STUDIES IN STEREOCHEMISTRY BY NUCLEAR MAGNETIC RESONANCE

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BY

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CONTENTS

ABSTRACT

Nuclear Magnetic Resonance Spectroscopy is used to help solve two independent problems:- (i) The kinetic isomerization of β-aminocrotononitrile in both solid and solution phases is studied by using the relative intensity of the cis and trans methyl peaks from the n.m.r. At temperatures below 46°C, a solid state equilibrium of > 95% cis isomer is formed, and above 46°C a 1:1 mixture of the two isomers forms as the compound slowly fuses. In solution, the trans isomer appears more stable at any temperature. The studies indicate β-aminocrotononitrile exists as either a pure cis monomer, or as a dimer or polymer of the cis and trans isomers. Dilution studies, acid catalysed kinetics, deuterium isotope effect studies, etc., support this observation. The structure of this dimer is proposed, and a reaction scheme supporting the experimental results suggested. (ii) Several ethyl ethers with an asymmetric centre next to the oxygen atom are studied by n.m.r. In each case, the methylene protons of the ethyl groups are non-equivalent, the chemical shift between them being about 20 cycles (at 60mc). This non-equivalence is attributed not only to the asymmetry of the carbon atom, but also to the induced asymmetry of the lone-pair electrons on the ether oxygen.

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PART I

β -Aminocrotononitrile,
A "Freely" Rotating Double Bond.

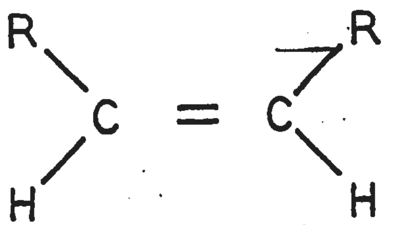
Chapter 1

Introduction

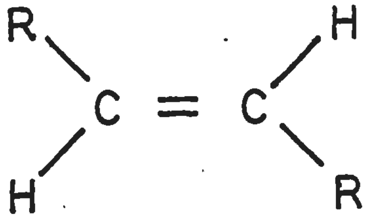
Cis-Trans Isomerization

Organic molecules containing a double bond and sufficient molecular asymmetry may exist in two or more forms, the so-called cis (I) and trans (II) forms. An equilibrium mixture of the two isomers can usually be obtained thermally, catalytically or photochemically. Photochemically induced reactions often result in the formation of the thermodynamically less favored isomer, i.e. the cis isomer. In photochemically induced transitions, the olefin molecule becomes excited to a state whose energy content is well above that of either the singlet or triplet levels. This energy (provided it is not lost immediately by fluorescence) is degraded into vibrational and rotational energy, and may set up a rotation about the olefinic bond. The velocity of rotation, however, will not be constant, as the excited state of the cis isomer is of higher energy than that of the trans, and thus the kinetic energy of rotation will be less in the cis state, resulting in the molecule spending more time in this state. Thus, when the molecule eventually loses this energy, there is a higher probability of the molecule returning to the cis ground state (provided the probability of the return of the molecule to the ground state is independent of the angle between the two halves of the molecule). Also, the trans isomer absorbs light more strongly than the cis because the trans excited state is a lower energy level, and is thus more easily converted to the cis form (1, p.345, 6 and references therin). When the molecule returns to the ground state, the isomer closest to the excited phase predominates, usually the "unstable" cis compound. An energy level diagram for the isomerization process is represented in figure 1 (2). Although E_1, the energy difference between the two isomers, may not be large, if E_2 is large, isomerization will be difficult. As this energy diagram is influenced by the electron density at the double bond, conjugated compounds isomerize more easily than non-conjugated olefins. The relative equilibrium concentration of each isomer (dependent on the difference in energy (E_1) of the troughs at 0° and 180° in figure I, provided the entropies are the same), is governed by steric hindrence (possibly causing a displacement of E_{min} from the 0° or 180° position), internal pseudo bonding (such as hydrogen bonding), etc. In most cases, however, the trans appears to be the more stable isomer. (Heats of hydrogenation and combustion of cis and trans isomers of some compounds are reported by Eliel (1, p.337ff). The trans isomer is usually more stable by around 1 to 10kcal./mole). An exception is 1,2-dichloroethylene, the cis form of which is the more stable by 0.25kcal./mole in the gaseous state.

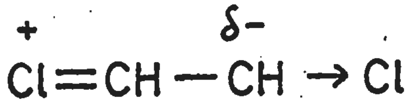
Fig. I Simple reaction curve for cis-trans isomerizations (from reference 2).



I

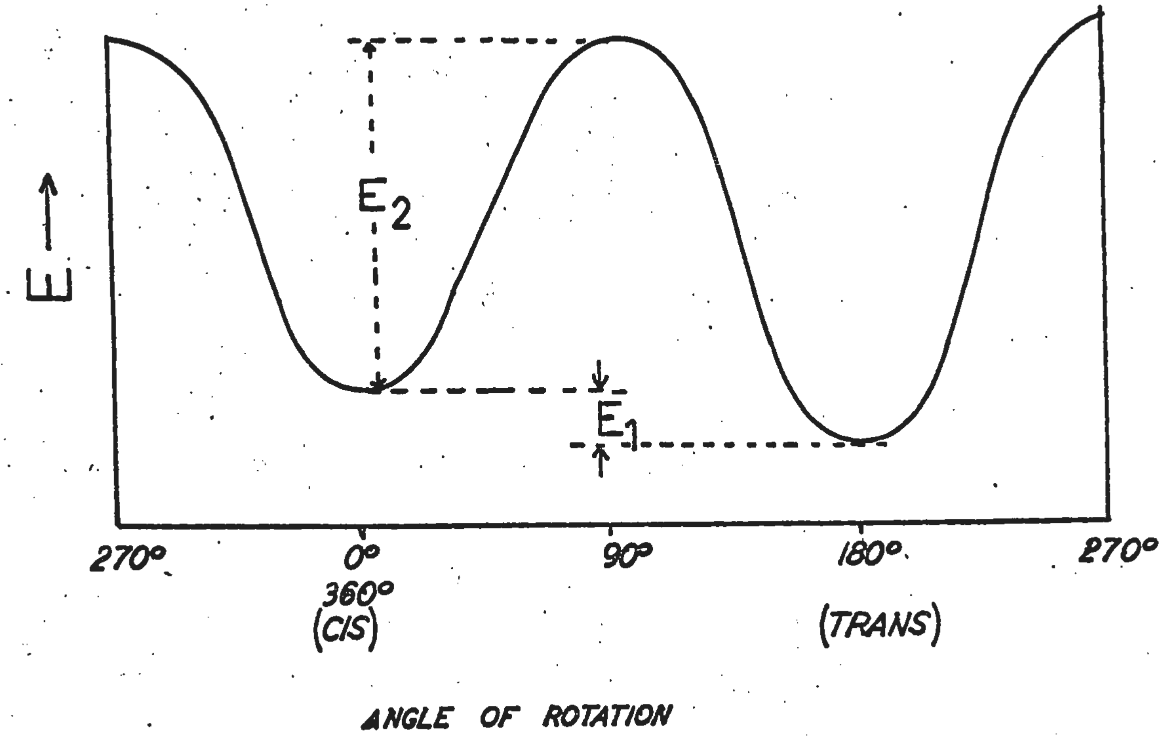


II


$\overset{+}{\mathrm{Cl}}=\mathrm{CH}-\overset{\delta-}{\mathrm{CH}}\rightarrow\mathrm{Cl}$

III

FIG. I



The difference in the standard free energy of formation ΔG_o of geometrical isomers, obtained from equilibrium constants, has also been used to determine the relative stabilities of geometrical isomers (1).

$$\Delta G_o = -2.3 \text{ RT} \log_{10} K \qquad (1)$$

Again, the trans form is favored, in most cases, cis 1,2-dichloroethylene being an exception.

Many studies on the kinetics of the thermal isomerization process have been attempted. The first such reported work appears to have been carried out by Hojendahl (3) on the conversion of maleic to fumaric acid in the fused state. Since thenm many more invesitgations on similar type systems have been done, both in the gaseous and solution phases. (See ref. 4 for a list of references).

Gas phase isomerizations have presented great experimental difficulties, as the systems appear to be affected by the surface properties of the glass used and by decomposition. This has been demonstrated with butene-2 (3). A "clean" glass or quartz reaction vessel gave faster rates than a vessel which had been exposed to a few cm. of butene-2 at the reaction temperature for about thirty minutes. This is probably due to polymeric material coating the active sites of the vessel. A high pressure of butene-2 in this "aged" vessel, however, produced high and non-reproducible results. The higher pressures probably produce free radicals, which then catalyse the reaction.

Another example of a surface reaction is the isomerization of 1,2-dichloroethylene, which is entirely a surface controlled chain reaction (6).

Solution reactions, however, appear to give relatively good results because surface effects are negligible. Also, analysis (by spectroscopy and dipole measurements) appears to be more reliable. There is, however, always the possibility of catalytic effects which could introduce systematic errors into the rate determinations. Cundall (4) states these systems should be subjected to a more detailed chemical analysis than has been previously carried out to ensure no catalytic effect is present. These systems appear to be sensitive to a variety of catalysts, several of which are (see ref. 2 for original references): nitrous acid (or Poutet's reagent, mercury and nitric acid), sulphur, selenium black, platinum black, alkali metals, halogen acids, sulphuric acid, phosphoric acid, red phosphorus and water, ammonia, primary and secondary amines, tetranitromethane, and more. Photosensitized halogen (usually iodine) can also be used.

Rate measurements are usually fitted to an "activation energy" (E_a) curve. Then, the rate constant is

$$k = Ae^{-Ea/RT} \qquad (2)$$

where A is the "frequency factor", R is the gas constant and T the absolute temperature. The reported results appear to fit two main classifications: those with low frequency factors ($\approx 10^4$) and activation energies ($\approx$ 25kcal./mole), and those with high frequency factors ($\approx 10^{12}$) and activation energies ($\approx$40kcal./mole). These differences have been explained by a difference in isomerization mechanism(7).

In a molecule containing a double bond, there exist the occupied ground state and unoccupied excited electronic energy levels. The levels of interest for this discussion are the singlet ground state (N), and the first excited triplet state (T). In thermal isomerizations, the ground state becomes vibrationally excited. (The ground singlet state has spin zero, so the two electrons in the molecular orbital are anti-parallel). A linear combination of the two atomic p orbitals can also form a high energy anti-bonding orbital.

The total electronic energy of the triplet state remains almost constant during rotation*, and the energy of the ground state rises considerably. If the total triplet energy at some point along the reaction path is less than the singlet energy, then the transition will tend to proceed via the lower energy route. The singlet-triplet transition then lowers the transition energy.

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* The triplet state has one electron in the bonding orbital and one in the anti-bonding orbital. Both the ground and excited

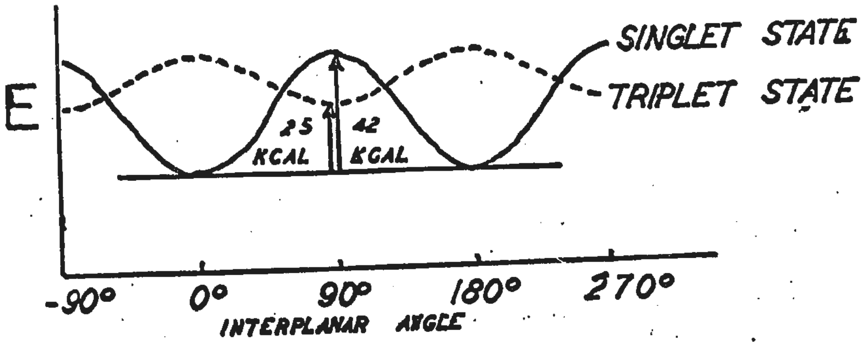
state energy levels change on rotation, but the combined energy of both levels remains almost the same. At 90°, the electrons form two non-bonding p orbitals of the same energy.

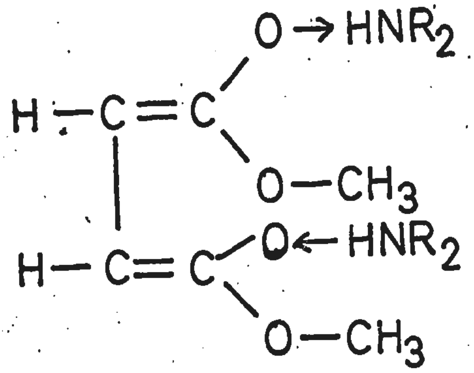
Normally, the atoms around a double bond lie in a plane. For isomerization to take place, the bond must twist a full 180°, and the singlet and triplet energy levels change during this twisting (see figure 2). At an angle of 90°, the triplet level is normally of less energy than the singlet, and thus a lower activation energy should be required if the isomerization took place via this biradical process, i.e. a triplet mechanism, than via the simpler, but more energetic singlet transition. The frequency factor of a singlet-singlet type transition, however, should be greater than that of a singlet-triplet, as the latter involves an electronic transition between orbitals and reversal of spin. Thus, the above is a possible explanation of the observed results.

Eliel (1, p.342), however, points out that originally butene-2 was suspected of isomerizing along the singlet-triplet path, but later results pointed out it is actually a singlet type transition. He thus cautions too easy acceptance of the triplet mechanism, and suggests some of the other systems, where this is suspected, should be reinvestigated. There appear to be no examples of the triplet mechanism in gas phase kinetics, as recent evidence dealing with photochemical isomerizations indicates that the triplet states of simple olefins have an energy of 60 - 80kcal./mole higher than the ground state. This,

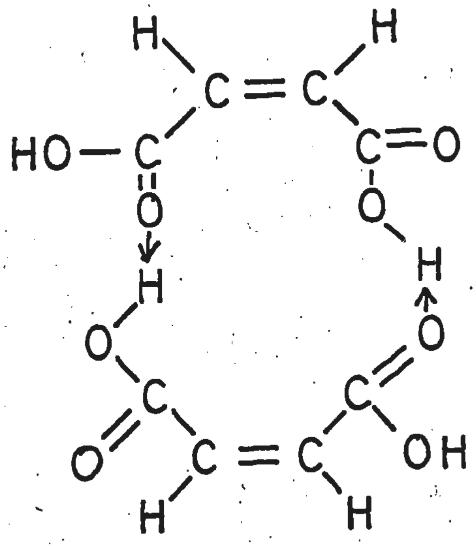
Figure 2. Cis-trans reaction curve showing both singlet and triplet energy curves and how the triplet state could take part in the reaction. (From reference 1).

FIG. 2


SINGLET STATE
TRIPLET STATE
E
25 KCAL
42 KCAL
-90°
0°
90°
180°
270°
INTERPLANAR ANGLE



IV



V

coupled with the low frequency factor, seems to rule out the triplet mechanism in simple ethylenic gases. But this explanation is useful for cis-trans isomerizations in solution, and also for more complicated gas phase reactions, such as the dimethyl maleate isomerization, (which perhaps should be reinvestigated).

Cundall (4) also briefly discusses the possibility of quantum mechanical tunnelling. The effect appears to be absent in any substituted ethylene, and will not be discussed further here.

Gold (8) states that the σ bonds, besides the π bonds, may contribute to the energy of activation. The length of the σ bond is compressed in a double bond, and thus when the interaction of the π electrons is stopped, the link will expand to the single bond distance and thus help to stabilize the 90° transition state. The lengths of the other bonds in the molecule will also adjust themselves to different lengths in the transition state because of the general redistribution of π electrons. This method has failed, however, to explain all isomerizations as purely singlet or purely triplet transitions, although a proper choice of the resonance integral (β) might give the correct results.

Davies and Evans (9) have investigated maleic-fumaric and cinnamic ester cis-trans isomerizations. The ester kinetics are all first order, with low frequency factor ($\simeq 10^{5}$) which changes with a change in solvent. This might indicate a solvent effect on the singlet-triplet transition probability. Rates could be a combination of the two effects:

$$k_{obs} = 10^5 e^{-E_t/RT} + 10^{12} e^{-Es/RT} \quad (3)$$

o-Methoxy cinnamate (9) gives different activation energies for different temperatures. The rate studies gave good first order kinetics. Effects such as decomposition catalysis would have been expected to lead to curved first order plots due to differing concentration of catalyst. If no unrecognizable experimental factor is present, it appears that the reaction changes from a singlet-triplet process at lower temperatures to the singlet-singlet mechanism at higher temperatures. The data, however, seem to indicate the resonance stabilization of the transition state, which is appreciable for phenyl derivatives of ethylene, is reduced in the o-methoxy compound.

Acid and base catalysis of maleic ester isomerizations are reported. A hydrogen type bond is found to be important in the transition state, which probably looks something like IV. This also explains the absence of observed deuterium exchange when DCl is used as a catalyst. The catalysed reaction appears not to be via the singlet-triplet transition with its low probability.

Studies by Calvin and Alter (10) on para substituted stilbenes showed that substitution gave values closer to a triplet type mechanism. They concluded substitution lowered E_{trip}, leaving E_{sing} unaffected.

Low activation energies and A factors have been reported (11) where resonance can stabilize the opening of the double bond.

As discussed above, cis trans isomerizations are subject to catalysis by a wide range of materials. Most of these are thought to catalyse the isomerization by addition in some way, thus reducing the π electron density of the double bond and permitting rotation (2). For the purposes of this introduction, acid and base catalysis will only be dealt with in detail. Suffice it to note that cis trans isomerization systems are subject to catalysis by a wide variety of other substances, thus introducing difficulty in the determination of "true" rate factors for a particular reaction.

Davies and Evans (9) have studied maleic and cinnamic acid isomerizations. The conversion of maleic to fumaric acid appears to be a second order process. They postulated an acceptor-donor type intermediate V involving two maleic molecules. This explains the low frequency factor (5×10^2), because of the difficulty two maleic acid molecules would have in aligning this way. The bond structure can then change, making isomerization easier. Although the singlet-triplet mechanism cannot be ruled out, the transition is certainly not a simple singlet transition. Studies using other acids as catalysts confirm (V) as a likely transition state, as now two acid groups must replace the one maleic acid group. The fumaric acid product cannot catalyse the reaction because it cannot form the ring type structure needed. Similar type results are reported with α-bromocinnamic acid, but in this case a singlet transition is possible. Again, however, reduced bond order seems to play an important role.

The maleic-fumaric acid isomerization results were the same in anisole and cyclohexanone, thus incidating these solvents give "true" isomerization rates.

The catalysed and uncatalysed isomerization of maleic to fumaric acid in water solution has also been studied by Davies and Evans (12). In this case, they suggest the scheme shown in figure 3 to explain the result. D can be either a maleic acid molecule (in the case of acid catalysis) or a water molecule (when HA = maleic acid). D acts in a donor capacity to stabilize the transition state.

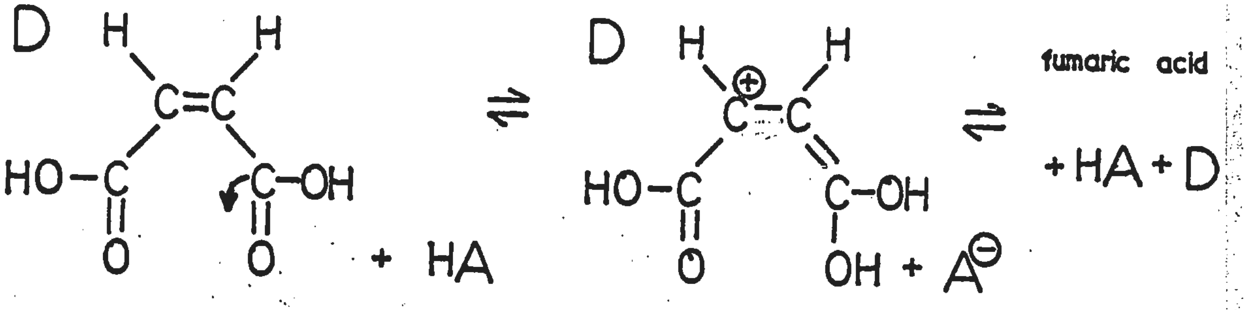
The thiocyanate catalysed isomerization of maleic acid 2, 3 - d_2 gives an isotope effect of $k_H/k_D \approx 0.9$ (13). This is taken as evidence for the above type reaction. The transition state appears to be a little more than half way between the trigonal and tetrahedral states of carbon. Again, no deuterium-hydrogen exchange between the unsaturated hydrogens was noted.

Recently, several reactions have been reported in which the catalyst directly attacks the double bond.

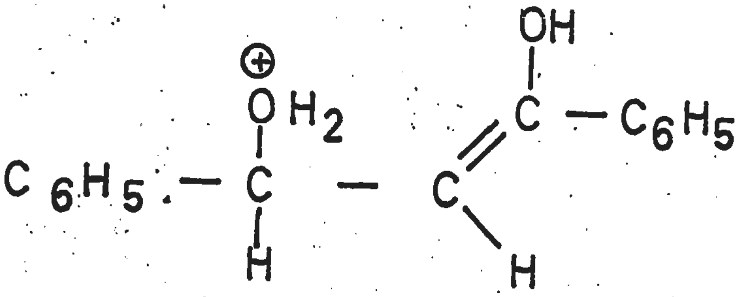
In the acid catalysed isomerization of cis-benzalacetophenone (chalcone) (14), a water molecule is thought to add directly to the double bond, producing the intermediate IX. This is

Figure 3. The catalysed and uncatalysed isomerization of maleic to fumaric acid in water solution.

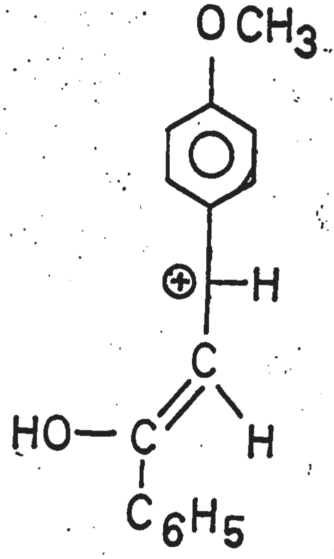
FIG. 3



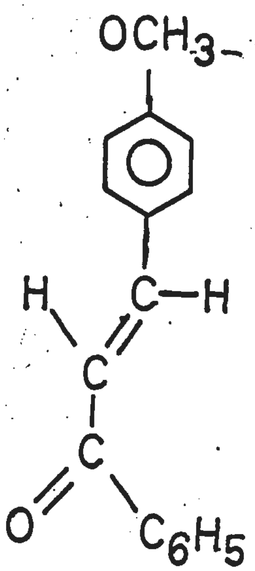
VI VII VIII



IX



X



XI

the rate determining step in the reaction. Kinetic isotope effects confirm this mechanism (15), and also show there is no deuterium addition to the double bond.

The isomerization of cis-4-chlorochalcone and cis-4-nitrochalcone is similar to chalcone, but cis-4-methoxychalcone appears to isomerize without direct addition to the double bond (16). The methoxy group supports the partial formation of the enol carbonium ion X with a reduced $\alpha \underline{=} \beta$ bond order, thus leading to rotation about the $\alpha - \beta$ bond giving the trans isomer XI. The other compounds studied cannot support this positive charge as easily, and thus water addition is postulated. Deuterium isotope effects in D_2O - D_2 SO_4 help confirm the above conclusions.

Cinnamic acid isomerization studies in fairly strong sulphuric acid (17) indicate an addition - elimination mechanism is operating (see figure 4).

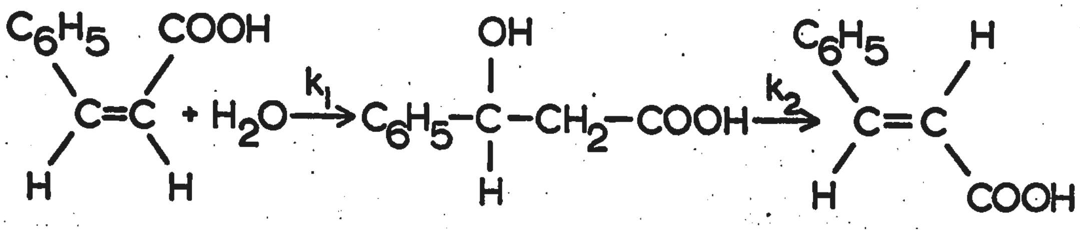
α-deuterium isotope studies suggest that deuterium - hydrogen exchange takes place during the isomerization process, and not subsequent to it. The large solvent isotope effect ($k_H/k_D \approx 6$) indicates direct proton transfer is the rate determining process. (18). The intermediate, β-phenol- β-hydroxy propionic acid, was further studied, and deuterium isotope effects indicate the rate determining step in formation of trans cinnamic acid is the loss of the α hydrogen. Isomerization studies with p-methoxy and p-chloro cinnamic acids (19) revealed a similar type mechanism. A correlation with Brown and Okamoto's (20) $\sigma^+ = -4.3$ indicates both important resonance interactions between the para substituent and the electron deficient centre of the transition state and a high degree of positive charge at the benzylic carbon. This would facilitate the scheme shown in figure 4.

Some work on the base catalysis of the cis trans isomerization of maleic esters has been carried out. (See earlier discussion on acid catalysis for case with R_2NH by Davies and Evans (9). Other schemes have been proposed but they involve:- (i) a five covalent carbon and four covalent nitrogen or (ii) the addition of an amine to the double bond - an unlikely process. Davies and Evans (9) acceptor - donor type complex appears to be the best explanation of both acid and base catalysis of maleic esters. Tertiary amines and pyridine are ineffective (4) thus indicating the importance of the proton in the catalysis.

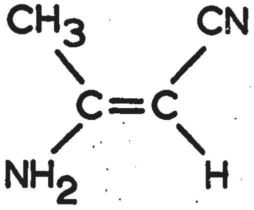
As β-aminocrotononitrile appears to be insensitive to visible light as a catalyst, photochemical processes are not important in this introduction, as they seem to introduce no errors in the system to be studied. Cundall (4) has an excellent review of photochemical isomerizations, and thus interested readers should refer there for further information.

Figure 4. Cinnamic acid isomerization in fairly strong sulphuric acid.

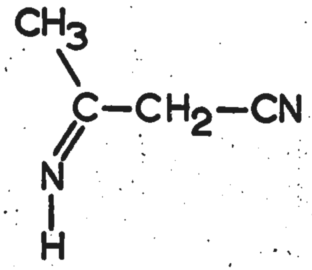
Figure 5. Some proposed resonance forms of β-aminocrotonitrile.



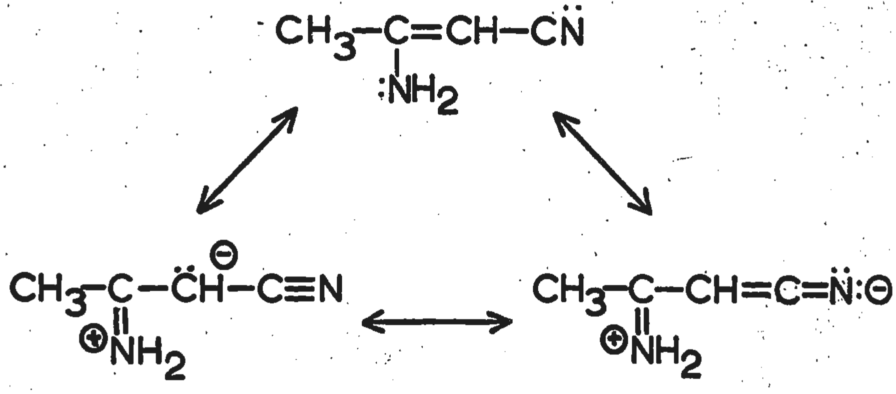
XII XIII XIV



XV



XVI



XVII XVIII

β-aminocrotononitrile

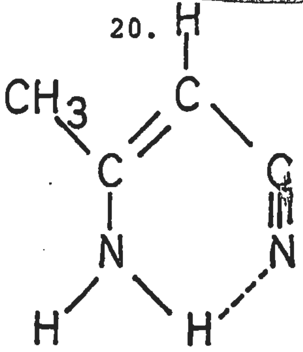
β-aminocrotononitrile was first made in 1889 by Holtzwart (21). Six years later, von Meyer (22) isolated two crystalline forms of the nitrile, a low melting (52-53°C) form and a high melting (79-83°C) form, the former having the higher solubility in benzene, and assigned them to the ketimine (XVI) and enamine (XV) tautomers. He later synthesized (23) a number of derivatives of the ketimine form. With semicarbazide, two isomeric uraminoacetodinitriles ($MeC(:NHCONH_2)CH_2CN$) were formed. Similar type compounds resulted from reaction with thiosemicarbazide and benzoylhydrazine. Also, reactions of the type:

$$ArNH_2 + \text{nitrile} \xrightarrow{HOAc} MeC(:NAr)CH_2CN$$

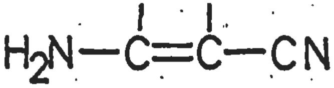
were reported. These reactions were taken to indicate the presence of the ketimine tautomer. (Note, an elimination mechanism is as plausible as the more usual condensation for these reactions, and thus the presence of even small equilibrium amounts of ketimine cannot be assumed from these results).

Von Auwers and Wunderling (24) have presented spectrochemical evidence for the enamine tautomer. Ketones of the type PhCOAlk normally show $E\Sigma_{Refr.} \approx 0.5$ and $E\Sigma_{Disp.} \approx 28\%$, and these values should not exceed 1.0 and 50% for this type compound. From the observations of Moreau and Mignonac, imides ($PhC(:NH)Alk$) behave similarly. Enamine nitriles (including β-aminocrotononitrile) have far greater exaltations than would be expected for the ketimine form, and thus (XV) is thought to be the stable form. This does not rule out the possibility of small amounts of XVI being present.

Conn and Taurins (25) have presented further evidence supporting XV as the stable form. Ultraviolet spectra indicate that both forms of the nitrile reported by von Meyer (22) have the same electronic configuration, corresponding to the enamine form. XV could exist as a resonance hybrid of XVII and XVIII (see figure 5). Also, if the two isolated forms are XV and XVI, the heats of solution at the melting point would be different. They are, however, the same. Enantiotropic and monotropic polymorphism were also ruled out. Thus, Conn and Taurins assumed the two crystalline forms of β-aminocrotononitrile are the cis and trans isomers, isomerization taking place via the hybrid forms XVII and XVIII. They postulated the low melting form to be the trans isomer XIX, stabilized by an internal hydrogen bond. Baldwin (26) points out, however, that intramolecular hydrogen bonding is impossible as cyanide bonds are linear. He states that enaminonitriles can exist as XX, XXI or XXII. The infrared spectrum indicates that XX is the form present. (Reported peak positions are:- NH_2 3450, 3350 1645cm^{-1}; C=N 2180cm^{-1}; C=C 1600cm^{-1}). The CN absorption bond is about 30cm^{-1} lower than normal conjugated nitriles because of increased interaction between the p- electrons of the nitrogen atom with the π electrons of the double bond, and in turn with the π electrons of the nitrile group itself - i.e. the



XIX

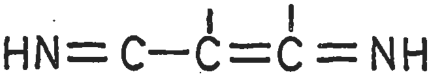


$H_2N-\overset{|}{C}=\overset{|}{C}-CN$

XX

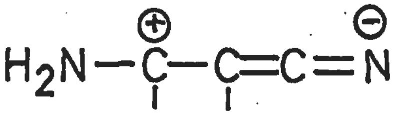
$HN=C-CH-CN$

XXI



$HN=C-\overset{|}{C}=\overset{|}{C}=NH$

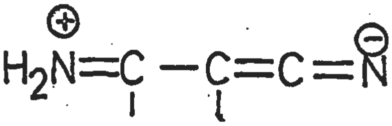
XXII



$H_2N-\underset{|}{\overset{\oplus}{C}}-\underset{|}{C}=C=\overset{\ominus}{N}$

XXIII

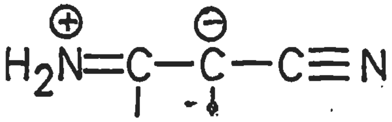
↔



$H_2\overset{\oplus}{N}=\underset{|}{C}-\underset{|}{C}=C=\overset{\ominus}{N}$

XXIV

↕



$H_2\overset{\oplus}{N}=\underset{|}{C}-\underset{|}{\overset{\ominus}{C}}-C\equiv N$

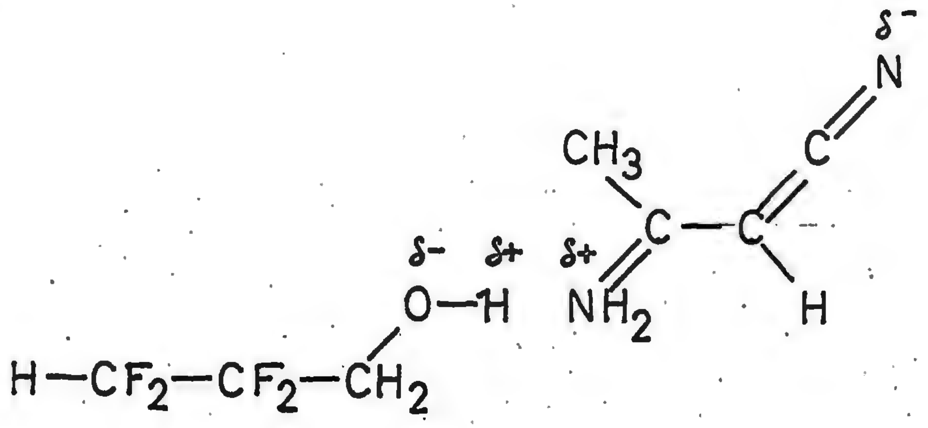
XXV

enaminonitrile structure allows charge separated resonance forms such as XXIII, XXIV and XXV to contribute to the ground state of the molecule. Structures XXIII and XXIV, with the C=C=N group, might be expected to show an IR band around 2045 cm.$^{-1}$, and thus these might contribute to the ground state. The iminonitrile structure XXI certainly could not explain the C=N band shift. Thus, the enaminonitrile structure is again inferred.

