-75% those of the corresponding  ${}^3J_{CH}$  values in 29. Specifically, for

(36) G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Phys. Chem.*, **65**, 1657 (1961).

(37) G. Miyazima, Y. Utsumi, and K. Takahashi, *J. Phys. Chem.* **73**, 1370 (1969).

(38) As has been pointed out,<sup>10</sup> the possibility of different conformer populations being responsible for random variations of  ${}^3J$  should be considered. However, it was noted<sup>10</sup> that in large numbers of propane derivatives the  ${}^3J_{HH}$  value is relatively constant. Although the proton nmr spectra of 19-27 were too complex to analyze completely, it is reasonable to assume that these butane derivatives also should have similar conformer populations as the substituent is changed. Compare the  ${}^3J_{CC}$  values for 20 and 25—the primary and tertiary alcohols—which differ by only 0.4 Hz.

(39) D. Doddrell, I. Burfitt, J. B. Grutzner, and M. Barfield, *J. Amer. Chem. Soc.*, **96**, 1241 (1974).

(40) R. R. Ernst, *Mol. Phys.*, **16**, 241 (1969); K. Hirao, H. Nakatsuji, and H. Kato, *J. Amer. Chem. Soc.*, **95**, 31 (1973).

(41) A. M. Ihrig and J. L. Marshall, *J. Amer. Chem. Soc.*, **94**, 1756 (1972).

$C_7 = CO_2H$  (the group closely examined in our carbon-proton coupling studies<sup>6,7</sup>)  ${}^3J_{C_7-C_3} = 4.53$  Hz and  $J_{CC}/J_{CH} = 0.61$ . Thus,  $J_{CC}/J_{CH}$  is only slightly larger than  $J_{CH}/J_{HH}$ , and no surprises are encountered here. These  ${}^3J_{CC}$  values are probably positive,<sup>42</sup> and hence there appears to be good correspondence between  ${}^3J_{HH}$ ,  ${}^3J_{CH}$ , and  ${}^3J_{CC}$ .

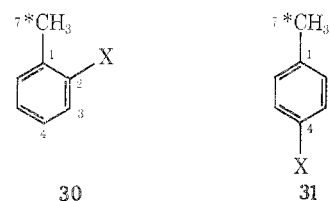


If  ${}^3J_{CC}$  in these systems is indeed positive and if the coupling mechanism is similar to that in  ${}^1J_{CH}$  where a Fermi contact term is dominant,<sup>10,43,44</sup> then  ${}^3J_{CC}$  should increase as the s character of  $C_7$  increases and as a substituent on  $C_7$  increases in electronegativity.<sup>45</sup> Inspection of the  ${}^3J_{CC}$  values<sup>41</sup> shows this is indeed the case.

(2)  ${}^2J_{CC}$  Values. It was pointed out above that aliphatic  ${}^2J_{CC}$  values were surprisingly low. However, the  ${}^2J_{CC}$  values found for **28** (i.e.,  ${}^2J_{C_7-C_2}$ ) were much larger (2.2–3.1 Hz), albeit the  ${}^2J_{CC}$  values were still smaller than the  ${}^3J_{CC}$  values. These  ${}^2J_{CC}$  values are to be contrasted with  ${}^2J_{CH}$  in benzene **29** (i.e.,  ${}^2J_{H_1-C_2}$ ), which is considerably smaller (+1.0 Hz).<sup>28</sup> These  ${}^2J_{CC}$  values increased as a  $C_7$  substituent increased in electronegativity, just as for  ${}^3J_{CC}$ ; however, in contrast to the  ${}^3J_{CC}$  values, an increase in the s character of  $C_7$  decreased  ${}^2J_{CC}$ . Model carbon-proton systems to examine these trends are difficult to find. These  ${}^2J_{CC}$  values are probably positive: as ethylene was used as a model compound to predict a positive  ${}^2J_{CH}$  in **29**,<sup>28,46,47</sup> acrylic acid derivatives (whose  ${}^2J_{CH}$  values are  $\sim +3$  Hz<sup>6</sup>) suggest the same sign for  ${}^2J_{CC}$  in **28**. Furthermore,  ${}^2J_{CC}$  for acetone is positive (+16.1 Hz<sup>48</sup>).

