

# APPLICATIONS OF DOUBLE RESONANCE AND FOURIER TRANSFORM NMR SPECTROSCOPY IN ORGANIC CHEMISTRY

W. VON PHILIPSBORN

*Institute of Organic Chemistry, University of Zurich, Switzerland*

## ABSTRACT

The non-routine use of homonuclear and heteronuclear double resonance in continuous wave and pulse-Fourier-transform proton and carbon spectroscopy is illustrated with examples from organic and organometallic chemistry.  $^1\text{H}$ - $\{^1\text{H}\}$  INDOR spectroscopy and relative signs of spin coupling constants are shown to yield stereochemical information (relative configurations) not obtainable by other n.m.r. techniques. The scope of FT  $^{13}\text{C}$  spectroscopy in structural chemistry is outlined with particular emphasis on proton-non-decoupled single-resonance spectra, and C, H coupling constants and their structural significance. Furthermore, chemical exchange processes (prototropic rearrangements) not amenable to proton n.m.r. are investigated by variable-temperature carbon spectroscopy.

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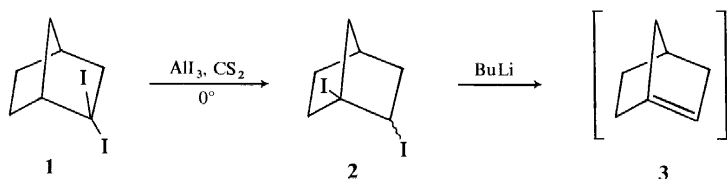
The first spectacular applications of n.m.r. spectroscopy in structural organic chemistry appeared in the literature between 1956 and 1958. For example, the structures of Feist's acid<sup>1</sup> and photosantonic acid<sup>2</sup> were firmly established by means of proton spectroscopy. Since then a vast material of experimental data on proton n.m.r. has been accumulated and many structural problems may now be solved in a routine fashion. The methods employed to evaluate n.m.r. spectra and to interpret their spectral parameters have not changed much during the last decade. What have changed dramatically, however, are the experimental or instrumental techniques used to obtain and analyse complex n.m.r. spectra. Homonuclear and heteronuclear double-resonance techniques and the combination of pulsed n.m.r. and Fourier transform methods are certainly the most significant developments to have occurred in the last few years. These methods are mainly responsible for the enormous increase in application and scope of high-resolution n.m.r. studies in structural chemistry. It is of particular importance for *organic* chemistry that the combination of pulse-FT techniques and double resonance has opened the new field of  $^{13}\text{C}$  spectroscopy. There can be little doubt that other non-abundant nuclei will become accessible in the future.

In this account of recent developments in the title field no attempt has been made to be comprehensive. Since several reviews on double-resonance<sup>3</sup> and Fourier transform spectroscopy<sup>4</sup> have recently been published, emphasis will lie on the chemical side. In the first part the non-routine use of less well-known

double-resonance methods in proton n.m.r. of complex organic molecules will be illustrated. The second part is mainly devoted to high-resolution  $^{13}\text{C}$  spectroscopy as applied to problems in structural chemistry.

Double irradiation with very low  $\text{H}_2$  power levels  $[(\gamma/2\pi)\text{H}_2] < 0.5 \text{ Hz}$  does not change the energy of the spin states but does influence their relative populations. As a result of such double-resonance experiments, intensity changes in the observed nuclear transitions are recorded. This generalized nuclear Overhauser effect (GOE) may be observed in the  $\omega_1$ - or  $\omega_2$ -sweep mode. Kaiser<sup>5</sup> and Kowalewski<sup>6</sup> have shown that INDOR spectra<sup>7</sup> obtained by sweeping the perturbing field  $\text{H}_2(\omega_2)$  are very useful in the analysis of multispin systems, yielding the relative signs of scalar coupling constants together with the appropriate energy level diagrams.

The INDOR method, however, has found very little use in structural studies, although it is ideally suited to the detection and precise frequency determination of hidden lines. As an example, the determination of the stereochemistry of 1,2-diiodonorbornane (**2**) will be discussed.



Compound **2** is formed<sup>8</sup> from the geminal diiodo compound **1** in a kinetically controlled reaction at  $0^\circ\text{C}$ , and therefore the *cis*-isomer may result in spite of the size of the iodine substituents. The configuration of the iodine atoms is of particular interest since halogen elimination by butyllithium leads to the strained norbornene-1 (**3**), which is a forbidden structure according to Bredt's rule but which could be trapped by a Diels–Alder addition to furan. The proton spectrum of **2** is illustrated in Figure 1. The eight H(1) transitions indicate that this proton is coupled to three other protons, those being the vicinal protons H(2) and H(3), and either H(4) or H(8). To derive the stereochemistry at C(2), since a planar zig-zag pathway is required for  $^4J_{\text{HH}} = 2.0 \text{ Hz}$ , it is necessary to decide whether H(1) is coupled to H(4) or H(8). In the first case ( $J_{1,4}$ ) the iodine atom will be *exo*, which makes the two iodines *cis* to each other. In the second case ( $J_{1,8}$ ) the iodine will be *endo* and therefore both iodines will be *trans*. When the well-resolved lines of H(1) are monitored while the perturbing field is swept through the rest of the spectrum, resonance lines of H(2), H(3) and the unknown proton are located which allow determination of the chemical shifts and coupling constants of these neighbours (Figure 1). The next important step is to monitor the INDOR frequencies in consecutive INDOR experiments<sup>9</sup>, in order to determine the transition frequencies of the nearest neighbours of H(2), H(3) and of the unknown proton spin-coupled to H(1). Figure 1 illustrates the detection of the geminal neighbour of the unknown proton. This new proton exhibits a doublet ( $^2J = -10.7 \text{ Hz}$ ) with triplet fine structure ( $^4J = 2.6\text{--}2.7 \text{ Hz}$ ). The rather small geminal coupling constant

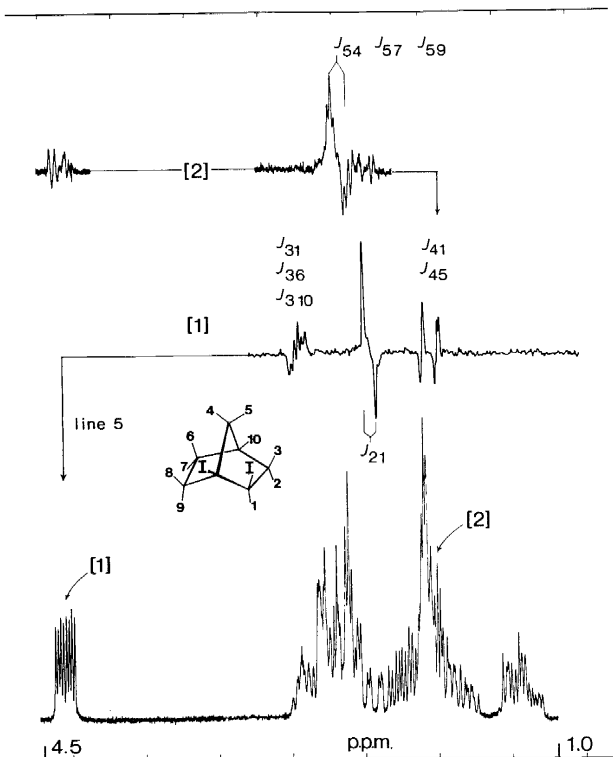
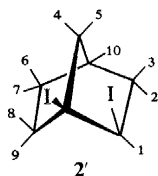


