AN ABSTRACT OF THE THESIS OF

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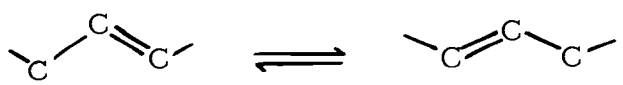
Title: PART I. SYNTHESIS AND COPE REARRANGEMENT OF SOME SUBSTITUTED HEXADIENES.

PART II. FORMATION OF N-PHENYL AND N-METHYL PYRIDINIUM SALTS FROM 1,7-DIAZA-1,3,5-HEPTATRIENES.

Abstract approved: Elliot N. Marvell

In many electrocyclic reactions there appear three atom groups which undergo a shift of a double



bond from one side of the central atom to the other during the course of the reaction. Frequently the geometric requirements in the electrocyclic transition state appear to force a deviation from the stereoelectronic ideal for this three atom process. An attempt to use the Cope rearrangement to establish a comparison standard for the influence of substituents attached to the central atom is described. A series of 3,3-dideuterio-2-(p-substituted phenyl)-1,5-hexadienes was

rearranged in cyclohexane-d_{12} and the rates determined by nmr. At 164° the rates for rearrangement to 1,1-dideuterio-2-(p-substituted phenyl)-1,5-hexadiene were X=H 5.30×10^{-5} sec.$^{-1}$; X=CH_3, 2.33×10^{-5} sec.$^{-1}$; X=OCH_3, 2.98×10^{-5} sec.$^{-1}$; X=Cl, 6.60×10^{-5} sec.$^{-1}$ (where X = the p-substituent).

The results show an unexpectedly large rate enhancement (50-100 fold) for aromatic substituents at C_2. The para substituents cause only minor effects and no correlation with sigma constants is observed. Possible changes in mechanism for the Cope rearrangement of these dienes were considered. A mechanistic continuum varying from complete scission into two allylic radicals at one extreme to formation of a 1,4-cyclohexadiyl diradical at the other was proposed.

In a second program the mechanism of the ring closure of 5-anilino-N-phenyl-2,4-pentadienylideniminium chloride in acid solution was investigated. An acid catalyzed process was identified and was shown to give N-phenylpyridinium chloride and anilinium ion. The two protons in enamine positions (carbons 2 and 5 of the pentadiene chain) were observed to undergo a very rapid exchange in deuterated TFA. In DMSO-d_6 containing 20% TFA-d_1 the exchange rate is 1.5×10^{-5} sec.$^{-1}$ at 24°C. When ring closure is carried out in deuterated acetic acid using D_2SO_4 as catalyst, the N-phenylpyridinium ion contains deuterium in the 3- and 5-positions on the pyridine ring. In this medium a solvent isotope effect of $k_D/k_H = 2.4$

was found. Two possible mechanisms were considered, and the electrocyclic closure of a doubly charged ion protonated on nitrogen was preferred.

Study of the ring closure reactions of 5-methylamino-N-(2,4-dinitrophenyl)-2,4-pentadienylideniminium chloride was initiated. In DMSO this unsymmetrical salt reacted cleanly to give N-methylpyridinium chloride and 2,4-dinitroaniline by a first order process, $k_1 = 2.27 \times 10^{-4}$ sec.$^{-1}$ at 40°. Careful nmr studies in both DMSO and TFA showed that a rapid pH sensitive equilibrium between the unsymmetrical salt and 2,4-dinitrophenylpyridinium ion plus methylamine was established almost instantly either by mixing the two components in DMSO or on dissolving the unsymmetrical salt in that solvent. In TFA no equilibrium mixture is formed. Further work will be needed to ascertain mechanistic detail.

Part I. Synthesis and Cope Rearrangement of Some Substituted Hexadienes

Part II. Formation of N-Phenyl and N-Methyl Pyridinium Salts from 1, 7-Diaza-1, 3, 5-heptatrienes

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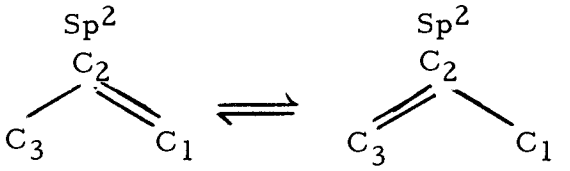
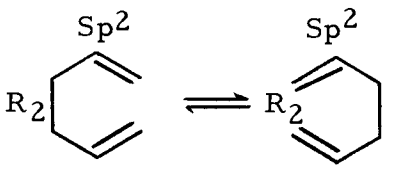
INTRODUCTION

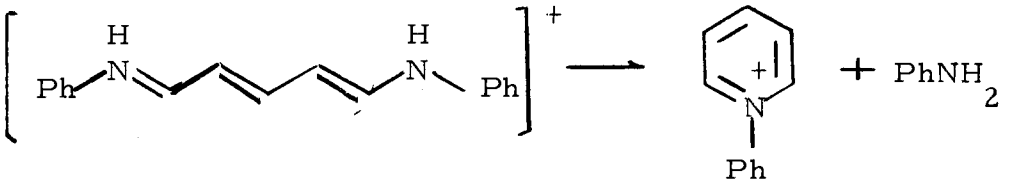
Much attention has been focused recently on the electrocyclic ring-closure of cis-trienes. As part of a general study on the influence of structure on the rate of this reaction, the first part of this thesis will consider an attempt to establish a standard of comparison for the influence of substituents attached to a carbon of the triene system which retains sp^2 hybridization during the electrocyclic reaction.



The Cope rearrangement of 2-substituted 1, 5-hexadienes was selected as a model system since the reaction is concerted and proceeds via a cyclic transition state where carbon 2 remains sp^2 hybridized.

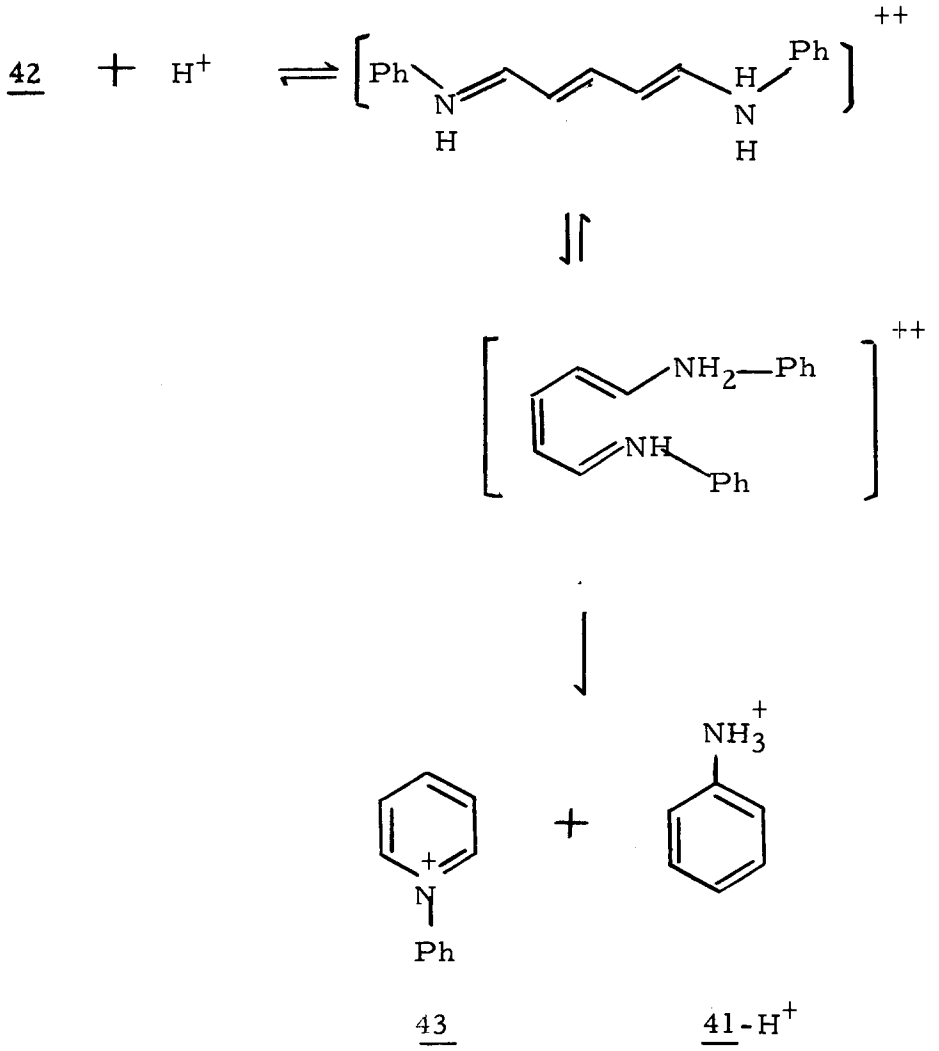


The second part of the thesis will treat the effect of a positive nitrogen at the terminal position of a cis-triene system. Previously studies of the valence isomerization of trienes having an oxygen or a nitrogen at a terminal position have been reported by this laboratory[45, 72, 73]. The electrocyclic ring closure of 42 in basic methanol



42 43 41

was shown to proceed faster than does that cyclization with a cis-dienone[45, 74]. This difference in reactivity of the heterocyclic system might be attributed either to the relative electronegativities of oxygen and nitrogen, or to participation by the lone pair of electrons on those atoms. A study of the reaction of 1,7-diazaheptatrienes in acidic media was initiated to distinguish these two alternatives. Thus, for example, if the reaction proceeds via the ring closure of a doubly charged ion as shown here, participation by the lone pair would be impossible.



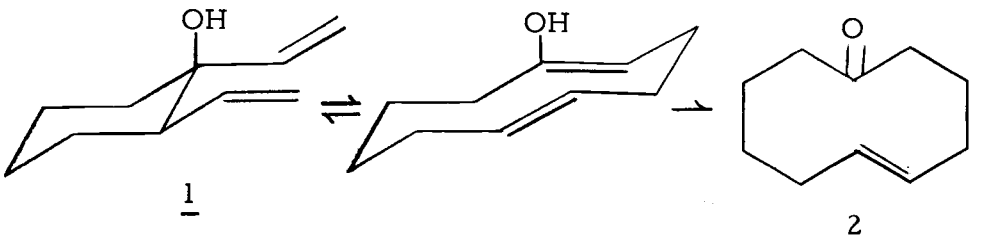
43 41-H^+

HISTORICAL

Part I. Synthesis and Cope Rearrangement of Some Substituted Hexadienes

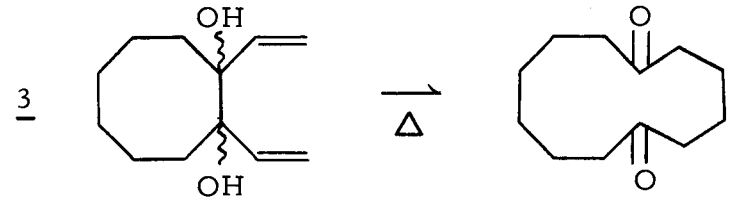
An enormous volume of work has been devoted to the Cope rearrangement since its discovery in 1940[1]. Several reviews on this reaction have been published[2, 3]. Despite this large volume of research, the full synthetic value of this rearrangement, certain details of its stereo course, and the precise nature of its transition state are still not completely understood. Some recent work pertinent to these points will be reviewed in this section. We will also survey some studies of its occurrence in certain natural products containing a ten-membered ring where its incursion under mild conditions raises the important issue of whether the related six-membered ring sesquiterpenes do indeed occur in nature.

The synthetic utility of the Cope and the related Claisen rearrangement has been studied extensively. An interesting synthetic value of this rearrangement was reported by Marvell and Whalley[4], i.e., their novel synthesis of 5-cyclodecen-1-one (2) from 1,2-divinylcyclohexanol via a four-carbon ring expansion. A 90% yield of trans-2 was obtained from trans 1, while cis-1 gave only 50% of a 60:40 mixture of trans-2 and cis-2. The relationship of the stereochemistry of the products was suggested to be the result of a concerted



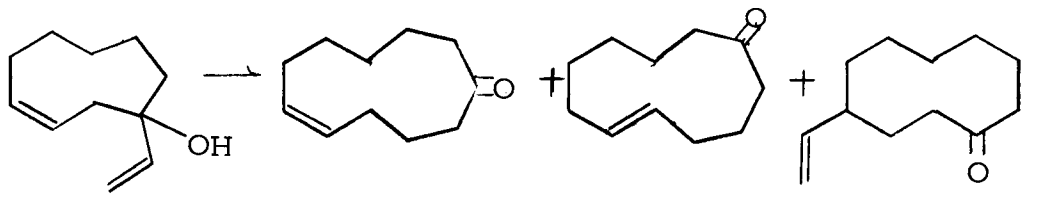
1 2

stereospecific Cope reaction via a chair-like transition state. A similar four carbon ring expansion had been reported earlier by Marvell and Tao[5] using the Cope reaction of 1,2-divinyl-1,2-cyclooctanediol (3).



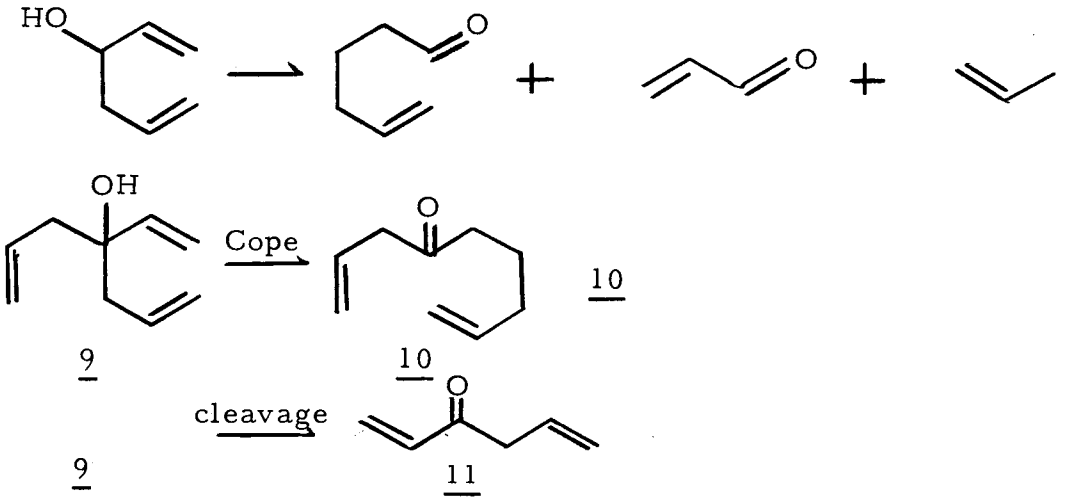
3

More recently a two carbon ring expansion was reported by Thies[6]. He studied the rearrangement of cis-1-vinylcyclonon-3-en-1-ol and its trimethylsiloxy derivative. The [3,3] sigmatropic shift only gave the minor product 8, whereas a [1,3] shift gave 76% of cis-5-cycloundecenone (6). A further value of the oxy-Cope reaction



5 6 (76%) 7 (12%) 8 (8%)

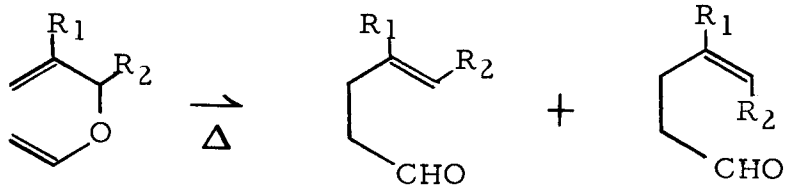
is for the synthesis of Δ^5-unsaturated carbonyl compounds and products derived therefrom. Viola and his coworkers[7,8] studied the vapor phase thermolysis of various methyl substituted 3-hydroxy-1,5-hexadienes and reported that this can serve as a general method for the preparation of Δ^5-unsaturated carbonyl compounds. However, yields are highly sensitive to substituent effects and reaction temperature. By-products from the competitive β-hydroxyolefin cleavage often make this route less attractive. Similarly, 4-vinyl-1,6-heptadien-4-ol (9), on heating, gave 1,8-nonadiene-4-one (10), along with



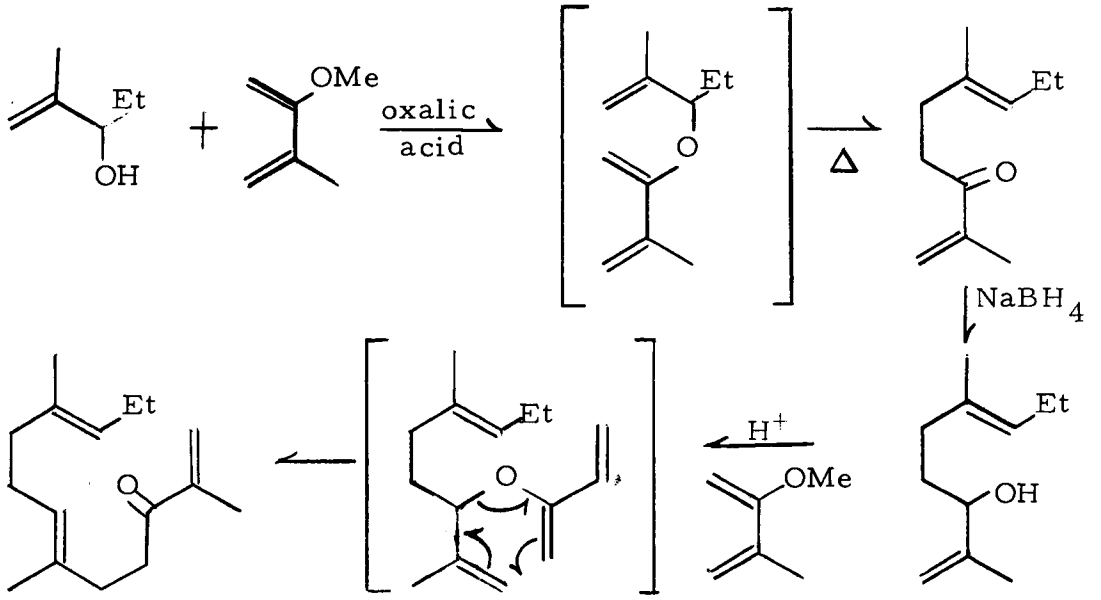
the cleavage product, 1,5-hexadiene-3-one (11). The ratios of the two products changed from 70% Cope and 30% cleavage at 370-375°C to 25% Cope and 75% cleavage at 400-402°C.

One of the most significant values of the Claisen rearrangement is for the stereoselective synthesis trisubstituted double bonds. Faulkner and Peterson[10] reported the Claisen rearrangement of various substituted allyl vinyl ethers to the corresponding unsaturated

aldehydes in quantitative yields. The ratio of the products is about 10:90. One major advantage of this route is that the process can be repetitive. The reaction later became known as the "methoxy-isoprene method."

