NMR SPECTROSCOPIC AND CHEMICAL STUDIES ON AROMATIC CHARACTER AND REACTIVITY

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by

G. GOPAKUMAR, M. Sc.

NATIONAL CHEMICAL LABORATORY
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C O N T E N T S

PART I

LONG RANGE SPIN-SPIN COUPLING IN THE STUDY OF AROMATIC PI-ELECTRONS

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INTRODUCTION

Although long range spin-spin coupling between protons on sp^3 hybridized carbon atoms and ring protons in aromatic compounds has been studied by a number of investigators[1-6], there has been no attempt to study the variation of this coupling (hereafter referred to merely as "benzylic coupling") with π-electron distribution. Other than complete determinations of structure by X-ray crystallography, the methods available at present to the chemist for ascertaining even the relative magnitudes of π-bond orders are very limited. The carbonyl stretching frequencies in O-hydroxy acetyl derivatives of aromatic compounds were found by Hunsberger, Ketcham and Gutowsky[8,9] to be a decreasing function of the mobile bond order between the substituted positions. Practical applications of this relationship are, however, attended by serious difficulties and uncertainties since they are complicated by steric and other factors[10,11]. Vicinal proton-proton coupling constants in aromatic systems have been shown to be linearly related to mobile bond order by Jonathan, Gordon and Bailey[12].

However, vicinal coupling is the sum of two factors. The larger part is due to coupling that proceeds entirely through σ -bonds and the smaller involves π-bonds. The margin of uncertainty for the first factor would make it difficult to use vicinal coupling constants for measuring bond orders[13]. It was therefore considered that a study of the variation of benzylic coupling as function of π-electron distribution would, in spite of the small magnitudes involved, be of considerable value. In order to set the present investigation in the proper perspective, the literature on benzylic and allylic coupling that was available at the start of this study is briefly reviewed below.

Long range spin-spin interactions between methyl protons and aromatic or olefinic protons in a large number of aromatic, olefinic and heterocyclic compounds were reported by Hoffman[1,14]. He observed that in the spectra of mesitylene and m-xylene the methyl protons are coupled to aromatic protons with J = 0.62 cps and 0.45 cps respectively. In orthosubstituted toluenes the spin coupling was found to be dependent on the nature of the substituent. He suggested that the main contribution to the long range

spin-spin interactions is due to hyperconjugation between the π-orbitals of the unsaturated systems and the C-H bond orbitals of the methyl group. As experimental proof of this argument, Hoffman[1] cited the examples of methyl substituted semiquinones, 1,4-naphthosemiquinone and dimesityl methyl, the electron resonance spectra of which revealed hyperfine splittings due to the methyl protons which were of the same order of magnitude as those due to ring protons.

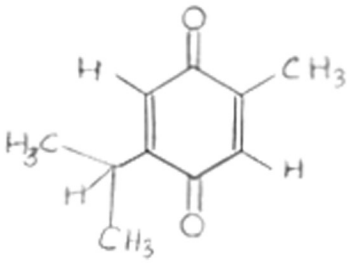
The multiplicity of the methyl signal in the NMR spectrum of 2,2' dimethyl-diphenyl ether which was explained by Shimizu, Fujiwara and Morino[2] as due to the nonequivalence of the methyl groups, was later shown by Tiers, Bovey and Shapiro[3] to be the result of long range spin-spin coupling of the methyl protons with the aromatic protons. Tiers et al. found that this separation between the two signals of the methyl is not temperature dependent and also that the gross peak half-width does not change as the radio-frequency varies from 40 to 60 Mc.

It was observed by Rottendorf and Sternhell[4] that in a number of para-disubstituted benzene derivatives, where one of the substituents is an sp^3 carbon atom carrying one, two or three hydrogens, the portion of the A_2B_2 pattern

assigned to the pair of ring protons ortho to the methyl, methylene or methine substituent is conspicuously broad. They concluded that this arises from long range interaction between the benzylic protons and the ring protons in the ortho position to the benzylic substituent. This was further supported by the measurement of the width of the methyl bands at half-height in the three isomeric methoxy toluenes and comparison of the methyl band widths with the methoxyl band widths.

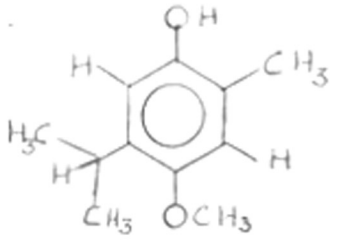
In the NMR spectrum of 3,5-di-t-butyl-4-hydroxy-toluene, the methyl was observed[5] to give a triplet with J = 0.60 cps.

That J, the coupling constant for interaction through four bonds, is dependent on the type of the double bond involved has been pointed out[6,7] through the interesting example of thymolquinone (I) and the monomethyl ether (II) of the corresponding quinol.



$J_{\text{long-range}}$ = 1.5 cps

I



$J_{\text{long range}}$ = 0 cps.

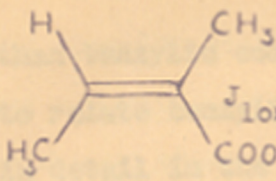
II

While in (I), where the 2-3 bond is very much like an ethylenic double bond there is observable splitting of the methyl, in II where the ring is fully aromatic in nature, there is no observable interaction between the aromatic protons and the side chain protons.

Long range spin-spin coupling between C_1 and C_3 protons in allylic systems (separated by four bonds), i.e. allylic coupling, has been extensively investigated[15,16]. Various olefinic hydrocarbons, aldehydes, acids and other derivatives have been examined in this connection and the allylic coupling in these systems have been found to vary from 0 to 3 cps. Generally the cis coupling is found to be slightly greater than the trans coupling[17]. Similar long range couplings between methyl and ring protons in heterocyclic systems have been observed by a number of workers[14,18-21]. Reviews on these and other types of long range interactions have appeared[15,16,17]. Some examples of unsaturated and heterocyclic systems with the corresponding J values are given in Fig.1.

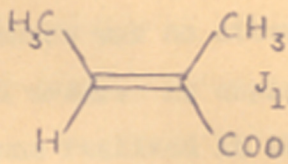
In compound (XI) the high value of the long range coupling constant is indicative of the absence of aromatic character.

From the foregoing it can be seen that indications were available that allylic coupling is usually stronger



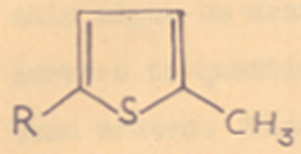
$J_{long\ range} = 1.2 - 1.3$ cps

III[14,22]



$J_{long\ range} = 1.4$ cps

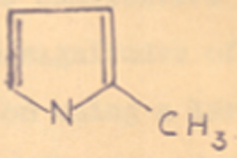
IV[14,22]



R= -D, -Br, $-SCH_3$, $-NO_2$, -CHO etc

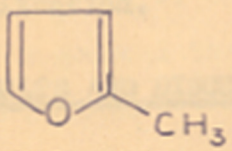
J = 1 - 1.15 cps

V[14]



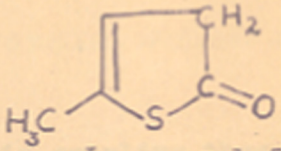
$J_{CH_3-H_3} = 0.6$ cps

VI[18]



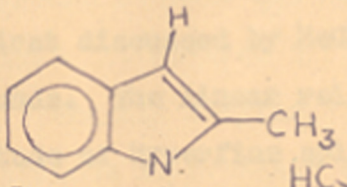
$J_{CH_3-H_3} = 0.9 - 1.1$ cps

VII[18,19]



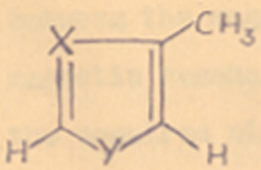
$J_{CH_3-H} = 1.5$ cps

VIII[14]



$J_{CH_3-H_3} = 1.0$ cps

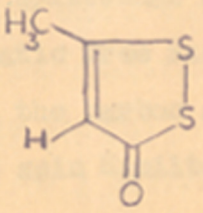
IX



X = N, Y = S; $J_{CH_3-H_5} = 1.0$ cps

X = N, Y = O; $J_{CH_3-H_5} = 1.28$ cps

X[23]



$J_{CH_3-H} = 2.9$ cps

XI[17,24]

FIG. I

than benzylic coupling. However, there was no attempt to relate benzylic coupling to bond order. As explained in detail in the next Section, it was realized at the beginning of this study that benzylic coupling should be proportional to the square of the mobile bond order between the aromatic carbon atoms involved and that this relationship might be useful in finding at least qualitative answers to questions involving relative magnitudes of mobile bond orders. The following investigation using a large number of methyl substituted aromatic compounds was undertaken with the object of testing the soundness of this proposition and defining the limitations in its application.

RESULTS AND DISCUSSION

Long range nuclear spin-spin coupling through π electrons was first discussed by McConnell[25] for the case of aromatic compounds. The linear relationship observed between the magnitude of hyperfine splittings in the paramagnetic resonance spectra of aromatic free radicals and the unpaired electron densities at the carbon atoms involved was used to formulate an effective spin Hamiltonian for

the coupling between π-electron spin and proton spin. The π contribution to the coupling between protons attached to carbon atoms M and M' was shown to be given by the expression,

$$J^{\pi}_{MM'} = (BQ)^2 \; P^2_{MM'} / \; h\,\Delta E \qquad \ldots\ldots \qquad (1)$$

where $P_{MM'}$ is the mobile bond order between the carbon atoms, Q the isotropic hyperfine splitting constant, B the Bohr magneton and ΔE an average electronic (singlet-triplet) excitation energy. Using the same technique, an expression of the same form was later derived by Karplus[26] for ethylenic systems which could be applied for cases involving coupling through four or five bonds. These treatments are modifications of the general theory of electron-coupled nuclear spin-spin interaction.[27]

In the background of this theoretical work it was realized[28] that equation (1) derived by McConnell could be made applicable to "benzylic coupling" i.e. coupling between benzylic and ring protons in aromatic compounds, if one of the Qs is replaced by the hyperfine splitting constant (Q') for the .C-X fragment where X is the benzylic carbon atom bearing protons. Making allowance for a possible σ-contribution benzylic coupling may therefore be expected to be

linearly related to the square of the mobile bond order (p). For all the compounds used in this study X is a freely rotating methyl group. The extension of equation (1) to the case of benzylic coupling was also suggested by Dewar and Fahey[29] by the time the preliminary results of this study were available.

The data describing the nature of the methyl signals of the 60 Mc PMR spectra of the methyl-substituted aromatic compounds that have been examined are presented in Table I. In most of the cases where clear splitting is observed, the signals display fine structure and only the largest coupling is readily estimated. In cases where visible splitting is not observed the width of the methyl signal at half height (band width) is used as a measure of benzylic coupling in a very limited way. Comparison of band widths is made only under comparable spectrometer conditions indicated by the width of the reference signal of tetramethylsilane. In the monomethyl derivatives, the π-electron distribution may be assumed, as a first approximation, to be nearly the same as in the parent compounds. The methyl signals of these compounds are clearly split in all cases where an aromatic C-C bond connecting the methyl group to an ortho proton has a large mobile bond order (p).

TABLE I

No.	Compound	J_{CH_3-Ar}	Band width in cps
1	Toluene	-	1.15
2	2-Bromotoluene	0.428	1.08
3	2-Deuterotoluene	-	0.85
4	1-Methylnaphthalene	0.7	1.5
5	2-Methylnaphthalene	0.7	2.0
6	1-Bromo-2-methyl-naphthalene	-	1.1
7	1-Deutero-2-methyl-naphthalene	-	1.2
8	1-Methyl-6-isopropyl-naphthalene	0.76	1.4
9	1-Methyl-7-isopropyl-naphthalene	-	1.4
10	1,6-Dimethyl-4-ethyl-naphthalene	1 .. -	1.5
		6 .. 0.4	1.9
11	1,6-Dimethyl naphthalene	1 .. 0.78	1.56
		6 .. 0.70	2.0
12	1,6-Dimethyl-4-isopropyl-naphthalene	1 .. -	1.6
		6 .. -	2.05
13	1,2-Dimethylnaphthalene	1 .. -	2.2
		2 .. -	2.2
14	2-Methylbenzanthrone	0.5	2.0
15	10-Methylbenzanthrone		1.85
16	4-Methylbenzanthrone	0.6	1.8

.....contd.

TABLE I (Contd.)

No.	Compound	J_{CH_3-Ar}	Band width in cps
17	16,17-Dimethyl-dibenzanthrone	-	2.6
18	2-Methylanthracene	0.8	2.6
19	9-Methylanthracene	0.625	1.4
20	10-Bromo-9-methylanthracene	-	0.6
21	2-Bromo-4-nitrotoluene	0.4	1.5

The author wishes to record his gratitude to Dr. Sukh Dev and Mr. J.R. Prahlad for sparing us samples of compounds 9, 10 and 11, to Dr. S.C. Bhattacharya and colleagues for samples 12 and 13 and to Dr. C.J. Sanchorwala for samples 15, 16, 17 and 18.

The methyl signals of 2-methyl-naphthalene, 1-bromo 2-methyl-naphthalene, 1-deutero 2-methylnaphthalene and 2-methyl-anthracene are shown in Fig.2 while those of 1-bromotoluene, toluene, 9-methyl-anthracene and 9-methyl 10-bromo anthracene are shown in Fig.3. For 2-methyl-naphthalene and 2-methyl-anthracene the observed couplings are to C_1 protons. On substitution of the 1-position in 2-methylnaphthalene with bromine or deuterium the splitting of the methyl signal disappears and the methyl band-width is decreased from 2.0 to 1.1 cps. The well known difference in the p values for the 1-2 bonds of naphthalene and anthracene is reflected in the observed splittings (0.7 and 0.8 cps respectively) for their 2-methyl derivatives. The couplings to the protons in the 3-positions in these compounds are very small as may be expected. 1-Methyl-naphthalene also shows a similar methyl spectrum although the band-shape is somewhat different. That the observed coupling in 2-bromotoluene is to the 6-proton and not to the 4-proton is clear from the presence of this coupling (0.4 cps) in 4-substituted 2-bromotoluene also.

The case of the three methyl benzanthrones studied provides a clear illustration of the bond order dependence of benzylic coupling. The molecular orbital calculations

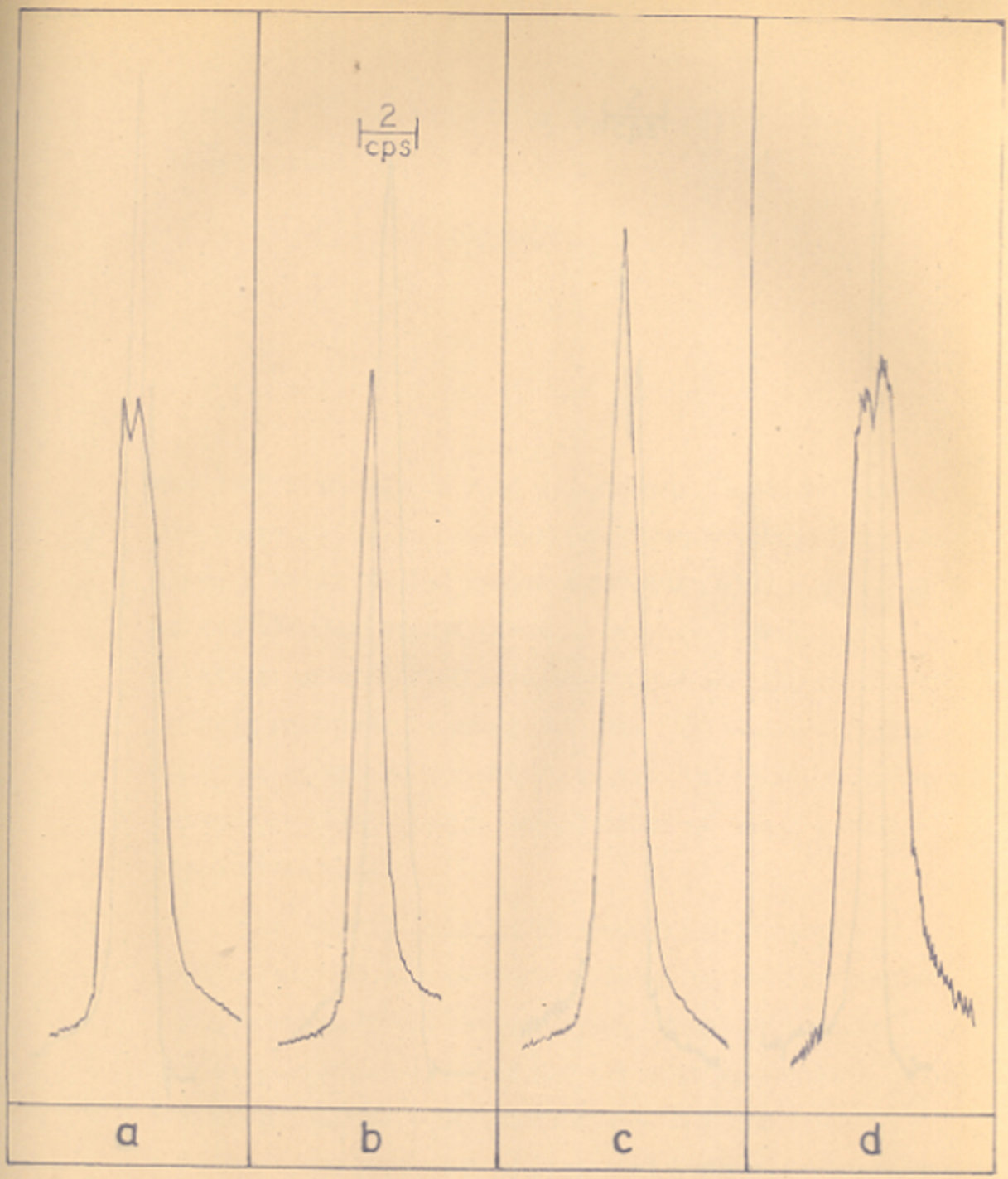
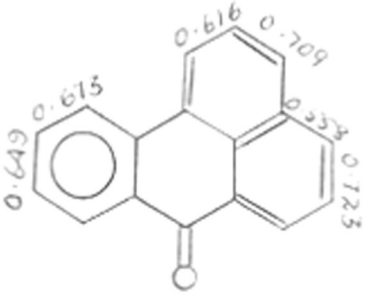


FIG.II - METHYL SIGNALS of (a) 2-methylnaphthalene (b) 1-bromo-2-methylnaphthalene (c) 1-deutero-2-methylnaphthalene and (d) 2-methylanthracene.

of Goodwin[30] give the following bond orders for benzanthrones



The methyl signals of 4,10 and 2 methyl benzanthrones are shown in Fig.4. Whereas the first of these compounds gives a clean doublet methyl absorption with a coupling of 0.6 cps, the second gives an unsplit signal. The behaviour of the third is intermediate and the corresponding splitting is about 0.5 cps. It is readily seen that the nature of the methyl signal reflects the different extents of "fixation" or localization of the π bonds in these three rings.

The α-methyl signals of 1-methyl 6-isopropyl naphthalene and 1,6 dimethyl naphthalene show splittings of 0.76 and 0.78 cps respectively. These values are higher than those observed for 1-methyl naphthalene itself. The approximation that substitution does not affect π-electron distribution is apparently not valid in these

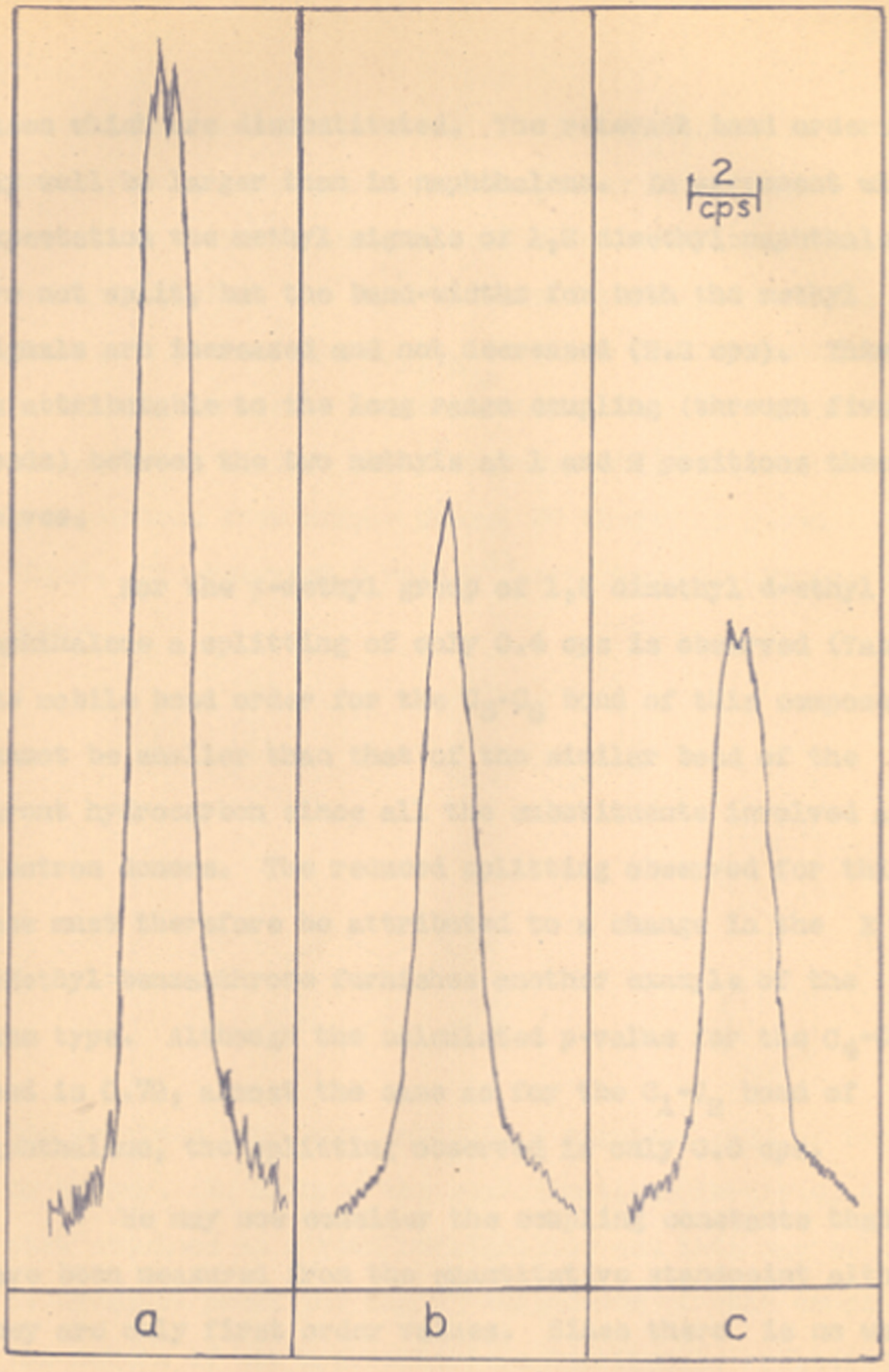


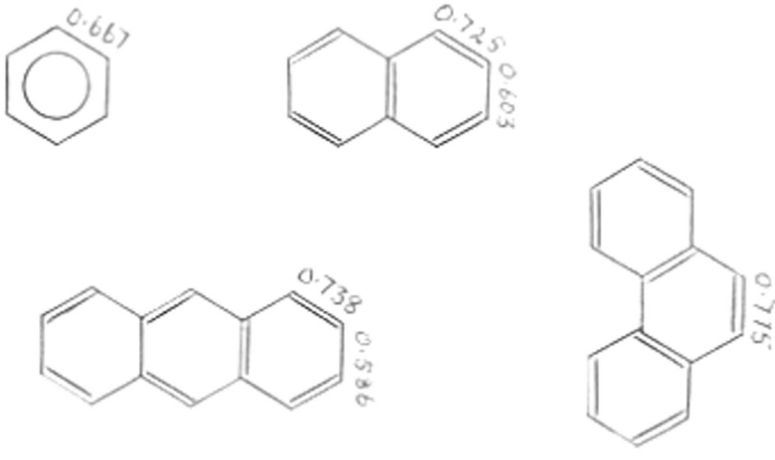
FIG. IV - METHYL SIGNALS OF (a) 4-methylbenzanthrone
(b) 10-methylbenzanthrone and (c) 2-methylbenzanthrone.

cases which are disubstituted. The relevant bond orders may well be larger than in naphthalene. In agreement with expectation the methyl signals of 1,2 dimethyl-naphthalene are not split, but the band-widths for both the methyl signals are increased and not decreased (2.2 cps). This is attributable to the long range coupling (through five bonds) between the two methyls at 1 and 2 positions themselves.

For the p-methyl group of 1,6 dimethyl 4-ethyl naphthalene a splitting of only 0.4 cps is observed (Table I). The mobile bond order for the C_5-C_6 bond of this compound cannot be smaller than that of the similar bond of the parent hydrocarbon since all the substituents involved are electron donors. The reduced splitting observed for this case must therefore be attributed to a change in the E value. 4-Methyl-benzanthrone furnishes another example of the same type. Although the calculated p-value for the C_4-C_5 bond is 0.72, almost the same as for the C_1-C_2 bond of naphthalene, the splitting observed is only 0.6 cps.

We may now consider the coupling constants that have been measured from the quantitative standpoint although they are only first order values. Since there is no way of correctly estimating Δ E values at present, a linear variation of $J_{CH_3\text{-}H_{Ar}}$ with p^2 can be demonstrated only for

a set of compounds for which ΔE is constant. In other words, closely related compounds have to be chosen to test the theory. Since the methyls are all freely rotating, the same Q' value would apply in all cases. A plot of the $J_{CH_3\text{-}H_{Ar}}$ values for 2-bromotoluene, 2-methylnaphthalene, 2-methylanthracene and 9-methylphenanthrene against the p^2 values obtained for the parent hydrocarbons from simple Hückel MO theory is given in Fig.5. The relevant p values[31] are shown in the formulae below.



