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1-3 dipolar cycloadditions of nitrile ylides

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I-3 DIPOLAR CYCLOADDITIONS OF NITRILE YLIDES

by


Steven P. Braff, *U.C. 1972*
" "

Senior Thesis Submitted
in Partial Fulfillment
of the Requirements for Graduation

DEPARTMENT OF CHEMISTRY

UNION COLLEGE

APRIL 13, 1972



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This Thesis
Submitted by

to the
Department of Chemistry of
Union College in Partial
Fulfillment of the Requirements
of the Degree of Bachelor of Science
with a Major in Biology,

is Approved by

Howard E. Sheffer

April 13, 1972

LB

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I would like to thank Professor Sheffer for his help, criticism, and his encouragement during the course of this work. I would also like to thank the other members of the chemistry department who gave their time to answer my many questions. Most of all, I wish to thank my wife Martha, without whose patience and interest this work would not have been completed.

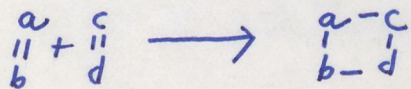
TABLE of CONTENTS

Historical.....1
Proposed Scheme.....5
Experimental.....7
Mechanisms and Discussion.....17
Spectra.....34
Footnotes.....45

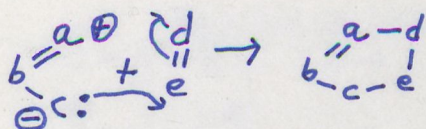
History

1-3 dipolar cycloaddition is the union of a 1-3 dipole, a-b-c, with a system containing a multiple bond, d-e, to form a five membered ring. In this scheme, center a contains an electron sextet, and concomitant positive charge, while center c contains an unshared pair of electrons and is the anionic center of the dipole. In the cycloaddition reaction, the 1-3 dipole and the multiple bond system (called the dipolarophile), collapse to form a five membered ring with loss of all formal charges. 1.

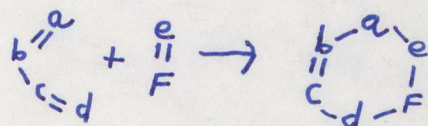
fig. 1 Some Cycloadditions



thermal and photochemical-dimerization of alkenes

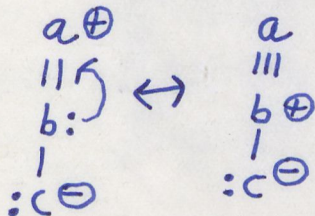


1-3 dipolar additions

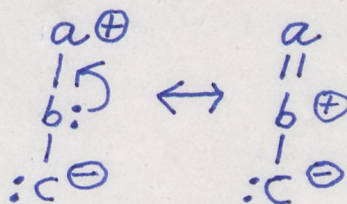


Diels- Alder reaction

fig. 2 1-3 Dipolar Systems



with double bond
b=N

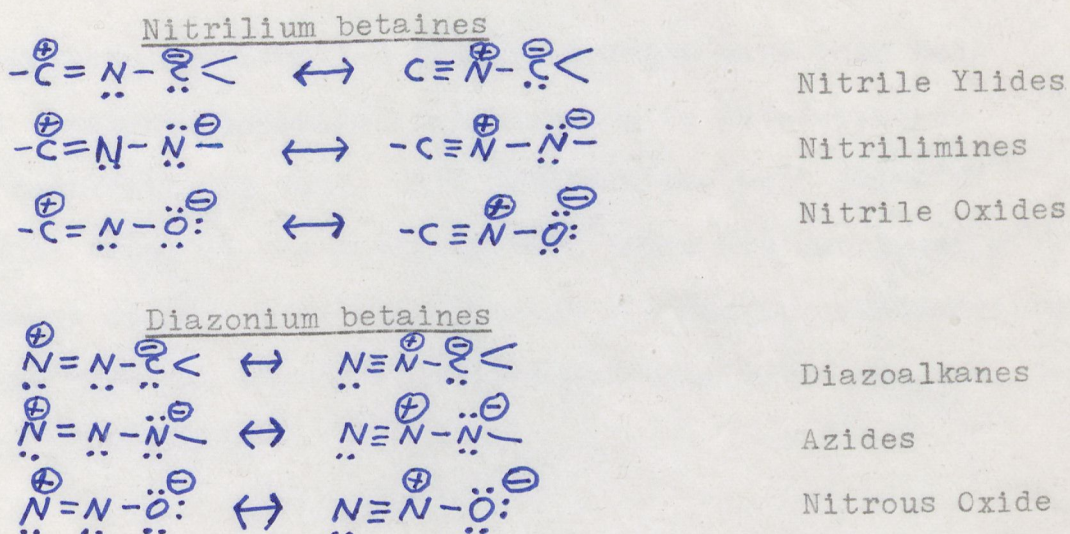


without double bond
b=N or b=O

1-3 dipoles with the positive center on electron deficient carbon, nitrogen or oxygen atoms are not capable of existence as stable substances.² In one resonance structure, atom b holds an unshared electron pair, which it is capable of donating to cationic center a by the formation of another bond, thus shifting the formal charge to b. If the unmasked 1-3 dipole contains a double bond, the middle atom b must be nitrogen. No other atom in the first row of the periodic table can accommodate a lone electron pair in the neutral tetravalent state.

We can also imagine an unmasked 1-3 dipole that doesn't contain a double bond. In this case, the middle atom b can now be nitrogen or oxygen. Once again, the lone pair from b must stabilize the electrophilic center through resonance.

fig. 3a 1-3 Dipolar Systems with double bonds³

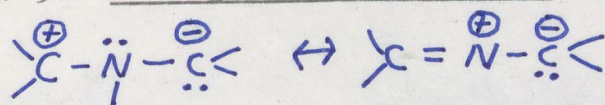


There are six conceivable 1-3 dipolar systems that contain a double bond. These are classified nitrilium and diazonium betaines. In each class of betaines, the anionic center varies

from carbon to nitrogen to oxygen. For each type, the all-octet resonance form is shown to the right while the canonical form indicating the 1-3 dipolar character of these compounds is shown to the left.

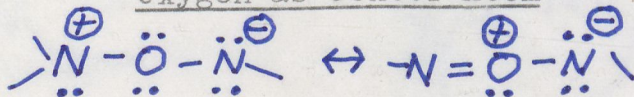
There are twelve classes of 1-3 dipolar compounds which do not contain a double bond in the sextet resonance form. Six of these systems have nitrogen as the central atom, while six have oxygen. Some of these have yet to be discovered. For the sake of brevity, only one example from each group will be shown.

fig. 3b Nitrogen as Center Atom



azomethine ylides
+ five others

Oxygen as Center Atom

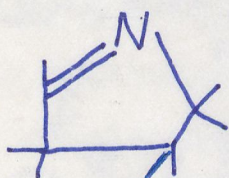


Nitroso Imines
+ five others

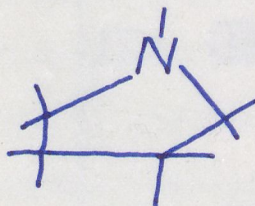
All together, eighteen 1-3 dipolar systems have been mentioned. The synthetic potential with respect to heterocyclic adducts is fantastic. In fact, this reaction may well prove to be as broad in scope as the Diels-Alder. Below are mentioned a few examples of adducts available through 1-3 dipolar cycloaddition. To date, more than one thousand analyzed adducts have been synthesized via this route.

fig. 4 Some Heterocyclic Systems available by 1-3 Addition

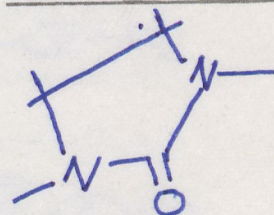
Pyrrolines



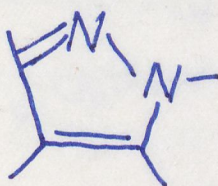
Pyrrolidines



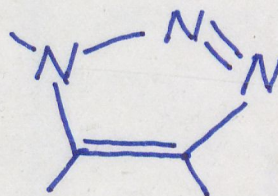
Imidazolidones



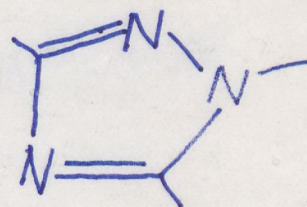
Pyrazoles



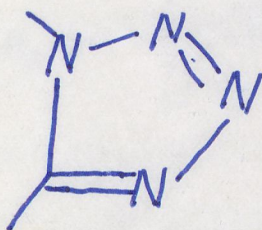
1,2,3-Triazoles



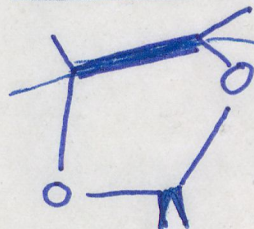
1,2,4-Triazoles



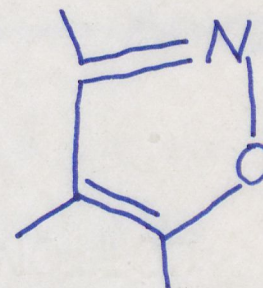
Tetrazoles



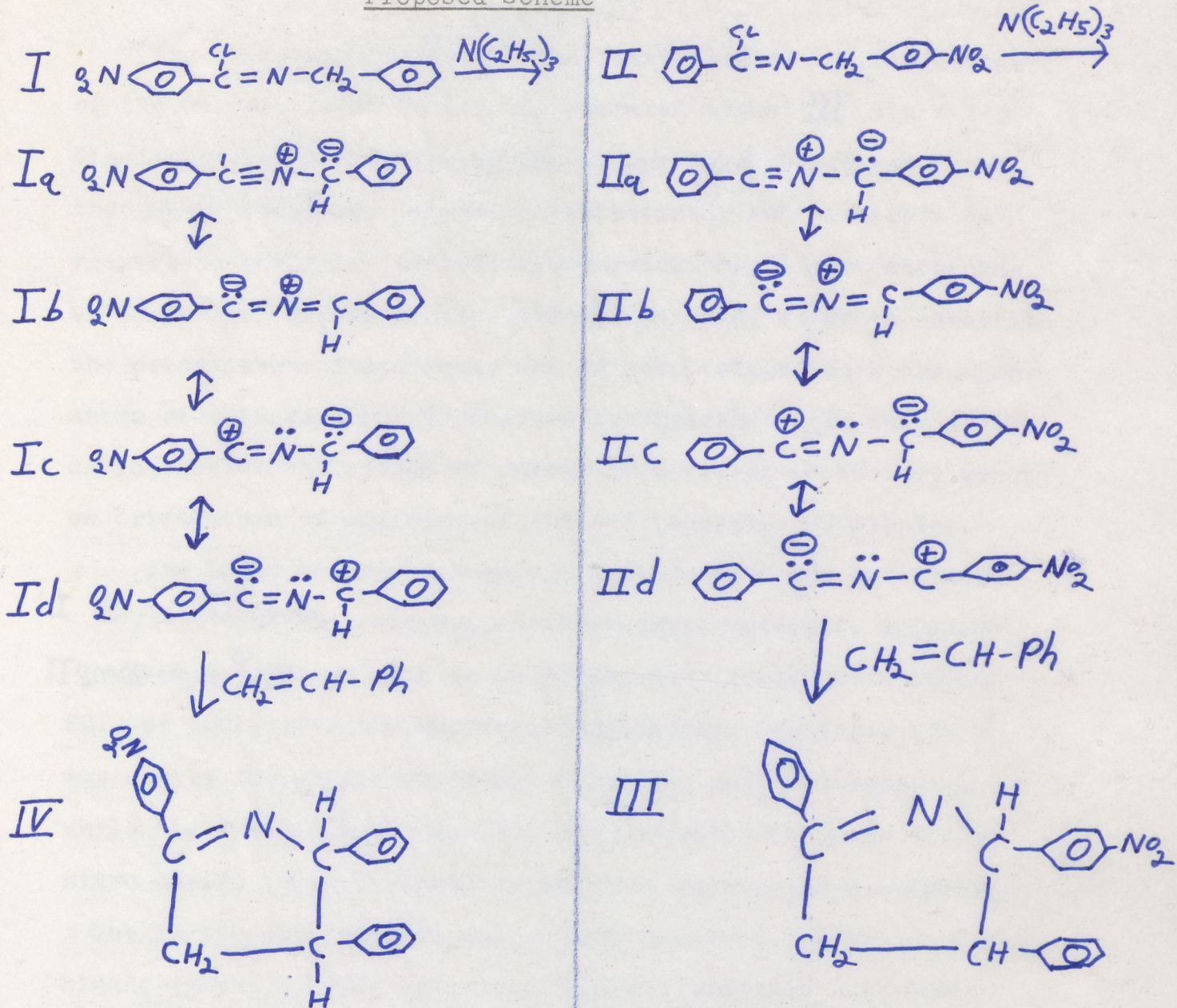
1,3-Dioxolans



Isoxazoles



Proposed Scheme

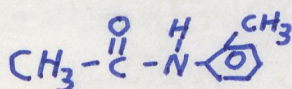


Compound **II** is an example of the Nitrile Ylide group of 1-3 dipoles. It is thus an octet stabilized dipole, with a double bond. The first Nitrile Ylide was obtained by H:Cl elimination from the imido chloride **II** with triethylamine at twenty degrees Centigrade. Triethyl ammonium chloride separates, and a solution of **II(a-d)** results.

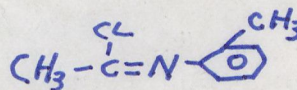
The intermediates $\text{II}(\alpha\text{-d})$ was first studied by Rolf Huisgen of the University of Munich. He prepared adduct III via a 1-3 dipolar route. During the course of our research it was hoped that $\text{I}(\alpha\text{-d})$ and $\text{II}(\alpha\text{-d})$ could be synthesized, and studied with respect to their 1-3 cycloaddition reaction. In this work, the unsymmetrical dipolarophile styrene was used, so as to ascertain the orientation of addition, and to help to elucidate the mechanism of this reaction (concerted or diradical). In this way we could observe the effect of change of position of the NO_2 group on orientation of addition of the two isomeric 1-3 dipoles.

The imido chlorides N-benzyl 4-nitrobenzimidido chloride I $\text{C}_6\text{H}_4(\text{NO}_2)\text{-CH}_2\text{-N}=\overset{\text{Cl}}{\text{C}}\text{-C}_6\text{H}_5$ and N-(p-nitro benzyl) benzimidido chloride II $\text{C}_6\text{H}_4(\text{NO}_2)\text{-CH}_2\text{-N}=\overset{\text{Cl}}{\text{C}}\text{-C}_6\text{H}_4(\text{NO}_2)$ were to be prepared by reaction of either PCl_5 or SOCl_2 with the corresponding amides. The amide for I was easily prepared from benzyl amine and p-nitro benzoyl chloride, while the amide for II required an elaborate synthesis of p-nitro benzyl amine followed by reaction with benzoyl chloride.

Due to the difficulties encountered in the preparation of the highly reactive imido chlorides, a model compound X (o-aceto Toluidide) was employed to make the corresponding imido chloride Y (o-tolyl-acetimido chloride). It was hoped that the use of a model compound would give us a better picture of the conditions under which the amides might be converted to the corresponding imido chlorides.



X



Y

Experimental

Reaction R-1 Preparation of N-benzyl 4-nitro benzamide

Using a method reported in Beilstein,⁶ 0.04 moles of benzyl amine and 0.04 moles of p-nitrobenzoyl chloride are dissolved in a solution of twenty ml. of acetone, containing 0.06 moles of pyridine. The reaction is run in a 250 ml. round bottom flask equipped with a water condenser, for a period of one hour at a temperature of 120 degrees. The product is then dissolved in chloroform and washed with dilute H:Cl and dilute NaOH in a separatory funnel to remove the pyridine and the unreacted benzyl amine. The chloroform is then evaporated off, leaving behind white crystals of m.p. 140-143 degrees. Recrystallization is effected from a solution of alcohol:water (2:1). The final product is 6.0 grams of crystals giving a 56% yield, and a literature melting point of 141-143 degrees. The product is soluble in ether and highly soluble in benzene. Please see spectra #5 and spectra #9 at the end of this report.

Sequence for Preparation of N-(4-nitrobenzyl) benzamide

Reaction R-2a Preparation of N-(4-nitrobenzyl) phthalimide

This method is a modification of the well known Gabriel Synthesis of pure primary amines. Ing and Mansk reported it in the Journal of the Chemical Society (London).