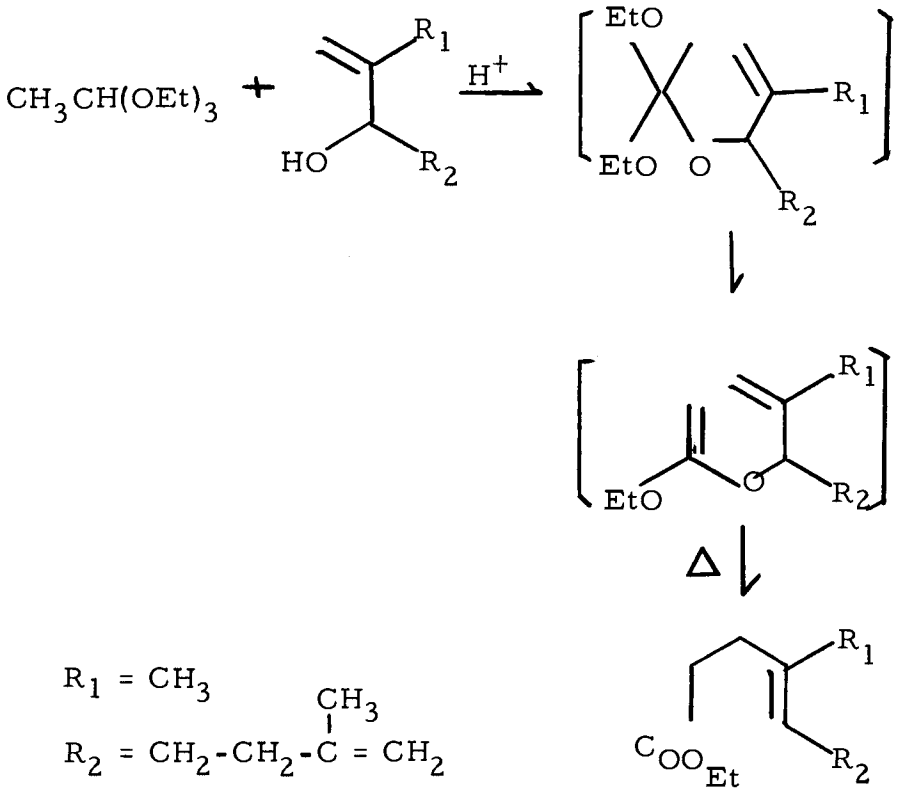


R_1	R_2	%	%
Me	Et	10	90
Me	i-Pr	7	93
Et	Et	10	90

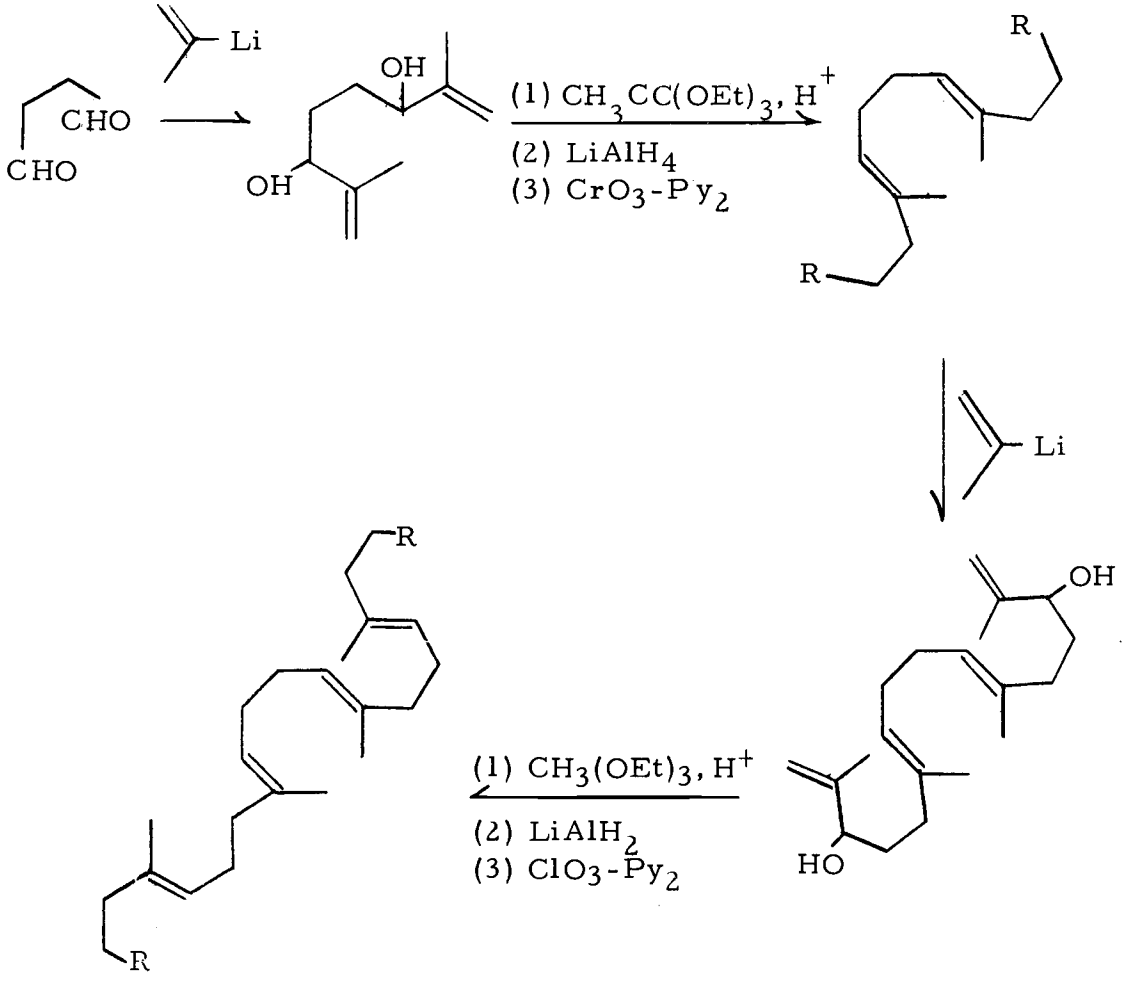


Similarly, the stereoselective synthesis of trisubstituted double bonds via the Claisen rearrangement of the orthoester of an allylic alcohol was reported by Johnson and his co-workers[11] in the synthesis of squalene. This orthoester process is simple to perform and the overall yield and stereoselectivity are higher than those of the

3-methoxyisoprene method.



Ortho-ester Claisen Reaction

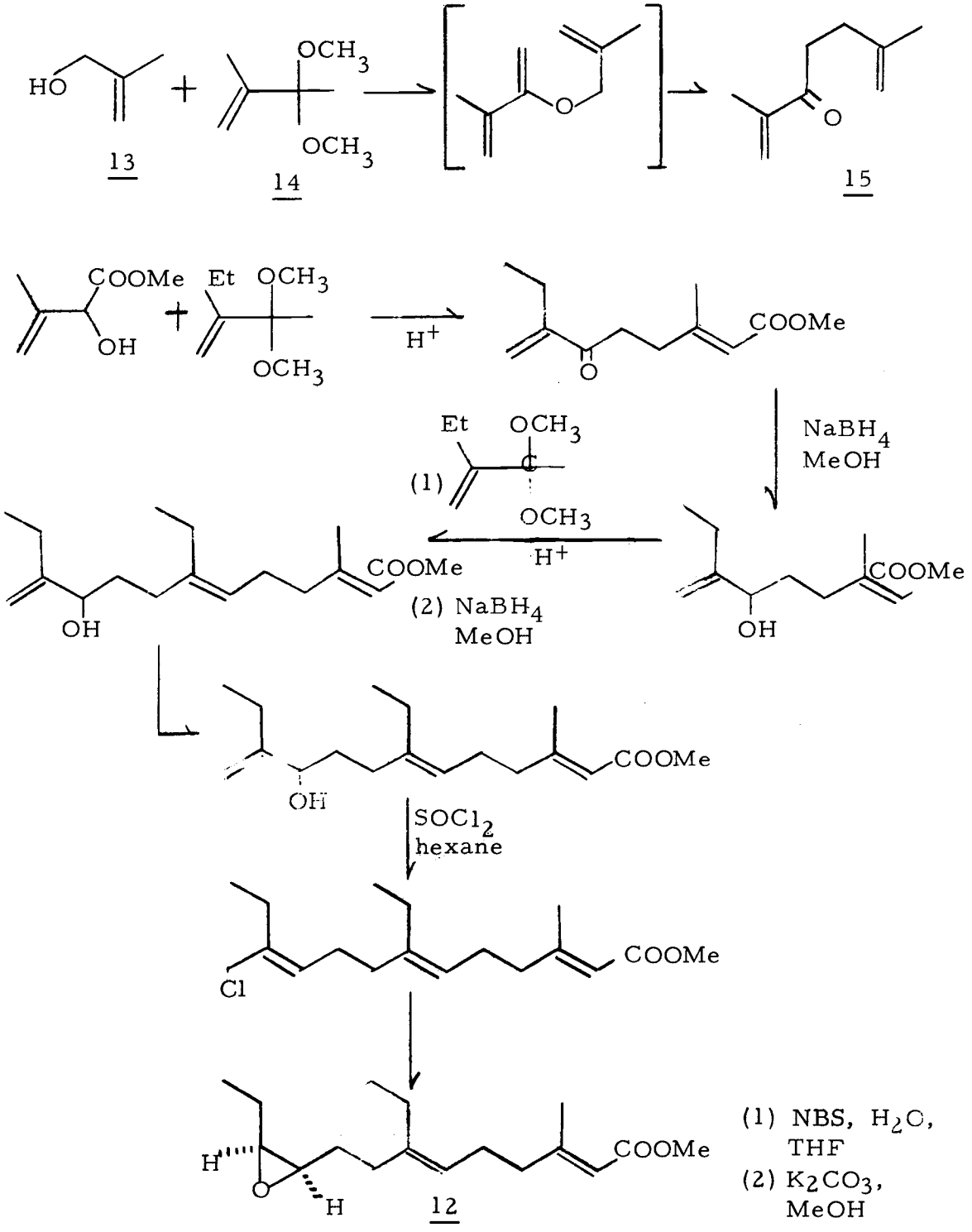


R = COOEt
R = CH_2OH
R = CHO

Synthesis of Squalene

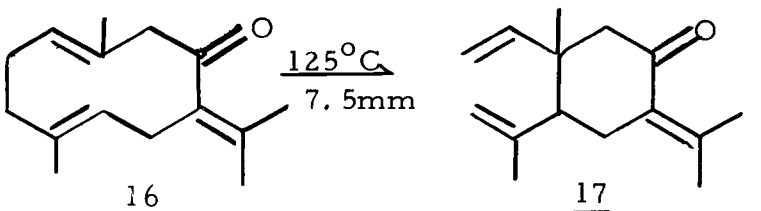
An improved Claisen rearrangement, involving a ketal which reacts at a lower temperature, a shorter reaction time and in weaker acid, was used by Johnson et al.[12] in the stereoselective synthesis of Juvenile hormone 12. The ketal Claisen involves heating an allyl alcohol 13 with a ketal to give an α,β-unsaturated ketone 15, which can be reduced to the corresponding alcohol. The process can

then be repeated and is useful for preparing trans-disubstituted, as well as trans-trisubstituted olefins in good yield. The scheme for the synthesis of juvenile hormone 12 is as follows:

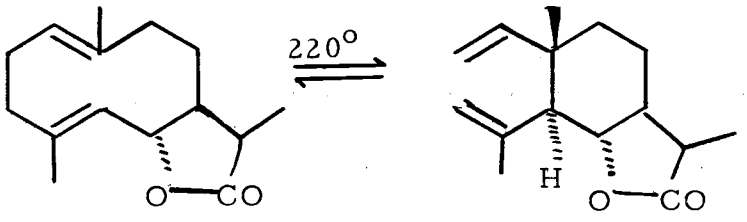


One of the most fascinating aspects of recent investigations of the Cope rearrangement is the discovery of its occurrence in ten-membered ring sesquiterpenes. The existence of these natural products had been assumed to be improbable since only one had been isolated up until 1957. However, a number of sesquiterpenes containing a divinylcyclohexane group had been found. The discovery that ten-membered ring sesquiterpenes can undergo the Cope rearrangement under unexpectedly mild conditions raised the interesting question as to whether the divinylcyclohexane type of sesquiterpenes occur in nature at all.

Sorm and his coworkers[13,14] first noted the Cope rearrangement of germacrone (16) to β-elemenone during vacuum distillation of 16. Shorterly thereafter Rao et al.[15] suggested that the six-membered ring sesquiterpene saussurealactone (19) does not occur in nature but was the result of a Cope reaction of dihydrocostunolide (18) during extraction. In fact, extraction at room temperature produced only traces of 19.

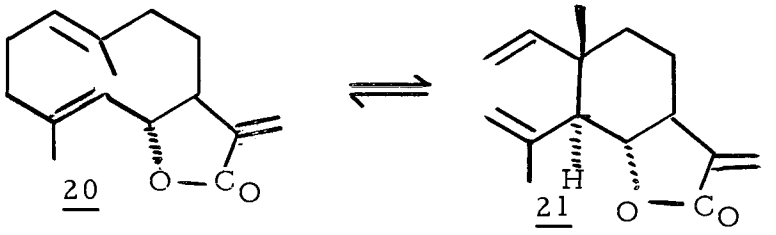


16 17



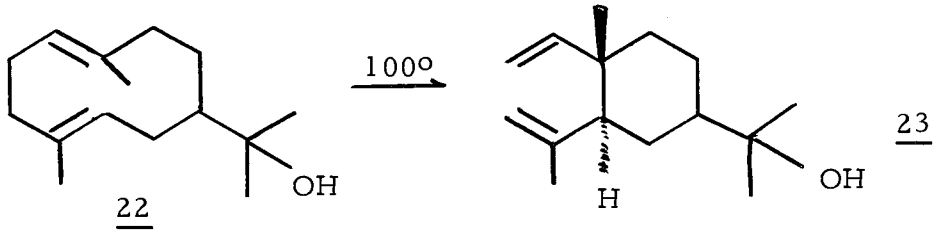
18 19

The Cope rearrangement of Costunolide (20) was reported by Jain and his co-workers[16]. They obtained the Cope product dehydrosaussurealactone (21) during the process of extracting 20 from costus root oil.



20 ⇌ 21

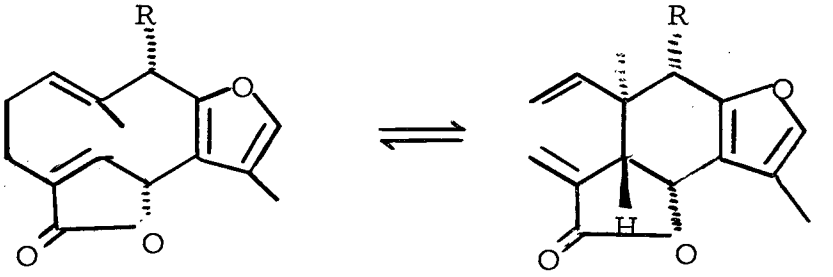
Another Cope rearrangement of a natural product was discovered by Sutherland et al.[17]. They observed the transformation of hedycaryol (22) to elemol (23) at 100°, and suggested this conversion might be possible in the plant itself.



22 → (100°) → 23

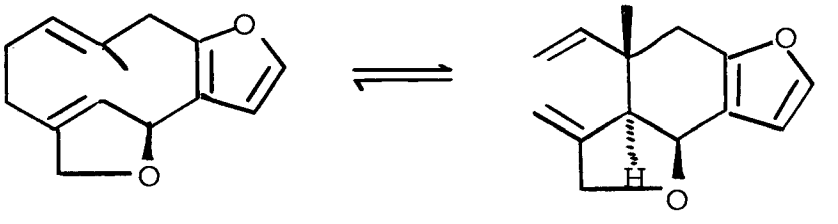
Cope rearrangements of ten-membered ring sesquiterpenes have also been reported in Tamaulipin-A[18], Chamissonin[19], and furanodiene[20]. Takeda and his coworkers[21,22,23,24] have done a thorough investigation of the reactions of linderalactone (24), litsealactone (25), the related diol 26, the ether 27 and the dimethoxy compound 28. The conformations of these ten-membered ring compounds have been studied using NOE (nuclear Overhauser effect)

techniques. Takeda suggested the stereochemistry of the rearranged products is controlled by the conformation of these ten-membered ring



24 R = H R = H

25 R = OAc R = OAc



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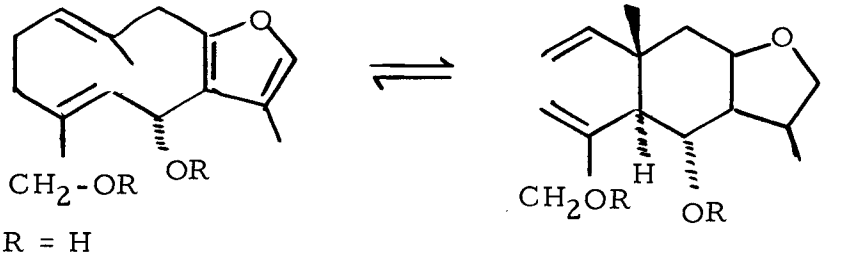
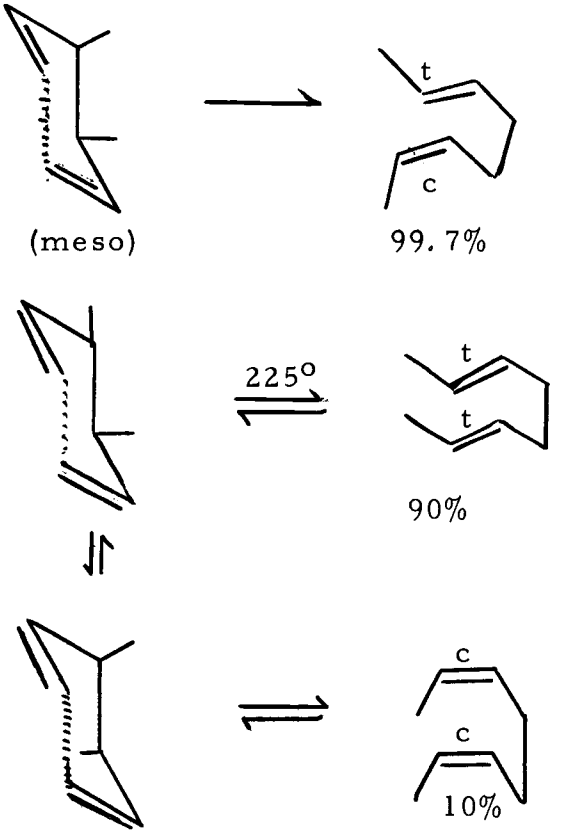


26 R = H

28 R = Me R = H, OMe

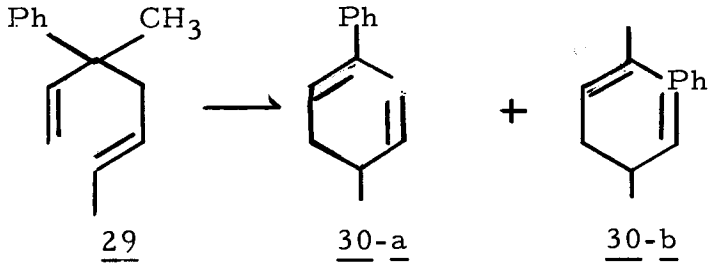
compounds. The Cope rearrangement of these germacrane-type sesquiterpenes, they suggest, has a preference for the chair-like transition state as predicted theoretically[25].

Two configurations are possible for the transition state of the Cope rearrangement, quasi-chair and quasi-boat, similar to the conformations of cyclohexane. In some cases, additional geometrical requirements lead to the quasi-boat form for the transition state as in the rearrangement of cis-divinylcyclopropanes[2,25]. However, the transition state generally prefers the quasi-chair configuration. Doering and Roth[26] have demonstrated elegantly using meso- and d,ℓ-3,4-dimethyl-1,5-hexadiene that the quasi-chair is favored by at least 5.7 Kcal/mole.

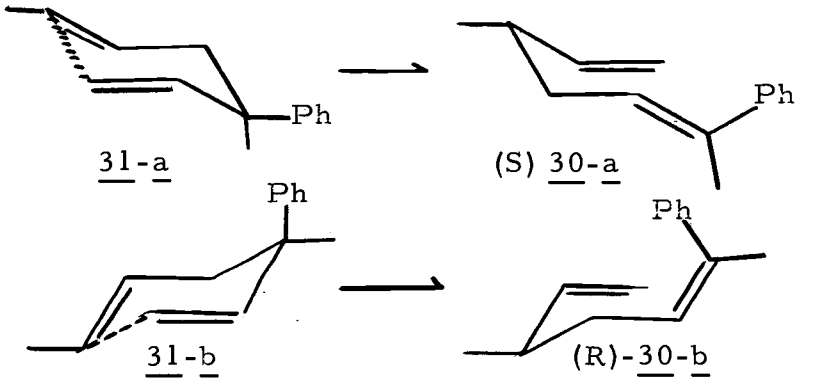


Other data leading to the same conclusion was provided by Hill and his coworkers[27] on the Cope rearrangement of

trans-3-methyl-3-phenylhepta-1,5-diene (29). An 87:13 mixture of cis- and trans-3-methyl-6-phenylhepta-1,5-diene (30-a) and (30-b) was obtained. Rearrangement of (R)-(+)-29 gave (S)-(+)-30-a and (R)-(+)-30-b of opposite configuration and with optical purities of 91% and 89%, respectively. These correspond to an optical yield of 94-96%. From this optical stereospecificity they suggested the preference for chair conformations 31-a and 31-b with an upper limit of 2-3% of reaction via the boat conformations.



