CHAPTER I

INTRODUCTION

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SECTION-A
The history of NMR spectroscopy is a classic example of the development of an original discovery in one branch of science to an excellent technique used in all the branches of chemical science. The first NMR signals were independently observed by two groups of physicists in 1945; Bloch, Hansen and Packard\textsuperscript{1} at Stanford University detected a signal from the protons of water, and Purcell, Torrey and Pound\textsuperscript{2} at Harvard University observed a signal from the protons in paraffin wax. In 1949 and 1950, a number of investigators noted that nuclei of the same species absorbed energy at different frequencies and the precise resonance condition for a given type of nucleus depends on its chemical environment\textsuperscript{3}. In 1951, separate absorption bands were resolved for chemically different protons in the same molecule\textsuperscript{4}. This finding led to the term "Chemical shift" to describe the differences in resonance conditions required for the same isotope in different chemical environments. With this development, NMR became a new method for the study of molecular structure, and over the past three decades it has been firmly established as one of the major analytical tools in several branches of
Most problems with which early $^{13}\text{C}$ spectroscopists were struggling were, in some way, associated with spectrometer sensitivity. Nuclear magnetic resonance is known to be an intrinsically insensitive technique when compared to optical or mass spectroscopy. This is so for basically two reasons. Firstly, the energy differences $\Delta E$ between the ground and excited states is comparatively small and so, consequently, are the population differences as expressed by the Boltzmann law:

$$\frac{N_2}{N_1} = \exp\left(\frac{-\Delta E}{kT}\right) = \frac{1 - \frac{\Delta E}{kT}}{1 - \frac{\Delta E}{kT}}$$  \hspace{1cm} (1)$$

where $N_1$ and $N_2$ represent the spin populations of the ground and excited states, respectively, $k$ is the Boltzmann constant and $T$ the absolute temperature.

All atomic nuclei have charge and mass, while many also possess angular momentum and magnetic moments; as a result, the latter behave as spinning bodies. Nuclear magnetic properties were first proposed by Pauli in 1924 to explain the hyperfine structure in
certain atomic spectra. These very small splittings were suggested to arise from interactions of the magnetic moments of electrons and nuclei in these atoms, and analysis of the hyperfine structure provided measurements of the angular momentum and magnetic moments of these nuclei. It is now established that nuclei with odd mass numbers have spins whose value, $I$, is an odd-integral multiple of $\frac{1}{2}$. Nuclei with even mass are spinless if the nuclear charge is even or have integral spin if the charge is odd. The maximum observable component of the angular momentum is $I$, the spin quantum number, and the permitted values of the vector moment along any specific axis are given, in terms of the magnetic quantum number $m$, as a series:

$$m = I, (I-1), (I-2), \ldots$$

It is often convenient to express $I$ in terms of the magnetic moment $\mu$, whereas the proportionality constant $\gamma$ is the gyromagnetic ratio. Thus, there are $(2I+1)$ possible orientations, or spin states, for a given nucleus. These states are degenerate in the absence of a magnetic field, but in the presence of an applied field these correspond to different potential
energy levels (Fig. 4.1). The two available energy states of an isolated nucleus of spin $\frac{1}{2}$ correspond to alignment with and against the field. Absorption of energy (resonance) occurs when the sample is irradiated with electromagnetic energy at a radiofrequency $\nu_0$. The magnetic component of the irradiation induces transitions between the two energy levels.

\[ AE = h\nu \]  

(2)

The nucleus comes into resonance when the precessional angular velocity $\omega_o$ is same as the velocity of rotating auxiliary field such that

\[ \omega_o = \gamma H_0 \]  

(3)

where $\gamma$ is gyromagnetic ratio and $H_0$ is the external applied field. The fundamental nuclear constant $\gamma$ is related to the nuclear spin by the equation (4):

\[ \gamma = \frac{2\pi\mu}{hI} \]  

(4)
where $\mu$ is the magnetic moment, $I$ is the spin number. The angular velocity $\omega_o$ is related to the frequency by the equation (5):

$$\omega_o = 2\pi \nu$$  \hspace{1cm} (5)

Substituting the value of $\omega_o$ in equation (3)

$$2\pi \nu = \gamma H_o$$  \hspace{1cm} (6)

Therefore, insertion of the difference in energy

$$\Delta E = h\gamma H_o/2\pi$$  \hspace{1cm} (7)

into equation (1) gives

$$N_2/N_1 \sim 1 - h\gamma H_o/2\pi kT$$  \hspace{1cm} (8)

where $h$ is Planck's constant, $\gamma$ the gyromagnetic ratio and $H_o$ the field strength. Since NMR transitions are typically observed in the radiofrequency region, $h\gamma H_o \ll kT$. In effect, only a very small fraction of the nuclei are accessible to the experiment:

$$\frac{N_1 - N_2}{N_1 + N_2} \sim 10^{-6}$$

This small excess gives rise to an observable NMR signal.

The second cause of the inherent low sensitivity of the NMR experiment lies in the long lifetimes of excited states (typically in the order of $10^{-3}$ to $10^3$ secs). This severely limits the power applicable to induce
a transition. If too large a power level is chosen, this rapidly leads to a situation where the spin populations of the upper and lower energy levels become equalized (saturation). This means that energy can no longer be absorbed by the NMR system.

Although, the low abundance in the past had been regarded as a major obstacle to the advent of routine $^{13}\text{C}$ NMR, nature's choice had been a very fortunate one. At a higher abundance, probably neither proton nor $^{13}\text{C}$ NMR would ever have become a meaningful technique for the organic chemist because of the greater complexity of spectra that would result from heteronuclear and homonuclear spin-spin couplings.

Earlier, the fast sweep rates implicit to this technique resulted in fairly low-resolution spectra. In the case where $^{13}\text{C}$ is coupled to protons, for example, it may be possible to monitor a proton transition ($^{13}\text{C}$ satellite), while simultaneously sweeping through the $^{13}\text{C}$ resonance region$^{6,7}$ with a weakly perturbing double resonance field.
Major progress was brought about in mid-1960s with the introduction of proton-noise decoupling\textsuperscript{8}, which resulted in a sensitivity gain of at least one order of magnitude and permitted henceforth the recording of spectra in the dispersion mode. The advent of electronic storage devices roughly falls in the same period. Signal averaging techniques\textsuperscript{9} are based on statistic properties of noise, while coherent signals add up linearly when a number of scans are accumulated, noise only increases with the square root of the number of passages. Signal averaging led to a further substantial improvement in signal-to-noise ratio which made samples of organic molecules down to concentrations of 1 mol/l accessible to the experiment\textsuperscript{10}. The crucial breakthrough was finally achieved with the development of Fourier Transform (FT) methods\textsuperscript{8,11}, which led to a rapid growth of the $^{13}$C technique.

**Time and Frequency Domain\textsuperscript{11,12}**.

The early and extensive development of the continuous wave method for high resolution experiments has accustomed us to being able to obtain this frequency spectrum directly. By contrast, the alternative
pulse method, which was also used from the beginnings of NMR, though not for high resolution work, provides the same information but in the time domain. Such information should be converted into the easily understood frequency domain. From a general point of view, the mathematical process of Fourier transformation enables to convert a function of time, \( f(t) \), into the corresponding function of frequency, \( F(\omega) \):

\[
F(\omega) = \int_{-\infty}^{\infty} f(t)e^{-i\omega t} \, dt \quad (9)
\]

and the inverse relationship holds:

\[
f(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F(\omega)e^{i\omega t} \, d\omega \quad (10)
\]

With the arrival of small commercial computers and fast Fourier Transform programmes, this time-to-frequency domain conversion can be made very easily and the pulse technique has now entered the field of NMR and become routine.

**The Different Excitation Modes:**

Owing to the phenomenon of chemical shift, nuclei of the same species in a molecule usually exhibit a number of resonances. In order to observe these
resonances, several modes of excitation of the spins I have been worked out. In the first mode the resonance conditions $\nu_i = \gamma |H_i|/2\pi$ are met successively for each resonance, either by slowly sweeping the frequency of the $H_y$ field, the strength of $H_0$ remaining constant, or by slowly varying the strength of $H_0$, the frequency of $H_1$ being fixed. In the slow passage conditions only one type of spin $i$ is excited at a time since $H_1$ field continuously applied in the time domain is monochromatic with frequency $\nu_i$ (Fig. 1.2a). Another possibility is to simultaneously irradiate all the $\nu_i$ resonances by means of an appropriate $H_1$ pulse. In (Fig. 1.2b), a $H_1$ field of frequency $\nu_o$ applied suddenly for a short time $T = P_w$ (pulse width), covers a range of frequencies $\Delta \nu_o$ centered at $\nu_o$ and extending from $\nu_o - 1/P_w$ to $\nu_o + 1/P_w$. Pulse width of the order of a few microseconds to several tenths of a microsecond are usually selected. Obviously, the responses to the CW and pulse excitation modes take different forms. In CW excitation mode, the frequency spectrum of the sample is obtained directly, whereas in the pulse excitation, an interferogram of the different resonance frequencies which have been simultaneously excited is obtained in the time domain.
Figure-1.2
the left hand side plots (a-c) represent different amplitude functions in the time domain, \( f(t) \), for an oscillation of frequency \( \nu_0 \). The right hand side plots represent the corresponding function in the frequency domain, \( F(\nu) \). These latter functions are centered at frequency \( \nu_0 \).

(a) To an oscillation \( f(t) \) of constant amplitude in the time domain, there corresponds a single line \( F(\nu) \) at frequency \( \nu_0 \) in the frequency domain.

(b) To a rectangular pulse of constant amplitude \( f(t) \), applied during the interval \( \tau \), there corresponds the function

\[
F(\nu) = A \tau \left( \sin \frac{\pi \nu \tau}{\nu_0} \right) \frac{1}{\pi \nu \tau} \text{ centered at } \nu_0. \quad (12)
\]

(c) A triangular pulse of duration \( 2\tau \) corresponds to the frequency function

\[
\int F(\nu) = A \tau \left( \sin \frac{\pi \nu \tau}{\nu_0} \right)^2 \left( \frac{\nu_0}{\nu \tau} \right)^2. \quad (13)
\]

(d) An exponentially decaying function \( f(t) = \exp(-t/T_2) \) corresponds to

\[
F(\nu) = \frac{T_2}{1 + (2\pi \nu T_2)^2} \quad \text{and} \quad i \frac{2\pi \nu (T_2)^2}{1 + (2\pi \nu T_2)^2} \quad (14)
\]

The curves have been drawn for \( T_2 = 1s \). Here \( \nu_0 \) is zero frequency.