We combined 0.175 moles of phthalimide, 0.088 moles of

anhydrous potassium carbonate, and 0.219 moles of 4-nitrobenzyl chloride, and refluxed for three hours in a 250 ml. round bottom boiling flask, equipped with a long air condenser. Next, the excess 4-nitrobenzyl chloride was distilled in a current of steam at its decomposition point of 170 degrees. The product charred each time this step was carried out. The product was next filtered off with water and recrystallized from glacial acetic acid. The melting point of 235-260 degrees indicated that the product consisted of impure phthalimide (m.p.=260). Rather than continue with this preparation, a literature search revealed another method.

Reaction R-2b Preparation of 4-nitrobenzyl phthalimide

In a 500 ml. pyrex beaker, 0.2 moles of phthalimide were dissolved in 140 gr. of dimethyl formamide. During the next fifteen minutes, 0.2 moles of potassium metal, cut into small pieces, was added to the solution. Stirring was effected with a magnetic stirrer, and the solution was heated on a hot plate, to the point where the reaction became visibly exothermic. The reaction was slowed down by immersing the beaker in an ice water bath, so as not to char the product. This first step was carried over forty minutes. Then 0.2 moles of 4-nitrobenzyl chloride was added to the reaction vessel and stirred for forty five minutes. After ten minutes, the solution turned dark brown, and it then became pink with a white precipitate. At this point, 200 cc of water were added to the solution. The 4-nitrobenzyl phthalimide was extracted two times, first with 200cc and then with 100 cc of chloroform.

The two chloroform solutions were combined and washed two times with water, and then dried over anhydrous sodium sulfate.

The chloroform was evaporated off, and the product was recrystallized from glacial acetic acid. The final yield was 17.0 grams (31%) of crystals of literature melting point (166-168).

Reaction R-2c Preparation of 4-nitrobenzyl amine·HCl

We dissolved 0.05 moles of finely powdered 4-nitrobenzyl phtalimide in 100 ml. of ethanol, and warmed the solution with 0.05 moles of hydrazine-hydrate (85% technical). The yellow solution is heated at reflux temperature using a water condenser for a period of two hours. At this time, five ml. of concentrated hydrochloric acid was added to the solution and the white phtalylhydrazide precipitates out. The solution is cooled and filtered, and the precipitate is washed with four, 10 ml. portions of ethyl alcohol. The filtrates are combined with the yellow solutions and concentrated to ten ml. Then fifty ml. of water is added, and any precipitate is filtered off. The solution is then concentrated to thirty ml. and once again filtered. Finally, the solution is evaporated to dryness. The resulting product is 7.55 grams of 4-nitrobenzyl amine·H:Cl of m.p. 250-253. (lit.=251-253) The yield is 80% of theoretical.

Reaction R-2d Preparation of N-(4-nitrobenzyl) benzamide

We dissolved 0.039 moles of finely powdered 4-nitrobenzyl amine·H:Cl and 0.148 moles of benzoyl chloride in 1.48 moles of two Normal sodium hydroxide. This solution is shaken in a

large corked Erlenmeyer flask for several minutes with frequent release of pressure. The product is filtered and recrystallized from alcohol. The melting point is 153-154, which is the same as the literature value. A 50% yield of product was obtained. It is important that the 4-nitrobenzyl amine·H:Cl be finely powdered in a mortar and pestel, since in basic solution, it has a tendency to stick together, lessening the extent of reaction and the percent yield. Please see spectra #3 and spectra #8 at the end of this report.

Reaction R-3a Attempted Preparation of N-(p-nitrobenzyl benzimidchloride

In Huisgen's work on 1-3 dipolar cycloadditions, he used the imido chloride N-(p-nitrobenzyl) benzimido chloride to produce an example of a nitrile ylide. The isomer of this imido chloride N-benzyl-4-nitro benzimido chloride was not mentioned in his work. One of the things we wanted to study in this research project was the change that variation in position of the NO₂ group would exert on the 1-3 dipolar cycloaddition reaction, as well as on the reaction leading to the formation of the imido chloride.

In the first attempt to synthesize the compound N-(p-nitrobenzyl)benzimidochloride,⁹ we combined 0.015 moles of N-(4-nitrobenzyl) benzamide with 0.015 moles of PCl₅ in 25 ml. of dry benzene. In a 100 ml. round bottom boiling flask, nitrogen was bubbled into the solution which was refluxed at 160 for a period of 1.5 hours. Next, the benzene and POCl₃ were removed at 2mm. pressure using an oil pump equipped with a dry ice-acetone trap.

Three more 25 ml. portions of dry benzene were added to the reaction flask. Each time, the product was dissolved in the benzene, and then the POCl_3 and benzene were removed *invacuo*. The product consisted of a frozen oil. It was dissolved in 15 ml. of dry ether, and recrystallization was attempted. The imido chloride could not be isolated in this manner. When working with a compound of the imido chloride family, all equipment and solvents must be free of water. The imido chloride will react with even trace amounts of water or with any solvent containing active hydrogen. For this reason, alcohols must not be used in recrystallization procedures. Any bases used in reactions with imido chlorides must be Lewis bases like pyridine or triethylamine. Two possibilities come to mind to explain the lack of success we had using this method to produce N-(p-nitrobenzyl) benzimido chloride. Either there was water in one of our reactants, or, the reactants were not refluxed for a long enough period of time to effect conversion of the amide. During the course of this research, it was also found that many imido chloride compounds decompose within 48 hours of the time they are synthesized. For this reason, they should be identified and used as quickly as possible.

Please see spectra #4. When compared with spectra #3, the disappearance of the NH peak of the amide is quite visible. This indicates strongly that there may, in fact, have been at least partial conversion to the imido chloride compound.

Reaction R-3b Preparation of N-(o-tolyl) acetimido chloride

We dissolved 0.033 moles of o-Acetotoluidide in 0.33 moles of SOCl_2 , and refluxed the solution for four hours in a round bottom boiling flask, equiped with a magnetic stirrer. The excess SOCl_2 was then removed by use of an aspirator overnight. O-Acetotoluidide is insoluble in room temperature hexane, while the corresponding imido chloride is reported to be soluble in hexane. There was no fraction of product found to be soluble in hexane or petroleum ether after careful column chromatography of the reaction product. At this point, a deeper literature search showed that several structural isomers of N-(O-tolyl) acetimido chloride were clear liquids with boiling points in the range of 120 at 15 mm. pressure. Up to this point, we had been looking for a solid product.

SOCl_2 was found to be an easier to use chlorinating reagent because both biproducts, SO_2 , and fuming HCl are eliminated from the reaction vessel in gaseous form. PCl_5 was a harsher reagent, in that the NMR spectra of products indicated that the PCl_5 was cleaving the amide to give p-nitrobenzyl amine as the major product. POCl_3 , a solid biproduct was also more troublesome to remove from the reaction vessel. As already mentioned, it had to be azeotroped off with benzene at 2 mm. pressure.

Reaction R-3c DMF Catalyst for N-(o-tolyl) acetimido chloride

Dimethyl Formamide $\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N} \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array}$ is reported in the

literature¹¹ to be an effective catalyst-solvent in reactions involving chlorination. The procedure used was essentially the same as in reaction R-3b, except that the amide was first dissolved in 0.016 moles of DMF. This reaction went uncontrollably throughout a range of temperatures. In one minute of reaction time, the product consisted of a black solid tar. There might have been a side reaction. However, using mylar backed thin layer chromatography, with a developer solution of dry benzene: absolute alcohol (10:1) it was found that the amide was being converted. The R.T. value of o-Acetotoluidide was 0.77, and the R.T. values for the tar product of this reaction were 0.77 and 0.32. Thin layer chromatography, and infra red spectra, proved to be useful tools to determine the extent of reaction. An especially useful peak to watch is the disappearance of the NH peak at 3100-3300 cm^{-1} , as well as the disappearance of the C=O peak at 1625-1635 cm^{-1} . The imido chloride should also have strong C-Cl absorption at 700-800 cm^{-1} .

Reaction R-3d Preparation of N-(o-tolyl) acetimido chloride

A deeper search of the literature indicated that the imido chloride reaction might be run with good yields in a Lewis base like pyridine, or dioxane or triethylamine. Apparently the pyridine forms some sort of complex with the SOCl_2 that favors the reaction going towards completion.

The o-Acetotoluidide was dissolved in a two equivalent excess of pyridine. Then, a molar proportion of SOCl_2 was added

dropwise over a period of fifteen minutes to the magnetically stirred pyridinal solution, which was kept at ice bath temperature. This procedure was carried on for ninety minutes, after which time the excess SOCl_2 and pyridine were aspirated off, and the oil like product remaining was dissolved in dry benzene and vacuum distilled at 15mm. 122-125 degrees. A clear liquid distilled over which was spectrally confirmed to be the imido chloride. The boiling point of the product is also in the same range as the boiling point of its structural isomers reported in the literature.

At the end of this report are appended the infra red and NMR spectra of o-Acetotoluidide (spectra #1, and #6), as well as the spectra of N-(o-tolyl) acetimido chloride prepared from this model compound (spectra #2, and #7). Note especially the disappearance of the NH peak on the NMR and IR spectra.

Reaction R-3e Preparation of N-benzyl 4-nitrobenzimidido chloride

At this point, we were fortunate to find new references for the preparation of the imido chloride compounds we wanted to obtain. One reported method was almost exactly like reaction R-3b in this report,¹² however, only two equivalents of SOCl_2 are used. The important fact to note in the following table is the large reflux time needed to effect conversion to N-(p-nitrophenyl) benzimidido chloride. $\text{C}_6\text{H}_5-\overset{\text{Cl}}{\text{C}}=\text{N}-\text{C}_6\text{H}_4\text{NO}_2$ In this method, the product is recrystallized from petroleum ether.

fig. 5 Preparation of R-C-Cl=N-R'

<u>R</u>	<u>R'</u>	<u>reflux time</u>	<u>% yield</u>
Ph....	Me.....	1 hour.....	76
Ph....	Ph.....	1 hour.....	88
Ph....	p-Cl-Ph	2 hour.....	82
Ph....	O ₂ N-Ph.	6 hour.....	88 (needles, m.p. 114-116)
Cl-Ph.	Ph.....	2 hour.....	62

Our reaction was run according to the method reported by Huisgen, Sauer, and Seidel in Chem. Berect. We combined 0.044 moles of SOCl₂ with 0.022 moles of N-benzyl p-nitro benzamide. The solution was refluxed for six hours time, and gave , according to NMR spectra a 20% yield.

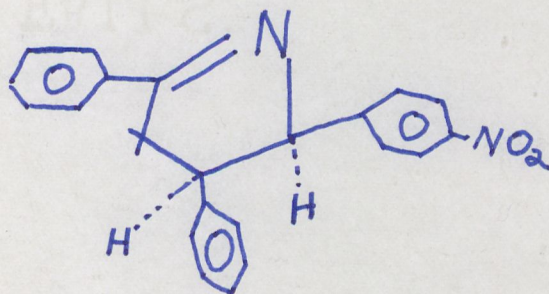
The next logical procedure to try, in an attempt to convert amides to imido chlorides, seems to be along the lines of reaction R-3d. Since we were able to get conversion of the model compound X to the imido chloride Y using pyridine as a solvent, this should also be tried for better yields in the conversion of the amides A and B to their corresponding imido chlorides **II** and **I**.

Please see spectra #10, #11, and #12. These spectra strongly indicate that we may have effected conversion of amide to imido chloride. When we compare the spectra of the amide (#9) with these other spectra, we can see the disappearance of the NH peak. It seems that we may have prepared the imido chloride compound. The major problem lies in purifying it.

Reaction R-4 Cycloaddition Reaction

Benzimidoyl chloride, with a p-nitrobenzyl group on the nitrogen atom, eliminates H:Cl on treatment with triethylamine in benzene at room temperature. The nitrile ylide can't be isolated, but is readily intercepted by dipolarophiles. With acrylonitrile, 1-3 addition yields two diastereomeric hindered 1-pyrrolines which can be dehydrogenated to an aromatic pyrrole derivative. Aldehyde groups and styrene are also suitable dipolarophiles.¹³

In the same article (reference 13), Huisgen reports that styrene containing N-(p-nitrobenzyl) benzimido chloride undergoes the cycloaddition reaction when treated for twenty hours at 15-20 degrees with triethylamine. The products were isolated at a temperature less than 20 degrees, and separated by preparative thin layer chromatography on silica gel. They consisted of 65:35 cis-pyrroline (m.p. 107.5-108.5) and trans pyrroline (m.p. 92-93). Both products dehydrogenated to the same triaryl pyrrole pictured below, after treatment with chloranil in boiling xylene.



Mechanism

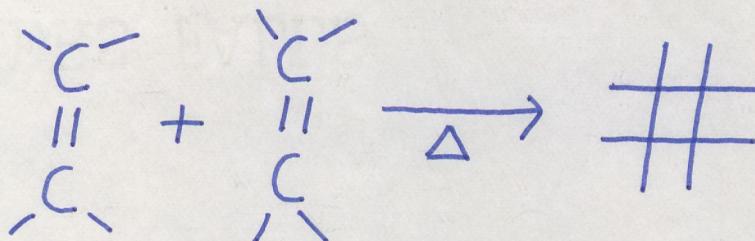
The concept of 1-3 dipolar cycloadditions was first suggested by Smith in 1938. But it was Rolf Huisgen who recognized the generality of the reaction in a series of brilliant researches.¹⁴

Huisgen feels that the mechanism is a single step, four centered cycloaddition, in which the two new sigma bonds are both partially formed in the transition state, to nearly the same extent.

On the other hand, Raymond Firestone has put forward a different mechanism to explain the 1-3 dipolar cycloaddition. He proposes a spin paired diradical intermediate in place of Huisgen's one step pathway with a single transition state. Firestone feels that the experimental data can be better explained by a two step mechanism, with a discrete intermediate, and the first step rate determining.

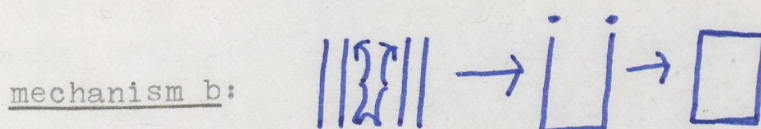
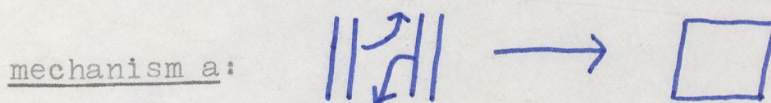
The idea of a diradical intermediate in thermal cycloadditions was first proposed by Kistiakowsky for the Diels-Alder reaction in 1937. A diradical intermediate has almost certainly been identified in the mechanism of dimerization of alkenes.¹⁵ For this reason, it might be useful to take a look at the evidence for the various mechanisms of these two reactions. Then we will discuss the proposed evidence and mechanisms for the 1-3 dipolar cycloaddition reaction. Finally, we will relate our research approach to the possible elucidation of the correct mechanism.

fig. 6 Dimerization of Olefins¹⁶

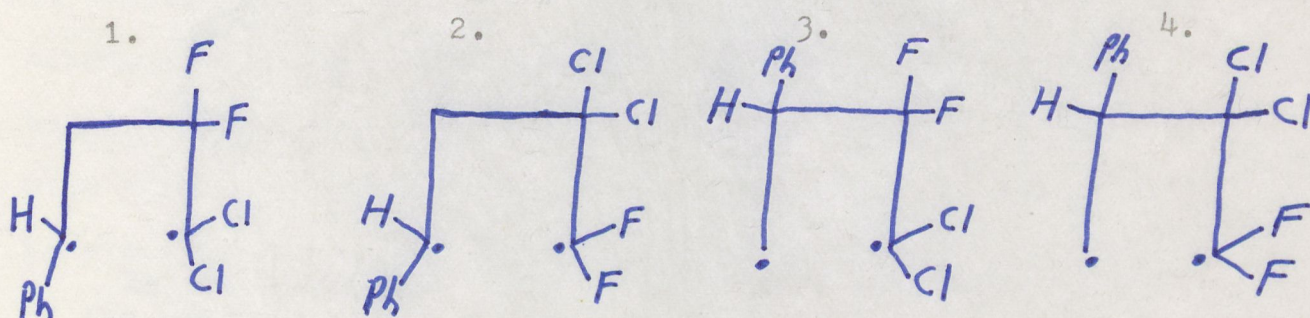


This is a reaction between two molecules of olefin to give a cyclobutane derivative. It is not a general reaction for olefins, as it occurs almost exclusively with $F_2C=CX_2$ ($X=F$ or Cl), as well as with styrene and acrylonitrile.