29 30-a 30-b



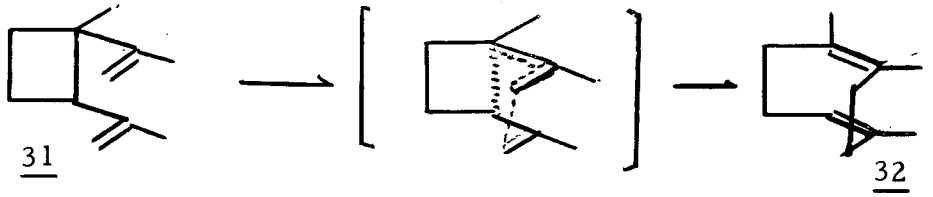
31-a (S) 30-a

31-b (R)-30-b

Other rearrangements, whose stereochemistry require a four-center, chair-like transition state, are those of cis, trans-cyclonona-1,5-diene[28] and cis, trans-cyclodeca-1,5-diene[29].

Rearrangement can occur readily through the boat-like transition state if the molecule is so constructed that the chair-like transition state is sterically unfavorable. An example of this is the Cope

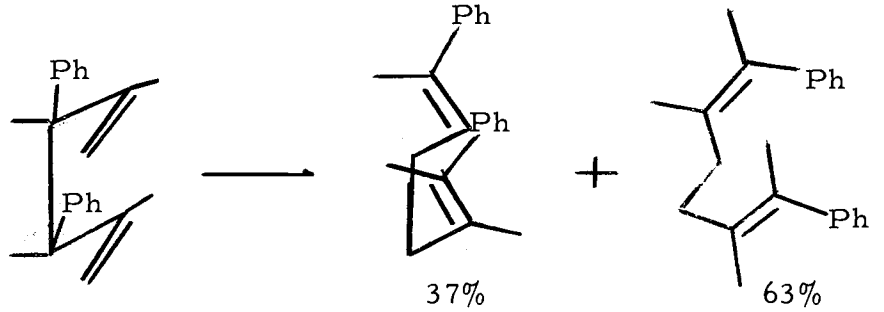
rearrangement of cis-1,2-divinylcyclobutane (31) to cis,cis-cycloocta-1,5-diene (32)[30]. Similarly, the well known Cope rearrangement of



31 32

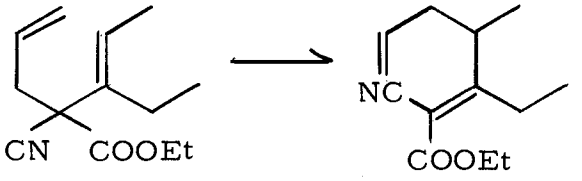
bullvalene[31] must proceed via the boat-like transition state owing to the structure of the molecule.

One interesting Cope rearrangement that utilizes both the boat-like and chair-like transition states is that of meso-3,4-diphenylhexa-1,5-diene (33) reported by Lutz and his coworkers[32]. The product is a mixture of cis,trans-1,6-diphenylhexa-1,5-diene (34-a) and trans,trans-1,6-diphenylhexa-1,5-diene (34-b). The authors suggest this exceptional behavior must be due to steric inhibition to coplanarity of the phenyl and allyl groups in the chair-like transition state.



33 34-b 34-a

Mechanistically, the Cope rearrangement has long been considered to be a concerted process with a cyclic transition state[1,3,26,27,33]. When proper geometric constraints exist, however, rearrangement can proceed through a pair of allylic radicals[25,28,34,35]. Crossover reaction products are usually observed when the reaction goes by this mechanism. A third possible mechanism, via an ion pair, was considered by Walling et al.[36] in 1962 for the Cope rearrangement of ethyl(1-ethylpropenyl)allylcyanoacetate (35) under high pressure. They suggested a cyclic transition state was more reasonable based on their experimental results.



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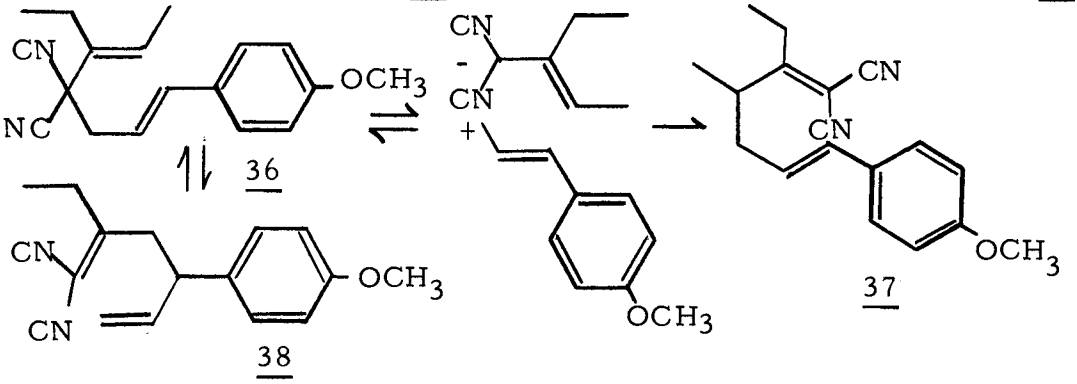
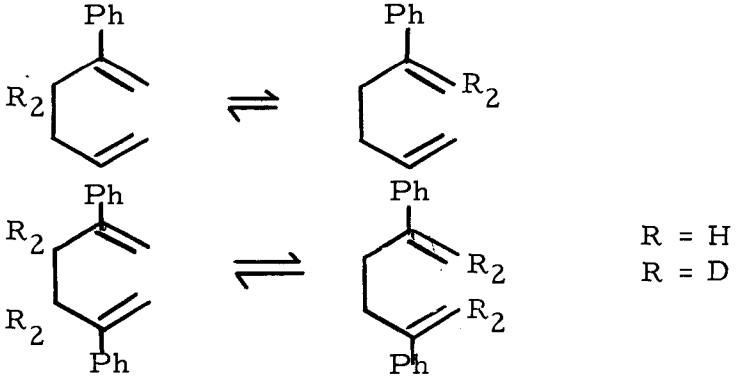
Wingfield and his coworkers[37,38] proposed ionic intermediates for the Cope reaction of 2-(1-ethyl-1-propenyl)-2-(3-p-methoxyphenylallyl)-malononitrile (36). Isolation of a crossover product (37),



in addition to the normal Cope product (38), indicated that the reaction proceeds either through ionic intermediates or a pair of allyl radicals. The latter was ruled out when CIDNP (chemically induced dynamic nuclear polarization) failed to detect any short-lived free radicals. Furthermore, the carbonium ion intermediate was trapped with thiophenoxide and hydride ions.

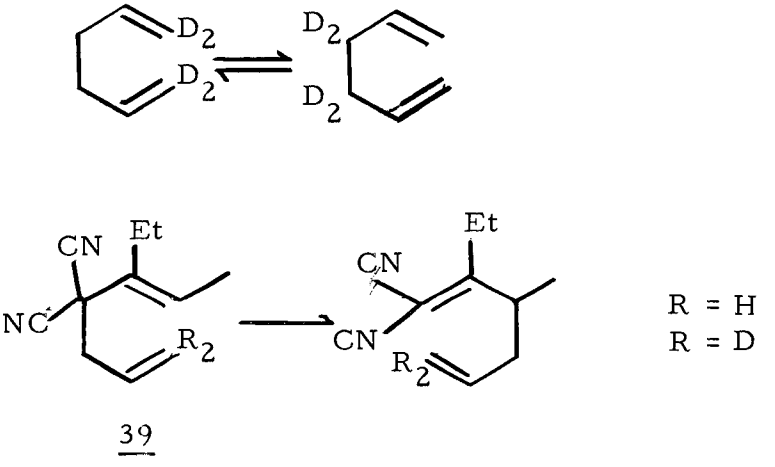
A fourth possible mechanism, i.e., via a cyclohexyl-1,4-diyl diradical has recently been suggested by Doering et al.[39] based on calculation of the heat of formation of this diradical. This led to an activation energy for formation of the diradical of 33.7 Kcal/mole, very close to the experimental activation energy of 33.5 ± 0.5 Kcal/mole for the Cope reaction of 1,1-dideuteriohexa-1,5-diene. From some rate studies, Dewar[40] has argued that this is the intermediate in the Cope rearrangement of 2-aryl substituted hexadienes. Dewar's suggestion of the diradical as the intermediate was based on the



greater rate enhancement by a phenyl group at carbon-2 compared with one at carbon-3. The Cope rearrangement of 3-phenyl-1,5-hexadiene proceeds through the concerted process, he argues, since

its rate is faster than that of 1, 5-hexadiene.

Neither Doering nor Dewar took account of the deuterium isotope effect on the rearrangement of deuterated 1, 5-hexadienes. However, recent work by Sunko[41] and his coworkers indicates the secondary deuterium isotope effect on the equilibrium constant is 1.10/per D for 1, 5-hexadiene-1, 1, 6, 6-d_4. A kinetic deuterium isotope effect of 1.10 is observed for the reaction of 3, 3-dicyano-2-ethyl-1-methyl-1, 5-hexadiene (39). No crossover reaction product was observed by mass spectroscopic analysis which eliminates the allylic radical route.



39

Part II. Formation of N-Phenyl and N-Methyl Pyridinium Salts from 1, 7-Diaza-1, 3, 5-Heptatrienes

Many investigations have been carried out on the ring opening of pyridinium ions since Zincke reported a series of these reactions

70 years ago[42]. His work drew attention to the reaction of the symmetrical red salt 42 when heated either with excess aniline or with ethanolic hydrogen chloride. The products of this process are aniline (41) and N-phenylpyridinium chloride (43) as shown in Figure 1.

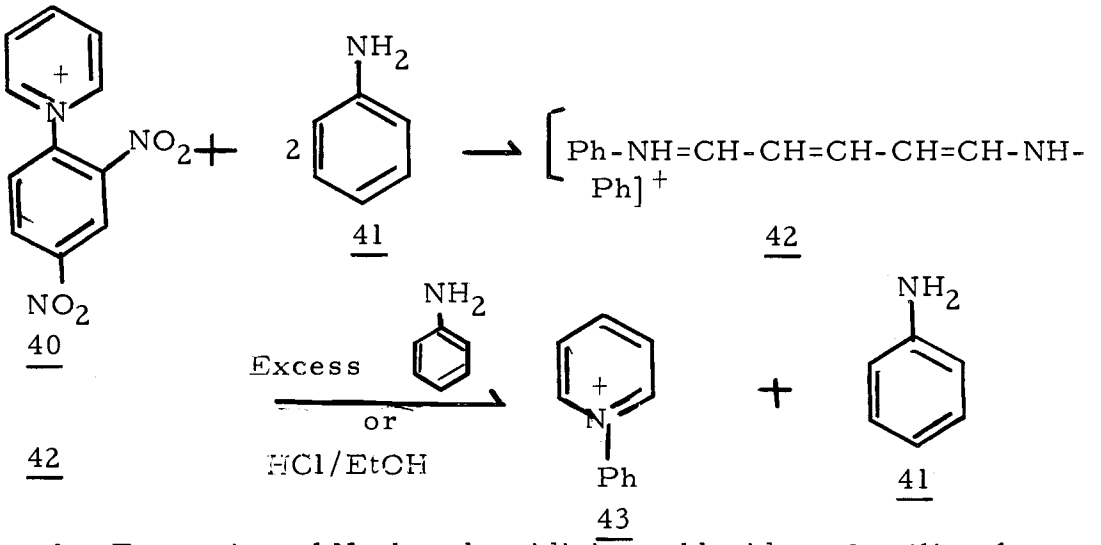
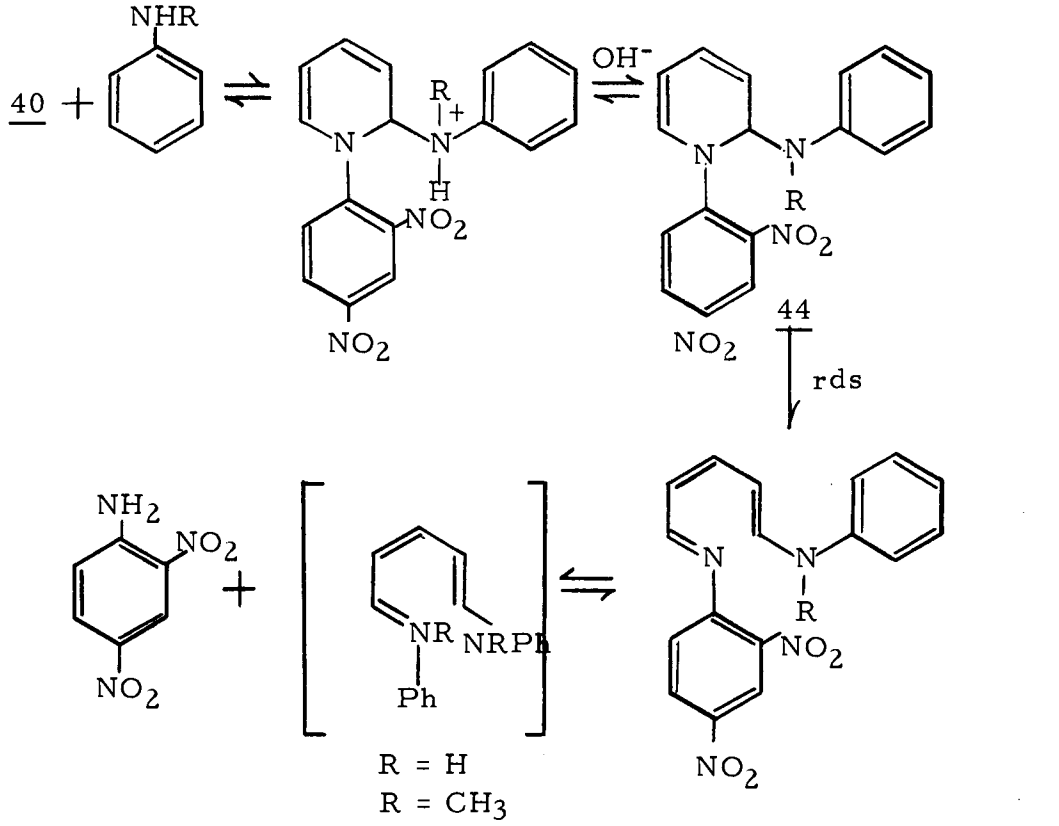
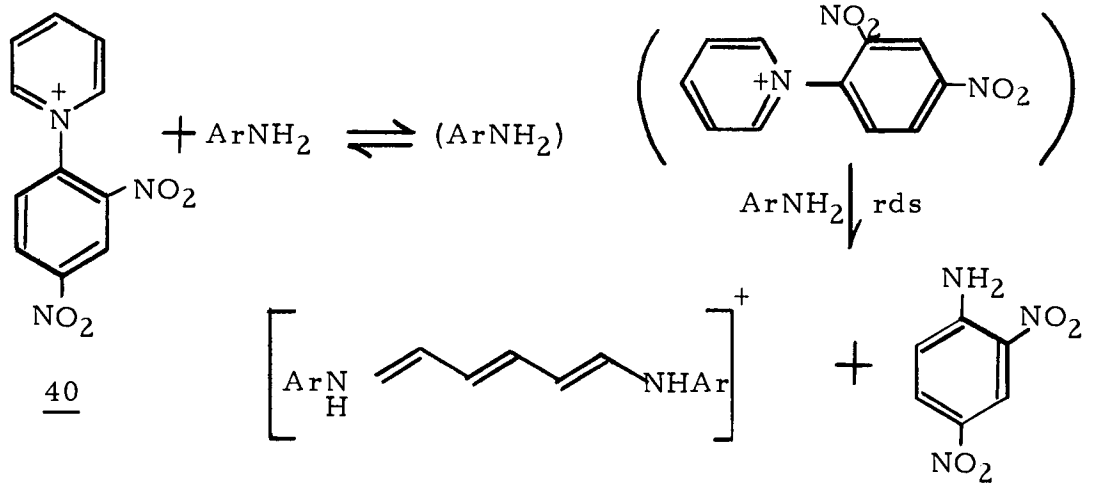


Figure 1. Formation of N-phenylpyridinium chloride and aniline from 2,4-dinitrophenylpyridinium chloride.

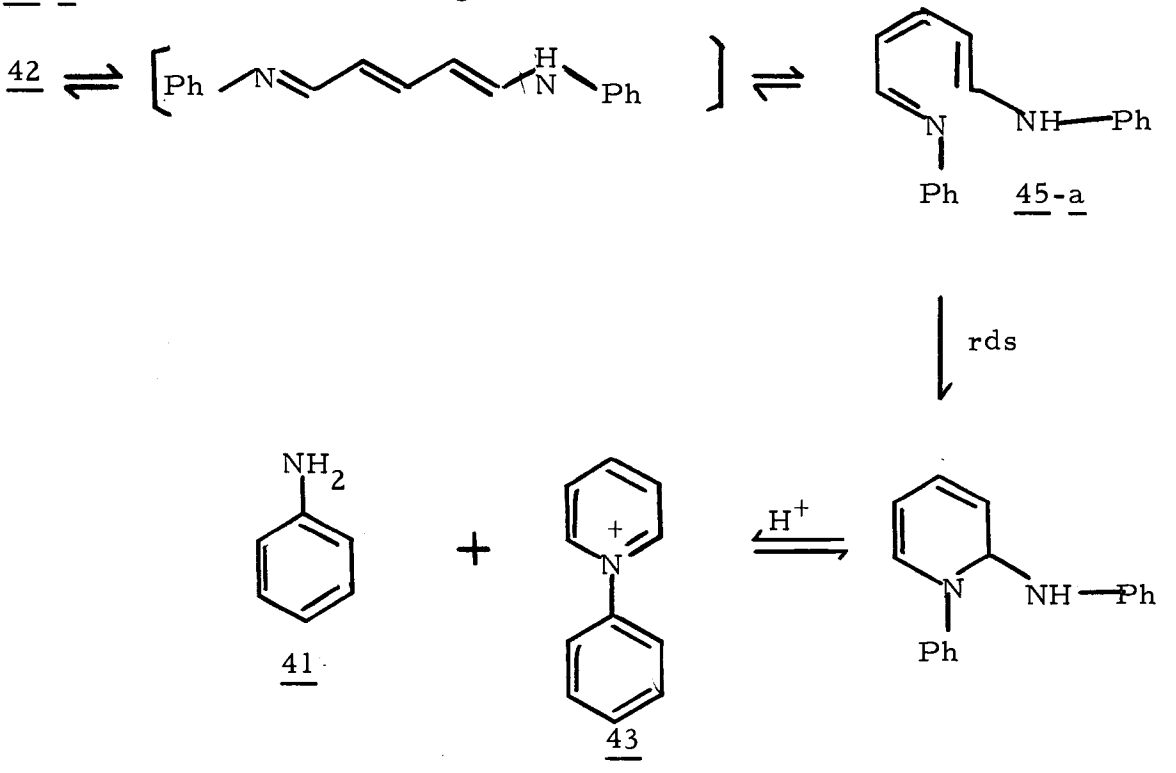
The mechanism of the ring opening of 40 with aromatic amines was first studied by Van den Dunghen et al.[43] in 1957. The reaction was shown to be first order in 40, hydroxide ion, and the amine at constant pH. Rate constants were not determined due to experimental difficulties. Ring opening of the dihydropyridine derivative 44 was proposed as the rate-determining step.



The reaction of 40 with a number of m- and p-substituted anilines in methanol was also studied by Oda and his coworkers[44]. They proposed a reaction mechanism involving the formation of a 1:1 complex as the first step, followed by a rate-determining reaction of this intermediate with aniline to form the products.