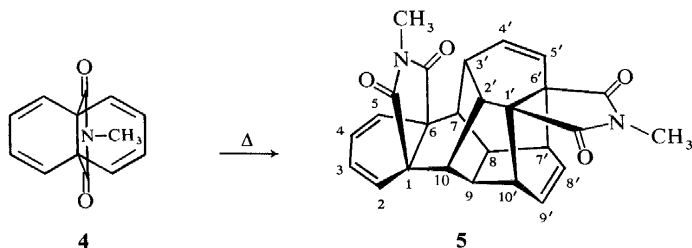
Figure 1. Proton spectrum (100 MHz) of *cis*-diiodonornbornane (2) and INDOR spectra; primary experiment [1] and consecutive experiment [2]

indicates<sup>10</sup> that the unknown proton is indeed H(4) and that its neighbour is H(5) on the methylene bridge, this being spin-coupled to the *endo*-protons H(7) and H(9). Further confirmation for this crucial assignment comes from the determination of all four geminal coupling constants  $J_{23}$ ,  $J_{89}$ ,  $J_{67}$  and  $J_{45}$  which result from a complete INDOR analysis of the norbornane system. Table 1 lists the chemical shifts of the 10 protons and their geminal, vicinal and long-range coupling constants. The  $^2J$  coupling constants of methylene protons in the six-membered ring are  $-14.2$ ,  $-13.6$  and  $-11.7$  Hz, and they reflect the position of the  $\text{CH}_2$  group with respect to the electronegative iodine substituents, because the latter increase  $^2J_{\text{HH}}$  of the methylene groups in the  $\alpha$ -position. The resonances of the methylene protons on the bridge are thus correctly assigned. The fact that both H(5) and H(4) exhibit two  $^4J$  interactions (2.0–2.8 Hz) with H(7) and H(9) and with H(1) and H(2), respectively, clearly establishes the *exo*-position of the iodine substituent and, hence, the sterically unfavourable *cis*-configuration of the compound. If H(1) were *exo*, a long-range coupling to H(8) analogous to  $J_{36}$  (2.8 Hz) would be expected.

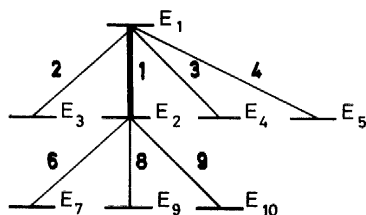
Table 1. Proton chemical shifts and coupling constants of *cis*-diiodonorbornane (2) (CDCl<sub>3</sub>)

Chemical shifts (p.p.m.)		Coupling constants (Hz)							
H(1)	4.35 ± 0.01	<sup>2</sup> J <sub>2,3</sub>	-14.2	<sup>2</sup> J <sub>8,9</sub>	-13.6	<sup>2</sup> J <sub>6,7</sub>	-11.7	<sup>2</sup> J <sub>4,5</sub>	-10.7
(3)	2.68 ± 0.05	<sup>3</sup> J <sub>6,8</sub> <sup>c</sup>	8.9	<sup>3</sup> J <sub>5,9</sub>	8.8	<sup>3</sup> J <sub>1,2</sub> <sup>c</sup>	7.7		
(8)	~2.6								
(5)	~2.5	<sup>3</sup> J <sub>1,3</sub> <sup>t</sup>	3.8	<sup>3</sup> J <sub>6,9</sub> <sup>t</sup>	4.2	<sup>3</sup> J <sub>7,8</sub> <sup>t</sup>	4.5		
(2)	2.31 ± 0.05								
(9)	2.01 ± 0.05	<sup>3</sup> J <sub>5,10</sub>	1.3	<sup>3</sup> J <sub>3,10</sub>	5.2				
(10)	~1.9	<sup>4</sup> J <sub>1,4</sub>	2.0	<sup>4</sup> J <sub>2,4</sub>	2.2				
(4)	~1.85								
(6)	1.68 ± 0.05	<sup>4</sup> J <sub>5,7</sub>	2.7	<sup>4</sup> J <sub>5,9</sub>	2.6				
(7)	1.25 ± 0.02	<sup>4</sup> J <sub>3,6</sub>	2.8						

Application of the INDOR method is not confined to first-order spectra if it is combined with computer calculations which allow identification of connected transitions. We were able to demonstrate this procedure in the case of a four-spin ABCD system with 56 transitions, from which only six lines were clearly resolved in the proton spectrum<sup>9</sup>. The four protons belong to a *cis*-diene system which is part of a complex cage structure (5) formed by the thermal dimerization of 11,13-dioxo-12-methyl-12-aza[4.4.3]propellane (4).



From six monitored lines of the diene system frequencies of 32 INDOR responses were obtained from primary and consecutive experiments. By use of a trial set of shift and coupling parameters, line frequencies were calculated and compared with the experimental INDOR frequencies. This comparison was made on the basis of two criteria, frequency and sign of the INDOR signal, since relative to a given monitored transition progressive transitions must correspond to positive INDOR signals and regressive transitions to negative signals, as is shown in Figure 2. In this way each monitored line leads



transition number	$\nu_{\text{INDOR}}$	$\nu_{\text{calc}}^*$
2	↓608.0	↓609.1
3	↓594.1	↓594.4
6	↑592.3	↑592.0
4	↓568.3	↓568.5
8	↑560.1	↑560.5
9	↑555.1	↑555.9

\* calculated from trial set of parameters

Figure 2. Assignment of INDOR frequencies to calculated transitions by means of partial energy level diagrams; ↓ denotes negative INDOR intensities from regressive transitions (2, 3 and 4); ↑ denotes positive responses from progressive transitions (6, 8 and 9)

to a fragment of the energy level diagram from which the complete energy level scheme can finally be constructed. After the successful assignment of experimental lines and INDOR lines, the final shift and coupling parameters were obtained by iterative computation using the 32 line frequencies. The parameters (Table 2) establish the presence of a *cis*-diene fragment in the dimeric propellane 5.

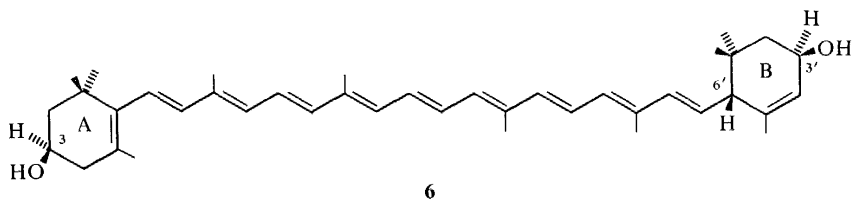
The limitations of the INDOR technique in structural studies result from a number of critical conditions. Firstly, some sharp well-resolved lines should

Table 2. Proton chemical shifts and coupling constants of the diene fragment in the dimeric propellane 5 (CDCl<sub>3</sub>)

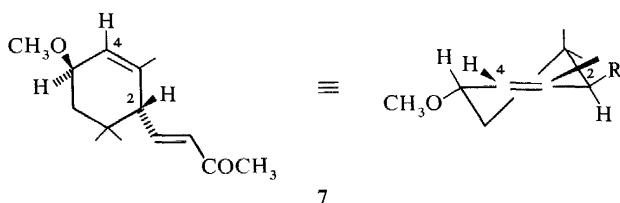
	Chemical shifts $\delta$ (p.p.m.)	Coupling constants (Hz)	
H <sub>A</sub>	5.904	$J_{AB}$	9.5
H <sub>B</sub>	5.991	$J_{CD}$	9.5
H <sub>C</sub>	6.103	$J_{BC}$	5.6
H <sub>D</sub>	5.634	$J_{AC}$	1.0
		$J_{BD}$	0.8
		$J_{AD}$	1.1

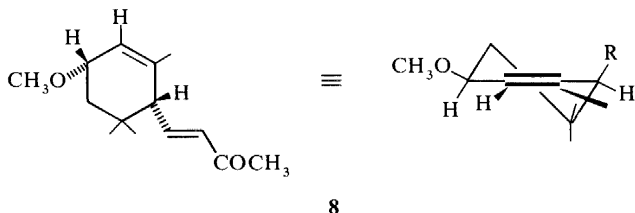
be available as primary monitored lines. Furthermore, the amplitudes of the  $H_1$  and  $H_2$  fields are critical, and for an optimum signal-to-noise ratio they require careful adjustment for each experiment. In particular, sufficient  $H_2$  power should be available from the swept oscillator. Finally, difficulties may arise with complex spin systems and computer methods must then be applied to derive the spectral parameters from the experimental frequencies. We have, however, applied the double-resonance method successfully in the structural analysis of carbohydrates, alkaloids, nucleosides and peptides. In the last case, NH signals can be used as monitored lines provided proton exchange is suppressed, as, for example, in dimethylsulphoxide solution.