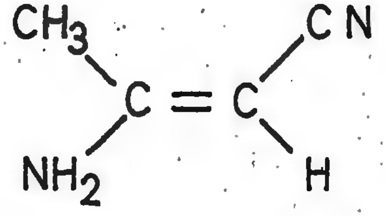
Hofmann et al (27) proposed that in weak acid solution (2,2,4,4-tetrafluoropropanol, pKa ≈ 11.4), uv light might cause the formation of XXVI, which could aid in the isomerization process. They also noted the melting point of the low melting form of β-aminocrotononitrile rises on standing in the solid phase. Bullock and Gregory (28) have recently described this effect as the solid state isomerization from a mixture of the two isomers (the low melting form) to the pure cis form. (The nomenclature used in this thesis is that from reference 28, as shown by compounds XXVII cis, XXVIII trans).

From molecular weight determination in benzene, they have described the low melting form as probably being a dimer, containing one molecule each of the cis XXVII and trans XXVIII isomer.

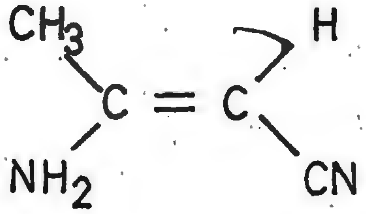
Cis-trans isomerization studies on compounds not unlike β-aminocrotononitrile have been carried out. The gas phase isomerization of crotononitrile (29) gives a first order rate constant of $k_1 = 10^{11} e^{-51.3/RT}$, $\Delta H = .17$ kcal./mole, and $\Delta S = -.39$e.u. The activation energy (51.3 kcal. / mole) is between that for 2-butene and dideuteroethylene, thus indicating that conjugation



XXVI



XXVII



XXVIII

in the side groups of an ethylenic bond lowers the activation energy of isomerization. The cis isomer is the most stable, and this is probably related to the negative entropy value, which is explained by the potential barrier to hindered rotation in the methyl group. (See ref. 1, footnote pages 339, 340).

The cis trans isomerization of enamino - ketones is closely analogous to that of β-aminocrotononitrile. Small amounts of the imino form have been proposed to account for this process (30). The prototropic character of the isomerization had been expected from the low activation energy (≈ 15kcal./mole) (31) and the deuterium isotope effect on the isomerization (32). Dabrowski (30) has observed an exchange of deuterium at the α hydrogen with isomerization in D_2O, and the deuterated enaminoketone exchanged its α deuterium for hydrogen in H_2O. The rate of exchange, however, is not nearly as fast as the rate of isomerization, and thus other mechanisms besides that involving the imine intermediate must be considered. That the N,N-dimethyl derivative does not isomerize is an indication a possible hydrogen transfer is important in this reaction.

The nuclear magnetic resonance spectra of cis and trans-β-aminocrotononitrile are reported in reference 28.

Chapter 2

Experimental (Kinetics)

(a) Solid state isomerization:

The solid state isomerization of cis β -aminocrotononitrile XXVII to a mixture XXIX of cis and trans isomers was studied at temperatures ranging from 47.5 to 100°C, and that of a mixture of the two isomers to the pure cis form from 0 to 45°C.

Preparation and purification of β-aminocrotononitrile:

To 127.5 gm. acetonitrile (freshly distilled from KOH), and 130 ml. anhydrous ether in a 1 litre, 3 neck flask equipped with stirrer and condenser, are added 25 gm. of freshly cut sodium (in small pieces) over 1 - 2 hours, keeping the reaction mixture gently refluxing. Extra ether (100 ml.) is then added, if necessary, and the mixture kept refluxing for four hours. The sodium salt is filtered off and washed with ether. Water is added dropwise to a slurry of the salt in ether at 0°C until most of the solid has disappeared. The reaction mixture is extracted well with ether, and the bulked ether extracts dried over $MgSO_4$, filtered and the ether removed in a flash evaporator. (The preparation must be finished to this stage in one day). The nitrile thus obtained was allowed to stand at room temperature overnight, and then recrystallized two to six times from benzene, until the melting point rose to 78 - 81°C. This material was recrystallized a further three times from spectro-grade benzene (Fisher), ground for two minutes in an agate mortar and dried in a vacuum desiccator (over silica gel) before using for kinetic experiments.

Material recovered from the benzene filtrate was found to give slower rates in solution, and thus the material used for the solution and acid catalyzed runs was purified by evaporating the filtrate, and recrystallizing the residue. The filtrate from this "second" purification was again treated as above, and used for the kinetic runs. Even then, repetitive results could not be obtained. (See Table VI and figure 20, results).

The material used for the low temperature runs (below 46°C) was prepared as above, except that after recrystallization the kinetic samples were fused for 4 to 10 minutes at around 100°C, ground for two minutes and dried as previously. This gave an approximately 50-50 mixture of the two isomers.

As there seems to be no rigorous standard of purity for β-aminocrotononitrile, material which had m.p. above 78° to 80°C and showed no extra peaks in the n.m.r. (anisole or concentrated d_6DMSO solution) was assumed to be pure.

Deuterated β-aminocrotononitrile:

The pure cis isomer (5 gm) was fused for 5 minutes on a steam bath. Heavy water (15 gm.) was added and the mixture shaken vigorously at 100°C for 1 minute. The mixture was cooled and extracted with pure ether (3 x 20 ml.). The solvent was removed immediately in a vacuum desiccator, and then drying was completed in this desiccator. The mixture obtained was analysed by n.m.r. ($CHCl_3$, d_6DMSO solutions), and, assuming no exchange of methyl hydrogens it was approximately 60% cis isomer.

15 ± 1% of the olefinic hydrogens were replaced by deuterium, and 80 ± 5% of the amine hydrogens appeared to be exchanged. (Note, NH integration in n.m.r. is imprecise because of the broad peak).

26 - 28 mg. samples were used in experiments on the kinetics of the isomerization. These samples were placed in clean n.m.r. tubes, which were used as the reaction vessels. They were sealed with plastic caps (Varian).

Except for the runs above 80°C, water or oil constant temperature baths controlling to ± 0.02°C were used. Those above 80°C were in oil or steam baths controlling to ± .2°C. The runs at 0°C were done in a cold room, and as the samples had to be left several months, the temperature necessarily varied (estimated temperatures were 2.5 ± 2°C).

Kinetic samples were analysed by dissolving in reagent grade (Fisher) anisole (b.p. 153.5 - 153.9°C) kept over molecular sieves, and the CH_3 peaks integrated on a Varian A-60 nuclear magnetic resonance spectrometer. Samples at the probe temperature (≃ 38°C) did not isomerize during the time taken for analysis. (See Table VI, results at 37.45°C). Five to eight integrations were taken for each sample, and graphs were plotted from an average of these. The rates given in Tables I to IV, VI and VIII, however, were obtained from a weighted least squares program run on an IBM1620 computer. (See below).

The samples for the deuterium isotope kinetics were analysed in commercial spectro grade chloroform (Fisher) which was freed from acid and ethanol by passage through a short column of chromatographic alumina. This solvent was kept for short periods in brown vessels.

As some of the runs were subjected to vibration by the bath stirring motor, which appeared to cause random results, a low and a high temperature run were done using a Blackstone ultrasonic probe. Standard runs were done at the same temperature using the same sample prepared as above. 20,000 cycle/sec. sound at the maximum intensity (100%) of the instrument was used. The samples (in n.m.r. tubes) were placed - 1 inch from the probe, water being used to transmit the sound.

Several checks were made on the reaction product of all solid state (and solution) runs, and no unexplained peaks could be found in the n.m.r. (anisole or d_6DMSO solution) of material that had not discolored, and all the rates reported are for such samples. Solid decomposition effects become obvious after two to three months with sample held at 25°C, and after three days at 45°C. The sample, however, always turns yellow before impurities can be detected in the n.m.r. spectrum, and none of the reported kinetic points are from yellowish samples.

Some good grade cis (m.p. 80.5 - 82°C) was placed in a micro test tube connected to a water-phenolphthalein manometer at 100°C and kept for 8 days. For the first two hours (a regular isomerisation at this temperature would be completed in (¼ hour) no detectable color was observed and no pressure change occured. After 5 hours, the pressure increased and the sample began to discolour. After 7 hours the water in the monometer turned pink, indicating that NH_3 was being liberated. After 8 days the sample was placed in a vacuum sublimation apparatus at 120 - 130°C for an additional two days. Three fractions were formed on the sides of the tube. The compounds have been tentatively identified as XXX, XXXI and nitrile. XXX and XXXI would produce ammonia (28), and this could catalyse the reaction, but this does not seem to occur until well after equilibrium has been reached.

Preliminary experimental work (and some of the above) was carried out by the author as an undergraduate, and used for an honours dissertation.

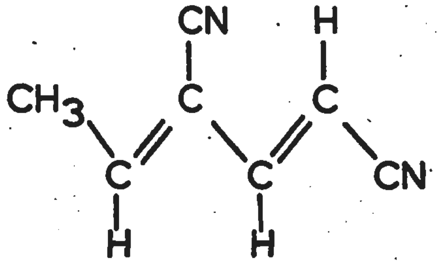
The rate of solid state reactions appears to be dependent on many factors, such as crystal size, sample size, mode of preparation, number of times recrystallized, age of the sample, and so on. Garner (33) reports the same sort of effect with other solid state reactions.

Crystal size:

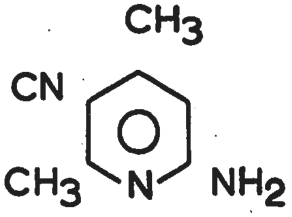
Different crystal sizes (obtained by sifting) gave different rates. As brass sieves were the only type available and the plots of the sifted vs. the non-sifted compound were not very smooth, impurities appeared to contaminate the sample during sifting. Grinding the material in an agate mortar for two minutes, however, gave consistent results.

Sample size:

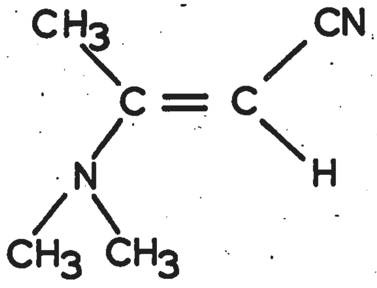
Smaller samples give faster rates, and thus a sample size of 26 - 28 mg. in an n.m.r. tube was found to be quite convenient,



XXX



XXXI



XXXII

as both reproducible results and an adequate n.m.r. signal were obtained.

Cis (m.p. 78 - 81°C) compound stored in a refrigerator kept a fair length of time without decomposition or isomerization (n.m.r. analysis), and after six months the melting point dropped to only 76 - 79°C. Impure material, however, decomposed on storing, and ammonia was obviously present upon opening the cap. (Bullock and Gregory (28) have discussed the self condensation of β -aminocrotononitrile, which liberates ammonia).

(b) Solution and Acid catalysed runs:

The β-aminocrotononitrile was prepared as described above. Solution runs were carried out mainly using the n.m.r. variable temperature probe as a constant temperature bath, while the acid catalysed runs were performed in a water (covered with 1 inch of oil) bath at 37.45 ± .02°C. A Sargent thermometer coupled with a thermistor was used for control. N.M.R. tubes (Varian) were again used as reaction vessels, but different rates were found with "new" and "aged" tubes (See results). A "new" tube is a tube as it comes from the package. It was neither washed nor heated before use. "Used" tubes were those, used solely for kinetics experiments, which were then washed well with water and acetone, heated ≃ 2 hours in concentrated nitric acid, rinsed with tap water, and steamed out 1 hour with steam from conductivity water. They were then rinsed with conductivity water and dried at 120°C in an oven. "Aged" tubes were "used" tubes which were rinsed with reagent grade anisole (Fisher) b.p. 153.4 - 153.9° C, aged in anisole in an oven at 160°C for 1 hour, and then rinsed with purified anisole, and allowed to "drip dry".

The solutions were prepared in volumetric flasks cleaned with nitric acid (room temperature, soaked ≈ 2 days), and then washed well with tap water. They were rinsed with conductivity water 20 times and soaked in this water for 1 day, this rinsing-soaking being repeated three times. They were then rinsed with spectro grade (Fisher) acetone, dried by drawing air through them for about 10 minutes with an aspirator, and then stored over silica gel in a desiccator. The pipettes used in making up and mixing the solutions were cleaned similarly. The most concentrated samples were weighed directly into the volumetric flasks using a Stanton or Sartorius 5 figure balance. (Weights accurate to ±.05mg.) The balance was allowed to settle to constant weight for each weighing. (Constant weight is taken as a change of not more than ±.02 mg. scale in 5 minutes). Anisole was then added, a four figure Stanton balance being used for weighing. The more dilute solutions were made by dilution techniques with a four figure Stanton balance. All concentrations reported are molalities (moles/ 1000 gm. solvent). All operations after the original weighing of the solid sample were performed in a simple dry box which was swept with dry nitrogen.

Anisole:'

Reagent grade anisole (Fisher) b.p. 152-153°C (800 - 900 ml.) was treated with an equivalent amount of 5% $FeSO_4$ and the mixture stirred for 24 hours. The anisole layer was dried over P_2O_5 for

24 hours, and then distilled using a Widmer column and fractionating distillation head in a stream of dry nitrogen. The purity of the distillate was checked by its index of refraction (Lit. 1.5179[20]).

For the acid catalysed runs, 2.00 ml. of a solution of the cis isomer was mixed in a 25 ml. erlenmeyer flask (cleaned by the same method as the "used" n.m.r. tubes with nitric acid) with 2.00 ml. of the phenol solution. ½ ml. aliquots from this mixture were placed in 8 reaction vessels (n.m.r. tubes). (New micro pipettes or cleaned pipettes were used for all transferring procedures.) Kinetic points were taken by removing the tube from the constant temperature bath and immediately running the integration of the methyl peaks. This takes about 100 seconds, and thus some error must be introduced by the temperature change. This is kept to a minimum, however, by using a reaction temperature (37.45°C) near the ambient temperature of the n.m.r. probe (≈ 38°C).

The acid catalysed series of runs were catalysis studies by four phenols. About six different concentrations of each phenol were used with four to six different concentrations of the substrate. After half the runs had been performed, fresh anisole was distilled, the compounds were recrystallized again, and fresh solutions made, to check the reproducibility of the results.

<u>Phenols:-</u>

The phenols used were commercial grade materials, and were recrystallized as follows:-

<u>p-Nitrophenol</u> - (Fluka, puriss) was recrystallized from solvent grade chloroform and once from spectro grade chloroform (Fisher).

It was dried over silica gel or P_2O_5 and vacuum for at least 4 hours, (m.p. 114.0 - 115.0°C). (Lit. 114°C).

m.-Nitrophenol - (Fluka, puriss) was recrystallized from solvent grade benzene, then once from spectro grade benzene (Fisher). It was dried over P_2O_5 or silica gel at least 4 hours. (m.p. 96.8 - 98.2°C, 97.0 - 97.7°C). (Lit. 97.0°C).

Sym-trichlorophenol - (Matheson, Coleman and Bell (Practical)) was recrystallized three times from petroleum spirit (Analar, b.p. 40 - 60°C, (m.p. 68.1 - 69.3°C, 68.4 - 68.9)(Lit. 68°C) and then dried under vacuum over silica gel.

p-Chlorophenol - (Matheson, Coleman and Bell, m.p. 42-44) was purified as sym-trichlorophenol (m.p. 42.9 - 44.4, 43.9 - 44.7°C) (Lit. 43°C). All phenols were stored in a desiccator in the dark, with silica gel as desiccant.

The rates were calculated as for the solid state runs, and again all the data were fitted to first order kinetic curves. The rates were plotted against catalyst concentration for each phenol. These rates were fitted to a parabolic equation by a polynomial least squares program on the computer. The catalytic rate is taken as the slope at infinite dilution, or the rate of reaction of 0.05 molal phenol. Most of the solutions of the cis isomer were made up using volumetric flasks with plastic stoppers. Although some good results appear to have been obtained with these solutions, the stoppers could be a source of error, leading to pseudo catalysis.

The non-catalysed runs were attempted in two ways. In the first, the solution containing only the cis isomer in anisole was placed in a clean n.m.r. tube, and the variable temperature probe of the n.m.r. Spectrometer was used as a temperature bath. (The constancy of the probe temperature is about ±1°C). In a second series of runs, various reaction vessels made of soft glass, pyrex and silica were used in water-oil or oil baths controlling to ±.02°C. In this case, aliquots were taken from the reaction mixture with new micro pipettes, and analysed as above. The soft glass containers had plastic seals, the pyrex ones had glass caps, and the silica container was open to the atmosphere. (These containers were cleaned as above for the "aged" n.m.r. tubes). Note, the second series of runs was not completely analysed because of the obvious non-reproducibility (see Table VII). Only one integration value was used for each time, and the reported rates are obtained from the graphs, and not from a computer analysis.

The effect of solvent and concentration on the n.m.r. peak positions and on the equilibrium concentration of the isomers of β-aminocrotononitrile were also studied. Five to nine concentrations of solute were used in each solvent. As previously, all measurements were made by weight (since 3 ml. volumetric flasks were used). A Stanton 0.1 mg. balance was used, and the original concentrated sample was diluted several times to obtain the desired range of concentrations. The nitrile used was good grade cis isomer (m.p. > 80°C). Results are reported for studies in anisole, benzene, chloroform and nitro-benzene. The nitrile is not sufficiently soluble in carbon tetrachloride or hexane to obtain suitable spectra. After recording the spectra to obtain peak positions, the solutions were allowed to stand either at room temperature, or in a bath at 40°C, for periods ranging from two to eight weeks, at which time equilibrium was most certainly reached. The methyl peaks were then integrated by n.m.r., and an estimate of the equilibrium concentration was obtained. As some of the samples became discolored, it is possible some decomposition does take place over extended periods in solution, even though no extra peaks show on the n.m.r. (This was verified by kinetic samples kept at 70 and 85°C, which decomposed in anisole solution after one month. The products appear to be XXX and XXXI from an n.m.r. analysis).

The spectra were run on a Varian A.60 analytical spectrometer, using 500 cps. sweep width. The calibration was checked with a TMS-$CHCl_3$ sample supplied by Varian Associates. Tetramethylsilane (TMS) (a weighed amount) was used as internal reference for each solvent. The solvents were purified as below.

Anisole as described above for solution runs, b.p. 152°C* uncorrected.

Chloroform - Spectro grade chloroform (Fisher) was freed from acid and ethanol by passing it through a column packed with chromatographic alumina.

Benzene - was redistilled and stored (≃ 6 months) over molecular sieve (Linde), and was filtered before use.

Nitro benzene - (Fisher cat. #N-90, mono rectified) was redistilled from molecular sieve (b.p. 82.2°C @ 9 m.m. mercury to 81.5°C @ 8 m.m. mercury).

* The reason for the low boiling point recorded is that nitrogen was passing through the system continuously.

PART I

Chapter 3

3. Results (Kinetics)

(a) Solid State

β -aminocrotononitrile can exist in one of two forms - the cis XXVII and trans XXVIII isomers. For this nomenclature, the compound is treated as a subsfituted cis or trans crotononitrile (28). At temperatures below 46°C, in the solid state, the nitrile exists almost entirely in the cis configuration (>95% equilibrium). At temperatures above 46°C, however, an equilibrium mixture of 50% cis, 50% trans is formed as the compound fuses. 46°C is the melting point of this mixture. Nitrile held at a specific temperature will eventually attain the stable equilibrium, and a study of this rate of isomerization has been attempted. All the rates appear to follow first order kinetics, and were treated as such. Tompkins (34), however, says the application of liquid and gaseous kinetic laws to solid state reactions is a dubious practice, and rarely is the interpretation of the solid state kinetics simple because reaction involves diffusion of ions through the solid and usually requires active sites. As these present studies follow fluid kinetics extremely well (for a particular preparation of sample) there is a good indication that the solid reaction involves only one molecule (or dimer) of the nitrile.

The isomerization of material deuterated preferentially on the nitrogen was studied between 25 and 45°C. The deuterium appeared to exchange between the nitrogen and the α carbon, and this exchange rate was also studied.

Some of the runs showed more scatter than others, and this was attributed to the vibration action of the stirring motor, which was attached to the constant temperature bath. To study the effect of stress and strain on the isomerization process, several runs were done whilst the sample was exposed to ultrasonic energy.

Several sets of kinetic data were obtained for the study of the solid state isomerization of β-aminocrotononitrile. These represent different samples used, as it proved difficult to repeat any results when a new batch of the nitrile was prepared. All sets are consistent for the particular sample used, and the latter sets (sample B in the tables) appear to be fairly reproducible, considering the difficulties involved. The rates obtained are given in tables I to IV and figures 15 and 16. Table 1 and figure 15 are compilations of all the rates obtained for low temperature runs, table II and figure 16 those for high temperature runs, table III those for deuterated runs, and table IV those for runs with the ultrasonic probe.

The rates reported were all obtained by fitting to a "best" straight line using a weighted least squares approximation on an IBM 1620 computer, plotting for a first order reaction, i.e. log concentration vs. time. The program averaged the several integrations obtained at a given time and computed the probable error of the average. Any values which deviated from the mean by more than five times the probable error (P.E.) were rejected and the mean recalculated. The new P.E. thus obtained was used

TABLE I

First order rate constants for low temperature (≤ 45°C) cis-trans isomerization of β-aminocrotononitrile

Temp. °C	K(1st order) sec^{-1}	Starting Material
2.5 (± 2°)	$2.625 \times 10^{-7} \pm 1.3\%$	Mixed Isomers A
24.91	$3.855 \times 10^{-6} \pm 2.4\%$	" " "
34.95	$1.674 \times 10^{-5} \pm .8\%$	" " "
40.00	$5.160 \times 10^{-5} \pm .7\%$	" " "
45.00	$7.243 \times 10^{-5} \pm .8\%$	" " "
2.5 (± 2°)	$1.339 \times 10^{-7} \pm 4.0\%$	Mixed Isomers B
25.00	$1.917 \times 10^{-6} \pm 2.4\%$	" " "
30.00	$3.615 \times 10^{-6} \pm 2.0\%$	" " "
35.00	$7.315 \times 10^{-6} \pm 1.5\%$	" " "
39.72	$1.578 \times 10^{-5} \pm 2.3\%$	" " "
45.00	$2.988 \times 10^{-5} \pm 1.1\%$	" " "

TABLE II

First order rate constants for high temperature (> 45°C) cis-trans isomerization of β-aminocrotononitrile.

Temp. °C	K(1st order) sec^{-1}	Starting Material
50.1	$1.325 \times 10^{-5} \pm 3.9\%$	Cis A
55.1	$5.468 \times 10^{-5} \pm 1.2\%$	" "
60.00	$1.196 \times 10^{-4} \pm 1.4\%$	" "
65.00	$2.236 \times 10^{-4} \pm 1.0\%$	" "
69.95	$3.691 \times 10^{-4} \pm 1.0\%$	" "
47.43	2.39×10^{-6} (error very large)	Cis B
55.00	$3.071 \times 10^{-5} \pm 1.7\%$	" "
64.64	$1.302 \times 10^{-4} \pm 0.9\%$	" "
74.64	$2.297 \times 10^{-4} \pm 2.4\%$	" "
84.6(±0.2°)	$4.668 \times 10^{-4} \pm 1.1\%$	" "
99.1(±0.2°)	$9.049 \times 10^{-4} \pm 1.1\%$	" "

TABLE III

First order constants for solid phase isomerization of N-deuterated β -aminocrotononitrile.

Temp.	k(1st order) sec^{-1}	k_H / k_D *
25.00 (a)	9.094×10^{-7} ±.16%	4.1 or 2.1
25.00 (b)	1.510×10^{-7} ± 9.5%	
35.00 (a)	3.174×10^{-6} ± 1.5%	5.3 or 2.3
35.00 (b)	5.500×10^{-7} ± 6.5%	
45.00 (a)	9.708×10^{-6} ± 2.3%	7.4 or 3.1
45.00 (b)	1.307×10^{-5} ± 7.9%	
45.00 (d)	1.642×10^{-7} ± 37.2%	

(a) Isomerization (b) H/D exchange

(c) Initial H/D exchange, (d) Final H/D exchange

* Values given relative to Samples A and B respectively, the deuterated material was made from the same starting material as sample B.

TABLE IV

First order rate constants for the solid phase isomerization of β-aminocrotononitrile subjected to ultrasonic sound. A new batch of nitrile was used, sample C.

Temp.	k(1st order) Sec^{-1}	starting material	type run
42.52	$9.090 \times 10^{-5} \pm 1.9\%$	mixed isomers, C	with ultrasonic sound
42.52	$9.226 \times 10^{-5} \pm 3.2\%$	" " , C	standard - no sound
69.30	$1.768 \times 10^{-4} \pm 2.1\%$	Cis " , C	with ultrasonic sound
69.37	$1.813 \times 10^{-4} \pm 4.4\%$	Cis , C	standard - no sound

TABLE V

Thermodynamic constants from the rate data

Temp. °C	Activation Energy	Frequency Factor	Entropy of Activation	Starting Material	Type Run
25.00	28.73 kcal./mole	$10^{15.7}$	13.1e.u.	mixture A	Low Temp.
35.00	"	"	13.0	" A	
45.00	"	"	13.0	" A	
25.00	26.38	$10^{18.6}$	3.70	mixture B	Low Temp.
35.00	"	"	3.63	" B	
45.00	"	"	3.57	" B	
50.00					
60.00					
70.00	14.31	$10^{5.4}$	-34.2	Cis B	
80.00	"	"	-34.3	" B	High
90.00	"	"	-34.3	" B	Temp.
99.99	"	"	-34.4	" B	
25.00	22.32	$10^{10.3}$	-11.3	deuterated	Low Temp.
35.00	"	"	-11.4	"	
45.00	"	"	-11.4	"	
37 to 130	≈ 12	≈ 10^3		Cis	solution

to calculate the weighing factor (W) for that particular time. Thus:

$$W \propto 1/(P.E.)^2 \qquad (4)$$

The log of the concentration (C_t) value is the y coordinate for each point, and if the experimental accuracy is the same for all points, then the accuracy of the logarithm for each point would vary as y^2 . Thus the total weighing factor for each point was

$$W = y^2 / (P.E.)^2 \qquad (5)$$

The differences between calculated and experimental points were used to find the P.E. of the difference, and if any difference was greater than five times the P.E., the point was rejected and the least squares line recalculated (35).

The computed slopes of the lines compare well with those determined graphically (45% in most cases). The method places more emphasis on the earlier points in the reaction than the later ones, and thus tends to reduce any slight "tailing off" effect which might not be noticeable in the graphic plots.

Any points which from the graphic plot were obviously off the line were rejected. Also, some of the runs show an induction period or a tailing-off period. The rates reported, however, represent the straight portion of the curve, as far as this is possible.

The errors reported in the rates are the weighed P.E. of the least squares fit, and represent the relative reliability of the data. The method of analysis itself introduces a large error into the results, as the individual n.m.r. integrations are only accurate to ± 2%, a best. Averaging certainly helps reduce this error, but there is the chance of a systematic error arising in the instrument. In the case of β-aminocrotononitrile, the cis olefinic peak is a singlet, but the trans hydrogen signal is split (0.7 cycles in anisole) by long range coupling with the methyl group. It is possible, though not likely, that this introduces a systematic error in the rates.

Errors in the solid state kinetics also arise due to the difficulty of preparing reproducible samples. Many batches of the nitrile were examined qualitatively, however, and they all behaved in the same way.

Figure 8 shows a concentration vs. time plot for several of the runs (with sample A). The run at 45°C appears unusual in that after 4 to 5 hours it tails off rapidly. The sample, however, became visibly fused on the edges at the start of the reaction, and it seems reasonable to assume the mixed isomers would remain in equilibrium. In the solid rapid formation of the cis isomer is occurring. This causes a rise in the melting point of the sample, and as the cis isomer diffuses into the molten material, the whole mass solidifies. Thus the resolidified melt might be expected to show a different isomerization rate than the powder.

Figure 9 is a plot of log % isomer (sample B) vs. time for some of the low temperature isomerizations. The reaction appears to be linear over one or two half lives, and this is

Figure 8. Representative plots of % trans isomer vs. time. These curves from the "low temperature" isomerization to the cis compound, and are for sample A.

Fig. 8.