(e) The Fourier Transform of the function

\[
f(t) = \exp(i2\pi\nu At) \exp(-t/T_2)
\]
\[ F(\nu) = \frac{T_2}{1 + \left[ 2\pi (\nu - \nu_A) T_2 \right]^2} - \frac{i}{1 + \left[ 2\pi (\nu - \nu_A) T_2 \right]^2} \frac{2\pi (\nu - \nu_A) T_2^2}{1 + \left[ 2\pi (\nu - \nu_A) T_2 \right]^2} \] (15)

A sinusoidal modulation of \( \nu_o \) by a frequency \( \nu_A \), whose amplitude decays exponentially with the time constant \( T_2 \), therefore, gives rise to the same frequency spectrum as in (d) but shifted by \( \nu_A \) with respect to the origin. Only the cosinusoidal part of the function \( f(t) \) is represented on the figure which is drawn for \( T_2 = 1 \)s and \( \nu_A = 2 \)Hz and only positive values of \( \nu_A \) are considered.

(f) To an infinite sequence of impulses at intervals \( T \) where corresponds an infinite number of discrete frequencies spaced at intervals \( 1/T \). The utility of the NMR method results from the sensitive variation of resonance frequency with chemical structure and molecular environment.

Two major classifications of NMR experiments exist, mainly because chemical-shift differences are small. In highly ordered systems such as solids, molecular motion is hindered and dipolar interactions between neighbouring magnetic nuclei tend to broaden the individual resonance lines, in which all the fine
structure of interest to the chemist disappears. In contrast, in liquids and gases, rapid molecular tumbling effectively averages these dipolar interactions to zero and sharp absorption signals may be resolved. The two categories are known as broad-line NMR and high-resolution NMR.

For the purpose of structure elucidation PMR offers three types of spectral information i.e. chemical shifts, coupling constants and peak area measurements giving information about the number of protons. In the $^{13}$C NMR spectral studies also, all the above types of informations i.e. chemical shifts, $^{13}$C — $^{13}$C coupling, $^{13}$C—H coupling and $^{13}$C — $^{13}$C-H couplings are available, but generally chemical shifts are the most useful parameters. Besides, these spin lattice relaxation time $T_1$ and spin-spin relaxation time $T_2$ also provide profitable information. Peak intensities can be utilized but the direct relationship between area measurement and the number of nuclei absorbing energy is often lost. In order to get the idea of number of carbons in a particular area, extra care has to be taken to keep the pulse delay timings greater than the $T_1$ values so that the intensity of the signals is
commensurate to the number of carbons in that area. For such an information facilities are available in FT NMR spectrometers using $^1$H gated decoupling, without NOE mode of irradiation called NNE. Spin-relaxation reagents $^{17,18}$ have been used to shorten and equalize $^{13}$C T$_1$'s and to suppress NOEs by circumventing normal $^{13}$C-H dipolar relaxation. For larger organic molecules, use of these reagents is not recommended because they can actually degrade results. Nuclear Overhauser effects may be effectively suppressed by using gated decoupling$^{19}$ with moderate delays between scans. For molecules with unfavourable relaxation characteristics, joint use of relaxation agents and gated $^1$H decoupling with short scan delays gives excellent results$^{20}$. Various "inert" relaxation agents have been used for organic samples, including tris-acetylacetonatochromium (III), Cr (acac)$_3$. A better agent is tris-dipivaloylmethanatochromium (III), Cr(dpm)$_3^{21}$, which is more soluble in nonpolar solutions and generally inert to hydrogen bonding interactions with hydroxylic substrates. Furthermore, it should be noted that Lanthanide chemical shift reagents do not yield the same level of benefits as they do in proton NMR since $^{13}$C resonances enjoy a far greater freedom from overlap than do proton resonances.
HMG (Homonuclear gated decoupling)

This method is used for suppression of solvent signals, NOE, pseudo INDOE etc. In NOE or INDOE measurements, a comparison of signal intensities is required; therefore, the pulse delay time (PD) must be longer than the time required for magnetization to return to thermal equilibrium.

Homospoil (Homogenuity spoiling technique)

It incorporates into the pulse sequence, a large $H_0$ field gradient, which is created by applying a current pulse to one of the magnet shim coils. The Homospoil pulse greatly accelerates dephasing of the transverse components and, therefore, destroys the residual response at each observed pulse. However, a serious disadvantage of this method is that the lock signal is put out of resonance during the homospoil pulse. This disturbance is completely quenched during data acquisition and may bring about distortion of the frequency spectrum.

At present the best available procedure uses a $180^\circ$ RF phase alteration of the observed RF pulse.
The FID signals then have alternating positive and negative phases; the positive signals are added to the memory and negative signals are subtracted so that the response signals will accumulate, while the residual signals and spin echoes are cancelled.

QFR (Off resonance)

In a single-frequency off-resonance decoupling experiment the $^1$H irradiation is kept at high power
levels, but the centre frequency is moved 500 to 1000 Hz away from the protons to be irradiated, and the excitation bandwidth generator is switched off. In these experiments one-bond $^{13}$C–H coupling patterns return, allowing spectral assignments of nonprotonated carbons, CH, CH$_2$ and CH$_3$ observed as singlets, doublets, triplets and quartets, respectively. The observed couplings in off-resonance decoupled experiments are not equal to the actual one-bond coupling constants but are reduced. In off-resonance $^1$H-decoupled $^{13}$C spectra, peak assignments are more easily made since overlap between adjacent carbon resonance bands is less likely. The observed residual coupling is a function of the actual $^{13}$C–H coupling, the decoupling power, and the decoupler offset. Suitable adjustment of the offset allows resolution of overlapping set of lines. These experiments show relatively high sensitivity since NOE is still present and because long-range $^{13}$C–$^{13}$C–H couplings are absent.

**NOE (Nuclear Overhauser Effect)**

Under conditions of proton noise decoupling the enhancement of the carbon signals is considerably
greater than would be expected from the collapse of the multiplet structure into a single line. This additional enhancement is known as the nuclear Overhauser effect (NOE) and has a maximum value of 2.988.

NOE is a by-product of proton irradiation in $^1$H-decoupled $^{13}$C NMR experiments. Irradiation of the protons in a sample disturbs the Boltzmann distribution of the upper and lower $^1$H energy levels. The carbon nuclei depend chiefly on the $^1$H nuclei for spin-lattice relaxation. The carbon nuclei react to the equalization of $^1$H energy-level populations by changing their own energy-level populations. This results in an equilibrium excess of nuclei in the lower $^{13}$C energy level relative to that specified by a Boltzmann distribution. Experimentally, this means that more radiofrequency (RF) energy will be absorbed by the $^{13}$C nuclei as a result of the larger excess population in the lower energy level.

In a $^{13}$C [1H] NMR experiment, the theoretical nuclear Overhauser enhancement factor (NOEF) is 1.988. This means that if the NOE is fully operative, each
carbon resonance will have a peak area of 2.988 times the total resonance signal area observed in the absence of $^1H$.

NOE is derived from the $^1H$-induced relaxation of $^{13}C$ nuclei. It is further dependent on the dominance of the $^{13}C—^1H$ dipole-dipole relaxation mechanism. Appreciable contribution to $^{13}C$ spin-lattice relaxation from other than dipole-dipole mechanism results in lower nuclear Overhauser enhancements. As a result of differing Overhauser enhancements in a single molecule, the integrated intensities of $^1H$-decoupled $^{13}C$ resonances can vary.

The time relation between the irradiation and observation pulses for the NOE mode is as shown below.

![Diagram of time relation between irradiation and observation pulses for NOE mode]

Here, PD: Pulse delay time
ACQTM: Sampling (acquisition) time of computer
$x$: Proton irradiation time

Fig. 1.4
Although there are large number of books available which define and discuss in detail the various terms used in the PMR and $^{13}$C NMR spectroscopy, however it will be appropriate from the point of view of this dissertation to define and discuss some of the most important terminologies at this place.

CHEMICAL SHIFT

The chemical shift is one of the most important spectral parameter which is defined as the nuclear shielding divided by the field i.e.

$$\delta = \frac{H(\text{reference}) - H(\text{sample})}{H(\text{reference}) \times 10^6} \text{ ppm} \quad (16)$$

where $H(\text{reference})$ is the magnetic field of the reference nuclei and $H(\text{sample})$ is the field at sample nucleus and this equation may be rewritten as

$$\delta = \left( \frac{\nu_{\text{sample}} - \nu_{\text{reference}}}{\nu_{\text{reference}}} \right) \times 10^6 \text{ ppm} \quad (17)$$

oscillator frequency in Hz

Chemical shift is only a function of the nucleus and its electronic environment i.e. it is a molecular
quantity. It is always measured from suitable reference compound, TMS, being the most widely used reference compound in organic solvents. However, in aqueous solvents TMS being insoluble may be used in a capillary tube as an external reference or another reference called DSS i.e. sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) in which the reference proton is the methyl proton which resonates at δ 0.0. The disadvantage of this reference compound is that it has a number of other protons/carbons which give signals in the important regions.

Besides the above two primary references there are some other secondary references whose chemical shifts with respect to TMS or DSS are known and hence these may be used as secondary references such as t-butyl alcohol, acetonitrile, toluene, benzene, DMSO, acetone etc. Standard values of solvents in respect to TMS are given in Table 11 and Table 12.

In the past decade extensive efforts have been made to theoretically calculate $^{13}C$ chemical shifts. Unfortunately, available theoretical treatments
still do not fully explain trends in $^{13}$C shieldings and the most accurate calculations are at present limited to small molecules containing only 1st and 2nd row elements.

### Table 1.1

TMS-Based $^{13}$C Chemical shifts for common standards and solvents.