Double-resonance experiments are often performed in order to determine the relative signs of the constants of indirect (scalar) spin coupling. Selective decoupling, spin tickling and the generalized nuclear Overhauser effect (for example, in the INDOR sweep mode) are the most common techniques used<sup>3</sup>. Although the relative (and absolute) signs of most types of H,H coupling are known today, so far very little use has been made of the considerable structural significance of this important parameter. Because of instrumental requirements and of several inherent difficulties associated with double-resonance experiments of this type, the relative signs of  $J_{HH}$  or  $J_{HX}$  are only considered when a structural problem cannot be solved by other means. As an example of this type, the stereochemistry of lutein was recently investigated in our laboratory in collaboration with Prof. C. H. Eugster. Lutein (= xanthophyll, **6**) is the most important hydroxylated  $\alpha$ -carotin in higher plants. The

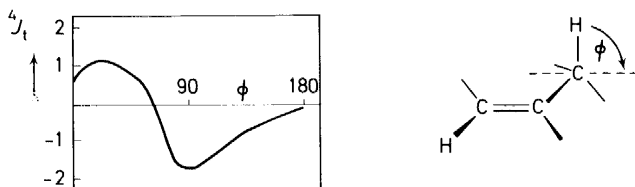


molecule contains three chiral centres, C(3), C(3') and C(6'). Whereas the R-configuration at C(3) and C(6') could be established by chemical correlations<sup>11</sup>, the absolute configuration at C(3') remained open. The problem was thus reduced to a determination of the *relative* (*cis* or *trans*) stereochemistry of the substituents at C(3') and C(6'). For this purpose the degradation product (+)-3-methoxy- $\alpha$ -ionone (**7**) containing only ring B was examined by high-resolution proton n.m.r. at 100 MHz<sup>12</sup>. The unnatural diastereoisomer **8** with





the opposite configuration at C(3') was also available. A conformational analysis of the two isomers shows that the preferred conformations of **7** and **8** in solution should correspond to the half-chair conformations illustrated. Whereas the vicinal coupling constant  $J_{4,5}$  is very similar in both isomers, and, hence, not a suitable parameter, the allylic coupling constant  $J_{2,4}$  should exhibit a significant difference in both magnitude and sign. The sign of  ${}^4J_t$  in allylic systems is known to depend upon  $\phi$ , the angle between the orientation of the C—H bond and the plane of the double bond, as shown in *Figure 3*. An inspection of Dreiding models reveals that for the *trans*-isomer  $\phi = 80^\circ$  and



*Figure 3.* Angular dependence of the sign of the allylic coupling constant  ${}^4J_{HH}^t$

for the *cis*-isomer  $\phi = 40^\circ$ . The angular dependence of the magnitude and sign of  ${}^4J_t$  is based on the predominance of the  $\sigma$  coupling mechanism for  $0^\circ < \phi < 60^\circ$  and that of the  $\pi$ -mechanism for  $60^\circ < \phi < 180^\circ$ . The curve in *Figure 3* was compiled from experimental data<sup>13</sup> and allows one to predict, for the *trans*-isomer, a rather large and *negative*  ${}^4J_t$ , whereas the *cis*-isomer should show a smaller and *positive* value. The magnitude of the allylic coupling constant was determined from a double-resonance spectrum (decoupling from the methyl protons) of the three-spin system H(2), H(4), H(5), whereas the sign was obtained from spin tickling experiments in the double-resonance spectrum of the three-spin system (i.e. from a triple-resonance experiment).  $J_{2,4} = -1.5$  Hz for the natural diastereoisomer is in excellent agreement in both magnitude and sign with the *trans* configuration **7**. Hence, the absolute configuration of C(3') in (+)-lutein is R and the total absolute configuration is 3R, 3'R, 6'R. The analysis of the spectrum of the unnatural diastereoisomer yielded  $|J_{2,4}| = 0.7$  Hz, but the sign could not be determined for experimental reasons. However, the magnitude of  $J_{2,4}$  is in good agreement with the model angle  $\phi = 40^\circ$ . The R-configuration at C(3') in lutein is at variance with a

proposal given by Weedon *et al.*<sup>14</sup> on the basis of biogenetic arguments, but a very recent chemical correlation by Jensen<sup>15</sup> fully confirms our conclusion.

With the advent of pulsed n.m.r. spectroscopy followed by Fourier transformation to obtain high-resolution spectra in the frequency domain<sup>16</sup>, the sensitivity of the n.m.r. experiment has increased by several orders of magnitude. More dilute solutions are now accessible for structural studies by proton spectroscopy. This also implies to a certain extent that larger molecular structures may be investigated which cannot be handled in the concentrations required for continuous wave (CW) experiments. In natural product chemistry, sample quantities are very often limited, particularly when a final product of a multi-step synthesis has to be identified and characterized. A rather spectacular example of this type is provided by the 100 MHz proton spectrum of the final product in the total synthesis of vitamin B<sub>12</sub>, cobyrinic acid hexamethylester-f-nitrile (**9**), which was kindly supplied by Prof. A. Eschenmoser (ETH, Zurich). 1.8 mg of the crystalline metal complex C<sub>53</sub>H<sub>70</sub>N<sub>7</sub>O<sub>12</sub>Co was dissolved in 2 ml of hexadeuterobenzene to yield a  $8 \times 10^{-4}$  M solution. The spectrum (Figure 4) obtained in 17 min total

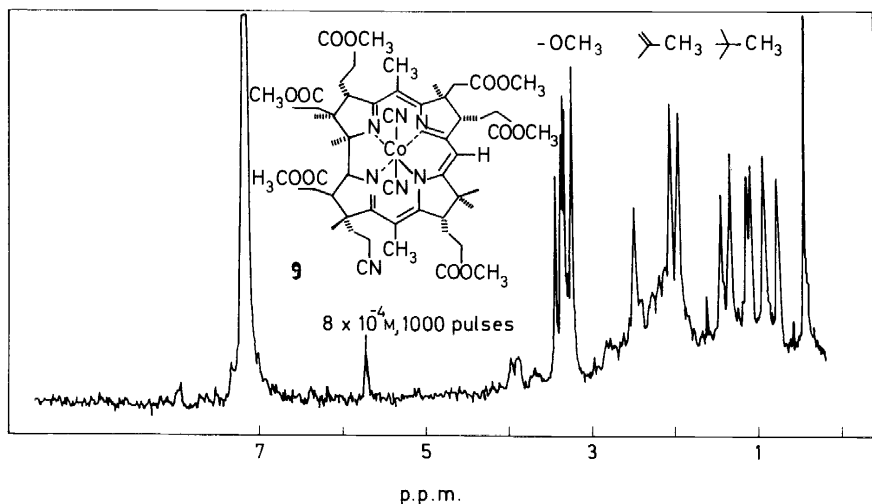


Figure 4. Proton FT spectrum (100 MHz) of cobyrinic acid hexamethylester-f-nitrile (**9**);  $8 \times 10^{-4}$  molar solution in hexadeuterobenzene; 1000 pulses; acquisition time 1.0 s

acquisition time clearly reveals the presence of a single vinyl proton resonance with a S/N ratio of 10:1. Furthermore, the six non-equivalent tertiary methyl groups and the six methoxy groups are well resolved. The spectrum proved identical with that of an authentic specimen of **9**.