The J-values have been assigned a negative sign as required by theory. In spite of the approximations involved, the plot obtained is a good straightline and this may be taken as adequate proof for the p^2 dependence of this coupling. The nature of the approximations involved is reflected in

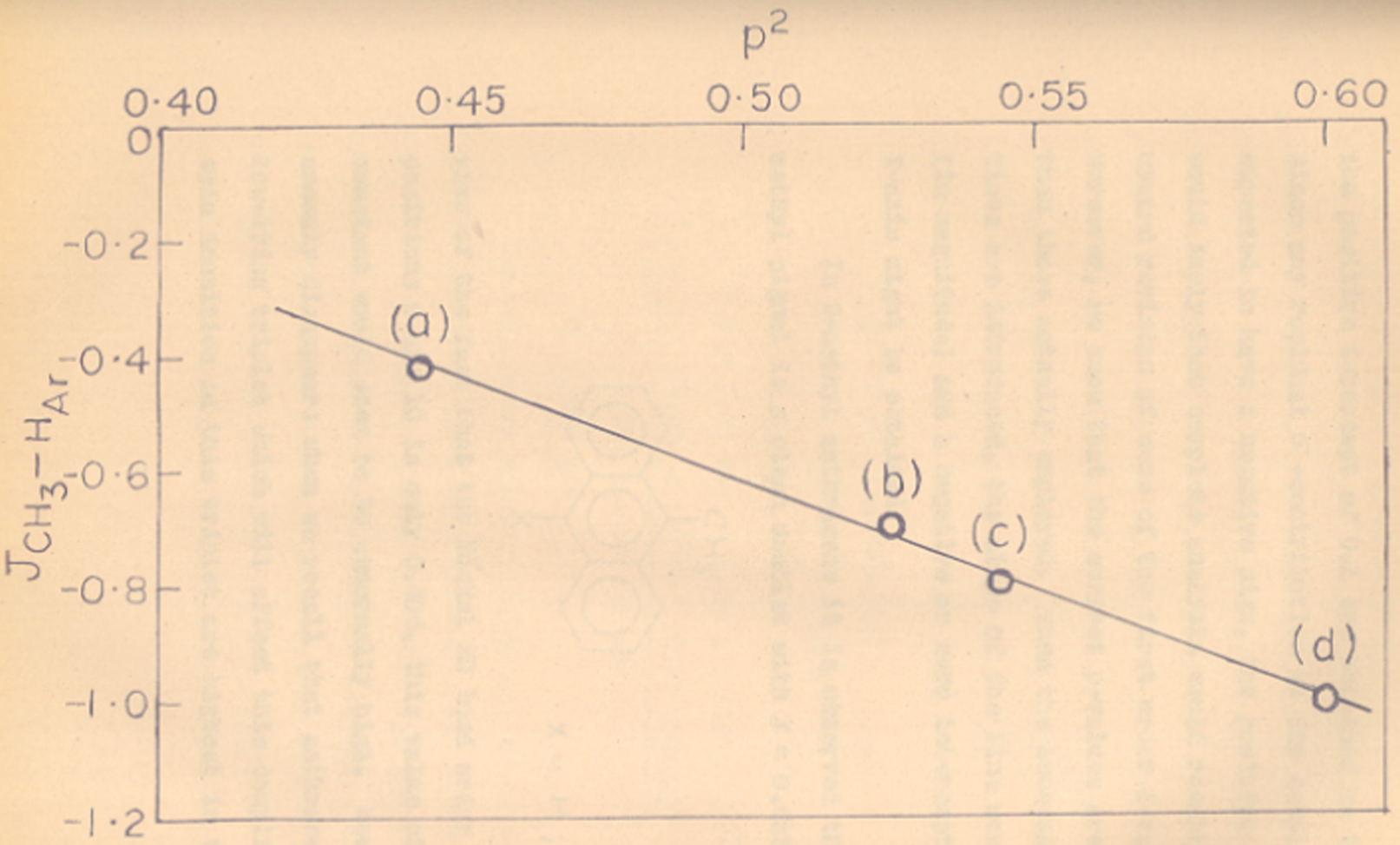
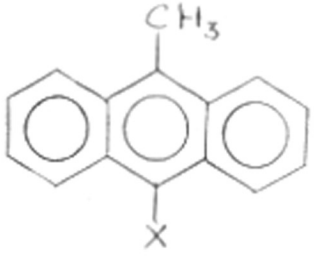


FIG.V. VARIATION OF BENZYLIC COUPLING WITH p^2

(a) 0-Bromotoluene (b) 2-Methylnaphthalene
(c) 2-Methylanthracene and (d) 9-Methylphenanthrene[33]

the positive intercept of 0.1 cps obtained on the Y-axis. Since any residual σ-contribution to the coupling is also expected to have a negative sign, the positive intercept would imply that complete analysis would result in an upward revision of some of the first order J-values. Moreover, we know that the correct p-values are larger than those actually employed. When the necessary corrections are introduced, the slope of the line would decrease (in magnitude) and a negative or zero intercept on the Y-axis might be obtained.

In 9-methyl anthracene it is observed that the methyl signal is a clean doublet with J = 0.625 cps. In



X = H ; Br.

view of the fact that the Hückel 9-10 bond order between positions 9 and 10 is only 0.404, this value of the coupling constant would seem to be abnormally high. However, the anomaly disappears when we recall that anthracene has a low-lying triplet which will affect this coupling. The spin densities in this triplet are highest in the 9 and 10

positions[32]. The energy of this state is 1.82 e.v. above that of the ground state. This is substantially lower than the average ΔE values that are ordinarily assumed in long range couplings of this type. The effect of the decreased p-value here is more than offset by the decrease in ΔE value. It will be of interest in this connection to calculate the $J_{CH_3\text{-}H_{10}}$ coupling constant on the assumption that only the lowest lying triplet need be taken into consideration. Assuming a value of 30 gauss for $\bar{Q}$ and Q', we have

$$\rho_{NN'} = -0.404 \text{ (calculated)}$$

$$\beta = 0.273 \times 10^{-21} \text{ ergs/gauss}$$

$$h = 6.624 \times 10^{-27}$$

$$\Delta E = 1.82 \text{ e.v.} = 1.82 \times 1.602 \times 10^{-12} \text{ ergs}$$

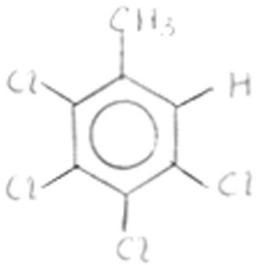
$$\therefore \left| J^{T}_{NN'} \right| = \frac{(9.273 \times 10^{-21})^2 \, (30)^2 \, (0.404)^2}{6.624 \times 1.82 \times 1.602}$$

$$= 0.653 \text{ cps}$$

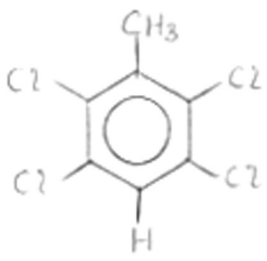
The calculated value of 0.653 cps is in good agreement with the observed value of J = 0.625 cps. There cannot be any doubt as to which proton the methyl is coupled to. 9-methyl 10-bromo anthracene gives an unsplit signal. The relative band-widths of the 9-methyl and 9-methyl 10-bromo derivative are 1.4 cps and 0.6 cps respectively. It is observed that in 9-methylanthracene the coupling of the methyl with protons

other than at the 10-position is negligible because the methyl band width in this case is nearly equal to that of TMS itself (0.4 cps).

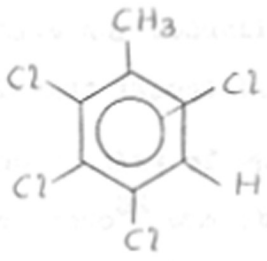
Quite some time after the publication of the preliminary results of this study[28a,b], Rottendorf and Sternhell[33] described some of their results on benzylic coupling. They prepared the three isomeric chlorotoluenes (XII, XIII, XIV) and measured the couplings of the methyl groups and the lone aromatic protons in these compounds.



XII



XIII

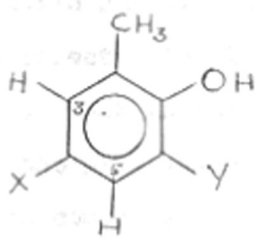


XIV

Both $J_{CH_3\text{-}H}$ ortho (for XII) and ~~XIII~~ and $J_{CH_3\text{-}H}$ para (for XIII) were found to be equal to 0.63 cps. The corresponding meta coupling was only 0.36 cps. On the basis of these and other data on benzylic and allylic coupling they concluded that benzylic coupling is somehow related to π-bond order. The measurements on tetrachlorotoluenes was presumably undertaken with the hope that they would throw some light on the variation of benzylic coupling. The nature of the results obtained

further illustrate the limitations that have been already pointed out regarding the value of measurements of benzylic coupling. Since substitution of strongly interacting groups alters the π-electron distributions of aromatic nuclei quite appreciably, the substitution method for isolating spin-spin interactions has serious limitations, when multiple substitution is involved. Secondly, any inference regarding relative magnitudes of bond orders from benzylic coupling constants can be made only if we can be reasonably sure that the corresponding ΔE values are comparable. These two factors have clearly conspired to make any deduction from the measurements on tetrachlorotoluenes impossible.

Another recent investigation, the results of which are of interest here, is that of Michio Kondo[34] who observed that the methyl at 2-position in 4,6-disubstituted o-cresols (XV) is spin coupled to the 3 and the 5 protons with $J_{CH_3-H_3}$ and $J_{CH_3-H_5}$ being 0.7 - 0.9 cps and 0.5 - 0.6 cps respectively.



XV

When X and Y are electron withdrawing substituents, the low field shift of the methyl signal was found to be proportional

to the benzylic coupling. Kondo concluded from this that the increased hyperconjugation resulting from electron withdrawing substituents is responsible both for the downfield shifts and for the enhanced benzylic coupling. However, no satisfactory explanation has been given for the high coupling constant for the 4,6-di-iodo derivative. Since the methyl group is meta to both X and Y, it is not directly hyperconjugated to these groups through the aromatic ring. The explanation advanced would, therefore, seem to be of doubtful validity. However, a better understanding of the observed variation will be possible only if the electron distributions in these systems can be ascertained.

One of the simplest and most important applications of the relationship between mobile bond order and benzylic coupling is in the study of controversial cases of bond fixation in aromatic rings. An example of this type is the Mills-Nixon effect which is studied in the next part of this thesis. What is involved in such a case is only a comparison of the p-values of two adjacent bonds of a suitably substituted compound. For this purpose the relative magnitudes of benzylic coupling constants may be used with considerable confidence. The reorganisation of

π-electrons that takes place on the introduction of strongly interacting substituents on the benzene ring leads to changes in the ring geometry. Measurements of benzylic coupling may also be used to probe such changes and such studies may add significantly to our knowledge of the properties of aromatic compounds.

E X P E R I M E N T A L

NMR measurements: NMR spectra were recorded on a Varian A-60 NMR Spectrometer operating at 60 Mc. Solutions (10-20%) were prepared in carbon tetrachloride or deuterochloroform for recording the NMR spectra. Tetramethylsilane (TMS) was used as a standard in band width measurements i.e. comparisons of band widths were made under spectrometer conditions which gave the same band width for the TMS signal. Calibrations of the Chart were done using TMS in $CDCl_3$ (436 cps).

Methyl signals were recorded at 100 or 50 cycles sweep width at 500 sec. sweep time. The splittings and band widths recorded are averages obtained from 5 to 10 independent scannings of the methyl signal in each case. RF and filter band width were adjusted so as to obtain optimum conditions i.e. best resolution and sufficiently low noise level.

Materials: Preparation and/or purification of the materials used are described below. Melting points and boiling points are uncorrected. The former were determined in pyrex capillaries in an electrically heated apparatus or on a Kofler Block.

Gas-liquid chromatographic analyses were carried out

on an Aerograph (Model A-350-B) using 5' x 0.25" columns packed with 20% diethylene glycol polysuccinate on Chromosorb W (60-80 mesh) - Column P-employing hydrogen as carrier gas. For preparative GLC a 6' x 1" column with the same packing was used on a Perkin-Elmer Vapour Fractometer (Model 154-D) using nitrogen as carrier gas.

Deuterochloroform for use as solvent in NMR measurements was prepared by a modified procedure starting from trichloroacetophenone in 88-93% yield. The product is of high isotopic purity (ca. 99.5%) and the isotopic dilusion during an experiment is negligible. The detailed procedure has been published[35].

Anhydrous sodium sulphate was used as drying agent in the preparations described.

Solvents of C.P. grade like toluene, benzene, carbon tetrachloride etc. were further purified and dried by the procedures described in Part II of this thesis. Pure dry ether (diethyl ether) was prepared by treating 10 parts ether with 1 part conc. sulphuric acid and distilling the ether from the mixture. The ether was protected from moisture with a gaurd tube. Sodium wire was pressed into it for removing residual moisture and the

solvent was also stored over sodium. This was further dried by distilling repeatedly from $LiAlH_4$, keeping over $LiAlH_4$ and filtering immediately before use.

O-Xylene (E.Merck) was used without further purification. 2-Methylnaphthalene (E.Merck) was distilled (b.p. 236-238°C) before use, using an air condenser. 1-Methylnaphthalene (Fluka A.G.) was repeatedly fractionated (b.p. 240-241°C) to remove 2-methylnaphthalene present as impurity.

2-Bromotoluene[36] was prepared by Sandmeyer's reaction on o-toluidine. Procedure followed was same as described by Vogel[37] for p-bromotoluene.
2-Bromotoluene, b.p. 175-177°C (lit.[36]: b.p. 178-181°C).

2-Deuterotoluene was prepared from 2-bromotoluene by a procedure similar to the one for deuterobenzene, C_6H_5D[38]. Lithium wire (1.2 g; .173 g atom) was pressed into dry ether (15 cc) in a 250 cc three-necked flask fitted with a mercury sealed mechanical stirrer, reflux condenser and dropping funnel. 2-Bromotoluene (14.22 g; .083 moles) in ether (15 cc) was added dropwise with vigorous stirring. The rate of addition was controlled such that a gentle reflux of ether was maintained. After all the bromotoluene was added the mixture was refluxed for 2 hrs with stirring.

D_2O (4-5 cc) was added dropwise, the mixture refluxed for one more hour and the ether layer separated. Ether extract was washed with water, dried and distilled. 2-Deuterotoluene (8.9 g) distilling at 108-110°C was collected. Product was found to have an isotopic purity of 99-99.5% by the NMR method.

1-Bromo 2-methylnaphthalene[39,40]: The method of Adams and Binder[39] was followed. A crystal of iodine and a pinch of iron powder were added to a solution of 2-methylnaphthalene (7.1 g; 0.5 moles) in CCl_4 cooled 0°C. In absence of light, bromine (80 g; 0.5 moles) in CCl_4 (150 cc) was added with stirring and the temperature maintained at 0°C. Working up as described gave the product (8.5 g) b.p. 156-158°C/14 mm; 143°C/6 mm (lit.[40]: b.p. 152-156°C/14 mm).

1,2-Dimethylnaphthalene[41]: Magnesium ribbon, cleaned and cut into small pieces (1.2 g; .05 g atom), in dry ether (10 cc) was taken in a 250 cc three-necked RB flask fitted with a stirrer, condenser and dropping funnel. 1-Bromo-2-methylnaphthalene (11 g; .05 moles) in dry ether (20 cc) was added dropwise with stirring. It was necessary to initiate the reaction with a crystal of iodine. Dimethyl sulphate (6.25 g; .05 mole) in dry ether (10 cc) was added

with ice-cooling. The mixture was then refluxed for two hours and decomposed with ice-cold dil. sulphuric acid. The product on distillation was found to be a mixture of 2-methyl-naphthalene (major component of Ist fraction b.p. 107-112°C/15 mm), 1,2-dimethyl-naphthalene (major component of 2nd fraction b.p. 112-138°C/15 mm) and 1-bromo 2-methyl-naphthalene (major component of last fraction b.p. 138-169°C/15 mm). Repeated fractional distillations gave a fraction (b.p. 135-140°C/15 mm) containing 1,2-dimethyl-naphthalene as the major component with traces of 2-methyl naphthalene and 1-bromo 2-methyl naphthalene. Pure 1,2 dimethylnaphthalene was obtained from this by preparative GLC. The compound thus obtained was found to be pure from its NMR spectrum.

<u>1-Deutero 2-methyl-naphthalene</u>: The Grignard from 1-bromo 2-methyl naphthalene was prepared as described above and was decomposed by the addition of a slight excess of D_2O. The product was worked up as usual and distilled under vacuum and the first fraction containing most of the 1-deutero 2-methyl-naphthalene was redistilled to obtain 45% yield of pure 1-deutero 2-methyl-naphthalene b.p. 112°C/60 mm. NMR spectrum of this product showed an isotopic purity of 90-95% by integration method.

9-Anthraldehyde: To anthracene (15 g; .084 moles) in dimethyl formamide (25 cc) taken in a 100 cc RB flask was added with cooling phosphorous oxychloride (14 g; .09 moles). The mixture was heated on a waterbath for two hours (silica gel guard tube), poured into excess water and the precipitate filtered off. Recrystallisation from glacial acetic acid gave 9-anthraldehyde (11.5 g) m.p. 101-103°C (lit.[42]: m.p. 104.5 - 106°C).

9-Methylanthracene[43]: The general method for Wolff-Kichner reduction reported by Huang-Minlon was followed[43]. 9-Anthraldehyde (4 g; .0194 mole) in diethylene glycol (20 cc) was refluxed for half an hour with 85% hydrazine hydrate (2 cc) and then a conc. aq. solution of sodium hydroxide (1.5 g) was added. The mixture was refluxed for 2 hours more, cooled and poured into cold water. The product was isolated by extraction with ether. It was recrystallised from alcohol and obtained as white plates (3.1 g), m.p. 78-79°C (lit.[43]: m.p. 80-81°C).

9-Bromo 10-methylanthracene[44]: Bromine (1.6 g; .01 mole) in CS_2 (5 cc) was added slowly into a well-cooled solution of 9-methyl anthracene (1.9 g; .01 mole) in CS_2 (5 cc). The

solid obtained on removal of the solvent was recrystallised twice from ethyl alcohol and then from benzene giving 9-bromo 10-methylanthracene (2.1 g) as yellow crystalline needles, m.p. 172-173°C (lit.[44]: m.p. 173°C).

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PART II

STUDIES ON THE MILLS-NIXON EFFECT AND RELATED PROBLEMS

CHAPTER I

"THE MILLS-NIXON EFFECT" —A REVIEW

"THE MILLS-NIXON EFFECT" - A REVIEW

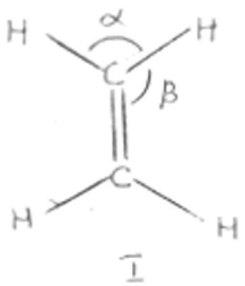
In 1865 Kekule[1] proposed the cyclic formula for benzene with alternating single and double bonds. It was immediately pointed out by Ladenburg[2] that the number of isomeric substitution products obtained experimentally are fewer than expected on the basis of the proposed structure. For example, while all known ortho-disubstituted benzenes are single compounds, two isomeric forms for them were predicted by the structure. Kekule[3] got over this difficulty by the suggestion that the double bonds are probably in a constant state of oscillation between the two forms. The great debate on the structure of benzene and aromatic character that was initiated, continued until the nineteen thirties when the quantum theory of molecular structure first took shape. The cyclic formula was soon accepted although there was no proper understanding of the peculiar properties of benzene as an unsaturated compound. Throughout the long period, during which the bonding in benzene was under discussion, interest in the two Kekule "forms" or "tautomers" continued. Victor Meyer[4] thought that the difference between the isomeric ortho-disubstituted benzenes would be so slight that it would escape detection. Graebe[5]

considered the possibility that if proper substituents are used one form may become stabler than the other. That the two forms used may be regarded as tautomeric was first suggested by Reddelein[6] who felt that introduction of heavy substituents may stabilize one "tautomer" to such an extent that it might be possible to detect it by a delicate test.

It was to this problem of the stabilization of the Kekule forms and their detection that Mills and Nixon[7] devoted their attention in their classic paper in the year 1930. They argued that the bond common to the two rings in the indane molecule should be single while in tetralin the corresponding bond should be double. The reasoning was as follows.

On the basis of Vant Hoff's tetrahedral theory of carbon valencies, it was assumed that in ethylene the angle (α) between each pair of single bonds is the same as the tetrahedral angle ($109^{\circ}\ 28'$). This would imply that the angle (β) between the double bond and the single bond would be about $125^{\circ}\ 16'$. On this basis the stable form of a compound in which the benzene ring is fused with an alicyclic five-membered ring (indane) would have a single bond common to the two rings (as in II) because the alicyclic five-membered ring would in this case include

two angles of the α-type and would be strain-free.



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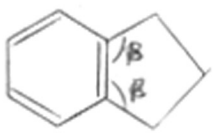
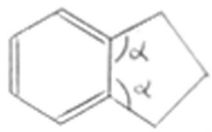


III

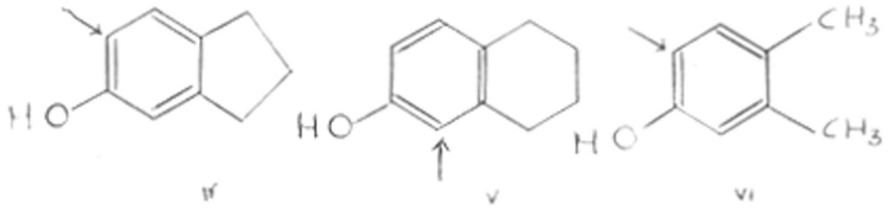


II

The alternative formulation (III) which has a double bond, common to the two rings, would include two angles of the type β, which are very much larger than the tetrahedral angle, in the five-membered ring. Structure (III) would therefore be relatively unstable and indane may be expected to have structure (II). Somewhat more involved reasons were given to show that when a six-membered alicyclic ring is fused to a benzene ring to give tetralin, the Kekule form in which the common bond is double would be preferred.

Mills and Nixon supported their arguments by experimental data on the bromination and diazo coupling reactions of 5-hydroxyindane (IV) and 6-hydroxytetralin (V). It was thought that the behaviour of these compounds should be comparable to those of enols and that the reactive positions in these would be those that are connected to the

hydroxyl group through double bonds. They observed



IV V VI

that in diazo coupling and bromination 5-hydroxyindane undergoes substitution almost exclusively at the 6-position while for 6-hydroxytetralin the more reactive of the 5- and 7-positions is the former. This was in agreement with expectation. 4-Hydroxy-o-xylene was found to behave like 5-hydroxyindane and this was considered to be normal because it should be, like 5-hydroxyindane, strain-free. 5-Acetamidoindane, 6-acetamidotetralin and 4-acetamido-o-xylene were also found to behave like the corresponding hydroxy compounds.

Considerable amount of experimental work[8,9] has been done, ever since 1930, on the problem of fixation of double bonds in indane and tetralin. Further studies on diazo coupling of other derivatives of indane and tetralin were made by Fieser and Lothrop[10] who concluded that there is fixation as suggested by Mills and Nixon in indane, but not in tetralin. However, they found

further[11] that 5-hydroxy-6-methylindane itself coupled under slightly modified conditions. The selectivity that was observed by Mills and Nixon was therefore regarded as arising from only a small difference in reactivity between the 4- and 6-positions.

This was soon followed by ozonolysis studies on indane, by Long and Fieser[12]. Ozonolysis of indane gave glyoxal and succinic acid. They suggested that succinic acid may be arising from cyclopenta 1,2 dione which itself might have arisen from the Kekule form (II). This led them to support the suggestion of Mills and Nixon. This interpretation was rendered uncertain by the observation that during the ozonolysis a considerable amount of indane is oxidised to indane-1-one (isolated from the product mixture), which itself can readily give rise to succinic acid.

A wave-mechanical treatment of the Mills-Nixon effect was put forward by Sutton and Pauling[13], in 1935. The effect of fused alicyclic rings upon the wave functions of the two Kekule structures was found by them to be in agreement with the formulae of Mills and Nixon although the effect was relatively small. The benzene ring was considered to be retaining the greater part of its resonance energy. They concluded that the wave-mechanical concept of the

structure of the benzene molecule is capable of accounting for the facts interpreted by Mills and Nixon in terms of stabilization of the individual Kekule structures.

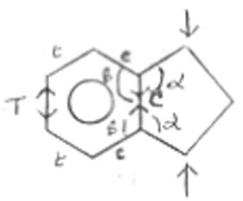
The studies of Sidgwick and Springall[14] gave dipole moment values of 1.78D, 2.11D, 2.13D and 2.11?D for 5,6-dibromoindane, 6,7-dibromotetralin, 4,5-dibromo-O-xylene and 1,2-dibromobenzene respectively for the Br-C=C-Br system. The data were strongly indicative of fixation of bonds in the case of indane and the absence of fixation in the other three systems. However, electron diffraction studies[15,16,17] of these dibromo derivatives later showed that the Br-Br distances in the above four dibromo compounds are the same. The dipole moment data have apparently not been correctly interpreted.

Lothrop's investigations[18] on the bond-fixation in indane by the use of Claisen rearrangement gave negative results. Both 5-allyloxy-6-methyl and 5-allyloxy-4,7-dimethylindanes gave rearranged products. Data on heats of hydrogenation[19] and acidities[20] of nitro-O-xylenols, nitroindanols and nitrotetralols gave results that did not offer any indication about fixation of bonds. The coupling and Skraup reaction studies of McLeish and Campbell[21] on

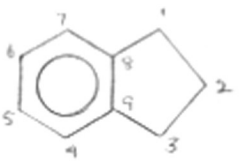
indane and tetralin derivatives did not fare better. Studies on ease of hydrolysis of bromoamino compounds by Bondin and Evans[22] also failed to give any definite indication of Mills-Nixon effect.

Conclusive evidence was available by 1942 to show that all the bond angles in ethylene are very nearly equal to 120° [23-26]. The basis on which the Mills-Nixon hypothesis was built was thus knocked off, but the problem of the reactivity of indane and its derivatives remained.

The problem was therefore taken afresh by Longuet-Higgins and Coulson[27]. In their hands the problem was reduced to one in classical statics. They showed that if there is any tendency at all for bond-fixation in indane it should be in the direction opposite to that postulated by Mills and Nixon (i.e. as in III).



VII



VIII

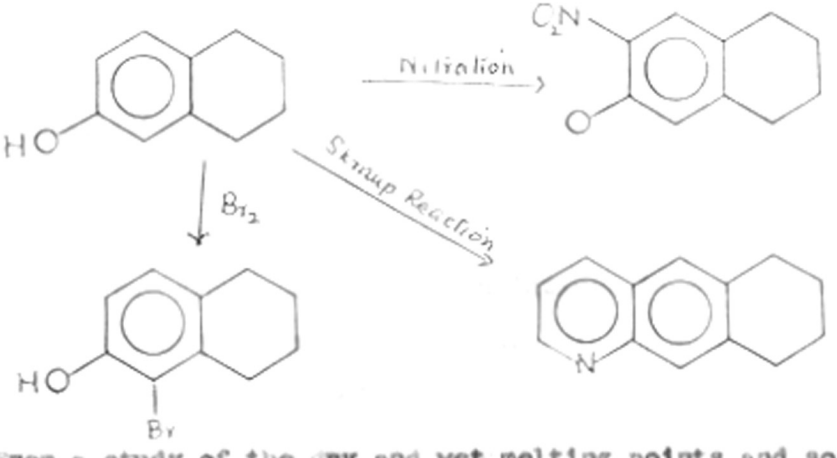
Their analysis showed that there is a stress on the 1 and 3 carbon atoms which will tend to decrease the angle ∝ and increase the angle β in VII. As a consequence the 8-9 bond

is compressed and the 5-6 bond is stretched. An increase in the 8-9 bond order and a decrease in the 5-6 bond order is thus expected. The effects of the trimethylene bridge on the aromatic bonds are shown in VII. T represents large tension and t, weak tension. Similarly C and c indicate large and small compressions. The susceptibility of 5-hydroxyindane to electrophilic attack at the 6-position was explained on the basis that in the transition state for such attack, the 5-6 bond would have more single bond character than in the transition state for attack at the 4-position.

That substitution reactions cannot be used for the study of bond-fixation was suggested by a number of workers, on the basis of the confusing and contradictory results obtained in different experiments and also because of the observation that electrophilic reagents prefer the positions of highest electronic charge for attack, this preference not having anything to do with bond fixation.

The experimental evidence of Mills and Nixon was shown to be unsatisfactory by Parkes[28] who found that the relative reactivities of the 2 and 6 positions in 3,4 dialkyl phenols, towards diazo coupling, is dependent on the nature of the alkyl substituent. Arnold[20] pointed out that the wave-mechanical treatment of the Mills-Nixon effect

problem leads to the conclusion that substitution reactions (with high activation energies) cannot be used to locate stabilized aromatic double bonds. That this conclusion is in accordance with experimental evidence is shown by the following reactions.

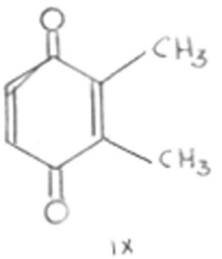


From a study of the dry and wet melting points and solubility and steam-volatility differences, Baker[29] arrived at the conclusion that 5-hydroxy-6-acetylindane is more strongly chelated than 5-hydroxy-4-acetylindane. However, these data have later been shown to be incorrect by more accurate (IR) measurements of chelation[46,47,48].