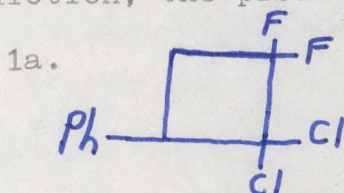
Two mechanisms have been proposed, and are pictorially represented below. Mechanism a is a thermal, concerted, one step process, whereas mechanism b is a diradical, two step process with a discrete diradical intermediate.



The evidence for the mechanism of the dimerization of olefins seems to point toward the diradical mechanism. When unsymmetrical olefins couple, the orientation of the product can always be predicted on the basis of the relative stability of the possible diradical intermediates:

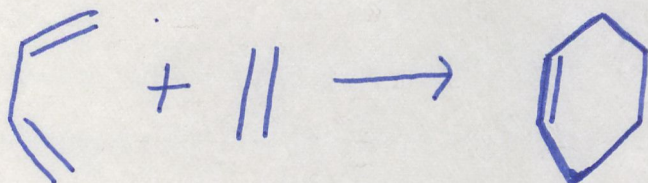
fig. 7 Possible Intermediates in Reaction of Styrene + $F_2C=CCl_2$ 

On the basis of relative radical stability, we may rule out intermediates 3 and 4, since in 1 and 2 there is resonance of an unpaired electron with a phenyl group. Intermediate 1 should be more stable than 2 since dichloromethyl type radicals should be more stable than difluoromethyl radicals. In accord with this prediction, the product is actually:



Additional evidence for the diradical mechanism is of two types; first, these reactions are not stereoselective. It will be shown in a later section of this report that a reaction that goes by a concerted mechanism should maintain stereoselectivity. Lastly, it has been shown that many olefins dimerize under ultraviolet light. This is a good way of producing radicals. Photochemical dimerization of this sort occurs even in the solid state, where only the electrons are free to move. This reaction is well suited to these limitations.

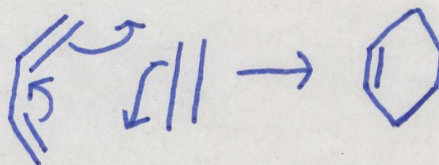
fig. 8 Diels Alder Reaction¹⁷



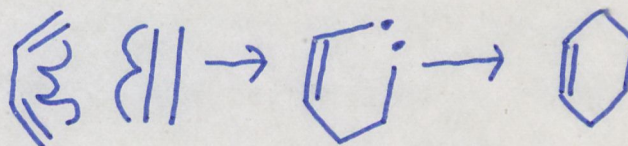
In the Diels Alder reaction, a double bond adds 1,4 to a conjugated diene so that the product is always a six membered ring.

Two mechanisms have been proposed for the Diels Alder reaction. In mechanism a there is a six centered transition state and no intermediate. The reaction is viewed as a single step concerted process. In mechanism b one end of the diene fastens to one end of the dienophile first, and then the other ends become fastened. If this diradical mechanism is correct, then the diradical intermediate must be spectrally singlet. (That is, the two unpaired electrons must have opposite spins.)

mechanism a:



mechanism b:



That the diradical intermediate must be spectrally single, may be proved by a similar argument that proves the structure of a carbene.

It can be shown that if the diradical intermediate in question is triplet in nature, there should be free rotation about the single bonds, and a mixture of cis and trans isomers should result. However, the Diels Alder reaction is cis stereospecific with respect to the dienophile, in every known reaction. This is pictured below, and confirms the spectrally singlet nature of the proposed intermediate.

fig. 9 Stereospecificity of the Diels Alder Reaction

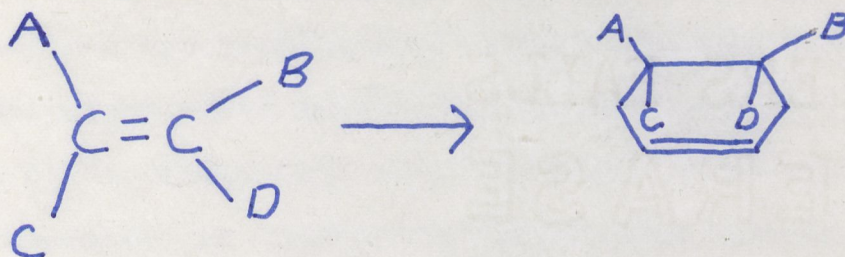
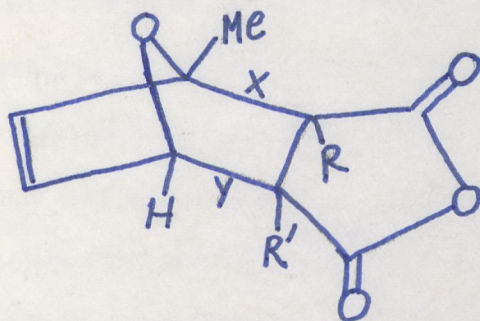


fig. 10 Evidence for Mechanism a



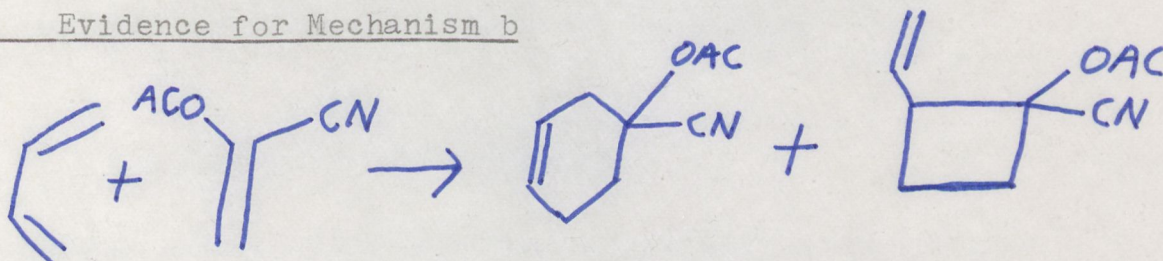
1: R=H, R'=D

2: R=D, R'=H

The isotope effect in the decomposition of this compound K_1/K_2 was equal to 1.00. If bond x broke before bond y, there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of x and y is simultaneous. This is the reverse of a Diels Alder reaction, and by the principle

of microscopic reversibility, the forward reaction should involve simultaneous formation of bonds x and y. In a similar experiment on the forward reaction, the result was the same.

fig. 11 Evidence for Mechanism b



Butadiene and 1-cyanovinyl acetate combine to give both the normal Diels Alder adduct and the four membered cyclization product. It is significant that the ratio of the two products (4:1) was not dependent on solvent or temperature, indicating a common transition state for both products. If there is a common state than one bond must be formed before the other, since a transition state in which considerable progress had been made toward the formation of both bonds couldn't explain both products.

Lastly, we must discuss the molecular orbital considerations with respect to the Diels Alder reaction. The principle of conservation of orbital symmetry states that thermal concerted reaction mechanisms are allowed only when all overlaps between the highest occupied molecular orbital of one reactant and the lowest unoccupied molecular orbital of the other reactant are such that a positive lobe overlaps only with another positive lobe, and a negative lobe only with another negative lobe. It has been

concluded that according to the principle of conservation of orbital symmetry, the Diels Alder reaction could go by a concerted thermal mechanism, and that the dimerization of olefins can not proceed by a concerted mechanism.

1-3 Dipolar Cycloaddition ¹⁸

In recent years, there has been considerable debate between two men, Rolf Huisgen and Raymond Firestone, as to the nature of the mechanism in 1-3 dipolar cycloaddition. As was pointed out in an earlier section, Huisgen feels that the mechanism is a single step concerted process, while Firestone thinks that a diradical two step mechanism better explains the experimental evidence. This controversy has by no means been settled. For this reason, we will first look at the experimental evidence for both reaction mechanisms, and we will lastly relate our particular experimental approach to the possible elucidation of the correct mechanism.

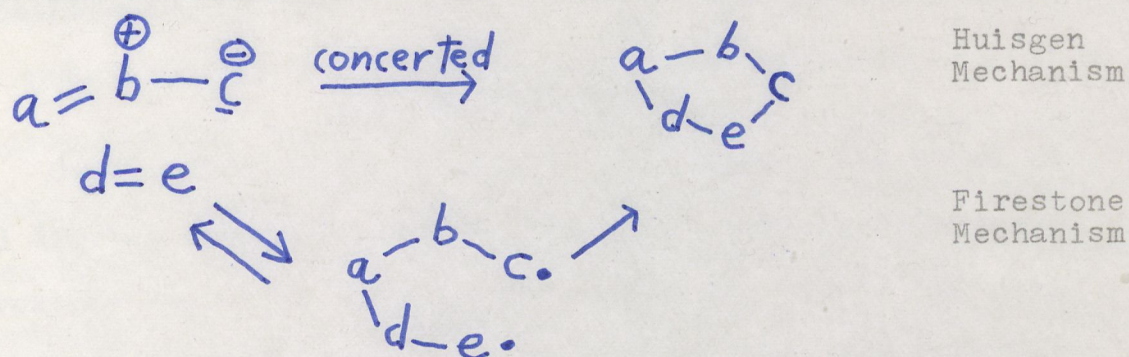
Stereospecificity

The 1-3 dipolar cycloaddition is strictly cis stereospecific. The geometrical relations of the substituents on both reactants are preserved in the product. This is required by a one step mechanism, but fits a two step mechanism only if the activation energy for single bond rotation in the intermediate is greater than that for either closure of the diradical or reversion to reactants.

Firestone feels that this is not unreasonable since the energy for rotation in ethane is 2.9 Kcal, and much larger values are anticipated for the comparatively encumbered intermediates proposed. He also thinks that the activation energy for ring closure of a spin paired diradical might approach zero. The energy for reversion to reactants is also small.

Huisgen feels that the stereospecificity of the 1-3 dipolar reaction is the greatest obstacle for the assumption of a diradical intermediate. He reasons that reversion to starting materials includes a change of hybridization at a and d. (see below) The bond a-d must undergo considerable stretching before the retrograde process can profit from the incipient formation of π bonds.

fig. 12 Proposed Mechanisms for 1-3 Dipolar Cycloaddition



Lastly, Huisgen calculated that by Firestone's mechanism, reversion of the diradical to reactants must be at least thirty times faster than rotation around d-e to account for the observed stereospecificity ($\ll 3\%$ of isomeric adduct).

Dipolarophile Structure

Conjugation exerts a promoting effect on the dipolarophilic activity of all multiple bonds. Firestone feels that this strongly supports a two step theory where the intermediate is stabilized by conjugation. However, in a concerted cycloaddition, the opposite would be expected; whatever stabilization energy the dipolarophile has should diminish steadily along the reaction coordinate as the π bond is consumed.

Huisgen says that conjugation increases the dipolarophilic activity of a multiple bond for two reasons; first, conjugation increases the polarizability of the π bond of the dipolarophile. Secondly, the two new sigma bonds are not formed synchronously. Unequal progress in bond formation of the transition state leads to partial charges which are stabilized by substituents.

Solvent Effects

Over a wide range of solvent polarities, the rates of 1-3 dipolar additions show a very small solvent dependence. Firestone says that this is not consistent with a one step mechanism in which the dipolarity of the starting material must be partially discharged in the transition state. He states that such a mechanism requires an inverse relation of rate to solvent polarity, the magnitude depending on the amount of charge dispersal. Yet the solvent effect is small, even with 1-3 dipoles of high polarity. In a two step mechanism, in which

only one bond is partially formed in the transition state, this species might reasonably be expected to have the same polarity as the orientation complex of the reactants, which would adequately explain the lack of solvent dependence.

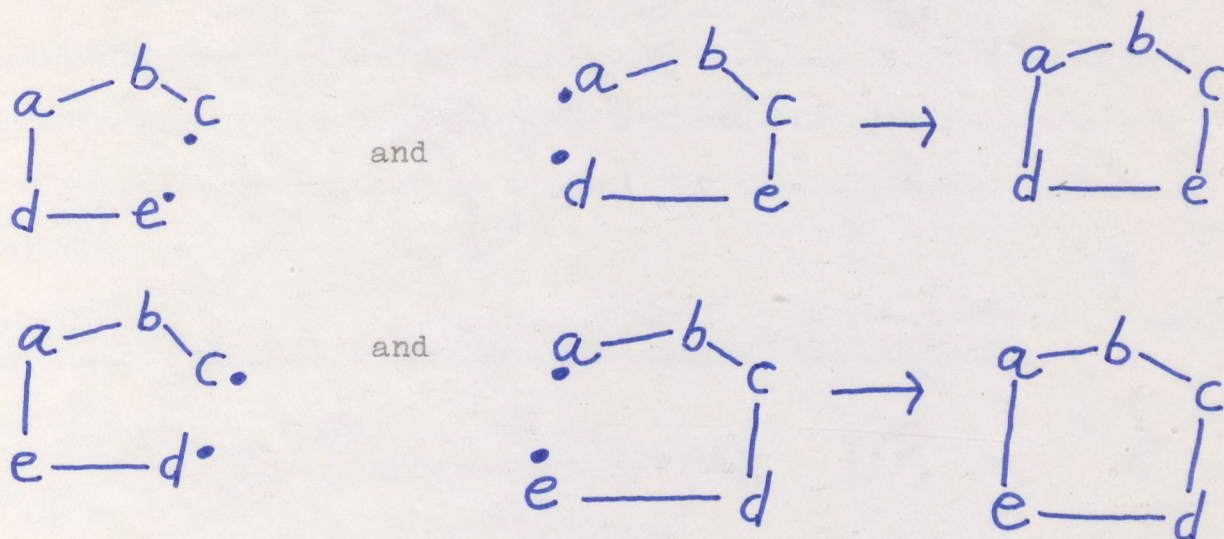
Huisgen feels that Firestone's assumption that disappearance of the dipole should bring about an inverse solvent dependence is wrong. A 1-3 dipole does not imply a large dipole moment. If one sums the resonance structures of the dipole, the anionic charge is distributed on either side of the positive center, giving a "tripole". These tripoles are poorly solvated. Huisgen regards the magnitude of solvent dependence as entirely adequate for a one step mechanism.

Orientation Phenomena

Unsymmetrical dipoles can add to unsymmetrical dipolarophiles in two directions, of which only one is usually found. An understanding of the problem requires consideration of both electronic and steric factors. Firestone contends that when other factors are controlled, the electronic factors should direct the course of a concerted cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole. For a two step cycloaddition with a dipolar intermediate, the prediction is the same. If the reaction proceeds through a diradical intermediate, the expected product sometimes has the opposite orientation from the one that would be formed through the other mechanisms. The method of prediction is to pick the best looking

of the four possible diradical intermediates. The chief difficulty is that the factors governing radical formation and stability are poorly understood.

fig 13 Possible Orientations of Addition with Diradical Intermediates

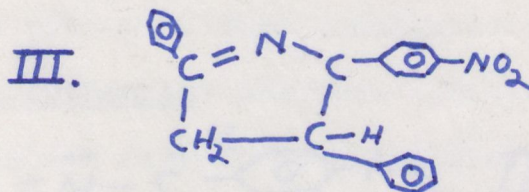


Huisgen says that the central argument of the diradical hypothesis is based on orientation. By supplementing known data with unpublished data, Huisgen shows that the experimental evidence approaches a statistical 50:50 of orientations consonant and dissonant with the diradical hypothesis. He also says that Firestone's assumption that the electrophilic end of the dipolarophile should link with the negative end of the dipole is wrong, since the formal negative charge of the 1-3 dipole is distributed on either side of the central substituent.