The major step forward towards a comprehensive n.m.r. spectroscopy of organic structures, however, is the combination of pulse spectroscopy and heteronuclear double resonance in <sup>13</sup>C magnetic resonance. Carbon, contrary to the peripheral hydrogen, is the building element of the skeleton of organic structures. <sup>13</sup>C offers a wide range of chemical shifts (~600 p.p.m. for



diamagnetic molecules) and sharp resonance lines, thus allowing high-resolution spectra to be obtained. The low natural abundance of the isotope (1.1 per cent) is responsible for the *de facto* absence of C-C spin coupling effects and, hence, under conditions of proton decoupling a single resonance line is obtained for each carbon atom. The pulse-FT method enables us to obtain such spectra on 0.1–0.3 M solutions within a reasonable time.

An excellent example for the potential of  $^{13}\text{C}$  n.m.r. for structural studies are the carbonyl resonances, which extend over a range of about 70 p.p.m., i.e. 1750 Hz at 25 MHz (Figure 5). Although conjugation effects tend to shift the

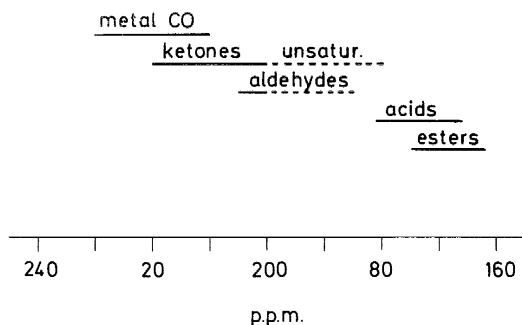
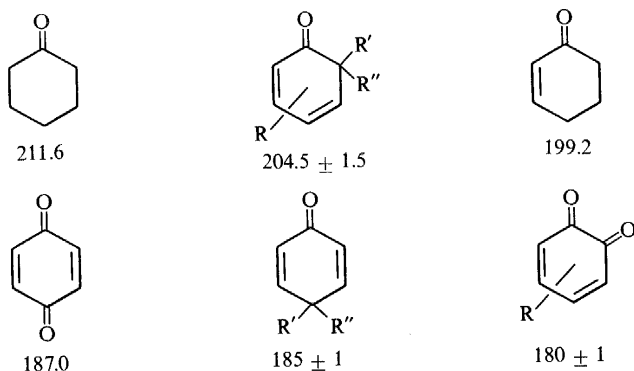


Figure 5.  $^{13}\text{C}$  chemical shifts (p.p.m.) of organic carbonyl compounds

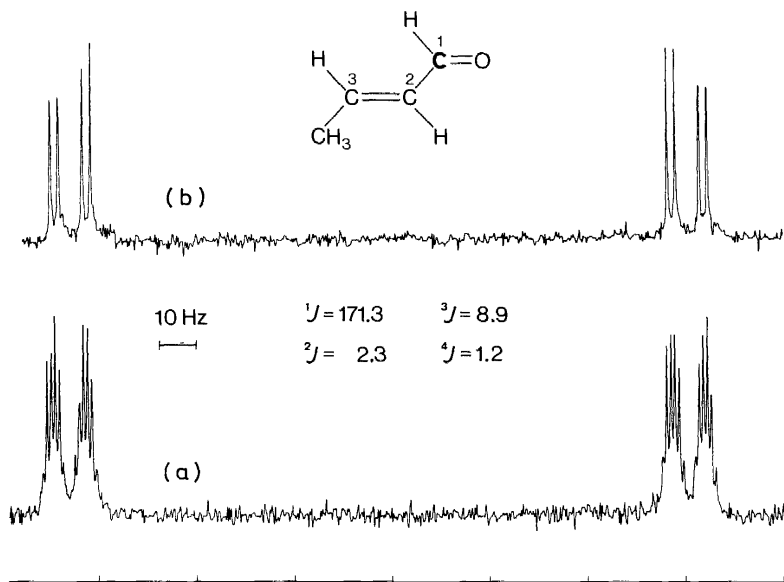
carbonyl resonance to lower frequencies, these effects are neither easily understood nor easily explained, as is shown by the chemical shifts of six-membered ketones<sup>17</sup>. Here the  $\alpha,\beta,\gamma,\delta$ -unsaturated ketone exhibits a carbonyl shift which lies between the saturated and  $\alpha,\beta$ -unsaturated ketone. The same



behaviour is shown by open-chain unsaturated ketones<sup>18</sup>. In the cyclic series the ketone with the lowest  $\pi \rightarrow \pi^*$  transition energy exhibits the lowest  $^{13}\text{C}$  carbonyl frequency. On the other hand, it has previously been shown<sup>19</sup> that in the cycloalkanone series the ketone with the lowest  $n \rightarrow \pi^*$  transition energy shows the highest carbonyl frequency, an effect which has been

attributed to the paramagnetic chemical shift term<sup>20</sup>. The above data clearly demonstrate the high diagnostic value of <sup>13</sup>C carbonyl shifts, especially in cases where i.r. and u.v. data cannot be decisive.

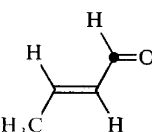
The potential of <sup>13</sup>C carbonyl data in structural studies becomes even clearer when proton-non-decoupled carbon spectra are considered. Such single-resonance carbon spectra exhibit a wealth of additional information in the form of <sup>13</sup>C, <sup>1</sup>H coupling constants, as shown in *Figure 6*, illustrating the spectra of the carbonyl group in *trans*-crotonaldehyde.



*Figure 6.* <sup>13</sup>C FT spectra of the carbonyl carbon of *trans*-crotonaldehyde (CD<sub>3</sub>OD); (a) single-resonance spectrum. (b) double-resonance spectrum with selective irradiation of the methyl protons. Acquisition time 4.0 s; 4 data points/Hz after Fourier transformation

The single-resonance spectrum (*Figure 6a*) can be analysed as the X-part of an A<sub>3</sub>KMX spin system according to first-order splitting rules. The assignment of the long-range C,H coupling constants (8.9 and 2.3 Hz), however, is not a trivial problem and may be solved by selective <sup>1</sup>H-irradiation at the resonance frequencies of H-C(2) and H-C(3) or by means of an off-resonance decoupling experiment. Irradiation at the methyl proton frequency simplifies the carbonyl spectrum to an eight-line pattern (*Figure 6b*) and yields reduced coupling constants of C(1) with the three remaining protons. Since the offset frequencies are in the order H-C(1) ≫ H-C(3) > H-C(2), <sup>2</sup>J<sub>CH</sub> should be reduced to a larger extent than <sup>3</sup>J<sub>CH</sub> and <sup>1</sup>J<sub>CH</sub>. The observed reduced J<sub>CH</sub> values (*Table 3*) constitute an unequivocal proof for the given assignment, namely that <sup>3</sup>J<sub>CH</sub> = 8.9 and <sup>2</sup>J<sub>CH</sub> = 2.3 Hz. Therefore the off-resonance irradiation technique normally used for the assignment of chemical shifts in

Table 3.  $^{13}\text{C}, ^1\text{H}$  coupling constants (Hz) of the carbonyl carbon of *trans*-crotonaldehyde ( $\text{CD}_3\text{OD}$ ) obtained from single- and double-resonance spectra (reduced coupling constants)

Single-resonance non-decoupled			Double-resonance $\text{CH}_3$ -irradiated	
$^1J$	171.3		165.5	(97%)
$^2J$	2.3	2.0	(87%)	
$^3J$	8.9	8.2	(92%)	
$^4J$	1.2	—		

$^{13}\text{C}$  resonance<sup>21</sup> may also be applied to assign C,H coupling constants, provided these data are measured with the necessary precision.