<table>
<thead>
<tr>
<th>Compound, Solvent</th>
<th>Protio Compound</th>
<th>Deuterio Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile (methyl carbon)</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Toluene (methyl carbon)</td>
<td>21.3</td>
<td>20.4</td>
</tr>
<tr>
<td>Acetone (methyl carbon)</td>
<td>30.4</td>
<td>29.2</td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td>40.5</td>
<td>39.6</td>
</tr>
<tr>
<td>Methanol</td>
<td>49.9</td>
<td>49.0</td>
</tr>
<tr>
<td>Dioxane</td>
<td>67.4</td>
<td>66.5</td>
</tr>
<tr>
<td>Chloroform</td>
<td>77.2</td>
<td>76.9</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>96.0</td>
<td>-</td>
</tr>
<tr>
<td>Benzene</td>
<td>128.5</td>
<td>128.0</td>
</tr>
<tr>
<td>CS$_2$</td>
<td>192.8</td>
<td>-</td>
</tr>
</tbody>
</table>

* In parts per million from internal TMS; $\pm$ 0.05 ppm at 38°C.
Table 1.2

$^{13}$C Chemical Shifts of Common Standards and Solvents

<table>
<thead>
<tr>
<th>ppm</th>
<th>200</th>
<th>160</th>
<th>120</th>
<th>80</th>
<th>40</th>
<th>0</th>
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<tr>
<td>207.3</td>
<td>(\text{C}_2\text{D}_5\text{N})</td>
<td>(\alpha)</td>
<td>(\beta)</td>
<td>(\gamma)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
</tr>
<tr>
<td>128.0</td>
<td>(\text{C}_6\text{H}_5\text{KO}_2)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>128.5</td>
<td>(\text{C}_6\text{D}_6)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>178.3</td>
<td>(\text{CH}_3\text{COOH})</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
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<tr>
<td>163.3</td>
<td>(\text{CF}_3\text{COOD})</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>192.6</td>
<td>(\text{CS}_2)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>207.3</td>
<td>(\text{(CD}_3\text{)}_2\text{CO})</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
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<td>123.5</td>
<td>(\text{CDCl}_3)</td>
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<td>(\epsilon)</td>
<td>(\delta)</td>
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</tr>
<tr>
<td>129.4</td>
<td>(\text{(CD}_2\text{)}_2\text{SO})</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>134.6</td>
<td>(\text{CCl}_4)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
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<td>140.2</td>
<td>(\text{CH}_3\text{OH})</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>130.5</td>
<td>(\text{C}_6\text{H}_5\text{Cl}_2)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
</tr>
<tr>
<td>132.6</td>
<td>(\text{CCl}_4)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
<td>(\delta)</td>
<td>(\epsilon)</td>
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RF = 24.99 MHz
Theory of Chemical Shift

In naturally occurring uncharged molecules the $^{13}$C chemical shift range is found to be slightly more than 200 ppm, whereas in the charged compounds the range may be up to 600 ppm. In analogy to PMR the $^{13}$C chemical shifts have contributions of various shielding constants which are additive:\(^{24}\)

$$\sigma_N = \sigma_d^N + \sigma_p^N + \sum_{B \neq N} \sigma_{NB}^N$$

(18)

where $\sigma_d^N$ represents the contribution from local diamagnetic electron currents at the site of the nucleus $N$, $\sigma_p^N$ relates to paramagnetic anisotropic nonspherical local electron circulations. The term $\sigma_{NB}^N$ describes the magnetic field at the site $N$ produced by the currents of electrons at neighbouring atoms or functional group $B$.

The local diamagnetic term $\sigma_d^N$ describes the isotropic circulation of electrons around the nucleus. This circulatory motion is perpendicular to the applied magnetic field, $H_0$, and according to Lenz's rule produces a secondary field $H_{local}^{dia}$ opposing...
the applied field. The greater the electron density at the nucleus, the greater the diamagnetic contribution, and further upfield the resonance occurs. For an isolated spherical atom $\sigma^d_N$ represents the only contribution and is given by the Lamb formula\(^\text{25}\)

$$\sigma^d_N (\text{free atom}) = \frac{e^2}{3mc^2} \sum_i (r_i^{-1})$$  \hspace{1cm} (19)

and in this equation the summation of the ground-state mean inverse distances $r_i$ is over all electrons $i$. An approximate calculation using this formula indicates that addition of an electron into a 2p orbital of a carbon atom would produce a shielding of 14 ppm. From this result it has been concluded\(^\text{26}\) that $\sigma^d_N$ inspite of its being numerically large on an absolute scale, can not be a dominant factor for $^{13}$C shieldings. However, it must be emphasised\(^\text{27-29}\) that in the molecules, equation (19) summation must be carried out over all electrons in the molecule. This can be satisfactorily achieved by using approximation method\(^\text{28}\) without adequate knowledge of ground-state molecular wave function by using the semiempirical relationship

$$\sigma^d_N = \sigma^d_N (\text{free atom}) + \frac{e^2}{3mc^2} \sum_{K=N} Z_K (R_{NK})^{-1}$$  \hspace{1cm} (20)
Z_K being the atomic no. of the nucleus K and \( R_{NK} \) representing the internuclear distance between K and N. Calculations\(^{28,30}\) have indicated that considerably larger variations in the \( \sigma^d_N \) term have to be considered when contributions from the adjacent atoms are taken into account. For example in a hydrocarbon, a simple replacement of a hydrogen atom by a carbon substituent increases \( \sigma^d_N \) term by 28 ppm\(^{28}\).

\( \sigma^p_N \) primarily depends upon the availability of low-lying electronic excited states of the carbon atom. A low value of \( \Delta E \) causes deshielding in the following equation given by Karplus and Pople\(^{31}\)

\[
\sigma^p_N = \frac{e^2 \hbar^2}{2m^2 c^2} (\Delta E)^{-1} \langle r^{-3} \rangle_{2p} \left[ Q_{NN}^+ \sum_{B \neq N} Q_{NB} \right]
\] (21)

The term \( \langle r^{-3} \rangle_{2p} \) stands for the expected value of the inverse cube of the distance between a 2p electron and the nucleus. The term \( Q \) stands for the elements of the charge density and bond order matrix. \( Q_{NN} \) assumes the value of 2 if the charge density in each 2p orbital is one, and the \( Q_{NB} \) represents multiple bond contributions.

The terms \( \Delta E, \langle r^{-3} \rangle_{2p} \) and \( Q_{NB} \) are mutually dependent, i.e. any change in the local electronic
structure of nucleus N affects all the terms in equation (21). In the UV spectra of alkanes the $\sigma \rightarrow \sigma^*$ transitions, which may be taken with some caution as a measure of $\Delta E$, move to longer wavelengths which means lower energies when substitution is increased\textsuperscript{28}.

This reflects the delocalisation or linear combination of $\sigma$ electrons. In view of this, the more highly substituted carbon atoms are found to resonate at lower fields in the $^{13}$C NMR spectrum. Since excited state energies are generally much lower in magnitude in the unsaturated system and, therefore, the unsaturated carbons are less shielded than the saturated carbons. The $\langle r^{-3} \rangle_{2p}$ term is very important for rationalization of $^{13}$C NMR chemical shifts and it primarily depends upon the effective nuclear charge on the nucleus N. An increase in electron density at a carbon atom leads to the expansion of the 2p orbitals and, therefore, the term $\langle r^{-3} \rangle_{2pN}$ is lowered. Therefore, a linear dependence of aromatic carbon chemical shift on local $\pi$-electron density has been established\textsuperscript{32}. This indicates that an addition of an electron to a 2p orbital causes, an upfield shift
of the corresponding carbon resonance by about 160 ppm.
and, therefore, it can be inferred that the dependence of the \( \sigma_N^b \) term is the cause for the large \(^{13}\text{C} \) chemical shift range. This term may be expected to reflect the influence of inductive effects, bond delocalisation and steric factors on \(^{13}\text{C} \) chemical shifts.

The term \( \sigma_{NB}^N \) (Equation (18)) also called the neighbouring group anisotropy effect, describes the effect of local electron circulations around the atoms \( B \) which surround carbon \( N \) under observation and of interatomic electron currents between atom \( B_1, B_2, \ldots, B_n \). McConnell\(^{33} \) and Pople\(^{34} \) derived a simple expression for \( \sigma_{NB}^N \) as follows:

\[
\sigma_{NB}^N = \frac{1}{3} R_{NB}^{-3} \Delta \chi_B^z (1 - \cos^2 \Theta_B)
\]

where \( R_{NB} \) is the distance between nucleus \( N \) and dipole \( B \), \( \Delta \chi_B^z = \chi_B^z - \chi_B^x \) is the magnetic susceptibility of the dipole \( B \) and \( \Theta_B \) is the angle between the symmetry axis of \( B \) and the NB distance vector. In this equation, an assumption has been made that these electronic currents may be approximated by point magnetic dipoles.

The shielding constant \( \sigma_N \) is also governed by
inter-and intra-molecular electronic effects. These very complex electronic effects have been rationalized in terms of quantities and this approach proves very useful for a qualitative understanding and prediction of $^{13}$C chemical shifts.

The most important shielding contributions in the $^{13}$C NMR may be envisaged as arising from:

(i) the hybridisation state of the nucleus under observation.
(ii) inductive effects of the substituents.
(iii) van der Waal's effects and steric effects between closely spaced nuclei.
(iv) electric fields originating from molecular dipoles or point charges.
(v) hyperconjugation.
(vi) mesomeric interactions in $\pi$-electron systems.
(vii) diamagnetic shielding due to heavy substituents (heavy-atom effect).
(viii) neighbouring group anisotropy effect and
(ix) isotopic effects.

Hybridisation

From literature survey it has been clearly
established that the state of hybridisation of the carbon nucleus under observation is a dominant factor in determining its chemical shift. As has been discussed earlier the $\Delta E$ and $\sum Q_{NB}$ (Equation (21)) combine to increase the paramagnetic term, the general trend, $\sigma(Sp^3) > \sigma(Sp) > \sigma(Sp^2)$ is parallel to the PMR spectral data. This coincidence is probably fortuitous since for hydrogen the chemical shift is dependent on the electronegativity of the carbon atom to which it is attached and the latter depends on the $S$-character which is of the order $Sp > Sp^2 > Sp^3$ and only by the hybridisation effect the order of the PMR chemical shifts of the hydrogens should be opposite to that of the order of $S$-character of the carbon atom. The experimental chemical shifts order $Sp^2 > Sp > Sp^3$ is a consequence of the neighbouring anisotropy term of the bonds (the $C=\CJK$ anisotropy shifts the order of the chemical shifts).

**Inductive effects**

Satisfactorily correlations of $^{13}$C NMR spectra can be easily drawn with the electronegativity of the substituent on the carbon atom under observation. The
effect can be understood due to the substituents property of removing electron density from the carbon 2p orbitals and this is associated with an increase in the term $\langle r^{-3} \rangle_{2p}$ (Equation (21)), and, therefore, a deshielding effect and this charge transfer\(^{35}\) is propagated along the carbon backbone, producing alternating effects and falling off with inverse third power of the distance i.e.

$$\delta^- \delta^+ \delta^- \delta^+ \ldots$$

Comparison of the experimental data clearly reveals that, apart from charge transfer, there must be some additional effects which are operative because no effect of the substituent electronegativity can be found at the $\beta$- or $\gamma$-atoms. And consequently, it will imply that the substituent induced shift of the $\alpha$-carbon atom can also only in part be due to an inductive effect.