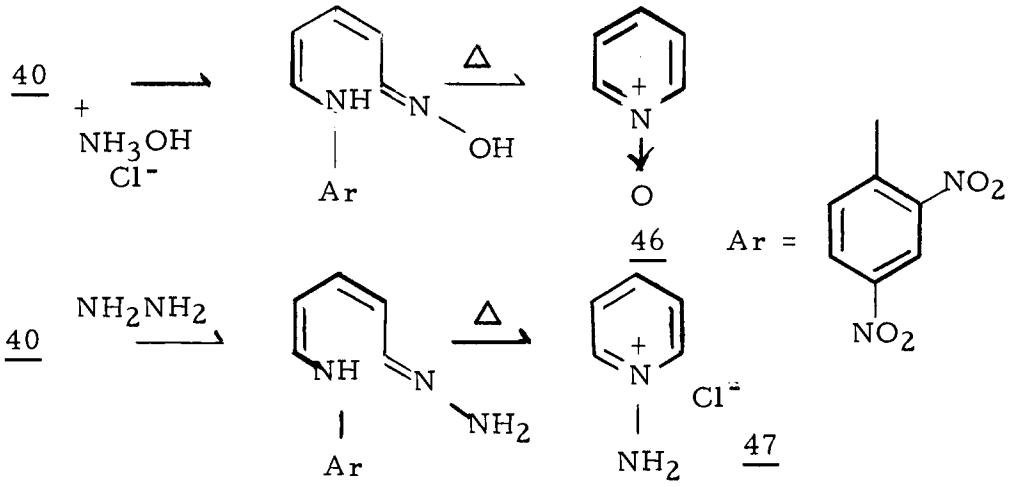


The mechanism of the ring-closure of the symmetrical diazatriene (42) in basic media was first reported by Marvell and his co-workers in 1970[45]. Kinetics were followed by the disappearance of the visible band at 407 nm for the base form 45 of 42. The reaction was first order in 45, with a rate constant of 3.5×10^{-4} sec.$^{-1}$ at 40°. The activation parameters for this reaction were also determined, ($\Delta H^{\ddagger} = 22.7$ kcal./mole and $\Delta S^{\ddagger} \approx 0$ e.u.). These workers suggested a reaction mechanism that involved an electrocyclic ring-closure of 45-a as the rate-determining step.



Ring opening reactions of pyridinium ions have been utilized extensively in the synthesis of azulenes and closely related heterocyclic compounds[46, 47]. More recently, use of this reaction for the synthesis of pyridine and iosquinoline N-oxides and N-imines from 40

was reported by Tamura et al.[48]. The overall yield was 92% for pyridine N-oxide (46), and 48% for 1-amino-pyridinium chloride (47). The lower yield in the latter case was thought to be due to the instability of the N-iminopyridinium betaine which reduced the yield in the



cyclization step. The N-oxides and N-imines of β and γ-picolines and 3,5-lutidine were also prepared in modest yield. This procedure for the synthesis of N-oxides and N-imines was also applied successfully in the isoquinoline series (Figure 2). The overall yield was 50% for this reaction. N-benzoylimino, N-carbamoylimino and N-arylimino-pyridinium and isoquinolinium betaines were prepared similarly in good yields by treating acylhydrazine and acylhydrazine derivatives with the pyridinium salt.

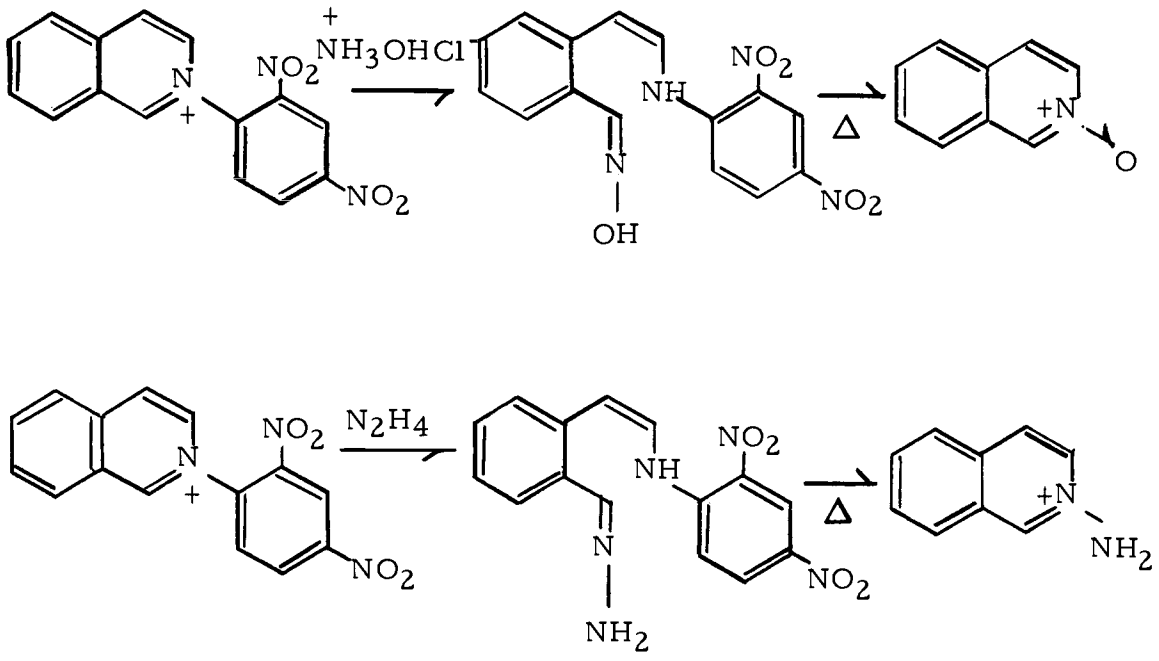
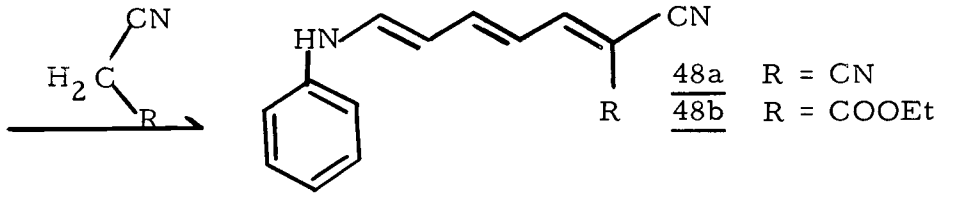
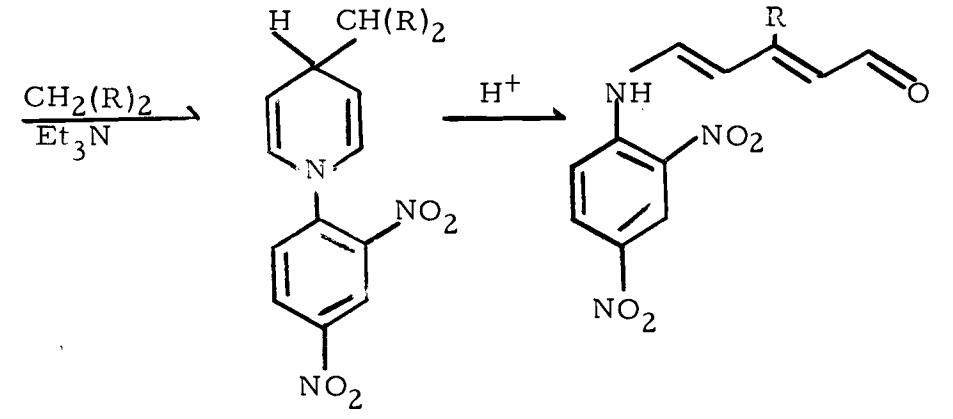


Figure 2. Synthesis of N-oxides, N-imines of isoquinoline.

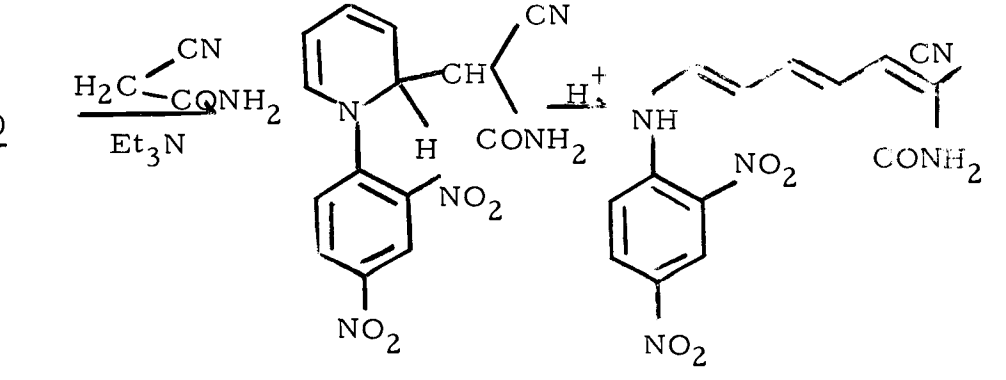
Tamura and his coworkers also investigated the reaction of 40 with active methylene compounds[49]. They reported that the reaction could proceed by three routes. (a) Malonodinitrile and ethyl cyanoacetate attacked the α-position of the pyridine ring and ring-opening gave the products 48 a, b. (b) Diethyl malonate and malonodiamide attacked the γ-position giving the dihydropyridine derivatives 49 a, b. Ring cleavage of 49 a, b in the presence of acetic acid gave the glutaconaldehyde derivative 50 a and b. (c) Cyanoacetamide added at the α-position also to give the 1,2-dihydropyridine derivative 51. Acid catalyzed ring-opening of 51 gave 52. The nmr spectra of compounds 48a, 49a and 49b were discussed. Compound 48a was assigned the all trans form, based on the large splitting constants.

(a) 

48a R = CN
48b R = COOEt

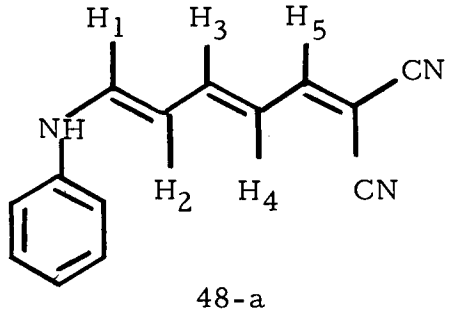
(b) 

49-a R = COOEt 50a R = COOEt
49-b R = $CONH_2$ 50b R = $CONH_2$

(c) 

51 52

($J_{1,2} = J_{2,3} = J_{4,5} = 12.3$; $J_{3,4} = 14.4$ cps.) No mechanism for this reaction was considered.



48-a

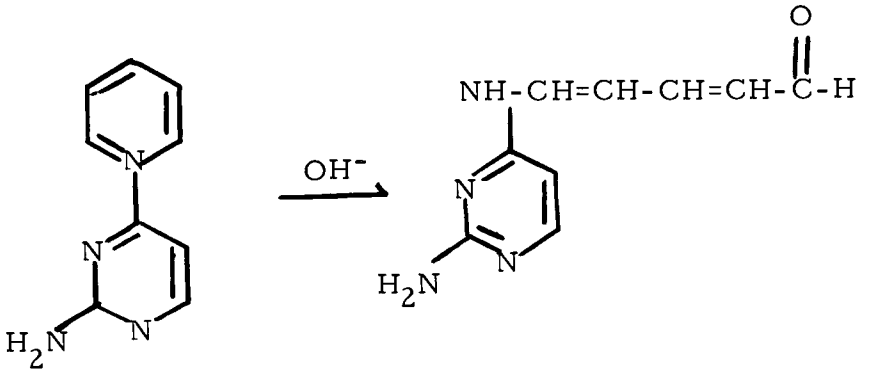
$J_{1,2} = 12.3$

$J_{2,3} = 12.3$

$J_{3,4} = 14.4$

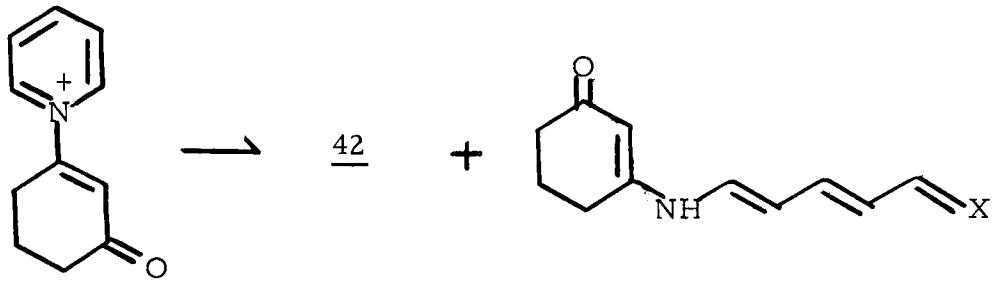
$J_{4,5} = 12.3$

Base catalyzed ring-opening of N-(2-amino-4-pyrimidinyl)-pyridinium chloride (53) has been investigated by Lira[50]. He reported cleavage of the pyridine ring by sodium hydroxide at pH 9 to give 5-(N-(2-amino-4-pyrimidinyl)-amino)-2, 4-pentadienal (54). Compound 53 was obtained when $BuSO_2Cl$ was added to 2-amino-4-hydroxy-pyrimidine in pyridine.

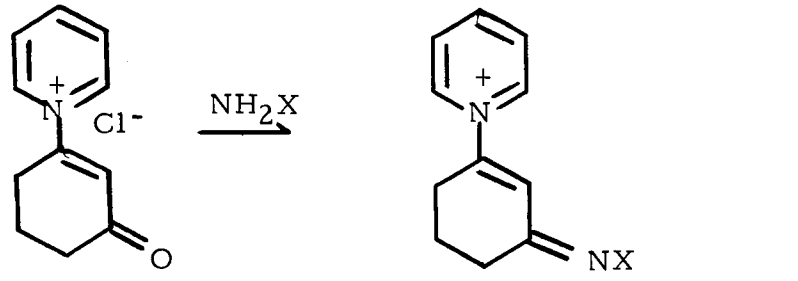


53 54

Reaction of N-(3-oxo-1-cyclohexenyl)-pyridinium chloride (55) with sodium hydroxide, aniline and active methylene compounds was reported by Tamura et al.[51]. Ring opening of 55 to form 42 and a glutaconaldehyde derivative 56, 57 occurred after addition to the C-N bond of the pyridine ring. Carbonyl reagents reacted with 55 to give



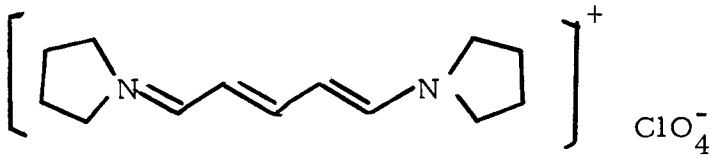
55 → 42 + 56 (X = O) / 57 (X = C(CN)COOEt)



55 → 58-a (X = NHCONH$_2$) / 58-b (X = NH-PH) / 58-c (X = OH)

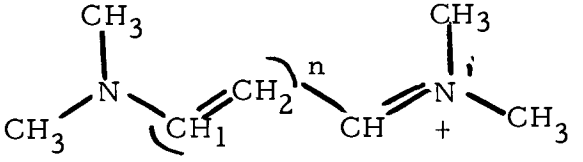
58 a-c only. No ring-opening of the pyridinium salt was observed.

The configuration of diazoheptatrienes had been shown to be all trans by x-ray and nmr studies. Hoppe and Baumgartner[52] first reported the geometry of compound 59 by x-ray studies. Scheibe and



59

his coworkers[53] confirmed the all trans configuration of the symmetrical red salts 60, 61 and 62 by nmr. Coupling constants of 11.8 and 12.7 cps were observed between H_1 and H_2, H_2 and H_3. Exchange of the enamine protons with deuterium has also been observed. A rough rate constant (2×10^{-4}) was reported for the exchange rate in 0.1 M D_2SO_4 in deuterium oxide, presumably for compound 66 at room

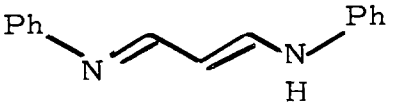


60 n = 1
61 n = 2
62 n = 3

temperature. Addition of acid speeded the rotation about the C'-N' bond, a reduction of E_a from 17 to 8.6 kcal./mole was observed for the cis-trans isomerization of 60 in the presence of 0.11% in sulfuric acid.

The cis-trans equilibrium of malonaldehyde dianil 63, its salt 64 and two related compounds 65 and 66 has been studied by Feldmann and his coworkers[54]. They established a relationship between charge, configuration and spectroscopic properties of the chromophoric system N-C-C-C-N containing 6-πelectrons. Spectroscopic (uv and nmr) data

indicated that this equilibrium was solvent and temperature dependent and could be affected by irradiation. The half-life for the interconversion of trans 63 to its cis isomer in n-hexane at room temperature was reported to be 140 msec. by flash spectroscopy.



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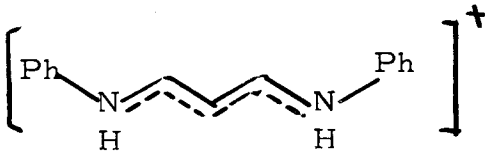

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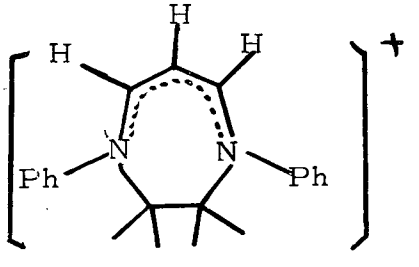
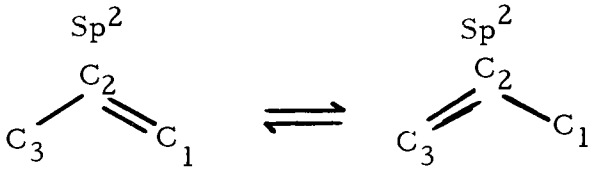


66

DISCUSSION

Introduction

This research is part of a broad program to study the influence of structure on the electrocyclic ring closure of cis-trienes. The first part of the thesis describes an attempt to find a standard against which to compare the influence of groups attached to the central carbons of the triene system. These carbons retain sp^2 hybridization, while the double bond migrates from one side of the carbon to the other. The second part of the thesis will examine the effect of nitrogen at the

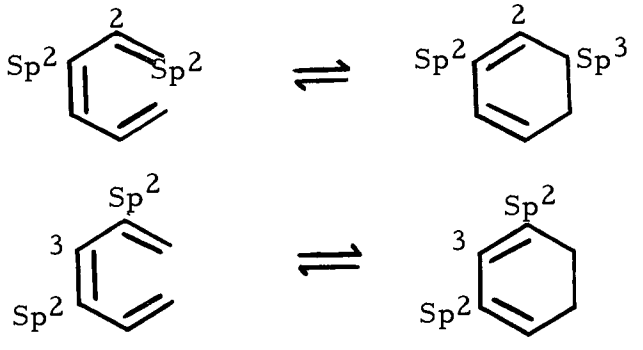


terminal position of the triene system on reaction rates.

Part I. Synthesis and Cope Rearrangement of Some Substituted Hexadienes

Woodward and Hoffmann[55] in their work on conservation of orbital symmetry, define the electrocyclic reaction as the formation of a single bond between the termini of a linear system containing k π electrons, and the reverse process. For the cis-trienes, thermal electrocyclic ring closure proceeds through a disrotatory

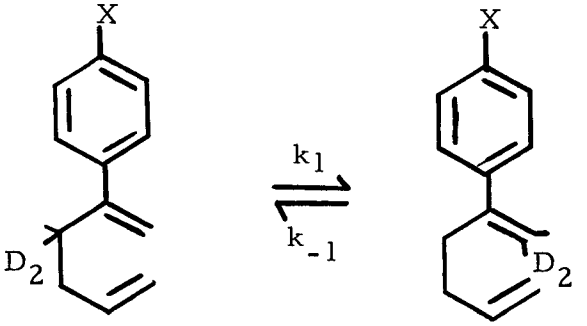
stereochemical route. As a result, geometric requirements will cause in some degree disruption of the overlap of the p-orbitals of the conjugated system still remaining at the transition state. One way to obtain some measure of this disruption would be to measure the influence of substituents on this reaction compared with the influence of those same substituents on some standard reaction having a simple, "normal" non-constrained transition state. Two problems arise: (a) There is no single simple standard reaction, and (b) the definition of "normal" must be clarified. The first problem arises because in any three atom groups the nature of the transition state depends not only on the central carbon, but also on the two terminal atoms. For example, in the triene below the three atom group $C_1C_2C_3$ has carbon two flanked by a pair of sp^2 carbons at the initial state, but one of them becomes sp^3 hybridized in the final state. Alternatively, the group $C_2C_3C_4$ has carbon three bordered by two carbons which remain sp^2 hybridized throughout the reaction.



