Studies of Barriers to Rotation in some 3-Arylcyclohexenone Derivatives: Effect of Substituents on the Free Energy of Activation.

Introduction: The present work is a continuation of a research programme first initiated in our laboratory in 1975 by Nasipuri and Mukherjee. It was observed by these workers that appropriately substituted 2-aryl-6-oxocyclohex-1-enylacetic acid derivatives (I) showed appreciable energy barrier to rotation about the aryl-cyclohexenone bond. The free energies of activation as determined by dynamic nuclear magnetic resonance spectroscopy were quite high (16-22 Kcal mol\(^{-1}\)) perhaps marginal for resolution into stable enantiomers but admirably suitable for study by d.n.m.r. Only three compounds (see later) were studied by these workers and the data were not sufficient to afford any reasonable conclusion to be drawn from them. In the past, attempts have been made to examine the effect of substituents on the barrier to rotation about single bonds both qualitatively\(^2,3\) and quantitatively\(^4,5\) but such studies have been confined mainly to biphenyl derivatives. The arylcyclohexenones mentioned above (as I) are easy to prepare, offer a reasonable variation of substitution patterns in

CHART I

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\begin{align*}
&\text{IIa} & \text{IIb} \\
&\text{TRANS} & \text{GAUCHE} & \text{GAUCHE}
\end{align*}
\]
the aromatic ring, and are thus convenient for such an investigation. About a dozen of these compounds have now been studied by d.n.m.r. and the free energy of activation of internal rotation has been determined in appropriate cases. The significance of steric and electronic factors on the energy of activation is discussed and an attempt made to explain an anomalous result encountered in a previous experiment.

Before presenting the results of investigations, the concept of restricted rotation about single bond in organic molecules and the principle by which the energy barrier is measured are discussed below.

Restricted Rotation about C-C Single Bond.

Actually the phenomenon of restricted rotation was known a long time back - as early as 1922 when 6,6'-dinitrodiphenic acid was resolved into two stable enantiomers (IIa) and (IIb). Subsequently, many o,o'-substituted biphenyls and styrene derivatives have been found to be resolvable giving rise to what is now known as atropisomerism. The principle behind the existence of this type of enantiomerism is very simple - the rotation of the two phenyl rings around the aryl-aryl bond is restricted so much so that at ordinary temperature one form cannot go into the other because in the planar transition state the bulky ortho-substituents cause considerable steric interaction. In the

early stage of investigation, there was no means to determine the energy barrier between the two enantiomers (actually two rotamers or conformers), except for the fact that the distance between the two ortho-positions could be determined and compared with the van der Waal's radii of different atoms and groups. These cases of restricted rotation about two \( sp^2 \)-hybridised carbon atoms leading to separation of two enantiomers have already been reviewed in various text-books\(^7,8\) and review articles\(^9\).

In contrast, it has long been believed that the rotation about two \( sp^3 \)-hybridised carbon atoms is completely free and it is only in 1936 that the concept of restricted rotation has to be brought in ethane type of molecule\(^10\) although even now the origin of this energy barrier is still not very clear. A typical example of this kind is the existence of three conformers of \( n \)-butane molecule, as shown in the Chart which are separated from each other by an energy barrier equal to 3.5 Kcal mol\(^{-1}\) which is too small to warrant their existence as separate entity but enough

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to affect various thermodynamical parameters of the molecule. Since then many investigations have been performed on the internal rotation in ethane derivatives making use of infra red and microwave spectroscopy. Restricted rotation has now been recognised as a universal phenomenon not only in carbon compounds but also in molecules containing other trigonal or tetrahedral atoms. Whether such restricted rotation could lead to additional stereoisomerism depends on the magnitude of the barrier. It is believed that atropisomerism is realised at room temperature only when the energy barrier to rotation about the bond in question is higher than 23 Kcal mol⁻¹ assuming the mean life time of 1 hour at 25°C and the frequency factor of 10⁻¹¹ sec⁻¹. Oki and coworkers have isolated several stable rotamers about sp³-sp³ carbon bonds which have been reviewed in a recent article.

Restricted Rotation and Dynamic Nuclear Magnetic Resonance.

Rotation about a single bond may be visualised as an intramolecular dynamic process characterised by rate constants depending on the energy barrier. Previously, molecules like biphenyl derivatives with appreciable energy barrier had to be resolved into enantiomers in order to investigate the rotation about the pivot bond and the polarimetry was the sole method of investigation. Now-a-days, however, it is possible to study