Huisgen states that it is not meaningful to assign an electrophilic and a nucleophilic end to a 1-3 dipole. The Molecular Orbital Theory description of concerted additions reveals

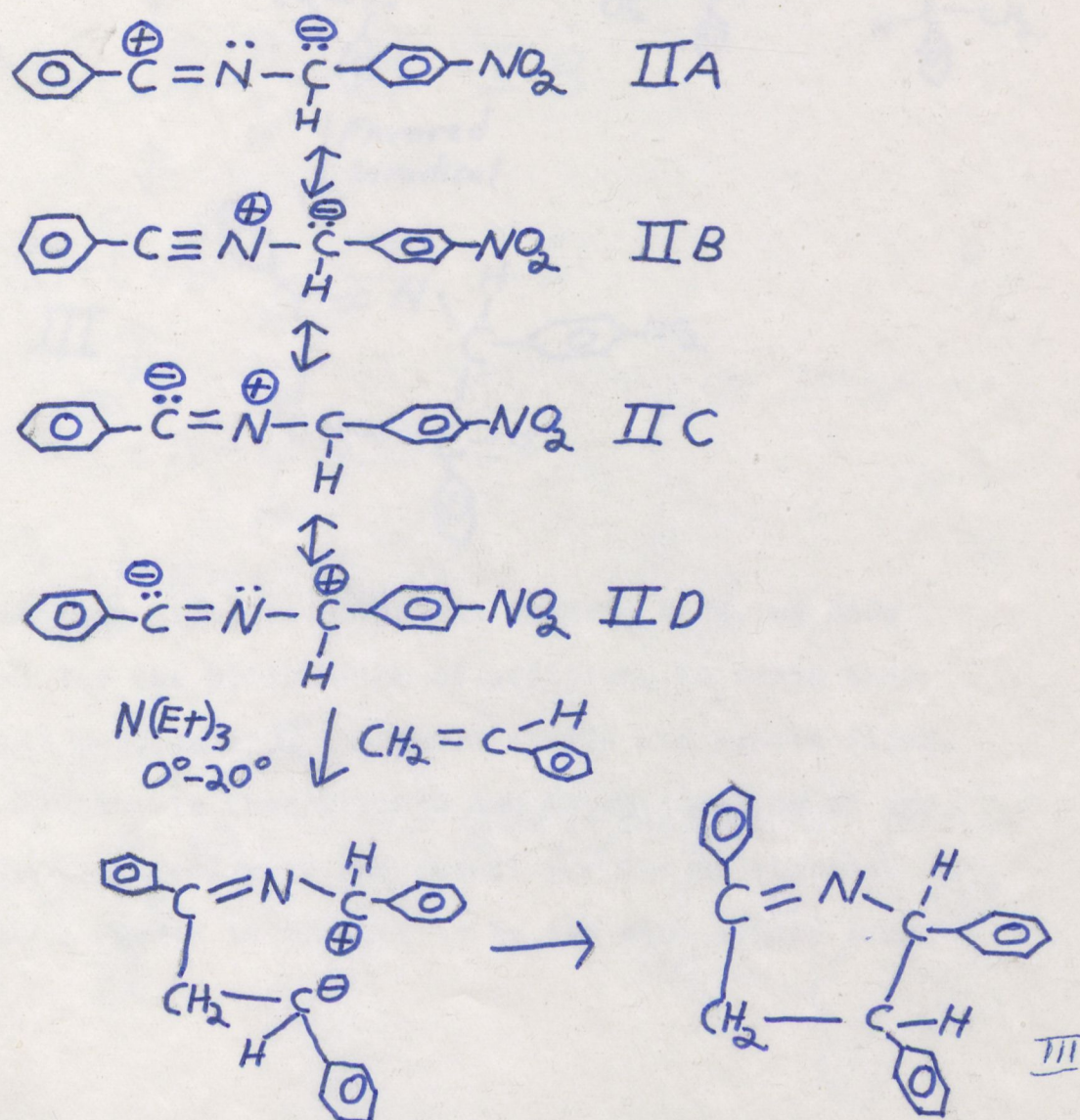
it is only meaningful to attribute a certain electron density to the incipient sigma bonds in the transition state. The major unsolved problem in both the Diels Alder and in 1-3 dipolar additions is that of orientation of addition.

Huisgen found, that in the cycloaddition reaction, the imido chloride **II**. $\text{C}_6\text{H}_5-\overset{\text{Cl}}{\text{C}}=\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-\text{NO}_2$ when reacted with styrene, gave the product



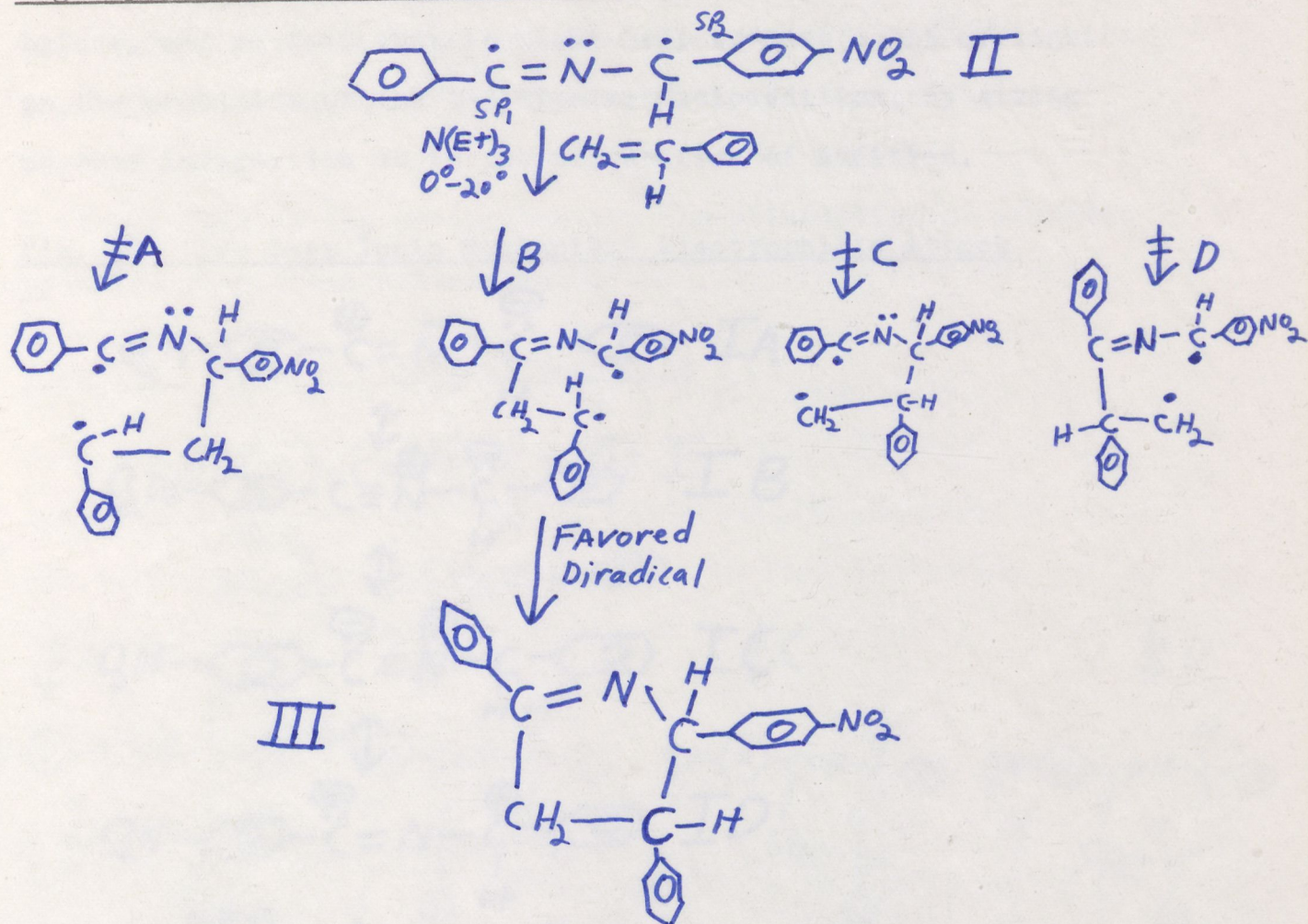
A one step concerted, or a diionic mechanism in which the electrophilic end of the dipolarophile attacks the more negative end of the dipole can easily account for this orientation of addition.

fig. 14 Two Step Ionic Mechanism- Electrophilic Attack



However, using the best diradical intermediate rule, a diradical mechanism can also account for the observed orientation of addition.

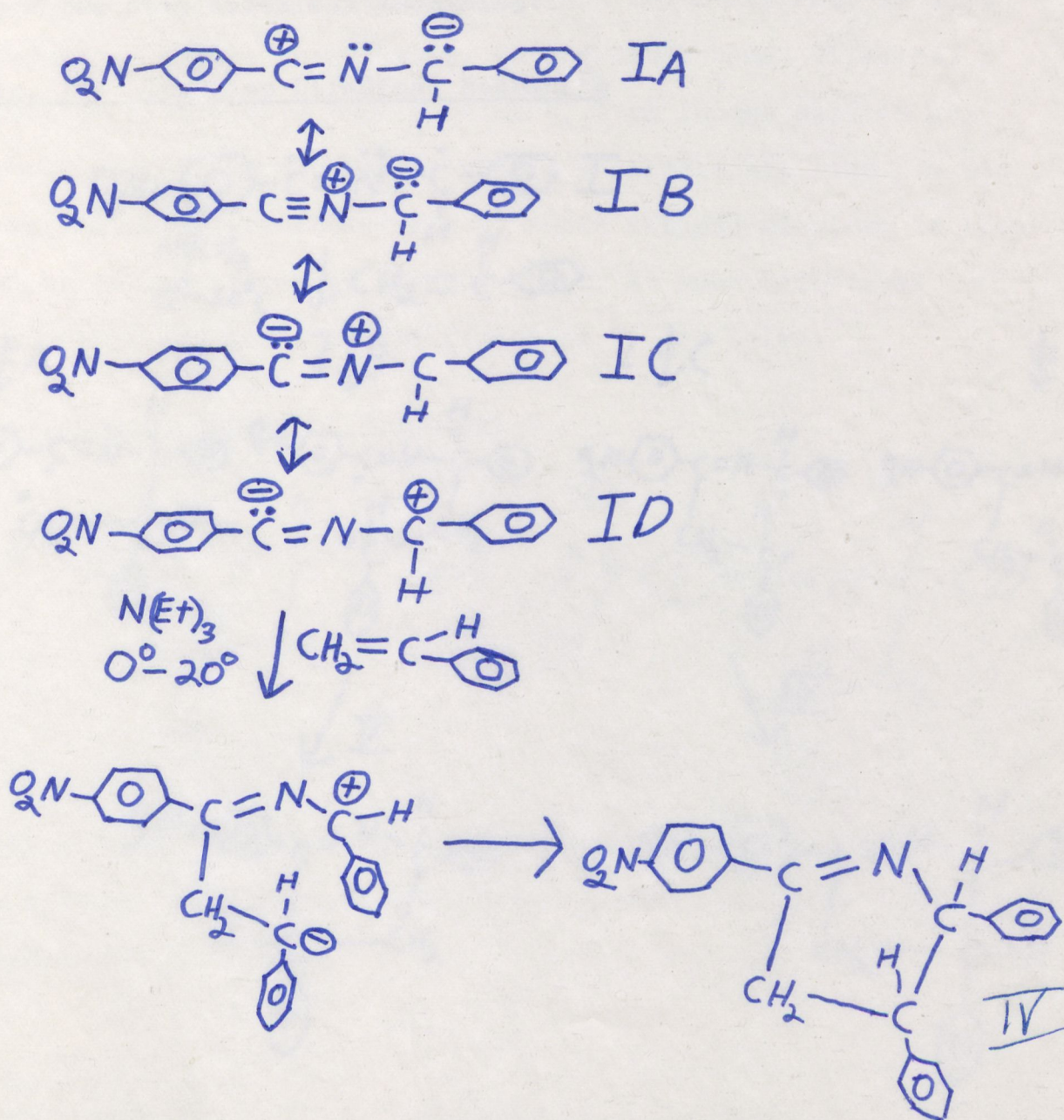
fig. 15 Two Step Diradical Mechanism



It may be seen that diradical B is the favored form, as only it can account for the orientation of addition. It seems that the SP_1 radical portion of **II** is least stable and reacts first. A and B are more stable than C and D due to conjugation of one portion of the diradical with the phenyl portion of styrene. The intermediate formed is thought to be the most stable one.

My research was directed at the synthesis of compound I O=[N+]([O-])c1ccc(C)cc1 and the study of this compound with respect to the cycloaddition reaction. This example of the nitrile ylide series of 1-3 dipoles has not been synthesized before, and we felt that it might help to cast a bit of light on the mechanism of the 1-3 dipolar cycloaddition, by giving us some information as to the orientation of addition.

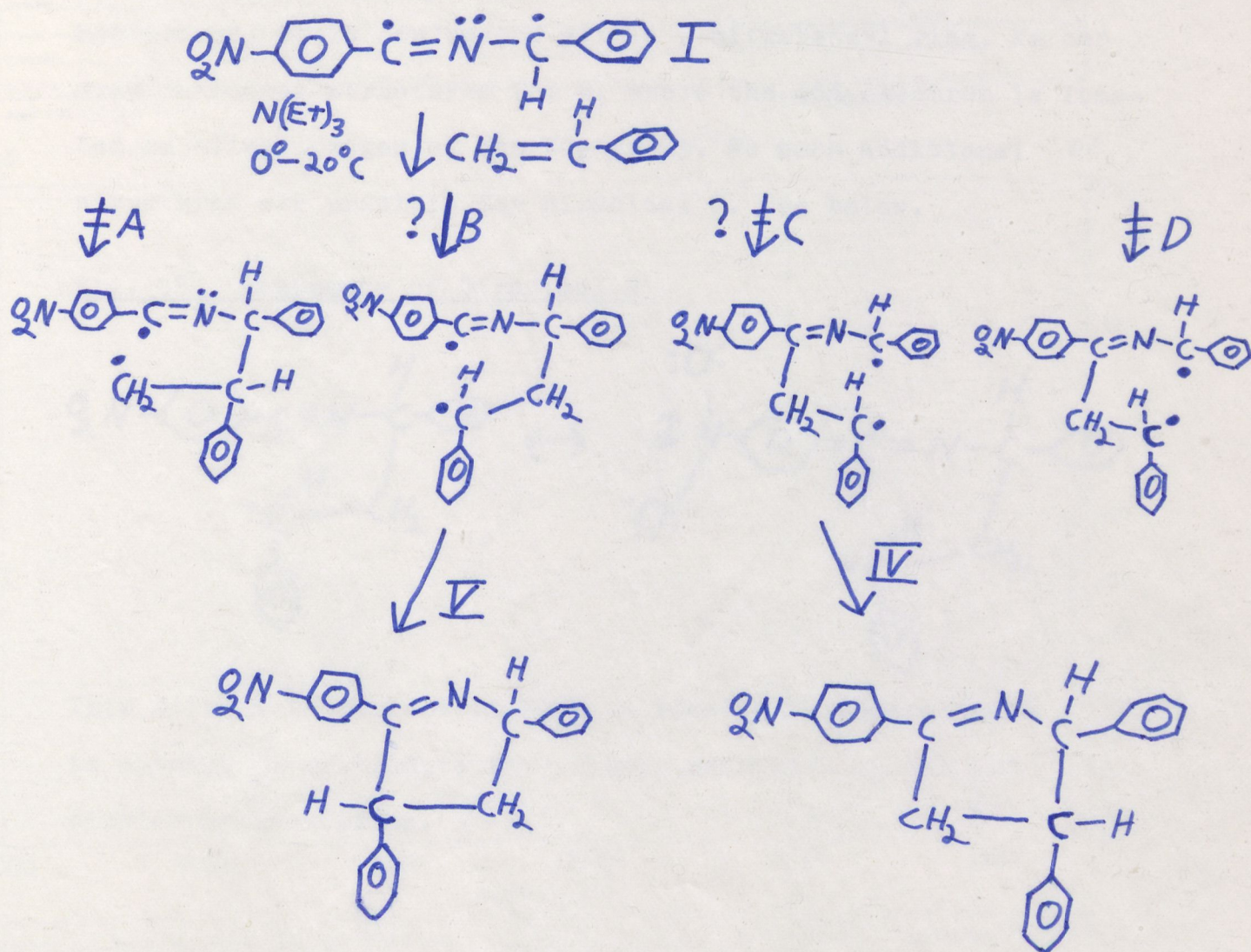
fig. 16 Two Step Ionic Mechanism- Electrophilic Attack



It seems that a concerted one step or a diionic mechanism would predict IV as the addition product. In this scheme, IC is the reactive resonance form, because the negative charge on this resonance form is supported by an SP_1 carbanion, which is the most stable carbanion. In the transition state, conjugation with the phenyl group of styrene helps to stabilize the negative charge.