**The Lindeman-Adams Rule\(^{36}\)**

Lindeman-Adams method remains the most convenient method for the determination of chemical shifts in alkanes. The chemical shifts of substituted alkanes may be estimated by calculating the shift of the
parent alkane and by adding the appropriate substituent parameters. Standard error for a set of 59 paraffins is $\pm 0.8$ ppm.

\[
\begin{array}{cccc}
\text{K} & \alpha & \beta & \gamma & \delta \\
\text{---CH}_n & \text{CH}_m & \text{C} & \text{C} & \text{C}
\end{array}
\]

\(n = \) number of hydrogens at carbon \(K\)
\(m = \) number of hydrogens at the \(\alpha\)-carbon
\(N_m = \) number of \(\text{CH}_m\) groups at \(\alpha\)-position \((m=0,1,2; \alpha-\text{CH}_3\) groups are ignored)\\
\(N^\gamma = \) number of \(\gamma\)-carbons
\(N^\delta = \) number of \(\delta\)-carbons

The chemical shift \(\delta_K(K)\) of carbon \(K\) can be calculated according to equation (23)

\[
\delta_K(K) = A_n + \sum_{m=0}^{2} N_m^\alpha \alpha_{nm} + N^\gamma \gamma_n + N^\delta \delta_n
\]  

(23)

where \(A_n, \alpha_{nm}, \gamma_n\) and \(\delta_n\) are constants.

An outstanding feature of \(^{13}\)C chemical shifts is the finding that substituent contributions are additive. This is particularly so for aliphatic carbons, where carbon shieldings can be divided into a number of additive contributions produced by substituents in \(\alpha\), \(\beta\), \(\gamma\) and \(\delta\)-positions.
Unsaturated carbon shifts are generally more straightforward to interpret because they primarily depend on the local $\pi$-electron density, which is more easily predictable and other contributions are often of secondary importance.

The $\alpha$-effect

The chemical shift of a directly substituted aliphatic carbon (an $\alpha$-carbon) mainly depends on substituent electronegativity, except the heavy halogen derivatives as discussed under the subheading "heavy atom effect". The effect is 10-20% smaller for secondary with respect to primary substituents again with the exception of Cl, Br and I.

The $\beta$-effect

With the exception of carbonyl, cyano and nitro groups, the substituent effects at the $\beta$-carbon are found to be fairly constant and independent of the nature of the substituent. Several attempts to interpret this effect have been made\textsuperscript{28,37,38} but a conclusive answer is lacking.
The γ-gauche effect

Carbons three bonds away from a substituent exhibit upfield shifts due to sterically induced polarization of C-H bonds. In rigid, cyclic systems the effect is zero for a trans arrangement and maximum when the substituent and the γ-carbon are in a gauche position.

The δ-effect

Substituent effects over four bonds are generally negligible in aliphatic systems (<1 ppm) since in the energetically favoured conformations, there is no nonbonded interaction, for the synaxial conformation, where the nonbonded internuclear distance is even smaller than in γ-gauche conformation, a strong steric effect is expected. The steric effect is, thus, of opposite sign to what would be predicted by analogy to the well-known γ-effect. The second order electric field effects due to fluctuating magnetic dipoles are responsible for the observed down-field shift.  


van der Waal's and steric effects

$^{13}$C chemical shifts are extremely sensitive to molecular geometry and consequently remote substituent effect i.e. carbons separated by several bonds strongly influence each other if they are close in space. There are in principal two types of short-range non-bonded interactions to explain these effects. Firstly, the attractive van der Waal's forces between closely spaced atoms lead to an expansion of orbitals. Such an effect would decrease the $\langle r^{-3} \rangle_{2p}$ term and hence produce upfield shifts. However, in the case of repulsive van der Waal's forces, the effect would be to increase $\langle r^{-3} \rangle_{2p}$ term and hence produce diamagnetic effect i.e. deshielding in the crowded molecules. Apart from causing distortion from electron distribution these interactions also effect the shielding constants indirectly by producing small changes in molecular geometry. These two components of steric effects are very difficult to separate.

As a qualitative tool the steric effects are a consequence of the polarizations of the C—H bonds. According to this concept, a steric perturbation of a bond leads to a drift of charge along the bonds towards
carbon thus causing orbital expansion and hence increased shielding. In practice the effect is observed whenever the two carbons bearing protons are gauche to each other. Although C—C bonds have polarizability similar to those of C—H bonds, no effect is expected for a carbon with perfect tetrahedral symmetry. C—C bond polarization will, therefore, not produce any change in net charge density on a quaternary carbon. The flow of a charge to a quaternary carbon along a C—C bond will be compensated by a loss of charge along the other C—C bond. The γ-gauche effect is also observed, though to a lesser extent, in conformationally mobile system. The Grants simple model predicts dependence of induced shift \( \Delta \delta_{st} \) not only on proton—proton distance \( r_{HH} \) but also on the angle between \( H...H \) axis and perturbed C—H bond.

\[
\Delta \delta_{st} = C.F_{HH}(r)\cos \Theta
\]

(24)

\( \Delta \delta_{st} \) is induced shift, \( r_{HH} \) is proton—proton
distance, angle $\Theta$ is the angle between H—H axis and the perturbed C—H bond. Depending upon the value of $\Theta$, $\Delta\delta_{st}$ can thus have positive or negative value.

**Electric field effects**

Another type of shielding has its origin in local electric fields$^{43-46}$. These may be generated at the site of the nucleus by an ionised group resulting from protonation. Due to concomitant polarization of carbon bonds, the local charge density is varied, affecting both the diamagnetic and paramagnetic contributions to the screening constant. It has been shown$^{46}$ that the electric field $\vec{E}$, at the site of carbon nucleus also plays an important role$^{44,45}$. Simplifying the assumption that $\vec{E}$ is uniform, a theory was developed$^{46}$ which allows us to estimate and separate the two contributions. Since no net charge is induced by a uniform electric field at a carbon of perfect tetrahedral bond symmetry, the first term vanishes for a quaternary carbon. The incremental shift observed upon introduction of the perturbation is thus solely caused by $\partial \Delta \delta / \partial \vec{E}$ term.

For the $\alpha$-carbon the observed shift is often
small, due to partial cancellation of the two contributions.

**Hyperconjugative effects**

The characteristic upfield shift caused by first row heteroatoms located at the γ-position and antiperiplanar to the ^13C nucleus observed has been explained by the phenomenon of hyperconjugation thus, in such a system C—γ resonances move upfield by calculated -2 to -6 ppm upon replacement of X=H or C by N, O or F, whereas classical mechanism such as σ bond polarization or through space electric field effects had to be excluded. The concept of hyperconjugative interactions of the lone pairs of X with Cα—Cβ bond is in good agreement with the observed effects as shown in figure. (Fig.1.6).

Fig.1.6

Such an interaction results in enhanced electron density at C-γ. Partial overlap of the lone electron
pairs of \( X \) with the \( p_{\pi} \) orbitals of \( C_{\alpha} \) is particularly favourable for \( X=N, O, F \) because \( C-X \) bond is short and the \( p_{\pi} \) orbital radii are comparable to that of carbon.

**Mesomeric effects**

This effect operates in unsaturated framework, where delocalisation of charge across the electron system produces large shielding changes due to the dependence of the paramagnetic shielding term on the effective nuclear charge. Various factors and mechanisms influence the local charge density of an aromatic carbon\(^{48} \) such as (i) overlap of the \( \pi \)-orbitals with substituent \( p \)(or \( d \)) orbitals of suitable size and symmetry called mesomeric effect, (ii) redistribution of \( \pi \)-electron density as a result of repulsive interaction between \( \pi \)-system and filled orbital of a substituent called orbital repulsion effect. Another governing effect is (iii) the polarization of the \( \pi \)-system by a polar substituent called \( \pi \)-polarization effect\(^{49} \) and finally (iv) the polarization of a \( \sigma \)-electron system inducing alterations in the \( \pi \)-electron density called inducto-electromeric or \( \pi \)-inductive effect.
The mesomeric effects can be described in terms of contributions from canonical structures as shown in the figure (Fig. 1.7). The electron-donating \((-I, +M)\) substituents such as \(-\text{NH}_2, -\text{OH}, -\text{F}\) delocalize their lone electron pairs into the \(\pi\)-system, thus increasing the charge density at ortho and para carbons in the aromatic system and \(\alpha\)-and \(\gamma\)-carbon atoms in the unsaturated systems. On the other hand, electron-withdrawing substituents \((-I, -M)\) delocalise the \(\pi\)-electrons of the ring or the double \(\pi\) bonds of the acyclic system towards them, thereby decreasing the charge density at ortho and para carbon atoms. Such changes in the charge density at the aromatic carbons affect the paramagnetic shielding term as described in the equation (21). Thus the substituents with lone pairs shield the ortho and para carbon atoms while electron-attracting substituents have a deshielding influence on such carbons. The observed chemical shifts of the para carbons correlate very well with the total charge density calculated by CNDO/2 method. The ortho carbons, however, show no correlations because of other effects such as steric interactions and neighbouring group anisotropy, which make significant contributions to the shielding. Good correlation of
Fig. 1.7

Substituted benzenes. Plot of $^{13}$C chemical shift of para carbon vs. Hammett $\sigma^+$ parameter.
aromatic carbon shifts have also been obtained with appropriate Hammett $\sigma$-constant's. These coefficients according to the Swain-Lupton represent a two third contribution of resonance to the charge density and one third being due to inductive effects. Thus, in aromatic hydrocarbons the $\Delta\mathcal{C}$ of para carbon is found to correlate with $\sigma^+_p$ as shown in figure (Fig.1.8). However, in the case of heterocyclic aromatics, the situation gets altered due to the heteroatoms. The meta carbon substituent shifts are found to correlate well with $\sigma^-_m$. The values for substituents with filled nonbonded p (or d) orbitals and those substituents without lone electron pairs fall on two different lines suggesting the presence of additional effects (other than mesomeric). However, the meta carbon chemical shifts don't vary more than 3 ppm, the effect is of little practical importance.