We chose the Cope rearrangement of 1, 5-hexadiene as a reasonable experimental model since it defines a "normal" state quite

appropriately. The reaction is concerted, and proceeds via a cyclic transition state, and the $C_1C_2C_3$ group has carbon two maintaining sp^2 hybridization while its attached pair of carbons undergo $sp^2 \rightharpoonup sp^3$ or $Sp^3 \rightharpoonup sp^2$ rehybridization. No serious geometric constraint is imposed on the orbital overlap pattern in this simple model system.

The Cope rearrangement of 2-substituted 1, 5-hexadienes is a degenerate process which requires deuterium labelling to follow the



69-a	X = H	72-a	X = H
69-b	X = CH_3	72-b	X = CH_3
69-c	X = OCH_3	72-c	X = OCH_3
69-d	X = Cl	72-d	X = Cl

rate of the reaction. Several 2-(p-substituted aryl)-1, 5-hexadienes have been prepared, and the rates of their Cope rearrangements have been determined.

Synthesis and Structure Proof

The substituted hexadienes were prepared by the simple route shown in Figure 3. Reaction of the proper substituted acetophenone with allyl bromide in the presence of t-amylate gave a mixture of mono and diallylated products which were separated by fractional distillation.

Spectral data for 67-a were in complete agreement with those published. Exchange was carried out with deuterium oxide in dioxane containing triethylamine until the methylene signal at 2.90 had disappeared and the multiplet at 2.42 for the allylic methylene was collapsed to a clean doublet. The carbonyl group was converted to the desired methylene moiety via the Wittig reaction. No loss of deuterium which could be measured by nmr spectroscopy occurred during this process when the reaction was carried out in ether/benzene solution.

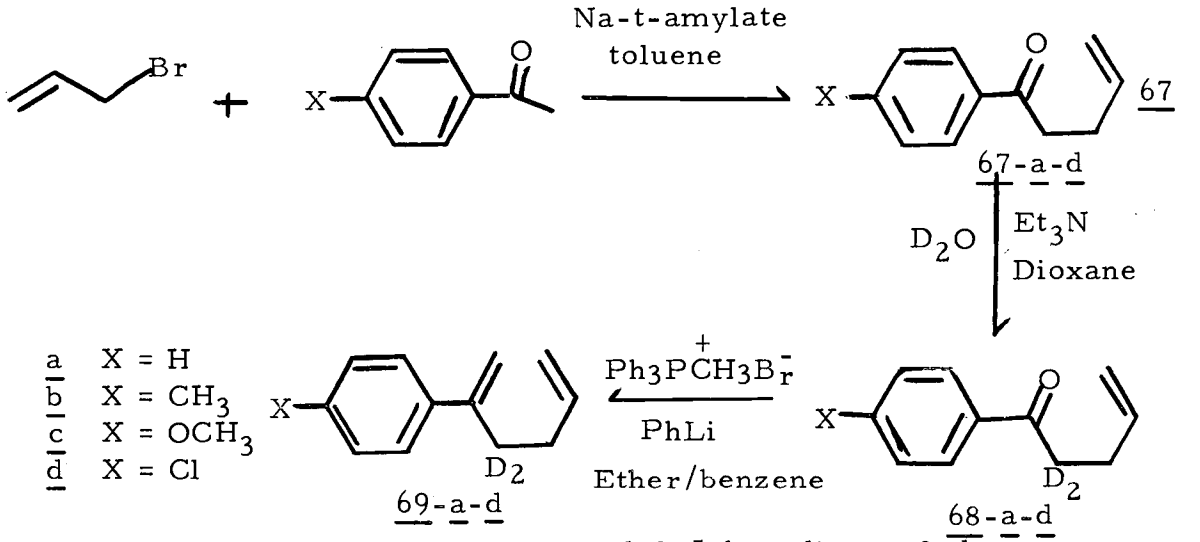
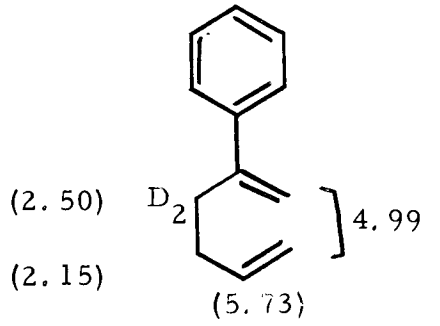


Figure 3. Synthesis of 2-substituted-1,5-hexadienes-3-d_2.

Structural assignments for 69-a-d were based on spectral studies, and only 69-a as a prototype will be discussed in detail. The nmr spectrum of 69-a has a multiplet at 7.23 (relative area 5 for the phenyl protons), a multiplet at 5.73 (proton at C_5) of relative area 1.0, a complex set of bands centered at 4.99 which integrates

for four protons and a doublet at 2.15 of area 2. The olefinic complex is assigned to the four terminal methylene protons, and the doublet to the allylic methylene group at C_4. The non-deuterated molecule



shows two changes from this nmr spectrum, (1) the doublet at 2.15 appears as a complex multiplet and (2) a triplet appears at 2.50 ppm with the relative area 2.

The ultraviolet spectrum for 69-a shows a strong band at 238 nm, which can be compared with the band at 242 in α-methylstyrene. The infrared spectrum shows the expected bands at 2210, 2110 (CD_2), 1645 (C = C str.), and 1000, 910 (CH = CH_2). Given the mode of synthesis and the spectral data here, there is no doubt about the structure of the molecule. Compound 69-a has been made previously, but has not been completely characterized spectrally. Structural assignments for 69-b-d were made in comparable manner.

Since it seemed desirable to provide at least one non-degenerate example permitting measurement of the rate influence of a phenyl group, compound 69-e was also prepared. The synthesis was achieved by the route shown in Figure 4. Propiophenone was

monoallylated to give 70. The structure of 70 is indicated by its nmr spectrum which has a multiplet (5H) between 7.40-7.86 (Ph-), a multiplet at 5.72 (1H, olefinic H), a multiplet at 4.98 (2H, olefinic H), a multiplet at 3.41 (1H, $\overset{O}{\overset{\|}{C}}$-CH), two multiplets at 2.51 and 2.16 (2H, $-CH_2-C=C$) and a doublet at 1.16 (3H, CH_3). The doublet for the methyl group and diastereotopic character of the allylic methylene hydrogens are clearly diagnostic for the monoallylation. Conversion of the ketone to a terminal olefinic group via the Wittig reaction gave 69-e. The nmr spectrum of 69-e has a strong resemblance to that of 70, with the expected changes, i.e., the multiplet at 4.98 now contains four protons, the single proton multiplet at 3.41 in the ketone shifts upfield to 2.71 and the chemical shift between the diastereotopic protons is markedly reduced. It is interesting that the addition of the methyl group which converts 69-a to 69-e forces the phenyl group to twist further from coplanarity with the double bond as is indicated by the shift from 238 to 233 nm for the ultraviolet maximum.

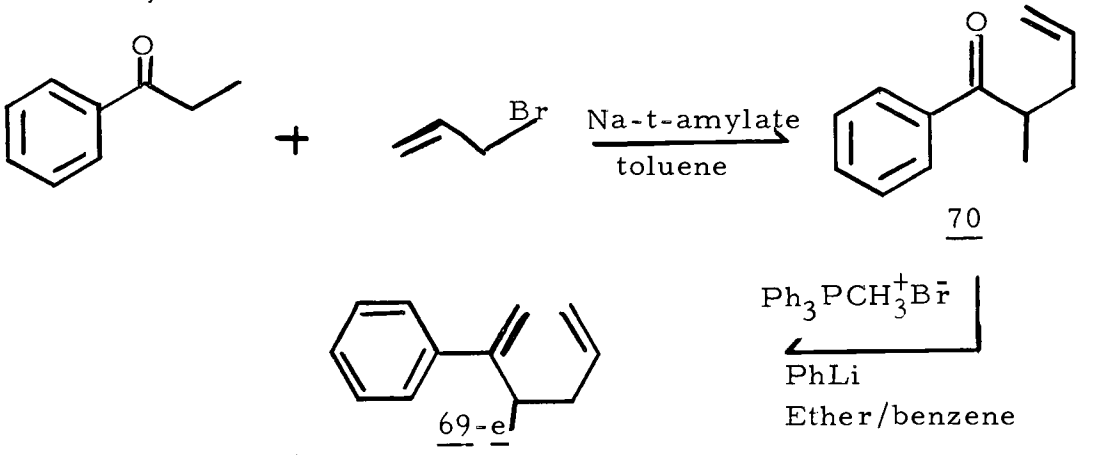
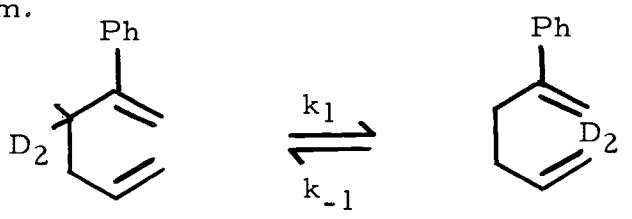


Figure 4. Synthesis of 3-methyl-2-phenyl-1,5-hexadiene.

Kinetics

All kinetic studies were carried out by an ampoule technique. The glass ampoules were treated to remove acids and solutions were degassed by a freeze-thaw procedure. Rearrangements of 69-a-d were carried out in dilute solution in cyclohexane-d_{12} containing a small amount of diphenylamine to minimize polymerization. Reaction was followed by the decrease in number of the olefinic protons in the nmr spectrum.



Rate constants were calculated according to the equation

$$(k_1 + k_{-1})t = 2.3 \log \frac{A_o - A_e}{A - A_e}$$

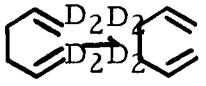
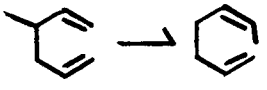
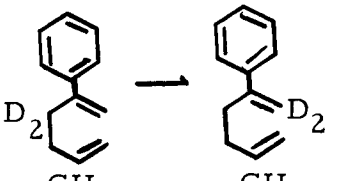
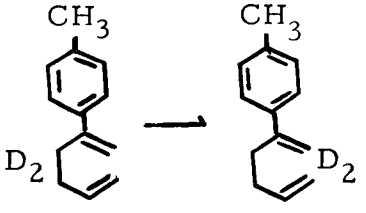
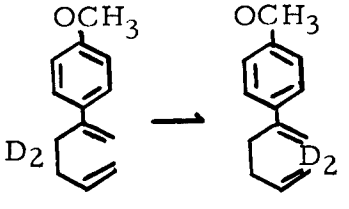
A_o = area corresponding to protons at 4.98 at t = 0

A_e = area for vinyl protons at equilibrium

A = area for vinyl protons at time t.

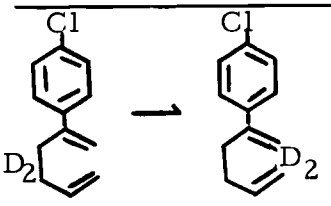
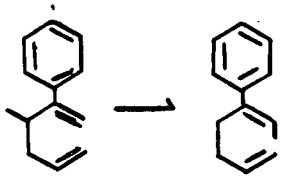
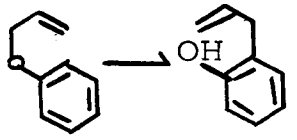
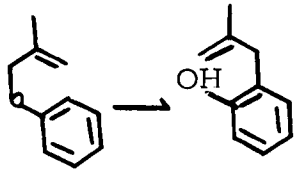
The value for A_e was obtained by heating the solution at 164° until no further change in the area occurred (12-14 hrs.) Generally the value obtained was near 3.05. The values for k_1 are listed in Table 1.

Table 1. Effects of substituents on rate of Cope rearrangement of 1,5-hexadienes and Claisen rearrangement of β-methylallyl phenyl ether.

Reaction	Relative Rate	Temp. (°C)	k (sec.$^{-1}$)	Ref.
	--	150	1.88×10^{-7}	41
Reverse	--	150	1.48×10^{-7}	41
	1	164	5.88×10^{-7}	calc'd
	1.26	164	7.40×10^{-7}	56
Reverse	0.12	164	6.90×10^{-8}	56
	0.105	164	6.16×10^{-8}	56
Reverse	0.044	164	2.56×10^{-8}	56
	1.15	164	6.75×10^{-7}	97
Reverse	0.019	164	1.10×10^{-8}	97
	90	164	5.30×10^{-5}	This work*
	40	164	2.33×10^{-5}	This work*
	50	164	2.98×10^{-5}	This work*

*Deuterium isotope effect was not taken into account for the calculations of rate constants.

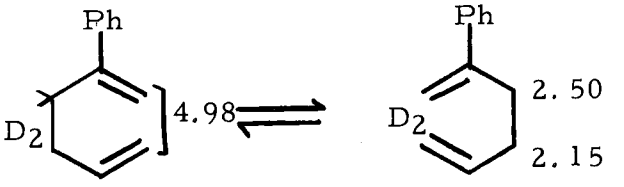
Table 1. (Continued)

Reaction	Relative Rate	Temp. (°C)	k (sec.$^{-1}$)	Ref.
	110	164	6.60×10^{-5}	This work*
	55	164	3.26×10^{-5}	This work*
	1	184.85	1.52×10^{-5}	101
	0.9	185	1.36×10^{-5}	This work

Rearrangement of 69-e was also carried out by an ampoule method with the rate being followed by gas chromatography using biphenyl as an internal standard. A plot of log $\frac{A_o/A_s}{A_t/A_s}$ vs. time was linear showing that the rate was first order in 69-e (A_o = area for 69-e at t_o, A_s = area for biphenyl, A_t = area for 69-e at time t). Finally the rate of the Claisen rearrangement of 71 was also measured by a similar procedure. The rates for 69-e and 71 are also shown in Table 1.

Structures of the Cope Rearrangement Products

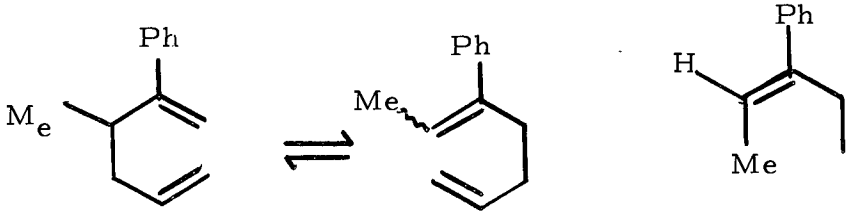
The rearrangement of 69-a is expected to give a mixture of 69-a and 72-a in nearly equal amounts. The nmr spectrum of the equilibrium mixture obtained after heating 69-a for ca. 12 hrs. is in agreement



69-a 72-a

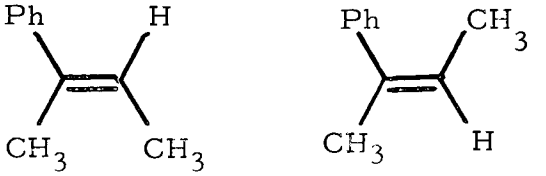
with expectation. No change occurs in the phenyl multiplet or in the multiplet at 5.74 assigned to the proton at C_5. The complex series of bands at 4.98 is reduced in area by about one-fourth (from rel. area 4.0 to 3.05). A new multiplet appears at 2.50 of relative area of 0.86 while the doublet at 2.15 shrinks in area and a poor resolved multiplet rises under that band, the entire signal reaching a final relative area of 2.06. No additional signals appear in other sections of the spectrum. The results for compounds 69-b-d are quite comparable with the exception of the different sort of multiplet in the aromatic region.

The product of the rearrangement of 69-e has an nmr spectrum consisting of a singlet at 7.2 (phenyl), a very complex set of bands at 5.74 (rel. area 2) from which one can extract a quartet overlapping a multiplet (CH_3-CH- and =CH), a triplet at 2.56 (rel. area 2, CH_2-C=), a multiplet at 4.92 (rel. area 2, HC=), a multiplet at 2.06 (re. area 2, CH_2-C=) and a doublet at 1.80 (rel. area 3, CH_3-CH=). Clearly



69-e 73

the data confirm the presence of a CH_3-CH=C< grouping, two allylic CH_2 groups presumably directly attached as indicated by the clear triplet at 2.56. The presence of a terminal vinyl unit is shown by the bands at 910 and 990 cm^{-1} in the infrared. Combined, the information cleanly fixes the structure of the product as 73. Unfortunately the geometry of the trisubstituted double bond is not fixed by our data. However, the maximum in the ultraviolet appears at 240 nm for 73, and the maxima for the α,β-dimethylstyrene are at 235 and 243 nm as



243 nm 235 nm

shown. This suggests that our product is the (E) isomer.

The gas chromatographic data suggest that the product is a single isomer, since one single clean peak was obtained and the collected material had the spectral data noted above. Two unidentified products comprised about 0.3% of the product. Reaction does not proceed to completion, but a sample heated 40 hrs. at 190° gave an 80:20 mixture of 73:69e.

Conclusions

The intent of the work reported here was to provide information about the influence of substituents at C_2 of the 1,5-hexadiene system on the rate of the Cope rearrangement. It was hoped that these data would provide a sort of standard for the "normal" influence of substituents on the central carbon of a three atom grouping where the central carbon retains sp^2 hybridization while a double bond transfers from one side of that atom to the other. The problem arises from a consideration of the geometry of the transition state for triene electrocyclic reactions. Stereoelectronic considerations alone (ignoring orbital phase properties and other geometric requirement) suggest that the optimal transition state would hold the p-orbitals at C_2 and C_3 parallel and that orbital at C_1 which is being converted from p to sp^3 character should deviate only minimally from that parallel alignment. To the extent that other structural requirements force a

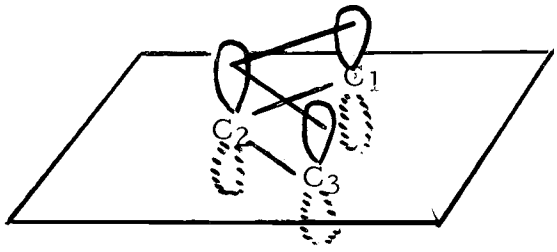
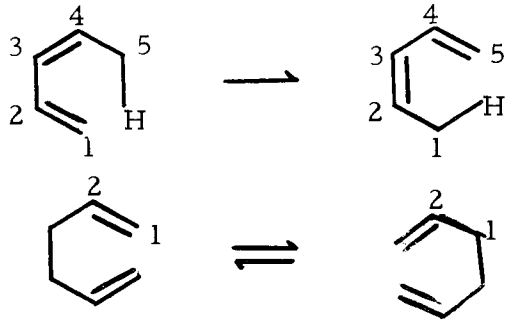


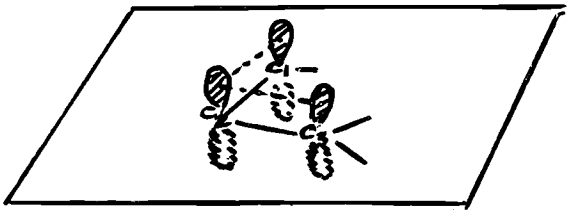
Figure 5. Ideal orbital system for transition state of electrocyclic reaction.

deviation from this ideal, the rate effect of substituents is expected to be altered. If the influence of substituents on the rate could be measured for this ideal case, i.e., the "normal" rate influence, the difference from "normality" be used as a measure of the deviation of the transition state structure from ideality. Hence the clear need for a standard which at least approaches the ideal. One might pick out the non-terminal C's in the electrocyclization of a tetraene, since it may be presumed that the transition state has a helix-like geometry. However, we preferred to have some standard completely separate from the electrocyclic reaction. Other possibilities which might be



advanced are the C_3 of a 1,5-hydrogen shift reaction or C_2 of the Cope rearrangement. We chose the latter for examination since the geometry of its transition state is more completely documented.