Non-decoupled  $^{13}\text{C}$  spectra of larger molecules may be very complex and are often characterized by rather poor signal-to-noise ratios. Pulse-FT methods are therefore essential to obtain such spectra in a reasonable time. Generally, at least 10 times as many pulses have to be applied compared with noise-decoupled spectra because of the absence of the NOE and the high multiplicity of the  $^{13}\text{C}$  resonances. The Overhauser effect can be partly retained in non-decoupled spectra if the decoupler output is gated as illustrated in Figure 7. The decoupler power is applied during the pulse delay

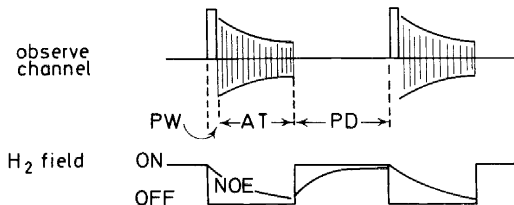
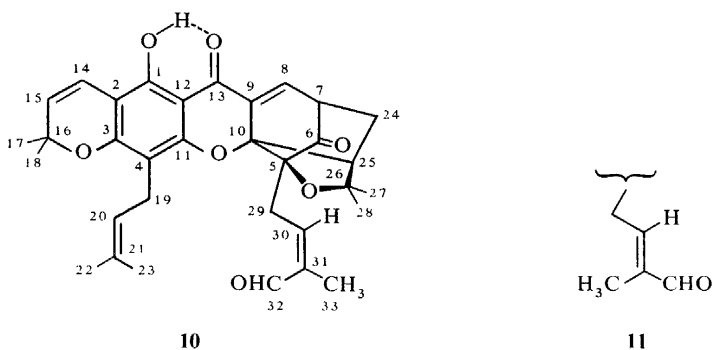


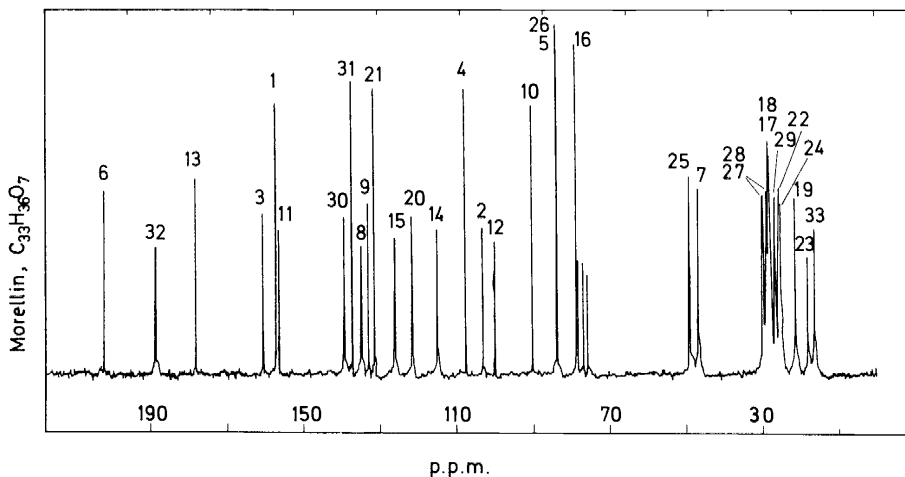
Figure 7. Schematic representation of the gated decoupler and its application in pulse sequences

time but switched off during acquisition of data. Since the decoupling effect only depends on the effective field  $H_0 + H_2$ , which breaks down instantaneously, while the NOE decays with the much longer time constant  $T_1$ , part of the Overhauser effect can be saved. The signal-to-noise improvement depends on  $T_1$  and varies from one carbon atom to another.

To obtain maximum information from non-decoupled spectra, expanded spectra with a high number of data points have to be recorded from certain spectral regions only. This is exemplified in the determination of the stereochemistry of trisubstituted double bonds by means of vicinal C,H coupling constants. Morellin, an antibiotic isolated from *Garcinia morella*, had been studied previously by chemical, spectroscopic and x-ray methods with the result that structure **10** was assigned to the molecule<sup>22</sup>.



Nevertheless, some doubts remain concerning the stereochemistry of the aldehyde side chain, particularly since morellin isomerizes to isomorellin (**11**) by base catalysis. The stereochemistry of the trisubstituted double bond is difficult to ascertain by proton n.m.r. from chemical shift arguments only<sup>2,3</sup>. The aldehyde carbon, however, should exhibit significantly different *trans* and *cis* vicinal coupling to the vinyl proton in morellin and isomorellin, respectively. The proton-noise-decoupled <sup>13</sup>C spectrum of morellin is illustrated in *Figure 8* together with an assignment of the 33 resonance lines.



*Figure 8.* <sup>13</sup>C FT spectrum of morellin (**10**) in CDCl<sub>3</sub>, chemical shifts relative to TMS; the numbering system is taken from ref. 25

Assignments are based upon off-resonance decoupling experiments, a partial analysis of the non-decoupled spectrum, selective decoupling experiments and spectral comparison with isomorellin. The long-range coupling constants <sup>3</sup>J<sub>CH</sub> of the aldehyde carbon were obtained from a selective decoupling experiment in which H<sub>2</sub>(ω<sub>2</sub>) was centred at or near the frequency of the methyl

group. The  $H_2$  power level and the offset frequency  $\nu_H - \nu_{CH_3}$  were kept constant for morellin and isomorellin to assure the same reduction of  ${}^3J_{CH}^{trans}$  and  ${}^3J_{CH}^{cis}$  †. The results obtained are summarized in *Table 4* together with the proton n.m.r. data. The first argument for the configuration of morellin may be based on the chemical shifts of the aldehyde carbon and the

*Table 4.*  ${}^{13}C$  and  ${}^1H$  chemical shifts and C,H coupling constants of the aldehyde side chain in morellin (**10**), isomorellin (**11**) and morellin (**12**)

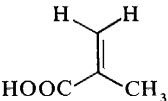
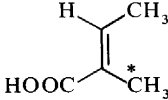
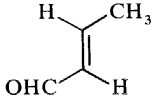
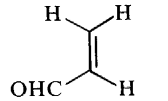
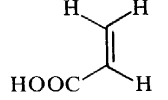
	Morellin ( <b>10</b> )	Moreollin ( <b>12</b> )	Isomorellin ( <b>11</b> )
$\delta_{CHO}$	189.1 p.p.m.	191.0 p.p.m.	194.1 p.p.m.
$\delta_{CHO}$	9.55	10.16	9.21
$\delta_{CH_3}$	16.0	16.1	8.1
$\delta_H$	6.02	6.87	6.36
${}^3J_{CHO, H}^{trans}$	9.8 Hz (red.)	9.9 Hz (red.)	—
${}^3J_{CHO, H}^{cis}$	—	—	7.8 Hz (red.)
${}^3J_{CH_1, H}^{trans}$	—	—	6.5
${}^3J_{CH_3, H}^{cis}$	6.1	—	—