On comparison of the mechanisms governing aromatic shieldings, it is clearly observed that the mesomeric effect dominates over other effects and the canonical structures represent useful aids for explaining chemical shifts in such systems. Carbonyl carbons are particularly important as the carbonyl carbon bears
a partial positive charge. This is the reason why carbonyl carbons resonate at the low-field end of the chemical shift scale. In $\alpha,\beta$-unsaturated carbonyl system, the positive charge can be delocalised from the carbonyl carbon and consequently the carbonyl resonance moves upfield in these derivatives. However, it should be kept in mind that for mesomeric effects to operate, coplanarity of the orbitals involved in delocalisation is a must and deviation from coplanarity leads to downfield shift due to steric inhibition of resonance.

**Heavy atom effect**

While the effects of most electronegative substituents upon the substituted aliphatic carbon shieldings have been shown to be mainly inductive, this does not apply for the heavier halogens. In the case of increased substitution with bromine and iodine, the heavy atom effect becomes very strikingly peculiar. Carbon-13 chemical shifts of halomethanes are given in Table 43. These effects are due to a diamagnetic shielding produced by the large number of electrons carried by heavy atoms.
Table 3

$^{13}$C Chemical shifts (in parts per million) of Halomethanes*

<table>
<thead>
<tr>
<th></th>
<th>CH$_3$F</th>
<th>CH$_3$Cl</th>
<th>CH$_3$Br</th>
<th>CH$_3$I</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>65.7</td>
<td>23.9</td>
<td>9.0</td>
<td>-21.7</td>
</tr>
<tr>
<td>(b)</td>
<td>104.4</td>
<td>52.9</td>
<td>20.4</td>
<td>-55.1</td>
</tr>
<tr>
<td>(c)</td>
<td>113.5</td>
<td>76.5</td>
<td>11.1</td>
<td>-140.9</td>
</tr>
<tr>
<td>(d)</td>
<td>117.5</td>
<td>95.4</td>
<td>-29.7</td>
<td>-293.5</td>
</tr>
</tbody>
</table>

* These values have been taken with respect to methane gas at zero density.$^{53}$

**Neighbouring Group Anisotropy Effect**

The anisotropic term depends only on the spatial relationship between the nucleus whose shift is being considered and the anisotropic group.

From the equation (22), it is evident that this
term is independent of the nature of the observed nucleus N and is thus of the same order of magnitude in PMR and $^{13}$C NMR. Since $^{13}$C chemical shifts occur over a far greater range than do proton shifts, therefore, by contrast, the anisotropic term, so important in PMR, is relatively less significant in $^{13}$C NMR, amounting generally to a few parts per million or less.

Ring-current effect is considered as a special case of neighbouring group anisotropy. Although proton shielding is markedly influenced by magnetic field-induced circulation of $\pi$-electrons in a close, conjugated system (aromatic ring-currents), the same influences ($\sim 5$ ppm) are less significant in determining $^{13}$C resonance positions$^{54}$. Günther and Schmickler$^{55}$ have summarized many of the arguments and limitations for ring-current effects on $^{13}$C shifts. DuVernet and Bockelheide$^{56}$ gave a definitive experimental determination of these influences. They measured proton and $^{13}$C chemical shifts for the R groups in figure 1.9a and 1.9b.

![Fig.1.9](image-url)
Both have essentially the same geometry but 'a' annulene, has a ring current, whereas 'b' does not. The effects of the ring current in 'a' are responsible for the differences in the measured shifts for protons and carbons in 'a' and 'b'. The magnitude of this effect depends principally on the position and the distance of the affected nucleus relative to the plane of delocalisation. DuVernet and Boekelheide\textsuperscript{56} found that the magnitude of the ring current effect was the same for both $^{13}\text{C}$ and $^1\text{H}$ and it was in good agreement with the theoretical predictions of Johnson and Bovey\textsuperscript{57}.

**Deuterium Isotope Effects**

The use of deuterium substitution for assignment of resonances in proton NMR spectroscopy has its parallel in $^{13}\text{C}$ NMR spectroscopy. Carbons bonded to deuterium generally display no NOE and are split by residual C–D coupling. Lines are frequently broadened because of effects of the deuterium quadrupole on $^{13}\text{C} T_2$. The combination of all these factors results in resonance lines for deuterated carbons that are substantially less intense than those of protonated ones. Hence, comparison of
spectra of specifically deuterated materials with the corresponding spectra of the protio compounds allows ready assignment of resonances.

It is well known that deuterium substitution changes resonance positions of the substituted carbons by small but measurable amounts. This "isotope shift" is almost always a shielding effect because of theoretical reasons as the heavy isotope lowers the potential energy of the molecule. The effect is $\sim 0.2$ ppm per deuterium atom for the substituted $\alpha$-carbon and $\sim 0.1$ ppm for the $\beta$-carbon. Effects further down a hydrocarbon chain and at more remote positions in cycloheptanone have been reported. Deuterium isotope effects on C—H or C—C couplings have not been reported yet.

**Spin-spin coupling involving carbon**

There are three types of carbon spin-spin interactions: $^{13}\text{C}—^1\text{H}$, $^{13}\text{C}—^{13}\text{C}$, $^{13}\text{C}—\text{X}$ coupling. The second one is not very probable in natural-abudance compounds for obvious reason that it is not necessary that the two adjacent carbons may be having $^{13}\text{C}$ isotope. Various theoretical calculations have been made for predicting $^{13}\text{C}—^1\text{H}$, $^{13}\text{C}—^{13}\text{C}$ and $^{13}\text{C}—\text{X}$
spin-spin coupling constants. The self-consistent field (SCF) finite-perturbation method utilizes the INDO molecular orbital approximation and has been used extensively in treating one bond $^{13}\text{C} - ^1\text{H}$ and $^{13}\text{C} - ^{13}\text{C}$ couplings. One-bond $^{13}\text{C} - ^{13}\text{C}$ coupling constants increase crudely with increasing 's' character of the two $^{13}\text{C}$ nuclei. However, cyclopropyl ring coupling constants show unusual nature.

Aromatics

$^{13}\text{C}$ NMR spectra of aromatic carbons assumed particular interest to organic chemists after the initial report of carbon chemical-shift dependence on substituent polarity. The carbons of benzene are found at 128.5 ppm, whereas $^{13}\text{C}$ chemical shifts of substituted aromatics appear over the wide range of 110 to 170 ppm. In 1961 Spiesecke and Schneider provided unequivocal proof for the assignment of aromatic chemical shifts and since then the literature is bulging with more and more information.

As presented earlier in equation (18), the $\sigma_{N}$ is approximated by a sum of three terms. As for the aliphatic systems and the aromatic system as well, $\sigma_{N}^P$
has been shown to be dominant for $^{13}$C chemical shifts$^{65,66a,24}$, although $\sigma_N$ has been important specially in the interpretation of small changes$^{28,66b}$. The principal factors affecting $\sigma_N$ are charge polarization, variation in bond order, and average excitation energy. When changes in bond order and/or the average excitation energy for related compounds do not vary much or vary in a mutually compensating way, a relationship with electron density may be apparent. Additional difficulties in seeking these correlations may arise from the approximations, often used for calculating electron densities, even in methods considered highly exact$^{67,68}$. It has been shown for the special case of benzene carbons para to a substituent that CNDO/2 charge densities correlate with $^{13}$C chemical shifts$^{65c}$.

The use of $^{13}$C chemical shifts as a probe in understanding the electronic nature of aromatic and aromatic-like systems has been further aided by use of Hammett $\sigma$ and related constants$^{65a,c}$, and, more recently, by dual-substituent parameter (DSP) treatments$^{51,69a,69b}$. Substituent chemical shifts (SCS) in benzene derivatives often may be correlated by a general DSP equation of the type

$$\delta(\text{SCS}) = K(P_1 + \lambda P_2)$$  (25)
where \( P_1 \) and \( P_2 \) are any pair of substituent reactivity parameters, for example, \( \sigma_f \) and \( \sigma_R \) or \( F \) and \( R \). As expected, the most successful correlations have been obtained for DSP treatments with para carbon chemical shifts in monosubstituted benzenes\(^{69a} \). Deviations observed with meta and, especially, ortho \( ^{13} \)C shifts are often rationalized through various combinations of steric, \( \pi \)-inductive, \( \sigma \)-inductive, and field effects\(^{71} \). When systems are carefully chosen, however, single-parameter correlations may be obtained and these may be used to verify reactivity parameters\(^{65c,72} \). In this case para carbon shifts of substituted benzenes\(^{65c} \) and the \( \beta \)-carbon of benzylidene malononitriles\(^{72} \) have been used.

Substituent effects in benzenes are approximately additive unless substituents are "ortho" with respect to each other. Therefore, no correction terms are usually required and chemical shifts may be estimated using the simple relationship.

\[
\delta_C(K) = 128.5 + \sum_i A_i(R)
\]

In equation (26), \( A_i(R) \) represents the chemical shift increment for a substituent \( R \) in the \( i \)th position (C—1, ortho, meta or para). Table\(^{44,64,65c,73} \) represents
the $^{13}$C chemical shifts for a number of substituted benzenes (p. 80-81).

**Solvent effects**

$\sigma^+$ values for a series of substituents may not remain constant in strongly interacting solvent media. In various solvents an individual substituent may behave quite differently and this should be reflected in the nature of electronic effect of the substituent attached on the aromatic ring. Some of the groups would be expected to interact strongly in protic solvents as compared to the non-protic solvents. For example, acetophenone is very prone to solvent effects and on addition of TFA, the para carbon of acetophenone is additionally deshielded by around 2 ppm up to 5:1 ratio of the acid and acetophenone$^{65c}$. A similar effect has been observed for a methoxy group and, therefore, the para carbons of these compounds are sensitive to solvents. For a substituent such as methyl, little solute-solvent interaction would be expected in most of the solvents. Infact, para $^{13}$C chemical shift in toluene remains constant for a wide range of solvents.
These solvent induced effects have been used to derive solvent-dependent $\sigma^+$ values, which may be used to predict the relative reactivity of aromatic systems with strongly solvated functional groups in reaction media of interest\textsuperscript{65c}. A DSP analysis carried out on the effect of aprotic solvents on para carbon shifts suggests that the effect depends mainly on the inductive rather than the resonance nature of the substituent\textsuperscript{74}. Enhanced substituent polarity in the more polar solvents leading to increased polarization of the π-system was suggested to explain these results. The spectrum of aniline\textsuperscript{65c} on protonation in methane-sulfonic acid changes significantly when compared with that of aniline in carbon tetrachloride. The ortho and para carbons are deshielded considerably and the meta position to a lesser extent (8.1, 11.4 and 1.06 respectively). The ipso carbon is strongly shielded by 17.6 ppm. The CNDO/2 calculated changes in charge density at each carbon agree quite well with the 'observed' changes in charge density derived from $^{13}$C chemical shift/charge-density correlations\textsuperscript{65c}. Similar results have been reported for substituted anilines\textsuperscript{75}.
The chemical interactions between aromatic substituents and various solvent systems can be probed by the large solvent-induced chemical shifts found for ring carbons. Another application for these large shifts and also for smaller generalized solvent-induced shifts is separation of accidentally coincident carbon resonances in analogy to the use of solvent-induced shifts in proton NMR. For example, in the $^{13}$C NMR spectrum of 3-bromobiphenyl with cyclohexane as solvent, three carbons appear as a singlet in 1000-Hz expansion, whereas in DMSO as solvent the three carbons are completely resolved.