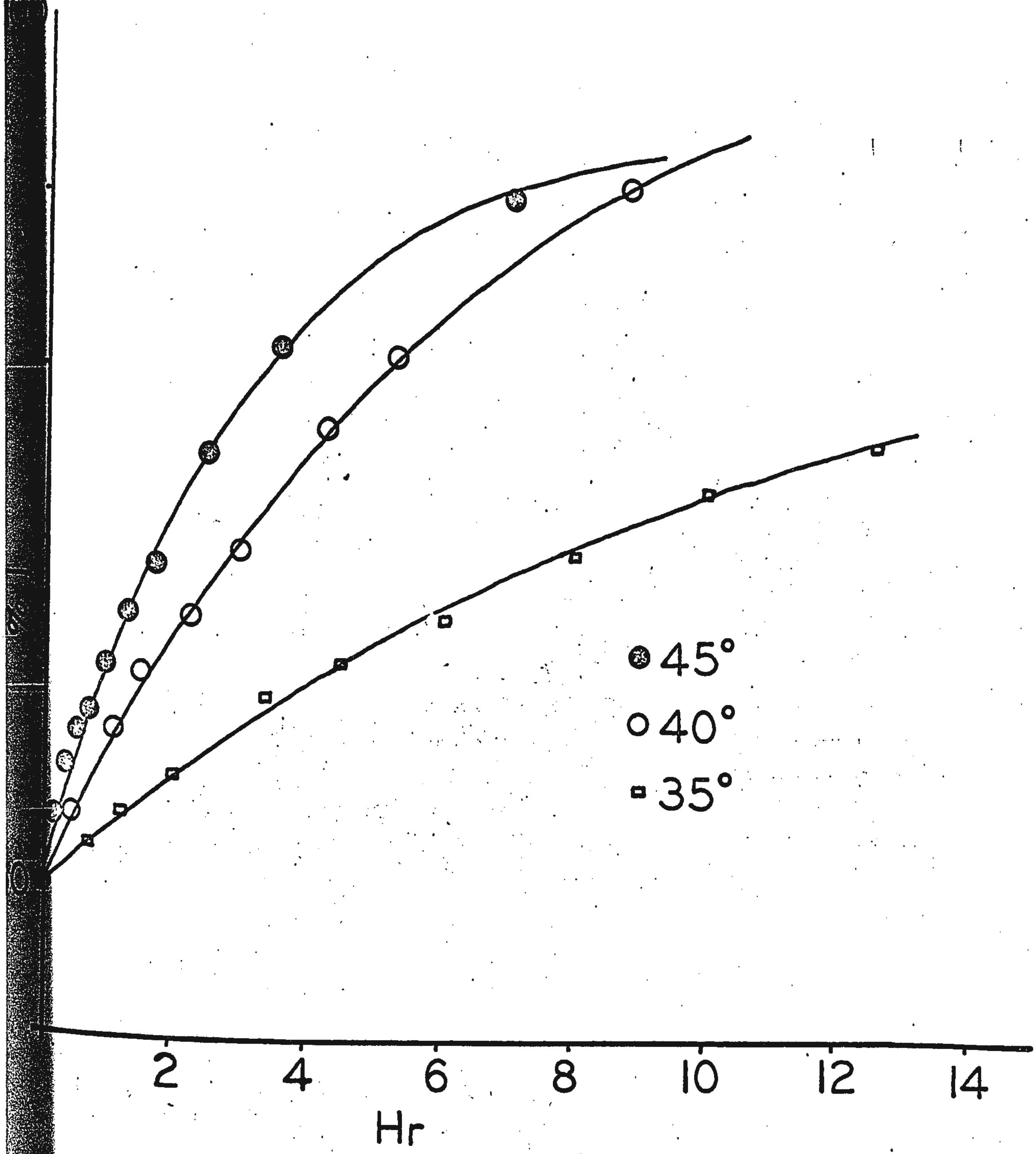
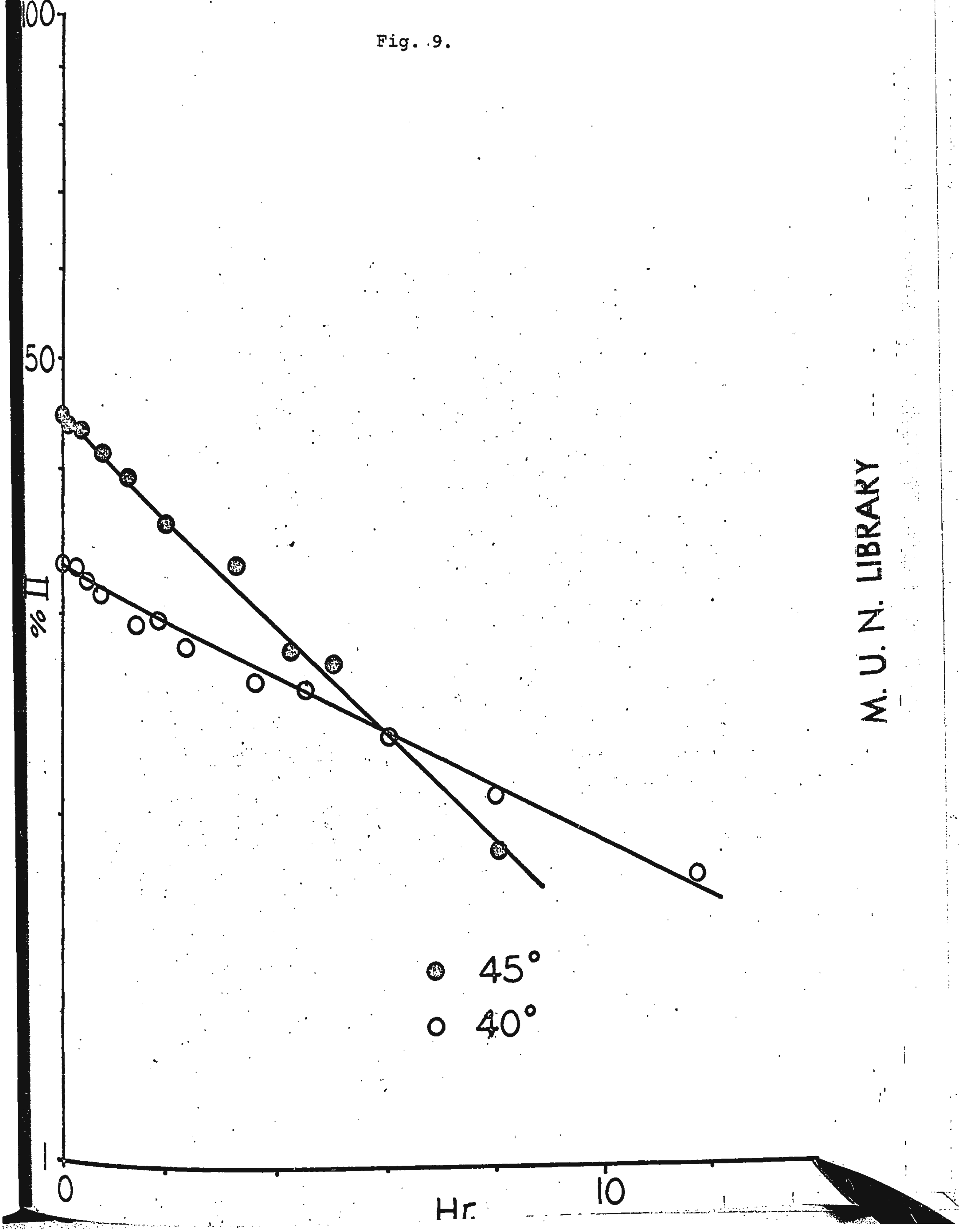


Figure 9. Solid state isomerization of mixture to cis-β -aminocrotonitrile below 45°C - first order rate plots of sample B.

Fig. 9.



sufficient for rate analysis. The points fall fairly well on a straight line, which is a little surprising considering the extreme dependence of the rate on sample size, etc. Figure 10 is an example of a run which was subjected to stirrer vibration, and the points are not nearly as good as those in figure 9. This must be attributed to random scattering of the sample particles, thus probably changing the heat conductivity of the whole, reducing or increasing the rate of reaction. The isomerization process below 46°C appears to be a true solid state process. Bawn (37) (p. 254) reports reactions where the appearance of a liquid state is usually accompanied by an increase in rate (see below, run at 65°C). These runs (0 to 40°C) show no induction period, and extremely good first order rate plots are obtained. Also, as the reaction proceeds, the melting point rises, lessening the possibility of liquid formation. That the reaction appears to be reversed in the fluid state (high temperature runs) is also an excellent indication that the low temperature runs are true solid state reactions.

Representative first order plots for "high temperature" runs are shown in figure 11. (Note, these are for sample B). The graphs seem to improve markedly with increased temperature. At 100°C, however, the reaction is completely in the fused state. (The sample takes 10 - 15 sec. to fuse, leaving $\approx$ 99% cis). The reaction at 55°C, on the other hand, is only $\approx$ 95% fused when there is 55% cis present. (See figure 12, where the progress

Figure 10. First order curve obtained when sample was being subjected to vibration from the stirrer.

FIG. 10

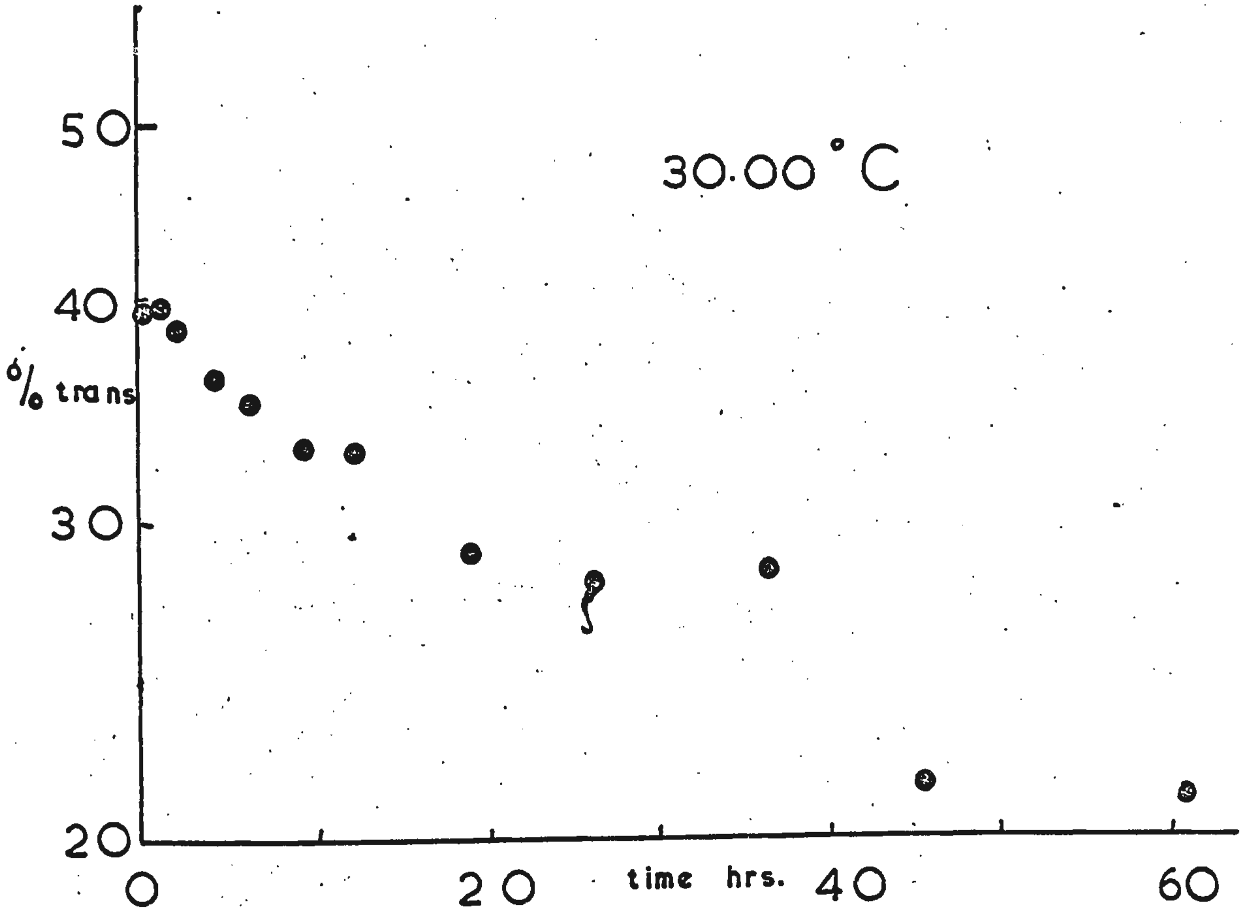


Figure 11. High temperature neat isomerization of solid cis-β-aminocrotononitrile (sample B) to the fused mixture at various temperatures.

Fig. 11a

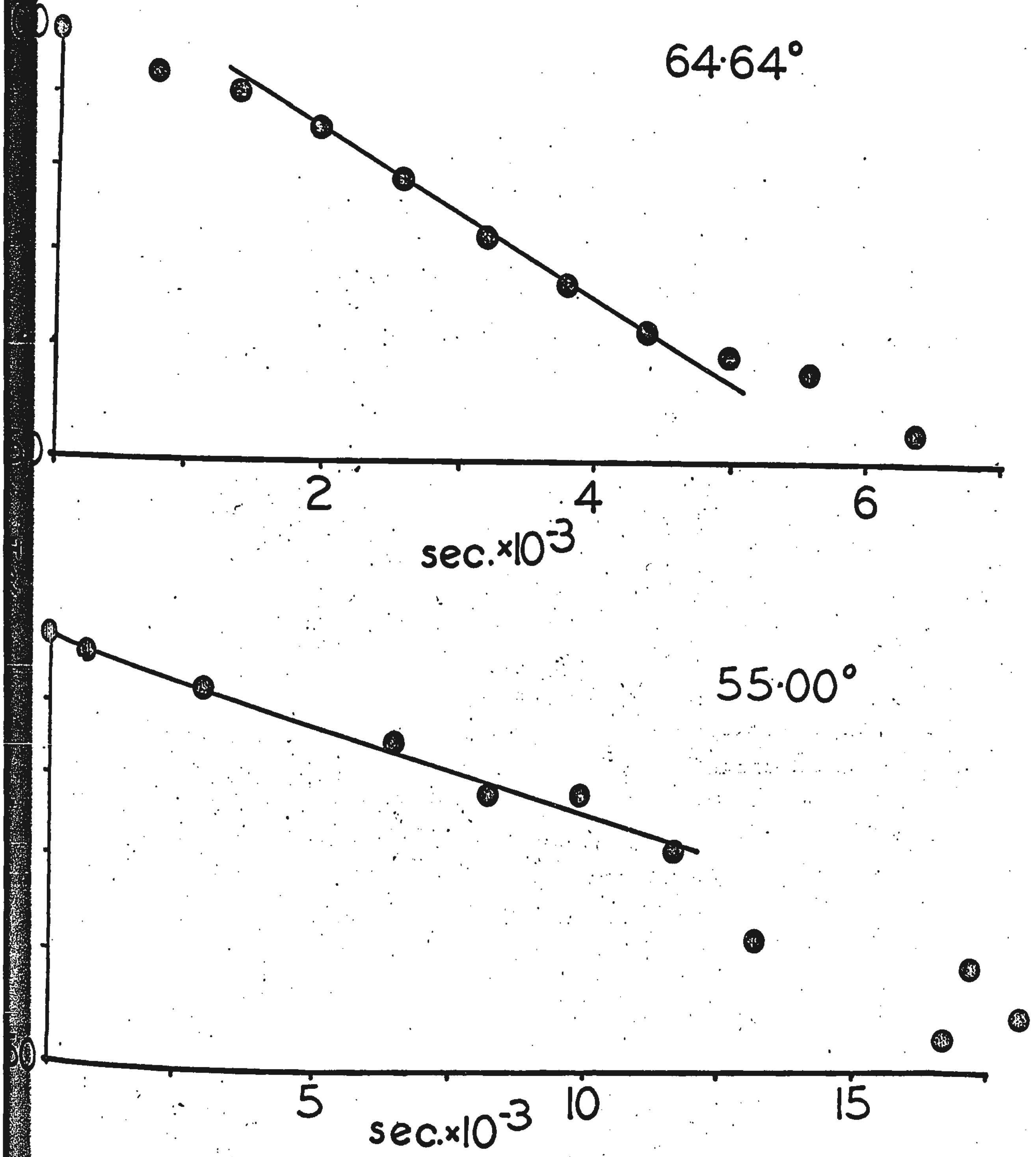


Fig. 11b.

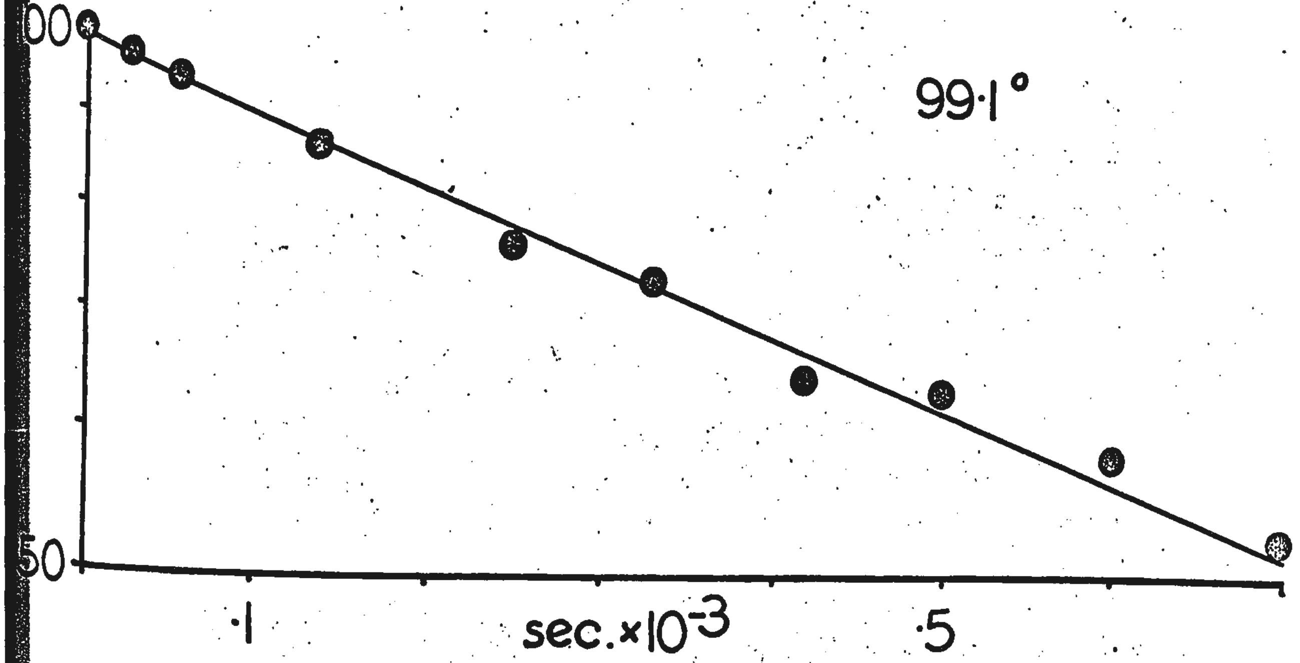
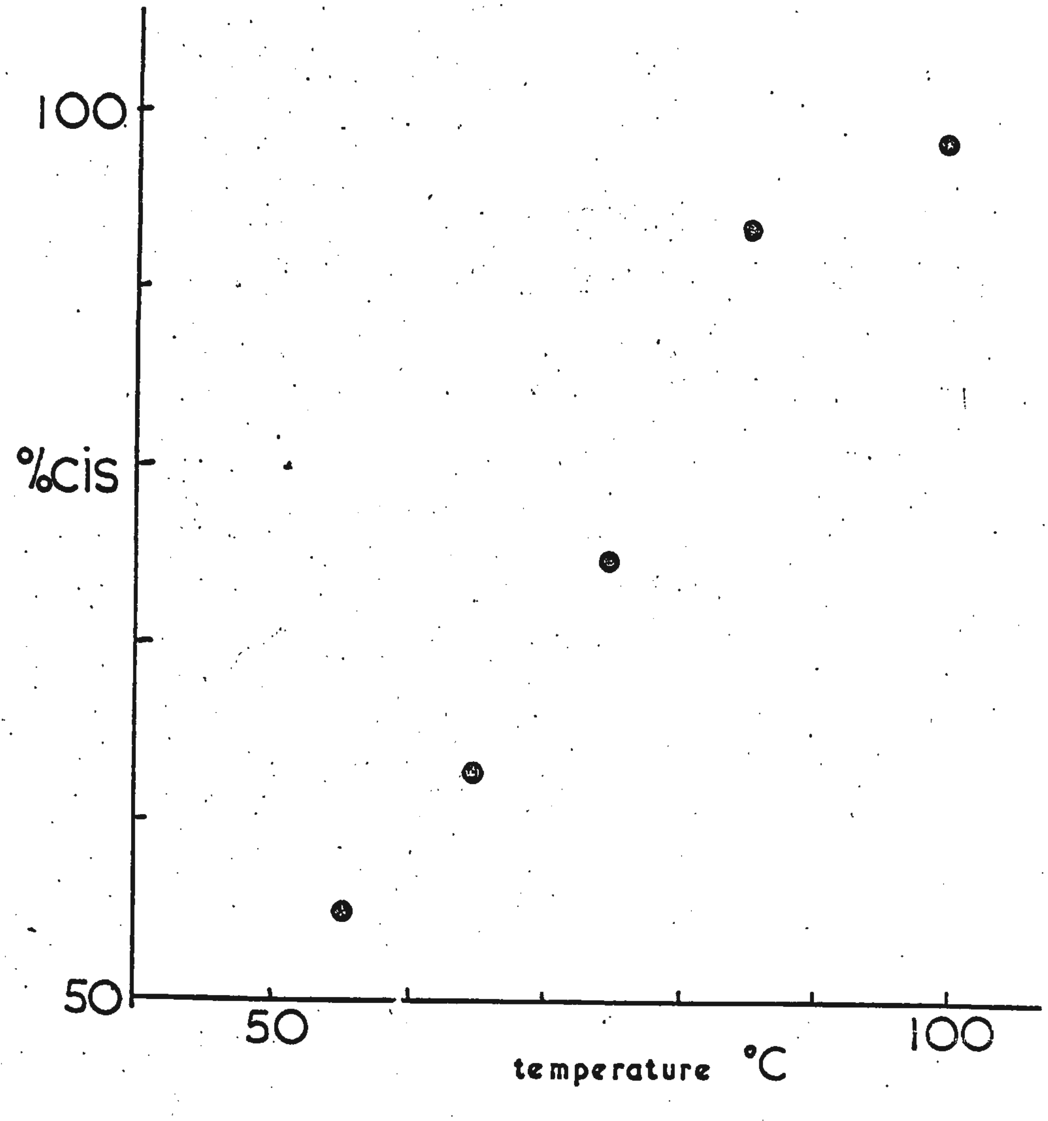


Figure 12. The point (approximate) in the reaction at which the nitrile is completely fused plotted against temperature of reaction (sample B).

FIG. 12



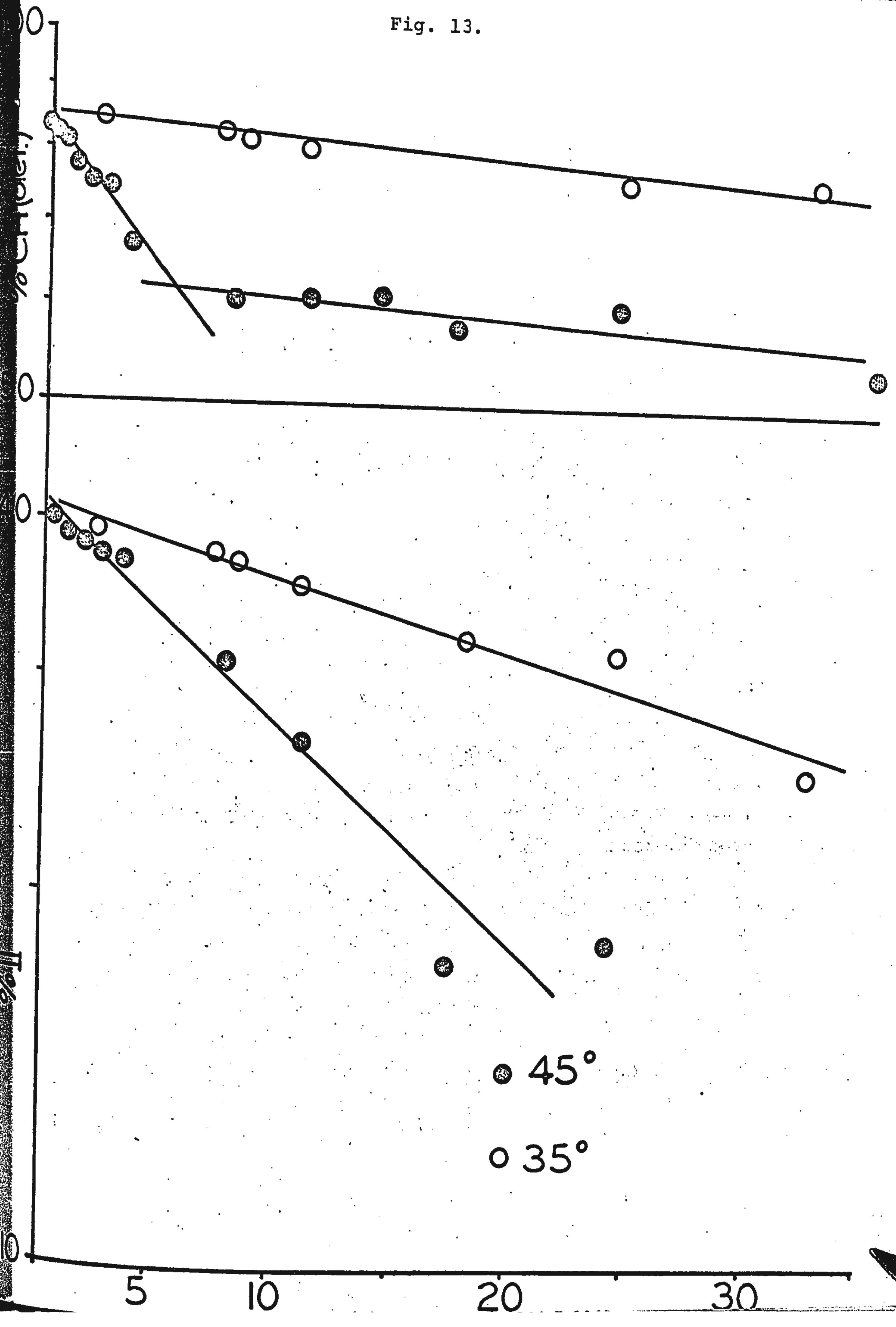
of the reaction is compared with the approximate point when the sample is completely fused). There appear to be two competitive reactions going on: isomerization in one direction in the solid state, and in the other direction in the fused state. At the lower temperatures, the solid state reaction is obviously more important, as a greater proportion of solid is present. This leads to the observed scattering. The higher temperature reactions appear to be closer to pure fused state reactions, when straight forward kinetics might be expected.

Figure 11a of the run at 65°C is particularly interesting. There appears to be an induction period. This might be caused by the necessity of some product nuclei to be present for the reaction to take place (38). The first traces of mixture (m.p. 46°C) formed would fuse and thus might dissolve additional cis isomer, enabling it to occupy another possible reaction site. That this appears to be a solid - liquid reaction also presents problems.

Some of the results of the kinetics using sample deuterated on the nitrogen are reported in figure 13. Figure 13b shows the first order curve obtained for the isomerization reaction, and figure 13a that of the rate of hydrogen deuterium exchange between the amine nitrogen and the α carbon atom. The curve representing the reaction at 35°C is unexceptional, though more scatter is to be expected than is observed with the isomerization type curves, since the integration on the CH portion of the spectrum is not as accurate as on the larger CH_3 peaks. (See experimental).

Figure 13. Isomerization of deuterated mixed β-aminocrotononitrile to the cis isomer; (a) $\log_{10}$ concentration of disappearing olefinic CH vs. time and (b) $\log_{10}$ change in total trans isomer vs. time.

Fig. 13.



The curve representing the 45°C run is interesting because the exchange takes place very fast at first, and then rapidly tails off. As noted above, a mixture of cis and trans isomers at 45°C first appears to fuse on the edges. In the fused state, intermolecular hydrogen exchange might be expected to be rapid. The second portion of the graph represents the exchange rate of the resolidified melt. This fusion might explain the slight pseudo induction period in figure 13b (at 45°C), and also the slight scatter.

Figure 14 represents the results obtained with the ultrasonic probe. At 42.5°C there was some difficulty controlling the bath containing the probe, yet both lines appear superimposable. The same is true of the high temperature runs (69.33°C), even though more scatter is noticeable here. This, again, is probably due to a mixture of fused and solid mode reactions. Thus, ultrasonic sound (20 Kcps.) appears not to influence this reaction, leading one to believe an intramolecular process must be involved in the solid state mixture to cis reaction.

Arrhenius type plots were made on the above data, and are reported in figures 15 and 16. Figure 15 is the low temperature plot using two different samples of mixture (see experimental), plus the deuterated samples. All the samples appear to give surprisingly good straight lines. (The runs at 0°C are not included, as they took over a month to carry out, and the likelihood of decomposition over such a period is high). For sample A,

Figure 14. First order reaction curves obtained with solid samples using the ultrasonic probe.

FIG. 14

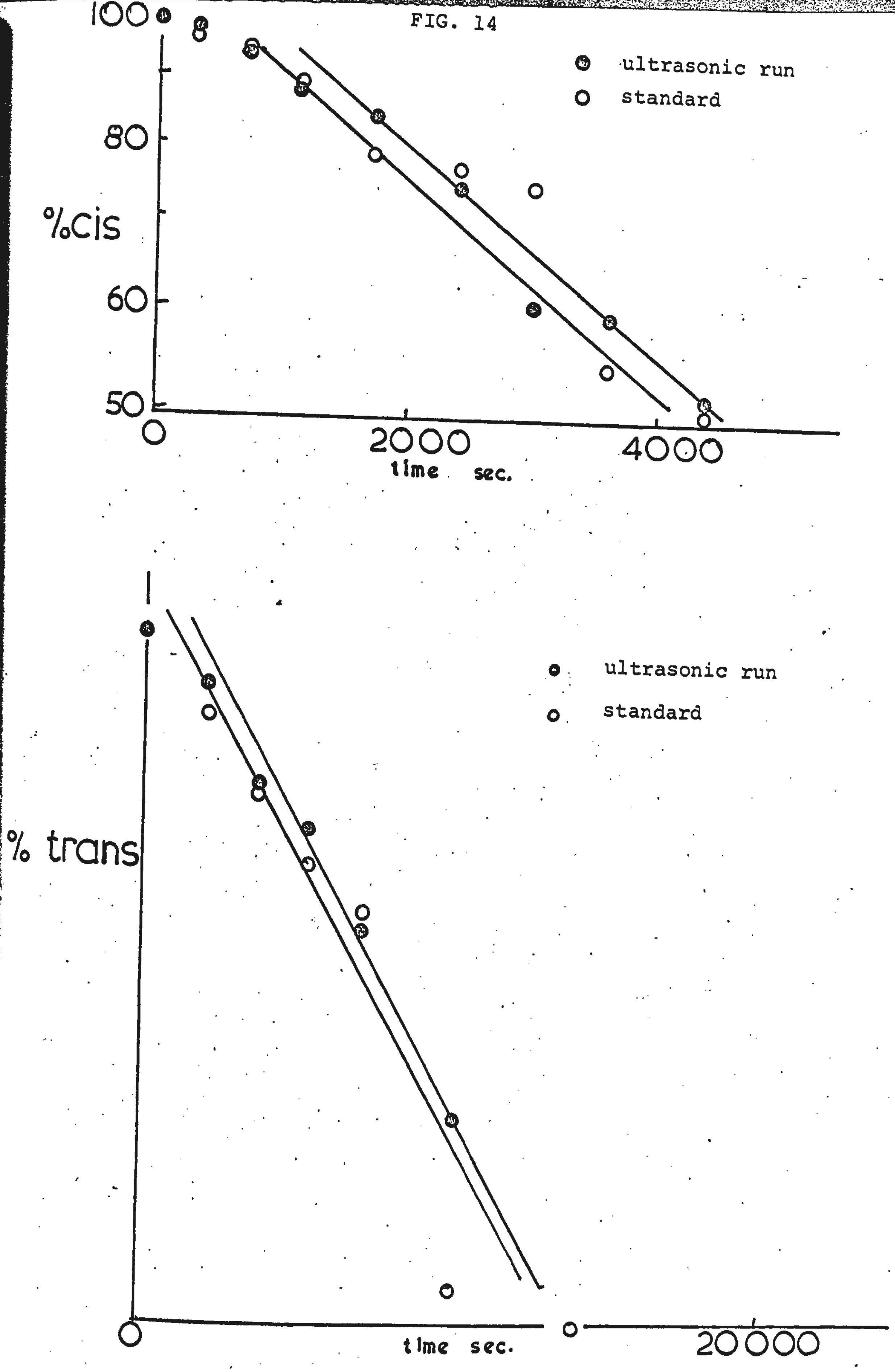
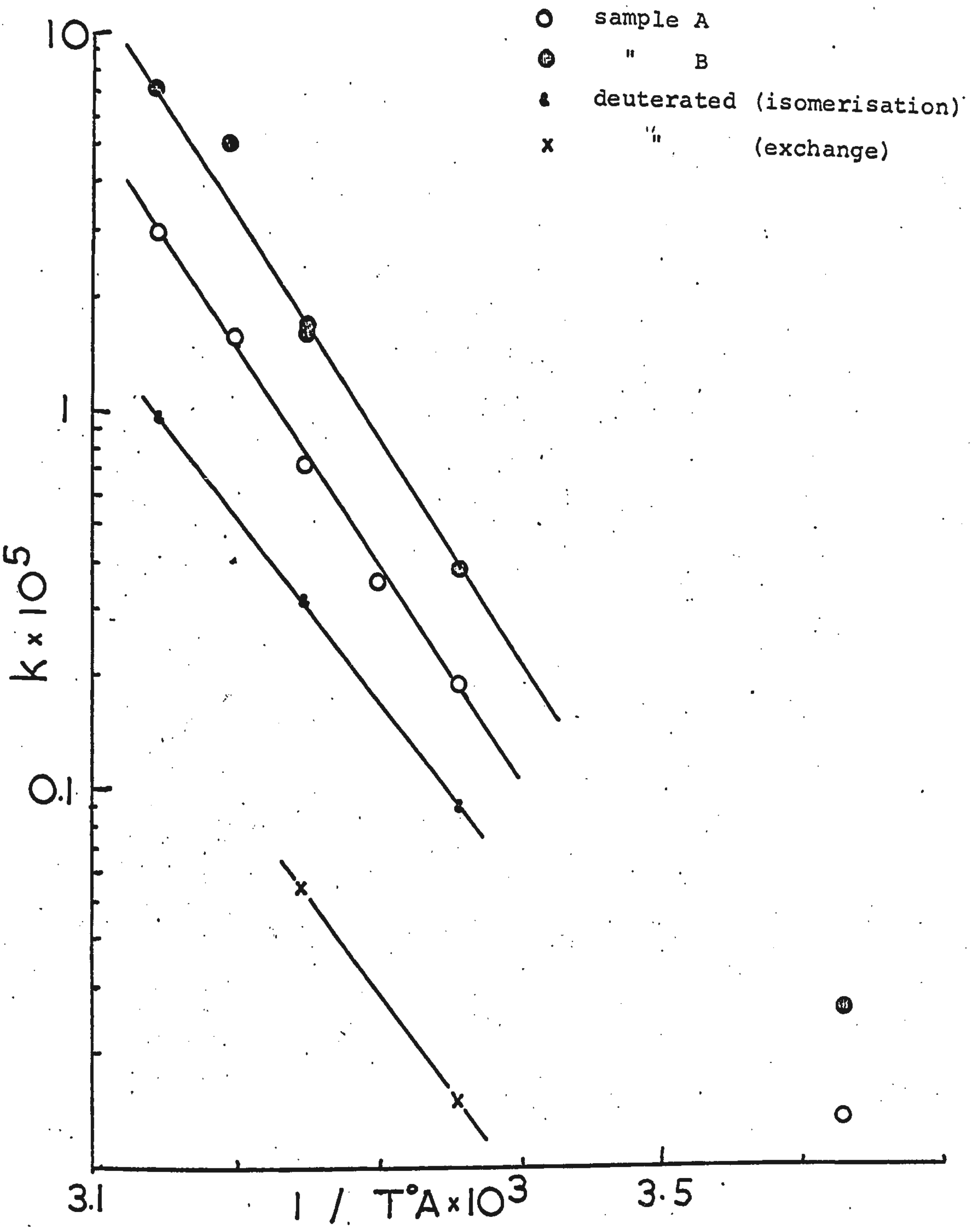

100
80
60
50
%cis
0
2000
4000
time sec.
● ultrasonic run
○ standard
% trans
0
time sec.
20000
● ultrasonic run
○ standard

Figure 15. $\log_{10}$ 1st order rate constant vs. reciprocal of absolute temperature for the low temperature solid state isomerization.