The situation at C_2 of the Cope rearrangement transition state differs slightly from that of the ideal defined above in that it has



orbitals at C_1 and C_3 which are both in the p-sp^3 interim and thus are not parallel to the p-orbital at C_2. The extent and direction of the effect this orbital change would have on the "ideal" is somewhat problematical. Clearly if the triad system had p-orbitals at all three atoms, as for example the allyl radical, there would be a node at the central carbon in the non-bonding orbital. The influence of substituents at that carbon would be expected to be very small. If both terminal atoms are partially bonded and have orbitals other than pure p-orbitals, the coefficient for the central atom will increase, and thus the sensitivity to substituent influence should also be enhanced. We assumed therefore that the Cope rearrangement as a model system might approximate the ideal, but in any event it should set an upper limit to the degree of influence.

The data in Table 1 show that introduction of one or two methyl groups at the C-3 position of the hexadiene system results in a slight increase in the rate of the Cope rearrangement. Substitution of methyl groups at the C-1 position has a much larger effect in slowing down the rate. The explanation for this is straightforward; both inductive and steric effects of the methyl groups are probably minor at the transition state, but are significant in the ground state. The methyl group at C-1 will stabilize the hexadiene at the ground state more than at the transition state. An increase in the energy of activation of 1-2 Kcal/mole has been reported for the Cope rearrangement of hexadiene with methyl at the C-1 position[56]. It is rather disturbing to note that the rate of rearrangement of 1,5-hexadiene, which is the comparison standard, has been measured by two groups and the values obtained differ by a factor of about four! Two points of difference in technique may be of some importance: (a) one study was clearly done in the gas phase while it is not clear whether the other was in the liquid or the vapor phase, and (b) the faster reaction occurred in the presence of a small amount of diphenylamine to reduce polymerization. Since our studies were carried out in the presence of diphenylamine relative rates are compared with the faster rate, and an additional factor of four could be introduced if the slower rate were used as a standard.

We did not measure the rate of 2-methyl-1, 5-hexadiene, but for convenience we measured the rate of the Claisen rearrangement of β-methylallylphenyl ether. In diphenyl ether the rate is about 10% slower than that of allyl phenyl ether. This factor is small enough to lie within the limits of experimental error, and for precise comparison it would be best to run the kinetics simultaneously in the same bath. It can be concluded that a methyl group in the 2-position exerts a relatively small influence on the rate of rearrangement. Goering found that a methyl group in the terminal position, i.e., trans-crotyl phenyl ether, also generates a very small retarding effect on the rate[57]. It may be presumed that the effect of a phenyl group on the rate of the Cope rearrangement will be larger than that of an alkyl group, and thus perhaps there could be a greater variability as the position of the phenyl substituent is altered. We were primarily concerned with the result for a phenyl group in the 2-position, and the table shows that a surprisingly large effect is found. In fact the rate is increased nearly 100-fold. Para substituents on the phenyl ring cause a relatively small further change in rate, but there is no simple correlation with σ constants. Electron donors such as methyl or methoxyl depress the rate slightly while chlorine increases the rate. An attempt to prepare a compound with a strong electron attracting substituent ($COOCH_3$) failed.

When this work was completed (1970), there seemed no reason to doubt that these results applied to a normal Cope rearrangement proceeding via a concerted cyclic transition state, a well documented mechanism. However, late in 1971 Doering[39] published some results which indicated that rearrangement via a 1,4-cyclohexyl diradical intermediate was energetically a readily accessible alternative, particularly in cases where one or more of the radicals receive strong stabilization. Finally, publication of a communication by Dewar[40] early in 1973 made it imperative that we reconsider our data in terms of two mechanisms for the Cope rearrangement which might be switched by substitution of a strong radical stabilizing substituent at C-2.

Possible Mechanisms

The remarkable elaboration of the mechanistic details of the Cope rearrangement forms one of the intellectually most pleasing chapters of modern chemistry. The basic requirement for this reaction in any simple system is a 1,5-diene structure. There exists three possible routes for the rearrangement to take place: (a) a concerted [3,3] sigmatropic shift with a cyclic transition state; (b) a dissociation of the C_3-C_4 sigma bond giving a pair of allylic radicals, and (c) formation of cyclohexa-1,4-diyl diradical as a reaction intermediate, followed by dissociation of the C_3 and C_4 sigma bond to form

the reaction products. These are represented in Figure 6.

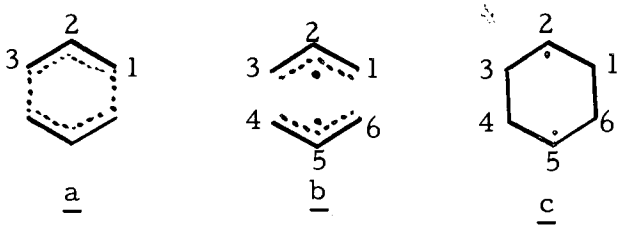


Figure 6. Possible transition state or reaction intermediates in the Cope rearrangement.

Concerted [3,3] Sigmatropic Shift with a Cyclic Transition State

It has been generally assumed that the Cope rearrangement is a concerted process which proceeds by a unimolecular mechanism with bonds broken and formed simultaneously. Woodward and Hoffman[58] called this reaction a [3,3] sigmatropic shift, and gave a theoretical justification for a four-center chair-like transition state. The reaction has been shown to be unaffected by radical sensitizers and inhibitors[3], and is characterized by first order kinetics and a low energy of activation.

One might expect that electronic effects on the rate of this reaction would be small if it indeed goes by a concerted unimolecular process. Thus the rate increase caused by the 2-phenyl substituent might be presumed to cast some doubt on the concerted mechanism

for that case. However, a rate enhancement of 90-fold for an S_N2 displacement of benzyl bromide in comparison with ethyl bromide has been reported[59]. Direct overlap of the π orbital of the aromatic ring with orbitals at the reacting center lowers the energy of the transition state, and hence increases the rate. This orbital-overlap can be illustrated in Figure 7, where X and Y are the leaving group and the nucleophile, respectively.

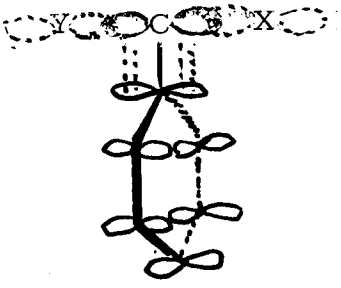


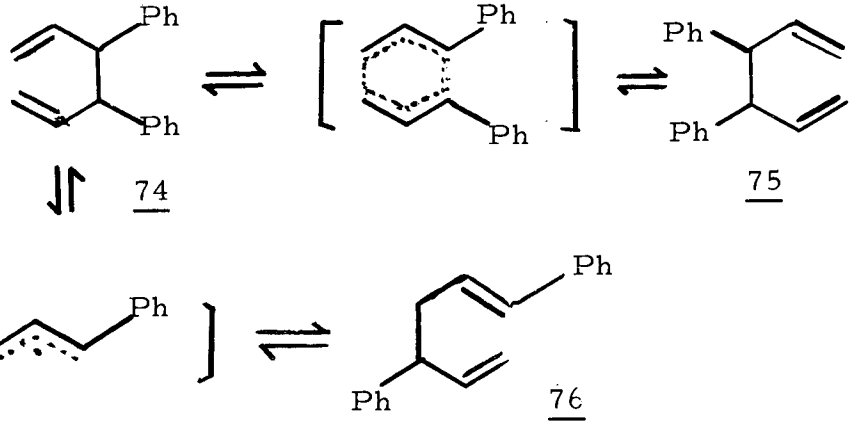
Figure 7. Orbital overlap in the transition state of an S_N2 displacement reaction of a benzyl halide.

It is clear that a phenyl group can stabilize in quite measureable degree, a p-like orbital which is also partially bonded to other entities in the transition state. The geometric-orbital situation at C-2 of the Cope transition state is quite analogous to that of the S_N2 state, except that the partial bonding is pi instead of sigma. There are six electrons to be fitted into six molecular orbitals in this state, and the extent of the stabilization by the phenyl group will be determined by the coefficient at C_2 of the highest occupied orbital or

orbitals (see below). It is possible, therefore, for the phenyl group to exert quite a large influence on the rate, and that magnitude is not readily predictable. One cannot, therefore, rule out this concerted process as a possible reaction mechanism based only on the rate data. Further investigation of substituent effects on the Cope rearrangement is required before one can make a prediction.

Dissociation into a Pair of Allylic Radicals as Intermediates

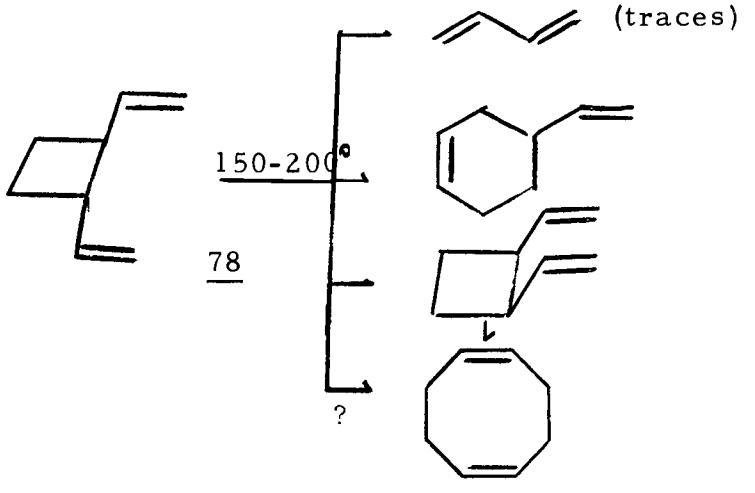
A second mechanism for the Cope rearrangement is the dissociation of the C_3-C_4 sigma bond with formation of a pair of allylic radicals. This process is non-concerted, and at least one other product would be expected from the recombination of these two radicals. The cross-reaction product from combination of a pair of allylic radicals has been reported in the rearrangement of 3,4-diphenyl-1,5-hexadiene (74)[35]. Two products, 1,4-diphenyl-1,5-hexadiene (75) and 1,6-diphenyl-1,5-hexadiene (76) were found in the ratio of 2:3. However, later work[32] has shown that this work was not correct.



Other examples that involve diradical intermediates have been reported in the Cope rearrangements of strained bicyclic, biallylic systems. The rearrangement of trans-1,2-divinylcyclopropane (77) at 200° to 1,4-cycloheptadiene is reported to involve this radical pair[60,61], since it is impossible for the trans isomer to react by a concerted process. Rearrangement of cis-77 gave the product under very mild conditions.

77

Trans-1,2-divinylcyclobutane (78), and trans-1,2-dimethyl-1,2-divinylcyclobutane (79) and trans-1-isopropenyl-2-methyl-2-vinylcyclobutane (80) are believed to rearrange through biradical intermediates, based on product studies and the enthalpies of activation[34]. The cis-1,2-divinylcyclobutane (81) rearranged to a single product, cis, cis-1,5-cyclooctadiene through a concerted process[34].



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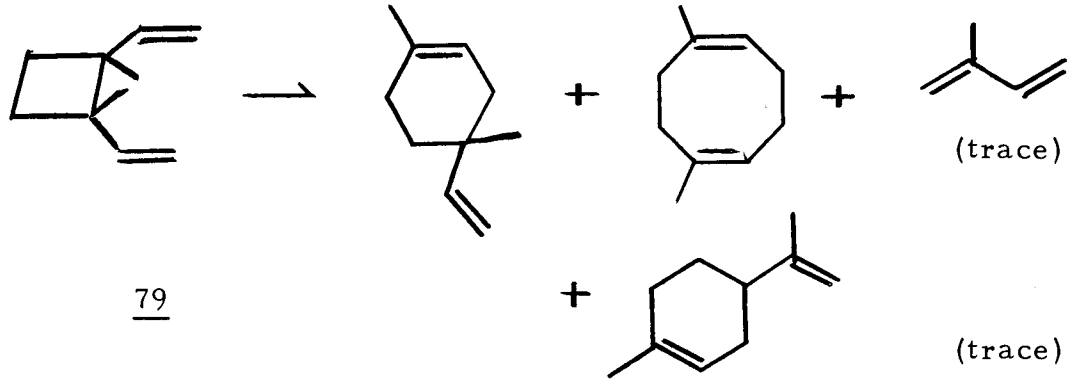

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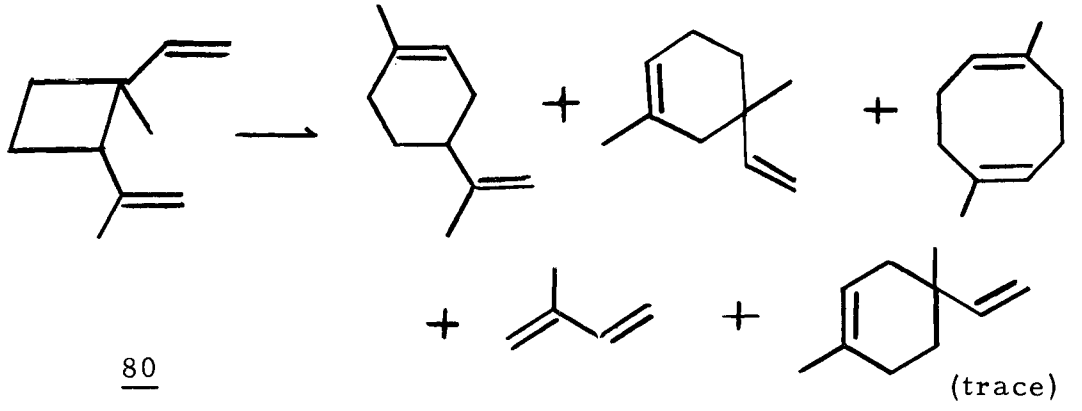

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81

One would expect little or no resonance effect at the C-2 position if the Cope rearrangement involved a pair of allylic radicals as intermediates. Simple Hückel molecular orbitals for the allylic

radical predict a node at the central carbon in the non-bonding orbital. There should be much larger effects at the terminal carbons for the reaction via a pair of allylic radicals.

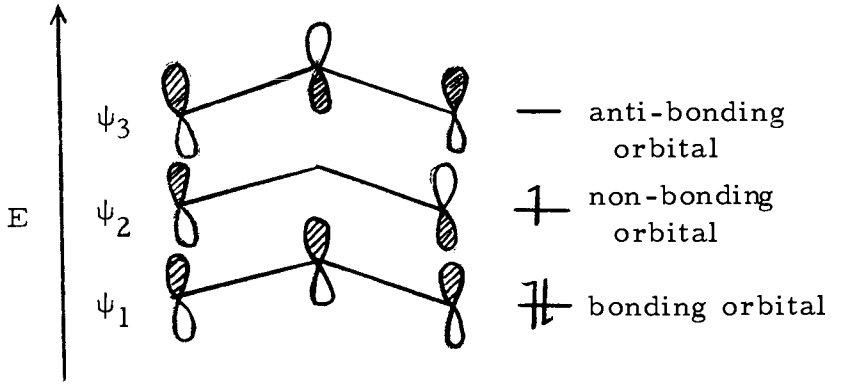


Figure 8. π molecular orbitals of the allylic system.

The Cope rearrangement via two allylic radicals has a much higher energy of activation than the concerted Cope pathway (E_a = 33 Kcal/mole)[63]. The bond dissociation energy of ethane is about 85 kcal/mole[64], and the resonance energy of an allylic radical is about 12 kcal/mole[65]. A rough estimate of the enthalpy required to break the bond between C_3 and C_4 of the hexadiene should be 61 kcal/mole. The enthalpy of activation for the formation of a pair of allylic radicals can be estimated from the heat of formation of 1, 5-hexadiene (H_f = 20.2 kcal/mole)[66] and of the allylic radicals. Several values for the heat of formation of allylic radicals have been reported, but the recent work by Tsang[67] (H_f = 77.8 kcal/mole) can be used here.

The enthalpy of activation for the formation of the allylic radicals is thus 57.6 kcal/mole. The enthalpy of activation has been reported to be 54.5 kcal/mole[39]. Normally then, the enthalpy of activation for Cope transition state is 23.3 kcal lower than that for formation of a pair of allylic radicals as shown in Figure 9.

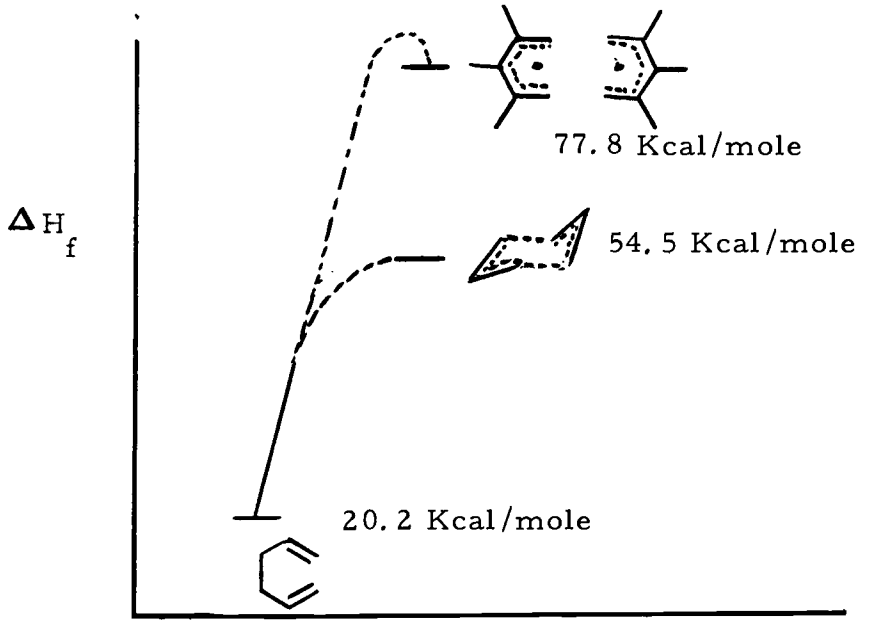


Figure 9. Energy diagram for Cope transition state vs. a pair of allylic radical intermediates.

Attempts to determine the energy of activation for cleavage of 1,5-hexadiene to a pair of allyl radicals experimentally have not been very successful. Doering has reported a $\Delta H^{\ddagger}$ of 49.6 kcal/mole[39]. Others have found values of 31.3, 44.1 and 62.6 kcal/mole[68,69,70]. The problem probably rests in a reaction which is not clean, and in failure to trap the radicals completely.

Cross products are not normally found in the Cope rearrangement unless special features are present which either lower the bond cleavage energy or increase the energy of the concerted process. Sunko et al.[41] reported the absence of any crossover product from the reaction of labelled 1,5-hexadiene by mass spectroscopic analysis of the succinic anhydride obtained by degradation of the equilibrium mixture. There was no sign of m/e 102 as shown in Figure 10.