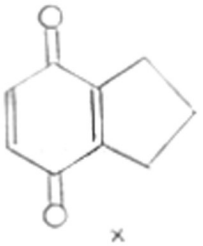
The investigations of Arnold and coworkers[30-36] on steric effect of methylene groups in indane and tetralin derivatives provided conclusive evidence for the distortion of the ortho valency angles and presence of increased strain in indane derivatives. Distortion of the two ortho-bonds

towards each other in indane derivatives was confirmed by the fact that the steric effect of the benzylic methylene group of a five-membered ring on the ortho-position on the benzenoid ring is much smaller than that of a six-membered ring. Enormous amount of chemical (e.g. haloform reaction, rates of saponification of esters etc.), ultraviolet (comparison of UV and near visible absorption spectra of p-substituted dimethylamino derivatives) and Raman spectral data have been presented by these authors in support of their statement. They found that the steric influence of methylene groups is minimum in indane, intermediate in tetralin and maximum in O-xylene. These data are in full support of the Mills-Nixon type distortion of valency angles, but the effect of this on the aromatic ring or the resulting deviation in bond character has not been discussed.

The oxidation-reduction potentials of O-xyloquinone (IX), 4,7-indanequinone (X) and 5,8-tetralinquinone (XI) were measured potentiometrically and polarographically[37].



IX



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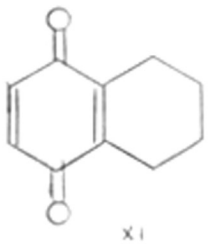
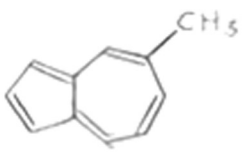


XI

The comparative study showed that indanequinone has a higher oxidation-reduction potential than the other two which have almost the same value. This has been explained as being due to the strain caused by the presence of the double bond in the five-membered ring.

A. Arnold[38] observed that the 4:5 bond in indane may have more double bond character than the 5:6 one, since indane on treatment with diazoacetic ester, followed by stepwise reduction gave 5-methylazulene (XII) which can be formed only if addition takes place across the 4:5 bond.

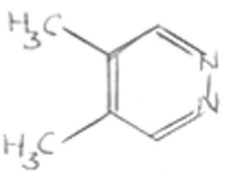


XII

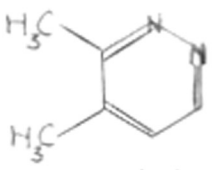
Though this evidence seemed interesting, it was considered inconclusive[9] because, the 4:5 and 6:7 bonds being identical, there is twice the chance that addition can occur across this bond rather than at the 5:6 bond and also because the crude product obtained by Arnold was a mixture.

Horning and Amstutz[39] made an attempt to tackle the problem of bond-multiplicity through UV spectral studies. They prepared 3,4- and 4,5-dimethyl-, 3,4- and

4,5-trimethylene- and 3,4 and 4,5-tetramethylene pyridazines (XIII - XVIII) and studied their spectra in iso-octane, ethanol,



XIII



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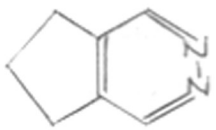

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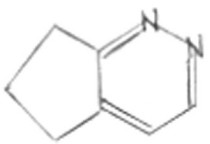
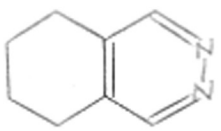
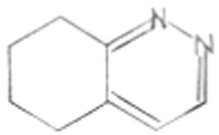


XVI



XVII

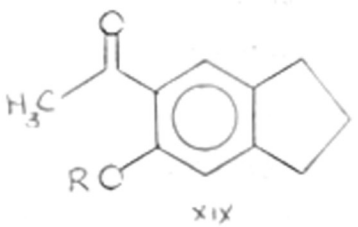


XVIII

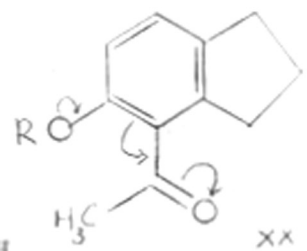
water and conc. H_2SO_4. The spectra of intermediate chloro and dichloro compounds were also obtained. If the parent hydrocarbons tetralin, indane and O-xylene cause the ratio of the mobile bond order of the 2 bond to the 1 bond to vary from unity, the E values (found as the energy differences between transition energies for isomers) will be different for the three isomers. These energy differences designated as E values, made it possible for the authors to arrange the parent hydrocarbons in the order of decreasing ratio of the bond orders (2/1) as tetralin, indane and O-xylene.

T.S. Wheeler and coworkers[40] studied the Baker-Venkataraman transformation of O-aroyloxy acetoarones into

o-hydroxy diaroylmethanes. They found that in the naphthalene series the transformation takes place more rapidly across the 2:3 (single) bond than across the 1:2 (double) bond. This they attributed to an ester type neutralization of the positive charge at the carbonyl carbon across the double bond and pointed out that this supports the view that the transformation involves a base-catalyzed intramolecular Claisen condensation. They observed that the transformation occurs more rapidly across the 5:6 bond than across the 4:5 bond in indane and across the 6:7 bond than across the 5:6 one in tetralin.



XIX



XX

R = C_6H_4CO; p-CH_3O-C_6H_4-CO; H

These results suggested that the 5:6 bond in indane derivatives is of a lower order than the 4:5 bond and similarly that the 6:7 bond in tetralin is of a lower order than the 5:6 bond.

41-43

The extensive researches of Wibaut and de Jong on the ozonolysis of the aromatic dimethyl derivatives of indane

tetralin and O-xylene are extremely interesting and have been claimed as providing unambiguous evidence in favour of partial bond fixation in indane, not as Mills and Nixon had originally suggested, but as the theoretical calculations of Coulson and L. Higgins[27] indicated. Their experimental procedure and results are summarized below.

Ozonolysis of indane, 4,7-dimethylindane, 5,6-dimethylindane, 5,8-dimethyltetralin and 6,7-dimethyltetralin and also p-xylene and durene (for reference) were performed and the dicarbonyl compounds produced, i.e. glyoxal, methylglyoxal, and dimethylglyoxal were identified and their yields quantitatively determined as the dioximes. The yield of dicarbonyl compounds in the case of 4,7-dimethylindane was 0.1 mol per mol of dimethylindane. Glyoxal and methylglyoxal were found to be present in this product mixture in the ratio 1.57: 1. The total yield for 5,6 dimethylindane was found to be .05 mol per mol of dimethylindane and the ratio of diacetyl to methylglyoxal was found to be 3.5:1. Though the results indicate that ozone attacks all the C-C bonds of the ring system, thus ruling out any possibility of complete 'fixation' of double bonds in the aromatic ring, the molecular ratio of the dicarbonyl compounds suggests that there is a marked

preference for the attack of the common C-C bond of the ring system and hence this bond has more double bond character than the adjacent C-C bonds in the aromatic ring.

On the other hand, 5,8-dimethyltetralin gave methylglyoxal and glyoxal in the ratio 3:1 and 6,7-dimethyltetralin gave methylglyoxal and diacetyl in the ratio 1.1:1 indicating the absence of any preference for attack of the common or any other C-C bond in the aromatic ring of tetralin. The reliability of the experimental procedure was confirmed by the ozonolysis of p-xylene and durene in which the former gave methylglyoxal and glyoxal in the ratio 2.15:1 and the latter gave methylglyoxal and diacetyl in the ratio 1.93:1 both as expected for the systems where there is no difference in double bond character among the 6 C-C bonds.

However, the admissibility of this evidence was open to doubt. It had been earlier pointed out[9] in criticism of Fieser's ozonolysis work that indane is readily oxidized to indane-1-one by ozone. The conclusions of de Jong and Wibaut can be correct only if it is certain that the amounts of dicarbonyl products obtained via the indanones are minor.

Measurements of the C=O stretching frequencies of a number of ortho-hydroxycarbonyl derivatives of benzene, naphthalene and anthracene led Hunsberger, Gutowsky and

co-workers[44,45] to the conclusion that conjugate chelation lowers the C=O frequency of these compounds by an amount which is directly proportional to the degree of double bond character of the bond between the carbon atoms holding the substituents. They attempted to solve the question of bond fixation in indane using this relationship.

It was observed[46,47,48] that the average $\Delta \nu$(C=O) value for the 4,5 derivative of indane is 50 cm^{-1} and that for the 5,6 derivative 44 cm^{-1} while the average Δ (C=O) value for benzene is 43.3 cm^{-1}. However the average Δ (C=O) values for the 3,4 and 4,5 derivatives of O-xylene (corresponding respectively to the 4,5 and 5,6 derivatives of indane) are 51 cm^{-1} and 42.3 cm^{-1} respectively. Examination of the data, including those for the corresponding tetralin derivatives, showed that steric factors are the primary cause of the differences between the two sets of values. Their analysis showed that the steric effect of methyl groups of O-xylene is intermediate between those of the α-methylene groups of indane and tetralin. It was concluded that the carbonyl frequency values would indicate little or no bond fixation in indane if allowance is made for "steric facilitation of chelation"[48].

It is of interest here to point out that the order

of steric effects found by Hunsberger et al. is not in agreement with the work of R. van Helden[49] and of Arnold and coworkers[30-36]. It is likely that the allowances made by Hunsberger et al. for steric facilitation are not quite correct.

Berthier and Pullman[50] put forward in 1950 an electronic theory for explaining the Mills-Nixon Effect. They suggested that hyperconjugation and inductive effect of the adjacent rings are causing certain modifications on the benzene rings in these compounds and attempted to explain the different behaviours of indane, tetralin and O-xylene towards electrophilic reagents.

It is clear from the foregoing survey that in spite of the numerous efforts that have been made to find an answer to the problem posed by Mills and Nixon, no definite conclusions could be reached in view of the contradictory results and doubtful interpretations. The problem is apparently complex and "a fairly precise evaluation of each contributing factor would be required before reliable conclusion can be reached"[51].

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CHAPTER II

BOND-FIXATION IN BENZOCYCLOALKENES

BOND-FIXATION IN BENZOCYCLOALKENES

INTRODUCTION

We have already seen in the previous Chapter that the studies that have so far been made on the Mills-Nixon Effect do not lead to a clear-cut answer to the question of fixation of bonds in indane and tetralin. Most of the evidence adduced is chemical and in chemical reactions we are really concerned only with the properties of transition states. As has already been pointed out by Pullman[1], the predominant contribution from either of the Kekulé structures to the resonance of the ground states of the molecules concerned is not proved by the ease with which substitution takes place at a particular position. The transition states in these reactions are excited states whose electronic configurations can be substantially different from those of the ground states. Hence the assumption that the differences in the rates of aromatic α- and β-substitution can be attributed to the nature of the ground state is not acceptable. For the same reason the ozonolysis studies of de Jong and Wibaut would also be ambiguous[2]. Even if the doubt, that the products of ozonolysis are those obtained via indan-1-one, is removed, still the objection remains that it may actually be an

excited state that undergoes ozonolysis to give the products in the ratios observed. In the case of indane, as Huckel has pointed out[3], ozone may be adding preferentially to an excited state which has a higher double bond character for the bond common to the two rings. "In effect the ozone molecule simply waits till the molecule is in this state and then adds on".[3] Hence any of these chemical investigations including those using double bond reagents may only be useful in studying the nature of the transition states involved. In contrast, by using physical methods like IR and NMR spectroscopy one may be able to observe the molecule in its ground state or in a state which is perturbed only very slightly. Even these methods can have drawbacks. For example the IR study of this problem by Hunsberger et al.[4] was complicated by the necessity to estimate steric effects[5,6]. However, an unambiguous method for the solution of this problem is suggested by the work described in Part I of this thesis[7] where a linear relationship between benzylic coupling and the square of the mobile bond order has been established.

RESULTS AND DISCUSSION

It will be convenient for us here to recall the nature of the methyl signals in the NMR spectra of the three methylbenzanthrones studied in Part I. 4-Methyl-

benzanthrone gives a clearly split methyl signal ($J = 0.6$ cps), while 10-methylbenzanthrone gives an unsplit signal for its methyl group. The nature of the methyl signal in 2-methylbenzanthrone is intermediate ($J = 0.5$ cps). It is clear from the calculated bond order values[8], given earlier, that the different extents of fixation of π bonds in the three aromatic rings are indicated by the magnitudes of benzylic coupling displayed by the methyl signals. The methyl signals of the three methylbenzanthrones are reproduced in Fig. I.

From the nature of these results as well as those discussed earlier in Part I of this thesis, the following conclusions may be drawn regarding the NMR absorption of a methyl group on an aromatic ring having protons in both ortho positions. When it is flanked by bonds whose p-values are comparatively small and not very different from each other, no splitting is expected for its resonance under the conditions of resolution obtaining. On the other hand, when there is considerable difference between the p values or when the p values are both quite large (as is indicated in the case of mesitylene)[9] clear splitting should be obtainable. However, the absence of splitting cannot, by itself, be taken to imply absence of appreciable benzylic coupling since weaker couplings to protons other than at the

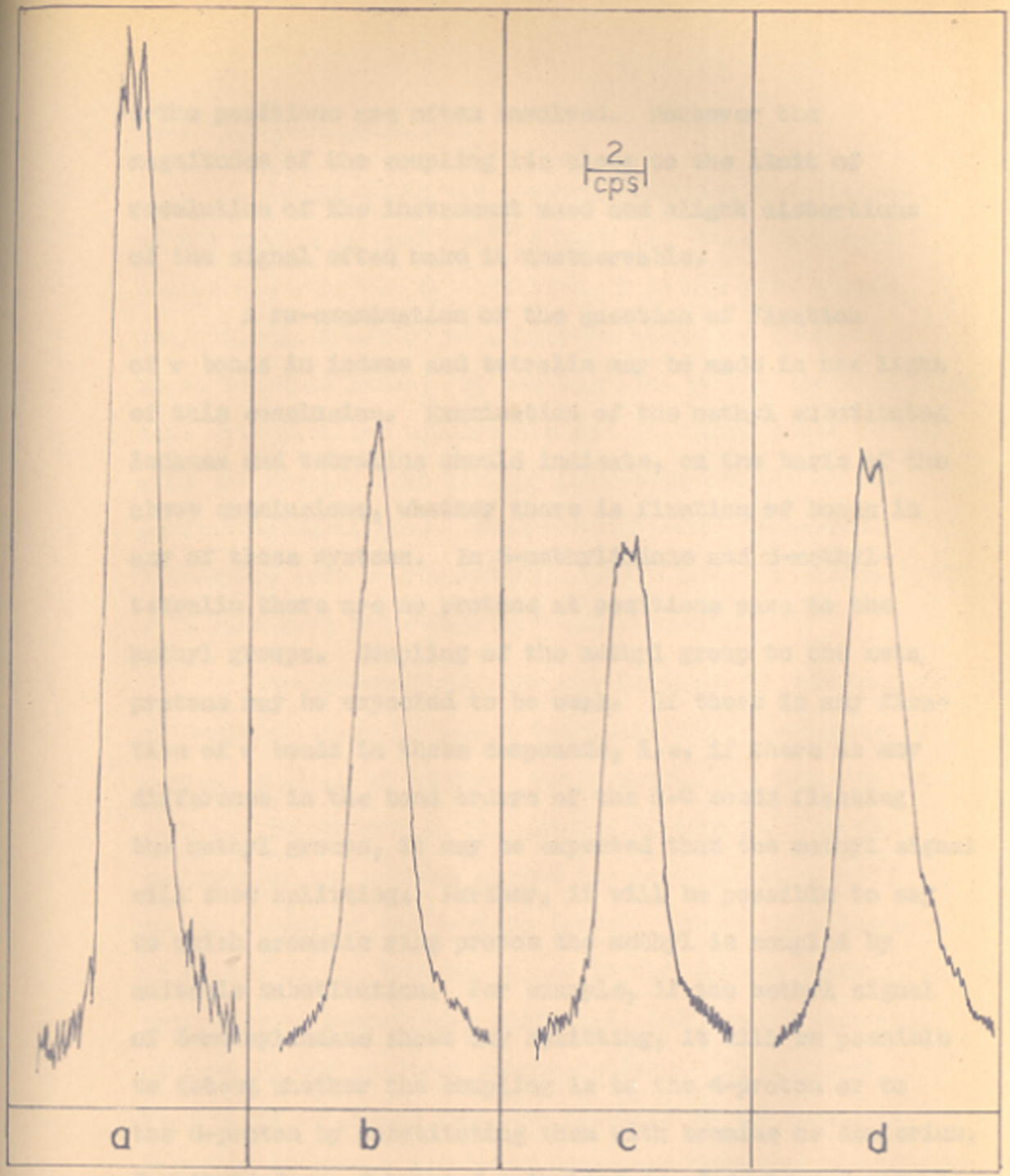


FIG.1 - METHYL SIGNALS OF (a) 4-methylbenzanthrone
(b) 10-methylbenzanthrone (c) 2-methylbenzanthrone and
(d) 5-methylindane

ortho positions are often involved. Moreover the magnitudes of the coupling lie close to the limit of resolution of the instrument used and slight distortions of the signal often make it unobservable.

A re-examination of the question of fixation of π bonds in indane and tetralin may be made in the light of this conclusion. Examination of the methyl substituted indanes and tetralins should indicate, on the basis of the above conclusions, whether there is fixation of bonds in any of these systems. In 5-methylindane and 6-methyltetralin there are no protons at positions para to the methyl groups. Coupling of the methyl group to the meta protons may be expected to be weak. If there is any fixation of π bonds in these compounds, i.e. if there is any difference in the bond orders of the C-C bonds flanking the methyl groups, it may be expected that the methyl signal will show splitting. Further, it will be possible to say to which aromatic ring proton the methyl is coupled by suitable substitution. For example, if the methyl signal of 5-methylindane shows any splitting, it will be possible to detect whether the coupling is to the 4-proton or to the 6-proton by substituting them with bromine or deuterium. 5-Methylindane, 6-bromo-5-methylindane, 6-deutero-5-methylindane, 4-bromo-5-methylindane and 4-deutero-5-methylindane

were therefore prepared.

5-Methylindane was prepared starting from indane by the method of Sukh Dev[10] (Chart I). Pure 5-acetylindane was obtained by acylation of indane with acetic anhydride in presence of anhydrous aluminium chloride in carbon disulphide. It was oxidised to the corresponding acid with alkaline hypobromite and the ethyl ester of the acid was reduced with lithium aluminium hydride to the corresponding alcohol. This alcohol with phosphorus tribromide gave 5-bromomethylindane which on hydrogenolysis with Pd/c gave the required 5-methylindane.

6-Bromo-5-methylindane was obtained by bromination of 5-methylindane in carbon tetrachloride in presence of a small crystal of iodine. The reaction was found to be slow and incomplete in the absence of iodine. The NMR spectrum of the product showed the presence of a small amount (< 5%) of the 4-bromo isomer. Since the removal of traces of the 4-bromo isomer in the 6-bromo derivative proved to be exceedingly difficult, the product was used as such in the spectral determinations. It appeared reasonable to assume that the presence of the isomeric impurity at such a low level would not have any significant effect on the measurements. 6-Deutero-5-methylindane was prepared from 6-bromo-5-methylindane by decomposing

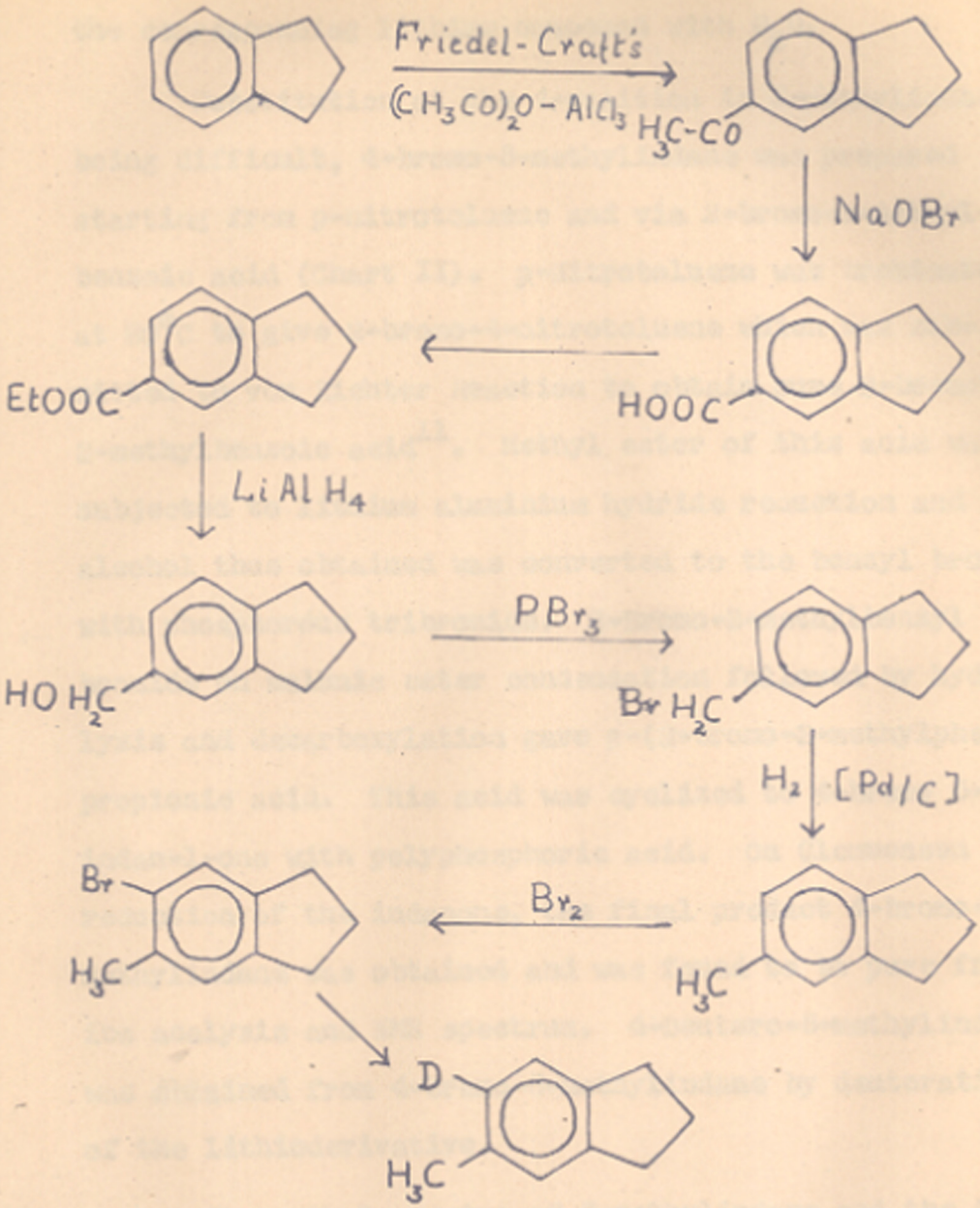

Friedel-Craft's
$(CH_3CO)_2O - AlCl_3$
H_3C-CO
NaOBr
HOOC
EtOOC
$LiAlH_4$
PBr_3
$HO\,H_2C$
$Br\,H_2C$
H_2 [Pd/C]
Br_2
Br
H_3C
D

CHART I

the corresponding lithium compound with D_2O.

Substitution at the 4-position in 5-methylindane being difficult, 4-bromo-5-methylindane was prepared starting from p-nitrotoluene and via 2-bromo-3-methylbenzoic acid (Chart II). p-Nitrotoluene was brominated at 80°C to give 2-bromo-4-nitrotoluene which was submitted to von Richter Reaction to obtain pure 2-bromo-3-methylbenzoic acid[11]. Methyl ester of this acid was subjected to lithium aluminium hydride reduction and the alcohol thus obtained was converted to the benzyl bromide with phosphorous tribromide. 2-Bromo-3-methylbenzyl bromide on malonic ester condensation followed by hydrolysis and decarboxylation gave β-(2-bromo-3-methylphenyl)-propionic acid. This acid was cyclized to 4-bromo 5-methylindan-1-one with polyphosphoric acid. On Clemmensen reduction of the indanone, the final product 4-bromo-5-methylindane was obtained and was found to be pure from its analysis and NMR spectrum. 4-Deutero-5-methylindane was obtained from 4-bromo-5-methylindane by deuteration of the lithioderivative.

The methyl spectra of 5-methylindane and the three methylbenzanthrones are shown in Fig.I. The latter are included only for purposes of comparison. The data on benzylic coupling and methyl band widths are given in

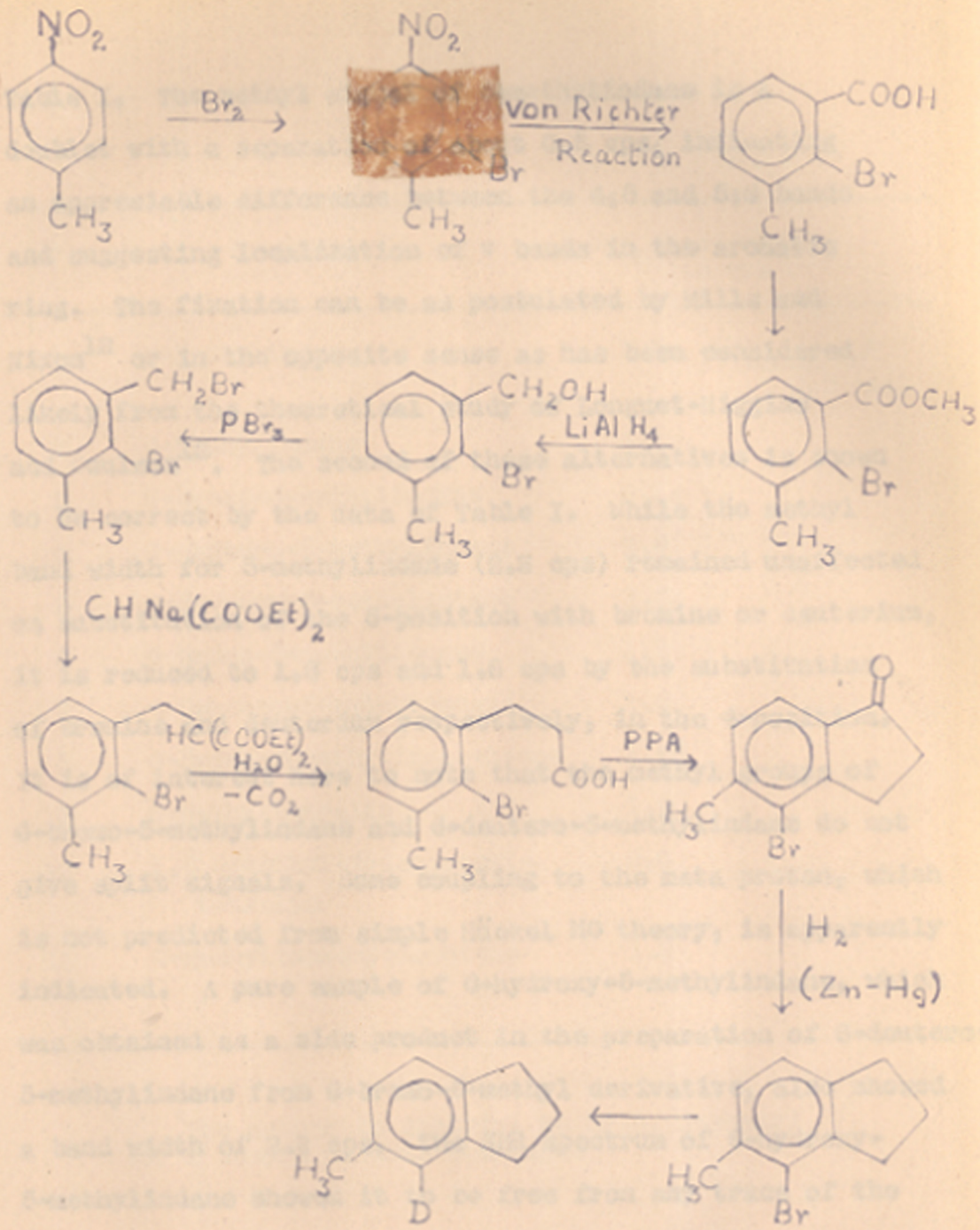

NO2
Br2
CH3
Br
von Richter
Reaction
COOH
Br
CH3
COOCH3
CH2OH
LiAlH4
CH2Br
PBr3
CH Na(COOEt)2
HC(COOEt)2
H2O
-CO2
COOH
PPA
H3C
H2
(Zn-Hg)
D

CHART II

Table I. The methyl signal of 5-methylindane is a doublet with a separation of about 0.5 cps, indicating an appreciable difference between the 4:5 and 5:6 bonds and suggesting localization of π bonds in the aromatic ring. The fixation can be as postulated by Mills and Nixon[12] or in the opposite sense as has been considered likely from the theoretical study of Longuet-Higgins and Coulson[13]. The second of these alternatives is shown to be correct by the data of Table I. While the methyl band width for 5-methylindane (2.2 cps) remained unaffected on substitution of the 6-position with bromine or deuterium, it is reduced to 1.6 cps and 1.8 cps by the substitution of bromine and deuterium respectively, in the 4-position. It is of interest here to note that the methyl groups of 6-bromo-5-methylindane and 6-deutero-5-methylindane do not give split signals. Some coupling to the meta proton, which is not predicted from simple Hückel MO theory, is apparently indicated. A pure sample of 6-hydroxy-5-methylindane, which was obtained as a side product in the preparation of 6-deutero-5-methylindane from 6-bromo-5-methyl derivative, also showed a band width of 2.2 cps. The NMR spectrum of 6-hydroxy-5-methylindane showed it to be free from any trace of the 4-hydroxy isomer. The identity of band widths for the 6-bromo- and 6-hydroxy- derivatives proved that the small

TABLE I

No.	Compound	$-CH_3$ band width in cps	
1	5-Methylindane	2.2	($J_{benzylic}$ = 0.5 cps)
2	4-Methylindane	2.1	
3	6-Bromo-5-methylindane	2.2	
4	6-Deutero-5-methylindane	2.2	
5	6-Hydroxy-5-methylindane	2.2	
6	4-Bromo-5-methylindane	1.8	
7	4-Deutero-5-methylindane	1.6	
8	4-Bromo-5-methylindan-1-one	1.65	
9	6-Methyltetralin	1.9	
10	1,6 Dimethyl-4-isopropyl-tetralin*	2.0	
11	4-Methylbenzocyclobutene	1.8	

*The author is grateful to Mr.R. Seshadri for a sample of this compound.