FIG. 15


○ sample A
● " B
• deuterated (isomerisation)
x " (exchange)
10
1
0.1
k × 10^5
3.1
3.5
1 / T°A × 10^3

the activation energy is 28.7 kcal./mole, and the frequency factor $10^{15.7}$; those for sample B 26.4 kcal./mole and $10^{13.6}$ respectively. From these plots, the entropy of activation at 25°C is ±13.1 e.u. for sample A +3.7 e.u. for sample B. (See also table 8).

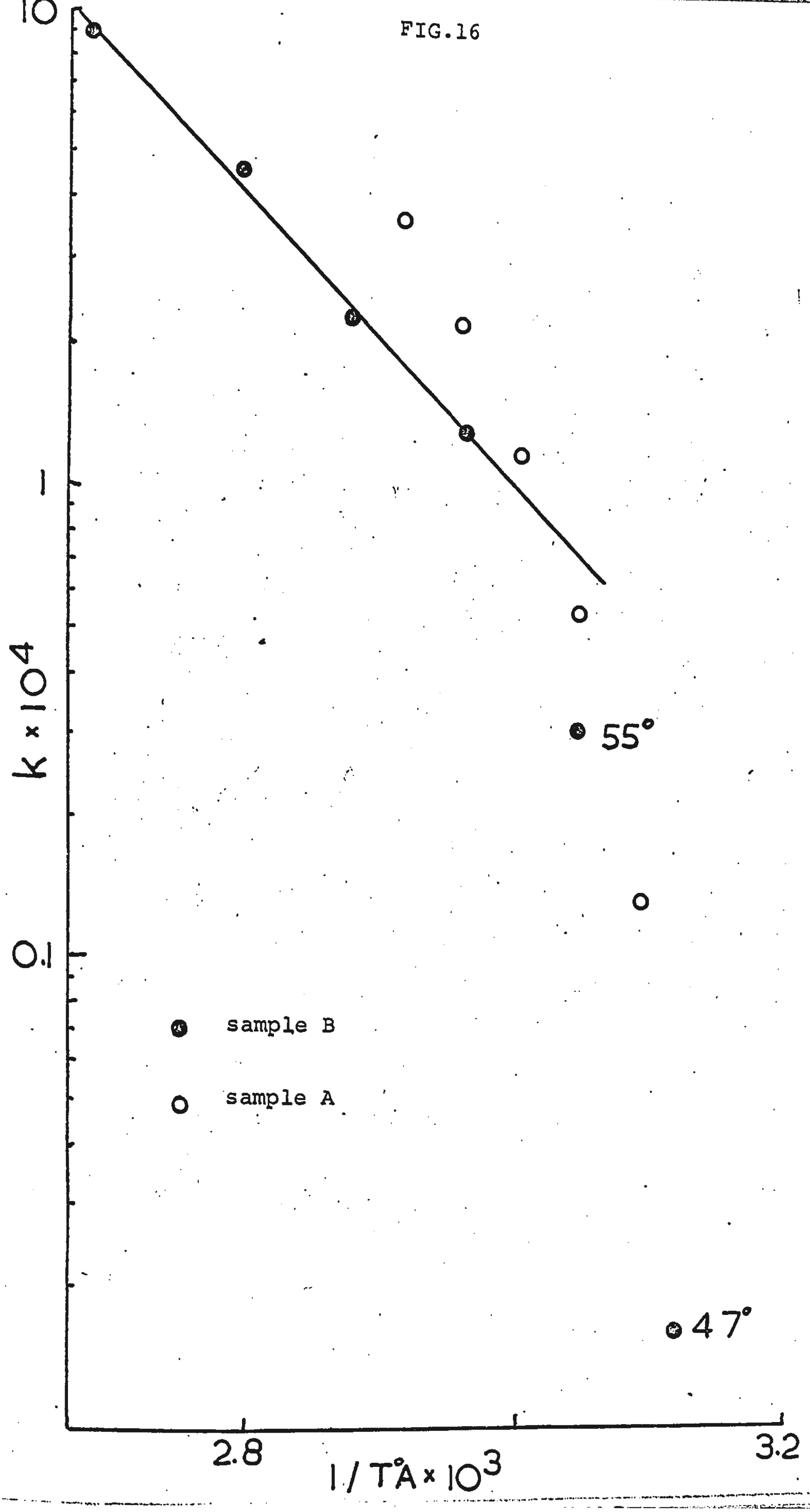
For the deuterated sample, the Arrhenius type plot gives E_a = 22.3 kcal./mole for the isomerization, and 23.6 kcal./mole for the exchange. (The E_a results were obtained by applying the rate results to a non weighted least squares type approximation). The frequency factors are $10^{10.3}$ and $10^{10.5}$ respectively.

From these results, there appears to be a deuterium isotope effect of k_H / k_D - 2.5, thus indicating hydrogen (deuterium) exchange is an important factor in the isomerization. As the deuterated sample could not be recrystallized from benzene because of the danger of further deuterium exchange to the carbon atom, the deuterated and nondeuterated samples might be expected to be of different purity, and thus give different rates. The presence of an isotope effect is thus not strictly proven and the value reported is almost certainly subject to great error. The rate of isomerization is about six times faster than the rate of deuterium exchange. As the compound is not purely deuterated on nitrogen and non-deuterated on the α carbon, there are many species present, all of which will isomerize at different rates. Thus, these results cannot be easily treated statistically. Also, the accuracy of k (exchange) is poor. (A rough statistical calculation assuming $k_H / k_D = 6$ predicts the rate of exchange to be ≈ 3.3 times slower than k (isomerization), not too far from the observed value of 6, considering no correction was applied for loss of deuterium from the nitrogen atom during isomerization).

The activation energy curve for the high temperature isomerization of samples A and B is shown in figure 16, and that of sample B (assumed to be purer) is linear from 65 to 100°C, indicating that these runs represent a fused state isomerization. The runs at 55°C and 47°C are considerably slower than would be expected, and lead to a curved Arrhenius plot. At the lower temperatures, however, as stated above, there appear to be competing reactions. In the solid state, β-aminocrotononitrile appears to attain a thermal equilibrium with > 95% of cis isomer. There is evidence (28) that mixture exists as a "dimer" containing one molecule of each isomer, this being the most stable (low energy) form. In the solid state, however, if there were a mechanism by which the dimer breaks down, the trans isomer being transferred into the cis isomer during the process, and if these two molecules now move apart by molecular collisions, then two molecules must collide to reform the mixture (and thus allow trans isomer to be formed again). The probability of this happening in the solid state is much less than in solution of the fused state. At temperatures above 46°C (m.p. of the mixture), a little mixture is formed, and then melts. This in turn dissolves more cis, which may react with solid (or fused) cis, forming more dimer, this process being slower than in the pure fused reaction, because of the extra energy required to dissolve

Figure 16. Log$_{10}$ 1st order constant vs. reciprocal of absolute temperature for the high temperature (neat) isomerization.

FIG.16



the material. There also must be reaction striving to reverse the process in the solid state, and thus the high temperature runs with solid material present might be expected to be slow, as in the case. The activation energy for the straight portion of the graph is 14.3 kcal./mole, and the frequency factor $10^{5.4}$. Other values for this system are reported in Table V.

(b) Solution

In solution β-aminocrotononitrile forms an equilibrium mixture containing an excess of the trans isomer. Thus, rate studies of the isomerization from the pure cis form were studied in anisole. The results were very discouraging, and seemed to be incapable of simple chemical explanation. The only reproducible results that could be obtgained were with samples from the same preparation of solution, and even this failed sometimes. The use of a new solution from the same materials gave a different rate. The data obtained are shown in Figure 17 and Table VI.

Several runs were attempted using different reaction vessels, cleaned out and aged as described in the experimental section. These results are given in Table VII. It is interesting that even a silica container supports a rate of reaction faster than that of a new n.m.r. tube.

The solution isomerization appears to be very "surface sensitive". The acid catalysed runs (see below)also show that the reaction is very sensitive to acidic impurities. As there are many other species which catalyse cis-trans isomerizations, this

Figure 17. Log$_{10}$ 1st order rate constant vs. reciprocal of absolute temperature for the isomerization of β-aminocrotononitrile in solution. (new n.m.r. tubes were used as reaction vessels).

FIG.17

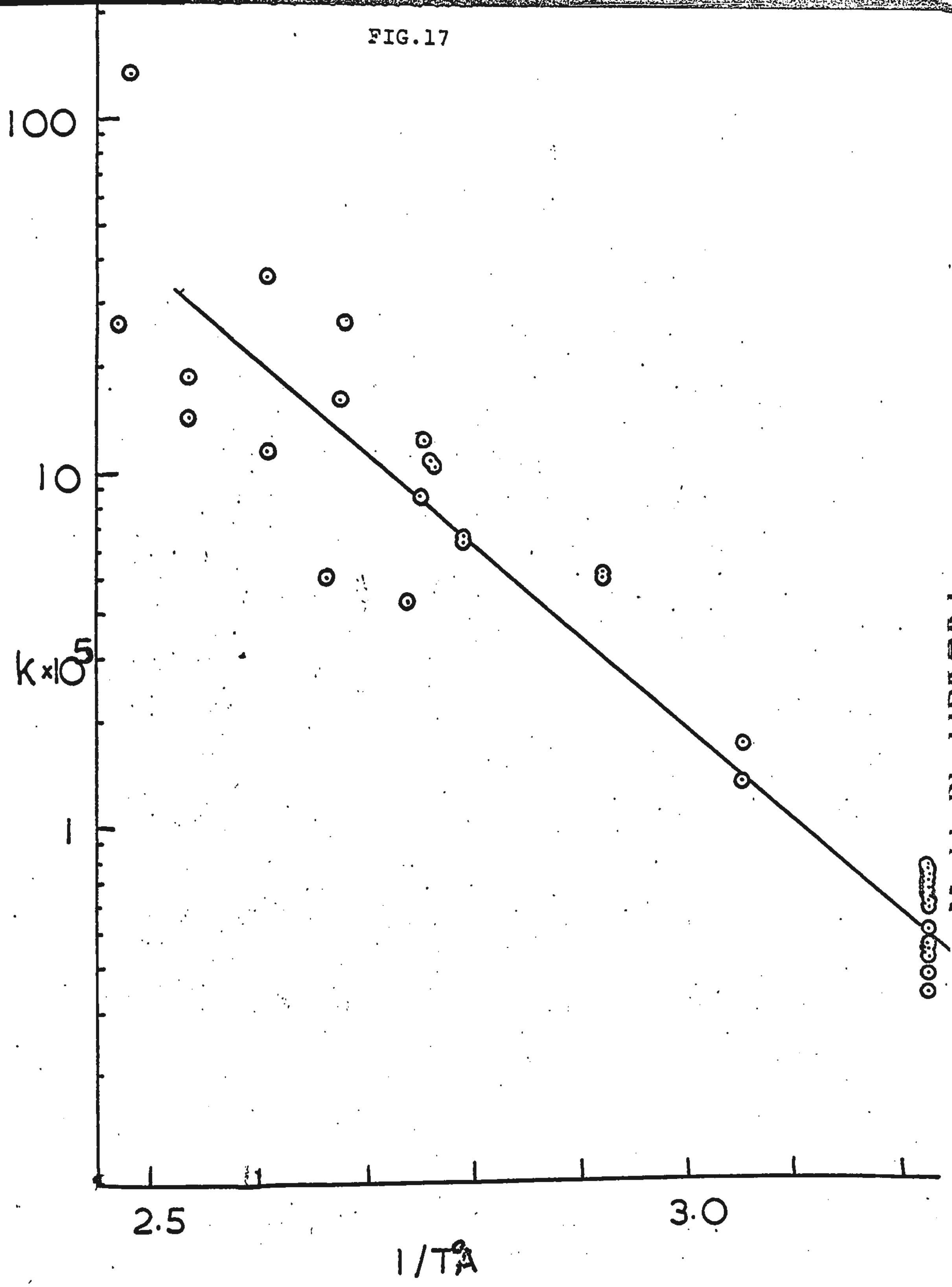


TABLE VI

First order rate constants for cis-trans isomerization of β-aminocrotononitrile in anisole solution, using "new" n.m.r. tubes as the reaction vessels.

Temp. °C	k 1st order	Concentration nitrile (Molal)	Comments
131.5 ± 1	2.654×10^{-4}	.3735	1
121.0	1.450×10^{-4}	"	1
110.5 ± 1	1.187×10^{-4}	"	1
102.6	5.059×10^{-5}	"	1
92.2	4.306×10^{-5}	"	1
130.0	1.342×10^{-3}	.1155	1
120.8	1.886×10^{-4}	"	1
110.5	3.657×10^{-4}	"	1
100.5	1.652×10^{-4}	"	1
91.0	8.681×10^{-5}	"	1
100 ± 1	2.671×10^{-4}	.255	1
90.5 ± 1	1.266×10^{-4}	"	1
89.5	1.075×10^{-4}	"	1
89.2	1.042×10^{-4}	"	1
54.73	1.026×10^{-5}	.4385	2
54.73	1.336×10^{-5}	.4211	2
69.35	4.094×10^{-5}	.4385	2
69.35	3.937×10^{-5}	.4211	2
85.50	5.132×10^{-5}	.4385	2
85.50	4.932×10^{-5}	.4211	2

TABLE VI Continued

Temp. °C	k 1st order	Concentration nitrile (molal)	Comments
37.45	7.767 x 10^{-6} ±	.3894	3
"	3.822 x 10^{-6} ± .96%	.3894	3
"	4.621 x 10^{-6} ±	.5653	3,4
"	4.280 x 10^{-6} ±	.5653	3,4
"	7.211 x 10^{-6} ±	.2097	3,4
"	4.536 x 10^{-6} ± 1.8%	.2097	3
"	7.620 x 10^{-6} ±	.4488	3
"	6.639 x 10^{-6} ± 2.4%	.6029	3
"	6.352 x 10^{-6} ± 1.9%	.1780	3
"	5.125 x 10^{-6} ± 1.4%	.2509	3
"	7.044 x 10^{-6} ± .88%	.3561	3
"	5.969 x 10^{-6} ± 1.4%	.3450	3
"	7.897 x 10^{-6} ± .39%	.5722	3
"	3.390 x 10^{-6} ± 1.4%	.1720	3

1. Runs in n.m.r. probe, rates calculated from graphs only.
2. Runs in constant temperature baths, rates roughly calculated from one point at each time (graph).
3. Runs in constant temperature bath, rates calculated by computer.
4. These rates are from "aged" tubes.

TABLE VII

Kinetics at 85.50°C of β -aminocrotononitrile isomerization in solution, using reaction vessels as indicated.

+

Type Pot	Rate* kx10^4	Concentration nitrile (molal)
Soft glass pot, treated with HNO_3 once Plastic stopper	2.415	.4385
Soft glass pot, treated with HNO_3 twice plastic stopper	4.584	.4385
Pyrex test tube, treated with HNO_3 once aged, ground glass stopper	2.848	.4211
Pyrex test tube, new, not treated, ground glass stopper	6.134	.4211
Silica container, no stopper, treated with HNO_3 and aged	2.032 1.147*	.3972
Silica container, no stopper, as above but aged again	2.065≠ 1.190*	.3972
new n.m.r. tube, untreated	.5132	.4385
" " " "	.4932	.4211

≠ These rates are only roughly calculated, usually using only one integration / time, and 6 to 10 times. They are graphical rates only, and not from least squares, thus no estimate of errors can be given.

* There are two rates reported for each reaction in silica pots because the reaction line is curved. The first rate reported is for the whole curve, and the second for the portion between 45 and 65% cis.

system has proved impossible, as yet, to deal with accurately.

To eliminate the surface effects, a silica container (with silica stopper) should be cleaned as described in experimental, and then baked out for several days in an oven set just below the fusion point of silica. After further ageing with the solvent, consistent results might be obtained.

The anisole appears to cause no catalytic effect, although minute traces of moisture which were present in some of the runs could catalyse the reaction. A test run indicated large quantities of water had no great effect on the system. This would be expected, as the K_A of water is only 1.79×10^{-16} (25°C) (39, p. 91). The acid catalysed results (see below) would seem to indicate the non-catalysed reaction would be faster than any expected catalytic effect from this source.

Another very important detail in the rate studies is the preparation of pure nitrile, as there are no absolute criteria of purity. The melting point is over a wide range due to isomerization. It is possible (though not likely) that some sodium hydroxide has remained in the reaction mixture, even after treatment with $MgSO_4$ and recrystallization. (The reaction is also base catalysed (28). Cundall (4) warns that some of the cis-trans isomerization rate studies reported in the literature might be on impure samples, thus leading to erroneous results).

Some of the runs (one full set from 90 - 130°C) (see figure 18 for example) did not give straight lines when plotted as first order graphs. These results, calculated as first order, represent the slowest (and thus best) set of results. It is possible, when no surface or catalytic effects are present, that the reaction is self-catalytic. The cis monomer would be a weak base because of the NH_2 group, and thus could catalyse the reaction. As the trans isomer is formed, and presumably as it forms the bonded dimer with the cis, the catalytic effect of the NH_2 group would decrease, and the curve of figure 18 would result. Unfortunately, attempts to repeat these results failed. If, however, the above explanation were correct, the reaction rate should be dependent upon the concentration of the substrate.

As these runs were done in "new" n.m.r. tubes, the surface composition of which is not known, there is a possibility that any coating might serve as a negative catalyst. A lot more work appears to be needed on the non-catalysed solution isomerization of β-aminocrotononitrile.

Different solutions at 37.45°C gave the graphs shown in figure 19. Figure 20 shows a rate versus concentration plot of runs at this temperature (done in "new" n.m.r. tubes), and the inherent difficulties in the system are obvious.

Assuming concentration of substrate has no effect, as seems to be the case, (if these reactions are catalysed by an unknown catalyst, a non-catalysed system would be very concentration dependent), an activation energy from figure 17 is roughly 12 kcal./mole with a frequency factor of 10^3, these values indicating the reaction is analogous to the high temperature "solid" state reaction.

Figure 18. First order plot obtained for a solution run (non catalysed in anisole) in the n.m.r. probe using the Varian variable temperature attachment as a constant temperature source.

Figure 19. First order rate plots for solution runs at 37.45°C showing the non-reproducibility of the results.

FIG. 18

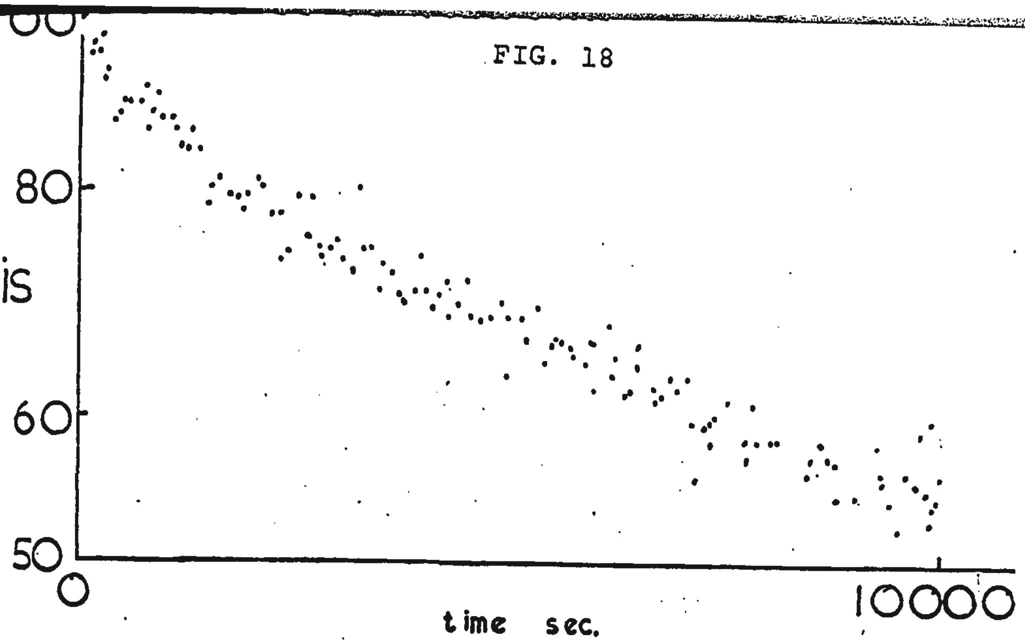

100
80
60
50
%cis
0
10000
time sec.

FIG.19

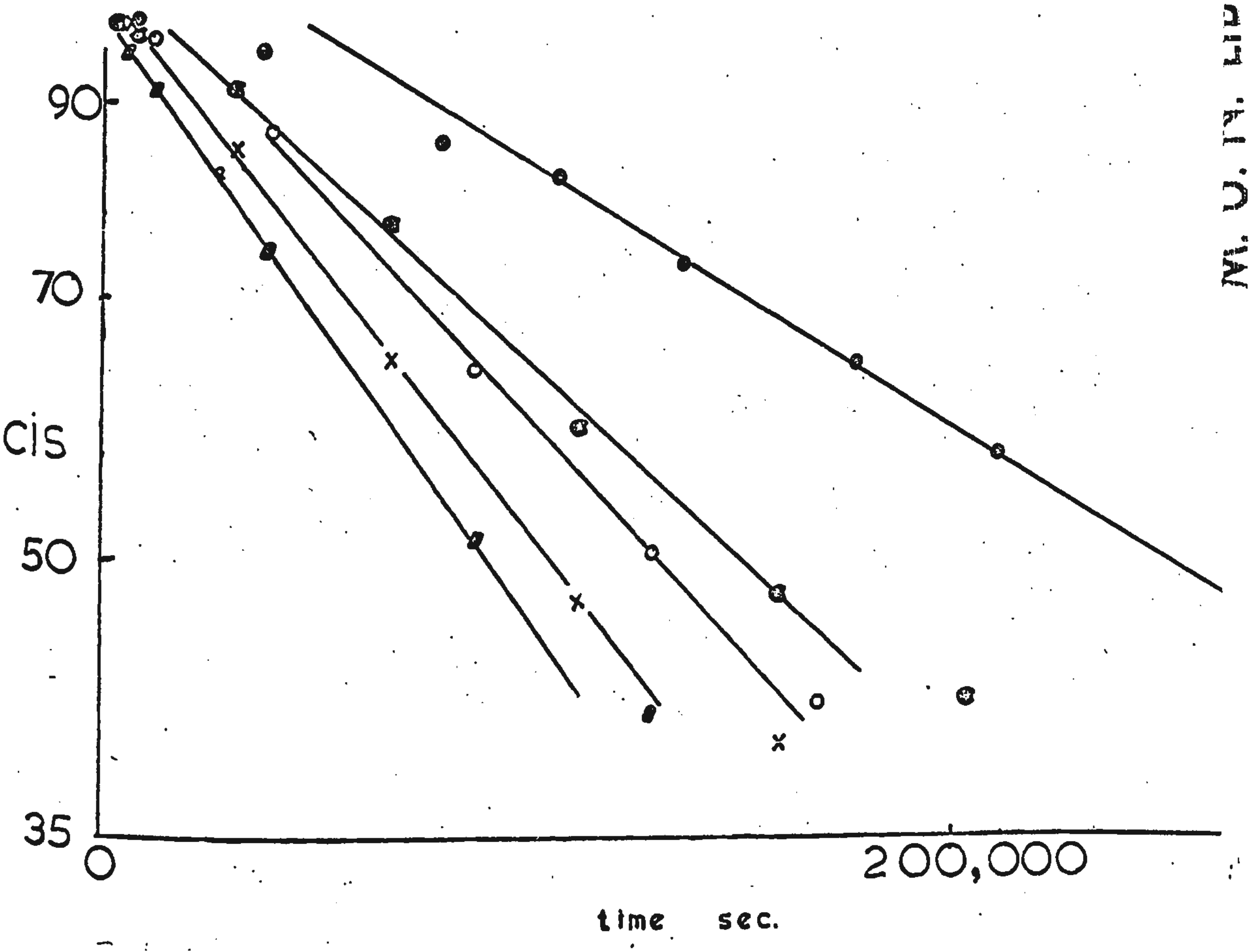
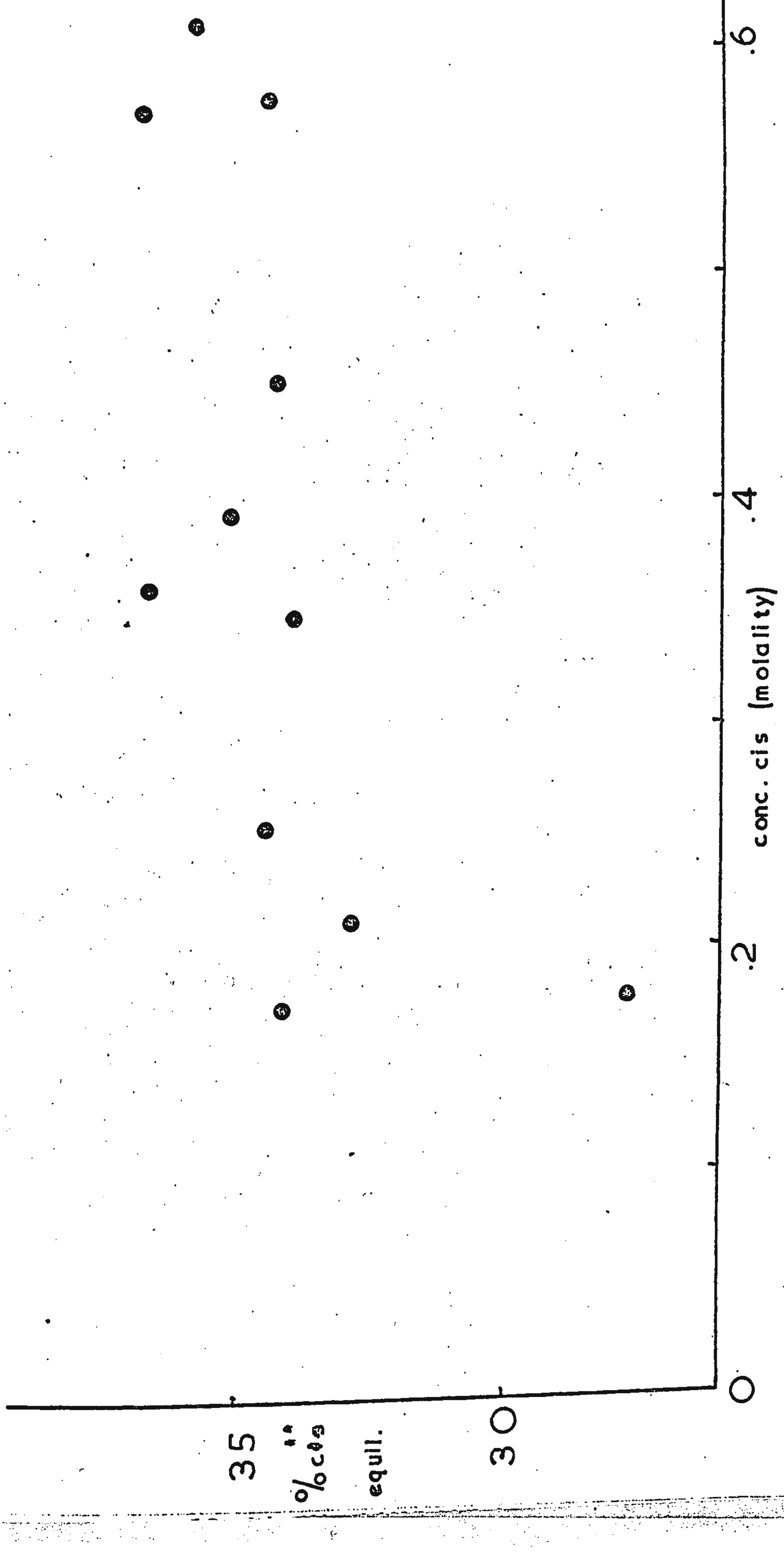

90
70
50
35
%cis
0
200,000
time sec.

Figure 20. Solution rate constants vs. concentration nitrile.

FIG. 20



(c) Acid catalysis

The rate of isomerization, with a series of phenols as catalysts, was studied to determine a Brönstead constant for the system.

Bell (39, p. 103) reports that in aprotic solvents, such as benzene, the velocity of an acid catalysed reaction is not simply proportional to the first power of the catalyst and substrate concentrations, but follows more complex laws. This non-linearity is caused both by the association phenomenon of carboxylic acids and in some cases by chemical association, and also kinetic medium effects due to dipole forces in solvents of low dielectric constant. That is, the effective behaviour of the catalyst is not linear with concentration, but shows an abnormal thermodynamic behaviour because of strong inter-dipole forces between the catalyst molecules. These dipole fields would not interact as strongly in solvents of higher dielectric constant, as the more ionic nature of the solvent would tend to lessen these effects.

Acid - base strength is dependent on the acid - base properties of the solvent, and ordinarily K measures the relative acid strength compared with that of the solvated proton. It is fortunate that for a series of acids of the same charge type, the relative strengths are approximately independent of the solvent. Deviations from this are rarely greater than a power of 10. As the Brönstead relation is an approximation in the first place, there is considerable justification for using K_{eq}. from water solutions in aprotic solvents.

An example of an aprotic solvent reaction is the acid catalysed rearrangement of N-bromacetanilide in chlorobenzene. Here, Bell fitted the results to the equation

$$k = ac - bc^2 \qquad (6)$$

where the constant a was taken as the catalytic constant, and c the concentration of catalyst. In the present case, an additional term is added to equation 4, and then:

$$k_{obs} = k^{o} + ck_{cat} + qc^{2} \qquad (7)$$

In both cases, the slope at infinite dilution (k_{cat}) is the catalytic rate constant. Surprisingly, with the inherent difficulties, consistent results are still obtained.

The rates obtained for the acid catalysed isomerization of β-aminocrotononitrile are shown in table VIII and figures 21 - 24. As they were not notably reproducible, only four phenols were used in the study. Some representative runs are plotted (as first order) in figures 25 to 28.