the hindered rotation by means of dynamic nuclear magnetic resonance (d.n.m.r.) when the energy barrier is just on the border line (18-23 Kcal/mol) where compounds become too unstable to be isolated chemically, down to a barrier of 5-6 Kcal mol\(^{-1}\) below which another powerful tool, microwave spectroscopy can be applied. The d.n.m.r. technique can be used to any process which is characterised by rate constants of an order of magnitude as the total spread (in cycles per second) of the n.m.r. spectra (typically 10\(^{-1}\) to 10\(^{5}\) sec\(^{-1}\))\(^{14}\). Rate process involving reversible intermolecular proton transfer, rotations around sterically crowded single bonds and single bonds with partial double bond character, inversion of lone electron pairs on nitrogen and phosphorus, inversion of carbocyclic and heterocyclic rings, and degenerate valence isomerisations, and intramolecular rearrangements are among the more common phenomena where d.n.m.r. technique is found to be very helpful. It will show changes of the shape of n.m.r. signals with change of temperature with consequent change of rate constants (changes in n.m.r. spectra could also be brought about by the variation of pH and magnetic field). If the average life time of a number of species (in the case of the biphenyls and analogues, the two enantiomeric forms and in the case of the ethane derivatives, the three rotamers) in equilibrium exceeds the n.m.r. time scale then the spectra will show them as individual entities. On the other hand, if the life times are short with respect to n.m.r.

time scale, a single spectrum will be obtained in which the chemical shifts and also the coupling constants are statistically weighted averages of the corresponding values of the exchanging species. An illustration may be given by the n.m.r. spectra of a compound typified by $\text{HCH}_2\text{CH}_2\text{Y}_2$ taken at various temperatures. The molecule exists in three conformers (IIIa), (IIIb), and (IIIc), two of which (IIIb) and (IIIc) are enantiomeric and will give identical n.m.r. spectra whereas the trans conformer (IIIa) will give a different one. These conformers are separated by low energy barrier and their population which is in dynamic equilibrium will depend on their relative free energies. At high temperatures, the rate of interconversion will be very fast on n.m.r. time scale, the three conformers will be almost equally populated, and the chemical shifts of the two protons and their coupling constant will be averaged out for the values of the three conformers, and the n.m.r. spectrum will be simple showing an AB-quartet. At very low temperature, the rate of interconversion may be slow on n.m.r. time-scale, and the spectrum will be a complex one due to superposition of the spectra of two gauche and one trans conformers. There will be two AB-quartets, one due to the gauche conformers and the other due to the trans conformer with a relative intensity of 2:1. At intermediate temperatures, a series of complex and broadened by exchange spectra will be obtained which provide information about the

In the case of biphenyl derivatives and the compounds of the type (I) to be discussed, the cause of nonequivalence lies in the rotation around a single bond being slow on n.m.r. time scale. As soon as the rotation becomes appreciable, the time-averaged environments of the two ligands (-CH₂- in case of I) are enantiotopic. At higher temperatures (or even at ambient), therefore, only a single signal will be observed. Unlike the chiral molecule (XVI), there will be no residual intrinsic nonequivalence in these compounds.

Application of Nuclear Magnetic Resonance Spectroscopy to Investigate Dynamic Molecular Stereochemistry.

A few examples collected from the vast literature regarding the application of temperature variant n.m.r. technique for studying the dynamic molecular stereochemistry are now given. As already pointed out, one of the first examples of biphenyl derivatives is due to Meyer and Meyer who determined the coalescence temperature (T_c) of the AB-quartet of 6,6'-diethyl-2,2'-bis(acetoxy-methyl) diphenyl (IV, page 7). From the examination of the shape of the outer peaks of the AB-quartet at intermediate temperatures where they first broaden and then disappear, the average lifetime of a molecule at 94° between rotation was calculated to be 4 sec. and the barrier to rotation to be 13 Kcal mol⁻¹.

1. Bridged Biphenyl Derivatives:

Kurland et al. studied the conformational rate processes in the bridged biphenyl (XVII; R = H, Y = O and S). The deviation

from coplanarity causes the methylene protons to give AB-quartet as soon as the rotation about the biphenyl and the concomitant ring inversion of the 1,3-cycloheptadienyl system become slow on the n.m.r. time scale. A complete line shape analysis for compounds (XVII, \( R = H \), and \( Y = O \) and S) gave activation energies of 9.2 and 16.1 Kcal mol\(^{-1}\) respectively.

A few other bridged biphenyls (XVIII) including doubly bridged compounds have been similarly studied by different groups of workers.\(^{26-28}\)

House and coworkers\(^{29}\) prepared a number of 1,8-diaryl-naphthalene derivatives (e.g., XIX and XX) and showed that they cannot be resolved into stable configurational isomers (diastereoisomers). D.n.m.r. studies of these derivatives indicated that \( \Delta G^\ddagger \) for rotation was 15-16 Kcal mol\(^{-1}\). In a subsequent paper\(^{30}\), they showed that in the 1,8-diarylnaphthalenes, the two phenyl rings are parallel to each other and perpendicular to naphthalene ring. The observed variation in C-Me signals with temperature in the compound (XXI) was simulated with a computer programme to allow determination of the pre-exchange life-times at various temperatures. From these the activation energy for rotation was

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CHART V

XXIa (cis)  
XXIib (trans)  
XXIII

XXIV

a : X = OMe, y = NO2  
b : x = y = OMe  
c : x = y = F  
d : x = y = Br  
e : x = y = CO2Me
calculated to be 16 Kcal mol\(^{-1}\) at 25\(^\circ\). Clough and Roberts\(^{31}\) have recently done d.n.m.r. studies on 1,8-di-o-tolylnaphthalene (XXII). The proton n.m.r. of compound (XXII) showed two sharp singlets for methyl separated by 2 Hz at 60 MHz. The two diastereoisomers (XXIIa) and (XXIIb) were separated and the equilibrium constant, \(\text{trans/cis}\) was found to be 3.21 which corresponded to a free energy difference of 0.73 Kcal mol\(^{-1}\) in favour of the trans isomer. The calculated \(\Delta G^\ddagger\) for rotation was found to be 24.1 Kcal mol\(^{-1}\), about 8 Kcal mol\(^{-1}\) greater than that of 1,8-diphenylnaphthalene derivatives lacking orthomethyl groups.