(3)  ${}^4J_{CC}$  Values. As for  ${}^4J_{CH}$  in **29**,  ${}^4J_{CC}$  values in **28** are small (0.6–1.6 Hz). These  ${}^4J_{CC}$  values appear to vary irregularly.

(4) *Substituted Aromatic Systems.* A study was conducted to determine the effect of a substituent on the aromatic ring of **28**. Specifically, a number of derivatives of the form **30** and **31** were investigated.<sup>49</sup> In general,  $J_{CC}$  values whose coupling passed through the substituted aromatic carbon (i.e.,  $J_{C_7-C_2}$  and  $J_{C_7-C_3}$  of **30**) were attenuated substantially (to ca. 50% of the former value where  $X = H$ ). These observations are to be compared with analogous  $J_{CH}$  values in aromatic systems;<sup>50,51</sup> these  $J_{CH}$  values become less positive (or more negative) as the benzene ring is substituted. These  $J_{CH}$  data are consistent with the  $J_{CC}$  data of **30** if a positive value is assumed for both  ${}^2J_{CC}$  and  ${}^3J_{CC}$  in **28**. It is to be recalled that

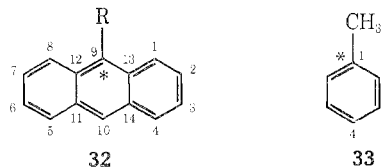


these positive signs were tentatively assigned (*vide supra*) for  ${}^2J_{CC}$  and  ${}^3J_{CC}$  in **28**.

**Carbon-Carbon Couplings in  $\pi$  Systems (Both Carbons  $sp^2$  Hybridized).** Three-bonded couplings in  $\pi$  systems are larger than olefinic proton-proton or carbon-proton models would predict, and thus an additional coupling mechanism through the  $\pi$  system is apparently operative. Typical  ${}^3J_{CC}$  values are: 9.05 Hz in 1,3-butadiene,<sup>52</sup> 9.45 Hz in toluene,<sup>53</sup> 7.6–8.6 Hz in monosubstituted benzene compounds,<sup>54</sup> 13.95 Hz in pyridine,<sup>54</sup> and 3.1–8.0 Hz in 9-substituted anthracene derivatives.<sup>55</sup>

On the other hand,  ${}^2J_{CC}$  values in  $\pi$  systems are quite small: <1 Hz in 1,3-butadiene<sup>52</sup> and toluene.<sup>53</sup> This attenuating effect on  ${}^2J_{CC}$  values of  $\pi$  systems has also been noted in isolated olefins.<sup>56</sup> The carbon-proton coupling in the model compound ethylene would also suggest a low value of  ${}^2J_{CC}$ .<sup>57</sup>

If an additional  $\pi$  mechanism is operating in the  ${}^3J_{CC}$  coupling in olefinic and aromatic systems, then bond order should be reflected in these couplings. This dependence has been noted in anthracene derivatives.<sup>55</sup> In compounds of structure **32** ( $R = CH_3, OCH_3$ ),  ${}^3J_{C_9-C_2}$  was larger than  ${}^3J_{C_9-C_4}$  (by ca. 60% average), attesting to the lower total  $\pi$ -bond order along the  $C_9-C_{13}-C_{14}-C_4$  route. This dependence of  ${}^3J_{CC}$  on the  $\pi$ -bond order is also seen with the cisoid couplings of 9-methylanthracene and toluene (i.e.,  $J_{C_9-C_{10}}$  of **32** and  $J_{C_1-C_4}$  of **33**): the  ${}^3J_{CC}$  of **33**, involving a larger total  $\pi$ -bond order, is larger by 12%. The transoid couplings of **32** are about one-half the cisoid coupling, in agreement with the idea that a dual mechanistic path is available for cisoid couplings in aromatic systems.<sup>54</sup> These cisoid couplings are to be compared with the large value of 1,3-butadiene,<sup>52</sup> in which a dual mechanistic path is *not* available. Thus, three-bonded carbon-carbon couplings appear to be more effective in olefins than in aromatics. This observation is analogous to  ${}^5J_{HH}$  values in homoallylic systems.<sup>58</sup>



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(46) M. Hansen and H. J. Jakobsen, *J. Magn. Resonance*, **10**, 74 (1973).