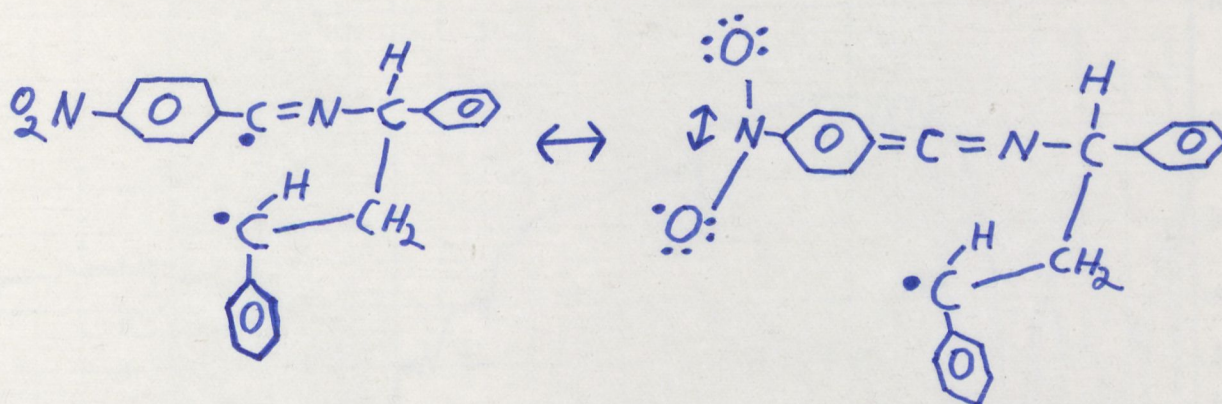
But what is the prediction for the orientation of addition by a two step diradical mechanism?

fig. 17 Two Step Diradical Mechanism

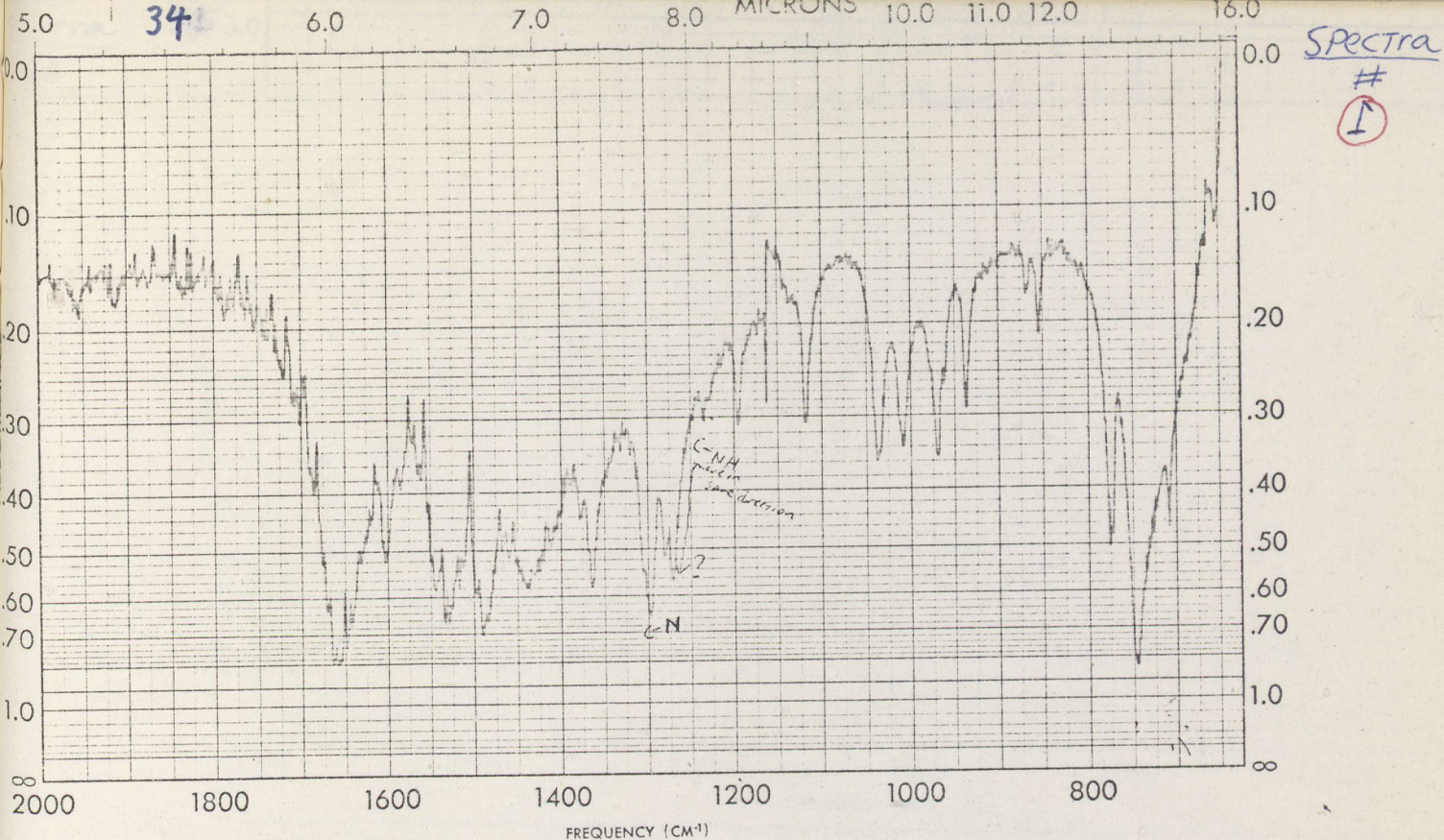


When we do run this reaction, if we get product IV as our adduct, we will have learned nothing about the mechanism of the 1-3 dipolar reaction. However, if we get the less expected adduct V, only the diradical mechanism could account for this orientation of addition. Whether it is product IV or V that is formed will depend on which diradical, C or B respectively, is more stable. The first reaction would be to pick diradical C as the most stable one because half of it is SP_2 hybridized and conjugated with a phenyl ring, and the other half is also conjugated with a phenyl ring. On the other hand, diradical B could be more stable than C because, even though half is SP_1 hybridized, it is conjugated with a p-nitrobenzyl ring. We can draw resonance structures for B, where the odd electron is located on either oxygen of the NO_2 group. No such additional structures are possible for diradical C. See below.

fig. 18 Resonance of Diradical B

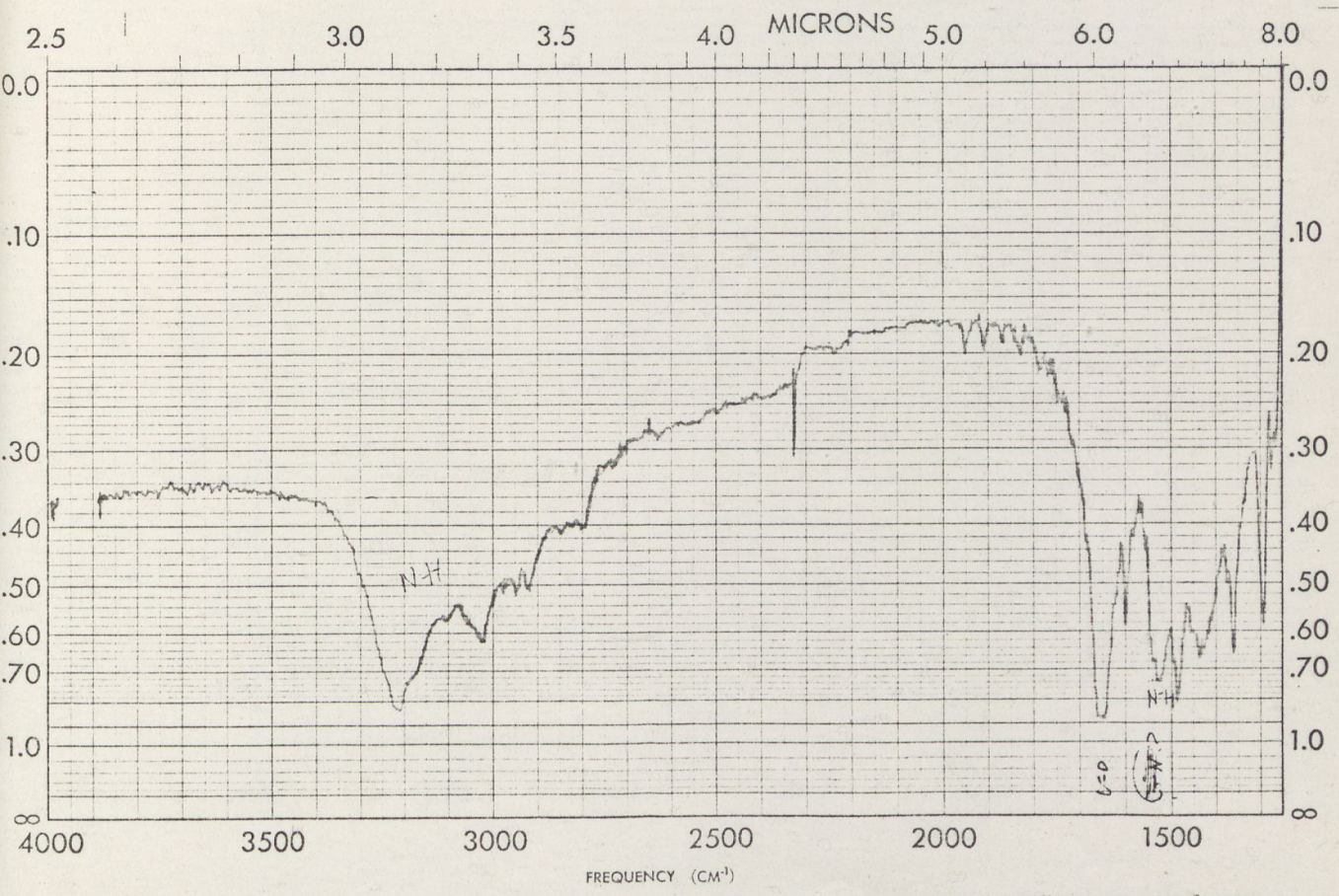


This situation provides us with an ideal experimental case to attempt to elucidate the correct mechanism in the 1-3 dipolar cycloaddition.



SAMPLE <chem>CH3-C(=O)-NH-C6H4-CH3</chem>	CURVE NO. _____	SCAN SPEED <i>fast</i>	OPERATOR _____
ORIGIN _____	CONC. _____	SLIT _____	DATE _____
SOLVENT <i>KBR cell</i>	CELL PATH _____	REMARKS _____	
REFERENCE _____	PERKIN-ELMER		

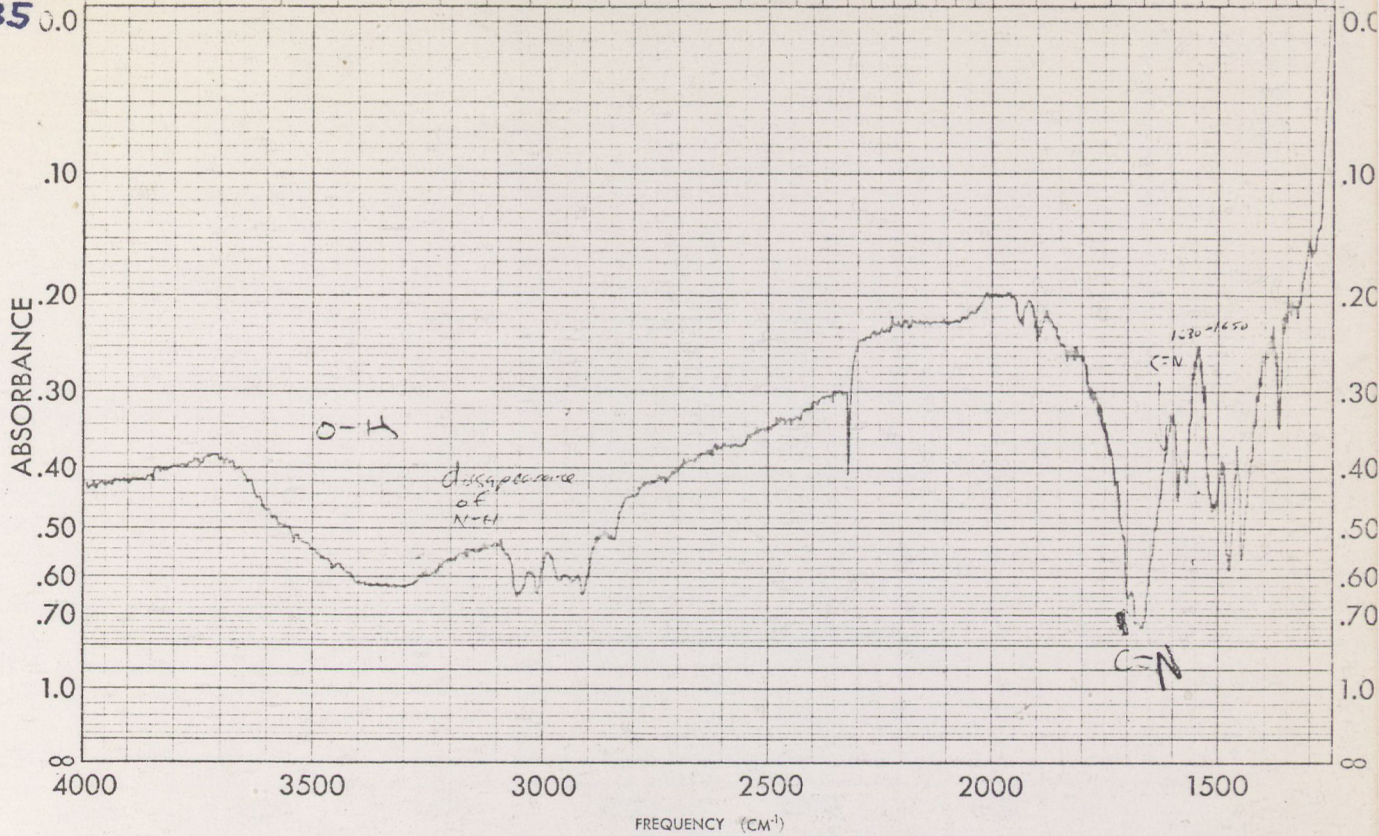
PART NO. 237-1033



SAMPLE <chem>CH3-C(=O)-NH-C6H4-CH3</chem> <i>acetamide</i>	CURVE NO. _____	SCAN SPEED <i>fast</i>	OPERATOR <i>Braff</i>
ORIGIN _____	CONC. _____	SLIT _____	DATE <i>7/25/71</i>
SOLVENT <i>KBR cell</i>	CELL PATH <i>look for C=O peak at 1650</i>	REMARKS <i>looks like acetamide KBR cell at 0560</i>	
REFERENCE _____			