Figure 25 is a first order rate plot of two of the runs with equal concentrations (.01713 m) of sym-trichlorophenol, but different concentrations of substrate. Both runs were with new n.m.r. tubes, and the slight difference in slope is attributed to some form of a systematic error, different for each system. Figure 26 shows a similar type plot for p-chlorophenol, but this time the lines are approximately parallel. (Note, these are representative runs for each system, and the type of plot shown for each phenol is not indicative of all the graphs obtained for that phenol). Similar graphs were obtained with m-nitrophenol (Figure 27 a & b). Figure 27b appears to represent curved lines. As this is not a general case, no attempt will be made to explain this effect. Probably some form of systematic error is involved. A run on the same solution (with p-nitrophenol), but using both

TABLE VIII

First Order Kinetic results for the acid catalysed isomerization of β-aminocrotononitrile in anisole solution, concentrations are molarities (at temperature of 37.45°).

Catalyst	Type n.m.r. Tube	(Catalyst)	(nitrile)	k $sec.^{-1}$	Equilibrium % cis
p-nitrophenol	b	.2978	.1947	1.508×10^{-3} ± 7.2%	40.19
	b	.2978	.2826	2.623×10^{-3}	39.06
	b	.2978	.1048	1.855×10^{-3} ± 6.3%	40.89
	b	.1262	.2244	7.442×10^{-4} ± 2.7%	36.18
	b	.1262	.3014	6.895×10^{-4} ± 2.5%	38.33
	b	.1262	.0890	4.986×10^{-4} ± 2.5%	35.42
	b	.0567	.1947	2.926×10^{-4} ± 1.4%	34.27
	b	.0567	.2826	*3.849×10^{-4} ± 1.6%	
	a	.0567	.2826	2.756×10^{-4}	
	a	.0567	.2826	*1.177×10^{-5} ± 12.0%	36.94
	b	.04144	.2244	1.577×10^{-4} ± 1.3%	34.36
	b	.04144	.3014	1.636×10^{-4} ± 1.3%	34.75
	b	.04144	.0890	8.838×10^{-5}	33.33
	a	.04144	.0890	8.514×10^{-5}	
	c	.02485	.2244	6.159×10^{-5} ± 1.9%	
	a	.02485	.2244	6.233×10^{-5}	35.39
		.02485	.3014	6.896×10^{-5} ± .96%	34.91
	d	.02485	.0890	5.877×10^{-5} ± 5.7%	
	a	.02485	.0890	4.776×10^{-5} ± 4.7%	32.86
	b	.01130	.1947	*4.731×10^{-5}	34.59
	a	.01130	.1947	2.745×10^{-5} ± 1.0%	34.60
	a	.01130	.2826	2.621×10^{-5} ± 7.8%	36.29
	c	.01130	.1048	*4.118×10^{-5} ± 4.7%	

TABLE VIII Continued

Catalyst	Type n.m.r. Tube	(Catalyst)	(nitrile)	k sec.$^{-1}$	Equilibrium % cis
	a	.01130	.1048	1.499×10^{-5}	36.67
	c	.01130	.1048	$2.099 \times 10^{-5} \pm 4.1\%$	34.05
	a	.01130	.1048	1.201×10^{-5}	
	b	.002276	.1947	$6.209 \times 10^{-6} \pm 1.6\%$	34.68
	a	.002276	.1947	7.757×10^{-6}	
m-nitrophenol	b	.3402	.1947	$5.369 \times 10^{-4} \pm 1.8\%$	40.21
	b	.3402	.2826	$5.720 \times 10^{-4} \pm 1.9\%$	
	b	.3402	.1048	$4.604 \times 10^{-4} \pm 2.2\%$	40.94
	b	.2002	.2244	$2.634 \times 10^{-4} \pm 1.4\%$	37.25
	b	.2002	.3014	$2.954 \times 10^{-4} \pm 1.3\%$	38.58
	b	.2002	.0890	$2.431 \times 10^{-4} \pm 2.3\%$	36.68
	b	.1158	.2244	$1.120 \times 10^{-4} \pm 1.1\%$	35.65?
	b	.1158	.3014	$1.136 \times 10^{-4} \pm 1.1\%$	38.78
	b	.1158	.0890	$1.117 \times 10^{-4} \pm 2.3\%$	35.07
	b	.0644	.1947	$*1.135 \times 10^{-4} \pm 1.3\%$	35.85
	b	.0644	.2826	$*9.717 \times 10^{-5} \pm 1.2\%$	
	a	.0644	.2826	5.165×10^{-5}	35.98
		.0644	.1048	5.206×10^{-5}	37.64?
	c	.03855	.2244	$*4.360 \times 10^{-5} \pm 4.2\%$	
	a	.03855	.2244	$2.844 \times 10^{-5} \pm 1.4\%$	34.00
	c	.03855	.3014	$*5.576 \times 10^{-5} \pm .93\%$	
	a	.03855	.3014	$3.756 \times 10^{-5} \pm 1.8\%$	36.00?
	d	.03855	.0890	$*9.827 \times 10^{-5}$	
	a	.03855	.0890	$4.445 \times 10^{-5} \pm 4.2\%$	32.91
	b	.01276	.1947	$*2.247 \times 10^{-5} \pm 2.4\%$	

TABLE VIII Continued

Catalyst	Type n.m.r. Tube	(Catalyst)	(nitrile)	k sec.$^{-1}$	Equilibrium % cis
	a	.01276	.1947	2.194×10^{-5}	36.27
	a	.01276	.2886	2.065×10^{-5} ± 1.2%	
	c	.01276	.1048	*3.014×10^{-5}?	
	a	.01276	.1048	1.830×10^{-5}	33.77
	c	.01276	.1048	1.687×10^{-5} ±6.5%	34.26
	a	.01276	.1048	1.398×10^{-5}	
p-chlorophenol	a	.6610?	.0860?	1.188×10^{-4} ±2.9%	32.70
	a	.6610	.1725	1.506×10^{-4} ± 1.9%	38.84
	a	.2444	.0860	2.405×10^{-5} ± 1.6%	32.74
	a	.2444	.1725	2.529×10^{-5} ± 1.7%	36.62
	a	.2326	.1254	2.769×10^{-5} ± 1.4%	33.76
	a	.2326	.1780	3.456×10^{-5} ± 1.3%	36.11
	a	.1192	.0860	8.718×10^{-6} ± 2.2%	34.29
	a	.1192	.1725	9.437×10^{-6} ± 1.4%	34.66
	a	.0759	.1254	6.239×10^{-6} ±2.3%	33.91
	a	.0759	.1780	5.858×10^{-6} ±1.4%	35.06
	a	.04461	.1254	4.158×10^{-6} ±1.2%	35.33
	a	.04461	.1780	4.277×10^{-6} ±1.7%	34.89
sym-trichloro-phenol	a & b	.0886	.1254	7.530×10^{-4} ±3.2%	29.64
	a & b	.0886	.1780	9.655×10^{-4} ±3.8%	35.47
	b	.04008	.0860	*3.962×10^{-4} ±5.3%	
	a	.04008	.0860	2.705×10^{-4} ±3.8%	24.68
	b	.04008	.1725	*4.179×10^{-4} ±2.2%	32.72

TABLE VIII Continued

Catalyst	Type n.m.r. Tube	(Catalyst)	(nitrile)	k $\sec^{-1}$	Equilibrium % cis
sym-trichlorophenol	a	.02748	.1254	$1.552 \times 10^{-4} \pm 2.0\%$	30.46
	a	.02748	.1780	$1.797 \times 10^{-4} \pm 2.9\%$	32.02
	a	.01713	.1254	$8.921 \times 10^{-5} \pm 3.3\%$	32.78
	a	.01713	.1780	$1.124 \times 10^{-4} \pm 2.1\%$	32.66
	a	.00794	.0860	$3.339 \times 10^{-5} \pm 2.4\%$	23.43
	b	.00794	.1725	*$8.505 \times 10^{-5} \pm 2.9\%$	
	a	.00794	.1725	$3.991 \times 10^{-5} \pm 2.0\%$	33.18?
	a	.00159	.0860	$6.178 \times 10^{-6} \pm 2.6\%$	31.44
	a	.00159	.1725	$8.374 \times 10^{-6} \pm 1.3\%$	30.98

* This rate not included in calculations

a new n.m.r. tube

b used n.m.r. tube, cleaned with HNO_3, etc.

c as b, but aged

d cleaned with ammonia, then aged

? doubtful result

Figure 21. First order rate constant (37.45°C) vs. concentration sym-trichlorophenol as catalyst in anisole solution.

FIG. 21

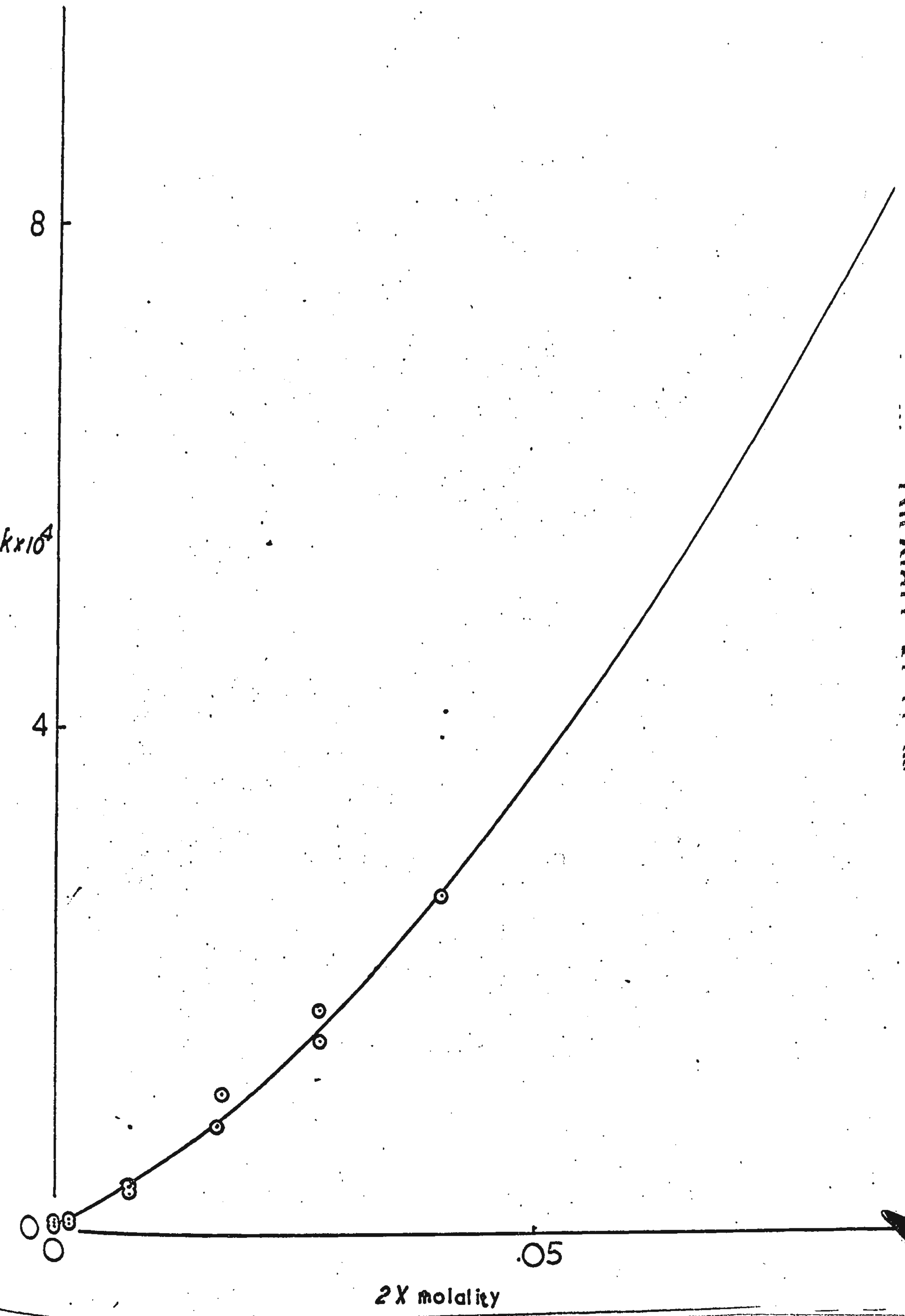


Figure 22. First order rate constant (37.45°C) vs. concentration p-nitrophenol as catalyst in anisole solution.

FIG. 22

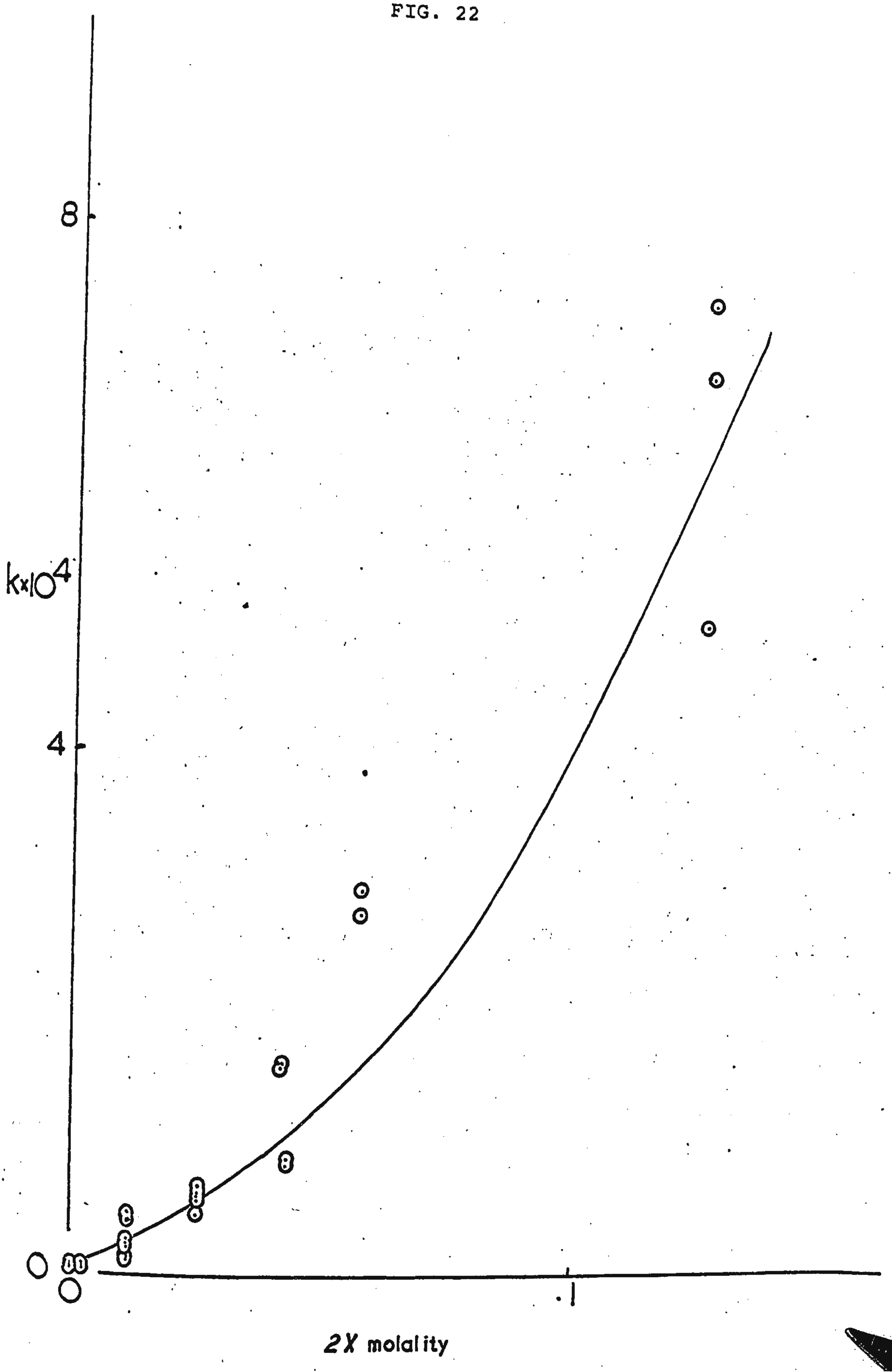


Figure 23. First order rate constant (37.45°C) vs. concentration m-nitrophenol as catalyst in anisole solution.

FIG. 23

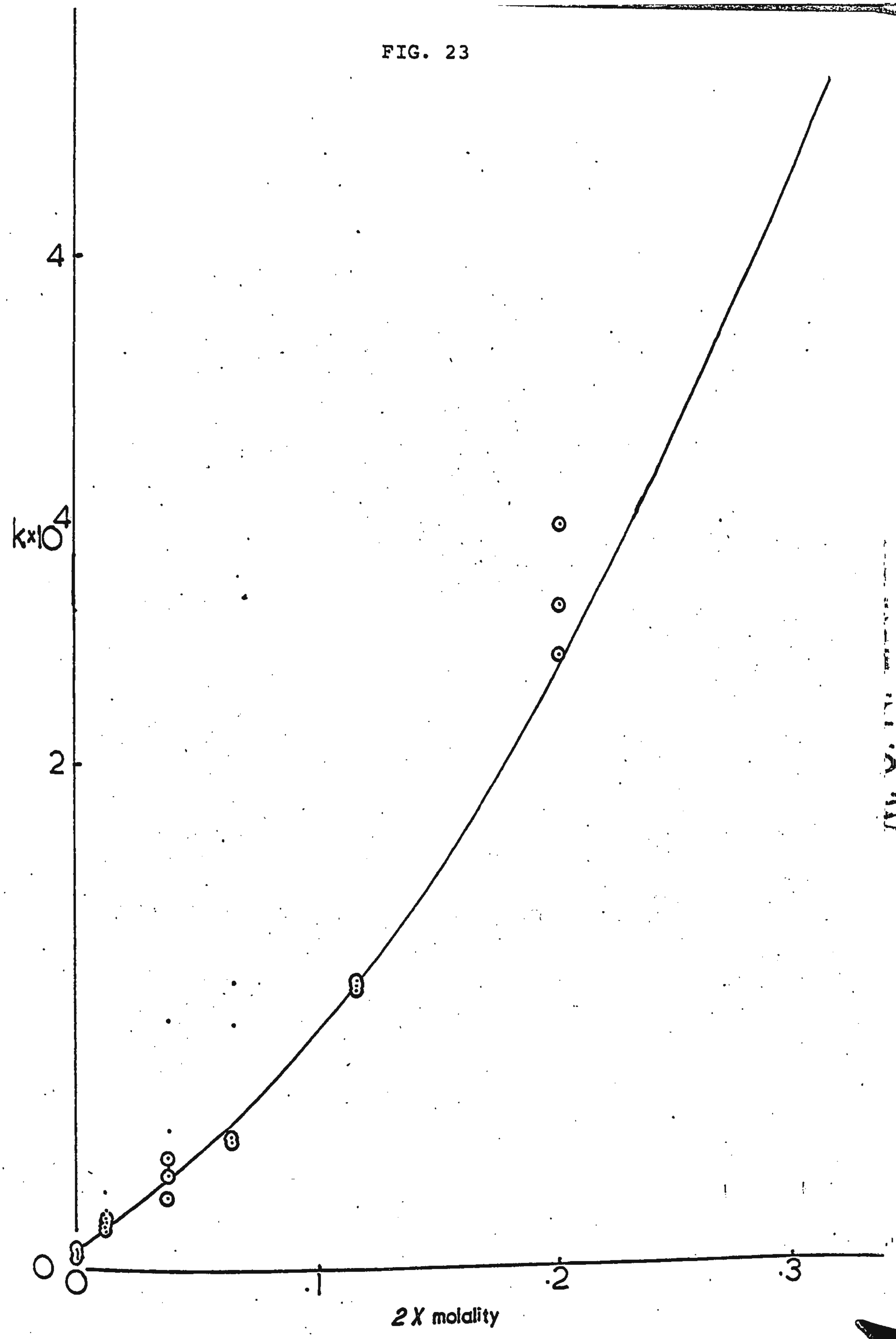


Figure 24. First order rate constant (37.45°C) vs. concentration p-chlorophenol as catalyst in anisole solution.

FIG. 24

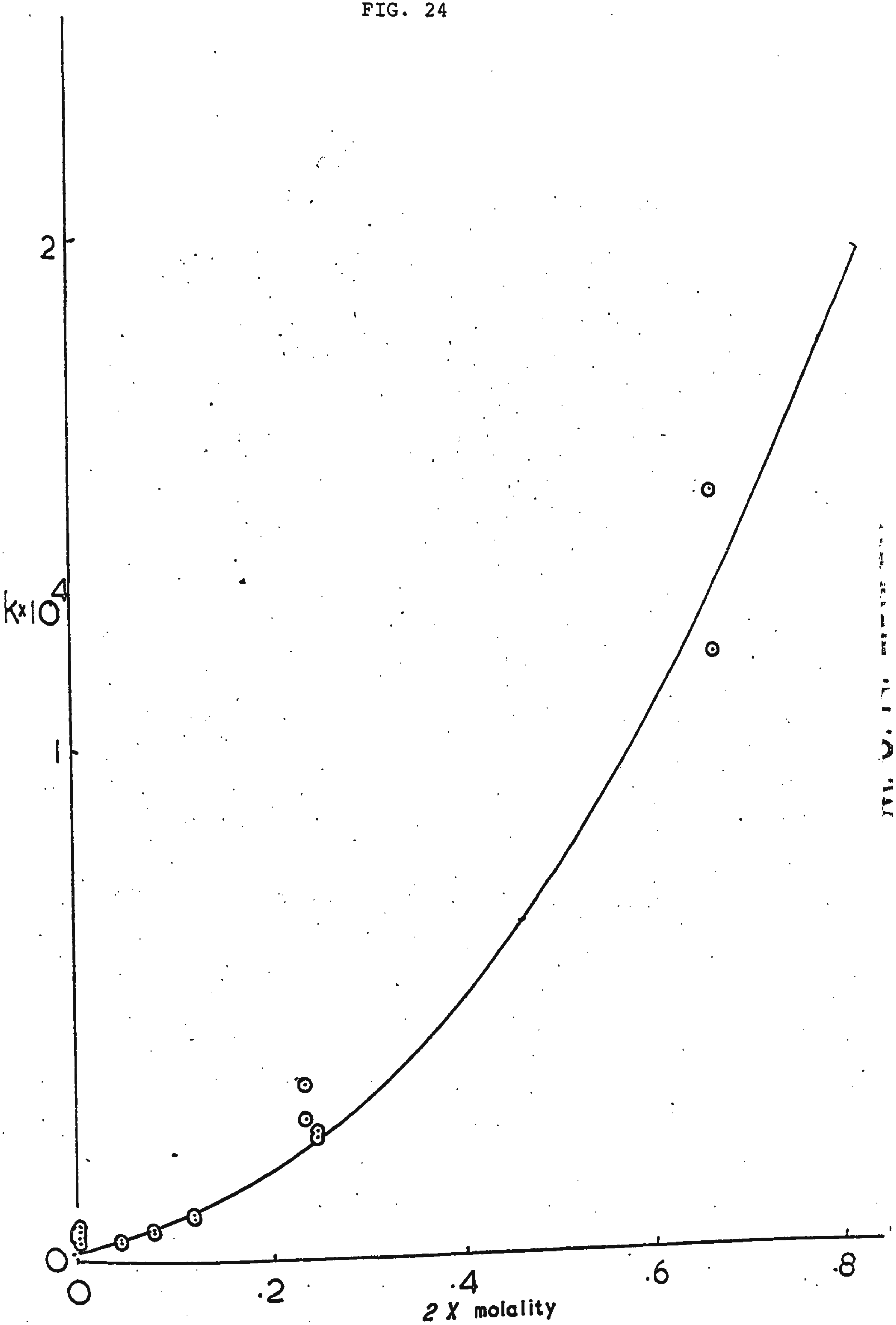


Figure 25. Example of acid catalysed first order rate plots sym-trichlorophenol catalyst.

Figure 26. Example of acid catalysed first order rate plots p-chlorophenol catalyst.

FIG. 25

"Solid and open circles are used to represent runs using different samples of the nitrile".

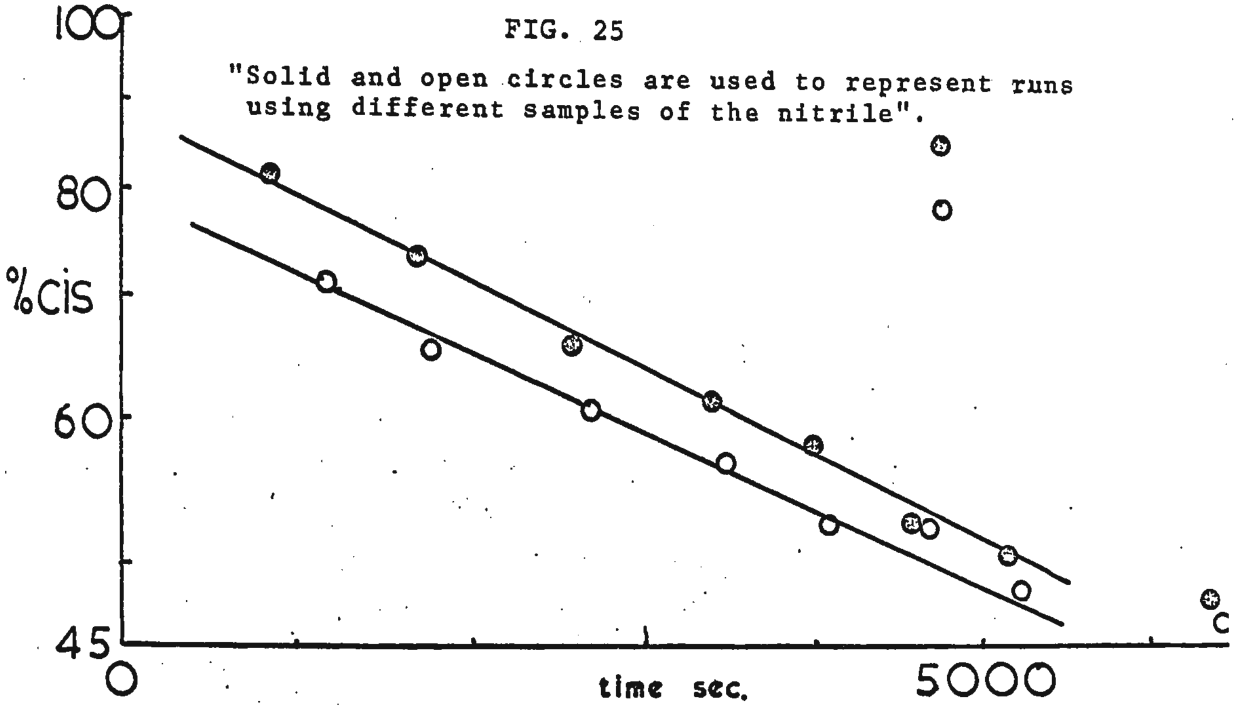


FIG. 26

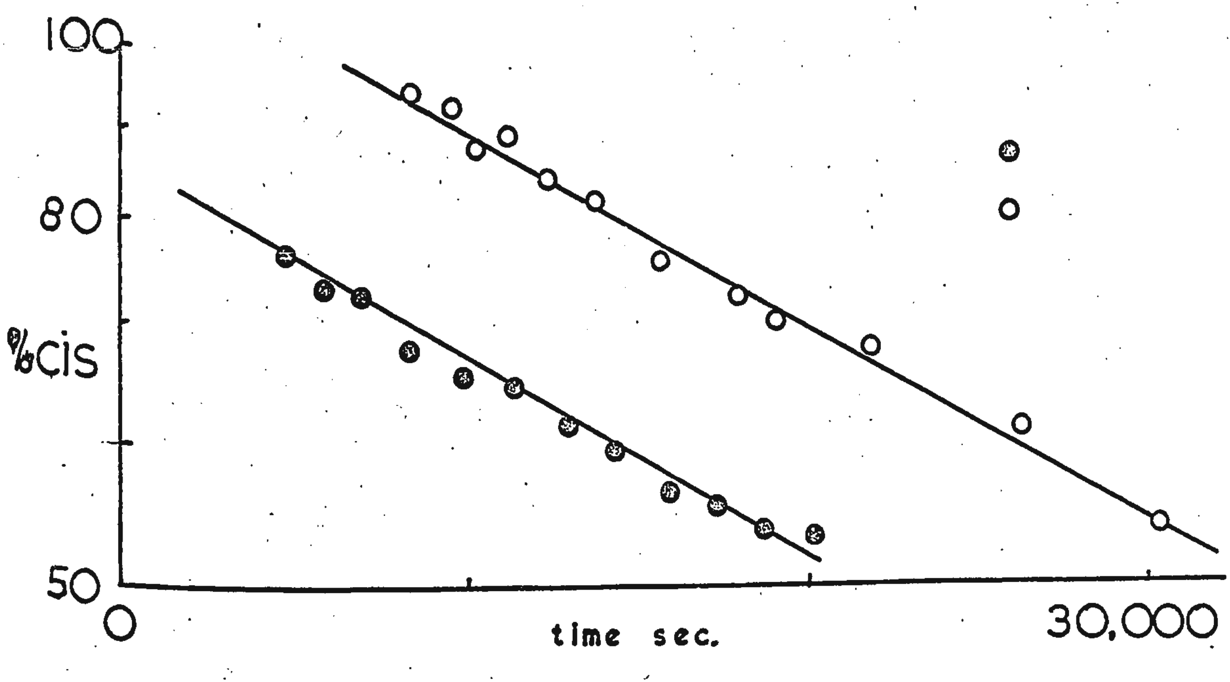
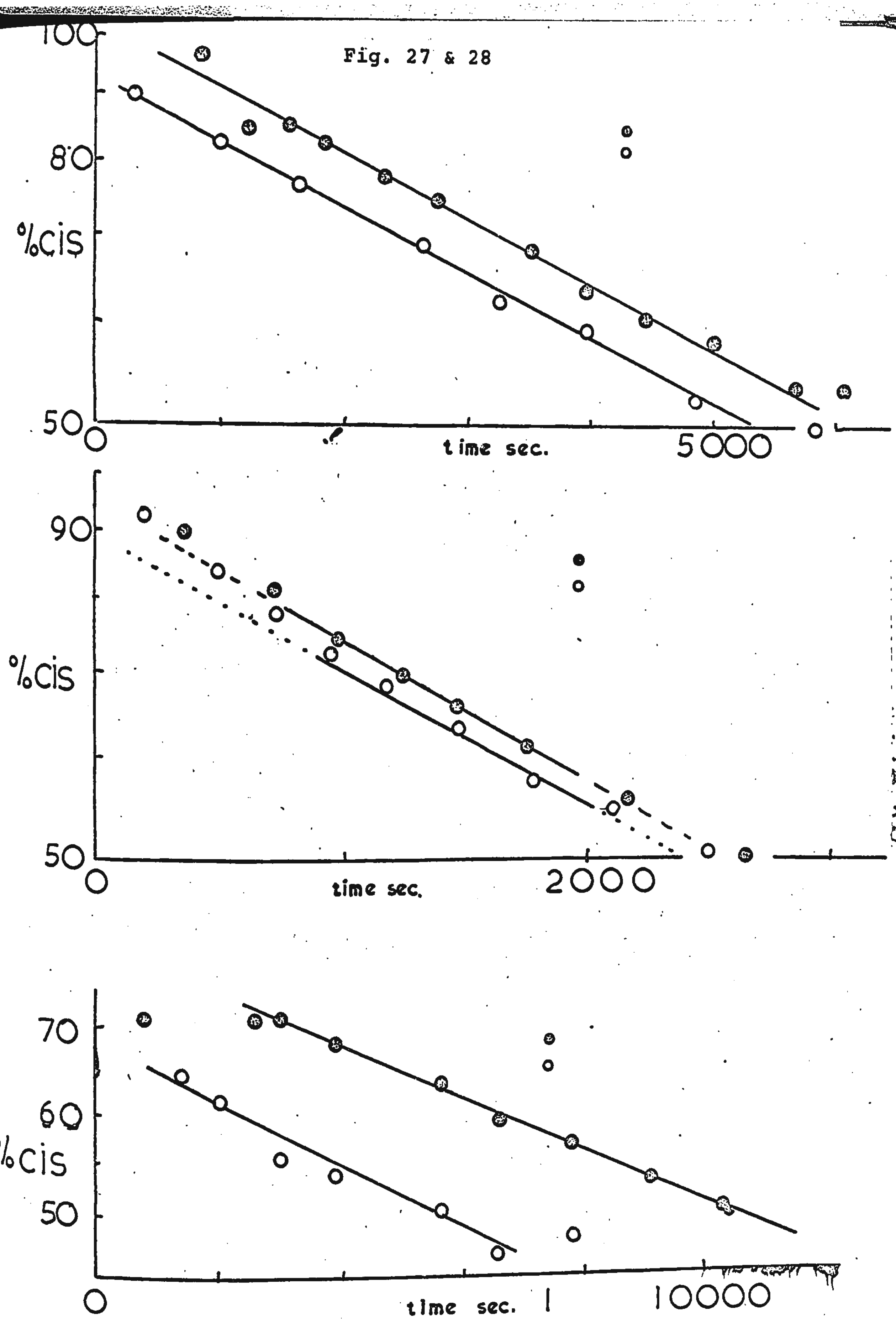


Figure 27. Example of acid catalysed first order rate plots m-nitrophenol catalyst.