Bergman and Chandler\(^{32}\) have determined barrier of rotation in some highly substituted ethers (XXIII).

Oki and coworkers have studied the effects of substituents on the energy barrier of inversion in some biphenyl as well as \(o, o'\)-bridged biphenyls. They synthesised the compounds (XXIV) and measured the n.m.r. spectra over a wide range of temperature. In each case the inversion rate \(k_c\) at \(T_c\) were calculated. From the line width \(W\) of the coalesced singlet, the approximate inversion rate \(k\) at various temperatures was obtained by means of the equation:

\[
k = \frac{\pi \Delta v^2}{2 (W - W_o)}
\]

where \(W_o\) is the extrapolated line width for \(k = \infty\). Arrhenius


Plots gave parameters $E_a$ and $\log A$ from which Eyring parameters were also calculated by appropriate equation.

Later, they prepared\textsuperscript{3,5} the two compounds (XXV) and (XXVI) and studied the coalescence of the double doublets of methyl group. In case of compound (XXV), the double doublets neither broadened nor coalesced up to $180^\circ$ indicating that the free energy of activation for rotation is higher than $27 \text{ Kcal mol}^{-1}$. The compound (XXVI) proved to be a suitable substrate for d.n.m.r. study. The methyl groups showed up as pair of doublets which coalesced to a broad singlet at $86^\circ (T_c)$ and then split into two sharp peaks at $150^\circ$. The intrinsic chemical shift difference without exchange varied almost linearly with temperature. Inversion rate $K_c$ at $T_c$ was calculated using the equation\textsuperscript{34}:

$$K_c = \frac{\pi \Delta \gamma^o}{\sqrt{2}}$$

where $\Delta \gamma^o$ represents the chemical shift difference of the two methyl groups without exchange; $\Delta \gamma^o$ was obtained by extrapolating the chemical shift difference at various temperatures up to $T_c$. Approximate inversion rate, $K$ at temperatures about $T_c$ was calculated following the fast exchange approximation:

$$K = \frac{\pi (\Delta \gamma^o)^2}{2(W - W_o)}$$

where $W$ and $W_o$ are the signal width at half height at a


given temperature and at a free exchange in the n.m.r. time scale respectively. The value of \( w \) at highest temperature was taken as \( W_0 \); \( K \) values were plotted against the reciprocal temperature which gave fairly good linearity. The inversion rate at 86° was obtained graphically from the plot and \( \Delta G^\ddagger_{86} \) was calculated as 18 Kcal mol\(^{-1} \).

2. \( o,o' \)-Disubstituted Aromatic Ketones:

Nakamura and Oki\(^{35} \) studied the rotational barrier of some \( o- \) and \( o,o' \)-disubstituted aromatic ketones as (XXVII) and (XXVIII) which can exist into two enantiomeric nonplanar conformers. For the benzyl ketone (XXVIII), \( \kappa_c \) and \( \Delta G^\ddagger_0 \) at \( T_c \) were calculated using the two equations:

\[
\kappa_c = \sqrt{\frac{\Delta \gamma^2 + 6j^2}{2}}
\]

\[
\Delta G^\ddagger = 4.57 \ T_c \left( 9.97 + \log \frac{T_c}{\sqrt{\Delta \gamma^2 + 6j^2}} \right)
\]

3. Systems Involving High Barriers to Rotation around Tetrahedral Atoms.

Molecules with appreciable energy barrier around single bond between two tetrahedral carbon atoms have also been prepared and in some cases, actual stereoisomers separated. The subject has been covered by a recent review by Oki\(^{13} \). Two examples are given below from his own work\(^{36} \).


CHART VI

XXV

XXVI

XXVII

XXVIII

XXIX

XXX
Compound (XXIX) showed two lines for the tert. butyl protons but the n.m.r. spectrum at 132° gave no sign of coalescence or line-broadening suggesting an energy barrier higher than 25 Kcal mol⁻¹. The steric conditions of the triptycene analogue (XXIX), therefore, meet the requirement for the resolution or isolation of rotamers as stable entities at room temperature (see also ref. 37). The activation energy for rotation of the isopropyl-analogue (XXX) was found to be 15 Kcal mol⁻¹. In view of the excellent review of Oki, we think it unnecessary to present any further data in this line. Moreover, this is not strictly relevant to our present investigations.