methyl carbon. Since it is well known that *cis*-substituents on an olefinic double bond lead to a shielding effect<sup>24</sup> (very probably via a van der Waals interaction of the hydrogens and subsequent polarization of the C—H bonds), the lower  $\delta$ -value of the CHO carbon (189.1 p.p.m.) must be assigned to the *cis*-configuration of CHO and  $CH_2$  groups (*Z* isomer) and the higher value (194.1 p.p.m.) to the *trans*- (or *E*) isomer. The reverse should apply for the  $\delta_{CH_3}$  values, and this is exactly what is observed, i.e. the methyl carbon in morellin (16.0 p.p.m.) is deshielded with respect to isomorellin (8.1 p.p.m.) This assignment is fully supported by the magnitudes of the vicinal C,H coupling constants of the aldehyde carbon,  ${}^3J_{CH}^{trans} = 9.8$  Hz (morellin) and  ${}^3J_{CH_3}^{cis} = 7.8$  Hz (isomorellin). Surprisingly, the corresponding coupling constants of the methyl carbon are only very slightly larger for the *trans*-interaction (6.5 Hz) than for the *cis*-interaction (6.1 Hz). For this reason we have investigated a number of model systems by the same procedure as outlined above and the C,H coupling constants are given in *Table 5*. It can be seen that whereas in monosubstituted and disubstituted ethylenes  ${}^3J_{CH}^{trans}$  is always much larger than  ${}^3J_{CH}^{cis}$ , the *trans*-interaction is considerably reduced in the trisubstituted double bond for the carbon atom having a *cis*-neighbour, as, for example, in tiglic acid and isomorellin.

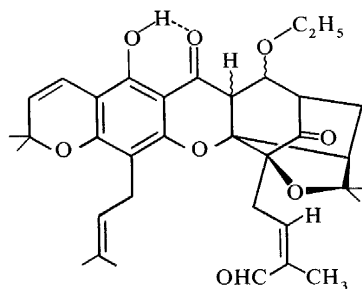
Since it is now firmly established that morellin corresponds to structure **10** and isomorellin to **11** we have been able to determine the stereochemistry of moreollin (**12**). Structure **12** results from an addition of the elements of ethanol to the double bond in the bicyclooctene ring. A compound of this type

† At the decoupling power used the vicinal C,H coupling constants are reduced by about 10 per cent (see *Table 3*).

Table 5. Vicinal  $^{13}\text{C}, ^1\text{H}$  coupling constants in  $\alpha,\beta$ -unsaturated aldehydes and acids

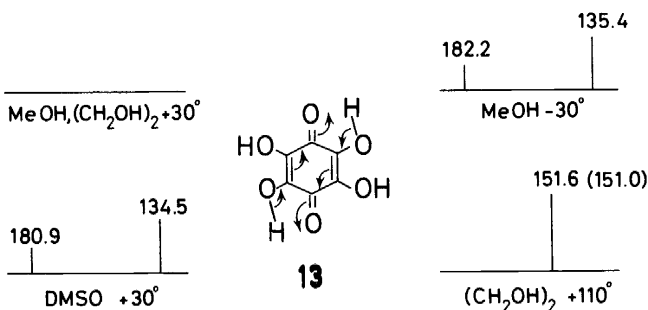
	$^3 J_{\text{CH}_3, \text{H}}^{\text{trans}} = 10.2$ $^3 J_{\text{CH}_3, \text{H}}^{\text{cis}} = 6.0$	$^3 J_{\text{COOH}, \text{H}}^{\text{trans}} = 12.4$ (red.) $^3 J_{\text{COOH}, \text{H}}^{\text{cis}} = 6.1$ (red.)
	$^3 J_{*\text{CH}_3, \text{H}}^{\text{trans}} = 7.7$	$^3 J_{\text{COOH}, \text{H}}^{\text{cis}} = 7.3$ (red.)
	$^3 J_{\text{CH}_3, \text{H}}^{\text{cis}} = 6.0$	$^3 J_{\text{CHO}, \text{H}}^{\text{cis}} = 8.9$
	$^3 J_{\text{CHO}, \text{H}}^{\text{trans}} = 15.9$	$^3 J_{\text{CHO}, \text{H}}^{\text{cis}} = 10.1$
	$^3 J_{\text{COOH}, \text{H}}^{\text{trans}} = 14.1$	$^3 J_{\text{COOH}, \text{H}}^{\text{cis}} = 7.6$

has previously been assigned<sup>25</sup> the ethoxydihydroisomorellin structure but a reinvestigation<sup>26</sup> showed that the primary ethanol adduct belongs to the morellin series. This is now confirmed by the magnitude of  $^3 J_{\text{CH}}$  of the aldehyde carbon (9.9 Hz), which corresponds to the value found for morellin (9.8 Hz) but not for isomorellin (7.8 Hz) (see Table 1). The use of vicinal C, H coupling constants is not only a valuable aid in stereochemical studies of olefins but also helps in the assignment of quaternary carbon atoms of aromatic and heteroaromatic compounds, such as pyrimidines and pteridines<sup>27</sup>.



An entirely different field for chemical applications of Fourier transform spectroscopy is provided by *dynamic* carbon resonance studies at variable temperature. The rather large  $^{13}\text{C}$  chemical shifts extend the range of rate constants which may be obtained from n.m.r. data by one or two orders of magnitude towards faster reactions. Conversely, chemical exchange reactions which require very low temperatures for proton n.m.r. studies may be studied in a more convenient temperature range. At lower temperature the sensitivity of the  $^{13}\text{C}$  resonance very often increases, since the shorter spin-lattice relaxation times reduce saturation effects in the pulse experiment. Furthermore, the low natural abundance of the  $^{13}\text{C}$  isotope and the use of proton-noise decoupling yields very simple spectra and makes any deuteration and similar experiments superfluous. It should be mentioned, however, that large chemical shifts may lead to difficulties in studying coalescence phenomena, and quite frequently no  $^{13}\text{C}$  absorption at all is observed in that temperature range. For this reason we have been able to detect an interesting prototropic rearrangement in hydroxy-*para*-benzoquinones.

The carbon spectra of 2,3,5,6-tetrahydroxy-*p*-benzoquinone (**13**) are illustrated in *Figure 9*. With methanol and ethylene glycol as solvents, no



*Figure 9.* Schematic  $^{13}\text{C}$  spectra of 2,3,5,6-tetrahydroxy-*para*-benzoquinone (**13**) at variable temperature and in different solvents

resonance is detectable at room temperature, whereas in methanolic solution at  $-30^\circ$  or in dimethylsulphoxide at  $+30^\circ$  two resonances with a relative intensity of 1:2 are observed. At  $+110^\circ$  in ethylene glycol a single sharp resonance line appears at the centre of gravity of the two resonances. The exchange phenomenon obviously involves a proton transfer, since in dimethylsulphoxide the reaction is slowed down because of hydrogen bond formation between substrate and solvent. There are several possible mechanisms for this process, since the substrate is a rather strong acid: (a) an *intermolecular* proton transfer from the OH group to the carbonyl oxygen, possibly via an anionic species and involving solvent protons; (b) an *intermolecular* [1,5]-proton shift corresponding to a *para*-quinone-*ortho*-quinone tautomerism; and (c) an *intramolecular*, concerted [1,4]- $\text{H}^+$  shift as indicated in *Figure 9*. The facts that 2,5-dihydroxy-*para*-quinone (**14**) shows an analogous exchange behaviour but that 2-hydroxy-*para*-quinone (**15**) is non-dynamic in the  $^{13}\text{C}$