**Steric effects in aromatics**

In substituted benzenes adjacent substituents may experience "steric" shifts in addition to the usual electronic effects. Substituent interactions in ortho di- and polysubstituted materials shield adjacent methyl carbons. The methyl group in o-Xylene is shielded by 1.9 ppm compared to that in the meta Xylene. Adjacent substituents need not both be alkyl. Deshielding $\delta$ effects are also displayed by disubstituted benzenes. The ring methyl carbon in
\textit{o-} \textit{tert.-butyl} \textit{toluene} is deshielded by 4 ppm in comparison to the methyl of \textit{o-xylene}, although the methyl resonance in \textit{o-ethyl-} and \textit{o-isopropyl} \textit{toluene} are not affected significantly\textsuperscript{78}. Chemical shifts of cyclophanes may also be interesting in terms of steric constraints.

Polynuclear aromatic hydrocarbons have been of considerable interest because of the case with which their $\pi$-electron system can be studied theoretically. Hansen\textsuperscript{79} has reviewed comprehensively theoretical work in this area. It has been found that in general, quaternary carbons are at lower field. It has also been observed that nonalternant hydrocarbons\textsuperscript{80} have a larger chemical-shift range (14 to 22 ppm) than do alternant hydrocarbons\textsuperscript{66a,81}. This difference in $^{13}\text{C}$ NMR behaviour offers experimental method for differentiation between the two classes i.e. alternant and non-alternant hydrocarbons. The correlations of $^{13}\text{C}$ chemical shifts with the theoretical calculated charge densities and other parameters show that $^{13}\text{C}$ shifts are not simply related to electronic charge but both $\pi$ and $\sigma$-charge variations play an important
role in both the categories of hydrocarbons.

**Heteroaromatics**

Heteroaromatic compounds have been of particular interest in the $^{13}$C NMR studies.

**Five-membered heterocyclics**

$^{13}$C NMR spectra of 5-membered heterocyclics have many of the qualitative features of substituted alkenes, yet the effect of the heteroatom is not as marked as for alkenes. The chemical shifts of $\alpha$-and $\beta$-carbons of furan differ by approximately 33 ppm, $\alpha$-carbon being downfield. For thiophene the $^{13}$C shifts of $\beta$-carbon is downfield as compared to that of the $\alpha$-carbon by approximately 1.7 ppm. This is an analogy with sulfur-substituted alkenes. In selenophene, the $\alpha$-carbon is downfield as compared to the $\beta$-carbon barely by 2 ppm. Pyrrole $^{13}$C resonances vary considerably more with solvent as compared to furan and thiophene. Selenium deshields both C—2 and C—3 relative to sulfur in thiophene, the chemical-shift differences are comparable but in
Six membered heterocycles

Amongst this class of compounds, pyridines are the first to be considered. Retcofsky and Friedel have presented extensive data on 2-,3- and 4-substituted pyridines. The three carbons of pyridine i.e. 2-,4-,6- are deshielded compared with those of pyrrole and behave more like those of substituted benzenes. Carbons para to the substituents in 2-substituted pyridines correlate in a linear fashion with $\sigma$ values. Ipso carbons in both 2- and 3- substituted pyridines correlate in a linear fashion with those of the corresponding monosubstituted benzenes. $^{13}$C chemical shifts of pyridinium ion exhibits $\alpha$-shielding, $\gamma$-deshielding and $\beta$- remains relatively unchanged as compared to those in pyridine.

Shielding of the $\alpha$-carbon on protonation is a common phenomenon for azabenzenes and has been attributed to both changes in N—C bond order and in average excitation energy. The corresponding deshielding of $^{13}$C on
N-methylation has been countered by an opposing $\beta$-effect, so that the net change is small. Formation of pyridine N-oxide offers a different situation. On the one hand, oxygen in a $\beta$-position to carbon C-2 is expected to rather markedly deshield that carbon but on the other hand, the formal negative charge is extensively delocalised on carbon C-2 and C-4, which are correspondingly shielded. This effect is enhanced by generation of a positively charged nitrogen and chemical shifts reflect a chemical balance between these effects$^{94}$.

The effects of phosphorus, arsenic and antimony in the six-membered ring are almost in the same direction as with pyridine and it is the $\alpha$-carbon that is influenced more strongly in the individual compounds.

Polynuclear heteroaromatics

Indole is perhaps the simplest of the polycyclic heteroaromatics and compared with the pyrrole the $\alpha$-carbon (C-2) is deshielded and $\beta$-carbon (C-3) is shielded. The effects of methyl substitution, on the
benzene moiety, have been clarified\textsuperscript{95}. For 1,2-dimethyl-indole, a combination of ortho-para directional effects, steric, and \(\alpha,\beta\)-alkene substituent effects appear operative. Chemical shifts of benzofuran\textsuperscript{96} and benzothiophene\textsuperscript{97} may be compared with the nonfused compounds. Other polycyclic 5-\textsuperscript{98}-104\ and 6-membered\textsuperscript{105-08} heterocyclics have been reported.

\(\textsuperscript{13}C\) NMR spectra of some monoalkyl, dialkyl, trialkyl- and tetraalkyl substituted pyridines have been recorded by Vicar et al.\textsuperscript{109}. \(\textsuperscript{13}C\) NMR shift increments for 3-substituted pyridine and 3,5-disubstituted pyridines have been assigned by Roger and his associates\textsuperscript{110}. 3-Acylpyridines and 3,5-diacylpyridines have also been studied. PMR, \(\textsuperscript{13}C\), and \(\textsuperscript{19}F\) spectral analysis of N-alkyl pyridinium salts and \(\sigma^-\) and \(\sigma^0\) values for N-pyridinium salts have been reported\textsuperscript{111}. Additivity of substituent effects in one bond \(\textsuperscript{13}C-\textsuperscript{1}H\) coupling constants in polysubstituted pyridines has been studied\textsuperscript{112}. The substituent effects on \(\textsuperscript{1}J\ \textsuperscript{13}C-\textsuperscript{1}H\) in polysubstituted pyridines is additive of the substituent shifts of monosubstituted pyridines. This additivity relationship has a diagnostic value in the assignment
of $^{13}$C resonances, where the chemical shift differences are small.

The $^{13}$C NMR spectra of pyridine oxide, quinoline oxide, isoquinoline oxide, quinoxaline mono and dioxide and phenazine dioxide were studied and the $^{13}$C chemical shifts were assigned$^{113}$. SCS of $\alpha$-, $\beta$- and $\gamma$-positions show that there was a strong shielding effect on the carbon in the peri position. Colletta and his co-workers$^{114}$ have given a simple additivity relationship for the substituent effect on the $^{13}$C NMR shifts for the pyridine ring in 2-, 3- and 4- azapyridines and other ethylene and styrylpyridines. $^{13}$C NMR spectroscopic investigations of m- and p- N- methylpyridinium iodides have been studied$^{115}$ and increased nitrogen $\pi$-electron densities in these compounds and its effects have been studied. Excellent correlation has been observed between substituent shift and Hammett substituent constant$^{51}$ when $\sigma_p$ values were used for donor substituents. Several other studies on pyridine derivatives have been carried out in recent years$^{116-119}$.

Zuika and his collaborators$^{120}$ studied the $^{13}$C substituent shifts of halogens, methyl, Me$_2$S-, -SH and
-NH₂ groups of 5- substituted quinolines. The substituent shifts linearly correlated with those for benzenes and correlations with F and R parameters were also found to be linear. They were also found in agreement with those obtained from theoretical calculations. The same authors studied the substituent effects of 8- mercaptoquinoline derivatives and it was observed that the effects are additive. Methyl quinolines and methyl isoquinolines with methyl groups at 7- or/ and 9- positions, 6- or/and 8- positions have been studied. The additivity of the substituent effects in these derivatives have been demonstrated. N- alkyl methyl quinolinium salts were compared with those of the methyl quinoline bases and the substituents effects at the nitrogen atom were studied.

Mc Nab Hamish studied carbon-13 NMR spectra of quinoxaline derivatives by consideration of their ¹H-coupled spectra. Assignments of ¹³C shifts have been accomplished by a first order analysis. Acceptable additivities of substituent effects have been found in the quinoxaline series. Musumarra and Ballistreri have studied ¹³C NMR and direct ¹³C-¹H coupling constants for 2-thienyl- and 2-furanylmethylene propane
dinitriles. Substituent chemical shifts for the heterocyclic ring carbons show similarities between propanedinitriles and the corresponding chalcone analogues.

Musummarra and Ballistreri\textsuperscript{126} have thoroughly studied the substituent effects on $^{13}$C chemical shifts in furan and thiophene chalcone analogues. The effect of substituents on $^{13}$C chemical shifts in phenyl and 5-membered heterocyclic ring have been discussed and these have been correlated with Hammett parameters and experimental substituent chemical shifts. For carbon C-1 to C-4, the substituent chemical shifts are relative to the phenyl-unsubstituted compound in the same series (X=H), while for carbons C-8 to C-11 of the heterocyclic ring, the substituent chemical shifts are relative to the thiophene or furan-unsubstituted derivatives.

$$
\begin{array}{c}
X=OCH_{3},-CH_{3},H,F,Cl,CN,NO_{2} \\
a \quad b \quad c \quad d \quad e \quad f \quad g
\end{array}
$$

$$
Y= -S/-O- \\
Ia \quad Ib
$$

$$
Z=H,CH_{3} \\
W=H,CH_{3},Br
$$

Extensive systematic studies of the influence of the
heteroatom and of other substituents on $^{13}$C NMR spectra of 5-membered heterocyclics have been carried out by Gronowitz and his co-workers$^{127}$. The chemical shift of the ring carbons caused by substituents were found to depend both on substituents and the heteroatom$^{127d}$. The substituent chemical shifts have been correlated to reactivity parameters by the Swain and Lupton$^{51a}$ equation. $^{13}$C substituent chemical shifts of $\alpha$- and $\beta$- carbons of thiophene$^{127b}$ and furan$^{127d}$ have been measured by these authors for a wide variety of 2- and 3- substituted derivatives. Their agreements are not as good as found for the phenyl ring carbons and this, probably, may be due to the inadequacy of the model compounds, which are monosubstituted derivatives measured in different solvents.