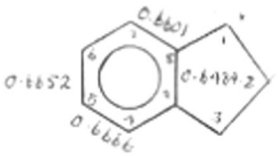
impurity in the former has not mattered very much.

We have also prepared 4-methylindane starting from o-xylene, by the method of Ekch Dev[10]. The band width of the methyl signal of this compound was found to be comparable (2.1 cps) to that of 5-methylindane. Bromination of 4-methylindane gave a mixture of three isomeric bromo-methylindanes.

In contrast to the behaviour of 5-methylindane, the resonance of the 6-methyl groups of 6-methyltetralin and 1,6-dimethyl-4-isopropyltetralin shows no tendency to split. The NMR data on tetralin is consistent with the accepted notion that there is little or no bond-fixation in tetralin.

An electronic theory to account for the difference in the reactivities of indane and tetralin has been put forward by Berthier and Pullman[14]. They felt that the steric influence of the saturated rings do not explain all the facts with regard to the Mills-Nixon Effect and hence suggested that hyperconjugation and inductive effect of the adjacent saturated rings may be responsible for the electronic changes in the benzene rings of indane, tetralin and O-xylene. According to their treatment the reactivity differences are traceable to electronic charge

densities at the various aromatic carbon atoms. The bond orders in indane and tetralin have also been calculated by them. These are as shown below.

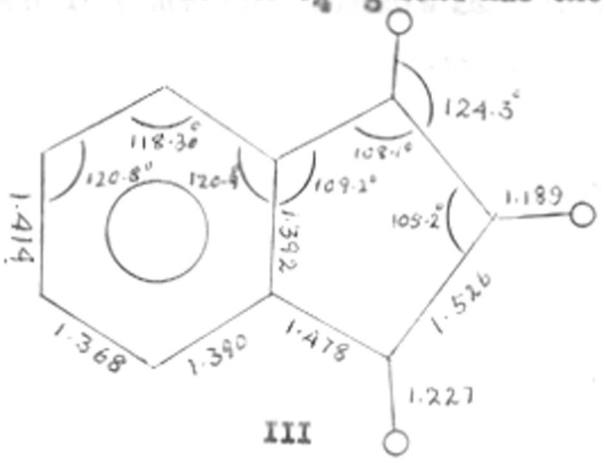


I

II

According to the above calculations, the difference between the bond orders of the 4;5 and 5;6 bonds in indane is extremely small. The present investigation clearly shows that this difference should be more pronounced than indicated by the calculations of Berthier and Pullman. Moreover, the recent X-ray study of the structure of triketoindane (ninhydrin) by William Bolton[15], further supports our observations. The experimentally measured bond distances of the molecule are shown in the formula (III) below. The longest of the aromatic bonds is between C_5 and C_6 and the shortest is between C_4 and C_5 (or C_6 and C_7). The linear inverse relationship between bond length and bond order has been demonstrated by Coulson[16]. On this basis, it can be concluded from the X-ray data that the C_5-C_6 bond has the smallest

mobile bond order while the C_4-C_5 bond has the highest

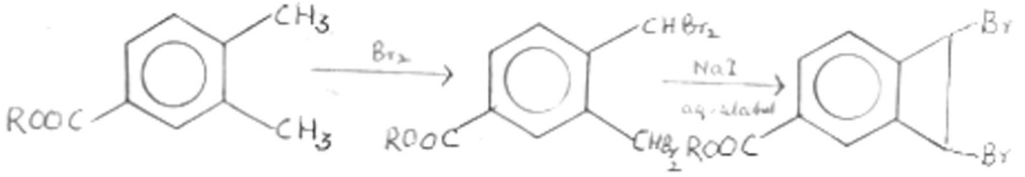


III

in the molecule. Though small differences in the bond angles and bond lengths may be expected for ninhydrin as compared with indane, the general nature of the aromatic system may be expected to remain unaffected. The fact that the bond order difference between the C_5-C_6 and C_4-C_5 bonds in indane is present in ninhydrin also, is worth considerable attention. This should mean that the electronic distribution and the π bond orders in the benzene ring in indane should be arising from some factor other than hyperconjugation because the 5-membered ring in ninhydrin carries only oxygen atoms. The effect common to both systems should therefore be the strain effect, as indicated by Longuet-Higgins and Coulson[13] and this may be expected to be slightly more pronounced in ninhydrin, because of the >C=O groups at 1-, 2- and 3-positions.

If indane is a strained molecule and the strain induces localization of the π electrons as suggested here, then it is of interest to investigate the lower homologue, benzocyclobutene, in which the effects of strain should be very much greater. For this purpose 4-methyl-benzocyclobutene, the analogue of 5-methylindane was prepared.

The ethyl ester of 3,4-dimethyl benzoic acid was brominated[17] with five equivalents of bromine at 125°C. Following Cava's procedure[17], ethyl α,α,α',α' tetrabromo-O-xylene carboxylate thus obtained was cyclized with sodium iodide in aqueous ethanol.



The NMR spectrum of the product clearly indicated that the required product, ethyl-1,2 dibromobenzocyclobutene-4-carboxylate has been formed. Separation of this compound from the mixture and conversion of the carbethoxy group to a bromomethyl group and removal of bromine by hydrogenolysis was planned. Since at this time, an authentic

sample (157 mgs) of benzocyclobutene-4-carboxylic acid[24] was received from Dr.P.A.Ongley*, we decided to prepare the final compound from this. The ethyl ester of this acid was reduced with lithium aluminium hydride and the alcohol obtained was converted to the corresponding benzyl bromide with phosphorous tribromide. On hydrogenolysis over Pd/c 4-methylbenzocyclobutene was obtained in pure form.

The methyl signal of 4-methylbenzocyclobutene showed no tendency to split and the band width of the methyl signal was found to be only 1.825 cps as compared with the value of 2.2 cps for 5-methylindane. This clearly indicated that there is comparatively little difference in the mobile bond order values for the C_3-C_4 and C_4-C_5 bonds. Further the aromatic ring seems to accommodate the strain due to the fused four-membered ring in a manner different from that in indane. It is interesting to compare the spin coupling between the para-(α-α') protons in the series: benzocyclohexene (tetralin),

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*The author is very grateful to Dr.P.A. Ongley and Dr.J.B.F. Lloyd of College of Advanced Technology, Birmingham for the sample of benzocyclobutene-4-carboxylic acid.

benzocyclopentene (indane), benzocyclobutene and benzocyclopropene. The relevant data are given in Table II.

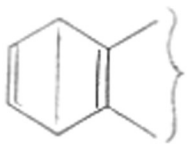
TABLE II

Systems with β(Ar) substituents	J_{para} (α-α') cps
Tetralin	0.0
Indane	0.5
Benzocyclobutene	1.0
Benzocyclopropene	1.9

The coupling between H_5 and H_8 protons in 6-substituted tetralins are found to be nearly zero while for indane para-coupling of ca. 0.5 cps was detected in some of its derivatives (e.g. 5-bromoindane). In ethyl benzocyclobutene-4-carboxylate we have found that the coupling between H_3 and H_8 is 1.0 cps. The NMR spectral data for 1,1 dimethyl benzocyclopropene-3-carboxylate (IV) has recently been reported by Anet and Anet[18].

IV

The value for the spin coupling between the para-protons in this compound was found to be 1.9 cps. This progressive increase in the para-coupling constants (0, 0.5, 1.0 and 1.9 cps) while going from tetralin to benzocyclopropene is indicative of an increasing contribution from the Dewar type resonance from (V) to the structure of the parent aromatic systems, the maximum being for benzocyclopropene.



V

Since this effect would be more pronounced in benzocyclobutene than in indane, it may be expected that the bonds flanking the 4-methyl group of this system will not display the same difference in bond order that has been observed for the similarly placed bonds of 5-methylindane. The value of the methyl band width observed for the former compound is consistent with such an interpretation.

E X P E R I M E N T A L

NMR spectra were recorded on a Varian A-60 NMR spectrometer. General experimental conditions and details regarding scanning of the spectra are described in Part I of this thesis.

<u>α-Bromo-O-xylene</u>:

In a 500 cc three-necked RB flask fitted with a mercury-seal mechanical stirrer, reflux condenser and dropping funnel and illuminated by a 300 watt lamp was placed O-xylene (E.Merck, 53 g, 0.5 mole). The flask was heated in an oil bath till the temperature of O-xylene reached about 125°C and remained constant. Bromine (88 g, 0.55 mole) was added dropwise with vigorous stirring. The addition took about an hour. The mixture was stirred and illuminated for another hour after which the excess bromine in the flask was sucked off (water-pump) and the product distilled under reduced pressure. The distilled material was slightly coloured and was therefore redistilled. The fraction boiling at 100-102°C/15 mm was collected and found to be pure O-xylyl monobromide (79 g, lit.[10]: b.p. 102°C/15 mm).

<u>β-O-Tolyl-propionic acid</u>: Procedure followed was similar to the one reported[10].

Sodium (6.95 g, 0.3 g atom) in dry toluene (250 cc) taken in a 1 lit. three-necked flask fitted with a stirrer, dropping funnel and reflux condenser (with silica gel guard-tube) was heated with vigorous stirring. The sodium was thoroughly dispersed and on cooling sodium sand in toluene was obtained. To the cooled sodium in toluene, freshly distilled diethylmalonate (67.5 cc, 0.42 mole) was added dropwise with stirring. Towards the end the reaction mixture became very viscous making stirring difficult. At this stage more toluene was added. The reaction mixture was gently heated and stirring made more vigorous to remove the coating on the sodium pieces. When the sodium had reacted completely, the reaction mixture was cooled in an ice bath and O-methylbenzyl bromide (55.784 g, 0.3 mole) was added in one lot. Toluene (25 cc) was used for washing in the last traces. After keeping for half an hour at room temperature, the reaction mixture was refluxed for 10 hours. It was then cooled and poured into water. The toluene layer was separated, washed with dil. acetic acid and with saturated ammonium sulphate solution. After drying, the solvent was removed.

The colourless oily residue was refluxed with conc. hydrochloric acid (175 cc), glacial acetic acid (115 cc) and water (21 cc) for 18 hours. The product was

cooled, diluted with cold water and filtered after allowing to stand for an hour. The acid collected in a buchner funnel was washed with water and dried. It was recrystallised from a mixture of acetic acid and water to obtain white crystalline plates of β- -tolyl-propionic acid (47.5 g), m.p. 103°C (lit.[10]: m.p. 104°C).

4-Methylindan-1-one:

Polyphosphoric acid was prepared by portionwise addition of 85% orthophosphoric acid (30 cc) into phosphorous pentoxide (150 g) in a RB flask, with occasional swirling and moderate cooling in cold water. The mixture was heated with occasional stirring on a steambath for 4 hours.

To the polyphosphoric acid, β-O-tolyl-propionic acid (15 g) was added in one lot. The reaction flask was closed with a calcium chloride guard tube and was gently heated over a free flame to get a clear solution and then heated on a waterbath for 2 hours. Working up and recrystallisation as reported[10] gave 4-methylindan-1-one (9.8 g) as colourless crystalline needles, m.p. 100°C (lit.[10]: m.p. 99-100°C).

4-Methylindane:

Zinc wool (20 g) was taken in a 500 cc RB flask and washed with acetone and distilled water. A solution of mercuric chloride (2 g) in distilled water (50 cc) containing

conc. HCl (2 cc) was added to the zinc wool and shaken for five minutes. The solution was decanted and the amalgamated zinc wool was covered with a mixture of water (30 cc), conc. hydrochloric acid (70 cc) and toluene (30 cc). To this 4-methylindan-1-one (7 g) and glacial acetic acid (2 cc) were added and the mixture refluxed for 24 hours. During the latter half of this period conc. hydrochloric acid (100 cc) was added in convenient lots. The product obtained after working up as usual, was purified by chromatography on Grade I alumina and distilled at reduced pressure to yield 4-methylindane (4.75 g), b.p. 112°C/50 mm (lit.[10]; b.p. 112°C/50 mm).

Bromination of 4-methylindane:

To a well-chilled solution of 4-methylindane (2.6 g, 0.02 mole) in CCl_4 (3 cc) were added a small crystal of iodine and bromine (3.2 g, 0.02 mole) in CCl_4 (3 cc). Evolution of HBr was quite vigorous. The mixture was left aside for two hours at the end of which water and ether were added to it. The ether layer was separated, washed with dil. sodium hydroxide and water and dried. The solvent was removed and the product distilled (105-115°C/10 mm). VPC and the NMR spectrum of the product (3.1 g) showed it to be a mixture of three components. These could not readily be

separated by fractional distillation.

5- and 6-Methyltetralins: Bromination of tetralin by a procedure[19] reported to yield pure 6-bromotetralin gave a mixture of 5- and 6-bromotetralins.

To a 100 cc three necked RB flask fitted with a stirrer, reflux condenser (with gaurd tube) and dropping funnel was added magnesium (1.415 g, 0.058 g. atom) cut into small pieces and dry ether (5 cc). Bromotetralin (12.25 g, 0.058 mole) in ether (10 cc) was added dropwise. A drop of methyl iodide was added to initiate the reaction. When all the magnesium had reacted, freshly distilled dimethyl sulphate (9.5 g, 0.075 mole) was added and the mixture refluxed for 2 hours on a waterbath. Dil. hydrochloric acid (10%, 125 cc) was added and the ether extract was washed with dil. sodium carbonate solution and with water. After drying the solvent was removed and the residual oil distilled. The fraction boiling at 101-102°C at 13 mm was found to be a mixture of 5- and 6-methyltetralins by NMR and VPC. Since the methyl signals of the two isomeric tetralins came separately this product was satisfactory for methyl band width measurements.

Indane: Indene was hydrogenated by a procedure similar to that of Alder and Wolff[20] using Raney Nickel catalyst

in a Parr High Pressure Hydrogenation Unit at 150 p.s.i. and 60°C. After the reaction was complete the catalyst was filtered off and the indane was taken up in pet.ether after adding a large amount of water to the alcohol solution. The dried pet. ether solution, on removal of solvent gave indane (in 90-95% yields) which was distilled under reduced pressure, b.p. 68-70°C/20 mm (lit.[20]: b.p. 70°C/20 mm).

5-Acetylindane: Indane (10 g, 0.085 mole) and acetyl chloride (7 g, 0.09 mole) in CS_2 (40 cc) was taken in a 100 cc three-necked flask well cooled in an ice-salt mixture. Aluminium chloride (12 g, 0.09 mole) was added to this in two lots in about half an hour. The stirred mixture was kept at 0-5°C for one hour and at room temperature for 2 hours. It was decomposed with cold dil. hydrochloric acid and was extracted with ether. The ether extract was washed with dil. sodium carbonate solution, dried and the product obtained after removal of solvent was distilled to yield pure 5-acetylindane (8.9 g), b.p. 143-144°C/13 mm; lit.[10]: b.p. 144°C/13 mm).

Indane-5-carboxylic acid: Bromine (25.6 g, 0.16 mole) and sodium hydroxide (17 g, 0.425 mole) was dissolved in water (150 cc). To the sodium hypobromite solution thus prepared was added 5-acetylindane (8.5 g, 0.053 mole) in dioxane (20 cc)

at 0°C with stirring. The temperature of the reaction mixture was allowed to rise gradually to 80°C by heating on a water bath and the mixture stirred for one hour at this temperature. The cooled solution was diluted with water and extracted with CCl_4. The aq. alkaline solution on acidification with conc. hydrochloric acid gave a white crystalline precipitate which was filtered and dried (6 g). On recrystallisation from acetic acid-water (60:100) indane-5-carboxylic acid (5.7 g) was obtained as white needles, m.p. 183°C (lit.[10]: m.p. 183-184°C).

Ethyl indane-5-carboxylate: Indane-5-carboxylic acid (5.5 g) benzene (9 cc), ethanol (5 cc) and conc. sulphuric acid (0.8 cc) were refluxed for 24 hours. The mixture was poured into cold water and the oily layer extracted with ether. The ether extract was washed with dil. sodium carbonate solution and dried. The residue left on removal of solvent was distilled at reduced pressure to yield a colourless pleasant smelling oil (4.6 g), b.p. 154-156°C/20 mm (lit.[10]: b.p. 156°C/20 mm).

5-Hydroxymethylindane: Ethyl indane-5-carboxylate (4.6 g, 0.028 mole) in dry ether was added to a slurry of $LiAlH_4$ (0.7 g, 0.018 mole) in dry ether (12 cc) during half an hour with stirring. When the addition was complete the reaction mixture was refluxed for two hours and left overnight. Water

was added dropwise with stirring to decompose excess $LiAlH_4$. The white precipitate of $Al(OH)_3$ which appeared was dissolved by addition of 10% sulphuric acid. The ether layer was separated, washed with dil. sodium carbonate solution and water and dried. White crystalline solid (3.3 g) obtained on removal of solvent was recrystallised from benzene to yield 5-hydroxymethylindane as white shining needles, m.p. 73°C (lit.[10]: m.p. 73.5-74.5°C).

5-Bromomethylindane: 5-Hydroxymethylindane (3.2 g, 0.0168 mole) was dissolved in a mixture of chloroform (6 cc) and benzene. A drop of pyridine was added to this. After chilling in ice-salt bath, PBr_3 (1.9 g, 0.007 mole) was introduced. The reaction flask was closed with a $CaCl_2$ gaurd tube. The mixture was kept at 0°C for 20 hours after which it was refluxed on a water bath for 6 hours. After cooling and diluting with water the product was ether extracted. The ether solution was washed with brine and cold water and dried. The solvent was removed and the residue distilled to yield 5-bromomethylindane (3.4 g) as a colourless lachrymatory oil, b.p. 117°C/4 mm (lit.[10]: b.p. 116-117°C/4 mm).

5-Methylindane: 5-Bromomethylindane (3.2 g) in ethyl alcohol (40 cc) was shaken in an atmosphere of hydrogen

in the presence of Pd/C (10%, 0.3 g), presaturated with hydrogen. A total volume of 843.7 cc of hydrogen was absorbed and no more absorption took place after about 1.5 hours. The catalyst was filtered off and washed with ether. The ether solution of the product was washed with brine and dried. After removal of solvent, the residue was distilled to obtain 5-methylindane (1.7 g) b.p. 111°C/50 mm (lit.[10]: b.p. 110°C/50 mm).

6-Bromo-5-methylindane: Bromination of 5-methylindane at low temperature in CCl_4 was found to proceed smoothly only in presence of a crystal of iodine. In absence of iodine very little reaction was observed even after 12 hours.

5-Methylindane (3.4 g, 0.026 mole) in CCl_4 (3 cc) was chilled with ice-salt mixture and bromine (4.1 g, 0.026 mole) was added dropwise with vigorous shaking. Copious evolution of HBr was noticed. After complete addition of bromine, the mixture was left at room temperature for 30 min., water was added and the product extracted after adding more CCl_4. The CCl_4 extract was washed with dil. sodium hydroxide and water. After drying and removal of solvent the residue obtained was distilled. The first fraction boiling below 100°C/10 mm was found to be 5-methylindane. The second fraction boiling at 110-112°C was found

to be the required product. This was redistilled to obtain 6-bromo-5-methylindane (4.0 g), b.p. 112°C/10 mm. The NMR spectrum of the product showed the presence of < 5% of the 4-bromoisomer. This could not be removed by repeated fractional distillations.

6-Deutero-5-methylindane: Lithium (E.Merck, 0.16 g, 0.024 g.atom) freshly cut in a dry box into small pea-size pieces and weighed without exposing to atmosphere, was taken in dry ether (5 cc) in a 250 cc three-necked flask fitted with a stirrer, reflux condenser (with magnesium perchlorate gaurd tube) and dropping funnel. 6-Bromo-5-methylindane (2.3 g, 0.011 mole) in dry ether (10 cc) was added dropwise with stirring. During the addition gentle reflux of the ether was observed. The reaction mixture was refluxed for three hours during which time almost all the lithium reacted. D_2O (2-3 cc) was added dropwise and when the decomposition was complete the reaction mixture was diluted with water. The ether layer was separated after addition of more ether. This was washed with very dil. HCl and dried. After removal of solvent, the residue was fractionally distilled. The fraction boiling at 100° at 40 mm was found to be pure 6-deutero-5-methylindane (1.2 g). This product was found to be more than 90% isotopically pure by the NMR integration

method. VPC showed this to be free from other impurities.

On discontinuing the distillation and cooling the unit, a white crystalline material was found in the distillation flask and at the lower parts of the condenser. This was recrystallised from pet. ether to obtain a white crystalline solid which was identified as 6-hydroxy-5-methylindane, m.p. 82-84°C (lit.[25]: m.p. 83-85°C). The NMR spectrum showed it to be a phenol, having two aromatic protons para to each other and conclusively proved the compound to be 5-hydroxy-6-methylindane. (Found: C, 80.81; H, 8.06; Calc. for $C_{10}H_{12}O$: C, 81.06; H, 8.17%).

2-Bromo-4-nitrotoluene: Bromination of p-nitrotoluene (68.5 g, 0.5 mole) was done with bromine (30.5 cc, 0.59 mole) in presence of iron powder (4 g) at 80°C as reported[11]. The mixture was poured into ice cold 10% sodium hydroxide solution and the crystalline product obtained was recrystallised from glacial acetic acid, 10% aq. acetic acid and finally from 1% sodium hydroxide solution. 2-Bromo-4-nitrotoluene (95 g), m.p. 75°C (lit.[11]: m.p. 75-76°C) was directly used for the next preparation.

2-Bromo-3-methylbenzoic acid: von Richter reaction was carried out on 2-bromo-4-nitrotoluene as reported[11]. Methyl cellosolve was used as solvent instead of cellosolve.

2-Bromo-4-nitrotoluene obtained from the above experiment, potassium cyanide (30 g), methyl cellulose (900 cc) and water (850 cc) were taken in a 5-lit. flask and refluxed for 16-18 hours on a heating mantle in a fuming cupboard. Water (1 lit.) was added and the mixture boiled. It was acidified with about 30 cc conc. hydrochloric acid and boiled for another 15 min. to expel all the hydrogen cyanide produced. The mixture was cooled to 40°C and a few g. of Fuller's earth were stirred in. It was filtered through a Buchner funnel pre-coated with Fuller's earth. The filtrate was extracted with chloroform (3 x 200 cc) and the combined chloroform extracts were further extracted with 5% ammonium carbonate solution (3 x 100 cc). The ammonium carbonate solution was acidified with conc. hydrochloric acid and cooled in an ice-bath. Yellow crystalline precipitate was obtained (no tarry material as reported[11] was obtained). The product was filtered, washed with water and dried. The dry product was refluxed with pet. ether (40-60, 500 cc), filtered hot and the filtrate concentrated. On cooling white crystals of 2-bromo-3-methyl-benzoic acid (7 g) separated, m.p. 134-136°C (lit.[11]: m.p. 134-136°C).

<u>Methyl 2-bromo-3-methylbenzoate:</u> 2-Bromo-3-methyl benzoic acid (20 g), benzene (40 cc), methanol (30 cc) and conc.

sulphuric acid (2 cc) were refluxed for 48 hours. Methanol was then removed by distillation. The residual mixture was cooled, diluted with water and ether extracted. The ether extract was washed with dil. sodium carbonate solution to remove unreacted acid and with water. Ether solution was dried and the solvent was removed. The oily residue (19.68 g) was distilled under reduced pressure, b.p. 113°C/6 mm (Found: C, 47.6; H, 4.08; Br, 34.53. Calc. for $C_9H_9BrO_2$: C, 47.2; H, 3.94; Br, 34.8%).

2-Bromo-3-methylbenzyl alcohol: Methyl 2-bromo-3-methylbenzoate (9.205 g, 0.04 mole) in dry ether (25 cc) was slowly added through a dropping funnel into a slurry of $LiAlH_4$ (1.2 g, 0.03 mole) in dry ether (25 cc) in a 500 cc three necked flask fitted with a stirrer, dropping funnel and reflux condenser. Addition was done during 30 min. with efficient stirring. The mixture was refluxed for one hour using a lamp source and left overnight. Water and 10% sulphuric acid were added dropwise with stirring till decomposition is complete. Ether layer was separated, washed with 1% sodium carbonate solution in brine and dried. On removal of solvent white crystalline needles of the alcohol were obtained. Recrystallisation from pet. ether-benzene (1:3) and from pet. ether gave 2-bromo-3-methylbenzyl

alcohol (7 g), m.p. 79.5°C. (Found: C, 47.96; H, 4.66; Br, 39.90. Calc. for C_8H_9BrO: C, 47.76; H, 4.48; Br, 39.8%).

2-Bromo-3-methylbenzyl bromide: 2-Bromo-3-methylbenzyl alcohol (6 g, 0.03 mole) was dissolved in a mixture of benzene (5 cc) and chloroform (15 cc) and a drop of anhydrous pyridine. This was cooled in an ice-bath and PBr_3 (2.75 g, 0.0101 mole) was added slowly with shaking. Reaction flask was closed with a calcium chloride guard tube and kept in a frigidaire for 20 hours. The reaction mixture was then refluxed on a water bath for six hours. After cooling and adding ether and water, the solvent layer was separated. It was washed with cold water (15 cc) and brine (15 cc) and dried. After removal of solvent, the oily residue was distilled under reduced pressure to obtain 2-bromo-3-methylbenzyl bromide (6.37 g), b.p. 114°C/5 mm. The product is lachrymatory.