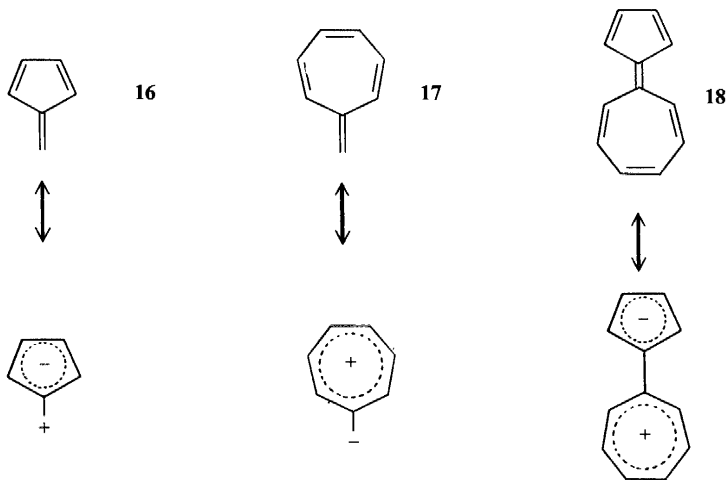
Table 6.  $^{13}\text{C}$  chemical shifts in hydroxybenzoquinones

	$\rightleftharpoons$ <b>14</b>		DMF, 30°	$\delta_c$ [p.p.m.]	172.2 C(1,5; 2,4) 105.6 C(3; 6)
	$\longleftrightarrow$ <b>14a</b>		D <sub>2</sub> O/NaOD 30°		183.0 C(1; 2; 4; 5) 102.5 C(3; 6)
	$\rightleftharpoons$ <b>?</b>		Ac-D <sub>6</sub> , 30°		189.0 } C(1; 4) 184.4 } 157.7 } C(2) 139.1 } C(5; 6) 134.4 } 109.4 } C(3)

spectrum (Table 6), constitute convincing arguments for the concerted mechanism (c). In addition, a second (*ortho*-quinone) species is not detectable at low temperature in the  $^{13}\text{C}$  or  $^1\text{H}$  spectra and the dianion species **14a** shows a chemical shift for the C(1), C(2), C(4), C(5) carbon atoms considerably different from that of the acid **14**. These proton transfer reactions in hydroxyquinones cannot be studied by proton resonance, since the proton remains on equivalent sites and, hence, no change in the chemical shift can be expected. A quantitative line shape analysis of the  $^{13}\text{C}$  lines to obtain activation parameters is in progress. The exchange phenomenon described is of considerable relevance to the  $^{13}\text{C}$  studies of biogenetic pathways in natural products containing similar moieties. For example, in the course of such a study on the biosynthesis of helicobasidin it has been reported<sup>28</sup> that the  $^{13}\text{C}$  label introduced into the carbonyl carbon of the 2,5-dihydroxy-*p*-quinone moiety is randomized between positions 1 and 5.

The relative simplicity of proton-noise-decoupled carbon spectra is a considerable advantage in the detection and identification of thermally unstable molecules which otherwise yield rather complex proton spectra. We were able to demonstrate this in a recent study of the structures of pentafulvene (**16**), heptafulvene (**17**) and sesquifulvalene (**18**). These molecules have always attracted the interest of synthetic organic chemists, spectroscopists and quantum chemists because it was assumed<sup>29</sup> that a potential relation to the well-known  $(4n + 2)$   $\pi$ -electron rule (E. Hückel) might be essential for an understanding of their chemical and physical properties. One of the main





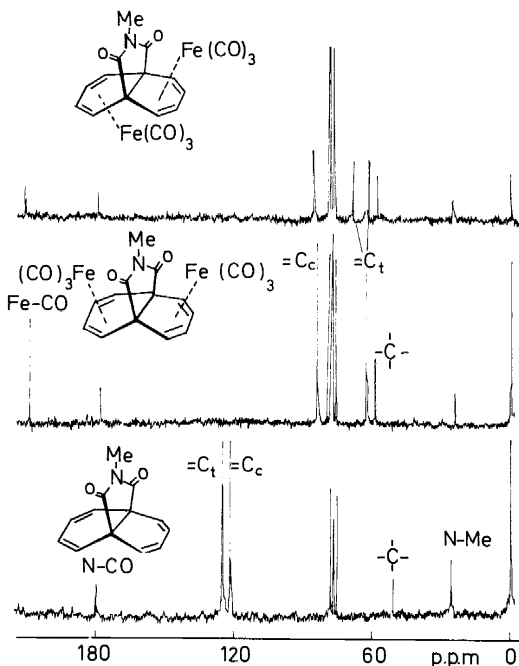
questions here is to what extent polar structures of potential aromatic character contribute to the electronic ground states.

Pentafulvene (**16**) has been known as a pure compound since 1964<sup>30</sup>, whereas neither heptafulvene (**17**) nor sesquifulvalene (**18**) had been prepared in quantity or purity until, very recently, Neuschwander and Schenk<sup>31</sup> succeeded in a general practical synthesis of compounds of this type. The

	exp.	calc.			
 <b>16</b>	134.3	129.7	 <b>17</b>	} 130.8 129.7	} 126.8 129.7
	124.9	130.8			
	152.6	151.8		138.3	130.8
	123.4	109.3		146.6	151.8
				111.9	109.3
 <b>19</b>	130.0	140.5	 <b>18</b>	} 129.9	} 118.6
	120.0				
	141.7			138.6	139.1
	160.2			146.5	139.1
		137.6	133.6		
			134.6		

Figure 10. Experimental (in  $\text{CDCl}_3$ ) and calculated<sup>34</sup>  $^{13}\text{C}$  chemical shifts in pentafulvene (**16**), heptafulvene (**17**), sesquifulvalene (**18**) and 6,6-hexamethylene-pentafulvene (**19**). For **18** and **19** only calculated shifts different from **16** and **17** are listed

proton spectrum of **16** is of the AA'BB'XX' type, and a complete analysis<sup>32</sup> has shown that in agreement with quantum chemical calculations<sup>33</sup> the  $\pi$ -bonds are largely localized. The  $^{13}\text{C}$  chemical shift data of the three fulvenes are illustrated in *Figure 10* and compared with calculated shifts obtained from additive shift increments for olefins (Savitsky and Namikawa<sup>34</sup>). The chemical shifts agree rather well for heptafulvene (**17**), thus supporting the purely olefinic character of this hydrocarbon, which is also reflected in its pronounced thermal instability at temperatures above  $-30^\circ$ . Pentafulvene, on the other hand, is considerably more stable and its carbon shift data do not agree with the calculated values. A particularly large deviation is found for the exocyclic carbon atom C(6) which is deshielded by 14 p.p.m. whereas C(2) and C(3) are shielded by 5–6 p.p.m. The same behaviour is shown by 6-substituted fulvenes, e.g. 6,6-hexamethylenefulvene (**19**), in which C(6) is deshielded by 20 p.p.m. These deshielding effects may be attributed to a partial positive charge at the terminal carbon. Based upon a value of 160 p.p.m./electron obtained from  $^{13}\text{C}$  shifts of non-benzenoid aromatic compounds<sup>35</sup>, the results on pentafulvene indicate that polar structures contribute about 10 per cent to the electronic ground state. The chemical shifts of the tertiary carbons in the five-membered ring of sesquifulvalene (**18**) agree very well with those of 6,6-hexamethylene-pentafulvene (**19**), which indicates that the  $\pi$ -polarization in **18** is not higher than in **19**†. The quaternary carbon



*Figure 11.*  $^{13}\text{C}$  FT spectra of 11,13-dioxo-12-methyl-12-aza[4.4.3]propellane (**4**) and its symmetrical and unsymmetrical bis(tricarbonyliron) complexes (in  $\text{CDCl}_3$ )

† The dipole moment (2.1 D) of sesquifulvalene is also rather small<sup>36</sup>.

atom C(6) in **18** is less deshielded (146.5 p.p.m.) relative to the calculated value (139.1 p.p.m.) than the corresponding carbon in **16**, which may be a consequence of delocalization of the positive charge into the seven-membered ring. From these results it appears that carbon chemical shifts can be a valuable criterion for  $\pi$ -electron delocalization in those cases where charge separations are involved. It should be noted that diamagnetic ring current effects are difficult to detect by carbon magnetic resonance, since they are relatively small on the carbon chemical shift scale<sup>37</sup>.