The chemical shifts of C-8 and C-11 correlate with the Hammett parameters for the substituents. The $\rho$ values for C-8 are negative, while those for C-11 are positive. The important feature of these studies are the long-range substituent effects in extended $\pi$-electron systems and these have been reported for the 'partially insulated' systems such as benzophenone$^{128}$ and for 'fully insulated' systems such as N-benzylidenebenzylamines$^{129}$. The
unusually high sensitivity to substituent effects at C-5 in thiophene relative to C-para in benzene, already noted by Grönowitz and his associates\textsuperscript{127b}, has been recently verified for arylcarbonium ions and discussed in relation to the calculated charges and other experimental probes of charge distribution\textsuperscript{130}. It has been suggested that any unusual sensitivity of the carbons adjacent to sulfur should be treated as a local effect\textsuperscript{130}.

A semiempirical expression for obtaining the substituent induced $^{13}$C NMR chemical shift in an aromatic side chain is applied to the $\alpha$-carbon atoms of substituted 2-phenylfuran and 2-phenylpyrroles\textsuperscript{131}. Electronic effects of 5-nitrofurans were studied by $^{13}$C NMR spectroscopy by Liepins et al.\textsuperscript{132}. $^{13}$C NMR chemical shifts of the title compounds have been correlated with the Swain-Lupton\textsuperscript{5ln} F and R parameters.

Belen'kii, and Karmonova\textsuperscript{133} have analysed carbon-13 NMR spectra and transmission of electronic substituent effects through furan and thiophene rings. The effects of carbonyl substituents in the 2-position of furan and thiophene on $^{13}$C NMR chemical shifts have been discussed.
Dana and his co-workers\textsuperscript{134} have studied substituent effects in carbon-13 NMR spectra of 2-phenylfuran and 2-phenylpyrrole derivatives. The $\alpha$- and $\beta$-carbons of the heterocycle, conjugated to the substituent X in the para position of the benzene ring, show variations in chemical shifts, which bear a simple relationship to the donor properties of X. This is rationalized by the change in electron density caused by this conjugation. Effect of conjugation is more important in the series of 2-phenylpyrroles than in the series of 2-phenylfurans especially if the behaviour of the $\alpha$-position is considered.

\begin{center}
\begin{tikzpicture}
\node at (0,0) \text{II } R=H \hspace{1cm} \text{III } R=\text{CH}_3 \hspace{1cm} \text{IV }
\end{tikzpicture}
\end{center}

These authors\textsuperscript{134} have thoroughly studied the substituent shifts in the cases of 5-(p-substituted phenyl)furan (II), its 2-methyl analogue, (III) and 5-(p-substituted phenyl)2-methylpyrrole (IV). They have shown that in 4-nitro substitution the carbon C-4 has been deshielded by ca. 3.80$\delta$ in II, the carbon C-3 has been deshielded by ca. 0.67$\delta$ only. The ipso
carbon of the furan ring (C-5) has been surprisingly shielded by ca. 2.50δ although the carbon C-2 has been deshielded by ca. 2.06. It has been exhibited that the electron withdrawing groups deshield the ipso carbon of furan ring (ca, CH₃, 0.59; -OCH₃, 0.25; NH₂, 0.37δ), whereas the carbon C-2 of the heterocyclic ring has been shielded as per the expectation from the mesomeric effect. These authors have drawn a correlation with ψ Hammett parameter values of the substituents and straight lines have been obtained when ψp and δ values were plotted. Similar trends have been observed in the 5-(p-substituted phenyl)-2-methylfuran (III) system as well as the 5-(p-substituted phenyl)-2-methylpyrrole (IV).

Influence of steric interactions in ¹³C NMR spectra of alkyl substituted furans has been studied by Kiewiet and his collaborators¹³⁵. ¹³C NMR spectra of furans substituted with methyl and/or Me₃C- groups showed that the effect of substituents on ring carbon chemical shifts has been found to be additive in nonsterically-hindered compounds. Ring carbon atoms with bulky neighbouring substituents have showed steric shifts. ¹³C NMR parameters have been detected
for 2- and 3- substituted furan derivatives containing strongly electron-attracting or strongly electron-donating substituents, as well as substituents of intermediate character such as $\text{Me}$ and halogens $^{127d}$. The substituent effect on the shifts for certain $^{13}C$ nuclei have been linearly related with those of thiophenes and selenophenes, and in this way, the variation of the total substituent effect with the heteroatom has been established. Electronegativity of the ring heteroatom has been found to be important in this connection. The $^{13}C$ chemical shifts of the furans also gave linear relations with the reactivity parameters, $F$ and $R$ of Swain and Lupton $^{51a}$. The influence of the inductive and mesomeric effects on the chemical shifts in furans, thiophenes and selenophenes were discussed. The substituent bearing carbon atoms, which gave no correlation with the reactivity parameters, $F$ and $R$ of Swain and Lupton equation $^{51a}$, could on the other hand be linearly related with the semiempirical parameter $Q^{51b}$.

$^{13}C$ NMR data were given for variously substituted 1-vinyl-2-arylpurrols $^{136}$ and a linear correlation with $\sigma$ constants has been described. It has been observed that transmission of the substituent effect was
increased owing to conformational effects if one substituent was vinyl group. The effect of substitution, lanthanide shift reagents, solvent changes and tautomerism on the $^{13}$C chemical shifts of pyrrole, pyrazole, imidazole, triazole and tetrazole has also been examined\textsuperscript{137}. The $^{13}$C NMR spectra of a large number of pyrroles have been reported and assigned\textsuperscript{138}. The pyrrole ring carbon chemical shifts were predicted nearest to $\sim 0.5$ ppm, on the basis of additive substituent effects and contributions from steric and conjugative effects. The substituent chemical shift parameters were analogous to those for thiophenes.

Takahashi and his co-workers\textsuperscript{139} have observed $^{13}$C resonances for monosubstituted thiophenes. These authors have drawn correlations between changes in chemical shifts of C-2 resonances, (a): the $\delta$ values of C-2 in 2- substituted thiophenes as ordinate vs. corresponding benzene values as abscissa, (b): $\delta$ C-2 values of 2-substituted thiophenes as ordinate vs. 3-substituted thiophenes as abscissa, (c): benzene derivatives vs. $\delta$ C-2 values of 3-substituted thiophenes (Fig.1.10). The $\Delta \delta$ is measured relative to the unsubstituted compounds. These authors have
observed large chemical shift deviations for the C-X (ipso carbon) of iodo- and methoxythiophenes. The chemical shift deviation from the unsubstituted compound is usually larger for the C-X atoms of 2-substituted compounds than for those of the corresponding 3-substituted compounds (Fig. 1.10). The effects of substituent on the chemical shift of C-X in these three series of compounds are not the same in magnitude but roughly similar in ratio and these deviations of the shifts of the C-X for the same substituent become increasing in the order benzene < 3-substituted thiophene < 2-substituted thiophene. The rationale for this has been advanced that this order may be due to the mutual interaction between the sulfur atom and the substituents. The substituent shift of the C-X increases in the order CH₃-O-<CHO <-CH₃ <-COOCH₃ <-Br and -I for both 2- and 3-substituted thiophenes. The observed range of the chemical shifts due to the position of the carbons in question becomes smaller in the order C-X > C-3 > C-5 > C-4 for 2-substituted thiophenes and in the order C-X > C-2 > C-4 > C-5 for 3-substituted thiophenes and the shift of C-4 in 2-substituted thiophenes falls into a narrow range of 5.26 ppm as compared to those of C-5 with a range of 21.16 ppm.
Fig. 1.10: Correlations between changes of chemical shifts of $\Delta \delta$ resonances: I, 2-substituted thiophene (ordinate) vs. corresponding benzene derivatives (abscissa); II, 2-substituted thiophenes (ordinate) vs. 3-substituted thiophenes (abscissa). III, benzene derivatives vs. 3-substituted thiophenes. The $\Delta \delta$ is measured relative to unsubstituted compound.

Fig.1.11
Similarly a narrow range of 6.206 ppm is also observed in the shift of carbon C-5 in 3-substituted thiophenes. Therefore, it can be concluded that the shift of carbons C-4 in 2-substituted thiophenes and C-5 in 3-substituted thiophenes are most insensitive to the nature of the substituents. A similar situation has been reported for benzene derivative by Spieceke and Schnider.\(^{140}\)

The insensitivity of the chemical shift of C-4 or C-5 in 2- or 3-substituted thiophenes, respectively may be ascribed to the resonance effect of the substituents (Fig.1.11).

The effect of amino and formyl substituents on the \(\Pi\) -electron structure of benzene, thiophene, thiazole and 1,3,4-thiadiazole has been examined via their \(^1\)H NMR, \(^{13}\)C NMR and UV spectra. The effect was especially strong when the ring contained both substituents, which imparted a marked merocyanine character to the compounds. Good agreement was obtained between \(^{13}\)C NMR chemical shifts and calculated \(\Pi\)-electron densities and calculated paramagnetic shielding constants.

Morel and his co-workers\(^{142}\) obtained NMR spectra of mono- and disubstituted selenophenes and analysed in
terms of additive increment effects of substituents. This permitted the calculation of substitution energies for a variety of substituents on the selenophene ring with excellent accuracy. Moegel and his associates\textsuperscript{143} have detected $^{13}$C NMR chemical shifts of some substituted pyrazoles and correlations with $\sigma_p$ constants have been obtained. The chemical shifts have also correlated well with $\Pi$-electron densities. Lam et al.\textsuperscript{144} have used $^{13}$C NMR as a probe for the structural assignment of two isomers of 1,4,5-trisubstituted imidazoles. Structural assignment has been made on the basis of statistical analysis of the $^{13}$C NMR values of the two isomers.