α-(2-Bromo-3-methylphenyl)propionic acid: Sodium sand in toluene was made from sodium (0.57 g, 0.0248 g.atom) in a 250 cc three necked flask as described earlier. Diethyl malonate (5.6 g, 0.035 mole) was added dropwise with stirring. The stirring was continued till the sodium reacted completely. This was cooled in ice bath and treated with 2-bromo-3-methyl benzyl bromide (6.37 g, 0.0241 mole) in one lot. After stirring

at room temperature for one hour, the mixture was heated on a steam bath for 2 hours and finally refluxed for 12 hours on a heating mantle. The reaction mixture was cooled and poured into water. The toluene layer was separated and washed with 2% acetic acid and with saturated ammonium sulphate solution. After drying and removal of solvent, the residual liquid was used for hydrolysis and decarboxylation reaction directly.

The above product was refluxed with conc. Hydrochloric acid (15 cc), acetic acid (10 cc) and water (3 cc) for 18 hours. The reaction mixture was cooled, diluted with cold water and was extracted with ether. The combined ether extracts were shaken with 10% sodium carbonate solution (2 x 25 cc). The alkaline extract was acidified with conc. hydrochloric acid and the precipitated acid was filtered through a Buchner funnel. After drying, the acid (4.1 g) was recrystallised from benzene-pet. ether (3:1) and again from benzene-pet.ether (1:1). β-(2-Bromo-3-methylphenyl) propionic acid was obtained as colourless crystalline plates (2.7 g), m.p. 122°C. (Found: C, 49.65; H, 4.43; Br, 32.58. Calc. for $C_{10}H_{11}BrO_2$: C, 49.38; H, 4.52; Br, 32.92%).

4-Bromo-5-methylindan-1-one: Polyphosphoric acid was

prepared from phosphorus pentoxide (14 g) and ortho-phosphoric acid (8 cc). β-(2-bromo-3-methylphenyl) propionic acid (2 g) was well powdered and introduced into the polyphosphoric acid. The mixture was heated upto 120°C on an oil bath, when the compound melted and an yellow colour developed which changed over to pink and then to red. When the reaction mixture became homogeneous, the flask was kept in an oil bath maintained at 100-105°C for about one hour. The product was worked up as described earlier. The ether solution was washed with dil. sodium carbonate solution and the alkaline extract was acidified with conc. hydrochloric acid, to recover the unreacted starting material (0.38 g). The ether extract, after washing with alkali, on concentration gave a solid, which on recrystallisation from pet. ether benzene (1:2) yielded 4-bromo-5-methylindan-1-one as colourless crystalline needles (1.5 g), m.p. 110°C. (Found: C, 53.51; H, 3.94; Br, 35.37. Calc. for $C_{10}H_9BrO$: C, 53.33; H, 4.00; Br, 35.55%).

4-Bromo-5-methylindane: To amalgamated zinc, prepared from zinc wool (1.9 g) and mercuric chloride (0.19 g) as described earlier, water (2.6 cc), conc. hydrochloric acid (6 cc) and toluene (3 cc) were added. The above indanone (1 g) was added to this, together with glacial acetic acid (0.2 cc). The

mixture was refluxed for 24 hours on a heating mantle. During the latter half of the refluxing period, conc. hydrochloric acid (8.6 cc) was added in small portions through the top of the condenser. The reaction mixture was cooled and extracted with ether. The zinc pieces were also rinsed with ether. The combined ether extracts were washed with brine and with water. After drying the solvent was removed. The pale yellow oil that remained, was distilled to obtain 4-bromo-5-methylindane (760 mg) as colourless liquid, b.p. 93-95°C/1.5 mm, n_D^{30} 1.5750. (Found: C, 56.98; H, 4.88; Br. 38.12. Calc. for $C_{10}H_{11}Br$: C, 56.87; H, 5.21; Br, 37.91%).

4-Deutero-5-methylindane: Lithium (0.105 g, 0.015 g.atom) cut into small pieces in a dry box, was taken in dry ether (10 cc) in a 100 cc three necked flask. 4-Bromo-5-methylindane (1.5 g, 0.071 mole) in dry ether (5 cc) was added dropwise with stirring. The mixture was refluxed for one hour after completion of addition. D_2O (5 cc) was added dropwise and stirring continued for half an hour. The reaction mixture was diluted with ether and water, ether layer was separated and washed with very dil. hydrochloric acid and water. After drying, the ether was removed. The residual liquid on distillation

yielded 4-deutero-5-methylindane (0.9 g), b.p. 109-110°C/ 50 mm. The product was found to be ca. 90% isotopically pure by NMR integration method.

4-Bromo-O-xylene: 4-Bromo-O-xylene was prepared by bromination of O-xylene by the procedure described in Organic Syntheses[21]. The product was distilled and the fraction boiling at 100-102°C at 18-20 mm was found to be 4-bromo-O-xylene (lit.[21]; b.p. 92-94°C/14-15 mm).

O-Xylene-4-carboxylic acid: Freshly cleaned magnesium ribbon (12.15 g, 0.5 g.atom), cut into small pieces and a crystal of iodine were taken in dry ether (20 cc) in a 1 lit. three necked flask fitted with a stirrer, reflux condenser (with gaurd tube) and dropping funnel. 4-Bromo-O-xylene (92.5 g, 0.5 mole) in dry ether (200 cc) was taken in the dropping funnel. 25 cc of this ether solution was added at a lot with vigorous stirring to start the reaction. The ethereal solution was then added dropwise with stirring. Continuous refluxing was observed. When the addition was over, the reaction mixture was externally heated to keep refluxing, till all the magnesium reacted. The Grignard thus obtained was poured into dry ice (about 100 g) in a 2 lit. beaker, with stirring. This was allowed to stand with excess Dry ice present for some time. This was then

decomposed by the addition of crushed ice and water containing conc. hydrochloric acid (ca. 50 cc). The mixture was extracted with ether and the ether layer was washed with cold water and with 10% sodium hydroxide solution (2 x 100 cc). The alkaline extract was acidified with 20% hydrochloric acid to give a white crystalline precipitate which was filtered, dried and recrystallised from benzene to furnish O-xylene-4-carboxylic acid (38 g) as colourless crystalline plates, m.p. 165°C (lit.[22]: m.p. 165°C). (Found: C, 72.74; H, 6.87. Calc. for $C_9H_{10}O_2$: C, 72.0; H, 6.67%).

4-Acetyl-O-xylene[22]: To camphor (100 g) in a 2 lit. flask was added conc. sulphuric acid (700 g) and the deep coloured mixture was heated at 105-110°C for one hour. Considerable amount of SO_2 was evolved and frothing had to be prevented by controlling the temperature. The product after cooling was added onto ice (1 kg) and the flask rinsed with cold water. This mixture was steam distilled till no more oily product came through. The distillate was extracted with ether and washed with 10% sodium hydroxide and with brine. The ether extract was dried and the solvent was removed. An yellow oil was obtained which was found to be a mixture of four products including the starting material and the required product, by NMR. 4-Acetyl-O-xylene was separated

from lower boiling impurities by fractional distillation. The fraction boiling at 127-128°C/22 mm was found to be pure 4-Acetyl-O-xylene (21 g) (lit.[22]: b.p. 126-128°C/22 mm).

O-Xylene-4-carboxylic acid from 4-Acetyl-O-xylene: 4-Acetyl-O-xylene (18.5 g, 0.125 mole) in 50 cc dioxane was added at 0°C to sodium hypobromite solution prepared from bromine (60 g) and sodium hydroxide (42 g) in water (350 cc). The temperature was then allowed to rise and the mixture was heated with stirring on a water bath for 2 hours. The reaction mixture was cooled and diluted with water. The aq. alkaline solution, after extraction with CCl_4, was acidified with conc. hydrochloric acid when the required acid was obtained as white crystalline solid. It was filtered, dried and recrystallised from benzene to obtain O-xylene 4-carboxylic acid (13.25 g) as colourless crystalline plates, m.p. 164°C (lit.[22]: m.p. 165-166°C).

Ethyl O-xylene-4-carboxylate: O-Xylene-4-carboxylic acid (14 g) was refluxed for 28 hours with benzene (24 cc), dry ethanol (14 cc) and conc. sulphuric acid (2 cc). Working up as usual and distillation under reduced pressure gave ethyl O-xylene-4-carboxylate (12.1 g) as colourless sweet-smelling liquid, b.p. 138-140°C/20 mm;

120-122°C/12 mm (lit.[23]: b.p. 120°/12 mm).

Ethyl 1,2 dibromo benzocyclobutene 4-carboxylate:

The above ester (11.5 g, 0.065 mole) was taken in a 250 cc three necked flask fitted with a stirrer, condenser and dropping funnel and illuminated by two 300 Watt tungsten lamps. The flask was heated in an oil bath till the temperature of the ester reached 125°C and bromine (16 cc; 0.3 mole) was added dropwise with vigorous stirring. The rate of addition was adjusted so that the bromine loss was minimum (about 40 min). The mixture was stored at the same temperature for one hour more and allowed to cool to 40-60°C. Suction (water pump) was applied to remove unreacted bromine and HBr evolved during the reaction. To the dark coloured residue was added sodium iodide (45 g), ethanol (150 cc) and a few drops of water. The mixture was refluxed with stirring for 48 hours after which the reflux condenser was replaced by a distillation unit and about half the solvent was removed. The mixture was cooled to room temp. and sulphur dioxide was passed through it till all the iodine was reduced. Crushed ice and water were added with stirring into the mixture. The product was extracted with chloroform. The chloroform extract was washed with cold water and dil. sodium bicarbonate solution (which on acidification gave 200 mg of a dark brown acid

product) and dried. After removal of solvent a brown syrupy liquid was obtained which on TLC showed itself to be a mixture of three products. This crude material was chromatographed through neutral alumina grade I, using pet. ether as eluent. The main fraction was found by NMR to be the required cyclised product. Since the required intermediate product benzocyclobutene 4-carboxylic acid[24] was made available to us at this stage by Dr.P.A. Ongley, further work on the purification of this dibromo compound was discontinued.

Methyl benzocyclobutene-4-carboxylate: Diazomethane was prepared from nitrosomethyl urea (10 g), potassium hydroxide solution (40%; 30 cc) and ether (100 cc) following the procedure in Organic Syntheses[11]. To a solution of the benzocyclobutene 4-carboxylic acid (0.1578 g) in ether (5 cc) was added diazomethane in ether solution till no more effervescence was observed and a pale yellow colour persisted. Ether was removed under suction at the water pump. CCl_4 was added and again the solvent was removed, the last traces under suction. The required ester was obtained as a colourless liquid (0.1557 g). This was found to be pure methyl benzocyclobutene-4-carboxylate from its NMR spectrum and was directly used for the next step.

4-Benzocyclobutenyl carbinol: In a 50 cc RB flask $LiAlH_4$ (100 mg); 0.0144 mole) in dry ether (3 cc) was taken and the ester (0.1557 g. 0.0009 mole) in dry ether (3 cc) was added. The mixture was refluxed for 24 hours after which the product was worked up as before. After removal of ether under suction, the product was recrystallised from CCl_4 to obtain 4-benzocyclobutenyl carbinol as white needles (0.1150 g), m.p. 68-70°C. The product was found to be pure from its NMR spectrum.

4-Bromomethyl benzocyclobutene: 4-Benzocyclobutenyl carbinol (0.1150 g) in benzene (0.1 cc) and chloroform (0.25 cc) was treated with PBr_3 (0.09 g) and kept in a frigidaire for 16 hours (with gaurd tube). It was then refluxed for 4 hours and worked up as described earlier. Traces of ether, benzene and chloroform were removed under suction at water pump and then at reduced pressure. The product (0.1212 g) was taken in CCl_4 and NMR spectrum recorded, which showed the product to be pure 4-bromomethyl benzocyclobutene. It is lachrymatory.

4-Methyl benzocyclobutene: Pd/C catalyst (5%; 0.05 g) in absolute alcohol (2.5 cc) in a 50 cc hydrogenation flask was saturated with hydrogen and the bromide (0.1212 g)

in absolute alcohol (2.5 cc) was introduced. When the absorption of calculated amount of hydrogen was over, the product was worked up as described earlier for 5-methyl indane. The colourless oil obtained after removal of solvent was distilled in a bulb under reduced pressure. The product distilled at 90-95°C(bath temp.)/ 40 mm. The distillate (0.057 g) was found to be pure 4-methyl benzocyclobutene from its NMR spectrum. The residue after distillation weighed 0.0231 g.

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CHAPTER III

NMR SPECTRA OF BENZOCYCLOALKENE DERIVATIVES

NMR SPECTRA OF BENZOCYCLOALKENE DERIVATIVES

INTRODUCTION

A systematic investigation of the NMR spectra of indane, tetralin, O-xylene and benzocyclobutene derivatives appeared worthwhile in the context of the conclusions arrived at in the previous Chapter. It was thought that the changes in π electron distribution brought about by the strain of alicyclic rings may be reflected in the chemical shifts of the protons of the aromatic rings or substituents. Information available in literature is very limited and their discussion incidental to other issues. NMR spectroscopy has been used together with other techniques for the determination of structure and conformation of certain indane derivatives with substituents in the five-membered ring[1-3]. NMR spectra of some benzocyclobutene derivatives have been reported[4-6] recently.

RESULTS AND DISCUSSION

The chemical shift and the spin coupling data from the NMR spectra* of a number of indane, tetralin, O-xylene

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*The NMR spectra are measured in CCl_4 or $CDCl_3$ on a Varian A-60 NMR Spectrometer. Tetramethylsilane (TMS) was used as internal reference unless otherwise mentioned. Chemical shifts are given as δ cps from TMS.

TABLE I

	Compound	cps	No.of protons	Assignment	Remarks
1	Indane	120.5	2	H_2	multiplet
		170.0	4	H_1, H_3	triplet J = 7 cps
		424.5	4	Ar-H	broad singlet b.w = 3.4 cps
2	Tetralin	102.5	4	H_2, H_3	unsym. quartet
		160.0	4	H_1, H_3	multiplet
		412.0	4	Ar-H	singlet b.w. = 1.2 cps
3	O-Xylene	127.5	6	$-CH_3$	singlet
		418.0	4	Ar-H	singlet b.w. = 1.1 cps
4	5-Acetylindane	123.0	2	H_2	quartet
		147.0	3	$-COCH_3$	singlet
		176.0	4	H_1, H_3	triplet; J = 7 cps
		432.0	1	H_7	doublet; $J_{H_7-H_6}$ = 9 cps.
		461.5	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 9 cps $J_{H_6-H_4}$ = 1.5 cps
		465.0	1	H_4	broad singlet

.....contd.

TABLE I (Contd)

	Compound	cps	No.of protons	Assignment	Remarks
5	6-Acetyltetralin	105.0	4	H_2,H_3	unresolved multiplet
		143.0	3	$-COCH_3$	singlet
		162.0	4	H_1,H_3	broad singlet
		418.0	1	H_8	doublet $J_{H_8-H_7}$ = 9 cps
		447.0	1	H_7	doublet of doublets $J_{H_7-H_8}$ = 9 cps; $J_{H_7-H_5}$ = 1 cps
		447.0	1	H_5	doublet $J_{H_5-H_7}$ = 1 cps
6	4-Acetyl-O-xylene	133.0	6	$-CH_3$	singlet
		147.0	3	$-COCH_3$	singlet
		425.2	1	H_6	doublet $J_{H_6-H_5}$ = 8.8 cps
		454.5	1	H_5	doublet of doublets $J_{H_5-H_6}$ = 8.8 cps; $J_{H_5-H_3}$ = 1.5 cps
		460.0	1	H_3	broad singlet
7	Indane-5-carboxylic acid.	125.0	2	H_2	quartet
		176.0	4	H_1,H_3	triplet; J = 7 cps
		438.0	1	H_7	doublet; $J_{H_7-H_6}$ = 8 cps
		474.0	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 8 cps; $J_{H_6-H_4}$ = 1.5 cps

...contd.

TABLE I (CONTD)

	Compound	cps	No.of protons	Assignment	Remarks
		479.0	1	H_4	broad singlet
		690.0	1	COOH	singlet
8	Tetralin-6-carboxylic acid.	110.0	4	H_2,H_3	broad singlet
		170.0	4	H_1, H_4	" "
		424.0	1	H_8	doublet $J_{H_8-H_7}$ = 8 cps
		467.0	1	H_7	doublet of doublets $J_{H_7-H_8}$ = 8 cps $J_{H_7-H_5}$ = 1 cps
		467.0	1	H_5	doublet $J_{H_5-H_7}$ = 1 cps
		720.0	1	-COOH	singlet
9	O-Xylene-4-carboxylic acid	136.0	6	$-CH_3$	singlet
		427.0	1	H_6	doublet; $J_{H_6-H_5}$ = 8 cps
		462.0	1	H_5	doublet of doublets $J_{H_6-H_5}$ = 8 cps $J_{H_5-H_3}$ = 1 cps
		466.0	1	H_3	singlet
		640.0	1	-COOH	singlet

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
10	Benzocyclobutene-4-carboxylic acid.	193.0	4	$-CH_2$	singlet
		428.0	1	H_6	doublet of doublets $J_{H_6-H_5}$ = 8 cps, $J_{H_6-H_3}$ = 1 cps
		468.0	1	H_3	doublet of doublets $J_{H_3-H_5}$ = 1.3 cps, $J_{H_3-H_6}$ = 1 cps
		481.5	1	H_5	doublet of doublets $J_{H_5-H_6}$ = 8 cps, $J_{H_5-H_3}$ = 1.3 cps
		670.0	1	-COOH	singlet
11	Methyl benzocyclobutene-4-carboxylate	187.0	4	$-CH_2$	singlet
		228.5	3	$-OCH_3$	"
		420.0	1	H_6	doublet of doublets $J_{H_6-H_5}$ = 8 cps, $J_{H_6-H_3}$ = 1 cps
		457.0	1	H_3	doublet of doublets $J_{H_3-H_6}$ = 1 cps, $J_{H_3-H_5}$ = 1.2 cps
		471.0	1	H_5	doublet of doublets $J_{H_5-H_6}$ = 8 cps, $J_{H_5-H_3}$ = 1.2 cps

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
12	Ethyl O-xylene -4-carboxylate	81.0	3	$-CH_2-\underline{CH_3}$	triplet; J = 7 cps
		132.5	6	$Ar-CH_3$	singlet
		258.0	2	$-CH_2-$	quartet; J = 7 cps
		427.5	1	H_6	doublet $J_{H_6-H_5}$ = 8 cps
		462.8	1	H_5	doublet $J_{H_5-H_6}$ = 8 cps
		486.2	1	H_3	broad singlet
13	5-Bromoindane	119	2	H_2	sextet
		163	4	H_1, H_3	triplet; J = 7 cps
		405.5	1	H_7	doublet of doublets $J_{H_7-H_6}$ = 8.5 cps $J_{H_7-H_4}$ = 0.5 cps
		413.5	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 8.5 cps $J_{H_6-H_4}$ = 1.9 cps
		420.2	1	H_4	broad singlet
14	6-Bromo-tetralin	102	4	H_2, H_3	multiplet
		157.8	4	H_1, H_4	unresolved multiplet
		404.5	1	H_8	doublet; $J_{H_8-H_7}$ = 9 cps
		420.0	2	H_5, H_7	multiplet centred at.

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
15	Ethyl 1,2-dibromo-benzocyclo-butene-4-carboxylate	81.0	3	$-CH_2-\underline{CH_3}$	triplet
		261.0	2	$-\underline{CH_2}-$	quartet
		325.0	2	-CHBr	singlet
		438.0	1	H_6	doublet; J = 8 cps
		472.0	1	H_5	doublet of doublets J = 8 cps J = ?
		481.0	1	H_3	broad singlet
16	5-Indanol	124.0	2	H_2	quartet
		168.0	4	H_1,H_3	triplet
		380.5	1	-OH	singlet
		394.5	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 7 cps $J_{H_6-H_4}$ = 2.2 cps
		397.2	1	H_4	broad singlet
		416.0	1	H_7	doublet; J = 7.8 cps
17	Sodium-5-indanolate	126.0	2	H_2	quartet
		170.0	4	H_1, H_3	triplet
		391.0	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 7.8 cps $J_{H_6-H_4}$ = 2.2 cps

.....contd.

TABLE I (Contd)

	Compound	cps	No.of protons	Assignment	Remarks
		398.7	1	H_4	doublet; J = 2.2 cps
		420.3	1	H_7	doublet; J = 7.8 cps
18	4-O-Xylenol	128.5	6	$-CH_3$	singlet
		379.5	1	-OH	"
		389.0	1	H_5	doublet; J = 8 cps
		392.5	1	H_3	singlet
		409.8	1	H_6	doublet; J = 8 cps
19	Sodium 4-O-Xylenolate	131 132	6	$-CH_3$	singlet "
		391	1	H_5	doublet of doublets $J_{H_5-H_6}$ = 7.5 cps $J_{H_5-H_3}$ = 1.5 cps
		394.8	1	H_3	singlet
		418.8	1	H_6	doublet $J_{H_6-H_5}$ = 7.5 cps
20	5-Acetoxy-indane	127.0	2	H_2	quartet
		131.5	3	$-COCH_3$	singlet
		173.0	4	H_1, H_3	triplet; J = 7 cps
		407.0	1	H_6	doublet of doublets $J_{H_6-H_7}$ = 8 cps $J_{H_6-H_4}$ = 2 cps

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
		412.0	1	H_4	doublet $J_{H_4-H_6}$ = 2 cps
		426.5	1	H_7	doublet $J_{H_7-H_6}$ = 8 cps
21	4-Acetoxy O-xylene	125.5	3	$-COCH_3$	singlet
		129.5	6	$-CH_3$	"
		404.0	1	H_5	doublet $J_{H_5-H_6}$ = 8.5 cps
		406.0	1	H_3	singlet
		416.5	1	H_6	doublet $J_{H_6-H_5}$ = 8.5 cps
22	4-Methylindane	122.0	2	H_2	multiplet
		132.0	3	CH_3	singlet
		169.0	4	H_1, H_3	quartet
		413.5	3	Ar-H	unresolved multiplet
23	5-Methylindane	121.5	2	H_2	multiplet
		135.0	3	$-CH_3$	doublet (J = 0.6 cps)
		168.5	4	H_1, H_3	triplet; J = 7 cps
		408.0	1	H_6 or H_7	doublet; J = 7.5 cps
		413.0	1	H_4	singlet
		414.0	1	H_6 or H_7	doublet; J = 7.5 cps

.....contd.

TABLE I (Contd)

	Compound	cps	No.of protons	Assignment	Remarks
24	6-Bromo-5-methylindane	121.5	2	H_2	multiplet
		138.0	3	$-CH_3$	singlet
		166.0	4	H_1, H_3	triplet
		416.0	1	H_4	singlet
		434.0	1	H_7	singlet
25	4-Bromo-5-methylindane	124.0	2	H_2	multiplet
		139.0	3	$-CH_3$	singlet
		174.0	4	H_1, H_3	triplet
		412.5	2	H_6, H_7	singlet
26	6-Hydroxy-5-methylindane	124.0	2	H_2	multiplet
		128.0	3	$-CH_3$	singlet
		166.0	4	H_1, H_3	triplet (J = 7 cps)
		287.0	1	OH	singlet
		388.0	1	H_7	singlet
		412.2	1	H_4	singlet
27	6-Deutero-5-methylindane	123.0	2	H_2	multiplet
		136.5	3	$-CH_3$	singlet
		169.8	4	H_1, H_3	triplet
		415.0	2	H_4, H_7	singlet

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
28	4-Deutero-5-methylindane	123.0	2	H_2	multiplet
		136.5	3	$-CH_3$	singlet
		169.5	4	H_1, H_3	triplet; J = 7 cps
		410.0	1	H_6	doublet $J_{H_6-H_7}$ = 8 cps
		417.5	1	H_7	doublet; J = 8 cps
29	4-Methylbenzocyclobutene	133.0	3	$-CH_3$	singlet
		181.2	4	$-CH_2$	singlet
		401.3	1	H_3	singlet
		405.8	2	H_5, H_6	singlet
30	4-Bromomethylbenzocyclobutene	184.5	4	$-CH_2$	singlet
		261.5	2	$-CH_2Br$	singlet
		422.5	3	Ar-H	multiplet
31	4-Hydroxymethylbenzocyclobutene	182.0	4	$-CH_2$	singlet
		206.0	1	-OH	broad singlet
		259.0	1	$-CH_2O$	singlet
		410.0	2	H_5, H_6	singlet
		412.5	1	H_3	singlet

.....contd.

TABLE I (Contd.)

	Compound	cps	No.of protons	Assignment	Remarks
32	Sym-Hydrindacene	114.0	4	H_2,H_2	quartet
		158.0	8	H_1,H_3, H_1,H_3	triplet; J = 7 cps
		407.0	2	H_4,H_7	singlet
33	Sym-Hydrindacene-1-one	127.0	2	H_2	quartet
		150.0	2	-CH_2-CO-	multiplet
		174.5	6	H_3,H_1, H_3	multiplet
		431.0	1	H_4	singlet
		446.0	1	H_7	singlet
34	β-(5-indane)propionic acid.	125.0	2	H_2	quartet
		158.0	2	-CH_2-CO	multiplet
		171.0	4	H_1,H_3, Ar-CH_2	multiplet
		419.5	3	Ar-H	broad singlet
		723.0	1	COOH	singlet
35	Indan 1,3-dione (in acetone)	194.5	2	>CH_2	singlet
		474.0	4	Ar-H	singlet

.....contd.

TABLE I (Contd)

	Compound	cps	No.of protons	Assignment	Remarks
36	4-Methylindan-1-one	144.0	3	$-CH_3$	singlet
		157.0	2	H_2	multiplet
		180.0	2	H_3	multiplet
		440	3	Ar-H	multiplet
37	6-Bromoindan-1-one	153.0	2	H_2	multiplet
		177.0	2	H_3	"
		433.0	1	H_4	doublet $J_{H_4-H_5}$ = 8 cps
		450.0	1	H_5	doublet of doublets $J_{H_5-H_4}$ = 8 cps $J_{H_5-H_7}$ = 1.8 cps
		459.0	1	H_7	singlet
38	5-Bromoindan-1-one	154.5	2	H_2	multiplet
		183.0	2	H_3	"
		438.0	1	H_4	singlet
		442.5	1	H_6	doublet $J_{H_6-H_7}$ = 9 cps
		448.5	1	H_7	doublet $J_{H_7-H_6}$ = 9 cps

.....contd.

TABLE I (Contd)

	Compound	cps	No.of protons	Assignment	Remarks
39	6-Hydroxy-indan-1-one	160.5	2	H_2	multiplet
		190.0	2	H_3	"
		408.0	1	H_5	doublet of doublets $J_{H_5-H_4}$ = 9.5 cps $J_{H_5-H_7}$ = 1.5 cps
		419	1	H_7	singlet
		452	1	H_4	doublet $J_{H_4-H_5}$ = 9.5 cps
40	4-Bromo-5-methylindan-1-one	148.5	3	$-CH_3$	singlet
		155.0	2	H_2	multiplet
		182.0	2	H_3	"
		431.0	1	H_6	doublet J = 8 cps
		445.0	1	H_7	doublet J = 8 cps
41	Thioketal of 6-bromo-indan-1-one.	168.0	4	H_2,H_3	multiplet
		204.0	4	$-SCH_2-$	singlet
		419.3	1	H_4	doublet $J_{H_4-H_5}$ = 8 cps
		434.7	1	H_5	doublet of doublets. $J_{H_5-H_4}$ = 8 cps $J_{H_5-H_7}$ = 1.8 cps

....contd.