Finally, I should like to emphasize the potential of carbon magnetic resonance studies in organometallic chemistry. The structure and stereochemistry of tricarbonylmetal complexes of olefins is a particularly interesting and rewarding field for such investigations, since unlike in proton n.m.r. structural information may also be obtained from the tricarbonylmetal ligand. The metal-to-carbon bonding situation, on the other hand, is reflected in the chemical shifts and  $^1J_{\text{CH}}$  coupling constants of the olefinic moiety.

Figure 11 illustrates the chemical shifts introduced upon tricarbonyliron complexation of *cis*-dienes incorporated in a propellane structure<sup>38</sup>. The terminal ( $C_1$ ) and central ( $C_2$ ) carbon atoms are shifted to lower frequencies by  $59 \pm 3$  and  $37 \pm 1$  p.p.m. respectively, whereby the *endo*- and *exo*-configurations of the tricarbonyliron ligand lead to significant shift differences, so that the symmetrical bis-*exo*-complex can be clearly distinguished from the *exo,endo*-complex. In addition, the latter exhibits two resonance lines for the non-equivalent tricarbonyliron moieties. Carbonyl resonances usually are

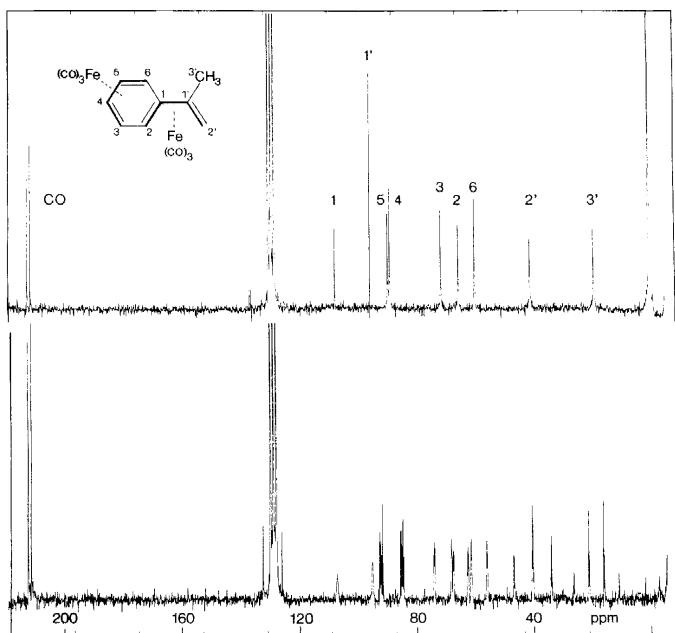


Figure 12(a)  $^1\text{H}$ -noise-decoupled and non-decoupled  $^{13}\text{C}$  FT spectra of bis(tricarbonyliron)-1'-methylstyrene (in  $\text{C}_6\text{D}_6$ )

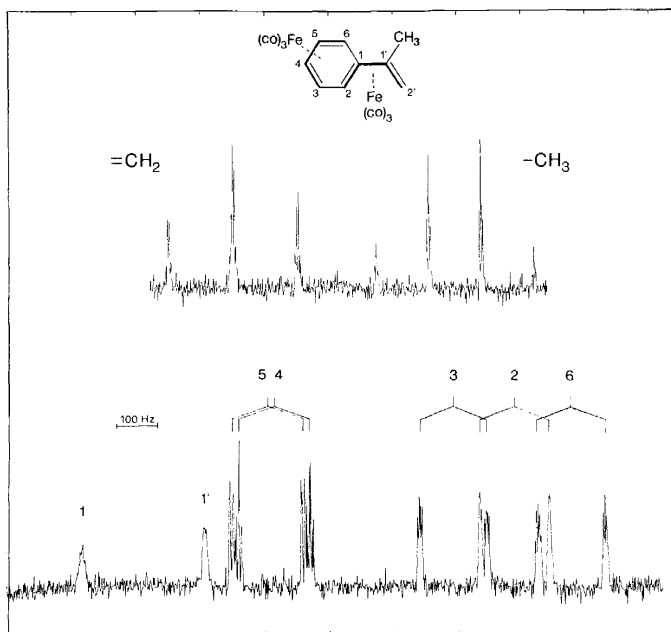


Figure 12(b) Non-decoupled  $^{13}\text{C}$  FT spectrum (expanded) of the olefinic region (without C(2)) of bis(tricarbonyliron)-1'-methylstyrene

sharp lines; in metal complexes, however, line broadening and eventually splitting of the CO resonance may indicate restricted rotation about the trigonal symmetry axis.

More subtle structural information about the geometry of the complexed diene, hybridization of the carbon atoms and  $\pi$ -bond orders may be obtained from non-decoupled  $^{13}\text{C}$  spectra. An example of this type from the series of bis-complexed styrenes<sup>40</sup> illustrates the quality and complexity of high-resolution carbon spectra of larger molecules (Figure 12a, b). Since the proton signals are well separated, the non-decoupled carbon spectrum is nearly first-order and analysis is straightforward. The one-bond C,H coupling constants of the terminal (t) and central (c) olefinic carbons are typical of  $\text{sp}^2$ -hybridized carbon atoms ( $C_t$ : 156.8–163.5 Hz;  $C_c$ : 174.3–176.1 Hz). These values seem to exclude extensive rehybridization upon complex formation of the styrene system ( $C_t$ : 156.8–160.1 Hz;  $C_c$ : 160.1–160.6 Hz) and illustrate similar bonding of the iron to the terminal and central carbon atoms of the diene systems. This is also reflected in the similar  $C_t$ -Fe and  $C_c$ -Fe bond lengths which have been determined by x-ray analysis of tricarbonyliron butadiene<sup>39</sup> and bis(tricarbonyliron)-1',3-dimethylstyrene<sup>41</sup>. The most interesting result of the x-ray analysis<sup>41</sup> is the folding of the benzene ring (Figure 13), so that the complex may be regarded as a combination of two

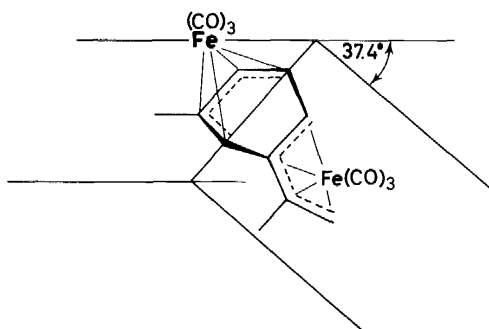


Figure 13. Geometry of bis(tricarbonyliron)-1,3-dimethylstyrene (after Herbstein and Reisner<sup>41</sup>)

tricarbonyliron isoprene complexes connected by two C—C bonds. The non-planar stereochemistry of the complex should be reflected in the vicinal C,H coupling constants  $^3J(=C-C-C-H)$  and  $^3J(C-C=C-H)$  which are expected to exhibit characteristic angular dependencies<sup>42</sup>. This aspect of the  $^{13}C$  spectra is presently under investigation.

In conclusion,  $^{13}C$  Fourier transform spectroscopy has opened up an entirely new field of structural investigations by nuclear magnetic resonance. The examples discussed in this article are necessarily incomplete, and such important applications as mechanistic and biosynthetic studies using  $^{13}C$ -labelled precursors have not been mentioned. Other important fields include polymer chemistry and the investigation of solids by special pulse techniques and heteronuclear spin-polarization transfer. Several other potential applications of Fourier spectroscopy may be envisaged for the near future, access to other non-abundant nuclei, such as  $^{15}N$ ,  $^{17}O$  and  $^2H$ , deserving particular attention.

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