2
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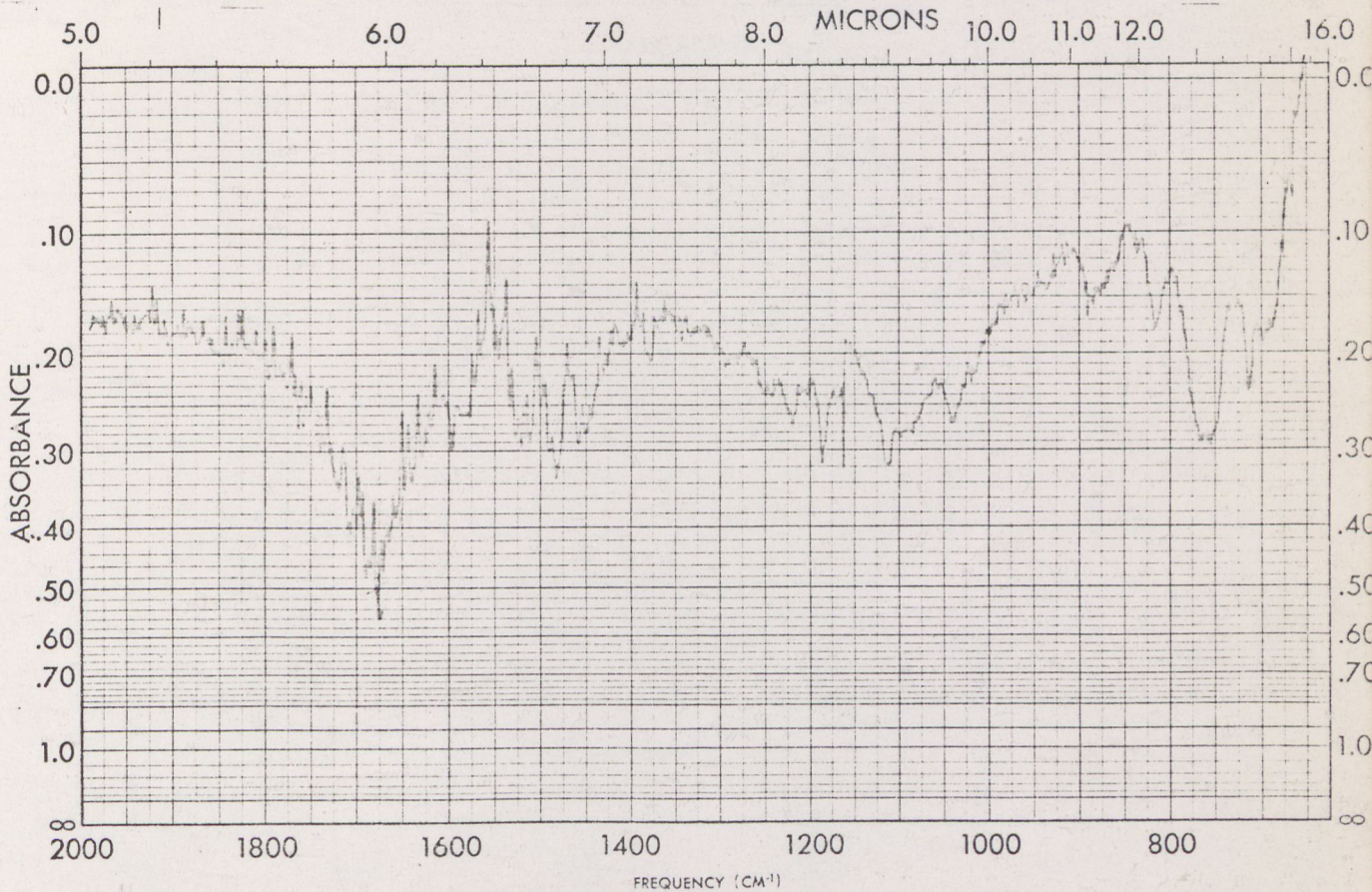
35 0.0



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SOLVENT <u>Acetone</u>	CELL PATH _____	REMARKS _____	
REFERENCE _____			

PART NO. 237-1032

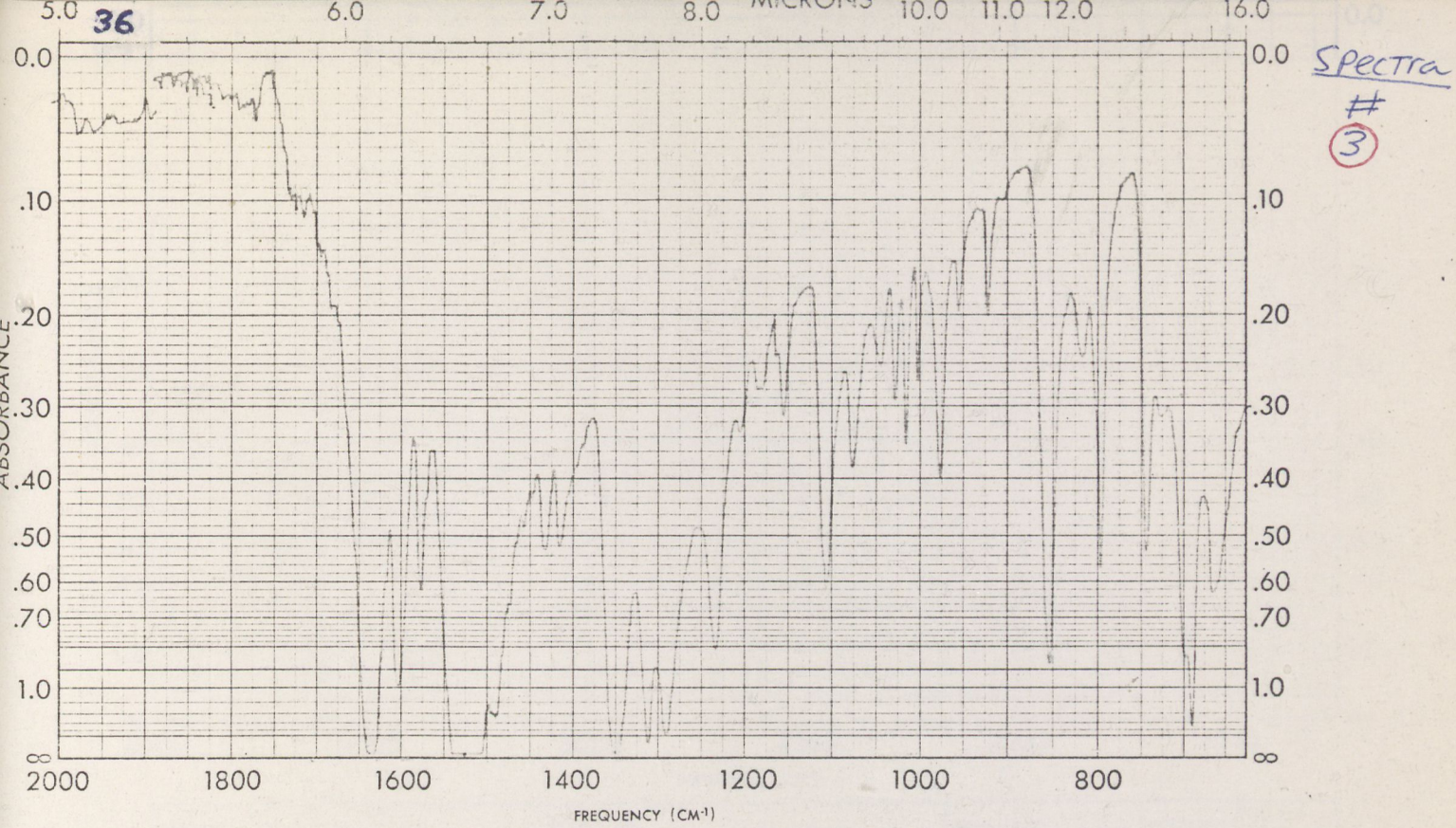
PERKIN-ELMER



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SOLVENT _____	CELL PATH _____	REMARKS _____	
REFERENCE _____			

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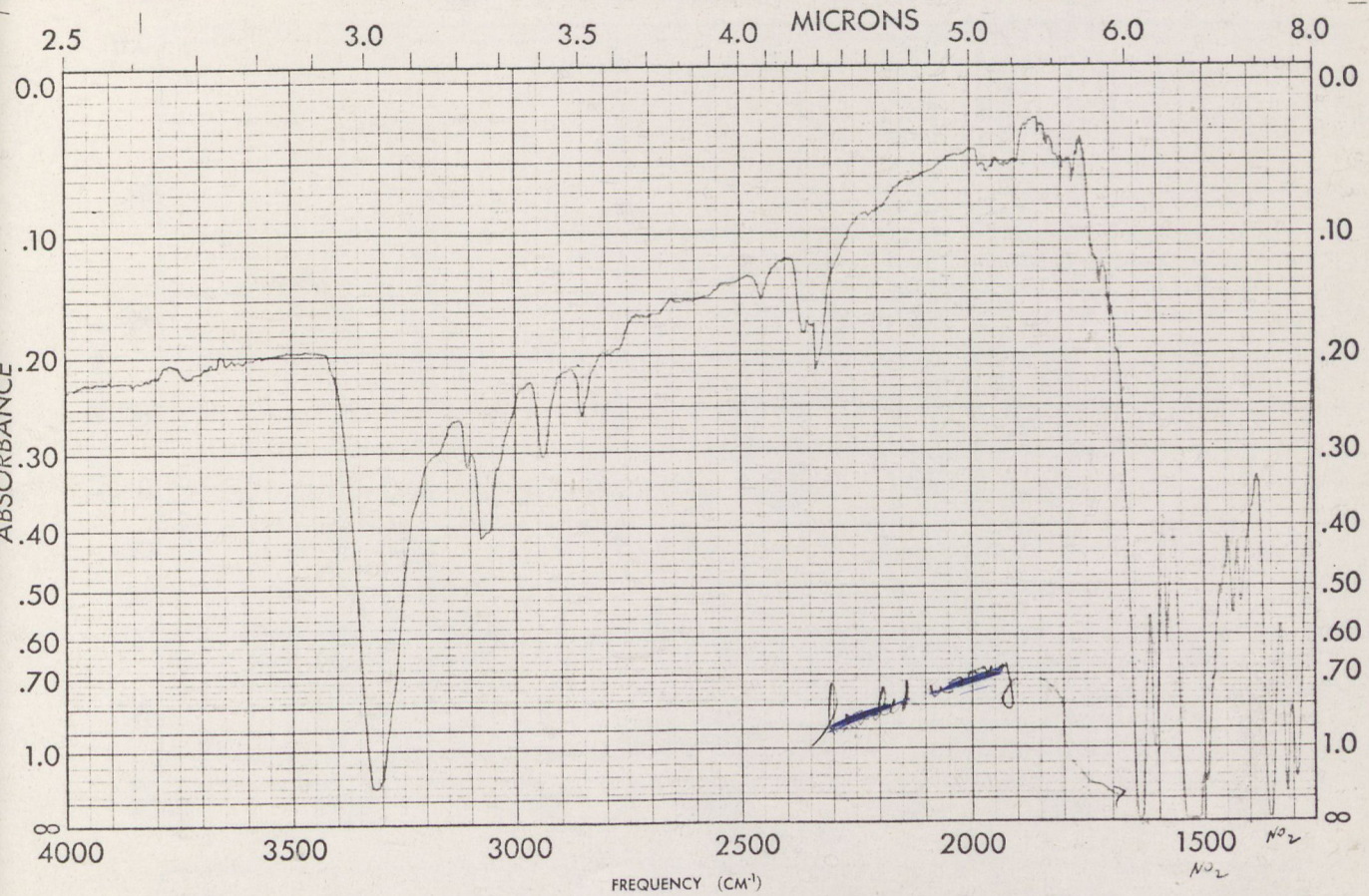
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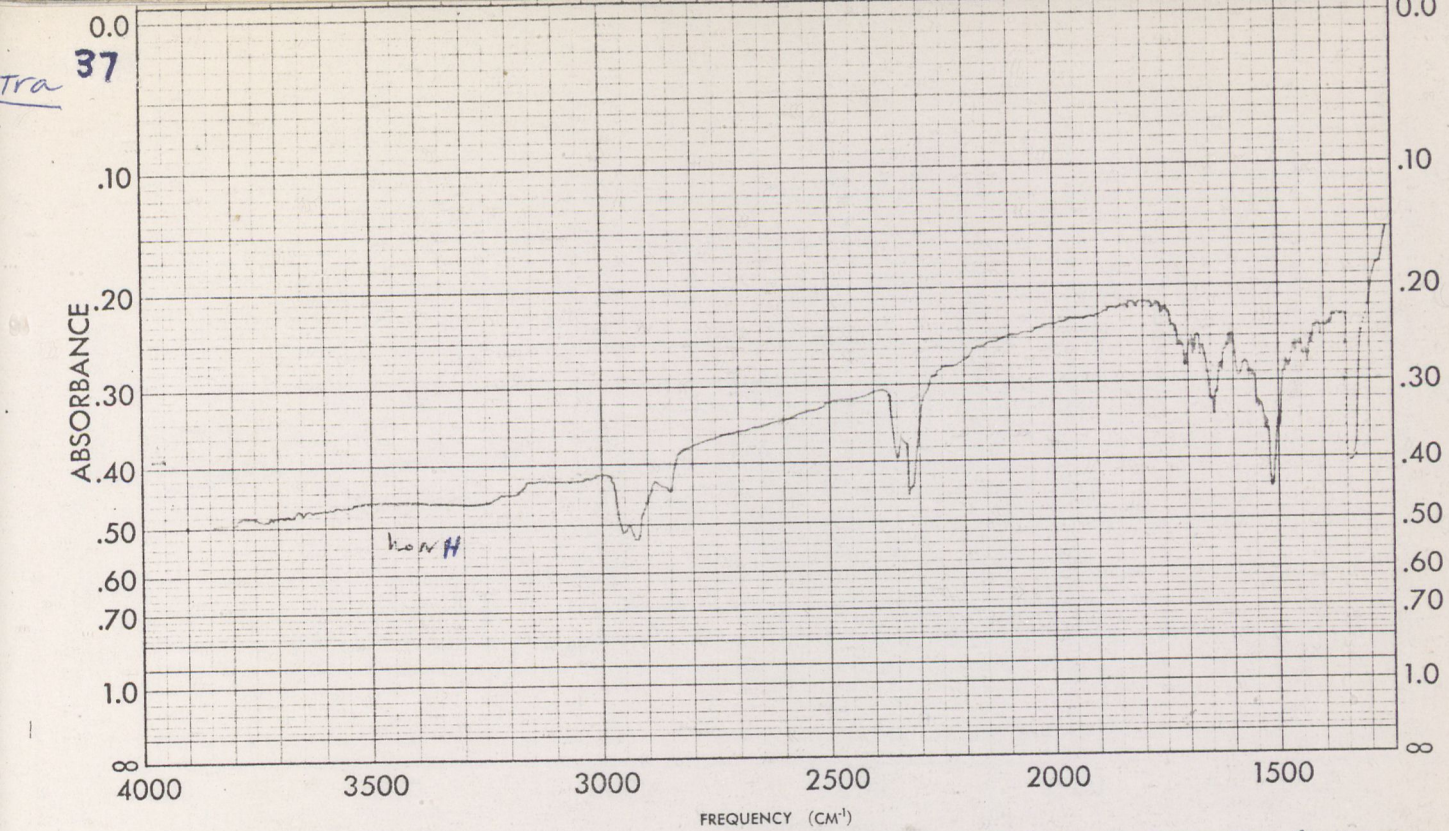
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SOLVENT _____	CELL PATH _____	REMARKS _____	
REFERENCE _____			

PART NO. 237-1033 24°

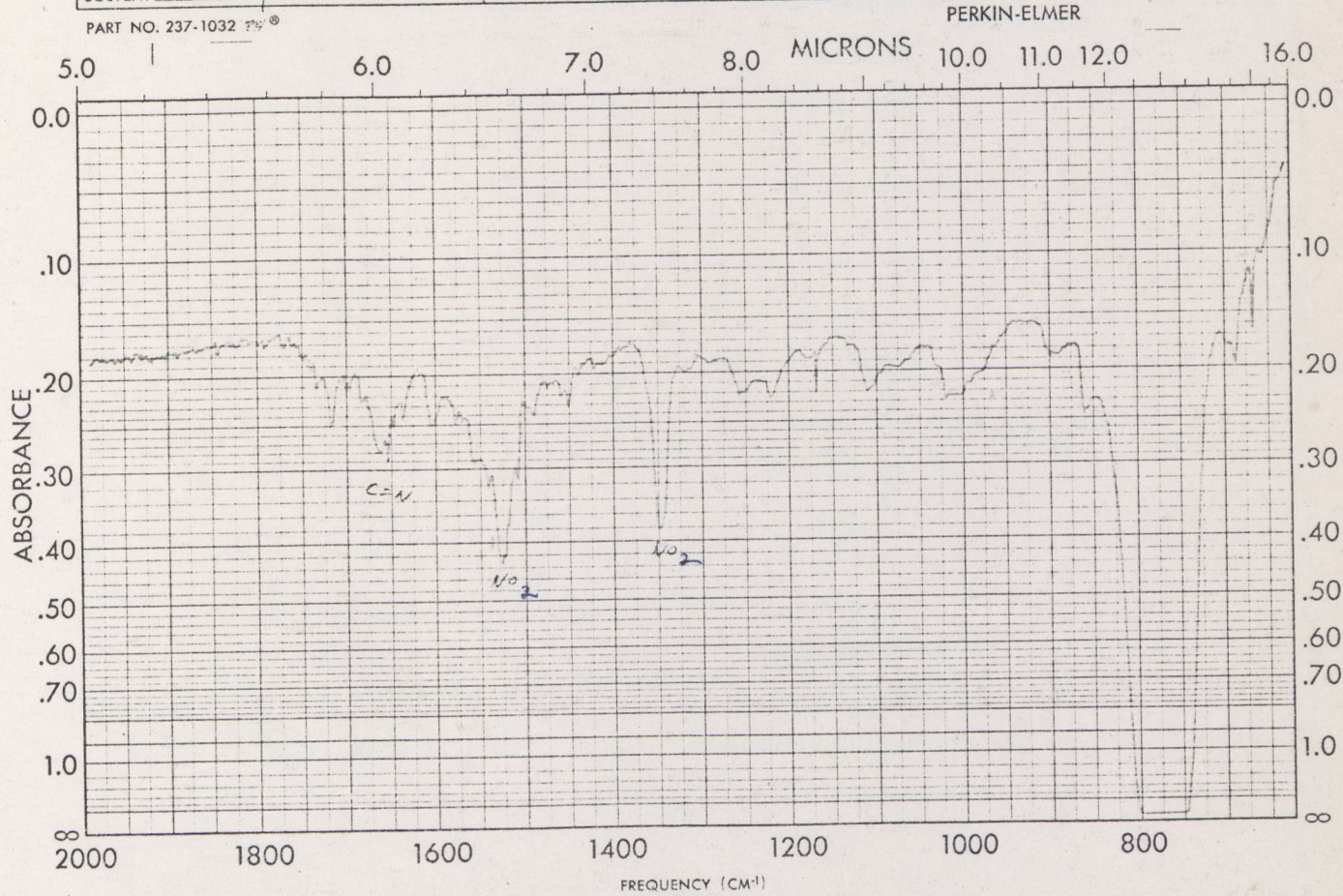
PERKIN-ELMER



SAMPLE <u>1-17-1</u> <chem>O=C(N)C(=O)N</chem>	CURVE NO. _____	SCAN SPEED _____	OPERATOR <u>Draff</u>
ORIGIN _____	CONC. _____	SLIT _____	DATE <u>3/11/71</u>
SOLVENT <u>KOR cell</u>	CELL PATH _____	REMARKS _____	
REFERENCE _____			