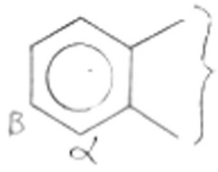
TABLE I (Contd)

Compound	cps	No. of protons	Assignment	Remarks
	455.5	1	H_7	doublet $J_{H_7-H_5}$ = 1.8 cps
42 Thioketal of 5-bromo-indan-1-one	160.5	2	H_2	Unsym. triplet
	174.0	2	H_3	"
	206.5	4	$-CH_2-S$	Singlet
	439	1	Ar-H	singlet
	442.5	2	Ar-H	singlet
43 4-Hydroxy-5-acetyl-O-xylene	133.5	3	$-CH_3$	singlet
	140.5	3	$-CH_3$	singlet
	150.0	3	$-COCH_3$	singlet
	476.0	1	H_3	singlet
	491.0	1	H_6	singlet
	478.0	1	-OH	singlet
44 5-Hydroxy-6-acetylindane	125.0	2	H_2	multiplet
	140.5	3	$-COCH_3$	singlet
	170	4	H_1, H_3	triplet; J = 7 cps
	440.0	1	H_4	singlet
	448.0	1	H_7	singlet
	730.0	1	-OH	singlet

and benzocyclobutene derivatives are given and discussed. The spectral data are presented in Table I.

The spectra of the parent hydrocarbons themselves are interesting. While the aromatic protons of tetralin and O-xylene appear as singlets at 412 and 415 cps respectively, those of indane (at 42.4.5 cps) give a band with fine structure. While the band width for the aromatic proton signals of tetralin and O-xylene are 1.4 and 1.1 cps respectively, indane aromatic signal has a band width of 3.4 cps. This is clearly indicative of the chemical shift difference between the A and B pairs of these A_2B_2 systems being larger for indane than for the other two. For tetralin and O-xylene this difference is nearly zero.

The pattern of the aromatic proton signals of indane, tetralin, O-xylene and benzocyclobutene derivatives substituted at the α-position (I) are of considerable



I

importance while indane and O-xylene derivatives give the same pattern, those of tetralin give a considerably different

pattern. The C_6-protons of 5-substituted indanes show their absorption invariably at higher fields than the C_4-protons, the absorptions of the corresponding protons of 6-substituted tetralins occur at the same field. Thus in the NMR spectra of 5-acetylindane, indane-5-carboxylic acid and its ethyl ester, 5-methylindane, 5-bromomethylindane, 5-hydroxymethylindane, 5-hydroxyindane, 5-bromoindane as well as in other 5-substituted indanes, the C_6-protons absorb at about 3 to 4 cycles upfield compared to the C_4-protons. The signals due to the C_5-protons of 6-substituted tetralins (which are meta-coupled) coincide with the mean positions of the C_7-proton doublet signals (ortho-coupled). On the basis of these observations we concluded[7] that the higher shielding at the 6-position in the 5-derivatives of indane is apparently a property of the indane ring system. The change from an electron donating to an electron withdrawing substituent does not alter the relative absorption positions of the aromatic protons. Whether this difference is arising from increased electron density at the 6-position in indane compared to the 4-position is not clear.

However, quite recently, after our preliminary results on these observations have been published[7], Zollinger and coworkers reported[8,9] the NMR spectra of 5-bromoindane,

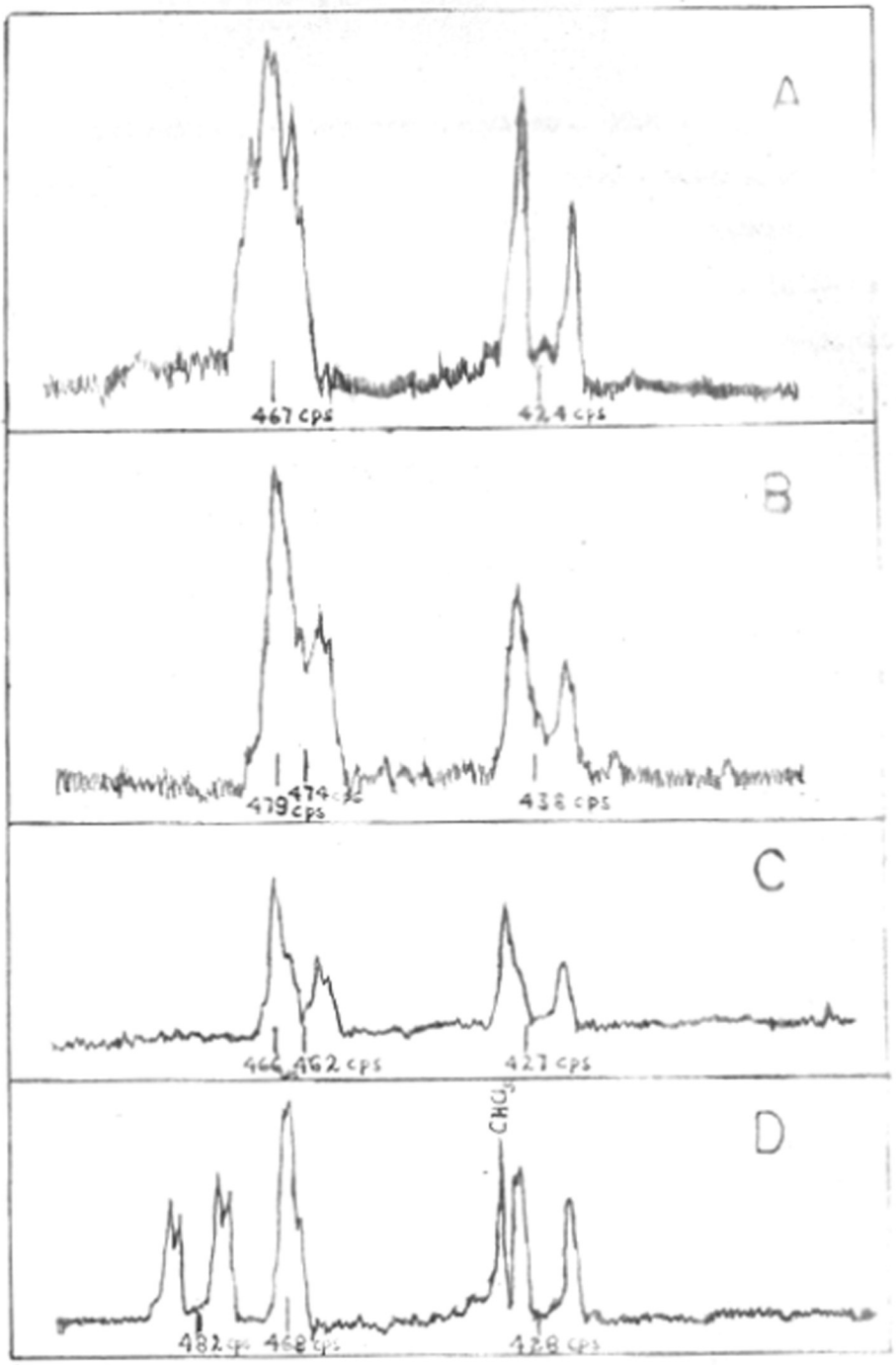


FIG.I - AROMATIC REGION OF THE NMR SPECTRA OF (A) tetralin-6-carboxylic acid (B) indane-5-carboxylic acid (C) O-xylene-4-carboxylic acid and (D) benzocyclobutene-4-carboxylic acid.

6-bromotetralin and 4-bromo-O-xylene. The spectra of 5-indanol and 6-tetralol and their anions were also reported by them and the chemical shift differences compared. They have suggested that the 6-position in 5-substituted indanes are more electron rich than the 4-position. They observed that on going from 5-hydroxyindane to 5-indanolate, while the C_4 and C_7 protons shift downfield by 3.2 and 3.6 cps respectively, the C_6-proton shifts upfield by 5.4 cps. On the otherhand, between 6-hydroxy tetralin and 6-tetralolate an upfield shift of 3.0 cps and 1.2 cps for the C_5 and C_7 protons, respectively, were observed while the C_8-proton was found to shift downfield by 3.0 cps. They concluded that by forming the anion of 5-hydroxyindane, the increase of electron density is maximum at position 6, while for the anion of 6-hydroxy-tetralin it is more at the 5-position compared to the 7-position. However, it is not at all clear particularly in view of the effects of strain demonstrated in the previous Chapter, if electronic charge density is the only factor that determines the NMR line positions in these compounds.

The absorption pattern for 4-substituted O-xylene derivatives is the same as that for 5-substituted indanes.

If the chemical shift difference between the protons ortho to the substituent in any of these systems is arising from electron density difference in the ground state, the same difference in electronic charge densities should be present in O-xylene derivatives also.

On extending Zollinger's arguments[8] to O-xylene-4-ol and comparing it with 5-hydroxy-indane we reach an anomalous position as described below. While shifts of the same nature, as reported, have been observed* for 5-hydroxyindane and its anion, 4-hydroxy-O-xylene and its anion behave differently. All the protons move downfield on going from O-xylene-4-ol to its anion. The shifts are 2.0, 2.3 and 9.0 cps for the C_5, C_3 and C_6 protons respectively. The methyls which have been coming together in O-xylene-4-ol appear resolved with a separation of 1 cps in the anion. In the first place it is not clear why the ortho protons here are showing paramagnetic shifts in going over from the hydroxy compound to the enolate. The corresponding shifts in indane and tetralin are diamagnetic. Moreover, while the downfield shift of

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*NMR spectra of 5-hydroxy indane and 4-hydroxy-O-xylene were measured in carbontetrachloride while those of their anions were measured in D_2O. For all these cases TMS was used as external reference.

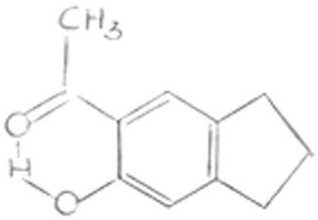
TABLE II

	H_4 indanol- H_4 indanolate	H_6 indanol- H0 indanolate	H_7 indanol- H_7 indanolate
5-Hydroxyindane	-1.5 cps	+3.5 cps	-3.7 cps
	$H_3$0-Xylenol- H_3 0-Xylenolate	H_5 0-xylenol - H_5 0-xylenolate	H_6 0-xylenol - H_6 0-xylenolate
4-Hydroxy-0-xylene	-2.3 cps	-2.0 cps	-9.0 cps

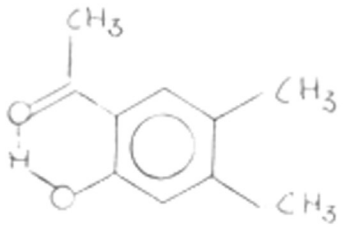
the C_6-proton of the anion of O-xylene-4-ol is 9 cps, the corresponding shifts of the indane and tetralin derivatives are only 3.6 and 3.0 cps respectively. The protons concerned are meta to the hydroxyl group and the pronounced difference noticed for the case of O-xylenol cannot be readily rationalized. There does not seem to be any one to one correspondence between the line positions and electron densities.

Though Hunsberger and co-workers[10,11] studied the IR spectra of chelated derivatives of indane, tetralin and O-xylene, due to complications arising from steric factors, their data could not be successfully applied to the study of bond-fixation. An NMR spectral investigation of O-carbonyl (acetyl, aldehydic, carboxylic) hydroxy derivatives of naphthalene, anthracene and phenanthrene has later been made by Porte, Gutowsky and Hunsberger[12]. They measured the chelated hydroxyl line positions in these compounds and concluded that the chemical shifts of the chelated hydroxyls can be used in studying the bond-order of the C-C bond between the carbon atoms carrying the hydroxyl and carbonyl functions. However, this investigation has not been extended to the indane and tetralin systems. We felt that if the two systems, 5-hydroxy-6-acetylindane (II) and 4-hydroxy-5-

acetyl-O-xylene (III) were compared by NMR, an idea of the extent of chelation could be obtained from the low-field hydroxyl line position. In these two systems



II

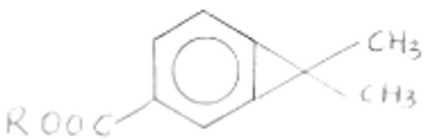


III

complications from steric factors are absent and the comparison will be free from effects other than hydrogen bonding. It was found that in the NMR spectrum of 4-hydroxy-5-acetyl-O-xylene the chelated hydroxyl appears 779 cps downfield from tetramethylsilane, while in that of 5-hydroxy-6-acetylindane it appears at 730.0 cps. On the basis of the observation[12] that strength of hydrogen bonding in such systems is directly proportional to the bond-order of the intervening aromatic bond, we conclude that in indane, the 5:6 bond is more single than in O-xylene, which can be regarded as a system in which, there is no fixation of bonds. This means that the 5:6 bond in indane should be longer than an average aromatic C-C bond. This is in support of our earlier conclusions based on long-range

spin-spin coupling.

The absorption pattern of the aromatic protons of 3-substituted benzocyclobutenes is considerably different from the patterns of the other similar benzocycloalkenes discussed above. While in the 5- derivatives of indane, the C_4-proton appears at a lower field than the C_6-proton, in the corresponding benzocycloalkenes (4-substituted), the C_3-proton appears at considerably higher fields than the C_5 protons. For example, in the spectrum of methyl benzocyclobutene-4-carboxylate the C_3-proton and C_5-proton appear at 457 and 471 cps respectively (see also Fig. ID). The same absorption pattern as for benzocyclobutene-4-carboxylate has been reported[13] for 1,1-dimethyl benzocyclopropene-3-carboxylate (IV).



IV

In this compound the C_2-proton appears at 462 cps while the C_4-proton doublet appears 8.5 cps further downfield. Though this difference in chemical shift between the two protons ortho to the substituent in this compound is smaller than in benzocyclobutene derivatives, the pattern

is essentially the same.

We had concluded in the previous Chapter on the basis of spin coupling data that the perturbations of the π-electron distribution caused by the four and three membered rings in benzocyclobutene and benzocyclopropene are quite serious while in indane the effect (of the five membered ring) is not so drastic. This was attributed to the increasing contributions of Dewar type structures in the resonance of the aromatic rings of lower homologues. It was pointed out that the methyl band width differences are in agreement with such an interpretation. The chemical shift data presented here also support the difference in the nature of the π electron distributions for two types of systems, one where the perturbation is minor (indane) and the other where the perturbation is large (benzocyclobutene and benzocyclopropene).

E X P E R I M E N T A L

NMR spectra were recorded on a Varian A-60 NMR spectrometer. Details regarding the scanning of the spectra, calibration of the chart and other experimental conditions are described in Part I. Except for compounds 16 to 19 in Table I, for all other compounds, tetramethylsilane (TMS) was used as internal reference. For compounds 16 to 19 TMS was used as external standard.

Methods of preparation of most of the compounds, the NMR spectral data of which are presented in Table I, are described in Chapters II and IV of this Part.

O-Xylene-4-ol and indan-5-ol were prepared by the method of Cook and Linstead[14]. 4-Hydroxy-5-acetyl-O-xylene and 5-hydroxy-6-acetylindane were prepared according to the method of Baker[15]. 5-Hydrindacene was obtained by a procedure, reported by Arnold and Barnes[16]. Cyclisation of β (5-indanyl)-propionic acid was done with polyphosphoric acid by a method similar to that described for β(O-tolyl)-propionic acid in Chapter II.

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CHAPTER IV

ELECTROPHILIC AND NULEOPHILIC SUBSTITUTION REACTIONS

ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION REACTIONS

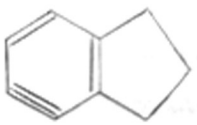
INTRODUCTION

We have seen in Chapter I that reactivity data obtained from electrophilic substitution reactions of hydroxy, amino acetamido and other derivatives of indane, tetralin and O-xylene have been used in the study of the Mills-Nixon effect. A comparison of the results of chloromethylation of indane, tetralin and benzosuberane has been made by Jukh Dev[1]. Except this, there has been no systematic study of the product ratios obtained in electrophilic substitution reactions of the parent hydrocarbons themselves, i.e. indane, tetralin and O-xylene. It was therefore considered worthwhile to make a comparative study of the product ratios obtained in bromination and Friedel-Crafts acylation of these systems.

It was also of interest to examine the nucleophilic reactivity of the aromatic ring from the point of view of the Mills-Nixon effect. Huisgen and co-workers[2] had determined the relative reactivities of the carbocyclic asynes dehydrobenzene, 1,2-dehydronaphthalene and 9,10-dehydrophenanthrene by measuring the selectivity in

the competitive addition of phenyl lithium and lithium piperidide. Their results indicated an increasing selectivity of the benzynes in the order, benzene > naphthalene > phenanthrene. Since the distance between the carbon atoms between which the extra bond is formed decreases in this order (1.39, 1.365 and 1.35 for the C-C bonds of benzene, 1,2 bond of naphthalene and 9-10 bond of phenanthrene), they concluded that the increasing selectivity of the aryne, which implies increasing stability, is due to an increasing overlap of the extra orbitals. However, experiments conducted by Kauffmann and coworkers[3] indicated that the 3,4-dehydropyridine is more selective (and hence more stable) than 1,2-dehydronaphthalene and dehydrobenzene. Since microwave measurements[4] had indicated that the 3-4 bond in pyridine is longer (1.4 Å) than the C-C bonds in benzene (1.39 Å), they reached the conclusion that the bond distances may not be the only stabilizing factor in benzynes. In the case of 3,4-dehydropyridine, however, there may be complications arising from the presence of the hetero-atom. The possibility that the stability of a benzyne is related to the length of the aromatic bond involved may still be true. It was therefore thought that it would be worthwhile to examine the nucleophilic reactivity of a suitable indane derivative. A 5-haloindane can theoretically give rise to

two benzynes, the 4-5 (I) and the 5-6 (II).



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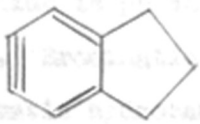


II

I will lead to 4- and 5- substituted products while II will give only 5-substituted products if the alicyclic ring is unsubstituted or unlabelled. However, the latter will give 5- and 6-substituted products if the 1-position is substituted. The extent of formation of 4-,5- and 6-substituted derivatives from the nucleophilic reaction of 5-haloindane is thus the relevant information required. Experiments with 1-alkoxyl and 1-halo derivatives were ruled out since these may be expected to undergo elimination and lead to other complications[5] under the conditions of the reaction. It was thought that a thioketal function at the 1-position may have reasonable stability under the conditions of an amination reaction using a lithium amide. The amination of 6-bromo and 5-bromo derivatives of the ethylene thioketal of indan-1-one with lithium piperidide was therefore proposed.

RESULTS AND DISCUSSION

Electrophilic substitution: Acylations were done with acetic anhydride in carbon disulphide in presence of anhydrous aluminium chloride at 0-5°C. Bromination was done by addition of bromine to the aromatic hydrocarbon at 0-5°C and keeping overnight at this temp. before working up. The products obtained from bromination and Friedel-Crafts acylation were worked up and the dried crude products distilled under reduced pressure. Any unreacted material present was removed by fractional distillation. The NMR spectrum of the distilled product was taken and the percentage ratios of the α and β products determined by the integration method using the deshielding effect of the substituent groups on the ortho-protons. Even when there was overlap between the ortho-proton absorptions of the α- and β-products, the integration method could be used successfully to detect the percentages because the α-product has only one ortho-hydrogen while in the β-product there are two such protons. By comparing the integrated intensity of the group of upfield protons with that of the downfield ones the ratio of the two products could be determined. The percentage ratios obtained on acylation and bromination are given in Table I.

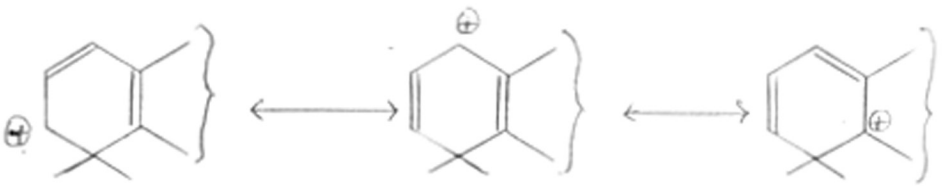
TABLE I

	Compound	Acylation		Bromination	
		% α	% β	% α	% β
1	Indane	0	100	25	75
2	Tetralin	10	90	60	40
3	O-Xylene	50	50	30	70

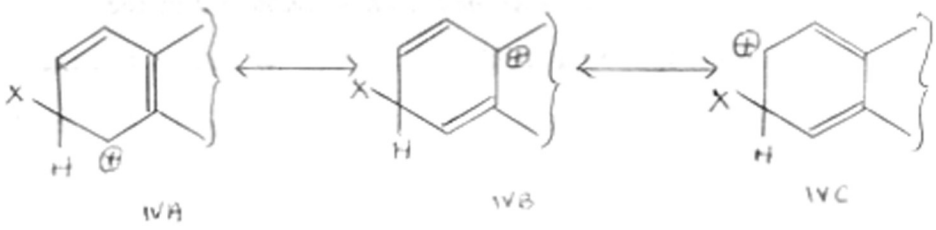
While indane gives predominantly β-products in both the reactions, tetralin gives more of the α-product in bromination and more of β-product in the acylation reaction. The product ratio in the latter case is comparable to that in the nitration of 6-hydroxy tetralin where 7-nitro product is formed predominantly[6]. On the other hand in bromination, the major product is 5-bromo-6-hydroxytetralin[6]. The higher percentage of β-product obtained in acylation of tetralin can be understood on the basis of the assumption that the steric effects in α-substitution may be more important for acylation reaction than for bromination. But the 50:50 ratio obtained in the case of O-xylene on acylation makes this explanation rather ambiguous. In the case of O-xylene the yield of β-product is more for bromination than for acylation. These reactions are, therefore, indicative of the fact that the product ratios obtained vary

from one reaction to another depending on various factors like the electronic and steric requirements of different reactions, and the nature of the transition state.

Very recently Vaughan et al.[7] have reported their results on bromination (with bromine in acetic acid and with hypobromous acid in acetic acid) and on nitration (with nitric acid-acetic anhydride) of indane, tetralin and O-xylene. Although they have taken note of the preliminary communication[8] of the results of the NMR study discussed elsewhere in this thesis, Vaughan et al. preferred to assume that bond-fixation in the transition state may be different from that in the ground state. Describing the resonance of the transition state to be analogous to that of the carbonium ions III and IV and assuming equal contributions from all possible resonance forms they suggested that in indane the transition state for β-substitution will have 1/3 double bond character for the 8-9 bond



III A III B III C



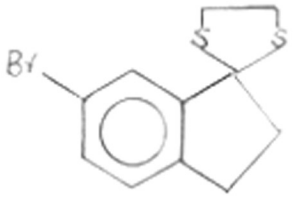
IVA IVB IVC

while α-substitution requires a transition state with 2/3 double bond character for the same bond. They assumed that the former will be more stable on the basis of Mills and Nixons' suggestion. We consider that the assumption that all resonance forms contribute equally to the transition state has no proper foundation. Further, the significance of the NMR study is not merely that the fixation of bonds in indane is in a sense opposite to that suggested by Mills and Nixon, but also that the effect of the 5-membered ring is to compress the 8-9 bond and to stretch the 5-6 bond. This effect must be the same in the ground state as well as in the transition state. It would therefore be more natural to accept the explanation advanced by Coulson and Longuet-Higgins[9]. The 5-6 bond of the transition state (V) for electrophilic attack at the β-position is a bond between sp^2 and

V VI

and sp^3 carbon atoms, while the same bond is between sp^2 carbon atoms in the transition state of attack at the α-position. The tendency of the 5-6 bond to stretch makes the former a lower energy transition state.

Nucleophilic substitution: 5-Bromo-indan-1-one and 6-bromoindan-1-one were prepared starting from m-bromotoluene and p-bromotoluene respectively. The thioketals of these ketones (III and IV) were obtained by treatment with ethane dithiol and BF_3-etherate. Lithium piperidide was prepared from butyl lithium and piperidine. The reaction conditions for the preparation of lithium piperidide and its reaction with the bromoindan-1-ones were similar to that reported by Huisgen. The reaction product was separated into the basic and neutral fractions and the amounts of product obtained and the starting material recovered were determined.



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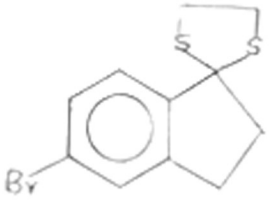

VIII

The thioketal of 6-bromoindan-1-one (VII) on treatment with lithium piperidide did not yield any

piperidino-derivative. About 95% of the starting material was recovered indicating stability of the ketal under reaction conditions. When the thioketal and bromobenzene were used in competition experiments nearly quantitative yield of n-phenyl piperidine was obtained while no detectable amount of piperidino-indane derivative was formed. However, the thioketal of 5-bromo-indan-1-one (VIII) reacted with lithium piperidide under the same reaction conditions. No starting material was recovered. The basic fraction on concentration gave a brownish solid product which appeared to be the required product complexed with some inorganic material. This material contained nitrogen and sulphur and the NMR spectrum in $CDCl_3$ showed signals in the aromatic region. Since the product was not obtained in a pure state, the ratio of the 4,5 and 6 piperidino derivatives could not be determined. However, the fact that the thioketal of 5-bromoindan-1-one underwent the reaction readily under conditions in which the thioketal of 6-bromo-indan-1-one was completely resistant to substitution is significant. In VII, the 7-position is sterically hindered. It would be expected that if the first step of attack of base can take place at the 5-position in VII, atleast some amount of the 5- or 6-piperidine products should be obtained. That none of this was actually formed

in the reaction, should mean that the attack of the base is possible only at the 7-position in VII and since this position is sterically hindered, no benzyne formation was taken place in this case. On the other hand, in VIII the 4-position is not affected by the thioketal group unlike in VII. Proton abstraction from the 4-position can readily proceed in VIII and the benzyne formation leading to thioketals of 4- and 5-piperidino indan-1-ones is possible. Though these experiments did not furnish all the expected data, the results obtained here indicate that further work on these lines would clearly give definite information regarding the benzynes formed. Our data are, however, not in agreement with those reported recently by Eigenmann and Zollinger[10]. They have given the rate factors for the 4- and 6-positions in 5-bromoindane by determining the ratios of 4 and 5-piperidino indanes formed. It is not clear whether the complication arising from the fact that both the 4;5 and 5;6 benzynes can give rise to the 5-substituted product is taken care of or not. Further experiments may be required before a definite conclusion on this can be reached.

E X P E R I M E N T A L

General experimental conditions are the same as described in Part I and Chapter II of this thesis.

6-Bromoindan-1-one and 5-bromoindan-1-one were prepared starting from p-bromotoluene and m-bromotoluene respectively.

p-Bromotoluene was prepared by Sandmeyers reaction on p-toluidine[11]. m-Bromotoluene was obtained from p-toluidine, by bromination of p-acetotoluidide followed by hydrolysis and deamination[11].

p- and m-Bromobenzyl bromide:

The procedure adopted for the preparation was similar to the one reported for p-iodobenzyl bromide[12]. Bromotoluene (200 g, 1.17 moles) in CCl_4 (250 cc) and bromine (215 g, 1.35 moles) in CCl_4 (200 cc) were mixed in a 2 lit. RB flask, illuminated by two 250 Watt Mazda lamps placed almost in contact with the flask. The flask was gently heated using a heating mantle to keep the mixture refluxing. Vigorous and continuous evolution of HBr was noticeable for about 3.5 hours. After the HBr evolution ceased, the mixture was refluxed with illumination for another 30 min. more. A few g. of potassium iodide and a solution of sodium thiosulphate (0.2N) in excess were

added till the CCl_4 layer became colourless. The CCl_4 layer was separated, washed and dried. After removal of solvent, the residue was distilled under reduced pressure. p-Bromotoluene gave p-bromobenzyl bromide (165 g), m.p. 64°C, b.p. 120°C/15 mm (lit.[13]: m.p. 61°C, b.p. 120-140°C/12-16 mm).