Belenkii and his co-workers\textsuperscript{145} have studied the electronic structure and carbon-13 NMR spectra of 2-phenyl- and 2-methyl-substituted derivatives of oxazole and thiazole. $^{13}$C chemical shift patterns have been related to the charge densities calculated by the CNDO/2 method. Lliñares et al.\textsuperscript{146} have analysed $^{13}$C NMR spectra of a large number of benzoxazoles, oxazole and aminophenols and all the signals have been attributed to substituent effects. The structures of products obtained after nitration of benzoxazole have also been detected by $^{13}$C NMR.
The shifts induced by substitution at 2-position have been discussed as a function of an empirical model by using the structural parameters $F, R_{51a}$ and $Q_{51b}$. $^{13}$C NMR spectra and reactivity of 9-alkenyl-carbazoles in electrophilic addition and cationic polymerization were studied by Filmonov and co-workers. $^{147}$ $^{13}$C NMR spectra of 3-and 3,6-substituted 9-vinylcarbazoles correlated well with Hammett substituent constants. $^{51a}$ $^{13}$C NMR of variously substituted phenylthiazoles were examined and the dihedral angle between the phenyl and thiazole system detected. Comparison of other heterocyclic ring systems with substituted phenylthiazoles indicated that the perturbation observed on phenyl substitution decreased with the increase in heteroatom electronegativity. Steric interactions were observed in 4,5-disubstituted phenylthiazoles and the substituent effects were non-additive; additivity was observed in 2,4- and 2,5-disubstituted phenylthiazoles.

Foster and Pestel $^{149}$ studied the dynamic $^{13}$C NMR spectra of 1-phenyl-3,3-tetramethylene-triazines and observed that $^{13}$C NMR spectra of a
series of para-substituted 1-phenyl-3,3-tetramethylene-triazines gave the band width in methanol which was dependent on temperature. Electron-releasing substituents were to enhance the rate of rotation about the N-2—N-3 bond, whereas the electron withdrawing groups retard the motion. The exchange averaging process in the $^{13}$C NMR studies was found to obey a linear free energy relationship when Hammett parameters were used for correlation.

$^{13}$C NMR studies have also been performed on pyrroline$^{150}$ and $\Delta^1$-pyrrolines$^{151}$ and useful correlation effects were reported. Phenarsazine-10-chloride$^{152}$ was subjected to $^{13}$C NMR studies and its structure elucidation and substituent effects were discussed. The effect of substitution on anisotropic reorientation of phenarsazine system proved that axis of anisotropic reorientation passes approximately through the centre of the molecule. In the case of benzo[c]phenarsazine-7-chloride, the axis of anisotropic reorientation is shifted by $23^\circ$ as compared to 3-chloro substituted system and the shift was found to be directed towards the benzene moiety.
Phenazines were subjected\textsuperscript{153} to \textsuperscript{13}C NMR spectral analysis and substituent shifts were calculated for methoxy, carbomethoxy and methyl derivatives. Oljan and his associates\textsuperscript{154} used \textsuperscript{13}C NMR spectral analysis for structure elucidation of 1,2,4-triaza
tines. \textsuperscript{13}C NMR studies were performed on 3-phenyl-as-
triazine-4-oxides by Bennett and his \textsuperscript{155}collaborators. The substituent chemical shifts of a series of para-substituted 3-phenyl-as-
triazine-4-oxides were ascertained using Swain and Lupton\textsuperscript{51a} and R values. On comparison of the data with those of para-substituted biphenyls, phenylpyrroles and phenylfuran
s, it was observed that the substituent chemicals shifts compared well with those of diphenyl systems.

\textsuperscript{13}C NMR spectra of 1,2,3-thiadiazoles were reported by Looker\textsuperscript{156}. 1,3,4-thiadiazoles were also subjected to \textsuperscript{13}C NMR studies and in DMSO-d\textsubscript{6} solution it was proved that 2-mercapto-5-methyl-
1,3,4-thiadiazole exists predominantly as the thione tautomer.

Breitmaier et al.\textsuperscript{157} have also studied
substituent shifts at various positions in phenazines and a good correlation was observed when compared with the substituent shifts in the benzene series. Phenothiazine, phenoxazine, pyridobenzothiazine and their derivatives were analysed\textsuperscript{158} by \textsuperscript{13}C NMR spectral analysis and it was observed that substituents influence only the \textsuperscript{13}C chemical shifts of the substituted carbocyclic ring while the chemical shifts of unsubstituted rings are not disturbed much.

Todashi and Takayuki\textsuperscript{159} have undertaken \textsuperscript{13}C NMR studies on benzo[\textsubscript{2,3-b}]furan derivatives having substituents at various positions and have studied the substituent shifts at C-2 in 5- and 6-substituted derivatives. They arrived at the conclusion that the substituent shifts obey modified Hammett equation, \( \delta = \rho_1 \sigma_1 + \rho_2 \sigma_2 \). According to their observation, the electronic effects were transmitted through the bond \textsubscript{3a-3}. The ground state electronic structure was similar to that of styrene rather than phenylvinyl ether.

Effect of methyl substituents additivity and steric effects on \textsuperscript{13}C NMR chemical shifts of
benzofurans has been reported by Nicole and his collaborators.\(^{160}\) \(^{13}\)C NMR studies of a series of 5-substituted benzimidazoles were carried out by Blackburn and his associates.\(^{161}\) The substituent shifts have been correlated with F and R values of Swain and Lupton\(^{51a}\) and Q* values of Schaefer\(^{51b}\).

Fruchier and his co-workers\(^{162}\) subjected benzimidazole derivatives to \(^{13}\)C NMR studies along with their benzimidazolium salts and substituent shifts were calculated. Investigation of transmission of the substituent effect in 2-substituted 1-methylbenzimidazoles were carried out by Lopyrev and his associates\(^{163}\) and the substituent shifts of various substitutions at the position-2 have been reported to be transmitted to C-4 and C-7 positions mainly by resonance mechanisms and to C-5, C-6 and N-methyl by approximately equal contribution of the resonance and inductive effects.

Benassi et al.\(^{164}\) undertook \(^{13}\)C NMR studies of benzimidazole, benzoaxazole, benzothiazole, N-methyl benzimidazole and 2-N, N-dimethylamino derivatives. They have studied the effect of N-protonation and N-methylation on \(^{13}\)C chemical shifts. Garnier
and his associates have thoroughly studied $^{13}$C NMR substituent shifts in mono, di- and trialkyl thiazoles. They also studied $^{13}$C–$^1$H values and concluded that these were insensitive to the position of substituent in the ring. Substituted 2-phenylbenzothiazoles when subjected to $^{13}$C NMR studies, the valuable information regarding the substituent shift correlated well with the calculated substituent shifts which were calculated by substituent additivity method. The relationship between $^{13}$C chemical shifts and the total charge densities of the corresponding carbon atoms were obtained by regression analysis. Charge densities were calculated by EHMO method.

$^{13}$C NMR spectral studies of benzothiazoles were undertaken by Faure et al. and $^{13}$C chemical shifts were assigned unambiguously in the 4-, 5-, 6- or 7-substituted benzothiazoles. The substituent shifts have been discussed as functions of nature of the substituent at C-2, annulation in benzo heterocyclic series, and prototropy in 2-hydroxy, 2-SH, 2-NH$_2$ substituted benzothiazoles.

Transmission of substituent effects in the substituted benzothiazole system were also reported
by Sawhney and Boykin\textsuperscript{169}. Correlation of chemical shifts with Hammett constants and slightly better correlations with linear combination of $\sigma_m$ and $\sigma_p$, Swain-Lupton\textsuperscript{51a} were determined for carbons C-2 and C-8. They concluded that resonance effects are primarily responsible for substituent effect on chemical shifts at these carbons. Transmission of substituent effect by sulfur atom is limited and the primary path of transmission of substituent effects to carbon-2 is through nitrogen by mesomerism.

Charge densities of 2-substituted pyrazines, 5-substituted pyrimidines or 4-substituted pyridazines were calculated by MINDO/2 method\textsuperscript{167,170}. The correlation of the ipso SCS with linear combination of substituent constants was found to be poor. Turner and Cheeseman\textsuperscript{171} reported $^{13}$C NMR spectra of pyrimidines and the substituent shifts were calculated with the $\eta$-electron densities. It was further observed that the substituents like $-\text{NH}_2$, $-\text{OMe}$ and $-\text{F}$ exerted more effect in the benzene series in comparison to that in pyridine and pyrimidine series. The effect of methyl and $-\text{NH}_2$ substituents on the chemical shifts were also reported by Riand and his associates\textsuperscript{172}. 
Turner and Cheeseman\textsuperscript{173} subjected monosubstituted pyrazines to \textsuperscript{13}C NMR studies and according to their observation, trends in \textsuperscript{13}C chemical shifts were parallel to those in monosubstituted benzenes and 2-substituted pyridines except that for the ipso carbon. Moreover, the substituent effects on the chemical shifts exhibited similar trend both in \textsuperscript{13}C NMR and PMR spectra.

Some papers have appeared on \textsuperscript{13}C NMR studies of coumarins\textsuperscript{174-181}. Some of these authors\textsuperscript{175} have applied Swain and Lupton\textsuperscript{51a} parameters to these compounds. Elgamal et al\textsuperscript{176} have reported \textsuperscript{13}C NMR spectral studies of furocoumarin derivatives. Correlation with Hammett constants in 6- and 7-substituted coumarins were reported by Gottlieb and his associates\textsuperscript{181}. The chemical shifts of the $\alpha_\beta$-unsaturated lactone system were correlated with the Hammett constants\textsuperscript{51a}. The electronic implications of these relations have been discussed by these authors\textsuperscript{181}. 
Table - 1.4

$^{13}$C Substituent effects of mono-substituted benzenes.

<table>
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<th>Substituent</th>
<th>C-1</th>
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<th>meta</th>
<th>para</th>
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a Parts per million relative to internal benzene standard; positive shifts deshielding, Solute concentration, 10% in CCl₄.
b Parts per million relative to benzene. Data obtained relative to internal TMS and converted using ¹JC=128.5 for benzene.

t Solute concentration 10% in CDCl₃.
c Neat liquids examined unless noted otherwise. Data converted using ¹JC=128.7 for benzene.
d In N, N-dimethylformamide.
e Original data obtained relative to CS₂. Conversion ¹JC=192.8 was used for CS₂.
f See Footnote e. Conversion ¹JC=193.7 was used for CS₂.
g Solvent unspecified.
h CF₃CO₂H solvent.