Figure 28. Example of acid catalysed first order rate plots p-nitrophenol catalyst.

Fig. 27 & 28


100
80
%cis
50
0
time sec.
5000
90
%cis
50
0
time sec.
2000
70
60
%cis
50
0
time sec.
10000

"new" and "old" n.m.r. tubes, is shown in figure 28. The new run appears to give a good straight line (after an unexplainable induction period). The "old" run, however, shows more scatter, and has a steeper slope. Generally, the results obtained using "old" n.m.r. tubes were more random than with the "new" tubes. This must be a surface effect - treatment with nitric acid either "activates" previously inactive sites, or leaves traces of HNO_3 at the surface. "New" n.m.r. tubes, although they give more consistent results, cannot be said to be free of surface effects, and thus the results obtained are far from being free of errors.

The rates for different concentrations of nitrile with the same concentration of catalyst appear to be reasonably constant, more so in fact than the non catalysed rates. The phenols shown had a pKa ranging from 6 to 9.5. The rate of isomerization was plotted against the concentration of phenol.

The rate of reaction in the catalysed runs is a combination of several factors. We shall assume it is a combination of the non catalysed reaction (k^o), the catalysed reaction (k_{cat}), plus other effects introduced by using an aprotic solvent (see above). Then, the observed rate is given by equation 7, where c is the concentration of catalyst. The slope of the plot of k_{obs} vs c at zero concentration (obtained from a polynomial least squares analysis by computer) gives k_{cat}, and this value is used in the Bronstead determination.

Figure 21 represents the rate data for catalysis by sym-trichlorophenol. The rates determined in new n.m.r. tubes lie on a smooth curve, except that this curve does not appear to pass through the zero concentration. The rate obtained at zero from this plot is probably quite good. (See table IX).

The data for the para-nitrophenol catalysed runs are collected in figure 22. This time, more runs were done at each concentration. There seems to be a fair scatter of points at higher phenol concentrations, and thus these values are not as reliable as the former set. Again, the runs with two different lots of material fall on the same curve, thus verifying that the results are fairly reproducible.

The plot (fig. 23) for m-nitrophenol is a little better than that for the p-nitrophenol, and again the results are reproducible.

p-chlorophenol (figure 24) appears to give an excellent curve, though the rates obtained for several of the lower concentrations of phenol are lower than those for the non-catalysed runs of the same sample at the same temperature. (All runs were done in "new" n.m.r. tubes). The rates are again very reproducible, much more so in fact than are the non-catalysed rates. It is possible that the phenols "cover up" the effect of another catalyst. Conceivably the phenol becomes associated with the active sites in the n.m.r. tubes, thus reducing both their catalytic effect and partially reducing the effect of the phenol. To settle these problems, much more work would have to be done on the system, and, as for the non-catalysed runs, baked out, aged silica containers would have to be used. For the present purposes, the results reported here are sufficiently accurate to give a rough Brönstead constant.

TABLE IX
Catalytic first order rate constants of phenols

Phenol	pKa	k(from slope at infinite dilution)	k from rate at 0.05 m -phenol
sym-trichloro	6.41	4.50×10^{-3} sec.$^{-1}$/mole	3.72×10^{-4}
p-nitro	7.14	3.92×10^{-3}	2.04×10^{-4}
m-nitro	8.35	7.87×10^{-4}	4.94×10^{-5}
p-chloro	9.38	6.40×10^{-5}	3.84×10^{-6}

The log of the initial rates obtained from figures 21 to 24 are plotted against the pKa of the phenol in figure 29a. The slope of this line gives the Brönstead constant, $\alpha = .63$ (least squares). The points do not lie well on a straight line, and this is to be expected from the nature of the reaction. Thus, the resulting Bronstead plot is good, considering the errors both axes measurements are subject to. (See page 74). The Brönstead plot taking the catalysis rate at 0.05 m phenol is shown in figure 29b. This time a better plot results. ($\alpha = .656$ least squares). A rough estimate of the error in these values of α would be ± 0.1.

A study of the n.m.r. spectrum of β-aminocrotononitrile in several solvents was made at normal probe temperature, and then the peak positions were plotted against concentration of the nitrile. The curves were extrapolated to infinite dilution of nitrile, and the values of the chemical shifts obtained for infinite dilution were plotted against the magnetic susceptibility of the solvent. (Figure 30).

Peak positions in normal n.m.r. spectra depend on the magnetic susceptibility of the solvent, and there appears to be a linear relationship. With normal solvents (such as $CHCl_3$, CCl_4), there is a straight line dependence between $\delta_1 - \delta_0$ and $X_o^{solute} - X_o^{solvent}$. ($\delta_1 - \delta_0$ is the chemical shift difference between the pure substance and infinite dilution in the solvent, X_o is the susceptibility) (40, p 422ff). Aromatic solvents do not in general lie on this line, but form a line of their own.

Aromatic compounds set up ring currents (40, p.180) which, from general induction theory, produce a field which opposes the

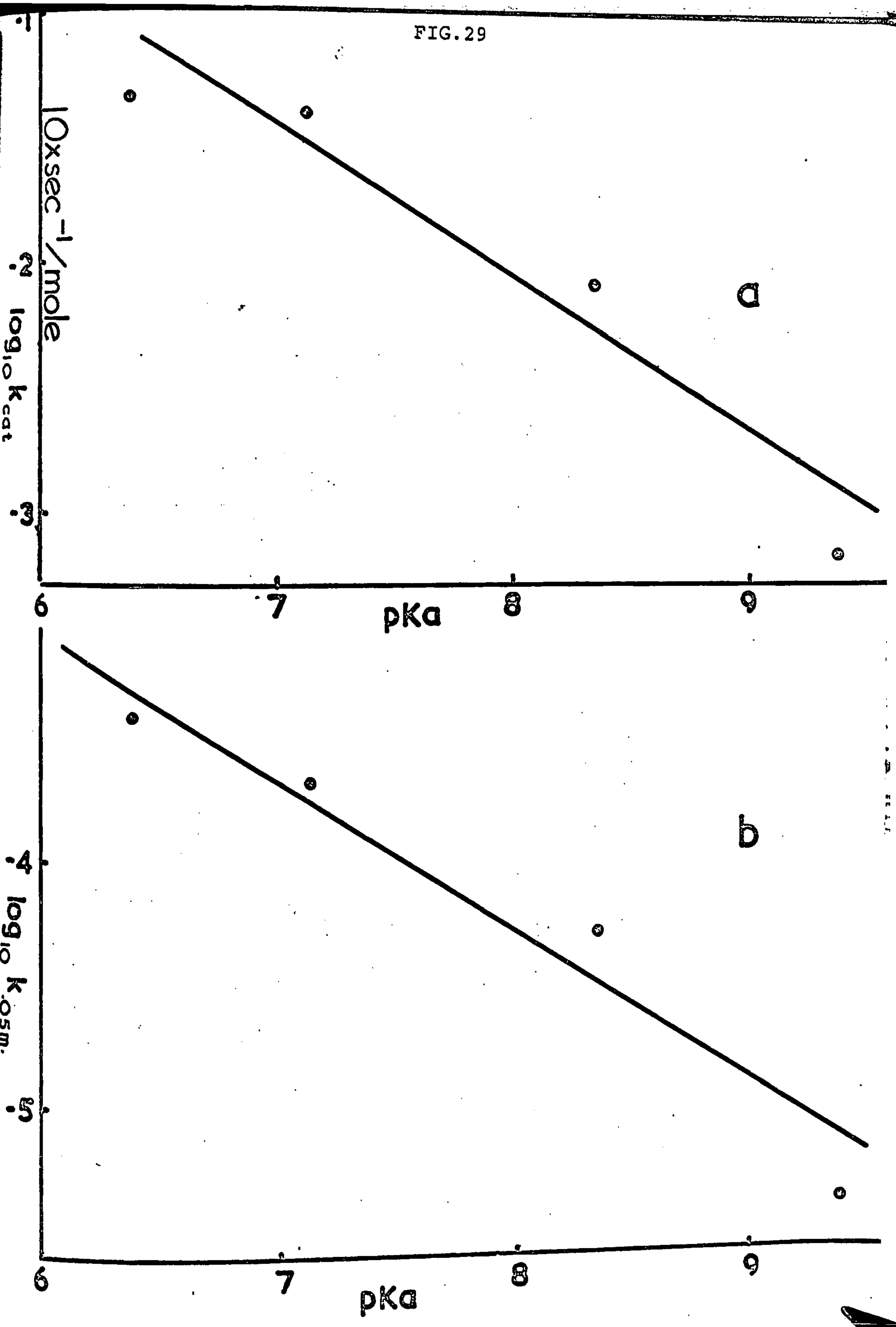
Figure 29. Bronsted plots from computer analysis of phenol-catalysed runs using K as

(a) rate at infinite dilution,

(b) rate at 0.05 molal phenol.

All rates obtained by polynomial least squares approximation.

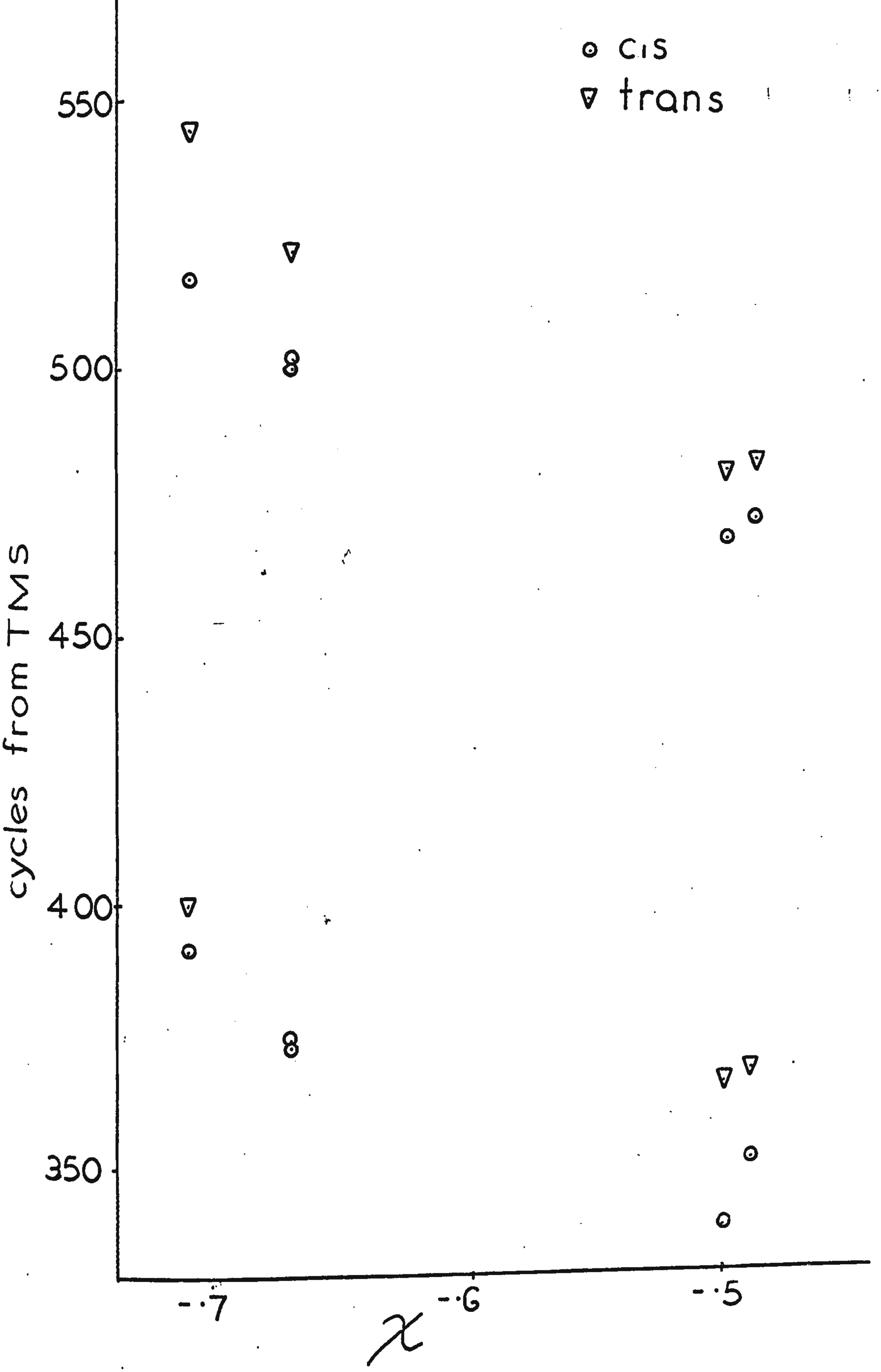
FIG.29



10xsec⁻¹/mole
·1
·2
·3
log₁₀ k_cat
6
7
8
9
pKa
a
·4
·5
log₁₀ k.05m.
6
7
8
9
pKa
b

Figure 30. Peak positions in β-aminocrotononitrile (at infinite dilution) vs. magnetic susceptibility of solvent.

FIG 30



main field. Thus, it is logical that molecules in an aromatic environment will require a larger main field to achieve resonance than the same molecules in a normal environment. Also, the effect of dilution in an organic solvent will be much greater, as on dilution the solute molecules, which in more concentrated solutions were under the influence of both solute and solvent, will be influenced even more by the solvent (aromatic) molecules. The upward curves which were obtained with anisole and benzene correspond with this hypothesis.

Pople, Schneider and Bernstein (40, p.430) report that nitrobenzene causes no appreciable shift. (Our curves for nitrobenzene are also fairly linear). Introduction of electron withdrawing groups reduces the π-donor capacity of the aromatic ring, but should not remove the effect completely. A type of competing association must occur, in which the oxygen atoms of the nitro group act as n-donors for the protons being investigated.

The curves obtained for chloroform slope down toward infinite dilution. This agrees with the observations of Pople, Schneider and Bernstein for similar systems. Note, as in the case of nitrobenzene, the effect of dilution is small. (The chemical shift only changes by 2 or 3 cycles over the dilutions studied, whereas in the case of anisole and benzene, the effect is more than 10 cycles).

In chloroform, benzene and nitrobenzene (fig. 31 for $CHCl_3$ example) the trans α-hydrogen peak changes at a different rate from the other peaks. This could imply a hydrogen bond of the trans α-hydrogen to a nitrogen in the dimer. (In anisole, this peak cannot be seen).

Figure 31. Peak position vs. concentration nitrile in chloroform.

FIG. 31

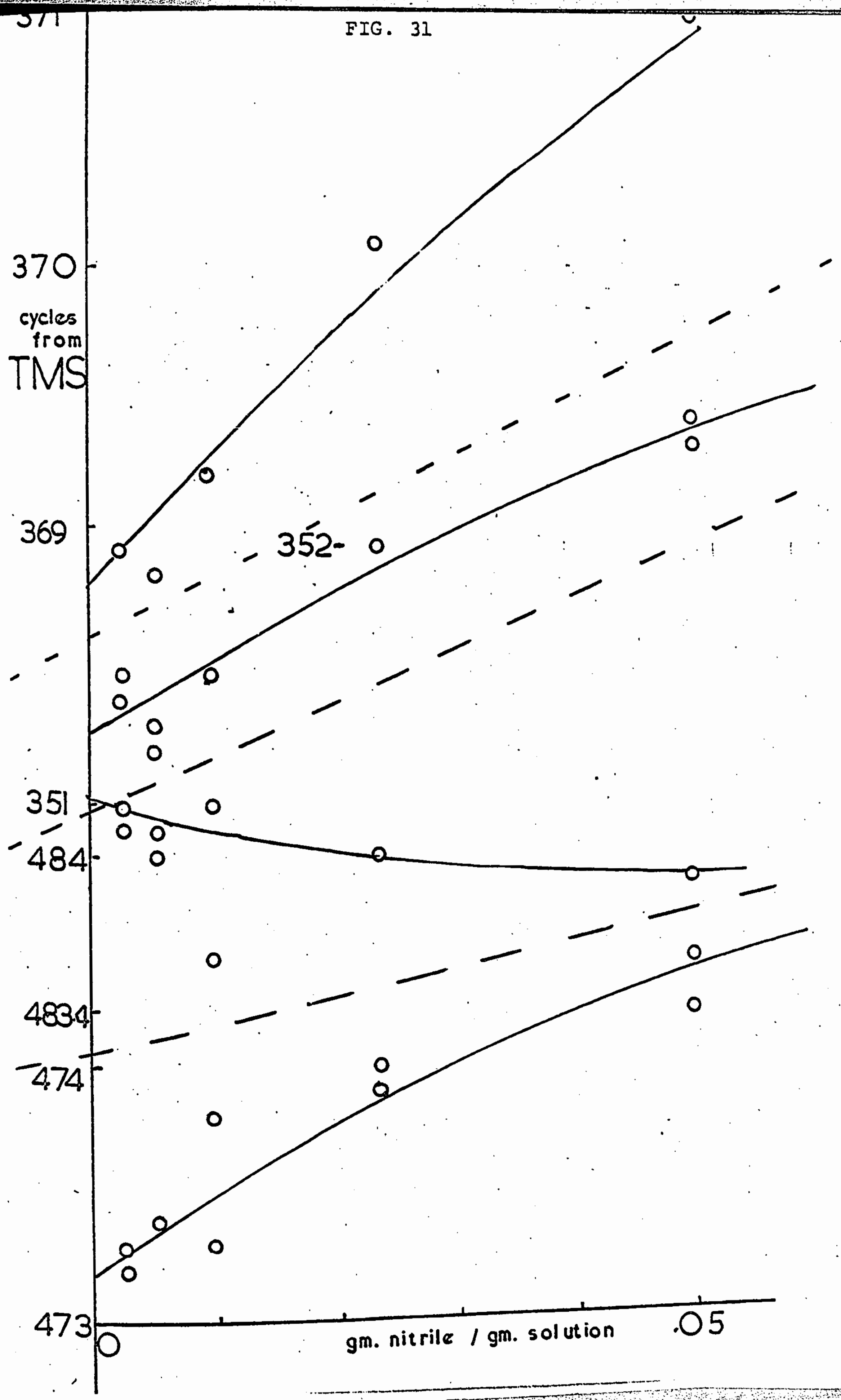

371
370
cycles
from
TMS
369
352-
351
484
4834
474
473
O
gm. nitrile / gm. solution
.05

Figure 30 is a plot of chemical shift vs. susceptibility and should be a straight line for the aromatic molecules, $CHCl_3$ should lie off this line. Thus, the result is what would be expected.

These spectra were recorded to see if any association effects could be detected which would give any evidence of the presence of a "dimer" of cis and trans isomers. In both benzene and anisole, the cis α-hydrogen peaks of the same solution of nitrile absorb at the same field (± .3 cycles), whether or not some of the trans isomer is present. The slight deviation is probably due to instrumental instability from day to day, as $CHCl_3$ - TMS calibration was not performed for all spectra. (Results for C_6H_6 are recorded for mixed isomers only. A seperate experiment was done to check the isomerization effect).

As the solvent shifts for the cis isomer are all normal, it appears that any dimer formed does not involve the methyl or the CH of the cis isomer. The trans hydrogen, however, probably takes part in such a phenomenon because, regardless of solvent, it appears to shift in the same direction on dilution (deshielded), and behaves differently than the other peaks.

The NH_2 peaks are very broad in all the solvents used. Qualitatively, however, no shift in the NH_2 peak was observed on isomerization in benzene or $CHCl_3$.

Equilibrium studies were carried out in a variety of solvents (figures 32 to 34). These were the solutions either from the solution runs or the peak position studies. The equilibrium in chloroform and benzene appears to be very concentration dependent (figure 32), whereas that in nitrobenzene (figure 33) varies only slightly in the concentration range studied, and that in anisole (figure 34) appears to be virtually independent of concentration.

The equilibrium concentrations of isomers from samples used in the acid catalysed runs were also studied. In these anisole solutions, the equilibrium constant appears to depend on the concentration of the catalyst, with a limiting value of about 34% cis isomer. These results are qualitative only because of the possible decomposition of nitrile kept in solution over long periods. (Some of these solutions were yellow). Similar solutions (containing no catalyst) kept at higher temperatures ($\approx 70^{\circ}C$) turned yellow and material precipitated out after one month. This impurity, from the n.m.r. spectrum, appears to be XXX, with perhaps some XXXI present as well. The condensation of nitrile to these products eliminates ammonia, and thus this could be a source of error in the solution runs. This condensation, although not detectable in most of the equilibria studies, could cause the "random" graphs. The important observation is that the equilibrium constant of β-aminocrotononitrile in solution is dependent on solvent, concentration and other dissolved materials. (See conclusions for an explanation).

Figure 32. Equilibrium % cis vs. concentration nitrile in chloroform and benzene.

FIG.32

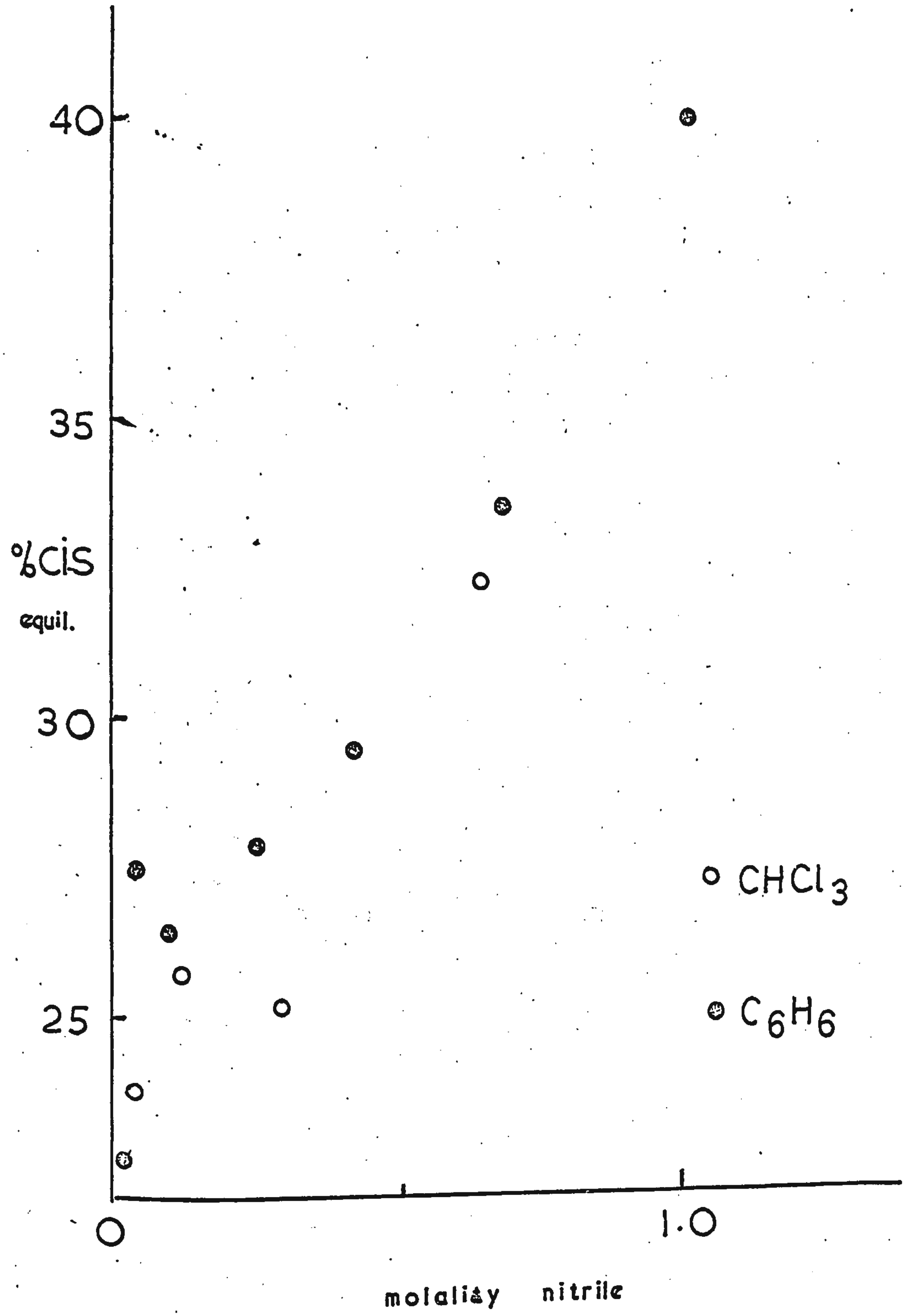


Figure 33. Equilibrium % cis vs. concentration nitrile in anisole and benzene.

Figure 34. Equilibrium % cis vs. concentration nitrile in nitrobenzene and benzene.

FIG. 33

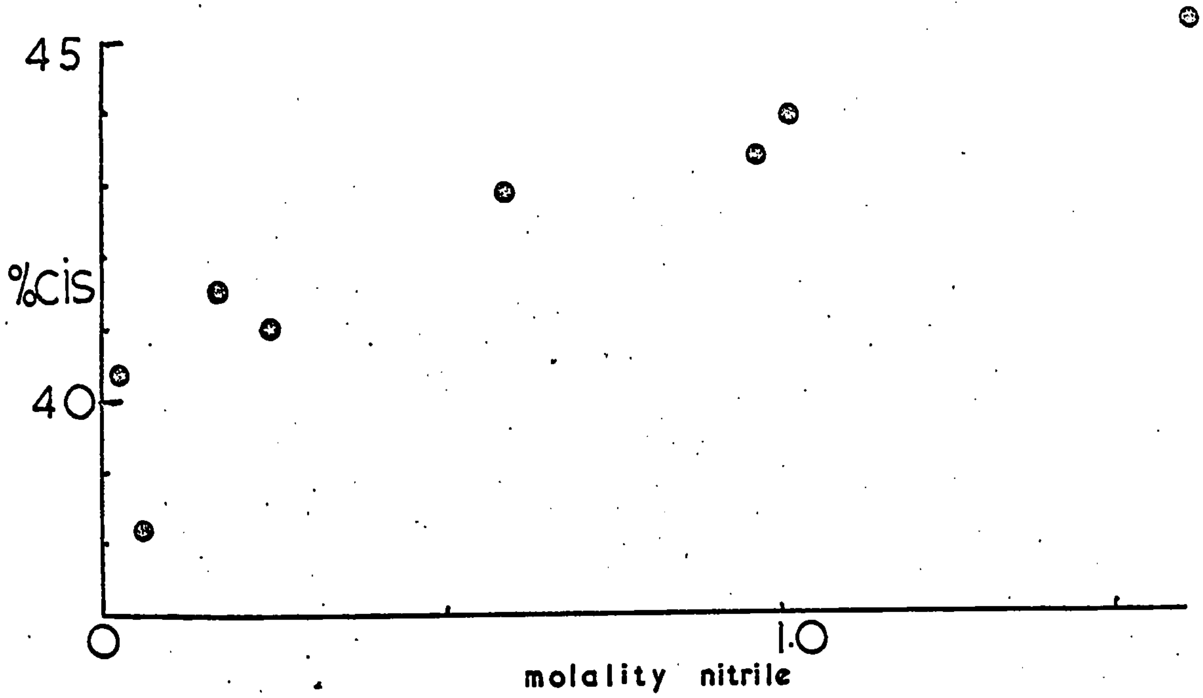
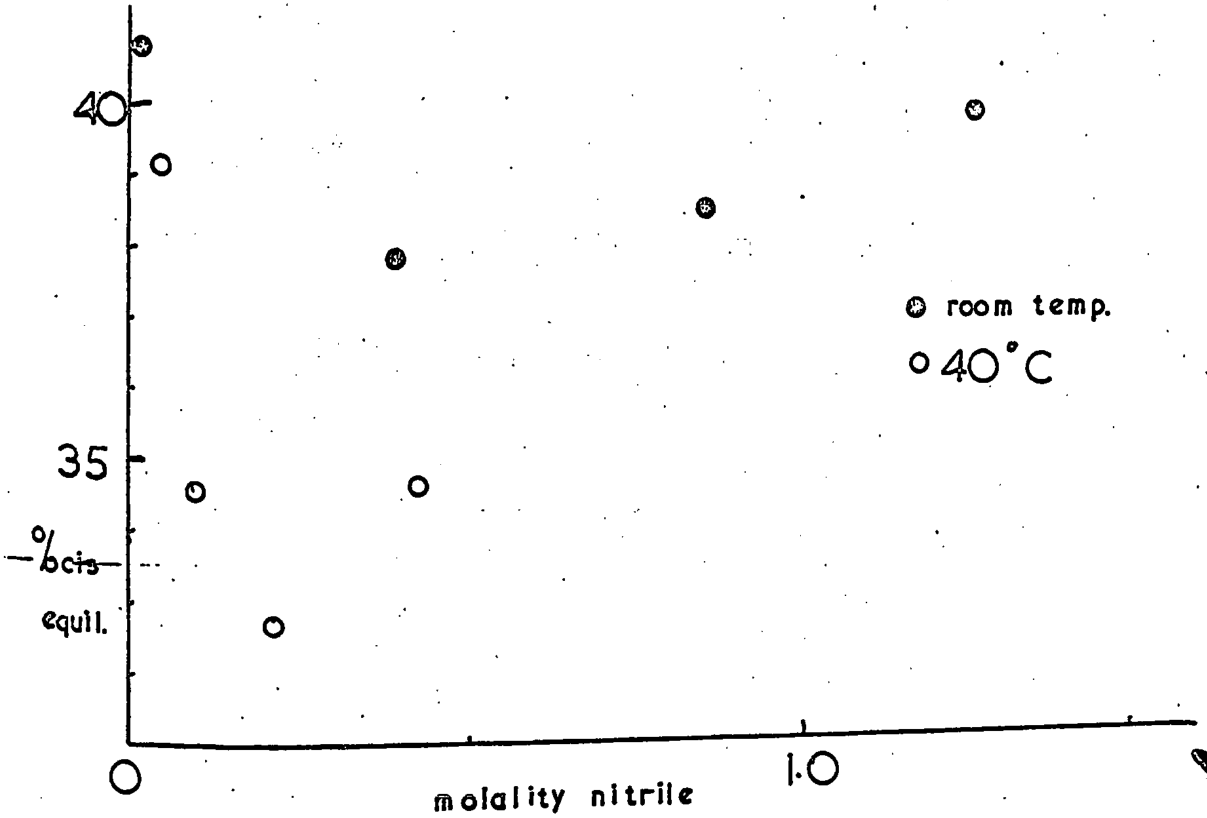

45
%cis
40
0
1.0
molality nitrile

FIG. 34


40
35
%cis
equil.
0
1.0
molality nitrile
● room temp.
○ 40°C

Chapter 4

Conclusions

The isomerization of β-aminocrotononitrile has presented some interesting problems. In the solid state, a mixture of the two isomers changes rapidly to > 95% of the cis isomer at temperatures below 46°C (the melting point of mixture), but above this temperature the reverse process is observed, the equilibrium being a 1:1 mixture of the two forms. Cryoscopic studies in benzene (28) have indicated the low melting form is a dimer or polymer of the two isomers. (Table X gives Bullock and Gregory's results. A very interesting observation is that the apparent molecular weight drops with increasing dilution). The equilibrium studies in solution indicate a definite dependence of $K_{eq.}$ on solvent and concentration, the trans isomer being more favored in the more dilute solutions.