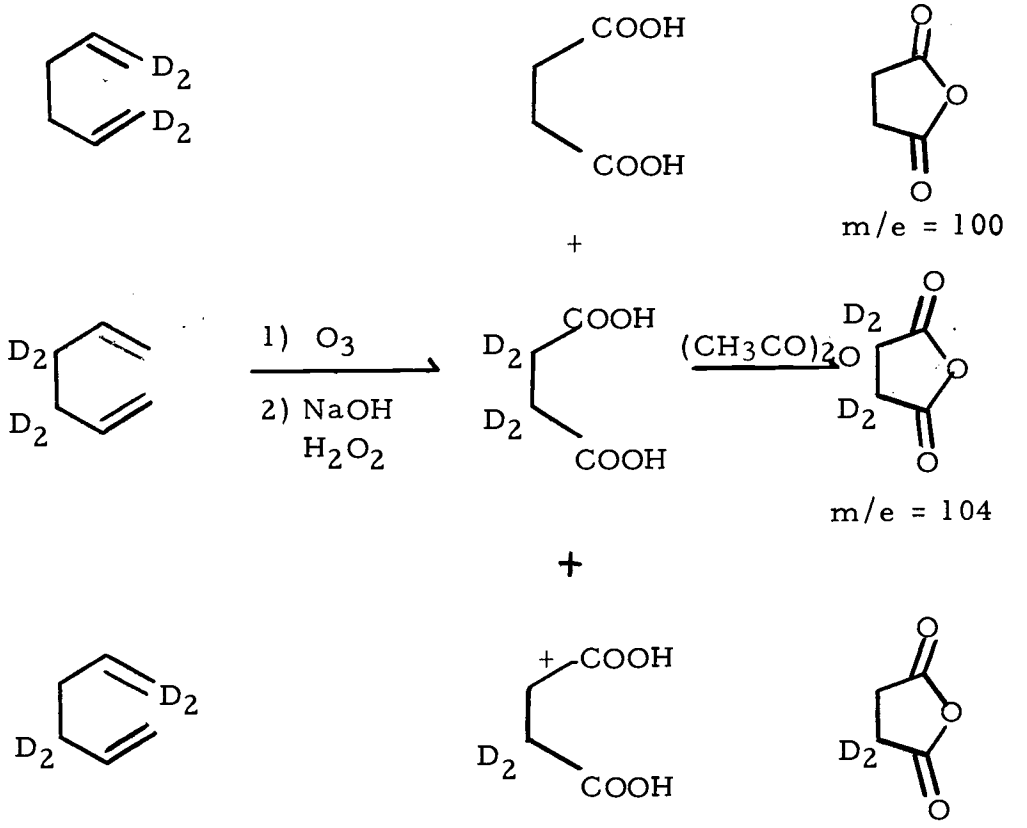


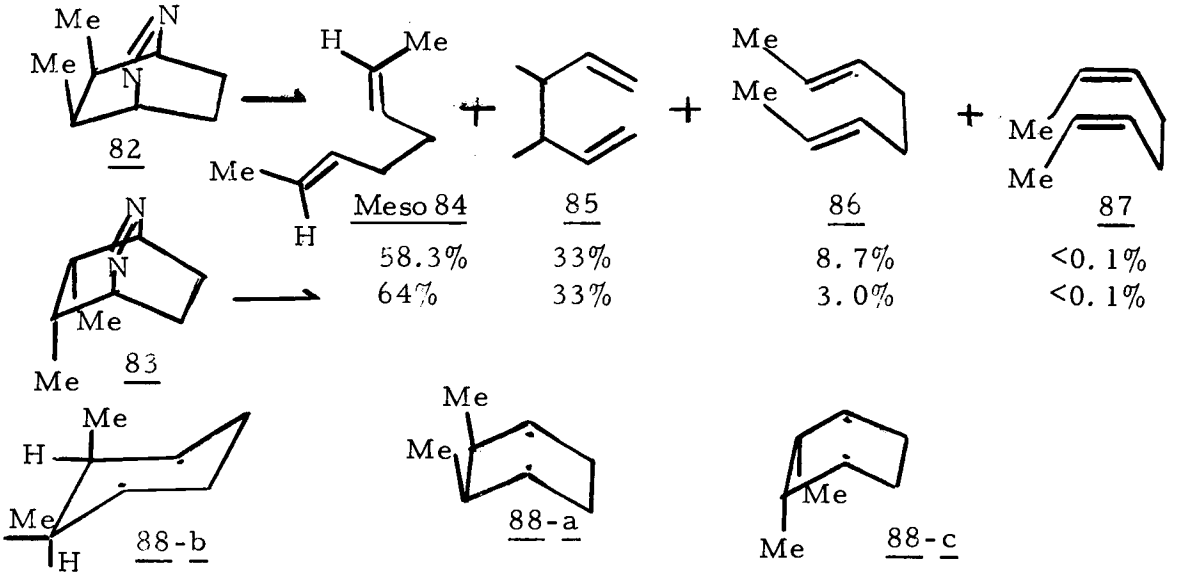
Figure 10. Scheme to detect crossover reaction products.

In summary, one would not expect the dissociation into allylic radicals as the reaction mechanism in the Cope rearrangement of the 2-Aryl-1,5-hexadiene system.

Formation of Cyclohexa-1,4-diyl Diradical Intermediates

The third possible mechanism involves formation of a sigma bond between C_1 and C_6 to give the cyclohexa-1,4-diyl diradical as an intermediate, followed by rupture of the C_3-C_4 bond to give the "rearranged" product. Doering et al.[39] have calculated the energy of activation for the formation of this diradical intermediate as 33.7 kcal/mole for the simple diene system. This is very close to their experimental enthalpy of activation of 33.3 $\pm$ 0.5 kcal/mole for this rearrangement, and therefore this diradical would be an acceptable intermediate energetically, provided the energy of activation for its cleavage to the product was negligible.

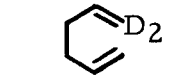
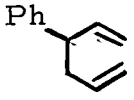
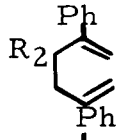
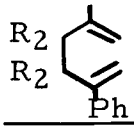
In the gas phase pyrolysis of exo,exo- and endo,endo-5,6-dimethyl-2,3-diazabicyclo 2.2.2-oct-2-ene (82) and (83), Roth[71] reported that the major products of the reaction were cis,trans-octa-2,6-diene (84) and meso-3,4-dimethyl-1.5-hexadiene (85). The author suggested the formation of the cyclohexa-1,4-diyl diradical 88-b which could be transformed from chair conformation into 84. Two minor products, trans,trans- and cis,cis-octa-2,6-diene (86), (87) were also formed, presumably from the two conformational diradical



intermediates 88-a and 88-c. Because of the presence of 86 and 87 Roth suggested the diradical 88-b could not be the intermediate in the Cope rearrangement since 85 had been reported to arrange exclusively into 84 (99.7%).

Dewar has recently proposed[40], based on the rate data shown in Table 2, that the Cope rearrangement of 2-aryl-1,5-hexadienes takes place via the cyclohexa-1,4-diyl diradical. The diradical is an intermediate since the activation energy is lowered by only 3.44 kcal/mole which is much less than the stabilization energy of a benzyl radical. He also notes that 3-phenyl-1,5-hexadiene must rearrange by the normal concerted process, since the phenyl group would have no effect on the rate if reaction proceeded via the diradical intermediate.

Table 2. Rate of Cope rearrangement of 2-aryl- and 2,5-diaryl-1,5-hexadienes at 189.8 ± 0.1°C.[40]

Compound		Relative Rate
		1
		18
		41
	R = H R = D	2000

Cope Mechanism - Triad or Continuum

With the addition of Prof. Dewar's evidence for the 1,4-cyclohexadiyl diradical route, there exists experimental information lending credence to the idea that 1,5-hexadienes can rearrange by three different mechanisms depending on the substitution pattern. In some ways this situation resembles the case of nucleophilic substitution at saturated carbon, where a duet is played to the tune of S_N1 and S_N2. What lies in between? Are there only two fixed processes with a mixture of S_N1 and S_N2 between, or is there a continuous variation from S_N1 to S_N2 with each molecule reacting by its one most favorable mechanism? One can ask the same question of the rearrangements of biallylic molecules. Are there three separate routes to rearrangement which can occur separately or in mixtures, or is there one continually variable sequence?

If we adopt the continuous variation idea, the following picture emerges from our results and those of Professors Dewar and Doering. With respect to the degenerate rearrangement of 1, 5-hexadiene the diagram of Figure 11 comes out of the data of Doering. The energy value which is given by the question mark relates to the energy of activation for decomposition of the 1, 4-cyclohexadiyl diradical into 1, 5-hexadiene. We can make an estimate of this value as follows. If it is assumed that this sort of diradical is formed in the decomposition of 2, 3-diaza-2-bicyclo[2. 2. 2] -octenes, then Roth's results show that the diradical is sufficiently long-lived to permit conformational interconversions between boat and chair forms. The barrier for this interconversion is unknown, but may be estimated from those of cyclohexane and of cyclohexanone to be about 5-6 kcal/mole[98]. Since this interchange apparently can occur several times prior to decomposition, it seems reasonable to set a lower limit to the question mark at 6 kcal/mole.

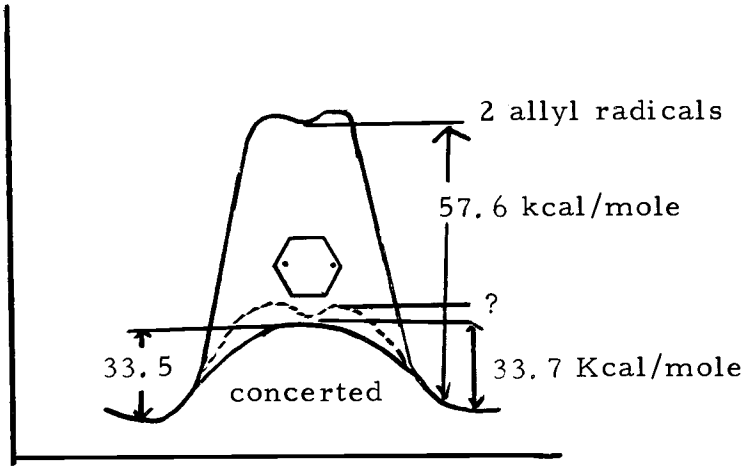


Figure 11. Energy diagram for Cope rearrangement of 1, 5-hexadiene.

To consider the influence of substituents at the various positions, let us consider the extremes first. For an alkyl radical substitution of an aryl group at C_1 or C_3 should stabilize the radical substantially. The benzyl radical is stabilized by about 12 kcal/mole[99], and by analogy with the cyclohexadienyl and allyl radicals which are stabilized by 24 and 12 kcal/mole, respectively[102,65,103], the phenyl group at C_1 or C_3 could stabilize the allyl radical about 12 kcal/mole as well. This is undoubtedly the upper boundary. On the other hand substitution of a phenyl at C_2 of the allyl radical should give a very small stabilizing effect since the non-bonding orbital has node at C_2. For the argument we will assume that it gives rise to no stabilization at all.

For the 1,4-cyclohexadiyl diradical substitution of a phenyl at C_2 or C_6 (note that in this molecule C_2 and C_6 are the equivalent of C_1 and C_3 of the allyl radical) should have no stabilizing influence at all, and the phenyl at C_1 should stabilize the radical by about 12 kcal/mole. Dewar has argued that the resonance stabilization is only about 8 kcal/mole[40] rather than 12-13 kcal/mole. In either event the stabilization is very large. Thus the substituent effect is very interesting in that as the reaction mechanism migrates from one extreme to the other the substituent effect at C_1 and C_3 of the hexadiene goes from a maximum to a minimum, while at C_2 it alters in reverse manner from minimum to maximum. Since these changes

need not be linear nor necessarily of identical curvature (though reversed in sign), it is not possible to predict accurately whether to expect a larger role for the phenyl at C_2 than C_3 for a concerted reaction whose position on the variation scale is unknown.

Now let us assume for the moment that as Professor Dewar suggests, the rearrangement of 2-phenyl-1, 5-hexadiene proceeds completely via the cyclohexane diradical route. The decrease in free energy of activation over the unsubstituted diene is 1.8 kcal/mole, the major portion of which can be equated to an enthalpy change. This means that the transition state for the formation of 1-phenyl-1, 4-cyclohexadiyl diradical is 1.8 kcal/mole below that of the concerted transition state for 1, 5-hexadiene, providing that the resonance stabilization of the ground state of 2-phenyl-1, 5-hexadiene is negligible. Even if the ground state stabilization is 2 kcal/mole (value given by Wheland for styrene) the transition state is only about 3.8 kcal/mole below that of the unsubstituted one. Since the original position of the diradical transition state was at least 6 kcal/mole above the unsubstituted one, the stabilization of the transition state is between 8-10 kcal/mole. Now the introduction of a second phenyl group at C_5 should give an equivalent stabilization of the transition state. Thus it should have increased the rate by enormously larger factor than did the first phenyl group. In fact that did not occur; the second phenyl had an influence which was almost exactly the same as the first. In

essence it would require a most improbable coincidence for the two phenyl groups to have equal influence on rate in terms of the complete change in mechanism picture.

On the other hand if we assume that a continuous variation in the transition state structure can occur, some calibration of where this transition state lies may be obtained from the influence of the 3-phenyl on the rate. The increase of 18 fold corresponds to a free energy decrease of about 0.57 kcal/mole, this small value suggests that the transition state has a considerable resemblance to the cyclohexadiyl diradical end of the scale. This means that the influence of a 2-phenyl group is approaching the maximum end for its influence, and that its effect is larger than the 3-phenyl is not at all surprising.

One further point should be considered. Lutz has given a half-life of ca. eight hrs. at 80° for the rearrangement of dl-3,4-diphenyl-1,5-hexadiene[32]. Converted to 164° by using E_a = 25 kcal/mole as an estimate, this corresponds roughly to a rate of 2×10^{-2} sec^{-1}. This estimate indicates a relative rate of ca. 50,000 for this compound! Thus the first phenyl increased the rate by 18 fold and the second by ca. 2800 fold. It might be suggested that the two phenyl groups interfere sterically and the transition state responds by lengthening the 3,4 and 1,6 bonds, i.e., it moves well toward the other end of the continuum and the magnitude of the 3-phenyl influence grows concomittantly.

Finally we should consider what conclusions could be reached from the present findings. The most important observation is that the rate changes caused by the various para substituents do not correlate with either σ or σ^+ constants. As Table 3 shows hydrogen abstraction from substituted toluenes, by various abstractors correlate with either σ or σ^+ depending on the case. Thus the results here do not offer clear cut support for the reaction via a cyclohexadiyl diradical. It must be noted, of course, that the rate influence is relatively small, and to draw any major conclusions from these data alone would be foolish. One possible explanation of the results observed is that the transition state may not involve an electron distribution which leaves all carbon atoms electrically neutral. Thus that one bearing the phenyl group may in the transition state increase its negative charge slightly. This would permit chlorine to stabilize that state more than hydrogen, and to the extent that the inductive effect of the methoxy dominates it might be less destabilizing than a methyl. We conclude that in general the idea of a mechanistic continuum provides a better rationalization of the data presently available.

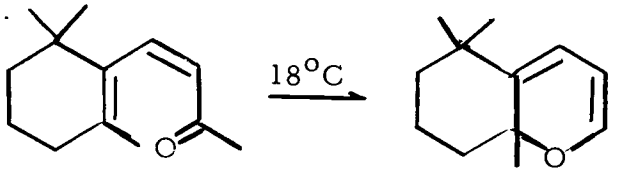
Table 3. Rho values for hydrogen abstraction from substituted toluenes[76].

Radical	Temp. °C	Solvent	Rho Sigma	r[(a)]	Rho Sigma Plus	r[(a)]
$\underline{t}$-C_4H_9	30	thiol	+0.99	0.96	--	--
CH_3	100	CCl_4	-0.121	--	-0.136	--
C_6H_5	60	CCl_4	-0.4	--	-0.3	--
$\underline{t}$-C_4H_9O	50	C_2Cl_3H and CF_2Cl-$CFCl_2$	-0.41	0.987	-0.35	0.974
Cl	60	CCl_4	-0.48	0.997	--	--
Br	80	CCl_4	-1.68	0.945	-1.38	0.977
CCl_3	50	$BrCCl_3$	--	--	-1.46	--

[(a)] Correlation coefficient.

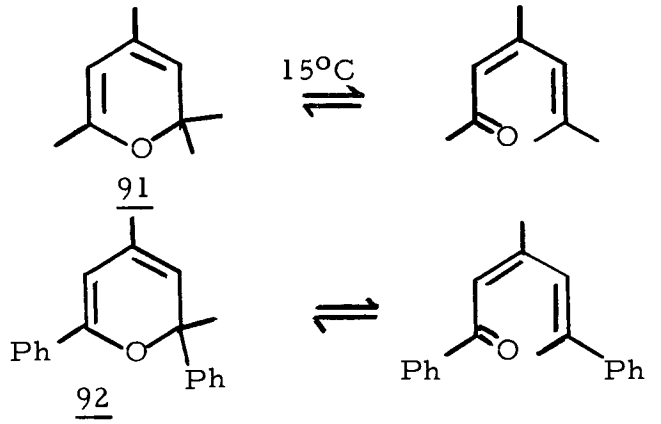
Part II. Formation of N-Phenyl and N-Methyl Pyridinium Salts from 1,7-Diaza-1,3,5-Heptatrienes

As a part of a general study of the influence of structure on the rates of electrocyclic ring closures of cis-trienes, the effects of oxygen and nitrogen at the terminal position of the triene system have been investigated. Marvell et al.[72] reported that the valence isomerization of the cis-dienone 89 to an α-pyran 90 has a rate constant of 1.4×10^{-3} sec^{-1} at 18°C.



89 90

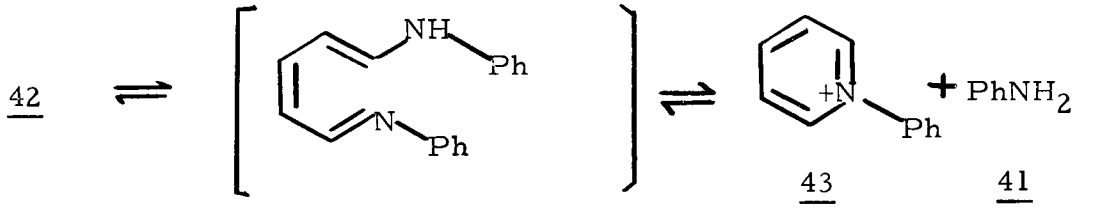
More recently, Marvell et al.[73] found that the rate of the retro-electrocyclic reaction of 91 at 15° was 1.6×10^{-4} sec^{-1} and that of the α-pyran 92 was 5.35×10^{-4} sec^{-1} under the same conditions. They used an indirect method to determine the rate of ring-opening since the dienone could not be observed directly. A rapid selective reduction of the cis-dienone with lithium aluminum hydride was used to trap that product. The rate enhancement caused by replacing the terminal carbon with oxygen is very large, that is, of the order of seven to eight powers of ten.



91

92

The influence of a nitrogen at the terminal position of a cis-triene system has also been explored. Marvell and his coworkers[45] reported that the electrocyclic ring-closure of diazatriene 42 has a rate constant of 3.5×10^{-4} sec^{-1} at 40°. If all rates are compared at a common temperature, this rate falls between the cis- trienes and cis-dienones. If, however, a minimum factor is introduced to

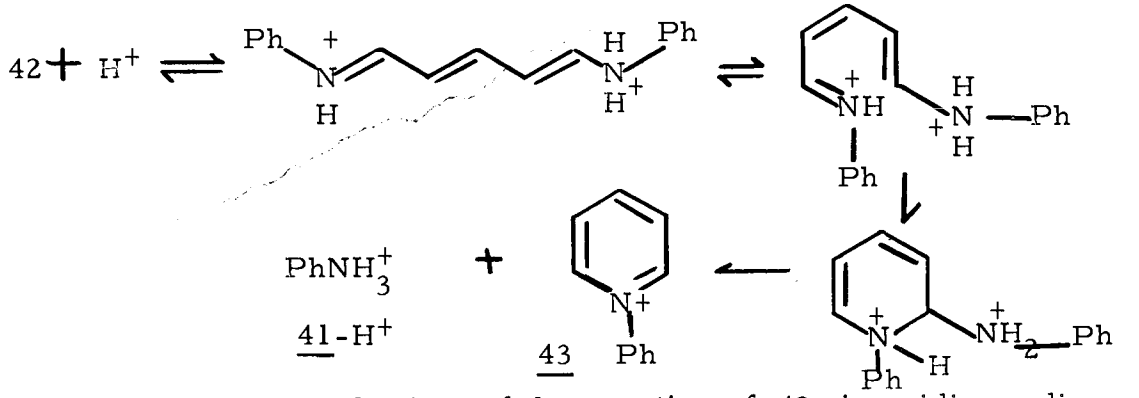


42 43 41

compensate for the trans ⇌ cis equilibrium for 42 , its intrinsic rate must be faster than that of the dienone. Two possible factors were suggested to account for this difference in reactivity[74]: (a) The higher electronegativity of oxygen and nitrogen compared to carbon leads to a polarization of the carbon-oxygen or carbon-nitrogen double bond. Thus the reaction rate would be increased because of the electrostatic attraction between the negative oxygen or nitrogen and

the more positive carbon five in the system. (b) Both oxygen and nitrogen might utilize a lone pair of electrons during the electrocyclic process. Hence either atom might have an enhancement in rate.