Similarly, m-bromotoluene yielded m-bromobenzyl bromide, m.p. 35-37°C, b.p. 132-134°C (lit.[14]: m.p. 36-38°C; b.p. 132-134°C).

ß-(p- and m-bromophenyl)-propionic acid:

Absolute alcohol (250 cc) was taken in a 1 lit. three-necked flask fitted with a stirrer, reflux condenser (with silica gel gaurd tube) and dropping funnel. Sodium (4.4 g, 0.409 mole) was cut into small pieces and added in small lots into the alcohol. After all the sodium had reacted, diethyl malonate (96 g, 0.6 mole) was added with stirring. p-Bromobenzylbromide (102.24 g, 0.409 mole) was introduced in convenient lots (about 10 g each) during about a period of about one hour. The mixture was refluxed with stirring until neutral to litmus (about 12 hrs). As much of alcohol as possible was distilled off. The residue was treated with water (500 cc) and shaken. Ether (50-100 cc) was added and the ether layer separated. It was washed with water and dried. The residual oil obtained

on removal of ether was distilled under reduced pressure. Diethyl ester of p-bromobenzyl malonic acid (58.6 g), b.p. 195-200°C/15 mm (lit.[15]: b.p. 193-198°C/14 mm) was collected. The undistilled material solidified on cooling was recrystallised from CCl_4. The white shining plates obtained was washed with pet. ether and dried. This material was identified as di(p-bromobenzyl) malonate, m.p. 103°C (lit.[15]: m.p. 104°C).

Diethyl (p-bromobenzyl) malonate (58 g) was refluxed with conc. HCl (175 cc), acetic acid (110 cc) and water (30 cc) for 18 hours. The mixture was cooled, poured into cold water and the solid crystalline precipitate was filtered off. After drying, the product was recrystallised from benzene to obtain β-(p-bromophenyl)-propionic acid as white crystalline needles, (30.5 g) m.p. 134-135°C (lit.[16]: m.p. 135°C).

β-(m-bromophenyl)-propionic acid, m.p. 74°C (lit.[17]: m.p. 74.5 - 75°C) was obtained from m-bromobenzylbromide by the same method.

6- and 5-bromoindan-1-ones:

Yields as well as the purity of the product was found to be better with conc. sulphuric acid than with polyphosphoric acid as the cyclising agent.

β-(p-bromophenyl) propionic acid (4 g) in conc. sulphuric acid (100 g) was heated to 145°C. It was then cooled to room temp. poured into ice and water and the crystalline solid was extracted with ether. The ether extract was washed with dil. sodium carbonate solution and water. After drying and removal of the solvent pale yellow crystals of the required product (3 g) was obtained. This on recrystallisation from benzene-pet. ether mixture (2:1) gave 6-bromoindan-1-one as colourless crystalline needles, m.p. 110°C (lit.[18]; m.p. 111-112°C).

β-(m-Bromophenyl) propionic acid by the same procedure gave 5-bromoindan-1-one, m.p. 124°C. Miller and Rohie reported the product, m.p. 122-123°C, to be a mixture of 5- and 7-bromoindan-1-ones. However, this product was found to be pure 5-bromoindan-1-one from its NMR spectrum.

Thioketals of 6- and 5-bromoindan-1-one:

Bromoindan-1-one (1 g), ethane dithiol (2 cc) and BF_3-etherate (2 cc) were mixed and kept at room temp. for half an hour. It was then diluted with chloroform (10 cc) and left overnight. The chloroform solution was washed with water and dil. sodium bicarbonate solution (10 cc). After drying, solvent was removed. The residual liquid was dissolved in pet. ether and kept in Frig.

Thioketal of 6-bromoindan-1-one was obtained as white crystalline plates (0.6 g), m.p. 70-71°C (Found: C, 46.26; H, 3.74; Br, 27.80; S, 22.20. Calc. for $C_{11}H_{11}S_2Br$: C, 45.99; H, 3.84; Br, 27.87; S, 22.30%).

Thioketal of 5-bromoindan-1-one was obtained, similarly, as white crystalline plates (0.54 g) m.p. 64°C (Found: C, 45.77; H, 4.03; Br, 28.45; S, 21.60. Calc. for $C_{11}H_{11}S_2Br$: C, 45.99; H, 3.84; Br, 27.87; S, 22.30%).

Reaction with lithium piperidide[20]:

Butyl lithium was prepared from lithium wire and butyl bromide by the procedure reported by Gilman et al.[21]. After the reaction the ether solution was filtered and the yield (80%) determined by titration.

The butyl lithium (1 equivalent) in ether was taken in a three necked flask, fitted with a stirrer, reflux condenser (with gaurd tube) and dropping funnel, and previously flushed with nitrogen. Piperidine (4 equivalents) was added dropwise with stirring. Thioketal of the bromoindan-1-one (1 equivalent) in ether solution was introduced. After stirring for half an hour at room temperature the mixture was refluxed for three hours and left overnight. The ether solution was filtered and shaken with conc. hydrochloric acid (5-10 cc). The ether solution

was concentrated to recover the starting material. The acid layer was separated, neutralised with sodium hydroxide solution and ether extracted. After drying the ether was removed by distillation.

In the case of the thioketal of 6-bromoindan-1-one no expected product (thioketal of piperidinoindan-1-one) was obtained. About 95% of the starting material was recovered in the neutral fraction.

Thioketal of 5-bromoindan-1-one did not give any neutral product in the ether solution after washing with hydrochloric acid, indicating that the reaction has proceeded to completion. However, the basic product was obtained as a brownish solid, containing inorganic material which could not be separated. This product contained nitrogen, sulphur and gave a residue on ignition. NMR spectrum in $CDCl_3$ showed signals in the aromatic region showing it to be an amino derivative of indan-1-one.

Friedel-Crafts acylation of indan, tetralin and O-xylene:

Acylations were done by a procedure similar to the one described for 4-acetyl o-xylene[22]. A mixture of the hydrocarbon (0.5 mole) and anhydrous aluminium chloride (0.55 mole) in CS_2 (250 cc) was taken in a three-necked flask fitted with a stirrer, reflux condenser and dropping

funnel. The mixture was well chilled in ice-salt bath and acetic anhydride (0.5 mole) was added dropwise with stirring. It was then refluxed for one hour and allowed to stand at room temp. for another hour. After decomposing with ice and hydrochloric acid and working up as described earlier (Chapter II) for 5-acetylindane, the product was distilled under reduced pressure. Ratios of α- and β-products were determined from the NMR spectra of the products, acetylindane, b.p. 143-144°C/13 mm (lit.[1]: b.p. 144°C/13 mm), acetyl tetralin, b.p. 150-152°C/12 mm (lit.[23]: b.p. 152°C/12 mm) and acetyl-O-xylene b.p. 122-129°C/21 mm (lit.[22]: b.p. 118-130°C/21 mm), by the integration method.

Bromination of indane, tetralin and O-xylene:

The hydrocarbon (1 mole) and iodine (2 g) were cooled to 0°C and bromine (1 mole) was added with stirring. After complete addition the reaction mixture was worked up as described earlier for the bromination of 4-methylindane (Chapter II). The product was fractionally distilled to remove the unconverted starting material. Product ratios of bromoindanes, b.p. 125-130°C/25 mm (lit.[24]: b.p. 128-131°C/25 mm), bromotetralins, b.p. 142-144°C/17 mm (lit.[25]: b.p. 144°C/17 mm), and bromo-O-xylenes, b.p. 92-95°C/15 mm (lit.[26]: b.p. 92-94°C/14-15 mm) were determined by NMR integration method.

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PART III

NMR SPECTROSCOPY IN THE STUDY OF SOLVENT EFFECTS IN AROMATIC HALOGENATION

SOLVENT EFFECTS IN PMR SPECTRA AND THE PROBLEM OF SOLVENT EFFECTS ON ISOMER DISTRIBUTION IN AROMATIC HYDROGENATION

It was reported some years ago by Stock and Himoe[1] that the ortho-para distribution of isomers in chlorination of toluene was remarkably dependent on the solvent used. They found that the variation of the ratio of the isomeric chlorotoluenes obtained was not related to the absolute rate of reaction. Both dry and wet acetic acid gave the same isomer ratio although the rates in these solvents differed by a factor of 3000. However, large variations of selectivity were observed in the other solvents employed. Recalling that unchanged selectivity in aromatic nitration and acetylation had been attributed earlier to common electrophilic intermediates, they suggested, in order to explain the observed variation, that the effective intermediate in the case of chlorination is a complex between chlorine and the solvent. While acetic acid and tert-butyl alcohol gave o:p ratios of 60:40 and 59:41, nitromethane and acetonitrile gave ratios of 34:66 and 38:62. The suggested explanation and the nature of these results would imply that the steric requirements of the complexes of chlorine with acetic acid

and tert-butyl alcohol are less than those of the complexes with nitromethane and acetonitrile. This does not look reasonable. Moreover, a later investigation[2] showed that nitrobenzene as solvent behaves like acetic acid. It is difficult to see any reason why any complex that chlorine may form with nitrobenzene should attack the ortho position of toluene more readily than the para. We felt that a rationalization of these data in terms of substrate-solvent interactions might prove to be more satisfactory.

In recent years much valuable information on solvent-solute interaction has been obtained through studies on solvent effects on PMR spectra[3,4-30]. Schneider and coworkers[4,5] have examined the influence of aromatic solvents on the spectra of many polar molecules including chloroform, acetonitrile, nitrobenzene and substituted toluenes, and obtained evidence for the formation of complexes. Very specific associations of N,N-dimethyl formamide, acetamide and mesityl oxide with solvent benzene have been detected[6,7] and they result in characteristic chemical shifts for the various groups of these molecules. It was of interest therefore to see if PMR studies would be of help in clarifying the nature of solvent effects on selectivity in aromatic halogenation.

The investigation which is described below has been undertaken with this aim.

The data available from the studies that have so far been made[4-30] are not adequate for our present purpose. Hydroxylic compounds whose interaction with aromatic systems is of special interest to the problem of selectivity in the chlorination reaction have not been covered by these studies except in a fragmentary way. Alcoholic hydroxylic groups have been known to form both inter- and intra-molecular hydrogen bonds to π-electrons[31-36]. However, since such a "π-hydrogen bond" is much weaker than the hydrogen bond between alcohol molecules, it is not clear if the former would be of much consequence when an alcohol is employed as solvent for an aromatic solute. Trimeric association of t-butyl alcohol has been suggested from PMR studies[9]. In the case of carboxylic acids which form dimers of appreciable strength[20-22] no π-hydrogen bond with aromatic compounds is to be expected. It is conceivable that in such cases other types of interaction may be important. In this study the PMR spectra of mixtures of t-butyl alcohol, acetic acid, ethyl acetate, dichloroacetic acid and methyl dichloroacetate with toluene have been examined over the entire concentration range between the pure materials. The latter three compounds were

chosen for purposes of comparison with acetic acid. Also included in the study are nitromethane ethylene dichloride and nitrobenzene for which measurements have been reported at only single concentrations[4].

RESULTS AND DISCUSSION

The factors that may contribute to the effect of a solvent on the chemical shift of a species in solution have been discussed by Buckingham, Schaefer and Schneider[12-14]. The solvent shift may be expressed by the equation:

$$\sigma_{solvent} = \sigma_b + \sigma_W + \sigma_a + \sigma_E + \sigma_{SI}$$

where σ_b represents the effect of the bulk susceptibility of the solvent and σ_W that of van der Waals forces. The term σ_a arises from the magnetic anisotropy of the solvent molecules and σ_E from the reaction field of the solute dipole in the solvent medium. The last term σ_{SI} represents specific interactions including hydrogen bonding. In the case of the binary mixtures of toluene with polar liquids, which are of primary interest in the present study, the last two terms may be expected to be dominant. Since all the measurements are made with tetramethylsilane as internal standard for data used are corrected for the bulk susceptibility factor (σ_b). It is our purpose here to see if either the specific or the dipole-induced dipole type

of interactions that may be indicated by the data can form an adequate basis for rationalisation of solvent effects on selectivity in aromatic halogenation.

In order to detect the interaction of hydroxylic compounds with toluene it is necessary to make adequate allowance for the effects of hydrogen bonding between molecules of the same hydroxylic species. This has been achieved by making parallel measurements on them using indifferent solvents like hexane and carbon tetrachloride in place of toluene. For each compound the variation of the chemical shifts of its proton bearing functions in mixtures with toluene and with an indifferent solvent are compared. Although all measurements were made with tetramethylsilane (TMS) as internal standard, the chemical shifts that we shall be concerned with are those with respect to the absorptions of the pure compounds (neat liquids). The absorption positions of the pure compounds themselves referred to TMS as internal standard are shown in Table I. Shifts upfield and downfield from the reference points are indicated by positive and negative signs respectively.

The data for t-butyl alcohol-toluene, t-butyl alcohol-carbon tetrachloride and t-butyl alcohol-hexane mixtures are given in Table II and shown graphically in Fig.1.

TABLE I - CHEMICAL SHIFT DATA OF PURE LIQUIDS WITH TMS AS INTERNAL STANDARD

Compound	Nature of H	Chemical shift, δ, in cps (downfield)
Toluene	ArH	422
	$-CH_3$	127.5
Acetic acid	-COOH	688
	$-CH_3$	124
Dichloroacetic acid	-COOH	670
	$-CH_3$	369
t-Butyl alcohol	-OH	271.5
	$-CH_3$	74.5
Ethyl Acetate	$-CO-CH_3$	116.7
	$-C-CH_3$	71.5
	$-CH_2-$	243.25
Methyldichloro acetate	$-CHCl_2$	369
	$-COOCH_3$	236
Nitrobenzene	o-H	484
	m-H	445
	p-H	453
Nitromethane	$-CH_3$	260
Ethylene dichloride	$-CH_2Cl$	224
Acetonitrile		117.5

For all three systems plots of the shifts of the hydroxyl group against the mole fraction of the alcohol give smooth curves which are steeper at the lower concentrations. The low concentration region has not been studied in detail to ascertain the limiting values of the hydroxyl shifts. It is interesting to note that the two 'indifferent' solvents behave differently. The shielding of the hydroxyl group is higher in carbon tetrachloride than in hexane. If hydrogen bonding effects are the same in both solvents the sequence expected for the two curves is the inverse of what is observed. On the basis of the results recorded by Buckingham, Schaefer and Schneider[12], the van der Waals term (σ_W) for carbon tetrachloride should be larger than the sum of σ_W and σ_a terms for hexane. The replacement of the latter solvent by the former should lead to a deshielding effect on these counts. Since the dielectric constants of the two solvents are nearly the same, the difference observed cannot arise from σ_E terms. It is thus clearly connected with the hydrogen bonding behaviour of the alcohol in the two solvents. Saunders and Hyne[9] have shown that the variation of hydroxyl shielding in carbon tetrachloride solutions of

t-butanol is best described by a monomer-trimer equilibrium with an association constant of 5.6. If the association constant is higher in hexane, as it appears to be, the break up of the bonded systems on dilution will be less and the upfield shifts of the hydroxyl resonance may be expected to be smaller.

Turning now to t-butanol-toluene mixtures we see that the upfield shifts of the hydroxyl absorption that accompany dilution are all much more pronounced in this system than in the other two. This difference increases with increasing dilution of the alcohol and is of the order of 61 cps for hexane and toluene solutions at a mole fraction of 0.1104. It cannot be rationalized in terms of a smaller formation constant for the trimer because the t-butyl group, which remains nearly unaffected in hexane and carbon tetrachloride solutions suffers an appreciable, though very much smaller, diamagnetic shift (Fig.1). The behaviour here is suggestive of π-hydrogen bonding of the alcohol with the aromatic solvent, the increased diamagnetic shift being very largely due to ring current. The relative magnitudes of the shifts of the OH and t-butyl groups are in agreement with the geometry of the hydrogen bonded complex (I). Unlike the OH group

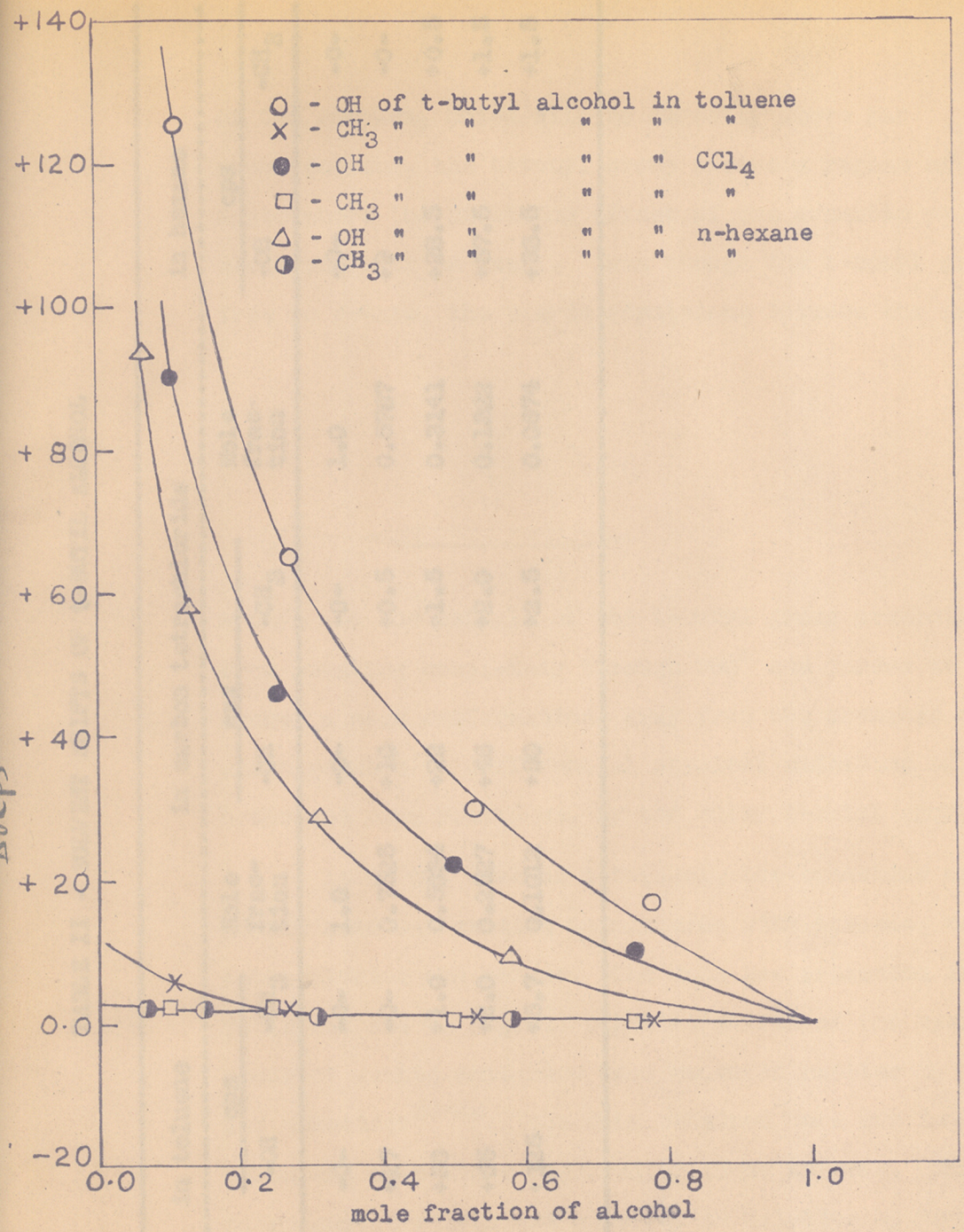
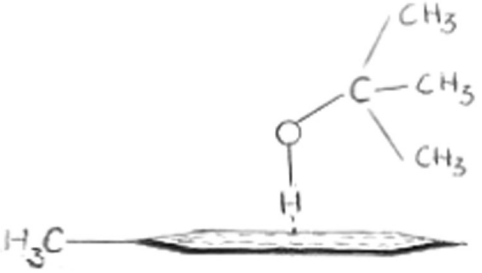


FIG.1. NMR·SOLVENT SHIFTS OF t-BUTYL ALCOHOL

TABLE II - SOLVENT SHIFTS OF t-BUTYL ALCOHOL

in toluene			in carbon tetrachloride			in hexane		
Mole fraction.	cps		Mole fraction	cps		Mole fraction	cps	
	-OH	$-CH_3$		-OH	$-CH_3$		-OH	$-CH_3$
1.0	-0-	-0-	1.0	-0-	-0-	1.0	-0-	-0-
0.7725	+17	-0-	0.7525	+19	+0.5	0.5787	+9	-0-
0.5279	+30	+1.0	0.5034	+22	+1.5	0.3141	+28.5	+0.5
0.2715	+65	+2.0	0.2527	+46	+2.0	0.1322	+57.5	+1.5
0.1104	+125	+5.7	0.1012	+90	+2.5	0.0674	+93.5	+1.5

of the complex, which will be directly above the aromatic ring, the t-butyl group sweeps a region of space where the shielding effect of the aromatic π-electrons will be small. Even though the t-butyl group is free to rotate, the steric repulsions between the aromatic



(I)

methyl and the methyls of the t-butyl group prevents it from rotating completely through 360° and forces it to assume a mean conformation, away from the aromatic methyl, which results in differential physical shielding of the ortho and para positions, by the bulky t-butyl group.

As in the case of t-butanol, the behaviour of acetic acid was studied in mixtures with toluene, carbon tetrachloride and hexane. The data are presented in Table III and in Fig.2. Dilution shifts of the hydroxyl group of acetic acid have been measured earlier by Reeves and Schneider[20-22]. The data obtained here are in good agreement with those reported by these workers. Increasing paramagnetic shifts are observed on dilution up to a limit beyond which strong diamagnetic effects come into play. The minimum of the dilution shift curve is in the low concentration region

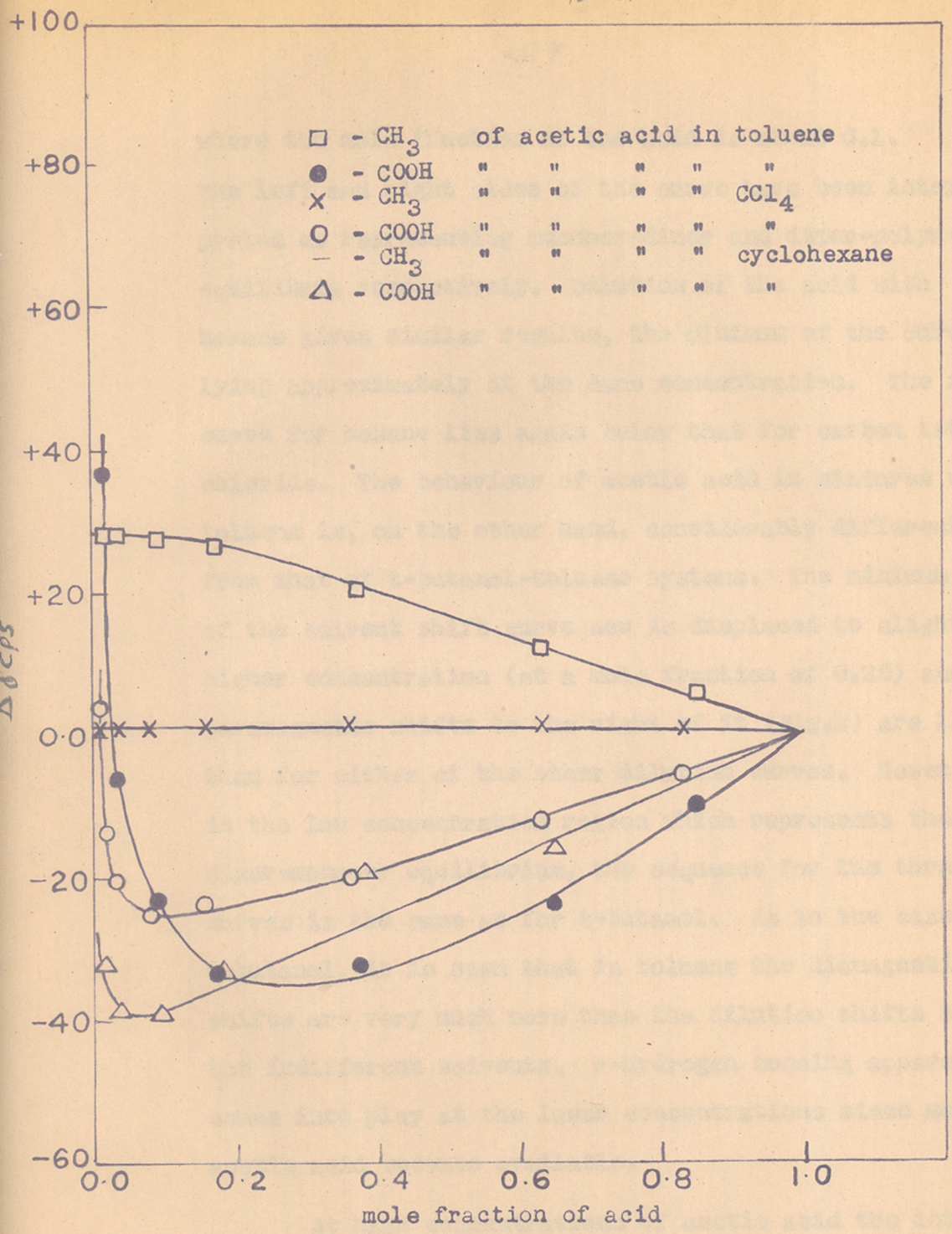


FIG.II. NMR SOLVENT SHIFTS OF ACETIC ACID

where the mole fraction of the acid is about 0.1. The left and right sides of the curve have been interpreted as representing monomer-dimer and dimer-polymer equilibria respectively. Dilution of the acid with hexane gives similar results, the minimum of the curve lying approximately at the same concentration. The shift curve for hexane lies again below that for carbon tetrachloride. The behaviour of acetic acid in mixtures with toluene is, on the other hand, considerably different from that of t-butanol-toluene systems. The minimum of the solvent shift curve now is displaced to slightly higher concentration (at a mole fraction of 0.25) and the paramagnetic shifts to the right of it (Fig.2) are larger than for either of the other dilution curves. However, in the low concentration region which represents the dimer-monomer equilibrium, the sequence for the three curves is the same as for t-butanol. As in the case of t-butanol, it is seen that in toluene the diamagnetic shifts are very much more than the dilution shifts in the indifferent solvents. π-Hydrogen bonding apparently comes into play at the lower concentrations since monomeric acetic acid becomes available.