Table X

Concentration (g./l)	Molecular weight
3.393	87.1
6.619	94.7
10.293	109.0
Theory	82.108

These seemingly anomalous results can be readily rationalized. The trans isomer XXVIII can exist only by associating with another molecule. (Bullock and Gregory (28) were unable to isolate XXVIII pure by sublimation, and the material they did obtain (≈ 90%) rapidly isomerized to mixture in chloroform). Thus, in the fused state, β-aminocrotononitrile assumes an equilibrium mixture of 50% of each isomer. This must be a hydrogen bonded species of some sort. The solid state isomerization of this "dimer" is caused by molecular collisions breaking up the hydrogen bonded species. The trans isomer, once separated from (or perhaps still loosely bound to) the cis, is extremely unstable, and undergoes isomerization easily. This explains the close agreement to first order kinetic data with "normal" *activation energy and frequency factor. The reverse reaction, however, is not nearly so simple, as now two or more cis molecules must "line up" in a specific way, facilitating the formation of the hydrogen bonded species. This however, seems an unlikely process in the solid state, as the mobility of organic molecules through the crystal lattice would be very slow, and thus the low temperature equilibrium with cis isomer is obtained.

At temperatures above 46°C, however, any small amount of dimer which might be formed will fuse. It is conceivable that this fused material could dissolve more cis isomer, thus making it more mobile, and more easily moved into the right position for isomerization. The lower temperature runs (Figures 11 & 16) demonstrate the randomness of this process.

*"Normal" activation energies for cis-trans isomerizations are ca.40kcal./mole. The experimental values (≃ 25kcal./mole) are lower because of an expected change in the multiplicity of the double bond by hydrogen transfer (see below).

H. Morawetz (36, p. 293) states it is quite possible in some cases involving a crystalline phase and a solution phase that the reaction is taking place within and at the surface of the crystals, and that it is therefore subject to some control by the geometry of the crystal lattice. At the higher temperatures, where the cis material fuses early in the reaction, this process becomes analogous to a Diels-Alder reaction, the important factor being the alignment of the molecules. This explains the observed low frequency factor ($10^{5.4}$).

The peak position studies and the equilibria studies help confirm the above proposal. The trans isomer can exist more readily with the support of a solvent molecule than can the cis. Thus, in the more dilute solutions, XXVIII becomes bonded to the solvent molecules, breaking away from the cis isomer in the dimer. The cis may then isomerize, or exist by itself. The effects observed with the phenols in solution are also a consequence of this, as they are certainly excellent centres for hydrogen bonded species. The different equilibrium constants obtained with different solvents may be partly due to a stabilization of the dipole moment.

should give an equilibrium at infinite dilution with the most cis isomer present. In fact, the value is largest (see figures 32 to 34). The extent of bonding to the solvent molecules must also depend on both the solvent's steric and electronic structures. In the neat liquid, one reason for a 50% mixture of each isomer might be the expected large dielectric constant of β-aminocrotononitrile, thus favoring the cis isomer.

The mechanism of this cis-trans isomerization, however, cannot be deduced completely from the above results. Kinetic experiments with the four phenols were performed to help solve this problem. A Brönsted constant α of 0.64(±.1) indicates that the isomerization is acid catalysed. According to Thornton's (41) definition of α, the transition state is neither reactant like ($\alpha = 0$) nor product like ($\alpha = 1$). One might say, however, that the phenols are "half" effective in catalysing the reaction. As acid catalysed reactions involve proton transfer, one might say the phenol proton is "half" transferred to the nitrile. This treatment of the Brönsted constant involves many approximations, and will thus not be discussed further.

The studies in acetic acid indicate the α hydrogen (probably the cis) undergoes exchange in strong acid solution, and that the amine protons are in very rapid exchange. (The NH_2 exchange with deuterium has been demonstrated in D_2O).

The kinetic runs with deuterated material indicate a primary isotope effect (≈ 2.5), and also show a deuterium exchange between the ND_2 and CH in the solid phase. Other solid state isomerizations have been reported (38, p. 294) and in particular the isomerization of isobutyl radicals trapped in the lattice of crystalline isobutyl halides to t-butyl radicals at -196°C is assumed to be due to an intra-molecular proton transfer. In the isomerization of β-aminocrotononitrile the α-H and ND_2 of the fused material appear to exchange very rapidly, as the run at 45°C (when the material partly fuses at first) demonstrates (figure 13). There appears to be a random exchange of hydrogen on the α carbon in the fused state. If the nitrile molecules are bonded together, a hydrogen transfer might be expected to change the multiplicity of the double bond, thus lowering the activation energy of isomerization from the "normal" 40kcal./mole to the experimental value of 25kcal./mole. Structures such as XVII or XVIII might be good intermediates for this reaction. The ketimine intermediate has been inferred for a similar solid state reaction (30, see also page 23 above).

Various intermediates have been described (see introduction) which would facilitate both the solution and solid phase isomerizations. From the present study, although these intermediates cannot be rules out, the ketimine XVI appears to be the most likely, although two or more first order processes involving different intermediates may be operating. If they occured statistically with similar activation energies, this duality of mechanism would not be detected by the kinetic results.

As $k_{\text{isomerization}} \simeq 6\ k_{\text{exchange}}$, and as k_{exchange} is not determined very accurately, it seems likely that a hydrogen transfer to the α carbon is involved in the isomerization, but other intermediates cannot be ruled out. From the n.m.r. spectra it appears that β-aminocrotononitrile undergoes no further α H-D exchange after reaching equilibrium in the solid phase, thus suggesting the proton for the isomerization must come from another molecule (another part of the dimer in the case of mixture). Intramolecular exchange of hydrogen from the amine group to the α carbon is doubtful. The non-catalysed reaction would then be represented by figure 35, and the catalysed by figure 36, the mixture XXIX here being represented by a tetramer, as the H- bonds in a dimer would be quite bent. Trifluroacetic acid destroys the compound, but most of the possible intermediates suggested in the discussion would be good candidates for destruction. Unfortunately, the structure of the dimer cannot be proposed with certainty. The α hydrogen of the trans portion appears to be bonded to the cis, and the cis appears to donate a proton to the trans in the solid state isomerization. XXIX, however, explains all the results, as it should break down (and isomerize) readily in the solid state with a high frequency factor, and the reverse reaction should have a low frequency factor. Whether or not formation of XXIX in solution should conform to first order kinetics cannot be predicted accurately, as a multi step reaction is probably involved, the rate determing step being first order (probably involving the combination of two dimer entites, each dimer consisting of two hydrogen bonded cis molecules). From the present study, all that can be said about the structure of the mixture is it must be a bonded species similar to XXIX, though not necessarily with the same number of molecular entites. It is possible the mixture is a true dimer, joined by only one hydrogen bond. The main reason for prefering a cyclic type structure is the low frequency factor of the high temperature solid and the solution results. Further work which might help elucidate this structure would be X-Ray crystallography. This, however, would present difficulties because of the low melting point of the mixture and the possibility of decomposition. Further work making inorganic complexes of the nitrile could possibly be of some use.

An interesting experiment would be to prepare N,N-dimethyl-β-aninocrotononitrile and compare its properties with those of the title compound. If hydrogen transfer from the amine group is an important step in the reaction (especially solid state), the N,N-dimethyl compound should not isomerize, thus supporting the idea of a ketimine intermediate. Changing the β-methyl group for phenyl, ethyl, etc. groups might also produce some useful results.

Much more work needs to be done on the non-catalysed solution experiments. Determination of the cause of the inconsistent results might help in determining mechanism and structure, especially if surface effects are important.

Figure 35. Proposed mechanism for non catalysed isomerization both neat and in solution.

FIGURE 35

Mechanism of solid state and non-catalysed reactions

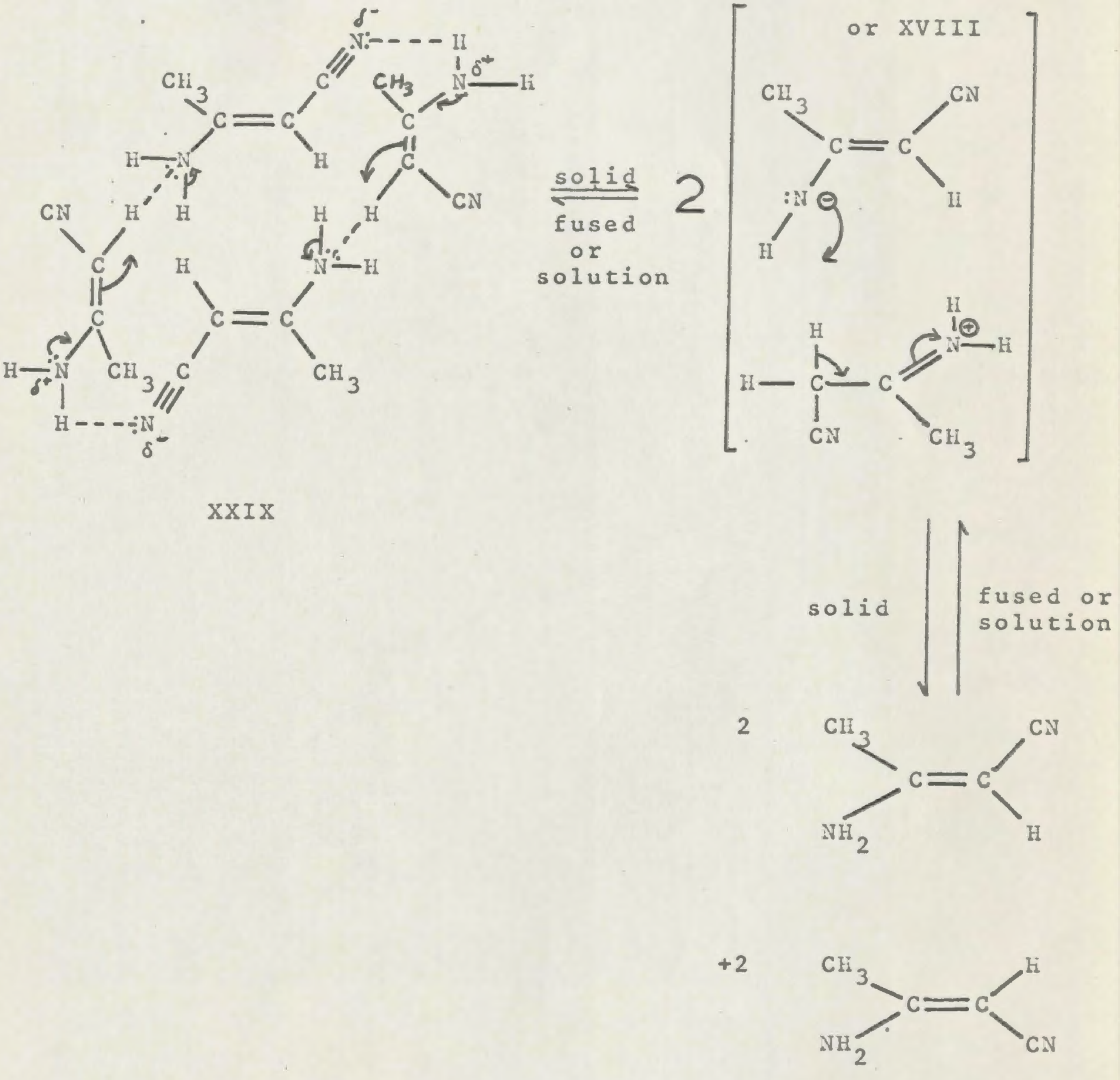
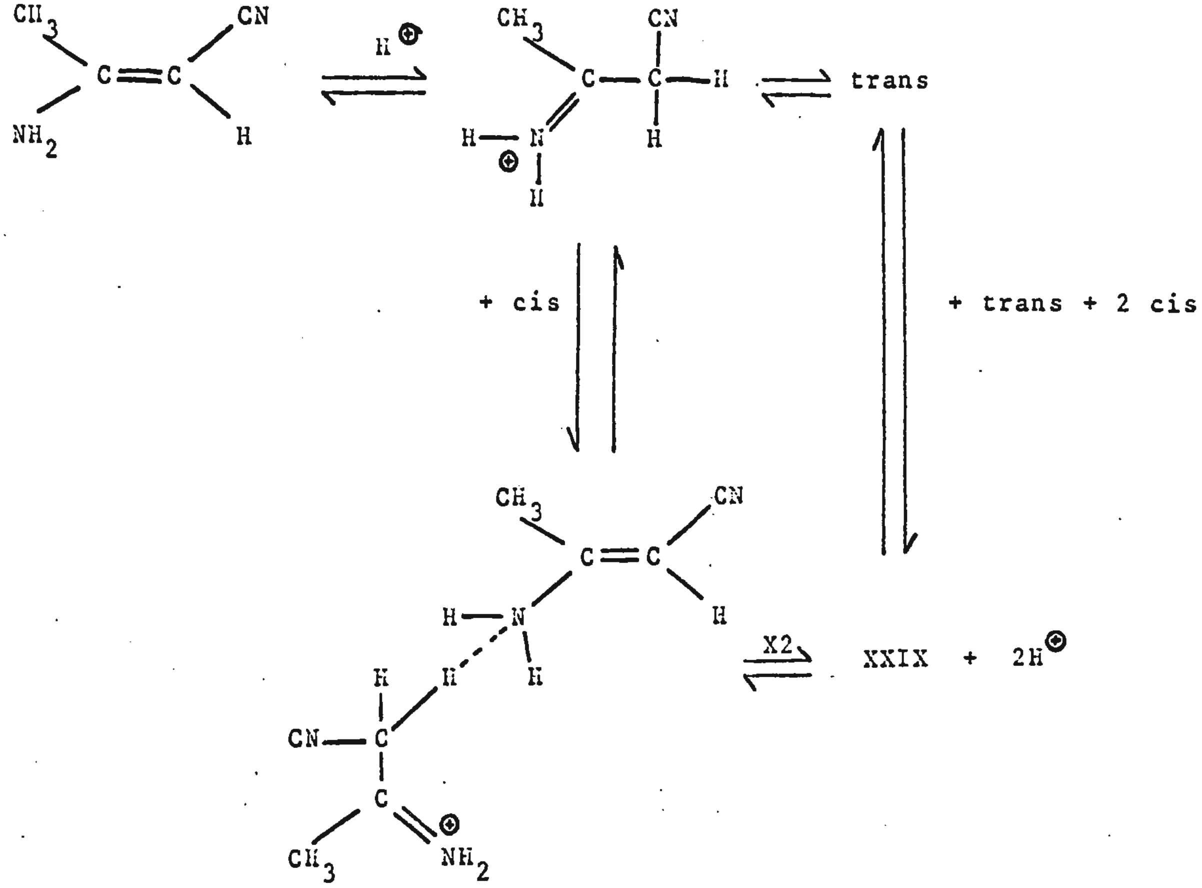


Figure 36. Proposed mechanism for acid catalysed isomerization of β-aminocrotononitrile.

FIGURE 36

Mechanism of acid catalysed reaction



PART II

NON-EQUIVALENT METHYLENE PROTONS IN ETHERS CONTAINING AN ASYMMETRIC CENTRE

Chapter 5

Introduction

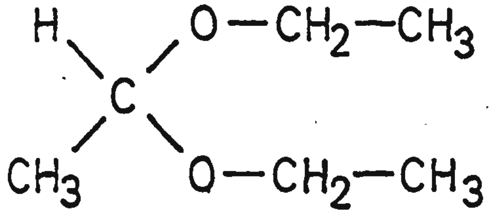
The second problem concerns a more theoretical aspect of nuclear magnetic resonance spectroscopy; the observation that two nuclei attached to the same centre may be magnetically non-equivalent. Many examples of this effect have been reported in the literature (42-67). Assuming that the molecular bonds are in relatively free rotation (this includes most saturated acyclic compounds), the sole requirement for non-equivalence is an apparent* asymmetric centre adjacent to or near a methylene group. Several chloro-and bromo-alkyl ethyl ethers with such a centre (e.g. compounds XL, XLI, XLIV, XLV and XLVI) were synthesized by Dr. B. Gregory** and the n.m.r. spectra were recorded and analysed by the author. The chemical shift between the two methylene protons of the ethyl group (around 20 cycles) was found to be much larger than most of those previously reported.

Nair and Roberta (43) appear to be the first to report non-equivalence due to an asymmetric centre. They postulated that restricted rotation with conformational preference about the C-C bond causes this effect. Rotation is, however, fast enough so that the n.m.r. signal for each proton averages out.

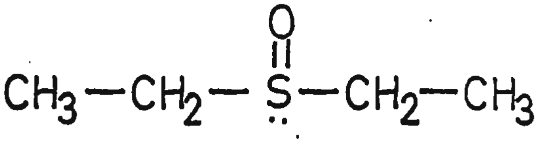
* Compounds such as XXXIII and XXXIV have non-equivalent methylenes because one CH_2 "sees" the active position attached to three different groups.

**Memorial University - post doctoral fellow, 1963-1965.

Figure 37. The three rotamers of a saturated compound with an asymmetric centre. (Note, there are three more for the opposite stereoisomer).



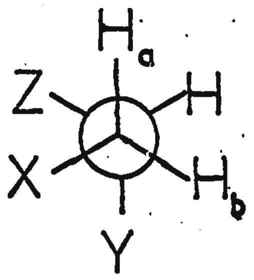
XXXIII



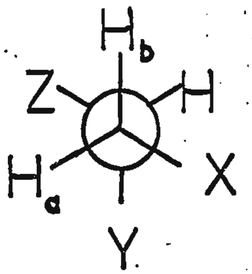
$CH_3-CH_2-\overset{\overset{O}{\|}}{\underset{\cdot\cdot}{S}}-CH_2-CH_3$

XXXIV

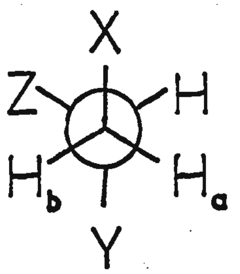
FIG. 37



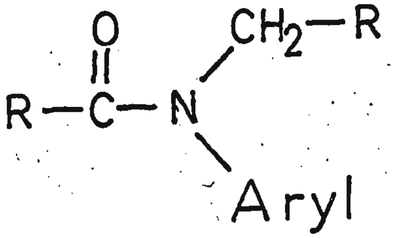
XXXV



XXXVI



XXXVII



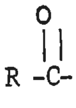
XXXVIII

Pople (68) has summarized the situation for substituted ethanes. For a compound with an asymmetric centre adjacent to a methylene group, there are three possible rotamers* of the d and l forms, (Note: H_a in the d form becomes H_b in the l form, and vice versa). Looking along the C-C bond, these can be pictured as in figure (37). The main argument is that if X, Y, Z are bulky groups (not hydrogen), there will be a barrier to rotation about the C-C bond. Also, some of the rotamers will be energetically more favored than the others, and thus the three will be populated to a different extent. The average environment of H_a and H_b will thus be quite different. For example, suppose XXXV is the least favored rotamer (this is reasonable as X, Y, Z are bulky groups which would interact most in this conformation). H_a spends more time near Y than H_b, and H_b spends more time near Z than H_a. (This assumes similar populations of XXXVI and XXXVIII). It is obvious that H_a and H_b would then be non-equivalent, provided Y and Z were anisotropically different.

Pople also pointed out that even if rotation is rapid, the methylene protons will still be non-equivalent because of the asymmetric centre. Careful inspection of figure 37 reveals

* Even in ethane, there is a 3kcal./mole difference between the staggered and eclipsed forms (1, p.124 plus references therein). Thus, in substituted ethanes the staggered forms (as shown in figure 37) are certainly energetically the most stable.

that the averaged environments of the protons would remain different even in fast rotation. Each of the terms in table XI represents a distinct average field, and no two are the same. If each conformation is equally populated, the average chemical shift should still be different for the two protons. Waugh and Cotton (48) extended this hypothesis to explain the non-equivalence of the methylene protons in diethyl sulfite (and similar type compounds). As pointed out by Roberts (58), however, the introduction of another atom (oxygen or sulfur) between the asymmetric centre and the methylene group results in an increase of the number of possible rotamers from three to nine, and thus each methylene signal now becomes an average of nine magnetic environments. Roberts considers the main cause of the non-equivalence is thus due to unequal populations in at least some of the possible conformations, and there is no doubt this accounts for some of the effect. (See discussion for a further explanation of the large non-equivalence in ethers).

Siddall and Prohaska (66) have reported n.m.r. spectra of compounds of type XXXVIII. When the aryl group is ortho-substituted the methylene protons are non-equivalent and the chemical shift is as large as 100 cycles. In this case restricted rotation appears to be very important, as the  $\mathrm{R}-\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-$ and ortho-aryl groups are both very bulky.

Gutowsky (69) derived a three term expression (11), including both of the above factors, to predict the magnitude

TABLE XI

CONFORMER ENVIRONMENT

PROTON	Ha	Hb	Conformer
Groups Proton	X Z, HH	XY, HH	XXXV
HA and HB are	XY, H Z	H Z, XH	XXXVI
adjacent to	HY, XH	X Z, HY	XXXVII

of the chemical shift. Using the three rotamers of figure 37, the rotationally averaged chemical shifts ν of the methylene protons are:-

$$\left\langle \nu_a \right\rangle = \sum_{n=1}^{3} x_n \nu_n^a \qquad \left\langle \nu_b \right\rangle = \sum_{n=1}^{3} x_n \nu_n^b \qquad (8)$$

x_n is the mole fraction of rotamer n, and ν_n^i is the resonance frequency, or chemical shift, of the i^{th} nucleus in rotamer n. Table XI shows why the six ν_n^i are different. If, however, X= H, then the three rotamers and their populations become identical. From table XI it is obvious $\nu_1^a = \nu_2^b$, $\nu_2^a = \nu_3^b$, $\nu_3^a = \nu_1^b$. Thus equation 8 becomes

$$\left\langle \nu_a \right\rangle = \left\langle \nu_b \right\rangle = \sum_{n=1}^{3} \frac{1}{3} \nu_n^a = \sum_{n=1}^{3} \frac{1}{3} \nu_n^b \qquad (9)$$

and $\left\langle \nu_a - \nu_b \right\rangle = 0$. . Thus, the three protons are magnetically equivalent (including X = H). The separate proton shifts, ν_1^i, ν_2^i and ν_3^i are, however, not equivalent, and in the case of X = H, C - C rotation must be prevented completely to see this. If X ≠ H, there is an increased asymmetry, and the energies and populations of the three rotameric pairs will differ, thus changing all ν_n^a and ν_n^b. Thus, the net chemical shift becomes

$$\left\langle \Delta\nu_H \right\rangle = \left\langle \nu_a - \nu_b \right\rangle = \sum_{n=1}^{3} x_n (\nu_n^a - \nu_n^b) \qquad (10)$$

or $$\left\langle \Delta\nu_H \right\rangle = \sum_{n=1}^{3} x_n (\Delta\nu^0 + \delta\nu_n)$$

We define $\Delta\nu_n^o$ as $(\nu_n^a - \nu_n^b)$ for the case X = H, and $\delta\nu_n$ as the change in $\Delta\nu_n$ caused by substituting X for H. Rearrangement, and the introduction of $\sum_{n=1}^{3} \frac{1}{3} \Delta\nu^0 = 0$ gives Gutowsky's three term equation:-

$$\langle \Delta\nu_H \rangle = \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \Delta\nu_n^0 + \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \delta\nu_n + \sum_{n=1}^{3} \tfrac{1}{3} \delta\nu_n \quad (11)$$

The first term depends upon the shifts caused by the "initial asymmetry" of the compound X = H, and the population differences introduced when X ≠ H; the second term depends both on the population differences and the shift changes introduced by having X ≠ H; and the last term is the "asymmetry effect", which would explain the non-equivalence were the populations of each of the rotamers the same.

Thus, methylene non-equivalence appears to be a combination of at least these two effects, sometimes one predominating, sometimes the other. The asymmetry effect must certainly be the predominant factor at high temperatures where free rotation might be expected. Unfortunately, experimental limitations restrict the use of n.m.r. spectrometers at high enough temperatures to allow observation of a pure asymmetry effect. Gutowsky estimated 6.7 cycles for "pure asymmetry" shift ($\delta F_a F_b$) in $CF_aF_bBrCFBrCl$.

Ethers with an asymmetric centre on one side of the oxygen atom and methylene on the other appear to show an unusually large non-equivalence. Roberts (58) has studied a number of compounds of this type. The observed chemical shielding, " σ ", of each methylene proton can be divided into two parts:

$$\sigma = \sigma_e + \sigma_d \qquad (12)$$

σ_e is the shielding due to the electrons in the methylene carbon hydrogen bond, σ_d that due to groups distant from the methylene carbon-hydrogen bonds. If the differences in shielding at the methylene protons were due to a difference in the orbital electronegativity of the carbon bonding orbitals directed toward them (i.e. to a difference in the s character of these orbitals) a difference in the $^{13}C - H$ coupling constants of the two non-equivalent protons would be expected. (58 and references therein). The $^{13}C- H$ coupling for both hydrogens is identical suggests that σ_e is of no importance in the chemical shift difference.

Several of the factors which might contribute toward σ_d are the magnetic anisotropies of the bonds in the molecule, the magnetic anistropy associated with unsaturated groups, both within the ether molecule and in the solvent molecules; the reaction fields induced in the medium by the solute; van der Waals interactions between solute and solvent; and hydrogen bonding or specific complex formation between solute and solvent. That the chemical shifts Roberts (58) reports for compounds of type (XLIX) dissolved in acetic acid are no larger than those in CCl_4 or cyclohexane suggests that intermolecular interactions involving the ether oxygen are negligible. Roberts further observes that solvents such as benzene, dimethyl sulfoxide and cyclohexane all give similar methylene chemical shifts, and thus to a first approximation solvent-solute interactions and reaction-field effects can be neglected. Thus, the shielding appears to arise solely from the anisotropy of the groups and bonds within the molecule.

Recently, Freymann (64) has suggested that the CH_2 non-equivalence in ethers with an asymmetric centre arises from "chelation" of the methylene protons with the oxygen. ("Chelation here means an intramolecular transfer of charge (from the lone pair of O or N to the CH) with the exchange term predominant, and not the classical hydrogen bond). Thus, there would exist two types of hydrogens: one far from the oxygen, non-perturbed; the other perturbed by the lone pair electrons.

Roberts (58) has discussed briefly the oxygen atom in ethers. For diethyl ether, the bond angle is $108 \pm 3^{\circ}$ (70), suggesting that the electronic hybridization around the ether oxygen is tetrahedral. Roberts also reports some electron diffraction studies carried out on chloromethyl chloroformate, diethyl terephthalate and potassium ethyl sulfate. These all suggest the bulky groups are trans, thus suggesting the lone pairs of electrons are "smaller" than an alkyl substituent attached to an ether oxygen.

Chapter 6

Experimental.

All spectra were run on a Varian 60 n.m.r. spectrometer at normal probe temperature. The samples were either neat + 2% tetramethylsilane (T.M.S.), or in a 30-50% CCl_4 solution (+ T.M.S.) as indicated in table X11. All coupling constants and chemical shifts are reported in cycles per second. T.M.S. was used as an internal reference, its absorption position being arbitrarily put = 0. The ethyl groups were analysed as ABX_3 spectra, even though Kaplan and Roberts(51) report ABC_3 analysis is necessary when J_{AB}, J_{AC} are of opposite sign, as appears to be the case. A good indication, however, of the chemical shifts and coupling constants can be obtained with a 1st order ABX_3 analysis (i.e. treating the CH_2 part as AB, and analysing the rest of the spectrum as a first order spectrum). J^*_{AB} was taken as the average of the splitting in the AB part of the spectrum. (A maximum of eight values were used). J_{AX} and J_{BX} were measured both from the X_3 and the AB parts of the spectrum, and agreed within experimental error in all cases. δAB (the chemical shift between the non-equivalent methylene protons) was an average of four determinations from the AB (split by X_3) portion of the spectrum. These are the least reliable results, *as there was around 1/4 cycle difference between the largest and the smallest determinations.

Most of the samples were prepared by Dr. B. Gregory from readily available compounds. The α, β-dichloroethyl ethyl ether was a Fisher product, and was redistilled before the spectra were recorded.

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*J_{AB} was measured as a positive coupling constant. It is, however, assumed to be negative, and thus the reported values are not strictly correct.

Chapter 7

Results

The results of the spectral analysis are reported in table Xll. The geminal and vicinal coupling constants are assumed to be of opposite sign, as seems to be the case in similar type compounds (51, 65, 71, 72). The spectra were analysed as ABX_3, and thus the values of the geminal coupling constants are not as accurate as would have been obtained using iterative methods with a computer. They are, however, consistent within themselves, and thus are adequate for the present work. As reported in the experimental section, the chemical shifts between the non-equivalent methylene protons are also subject to error, as they depend on the geminal coupling constants. The reported values are probably only accurate to ± 1 cycle. All other constants can be accurately found from a first order analysis (see experimental). An excellent indication that the vicinal coupling constants should be the same (necessitating the negative geminal coupling) is that the methyl signals (using 100 cps. recorder sweep width) are less than 0.8 cycle wide at half height, thus indicating only one peak, and thus only one coupling.

Several of the compounds studied are interesting in that they have two methylene groups adjacent to the asymmetric centre. In the first, α-chloropropyl ethyl ether XL, the A protons are non-equivalent (δ = 23.5 cycles), whereas the B protons, closer to the asymmetric centre, appear to be equivalent.

TABLE XII a

n.m.r. spectra of chloro and bromo ethers with asymmetric centres ≠

Compound	Solvent	Chemical Shift*			Δδ BC	J_{AB}	$J_{AC}-J_{BC}$	Chemical Shift*				MN	J_{LM}	J_{MO}
		A	B	C				L	M	N	O			
$CH_3CH_2OCHCH_2CH_3$ Cl	neat	72.4	235.5	211.9	23.5	7.07	9.54	333.4	118.7	118.7	60.7	0?	5.10	7.28
	CCl_4	73.5	235.9	211.1	24.72	7.07	9.56	330.6	118.7	118.7	61.2	0?	5.11	7.34
$CH_3CH_2OCHCH_2$ ClCl$_2$	neat	75.3	237.5	218.9	18.69	7.13	9.54	340.0	230.1	228.5	-	~1.6	5.68/ 5.42	-
	CCl_4	77.5	238.6	218.2	20.50	7.05	9.47	335.6	227.6	225.6	-	~2	5.96/ 5.32	-
$CH_3CH_2OCHCH_3$ Cl	neat	72.5	235.4	213.6	21.72	7.13	9.20	345.6 (358.8)	103.7 (105.5)	103.7 (105.5)	-	-	5.40 (5.60)	-
	CCl_4	73.9	236.2	211.8	24.48	7.12	9.54	340.9 (356.3)	104.3 (106.7)	104.3 (106.7)	-	-	5.40	-
$CH_3CH_2OCHCHCH_3$ ClCl	neat	75.3 (74.5)	237.8	218.0	19.79	7.04	9.66	341.8 (334.3)	252.9 (251.1)	-	95.7 (95.2)	-	2.80 (5/08)	6.72 (6/68)
$CH_3CH_2OCHCHCH_3$ BrBr	neat	77.0 (75.8)	236.3 (237.2)	218.5 (218.4)	17.84 (18.83)	7.12	9.86	376.0 (356.4)	220.0 (212.7)	-	110.7 (109.5)	-	1.96 (6.84)	6.80 (6/72)
	CCl_4	78.9 (77.5)	237.4	218.8	18.6	7.09 (7.13)	9.80	374.0 (353.5)	268.6 (261.0)	-	111.3 (110.0)	-	1.92 (7.04)	6.79 (6.75)

* Chemical shifts are measured in cycles from TMS=0, (a 60mc instrument was used). The letters refer to the protons indicated below.

≠ Values in brackets are for the compound of lower concentration where two compounds were detected.