(47) A positive  ${}^2J_{CH}$  has also been noted in various pyridines.<sup>29,46</sup>

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## Conclusions

From theoretical considerations, one would expect that the Fermi contact term would be dominant and that orbital and dipolar contributions would be small for light nuclei.<sup>59</sup> Thus, one might expect observations with proton-proton couplings would find analogy with carbon-proton and carbon-carbon couplings. The amount of carbon-proton and carbon-carbon data that is available does in fact show numerous parallels, and the similarity between  $J_{\text{HH}}$  values and  $J_{\text{CH}}$  and  $J_{\text{CC}}$  values is sufficiently clear to suggest that the use of  $J_{\text{HH}}$  values may be increasingly im-

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portant to help establish correlations between  $J_{\text{CH}}$  and  $J_{\text{CC}}$  values and molecular structure.

**Note Added in Proof.** Some recent high-resolution work with furan<sup>60</sup> indicates some proton-carbon coupling assignments in five-membered heteroaromatic compounds should be reversed (see ref 33).

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# Resonance Raman Spectroscopy: a New Structure Probe for Biological Chromophores

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The central challenge of modern biochemistry is to elucidate biological function in terms of molecular structure. A considerable catalog of information on biomolecular architecture is already available from X-ray diffraction studies on crystalline or partially ordered materials. Numerous spectroscopic methods have been introduced to monitor structural features and detect changes which accompany biological function. Among them, vibrational spectroscopy offers high promise, since vibrational frequencies, available from Raman or infrared spectra, are sensitive to geometric and bonding arrangements of localized groups of atoms in a molecule.

The study of vibrational spectra has played a leading role in structural investigations of small molecules, and a substantial body of systematic knowledge has been formed.<sup>1</sup> Application to biological materials is beset with difficulties, however. Water, the ubiquitous biological medium, is an excellent absorber of infrared radiation, leaving only restricted "windows" for infrared spectroscopy. These can be somewhat extended by using D<sub>2</sub>O as well as H<sub>2</sub>O solutions.<sup>2</sup> Raman spectroscopy does not suffer as much from this limitation, since water is a poor Raman scatterer. Lasers now provide the high light power density required for Raman spectroscopy and allow examina-

tion of minute quantities (microliters) of material. The chief obstacle encountered with biological materials, however, is their complexity. A molecule containing  $N$  atoms has  $3N - 6$  ( $3N - 5$  for linear molecules) normal modes of vibration. The macromolecules of biology contain thousands of atoms and have far too many vibrational frequencies to be resolved, let alone assigned in a normal Raman or infrared spectrum. Fortunately these frequencies tend to group themselves into more-or-less discrete bands, which can be identified with certain classes of structure. These bands can then be used to monitor changes in gross conformation, and this technique has been fruitfully applied to proteins, nucleic acids, and lipids.<sup>3,4</sup>

If one is interested in structural features of a specific site of biological function within a macromolecule, then the myriad vibrations of the whole molecule are a serious interference. What is needed is a selective technique that samples only the vibrations of the atoms in the vicinity of the site. This can be provided by *resonance* Raman spectroscopy, if the atoms in the site give rise to an isolated electronic absorption band. A normal Raman spectrum is obtained by illumination of the sample in a transparent region of its spectrum. In resonance Raman spectroscopy, the illumination is within an absorption band. Most of the Raman bands are attenuated by the ab-

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