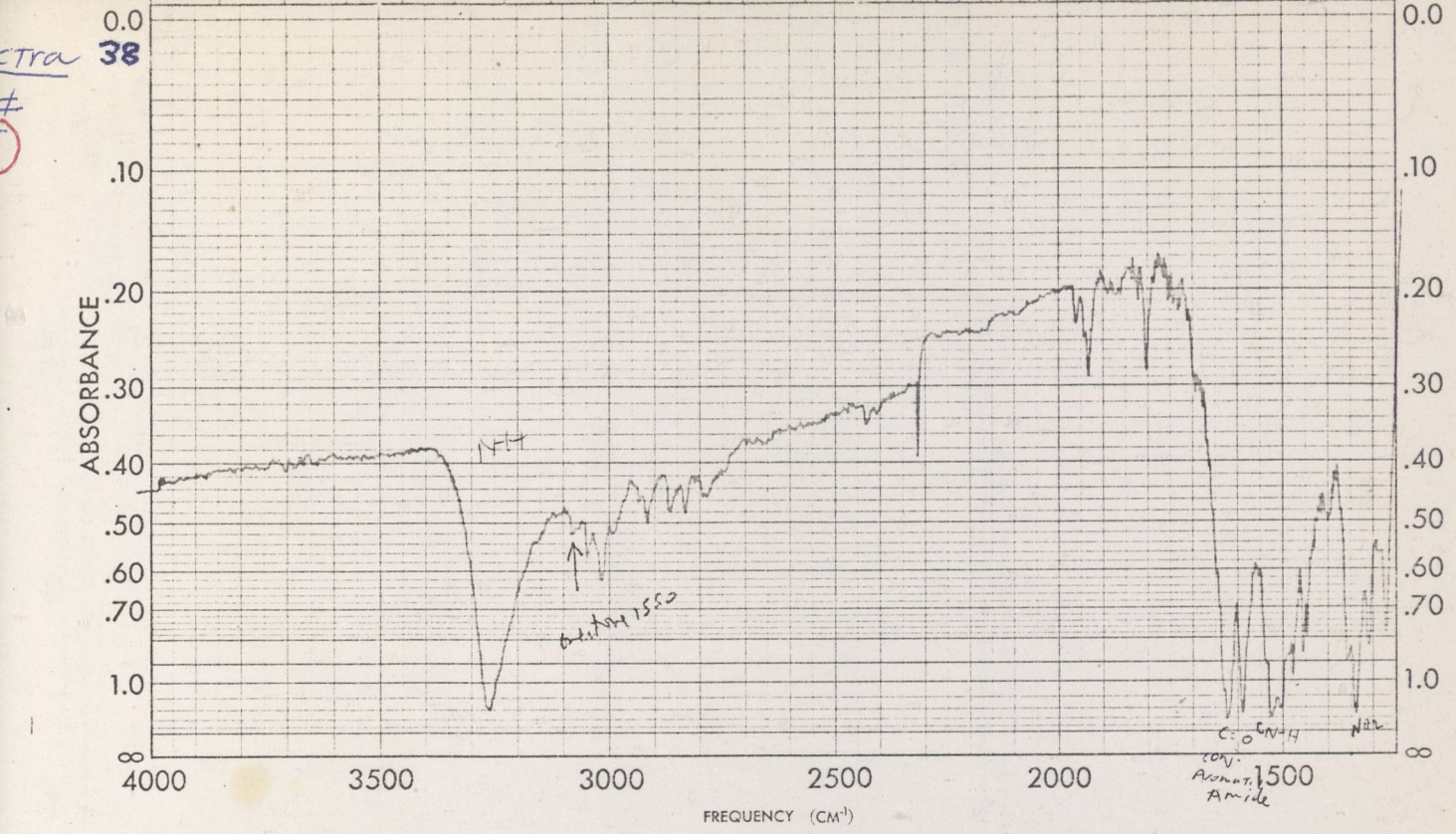


SAMPLE <chem>O=C1C=CC(=O)N1</chem>	CURVE NO. _____	SCAN SPEED _____	OPERATOR <i>Briff</i>
ORIGIN _____	CONC. _____	SLIT _____	DATE <i>11/8</i>
SOLVENT <i>CCl₄</i>	CELL PATH _____	REMARKS _____	
PART NO. 237-1032	REFERENCE _____		



SAMPLE <chem>O=C1C=CC(=O)N1</chem>	CURVE NO. _____	SCAN SPEED _____	OPERATOR _____
ORIGIN _____	CONC. _____	SLIT _____	DATE _____
SOLVENT _____	CELL PATH _____	REMARKS _____	
PART NO. 237-1033	REFERENCE _____		

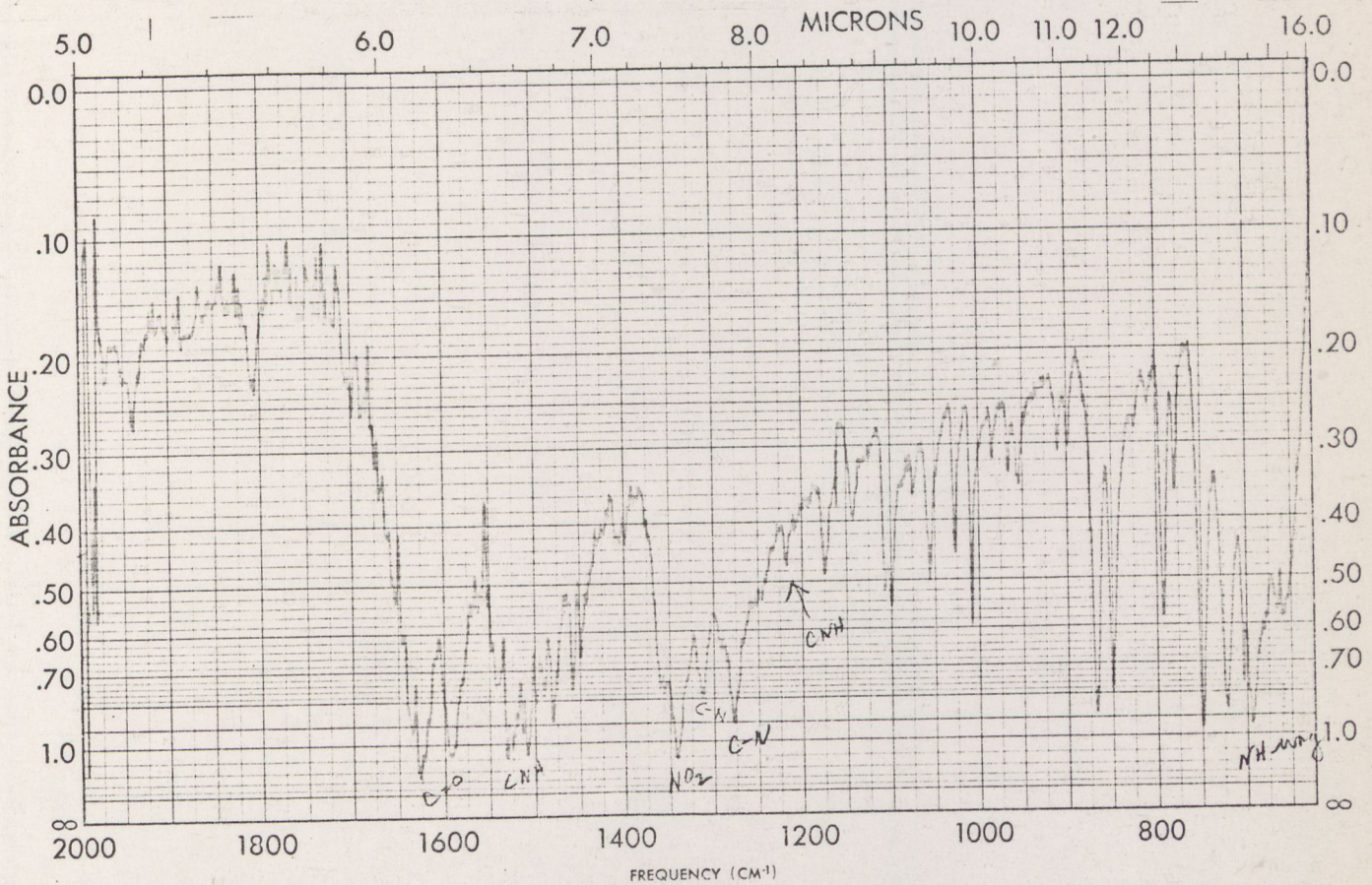
PERKIN-ELMER



SAMPLE <u>1-13-1 Amide</u>	CURVE NO. _____	SCAN SPEED _____	OPERATOR <u>Braff</u>
<chem>O=[N+]([O-])C(=O)Nc1ccc(O)cc1</chem>	CONC. _____	SLIT _____	DATE <u>7/30</u>
ORIGIN _____	CELL PATH _____	REMARKS _____	
SOLVENT <u>BR cell</u>	REFERENCE _____		

PART NO. 237-1032

PERKIN-ELMER



SAMPLE <u>1-13-1</u>	CURVE NO. _____	SCAN SPEED _____	OPERATOR <u>Braff</u>
	CONC. _____	SLIT _____	DATE <u>7/30</u>
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PART NO. 237-1033

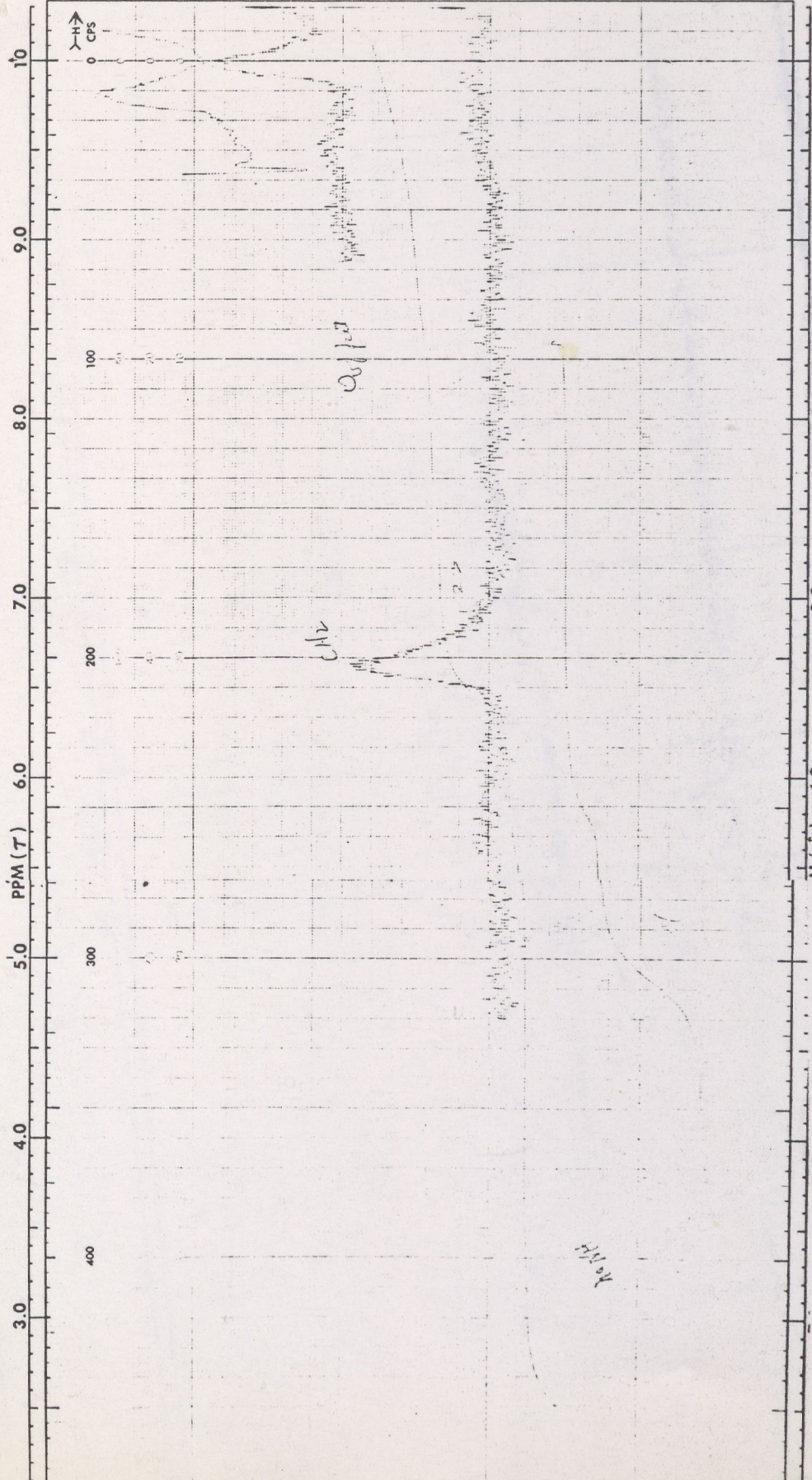
PERKIN-ELMER

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OPERATOR: J. J. J. DATE: 1-21-51
SAMPLE: 1-21-51