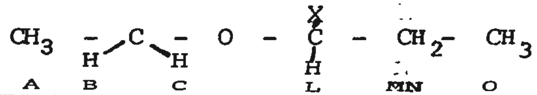
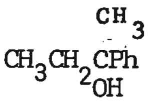
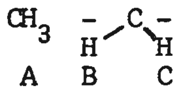

$CH_3-CH_2-O-CHX-CH_2-CH_3$

TABLE XII b

n.m.r. spectra of alkyl ethers with asymmetric centres

Compound	Solvent	Chemical Shift* A	B	C	Δ δBC	$J_{AB} = J_{AC}$	$-J_{BC}$	other protons
$CH_3CH_2OCH(CH_3)Ph$	CCl_4	66.8	199.1	?	≃ 2.7±2	7.1±2	?	CH_3=83.7; CH=260.9 J=6.5
 $CH_3CH_2C(CH_3)(OH)Ph$	neat	45.6	105.6	?	< 3#	7.2±.1	?	δOH=210.8; δCH_3^*=88.0**
	CCl_4	44.0	109.0	?	< 3#	7.26	?	180.2 86.7
	CCl_4(dil.)	44.2	104.2	?	< 3#	7.3	?	144.3 87.3**
$CH_3CH(CH_2CH_3)_x$ $O(CH_2CH_3)_y$	$(neat)_y$	67.5	202.1	210.5	8.4	7.08	8.79	δCH_3=64.3; J_{CH_3}=5.96≠
	$(neat)≠_x$	53.1	86.5≠	?	< 3≠	7.95≠	?	δCH=200.9; J_{CH-CH_2}=5.96≠

* Chemical shifts are measured in cycles from T.M.S. = 0. The letters refer to the ethyl protons as:-



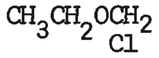
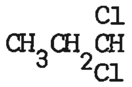
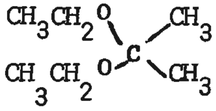
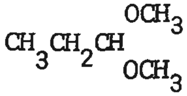
** From the spinning side bonds, there appear to be two peaks of unequal populations split by ~1.2(±.1) cycles.

\# There is a possibility these values are wrong.

≠ The x part of the spectrum is largely complicated with other parts of the spectrum, and thus the marked values should not be trusted. Note, there are several extra peaks in the BC part of the spectrum, probably from impurities (as sec-butanol).

TABLE XII c

n.m.r. spectra of ethers with no asymmetric centre

Compound	Solvent	Chemical Shift* A	B	C	Δδ BC	J_{AB} = J_{AC}	other protons
 $CH_3CH_2OCH_2Cl$	neat	73.5	224.3	224.3	0	7.06	δ = 331.2
	CCl_4	74.8	223.3	223.3	0	7.1±.1	δ = 328.3
 $CH_3CH_2CHCl_2$	neat	66.7	132.3	132.3	0	7.21	δ = 348.0; J_{CD} =5.68
	neat	65.9	205.6	205.6	0	7.09	δ = 75.7
 $CH_3CH_2CH(OCH_3)_2$	neat	51.9	94.1	94.1	0	≃ 7.2	δCH=254.8; J_{CH_2CH} = 5.58 δOCH_3=194.7(equivalent
$(CH_3CH_2O)_3PO$	$CDCl_3$	80.8	248.0	248.0	0	7.09	J_{BP}=7.91; J_{AP}=0.92
$(CH_3CH_2O)_2C(CH_2CH_3)_2$	neat	66.4	203.2	203.2	0	7.06	δCH_3=47.7; δCH_2=94.1 J = 7.32
	CCl_4	66.4	202.0	202.0	0	7.04	δCH_3=47.1; δCH_2=92.4 J=7.30
$(CH_3CH_2O)_3OCH_3$	neat	67.3	211.1	211.1	0	7.09	δCH_3=81.9

*Chemical shifts are measured in cycles from TMS=0, (a 60 Mc instrument was used). The letters refer to the protons indicated

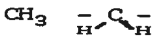
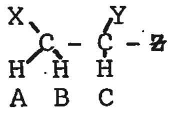


TABLE XII d

n.m.r. spectra of substituted ethanes reported by Snyder (65). (See the original paper for others).

Compound	Solvent	Chemical Shift*							Remarks
		A	B	C	Δδ AB	J_{AB}	J_{AC}	J_{BC}	
$CH_2ClCHClCN$	CCl_4	-	-	-	-	-	-	-	Too degenerate for analysis
	neat	59.93	63.06	6.43	3.13	-11.78	5.39	6.81	
$CH_2CHCO_2CH_2CH_3$ ClCl	CCl_4	32.41	43.40	7.96	10.99	-11.08	8.90	5.29	
	neat	39.85	45.95	7.25	6.10	-11,28	7.78	5.52	
$CNCH_2CHC_6H_5$ $CO_2C_2H_5$	CCl_4	65.97	78.94	7.90	12.97	-16.73	7.54	7.44	The ethoxy methane protons are also non-equivalent

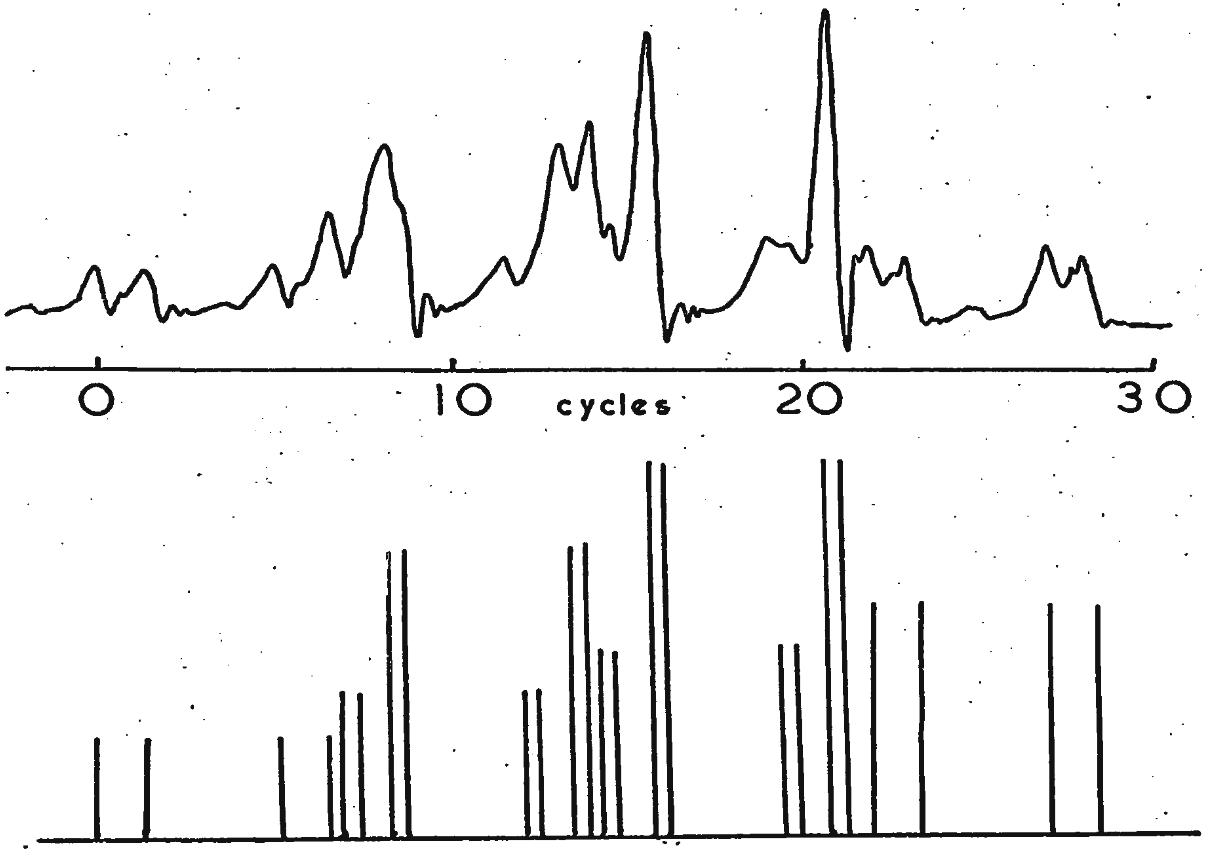
* Relative to some arbitrary zero. The letters represent the protons as:-



(A perturbation method (40. p. 154) was used to calculate both line positions and intensities of the B protons). The calculated and actual spectra agree within experimental error (see fig. 38). Thus, if the protons are non-equivalent, the chemical shift is less than three cycles. The A protons see the asymmetric carbon attached to hydrogen, chlorine and ethyl; the magnetic anisotropy of these three groups should be quite different. The B protons, however, see hydrogen,chlorine and ethoxy attached to the asymmetric carbon. If the magnetic anisotropy of C- chlorine and C- ethoxy bonds are similar, or the same, the B protons would appear to be adjacent to a magnetically compensating centre, and thus would seem equivalent. They might, however, become non-equivalent in some solvents. (Roberts (58, 61) and Snyder (65) have done extensive solvent studies on similiar type compounds, and have found that the chemical shifts and coupling constants often depend on solvent). The reported anisotropy of Cl and -OEt (73) in the gas phase (referenced to methane gas as 0) indicates the hydrogens β to the Cl or -OEt should resonate at slightly different frequencies. The spectra of two compounds, 1,1-dichloropropane and 1,1-dimethoxypropane, also indicate this. (See table XIIc). The chemical shift, however, is a combination of inductive and anisotropic effects. The chlorine appears to shield the β protons more than the oxygen, the effect of the oxygen being mainly inductive (in the gas phase). This is reasonable, as chlorine has a larger electronic shell than oxygen. Thus, the fields around these

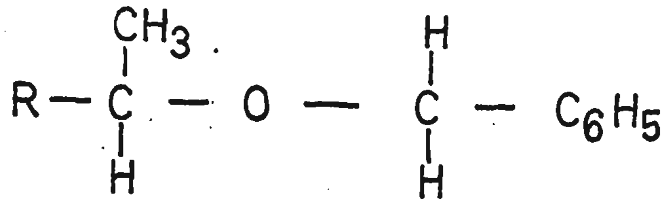
Figure 38. Observed and calculated spectra of the B-CH_2 protons of α-chloropropyl ethyl ether.

FIG. 38



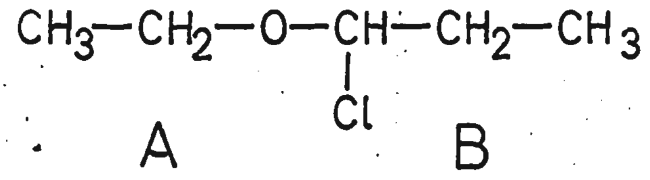
two groups must in some way interact and average out. That this effect could be sensitive to changes in solvent is quite possible. Thus, two experiments that should be performed are solvent studies on the spectra, and the preparation of ethyl 2-chlorobutanoate or ethyl 2-ethoxybutanoate. The anisotropic effect of the -COOEt group should be quite different from that of either ethoxy or chloro. Also, temperature studies could be performed. The latter type of experiment is discussed below for the 2-chloroethane series.

α,β-dichloroethyl ethyl ether XLI is similar to XL in that it has two sets of methylene protons adjacent to the asymmetric centre. In this case, however, a slight chemical shift ($\approx$ 2 cycles in CCl_4, $\approx$ 1.6 cycles neat) has been detected between the B protons. (Note, that as the B protons here are not further split by a methyl group, as in the previous case, non-equivalence is more easily observed and measured. That this shift is small indicates that the above argument is probably correct, i.e. the chloro and ethoxy substituents act as similar groups in this particular situation. The vicinal coupling constants are different. Snyder (65) has reported this for similar compounds of the type XCH_2CHYZ (see table XIId for examples). The spectra of 1,2-dichloro-1-cyanoethane XLII and ethyl 2,3-dichloropropionate XLlll, which are analogues of XLl, with the ethoxy group replaced by the cyano and



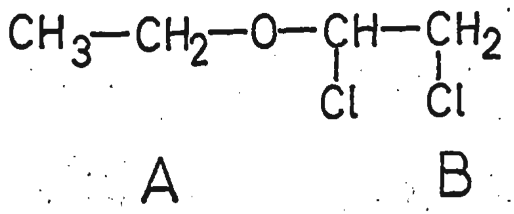
$$\mathrm{R-\overset{CH_3}{\underset{H}{C}}-O-\overset{H}{\underset{H}{C}}-C_6H_5}$$

XLIX



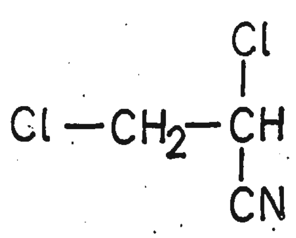
$$\mathrm{CH_3-CH_2-O-\underset{Cl}{CH}-CH_2-CH_3}$$

XL



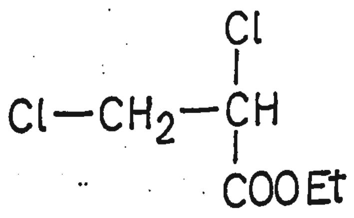
$$\mathrm{CH_3-CH_2-O-\underset{Cl}{CH}-\underset{Cl}{CH_2}}$$

XLI



$$\mathrm{Cl-CH_2-\overset{Cl}{\underset{CN}{CH}}}$$

XLII



$$\mathrm{Cl-CH_2-\overset{Cl}{\underset{COOEt}{CH}}}$$

XLIII

-COOEt groups respectively, are worthy of inspection.

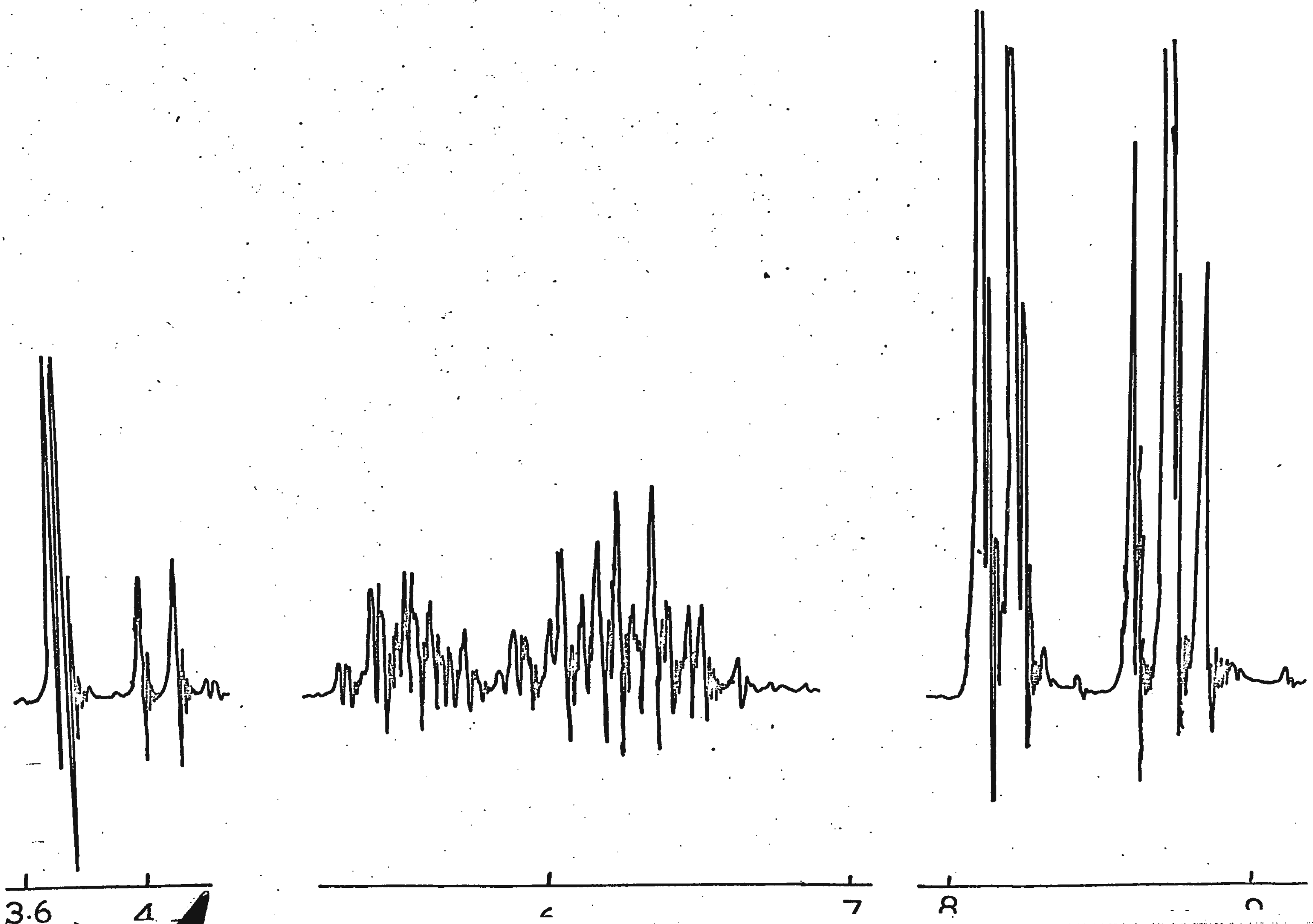
There is a 3.5 cycle shift between the methylene protons of XLll and an 11 cycle shift between the methylene protons of XLlll. Thus, the cyano and ethoxy groups appear to have about the same anisotropy as the chloro group, whilst the ester group introduces a large non-equivalence in the methylene protons. Thus, ethyl-2-chlorobutyrate should contain two non-equivalent CH_2 groups. This should be checked, and the propyl part of the spectrum should be compared with that of α -chloropropyl ethyl ether.

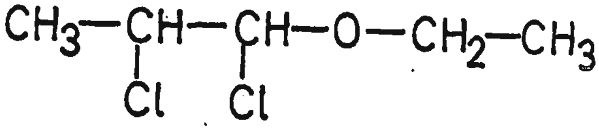
The spectra of α,β-dichloropropyl ethyl ether XLlV and α,β -dibromopropyl ethyl ether XLV present further variations. In both cases there appear to be two different compounds present (≈ 70% : 30%, both neat and in CCl_4), with different chemical shifts and coupling constants. (See figure 39). Although one of these might be an unrelated impurity, this seems very unlikely. In both cases the compounds could not be separated and the composition did not change on distillation. The spectrum of each compound corresponds to that of the assumed structure, both in line positions and integration. These compounds (XLlV and XLV), however, have two asymmetric centres, and thus there are four possible stereoisomers, or two pairs of enantiomers. The two compounds detected are probably the two sets of enantiomers.

Siddall and Prohaska (66) state that with two asymmetric centres, all that is required to develop two complete, distinct

Figure 39. Observed spectrum of α,β-dichloropropyl ethyl ether.

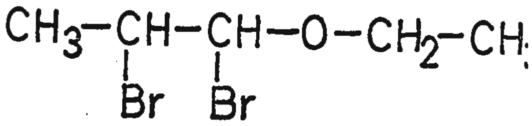
FIG. 39





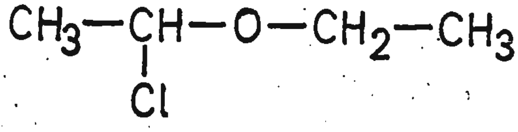
$CH_3-\underset{Cl}{CH}-\underset{Cl}{CH}-O-CH_2-CH_3$

XLIV



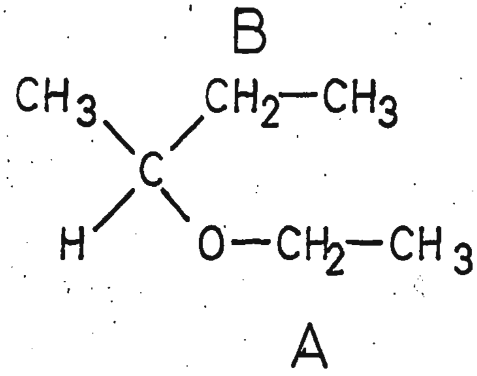
$CH_3-\underset{Br}{CH}-\underset{Br}{CH}-O-CH_2-CH$

XLV



$CH_3-\underset{Cl}{CH}-O-CH_2-CH_3$

XLVI



XLVII

sets of signals are groups with large enough electric and / or magnetic fields within the molecules. Chlorine and bromine are obviously suitable groups.

The spectrum of α-chloroethyl ethyl ether XLV1 also appears to show the presence of two compounds, but now there is only one asymmetric centre. In this case, either there is an impurity present, or the molecule is not in free rotation. From the integration of the spectrum, the extra peaks appear to be an impurity.

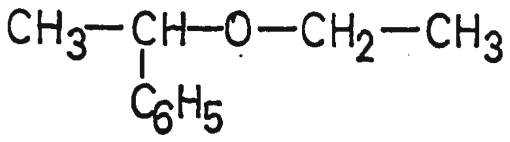
Probably the most interesting compound studied is sec-butyl ethyl ether XLV11. Although this compound could not be purified completely by redistillation (the impurity being sec-butyl alcohol), a reasonable spectrum (estimate 80 - 90% ether) was obtained, and analysed. The A protons are non-equivalent, the chemical shift between them being 8.4 cycles. The protons of the B methylene group were, however, equivalent. This is the complete opposite of what might be expected, as the A protons "see" the asymmetric carbon attached to hydrogen, methyl and ethyl, the latter being anisotropically fairly similar groups; whilst the B protons "see" methyl, hydrogen and ethoxy, three magnetically different groups. Thus, the oxygen must be important in the observation of non-equivalence in this compound. It is also surprising that both the A protons resonate at a lower field than the CH proton. No logical reason can be found to explain this, as tetriary protons usually resonate to lower fields than secondary protons in similar environments in saturated compounds.

The large methylene chemical shift of XLV11 is even more interesting when XLV111 and L are considered.

α -phenylethyl ethyl ether XLV111 would be expected to have a large CH_2 non-equivalence. In CCl_4 solution, however, a shift of 2.7 ± 2 cycles was measured (Roberts (58) reports for this compound shifts in :- CCl_4, acetone < 2 cycles, C_6H_6 ≈ 3 cycles. Only in XL1X did he find a large methylene chemical shift (≅10 cycles CCl_4, C_6H_6; ≈2.5 cycles acetone). The phenyl group is associated with a large anisotropy, and thus XLV111 would be expected to show a much larger methylene non-equivalence than XLV11.

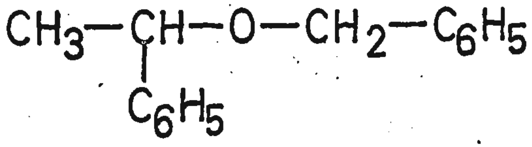
β-phenyl- β -hydroxybutaneXL is the last compound containing an asymmetric centre studied. In this case the methylene protons see an asymmetric carbon attached to phenyl, methyl and hydroxy ,three magnetically and electrically different groups. No non-equivalence could be detected (neat and CCl_4 solutions), and thus an upper limit of 3 cycles has been set on any possible chemical shift. In this case, the methylene group is adjacent to the asymmetric centre, with no oxygen in between. This again indicates the probable importance of the oxygen atom in the non-equivalence problem.

Data for several compounds containing no asymmetric centre have been included in table X11c. In each case, however,their methylene protons are equivalent. They are included solely for the purpose of comparison.



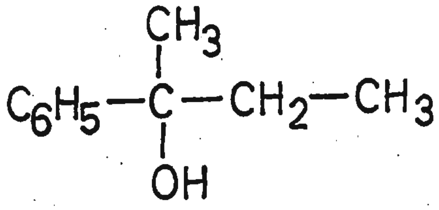
$$\underset{\displaystyle C_6H_5}{CH_3-\underset{|}{C}H}-O-CH_2-CH_3$$

XLVIII



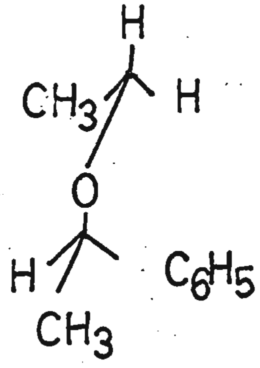
$$\underset{\displaystyle C_6H_5}{CH_3-\underset{|}{C}H}-O-CH_2-C_6H_5$$

XLIX



$$C_6H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-CH_2-CH_3$$

L



LI

Chapter 8

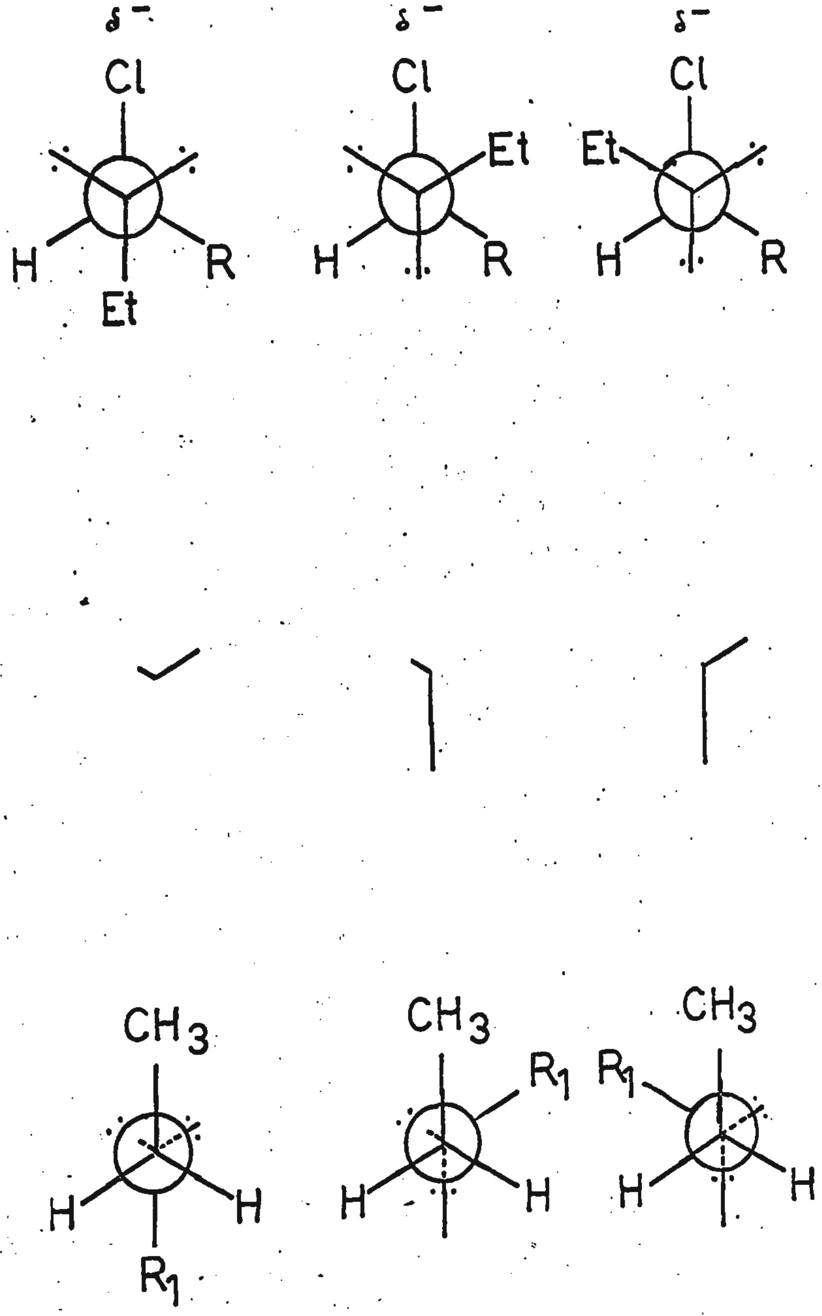
Discussion

As yet, there seems to be no unambiguous explanation of methylene splitting in asymmetric molecules, although Gutowsky's method (69) seems the most reasonable. Freymann's chelation of the CH_2 protons with the oxygen (see introduction and 64) is another possible contributing factor.

The oxygen, which is a highly polarizable centre, must contribute toward the large geminal chemical shifts in the ethyl ethers. The oxygen appears to become an "induced asymmetric centre". The groups on the true asymmetric centre affect the two sets of oxygen lone pair electrons to a different extent, whether or not free rotation occurs, that is, the lone pairs are in different averaged environments. Thus the oxygen, assuming it has an approximately tetrahedral electronic arrangement, becomes asymmetric itself. (See figure 40). This is the same as normal methylene non-equivalence as described by Pople (68), except that now the electron orbitals, and not the protons, become non-equivalent. Thus, the molecule has two asymmetric centres and nine, instead of three, possible rotamers. This means the two methylene hydrogen shifts are more likely to be different, with or without free rotation. Randall et al (57) suggested a similar type effect with N, N-dimethyl benzyl amines with an asymmetric centre in the o- or m- position. They stated : "One might have to consider not only the field effects through space, such as for con-

Figure 40. Asymmetric amplification in saturated ethers containing an asymmetric centre.

FIG. 40



formers, but also the possible influence of asymmetry introduced in the electronic system of the molecule by the asymmetric group". Thus, the ether methylene protons see, besides the true asymmetric centre, an additional asymmetry in the oxygen atom. This explains the large geminal chemical shifts. Gutowsky's equation (equation 11) could probably be applied twice to this system; the first time for the effect of the asymmetric carbon, and then for the effect of the "induced asymmetric" oxygen. The effect of the carbon on the methylene protons would be:

$$\langle \Delta\nu_H \rangle_{C*} = \sum_{n=1}^{9} (x_n - \tfrac{1}{3}) \Delta\nu_n^0 + \sum_{n=1}^{9} (x_n - \tfrac{1}{3}) \delta\nu_n + \sum_{n=1}^{9} \tfrac{1}{3} \delta\nu_n \qquad (13)$$

Where there are 9 possible rotamers (figure 40), $\Delta\nu_n^0$ is the chemical shift that would be reported between the methylene protons if the CH_3 of the ethyl group were replaced by H. $\delta\nu_n$ is the effect of replacing H by CH_3, and x_n is the population in rotamer n (see introduction and (69). Similarly, the asymmetric centre would induce a non-equivalence on the oxygen lone pair electrons, where the induced difference in average electron density, $\langle \Delta e \rangle$, between the two electron pairs would be, using the analogy of Gutowsky's equation,

$$\langle \Delta e \rangle = \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \Delta e_n^o + \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \delta e_n + \sum_{n=1}^{3} \delta e_n \qquad (14)$$

Δe_n^o is the electron density of the two lone pairs were the ethyl group replaced by a lone pair of electrons, and δe_n represents the change in Δe_n^o by the additional asymmetry of the ethyl group. (Note, n = 3 as there are 3 possible rotamers, of figure 37). Then, applying Gutowsky's equation a third time, using the oxygen as the asymmetric centre, another chemical shift can be obtained. (n = 3 for 3 possible rotamers, as in figure 37).

$$\left\langle \Delta\nu_H^{1} \right\rangle_{\ddot{O}} = \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \Delta\nu_n^{1\,0} + \sum_{n=1}^{3} (x_n - \tfrac{1}{3}) \delta\nu_n^{1} + \sum_{n=1}^{3} \tfrac{1}{3} \delta\nu_n^{1} \qquad (15)$$

The symbols have their usual significance. Thus, the observed methylene shift should be

$$\left\langle \Delta\nu_H^{obs.} \right\rangle = \left\langle \Delta\nu_H \right\rangle_{C*} + \left\langle \Delta\nu_H \right\rangle_{\ddot{O}:} \qquad (16)$$

Thus, the ether oxygen introduces a perturbation term into the original equation (11), and seems to "amplify" the effect of an asymmetric centre. As pointed out by Gutowsky, temperature studies might be able to separate the contribution of the pure asymmetry term from the other terms, and future experiments of this nature might well prove interesting. Roberts (47), however, found no change in the spectrum of acetaldehyde diethyl acetal at - 80°C.

The spectra of most of the ethers fit this hypothesis. β -phenylethyl ethyl ether XLV111 is odd, and would be expected to have a large methylene non-equivalence. In this case, either some of the factors in equation 16 cancel, or the phenyl ring is oriented in such a way as to minimize its effect. Roberts (58), using the theory of preferred conformations, suggests that this lack of non-equivalence is due to a very small contribution from the conformer L1 with H near the benzene ring. This seems a simplification of the whole problem, as intuitively it would seem there should be fairly free rotation around the ether C - 0 bonds. Also, Ll would appear (intuitively) to be a favored conformation.

That the compounds with a methylene group immediately adjacent to the asymmetric centre do not show a large methylene non-equivalence, strengthens the "induced asymmetric oxygen" hypothesis. β-phenyl- β -hydroxy butane L is a good example of this, with a geminal shift < 3 cycles. Snyder (65) reports several substituted ethanes with non-equivalent methylene groups. They have, however, bulky groups in both the α and β positions, and thus conformer perference is inevitably a more important factor here.

Sec-butyl ethyl ether XLVll seems to be an excellent example of oxygen "amplification", as the three groups on the asymmetric centre (Et, Me, H) should not be greatly different magnetically. The observed value of Δδ (8.4 cycles), however, seems a bit high, and another explanation for the large non-equivalence in this compound might well be correct. Chelation (64) cannot be ruled out.

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* Professor of Theoretical Chemistry, University of Bristol.

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