At high concentrations of acetic acid the interaction

TABLE III - SOLVENT SHIFTS OF ACETIC ACID

in toluene			in carbon tetrachloride			in cyclohexane		
Mole Fraction	cps -COOH	cps $-CH_3$	Mole fraction	cps -COOH	cps $-CH_3$	Mole fraction	cps -COOH	cps $-CH_3$
1.0	-0-	-0-	1.0	-0-	-0-	1.0	-0-	-0-
0.848	-10	+5.5	0.834	-6	+.5	0.6512	-16	+5
0.650	-24	+11.5	0.628	-12	+1	0.3748	-19.5	+8
0.368	-32	+20	0.360	-20	+1	0.1734	-34	+11
0.171	-33	+27	0.158	-23.8	+1	0.090	-39	?
0.089	-23	+27.5	0.081	-25	+1	0.370	-38.5	?
0.0366	-6	+28	0.033	-20	+1	0.0187	-32	?
0.0184	+36.5	+28	0.1675	-14	+1			
			0.0084	+4	+1			

with toluene is apparently of a different type, since it is the paramagnetic dilution shift that is increased in this region. Since acetic acid is in polymeric form in these solutions, the hydroxyl may not be expected to be directly involved in this interaction in mixtures of the acid with toluene. This group shows a diamagnetic shift that increases monotonically with increasing dilution. This shift has been attributed[30] previously to the same type of hydrogen bonding interaction (II), as postulated by Schneider for chloroform, acetonitrile and nitromethane[4]. Hydrogen bonding tendency in these compounds is related to

II

the presence of strongly electronegative functions on the α-carbon atoms which increase the polarity of the C-H bonds involved. If acetic acid is involved in this type of bonding it may be expected that ethyl acetate would behave similarly. When a carboxyl group is esterified, the acidity of the hydrogens of the carbon atom increases because of the increased effective positive charge at the carboxyl carbon atom. Therefore ethyl acetate should be more

effective than acetic acid in this type of hydrogen bonding if it is present. Actually it is seen that the corresponding diamagnetic shifts of the acetyl methyl of ethyl acetate in mixtures with toluene are very much weaker (Table IV), only about half as much as for acetic acid. It is therefore clear that hydrogen bonding of the type postulated earlier by Shimizu and Fujiwara[30] is not an acceptable interpretation. Since the hydroxyl and methyl groups of acetic acid are thus excluded, the interacting function must be the carboxyl group (in concentrated solutions). It appears that the observed solvent shifts have to be attributed to a combination of dipole-dipole and dipole-induced dipole types of interactions. The latter is probably the stronger. The small dipole moment of toluene would make it more polarizable along the two-fold symmetry axis than in other directions. The interactions between acetic acid and toluene may therefore lead to an association with a specific geometry. The specificity thus resulting has important consequences for the reactivity of toluene in acetic acid solutions. This is considered later.

Dichloroacetic acid does not behave in quite the same way as acetic acid. This is only to be expected

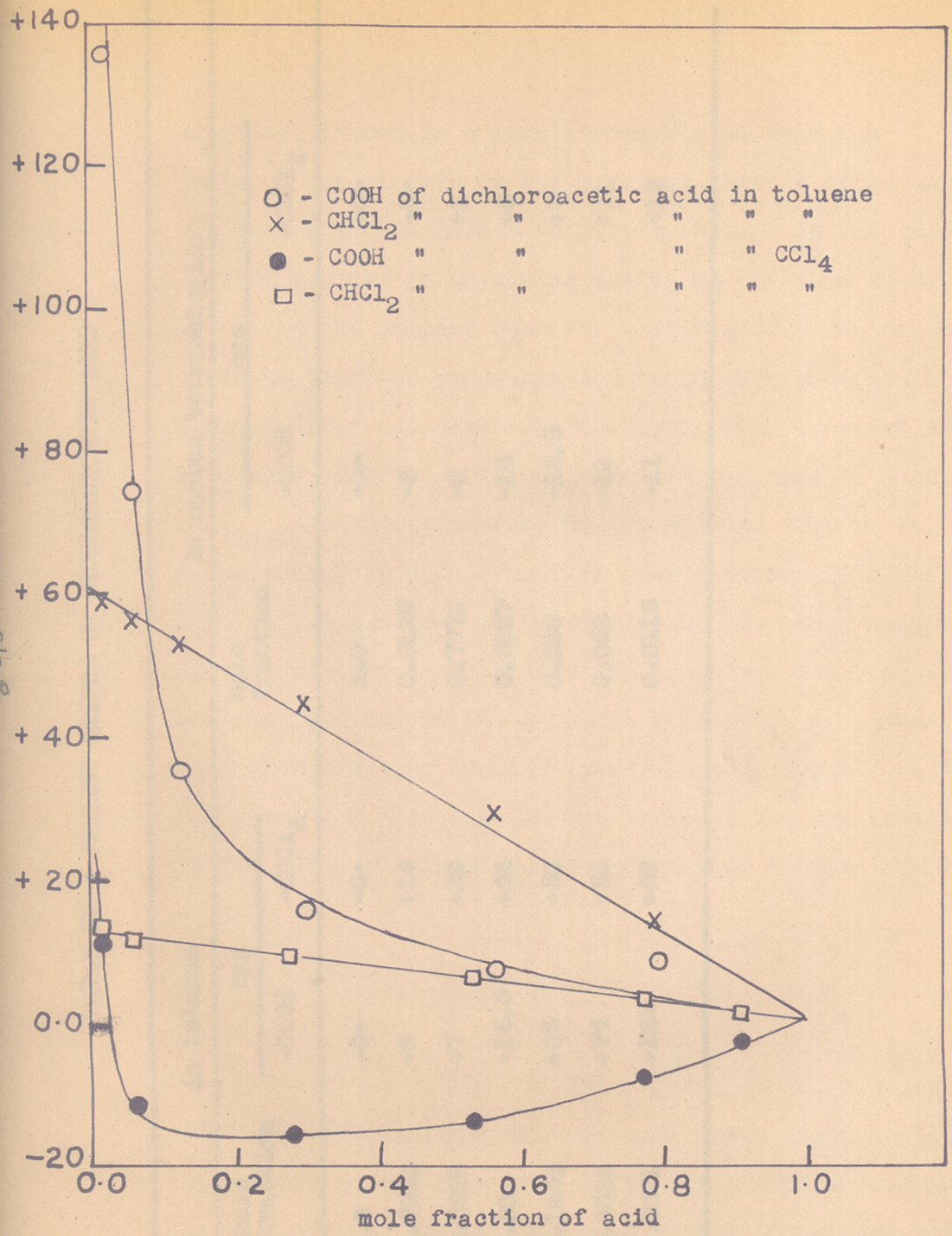
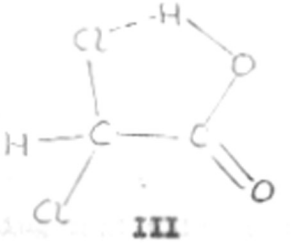


FIG.III. NMR SOLVENT SHIFTS OF DICHLOROACETIC ACID

TABLE IV - SOLVENT SHIFTS OF DICHLOROACETIC ACID

in toluene			in carbon tetrachloride		
Mole fraction	cps		Mole fraction	cps	
	-COOH	$-CHCl_2$		-COOH	$-CHCl_2$
1.0	-0-	-0-	1.0	-0-	-0-
0.7943	+8	+14	0.9126	-3	-0-
0.5628	+7	+29	0.7772	-8	+3
0.30	+15.5	+44	0.5387	-14	+6
0.1250	+35	+53	0.280	-15.5	+9
0.0634	+74	+56	0.058	-12	+11
0.0271	+135	+59	0.0116	-11	+13

since the former is a much stronger acid than the latter. The minimum of the hydroxyl solvent shift curve for carbon tetrachloride solutions (Fig.3) is not sharply defined and the paramagnetic shifts in the more concentrated solutions are smaller than for acetic acid. The curve suggests that the concentration range over which both monomer-dimer and dimer-polymer equilibria co-exist is very much wider in this case than in the case of acetic acid. Appreciable amounts of the monomer seem to be present in pure dichloroacetic acid itself. This difference from acetic acid may be traced to the increased strength of the dichloro derivative which decreases the hydrogen bonding tendency of the carboxyl carbonyl. An intramolecular hydrogen bonding interaction as shown in (III) may also be a factor . On the basis of the availability of the monomeric form and the π-hydrogen bonding demonstrated



III

for the hydroxyl function, one may expect that on dilution with toluene, the hydroxyl shifts may show the same behaviour as in t-butanol-toluene mixtures. This is in fact what is

observed (Fig.III). Diamagnetic shifts are seen even at low dilutions and they increase with increasing dilution. As in the case of acetic acid, the curve takes a sharp upward turn in the low concentration region. However, interactions of the hydroxyl groups with >C=O groups or with toluene, have little to do with the diamagnetic shifts of the $CHCl_2$ group which are equally pronounced for the methyl ester of the acid (Table V; Fig.IV). These shifts apparently arise from independent interactions with the solvent. The diamagnetic shifts of the $CHCl_2$ group in mixtures with toluene are nearly twice as large as for the methyl group of acetic acid. Moreover, while the toluene solvent shifts for the $CHCl_2$ group are nearly the same in the acid and ester forms, those for the acetyl methyl groups of acetic acid and its ester are quite different from each other. This furnishes further support to the conclusion that has been reached earlier with regard to acetic acid. The interaction of the $CHCl_2$ group of dichloroacetic acid and its ester with toluene are presumably similar to that of chloroform with benzene. It may be noted in passing that this group shows a very weak diamagnetic shift (Fig.IV) on mere dilution with carbon tetrachloride. Ethyl acetate does not exhibit a similar shift (Table VI). The presence of $CHCl_2$ and C=O functions

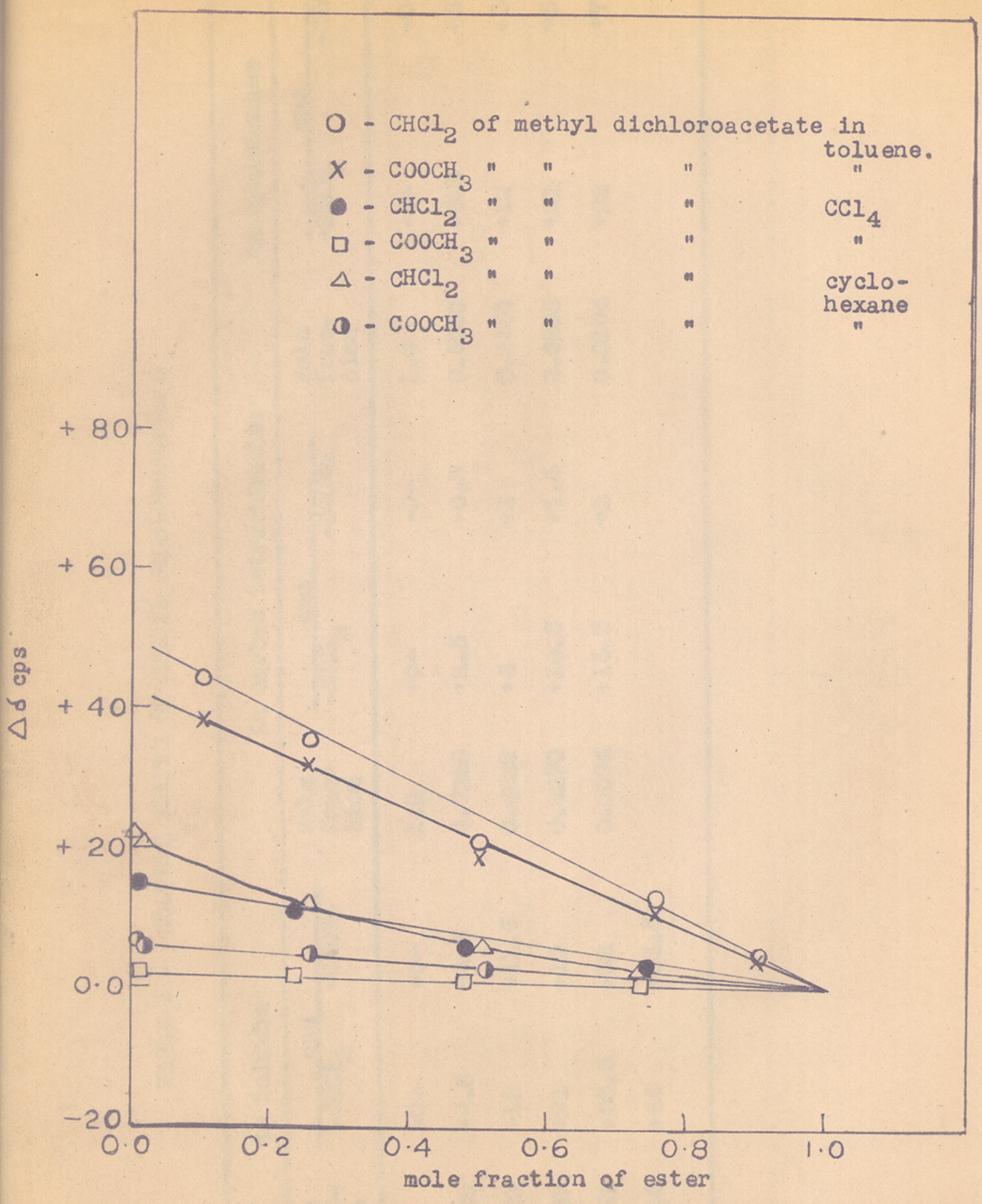


FIG. IV. NMR SOLVENT SHIFTS OF METHYL DICHLOROACETATE

TABLE V - SOLVENT SHIFTS OF METHYL DICHLOROACETATE

in toluene			in carbon tetrachloride			in cyclohexane		
Mole fraction	cps $-CHCl_2$	cps $-COOMe$	Mole fraction	cps $-CHCl_2$	cps $-COOMe$	Mole fraction	cps $-CHCl_2$	cps $-COOMe$
1.0	-0-	-0-	1.0	-0-	-0-	1.0	-0-	-0-
0.9036	+4.8	+4.5	0.7358	+2.5	+0.5	0.5080	+6.5	+3
0.7550	+13	+11.5	0.4829	+6	+1	0.2560	+12	+5
0.5067	+21	+19	0.2370	+10.5	+1.5	0.0208	+21	+6
0.2560	+35.5	+32	0.0094	+15.5	+2	0.0104	+22	+7
0.1024	+44	+38.5						

TABLE VI - SOLVENT SHIFTS OF ETHYL ACETATE

in toluene				in carbon tetrachloride			
Mole fraction	cps			Mole fraction	cps		
	$-COCH_3$	$-CH_3$	$-CH_2$		$-COCH_3$	$-CH_3$	$-CH_2$
1.0	-0-	-0-	-0-	1.0	-0-	-0-	-0-
0.907	+0.9	+1.0	+0.55	0.4965	-0-	-1.0	-0-
0.7653	+2.5	+2.5	+1.5	0.0099	+0.5	-1.0	+0.5
0.520	+6.7	+5.5	+3.75				
0.2659	+11.7	+9.5	+6.45				
0.1077	+14.8	+12.5	+8.45				
0.0541	+16.6	+13.5	+9.25				

would suggest that this shift represents the hydrogen bonding interaction (inter molecular) between them, the diamagnetic shift arising from the break up of the bonding.

On dilution of nitrobenzene with toluene to a mole fraction of 0.05 it is found that the ortho-, meta-, and para- protons of the former move upfield by 21, 38 and 39 cps respectively (Table VII). These upfield shifts were linear functions of concentration. However, no shifts were observed for any of these protons on diluting nitrobenzene with carbon tetrachloride. Themagnitude and direction of the solvent shifts observed here are nearly the same as those obtained by Schneider[4] from a comparison of 5% solutions of nitrobenzene in benzene and neopentane. The observed shifts can well be rationalized on the basis of a complex (IV) between nitrobenzene and toluene. The methyl

(IV)

and nitro groups of the two benzene rings might keep away from each other, as shown, due to steric factors. There will, however, be much freedom of rotation for the two

TABLE VII - SOLVENT SHIFTS OF NITROBENZENE IN TOLUENE

Mole fraction	cps		
	H_{ortho}	H_{meta}	H_{para}
1.0	-0-	-0-	-0-
0.99	+0.3	+0.5	+0.5
0.9518	+1.0	+1.0	+1.5
0.9127	+1.5	+2.0	+2.5
0.7573	+4.8	+8.0	+8.0
0.510	+11.0	+16.0	+19.0
0.2575	+15.5	?	+29.0
0.1036	+19.5	?	+32.0
0.0519	+21	+38.0	+39.0

aromatic rings and the observed shifts probably represent average effects. In such a π-complex the ortho-protons of nitrobenzene will be less shielded than the meta- and para- protons. The aromatic and methyl protons of toluene move downfield by 8 and 8.2 cps respectively on dilution of toluene with nitrobenzene. However, these shifts are very small and are comparable with the dilution shifts of toluene (.5 and 12.5 cps for aromatic and methyl protons respectively) observed in carbon tetrachloride itself.

Similar diamagnetic shifts are observed for acetonitrile, nitromethane and ethylene dichloride on dilution with toluene (Tables VIII, IX and X). The variation of the shifts is roughly linear with concentration. The limiting values (at infinite dilution in toluene) read out from the graphs are 76, 68 and 49 cps respectively. These values are comparable to those observed by Schneider for these systems i.e. between 5% solutions in benzene and neopentane. The dilution shifts in carbon tetrachloride are negligible. It has been suggested by Schneider that these shifts may be rationalized in terms of complexes of the type represented by V, VI and VII. If there are one to one complexes and the NMR line position observed is an average of the complexed and uncomplexed species, we may

TABLE VIII - SOLVENT SHIFTS OF ACETONITRILE

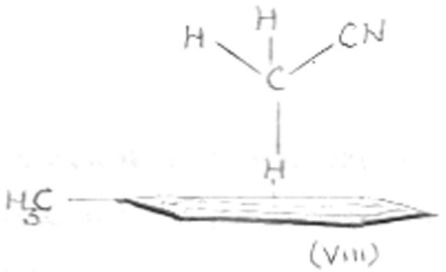
in toluene		in carbon tetrachloride	
Mole fraction	cps CH_3CN	Mole Fraction	cps CH_3CN
1.0	-0-	1.0	-0-
0.8589	+7.0	0.8466	-0-
0.6699	+18.5	0.6418	-0-
0.4035	+34.5		
0.0965	+60.5	0.1860	+0.5
0.020	+71		

TABLE IX - SOLVENT SHIFTS OF NITROMETHANE

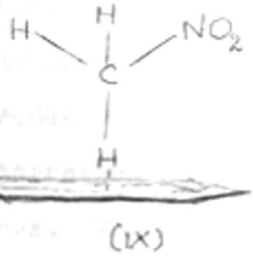
in toluene		in carbon tetrachloride	
Mole fraction	cps CH_3NO_2	Mole fraction	cps CH_3NO_2
1.0	-0-	1.0	-0-
0.9499	+3.5	0.8429	+2.2
0.8554	+11.5	0.6414	+2.8
0.6633	+20.5	0.1657	+5.0
0.3965	+39.9	0.0177	+6.0
0.1797	+57		

TABLE X - SOLVENT SHIFTS OF ETHYLENE DICHLORIDE

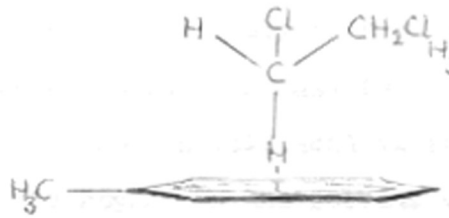
in toluene		in carbon tetrachloride	
Mole fraction	cps $-CH_2Cl$	Mole Fraction	cps $-CH_2Cl$
1.0	-0-	1.0	-0-
0.9238	+4.0	0.9166	+1
0.8014	+11.0	0.7849	+1.5
0.5739	+22.0	0.550	+3.0
0.3098	+34.0	0.2894	+3.5
0.130	+42.5	0.1195	+4.0
0.0066	+47.5		



(VIII)



(IX)



(X)

represent the situation by the equilibrium,

$$X + S \rightarrow XS$$

where S is the aromatic solvent and X, the interacting species. The concentration of XS will thus be

$$[XS] = K [X] [S]$$

A departure from linearity should therefore be expected for the solvent shifts at low concentrations of X. The linear variation observed would thus rule out one to one complexes. However an interaction of the type suggested seems to be present.

We may now examine the significance of the conclusions of the study of the NMR solvent shifts for solvent effects in aromatic chlorination. Stock and Himoe[1,2] had observed as mentioned earlier that the o-p ratios of monochlorotoluenes obtained as product is

dependent on the nature of the solvent. The solvents used and the percentages of ortho and para products obtained by Stock and Himoe are reproduced in Table XI. Water may be excluded from our consideration since the reaction in this case is heterogeneous. The behaviour of aqueous acetic acid is similar to that of acetic acid, with regard to the solvent shifts in toluene.

As pointed out earlier, the suggestion of Stock and Himoe[1,2] that the observed changes in selectivity can be attributed to complexation of chlorine with the solvents is totally unacceptable. It is inconceivable that such complexes would under any circumstances favour attack at the ortho position than at the para position, since the normal steric effect of the methyl group of toluene should be operative. The hydroxylic solvents of Table XI have similar effects. However the observed o-p distribution for these cannot be attributed to the properties of the hydroxyl function, since a similar distribution is obtained in solvent nitrobenzene. It would appear that the deciding factor is a geometrical one, arising from the "complexation" or interaction of the substrate (toluene) with the solvents. In a non-interacting solvent, the operation of the steric effect of the methyl group of toluene would make it more

TABLE XI

	Solvent	% ortho	% para
1	Acetic acid	60	40
2	" + 15.3M H_2O	61	39
3	Pivalic acid	64	36
4	Trifluoroacetic acid	67	33
5	t-Butyl alcohol	59	41
6	Nitromethane	34	66
7	2-Nitropropane	47	53
8	Acetonitrile	38	62
9	Ethylene dichloride	41	59
10	Nitrobenzene	61.6	38.4
11	Chlorobenzene	53.6	46.4
12	Acetic anhydride	49.0	51.0

susceptible to para attack than ortho attack. When it is either complexed with the solvent or interacting with it in a weaker manner, a differential physical shielding of the ortho and para positions can arise depending on the nature of such association. It is of interest to note in this connection that when the solvent is a flat polar molecule or contains flat polar functions, it favours ortho attack. The association between such a solvent and toluene may reasonably be expected to shield the para position more than the ortho position as indicated in IV. When the association is of the other type, represented by (V), the differential shielding may result from the tendency of the bulky groups of the solvent to avoid the methyl group of toluene. While nitromethane gives an o-p ratio of 34:66 in 2-nitropropane the ratio is 47:53. Introduction of two methyl groups in the interacting species increases the ortho percentage by 13, indicating the operation of a steric factor in this case.

E X P E R I M E N T A L

Purification of Materials:

n-Hexane (b.p. 67.5°C) cyclohexane (b.p. 79-80°C), nitromethane (b.p. 99°C), nitrobenzene (b.p. 206-208°C, and acetonitrile (b.p. 80°C) were obtained by distillation of C.P. grade materials at atmospheric pressure (715-720 mm).

Ethylene dichloride and carbon tetrachloride were washed with dilute sodium hydroxide and water. After drying over anhydrous calcium sulphate the materials were distilled (b.ps. 82°C and 74.5 - 75.5°C respectively). Ethyl acetate (b.p. 76°C) was treated similarly using sodium carbonate instead of sodium hydroxide.

Toluene (10 parts by volume) was washed with ice-cold conc. sulphuric acid (1 part) repeatedly until the acid layer was no longer coloured. After washing with aqueous sodium carbonate and water, it was dried over anhydrous sodium sulphate and distilled. The middle fraction boiling at 108.5 to 109°C was collected and stored over sodium wire.

Commercial acetic acid was frozen partially by cooling with ice and the liquid portion (about half the total amount) rejected. The frozen part was remelted, refluxed with chromic anhydride for about 5 hours and distilled. The

fraction distilling at a constant temperature of 117°C was collected.

t-Butyl alcohol was also first submitted to the partial freezing procedure, the crystalline alcohol being separated by decantation. After remelting it was dried over lime filtered and distilled over sodium (b.p. 81-82°C).

Dichloroacetic acid prepared from chloral hydrate, was dried in ether solution with anhydrous sodium sulphate and distilled (b.p. 104°/23 mm, 190-191°/715 mm). Esterification with methanol and sulphuric acid gave methyl dichloroacetate (b.p. 142-143°/715 mm).

NMR spectra

All spectra were recorded on a Varian A-60 NMR spectrometer using tetramethylsilane as internal standard. Solutions were prepared by mixing suitable volumes of pure materials measured with micro pipettes and mole fractions of the components were calculated using density data.

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SUMMARY

PART I - LONG RANGE SPIN-SPIN COUPLING IN THE STUDY OF AROMATIC π-ELECTRONS

The variation of benzylic coupling with changes in π electron distribution in a variety of methyl substituted aromatic compounds has been studied and it has been found that the coupling is a function of π bond order. It is pointed out that McConnell's treatment of the π-contribution to the coupling between aromatic protons can be extended to the benzylic coupling and that this coupling may be expected to vary linearly with the square of the mobile bond order (p^2) and inversely with ΔE which is an average singlet-triplet excitation energy. In agreement with expectation, when the square of the mobile bond order for a set of closely related compounds is plotted against $J_{CH_3\text{-}H_{Ar}}$ a good straight line is obtained. Indications of the inverse ΔE dependence have also been obtained. The calculated value of $J_{CH_3\text{-}H_{10}}$ for 9-methylanthracene is found to be in good agreement with the observed value of 0.625 cps.

The value of the relationship between mobile bond order and benzylic coupling for the study of π electron distribution in aromatic compounds, particularly fixation of bonds is discussed.

PART II - STUDIES ON THE MILLS-NIXON EFFECT AND RELATED PROBLEMS

A critical review of the experimental and theoretical investigations on the Mills-Nixon Effect is presented. A reinvestigation of the problem using benzylic coupling measurements is described. 5-Methylindane, 4-methylindane, 6-bromo-5-methylindane, 6-deutero-5-methylindane have been prepared in this connection. The third and fifth compounds mentioned above have not been described earlier. The methyl absorption of 5-methylindane appeared as a doublet with a separation of 0.5 cps. The band width of the signal (2.2 cps) remained unaffected on substitution of the 6-position, while it was reduced to 1.6 and 1.8 cps on substitution of the 4-position with bromine and deuterium respectively. The data indicate that the fixation of bonds in indane (benzocyclopentene) is not as postulated by Mills and Nixon, but in the opposite direction, as has been considered likely by Longuet-Higgins and Coulson.

4-Methyl benzocyclobutene has been prepared. The band width of the methyl signal was only 1.85 cps indicating that the effect of the strain of the 4-membered ring on the π electron distribution is considerably different from that of the 5-membered ring. Comparison of the NMR spectra of the benzocycloalkenes with carboxyl groups in the β(ar)-position showed that the para-coupling (α-α') increases as

the alicyclic ring-size decreases. This is attributed to the increasing contribution of Dewar-type structures (with bonds between α(ar)-carbons) to the resonance of these systems.

The NMR spectral data of a number of indane, tetralin, O-xylene and benzocyclobutene derivatives are presented and discussed. A comparison of the hydroxyl absorptions of 4-hydroxy-5-acetyl-O-xylene and 5-hydroxy-6-acetylindane has shown that the intramolecular hydrogen bonding is weaker in the latter indicating a smaller π-bond order between the carbon atoms carrying the hydroxyl and acetyl functions in this compound.

A study of the bromination and Friedel Crafts acylation on indane, tetralin and O-xylene is described. The product ratios do not show any regular trends. The complex behaviour observed has its origin in the superposition of at least two controlling factors viz. steric and electronic. Some experiments on nucleophilic aromatic substitution in indane derivatives are also described and discussed.

PART III - NMR SPECTROSCOPY IN THE STUDY OF SOLVENT EFFECTS IN AROMATIC HALOGENATION

It has been reported that in the chlorination of

toluene, variation of solvents has an effect on the ortho-para ratio of the mono-substitution products formed. This has been explained as resulting solely from an interaction between the reagent and the solvent and not from any interaction between solvent and the substrate. The NMR spectra of mixtures of the substrate with various solvents have been examined and the solvent shifts observed are discussed. The results obtained suggest that there are strong interactions between the solvents and the substrate and that these may be responsible for the solvent shifts observed from isomer distribution in the reaction.

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G. Gopakumar

NCL, Poona 8

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