ET-CM, H=C-E

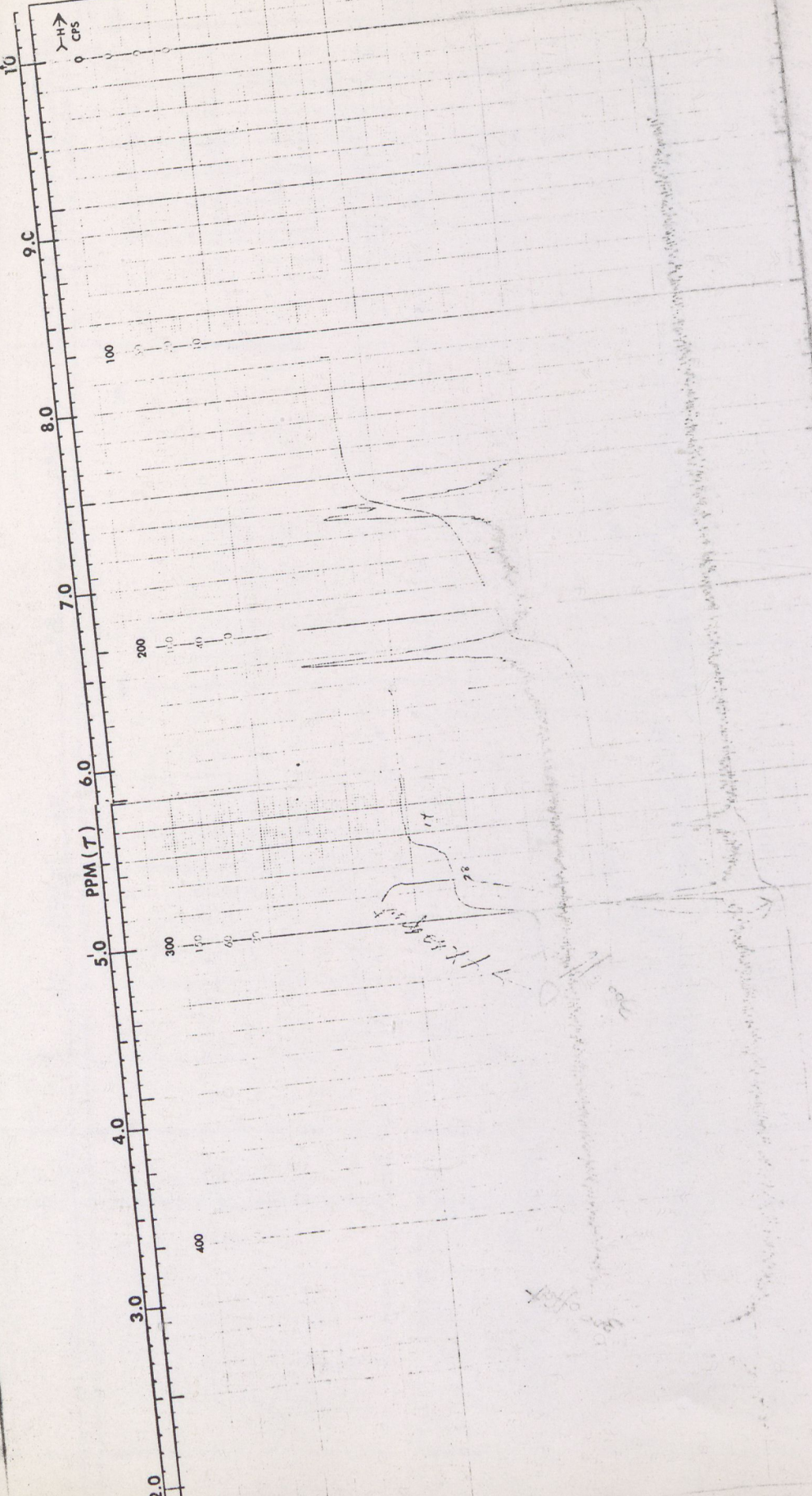
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FILTER BANDWIDTH: 20
RF FIELD: 20
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SWEEP OFFSET: 20
SPECTRUM AMP.: 20
INTEGRAL AMP.: 20
REMARKS:

PERFORMED BY: J. J. J.
DATE: 1-21-51
NO. VN 1003



#10
 60 MC NMR
 SPECTRUM NO. 10
 OPERATOR: J. J. ...
 SAMPLE: ...

SOLVENT
 TEMPERATURE
 FILTER BANDWIDTH
 RF FIELD
 SWEEP TIME
 SWEEP WIDTH
 SWEEP OFFSET
 SPECTRUM AMP.
 INTEGRAL AMP.
 REMARKS



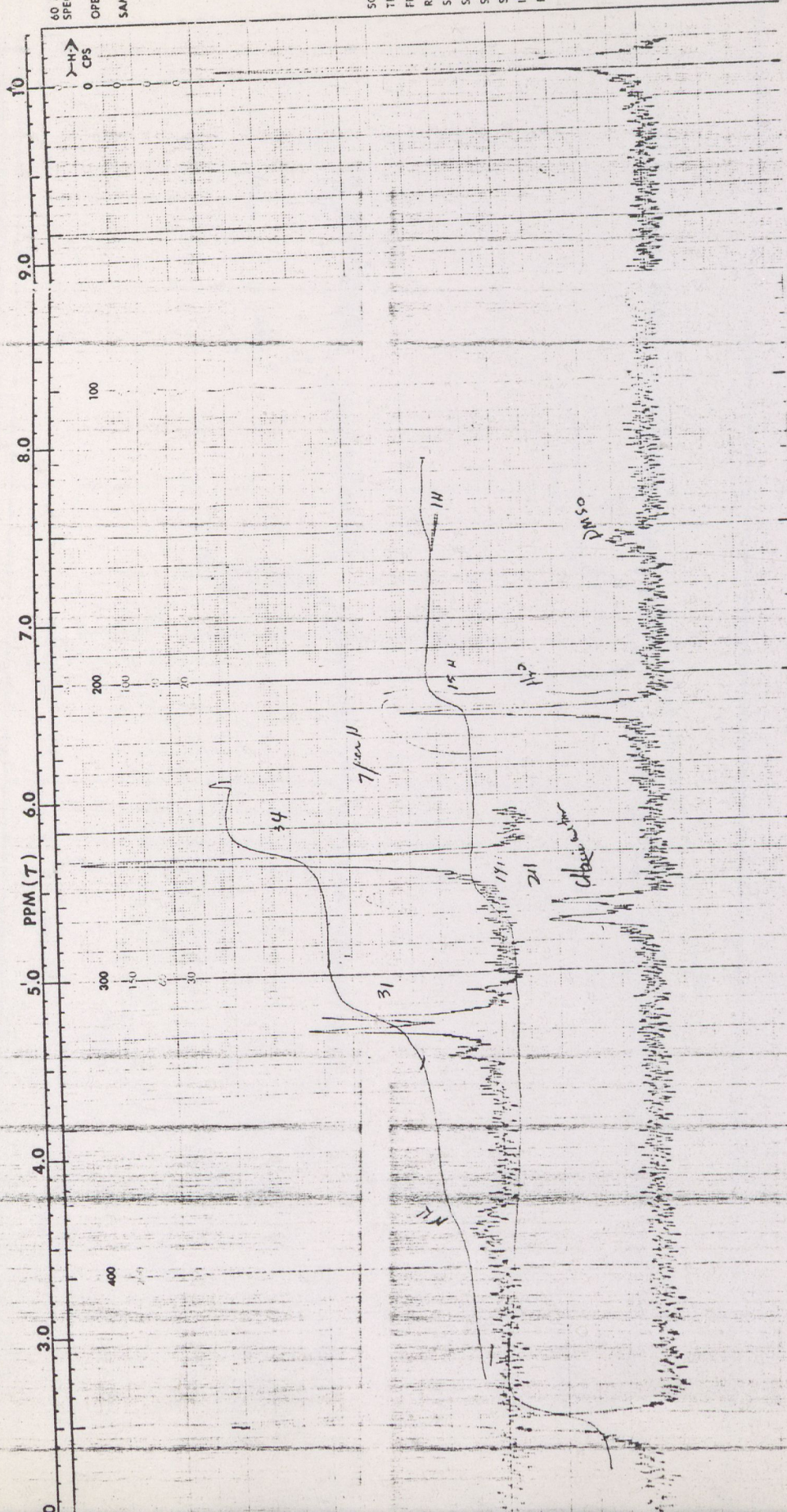
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 OPERATOR: *St. J.* DATE: *1-13-51*
 SAMPLE: *B-11*

ON 2-1-51 at 11:00 AM

SOLVENT	<i>B.C.</i>
TEMPERATURE	<i>11</i>
FILTER BANDWIDTH	<i>5</i>
R.F. FIELD	<i>100</i>
SWEEP TIME	<i>0</i>
SWEEP WIDTH	<i>11.5</i>
SWEEP OFFSET	<i>10</i>
SPECTRUM AMP.	
INTEGRAL AMP.	
REMARKS:	

200/1000
CH₃-S-CH₃

SPENCER CORP.
 MODEL 5000



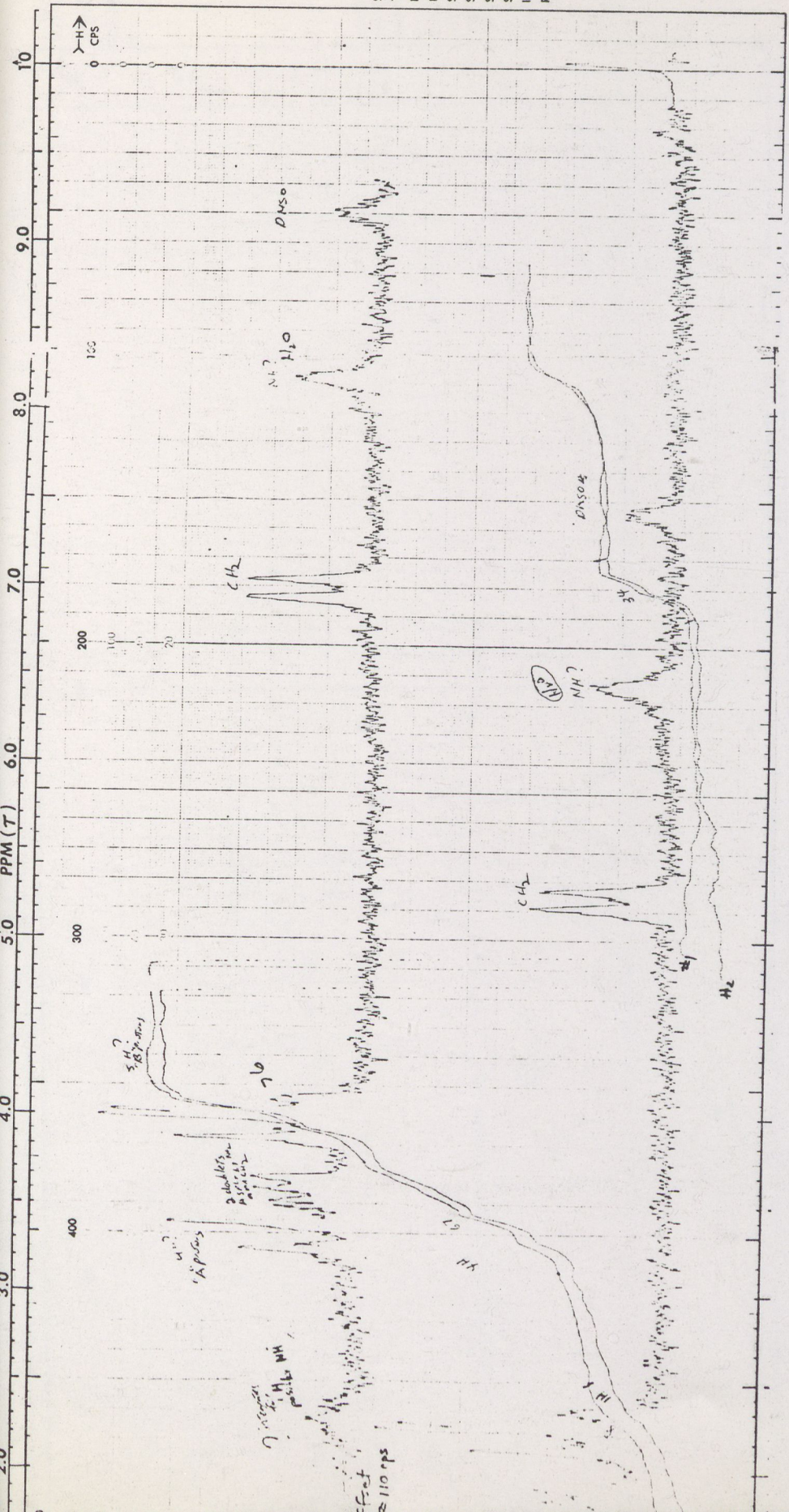
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OPERATOR: DATE: SAMPLE: 1-17-1-5110

1-17-1-5110

SOLVENT	DMSO-d ₆
TEMPERATURE	
FILTER BANDWIDTH	2
R F FIELD	0.015
SWEEP TIME	250
SWEEP WIDTH	500
SWEEP OFFSET	
SPECTRUM AMP.	
INTEGRAL AMP.	
REMARKS:	

RECORDED BY: DATE:

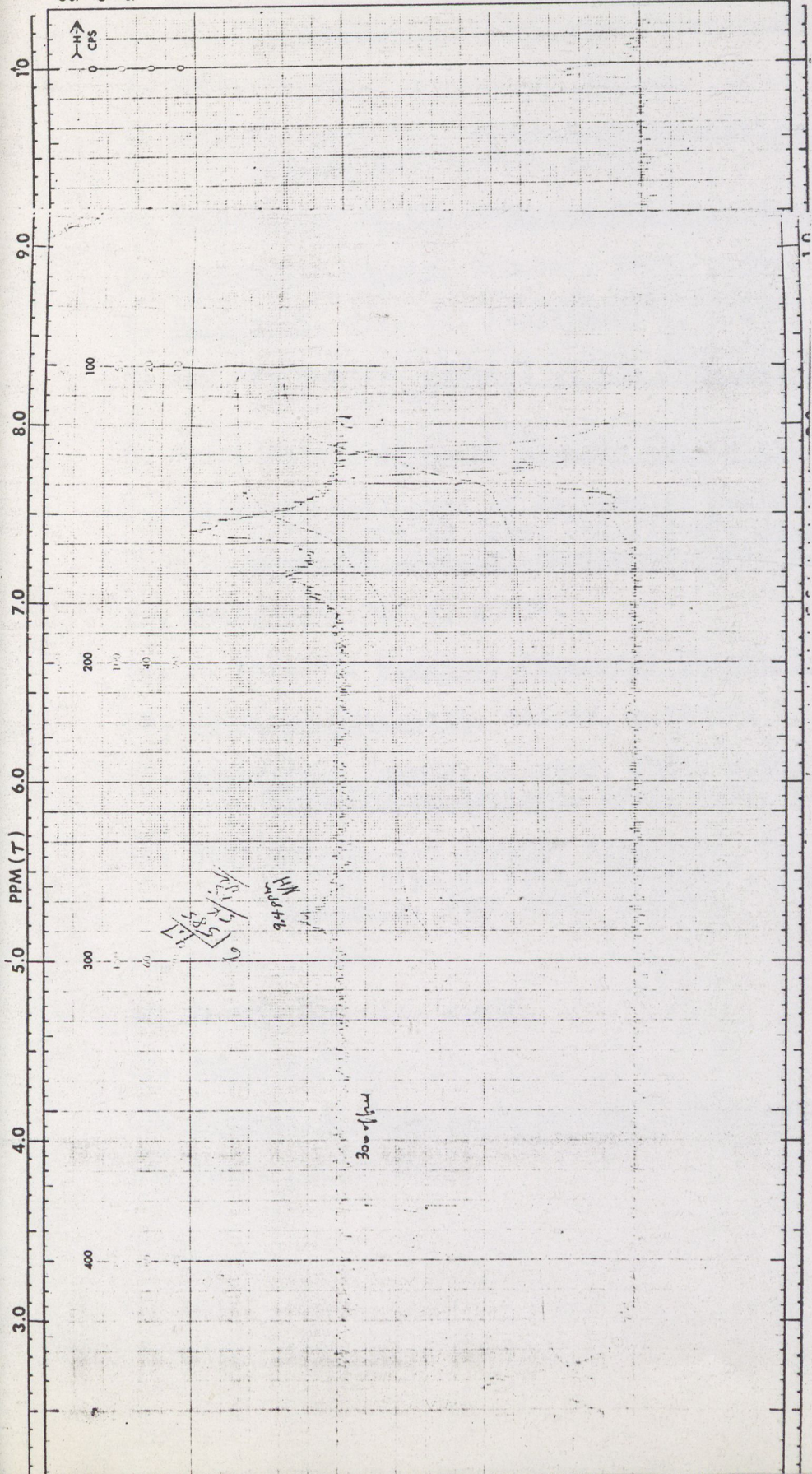


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Handwritten notes:
M3
L-1-N-C-44
59 2:35 PM

SOLVENT	
TEMPERATURE	
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R.F. FIELD	
SWEEP TIME	2.0
SWEEP WIDTH	2.0
SWEEP OFFSET	
SPECTRUM AMP.	10
INTEGRAL AMP.	
REMARKS:	

PERKINELMER
SPECTROSCOPY CORPORATION
SHELTON, CONNECTICUT
NO. VN 1003



Footnotes

1. Rolf Huisgen, "1-3 Dipolar Cycloadditions", in The Proceedings of the Chemical Society, October, 1961, p.359.
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9. "Nitrogen Analogues of Ketenes by Dehydrochlorination of Corresponding Imino Chlorides", Journal of the American Chemical Society, September, 1964, p.4400.
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19. Ibid. p.2291-2297.

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