Since Zincke had reported that 42 undergoes ring closure to N-phenylpyridinium ion in acidic solution, it appeared possible that this reaction could occur via the electrocyclic reaction of a doubly positive ion. Thus it would be possible to distinguish between the two alternatives (a) and (b) above. The purpose of this investigation was

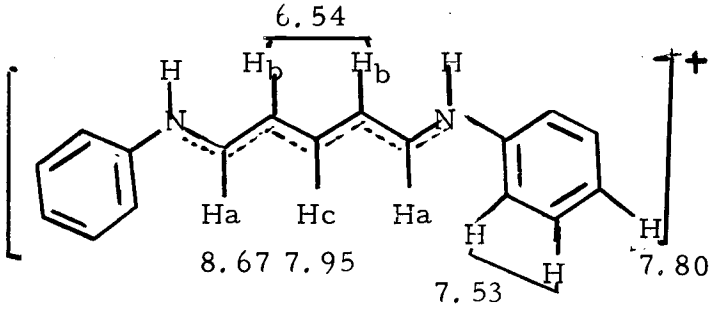


to ascertain the mechanism of the reaction of 42 in acidic media. In addition some study of the reactions of unsymmetrically substituted diazatrienes was contemplated.

Reaction of 5-Anilino-N-Phenyl-2, 4-pentadienylidenimium Chloride (42) in DMSO.

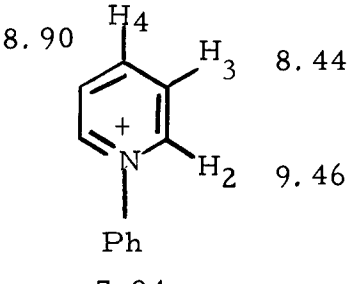
Initially the use of DMSO as a solvent for investigation of the acid catalyzed reaction 42 appeared to be promising since 42 is relatively soluble in DMSO and nmr could thus be employed as an investigative tool. In fact the spectrum of 42 in DMSO-d_6 was easily

obtained and can be interpreted readily by first order analysis. The spectrum is composed of a triplet at 6.54 (H_b, $J \simeq$ 12 Hz), a multiplet



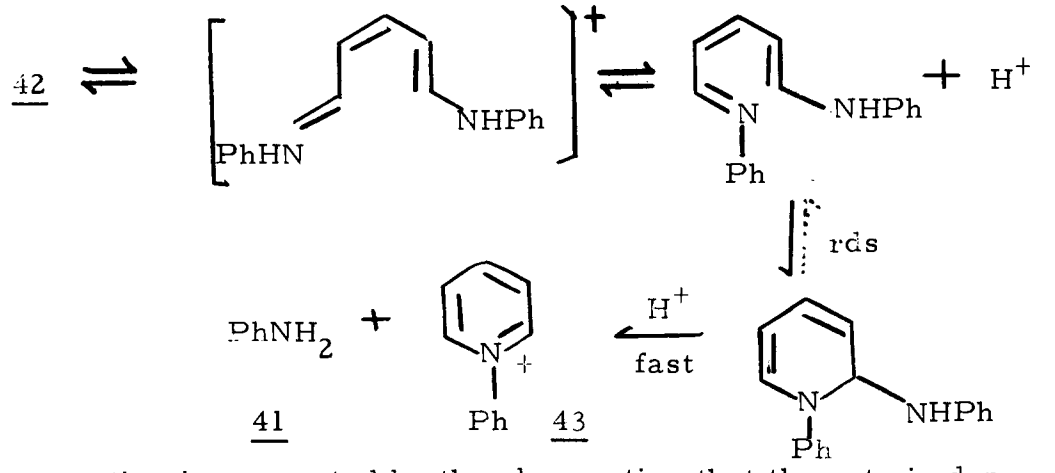
at 7.40 (2H, p-phenyl), a pair of sharp peaks centered at 7.53 (8H, o- and m-phenyl), a triplet at 7.95 ($1H_c$, $J \simeq$ 12 Hz) and a doublet at 8.67 ($2H_a$, $J \simeq$ 12 Hz). Addition of trifluoroacetic acid (TFA) revealed no evidence for a doubly protonated species, but the doublet at 8.67 was converted to a triplet and a broad doublet appeared at 11.68 (2 NH, $J \simeq$ 12 Hz). The lowered rate of NH exchange in acidic solution is expected[100].

Compound 42 reacts slowly in DMSO solution to give N-phenylpyridinium ion and aniline as the sole identifiable products. N-phenylpyridinium ion has an nmr spectrum with a triplet at 8.44 (2 H_{3+5}, $J \simeq$ 7 Hz), a triplet at 8.90 (1 H_4, $J \simeq$ 7 Hz) and a doublet at 9.46 (2 H_{2+6}, $J \simeq$ 7 Hz). The reaction product has an nmr spectrum which



matches exactly with that of a 1:1 mixture of N-phenylpyridinium chloride and aniline. The rate of the reaction was measured in DMSO alone and in the presence of added TFA. First order kinetics were followed to about two half lives, and the rate was depressed by added TFA. No evidence for acid catalysis could be obtained in DMSO solution.

The rate of reaction in DMSO was followed by the disappearance of the intense band in the visible region for 42 In DMSO 42 is in equilibrium with some of the non-charged base form as indicated by the presence of two bands at 495 nm and at 405 nm in the visible spectrum. Since the rate in DMSO is very close to that in methanol, the mechanism is probably the same as in neutral methanol. This



suggestion is supported by the observation that the rate is depressed by added TFA. The mechanism is shown above. It has been shown[75] that the rate of cis⇌ trans isomerization is rapid in acid solution in particular so the isomerization step cannot be rate-determining. The mechanism corresponds then to the process

$$SH^+ \underset{\leftarrow}{\overset{K_1}{\rightleftharpoons}} S + H^+$$

$$S \xrightarrow[k_2]{rds} S'$$

$$S' + H^+ \xrightarrow[k_3]{fast} P + Q$$

and since measurement was made in terms of equilibrium $[SH^+]$ at any time, then we can write

$$\text{rate} = -\frac{d[SH^+]}{dt} = \frac{d[P]}{dt} = k_3[S'][H^+]$$

$$\text{but} \quad K_1 = \frac{[S][H^+]}{[SH^+]}$$

and if S' is a steady state intermediate

$$\frac{d[S']}{dt} = 0 = k_2[S] - k_3[S'][H^+]$$

$$\text{or } k_3[S'][H^+] = k_2[S]$$

$$\text{and so, rate} = K_1 k_2 \frac{[SH^+]}{[H^+]}$$

In any run the $[H^+]$ remains constant and first order kinetics are observed, but with added TFA the rate is decreased as expected. Consequently it was necessary to study the acid catalyzed reaction in other solvents.

Reaction of 5-Anilino-N-Phenyl-2, 4-pentadienylideniminium Chloride (42) in Acetic Acid

In order to use some solvent which would permit high concentrations of strong acid without inducing decomposition of the solvent, and at the same time to employ one with known data on the H_o function, we chose to employ acetic acid in place of methanol which had been used by Zincke. Water was avoided to simplify the chemistry since hydrolysis of 42 can become a competing reaction in aqueous media.

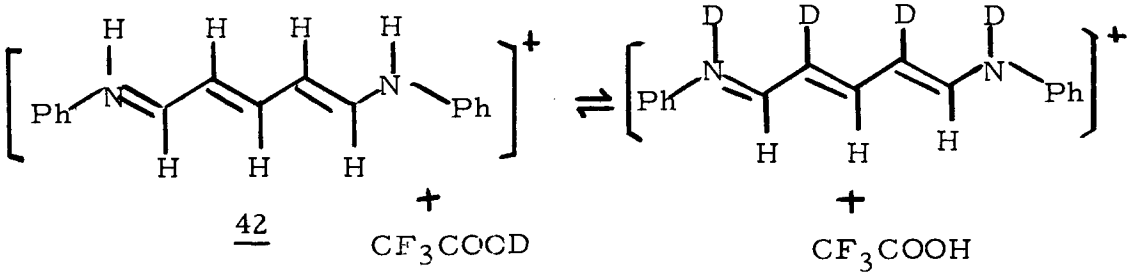
Reaction of 42 in acetic acid apparently proceeds largely by the known mechanism given above involving the uncharged base form of 42. Addition of sulfuric acid in low concentration leads to a further rate depression, but as the acid concentration is further increased the rate passes through a minimum and rises again until at about 0.3 M sulfuric acid the rate is about ten times faster than in pure acetic acid. At that point it is about as fast as the reaction of 42 in pure DMSO or neutral methanol. The increase in rate is too large to be purely a medium effect, so an acid catalyzed reaction must be occurring. The rate in any given medium is first order in 42 and independent of the acid concentration. The data in Table 6 show that the rate is not first order in sulfuric acid concentration, and in fact plots of log k vs. log $[H_2SO_4]$ or log k vs. $-H_o$ are not clean straight lines. The deviations observed are certainly partly experimental (see below).

During the early stages of our study of the kinetics of 42 in $HOAc/H_2SO_4$, some runs were made by Dr. Paik. This brought to light the fact that the reaction was giving nonreproducible results, that is the first order rate constants under apparently identical conditions could vary by factors up to two or more. Investigation revealed that the "anhydrous" acetic acid used by Dr. Paik was prepared in a different way. Further study showed that the reaction rate was very sensitive to traces of acetic anhydride or of water in the acetic acid. As Table 9 shows 1% of water depresses the rate to about half the "normal" rate, and 1% of acetic anhydride increases the rate by about 15 times. Consequently all final rate constants were taken from runs using acetic acid recrystallized to a constant melting point matching the literature value[77], and sulfuric acid was also purified by recrystallization.

Reaction in the presence of ca. 1% of acetic anhydride leads to a change in product. Acetanilide is obtained instead of aniline, a result that occasions no surprise. The product of the ring closure N-phenyl-3,5-diacetylpyridinium ion was separated from the mixture and had the following nmr spectrum. There is a multiplet at 8.06 (3H, o- and p-phenyl), a second multiplet at 8.24 (2H, m-phenyl), a singlet at 9.16 (1H, C_4H), a singlet at 9.43 (2H, C_2 and C_6 H's) in DMSO-d_6. The resonance of the methyl protons of the acetyl groups at C_3 and C_5 apparently lie under the signal of the residual DMSO protons which

appeared as a singlet at 2.80. In TFA these six protons give a singlet at 1.85 (935 cps from TFA acid proton). Presence of the acetyl groups is confirmed by the strong band at 1690 cm^{-1} in the infrared spectrum of this product.

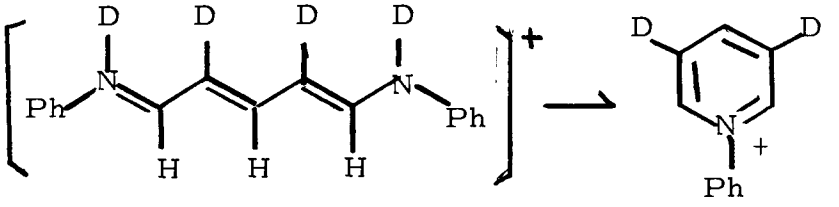
With the acid catalyzed reaction established, the next concern was the point of protonation. Some earlier studies in this laboratory[78] had established that the doubly-protonated species was not developed in sufficient concentration to be identified spectrally. Consequently we were forced to employ deuterated solvents to try to solve that problem. In TFA-d_1, even at -12°C, the first observable nmr spectrum finds the triplet at 7.56 and the doublet at 7.87 collapsed into singlets and the triplet at 6.54 has completely disappeared. Complete exchange of the C_2 and C_4 protons has occurred under these conditions.



42 CF_3COOD CF_3COOH

In view of the known position for protonation of enamines, this does not seem very surprising except for the rate of the reaction. In DMSO-d_6 containing 20% TFA-d_1 at 24° the exchange rate is slow enough to be measured and a rough first order rate of 1.5×10^{-5} sec^{-1} was found. The rate was followed by disappearance of the 6.54 triplet resonance in the nmr.

When the acid catalyzed reaction was carried out in DOAc/ D_2SO_4, the N-phenylpyridinium ion obtained was completely deuterated at C_3 and C_5. More significantly the rate was altered in the deuterated medium. A value $k_D/k_H = 2.4$ was obtained by careful and repeated rate measurement under as nearly identical conditions as we were able to achieve. This value is too large to be an inverse secondary deuterium isotope effect, and must, therefore, be a solvent isotope effect. The maximum solvent isotope effect for an acid catalyzed reaction in acetic acid calculated by the fractionation factor method[79] is 2.3.



Less complete studies of the reaction of 42 in acetic acid catalyzed by p-toluenesulfonic acid were also carried out. As Table 7 illustrates the addition of strong acid first reduces and then increases the rate. Generally the influence of the p-toluenesulfonic acid and sulfuric acid is essentially the same since the slope of a log k vs. log (conc.) is about the same, i.e., 0.75 for each acid. For the plot with the p-toluenesulfonic acid data the first point (lowest acid concentration) was ignored. Apparently this reaction proceeds in large measure via the uncharged base in that medium, and as a result it appears

much too fast compared to reactions proceeding purely via acid catalysis. Clearly the acid catalyzed reaction is proceeding by the same mechanism whether catalyzed by sulfuric or p-toluenesulfonic acid. Furthermore this equivalence of the slope of rate vs. concentration for the two acids suggests that sulfuric acid utilizes only a single proton in acetic acid.

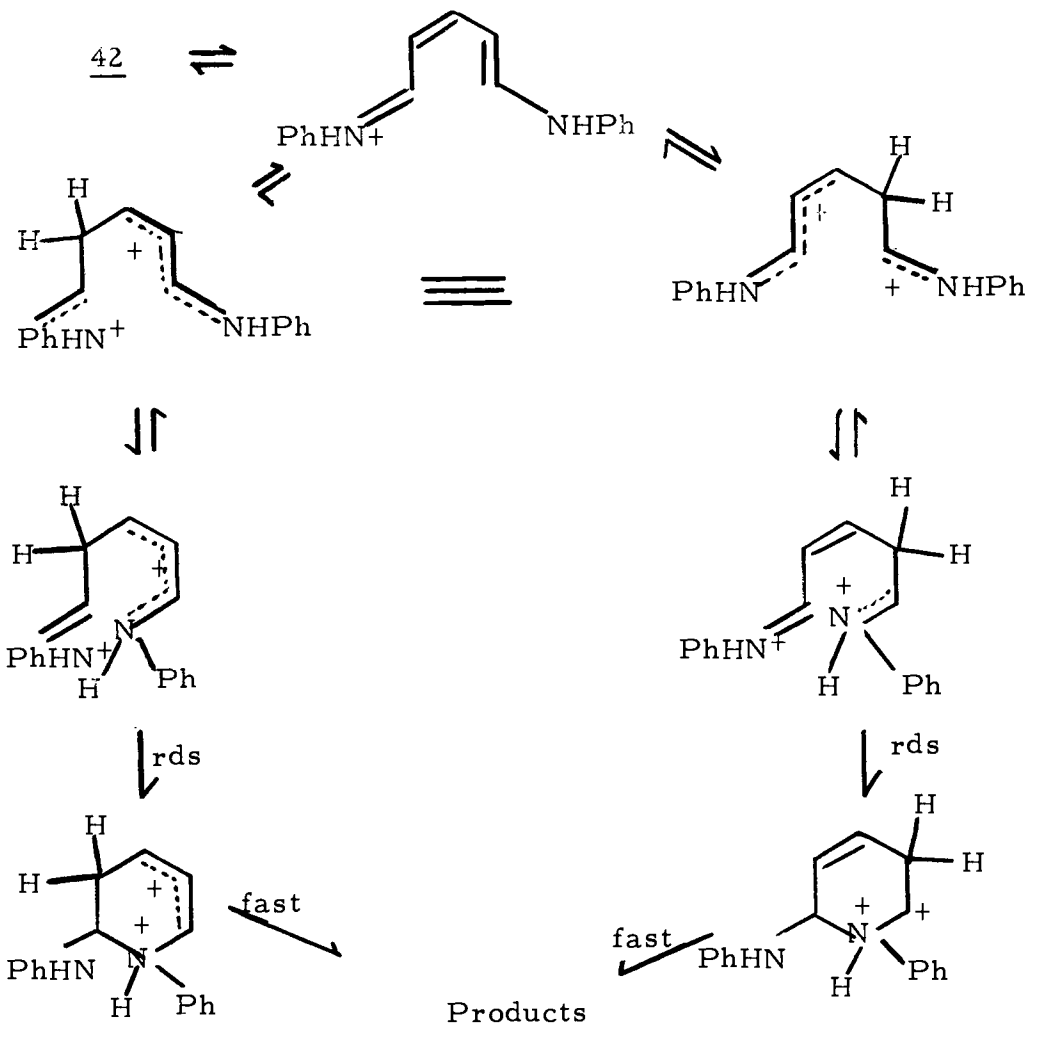
Products obtained by isolation from the p-toluenesulfonic acid catalyzed reaction were identical with those from the sulfuric acid catalyzed process. However, the ultraviolet spectrum of the final reaction mixture at higher concentration (1M) in the former case showed a band at 360 nm. This absorption band disappeared when water was added to the mixture, but was not attributable to any isolable product.

Certain conclusions can be reached about the mechanism of ring closure of 42 in acid solution on the basis of the data noted above. Since kinetically the reaction involves both 42 and proton, the transition state at the rate determining step must contain both entities. The solvent deuterium isotope effect requires a rapid equilibrium protonation step followed by a rate-determining step which cannot involve loss of the added proton. This is also in accord with the absence of a primary isotope effect, which eliminates addition or removal of a proton in the rate determining step. If protonation leading to reaction involves any position other than C_2, C_4 or N in 42 ,

then the proton added must be the one lost, i.e., it cannot become equivalent with the hydrogen atom already present at any stage of the reaction. Finally the mechanism must account for the first order kinetics in any run (pseudo first order) and the lack of first order in the acid catalyst.

In the discussion here we shall make the assumption that the requirement for acid catalysis involving protonation at some position other than at C_2, C_4 or N is too restrictive to be met, and all mechanisms must place protons at one or the other of those positions. The rapid exchange processes which occur at N or at C_2 and C_4 do not permit us to ascertain whether one of the other of these is mechanistically significant. Consequently two mechanisms can be advanced. One of these we shall call the enamine protonation route, the other the amine protonation route. Since both routes necessitate conversion of the all trans 42 to a mono cis form, the high rate of exchange compared with the ring closure rate is quite reasonable. In either case we postulate that the main role for protonation, as is also the case for deprotonation in the route via the uncharged base, is to remove the stabilization due to delocalization in the symmetrical salt 42.

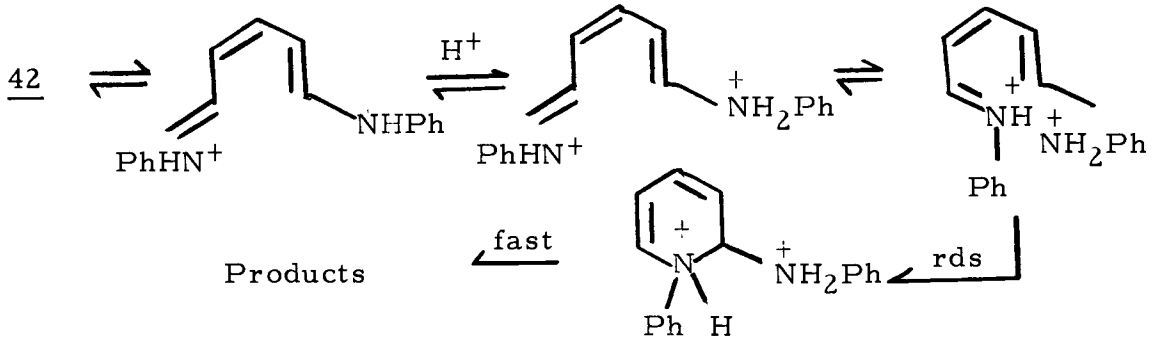
The enamine route involves protonation at carbon, shown here with 42 in the cis form, and with protonation occurring at either of the two originally equivalent carbons. The diprotonated form can conceivably react in two different ways. Rotation is now necessary to



bring the future ring nitrogen into the proper position for ring closure. Since the two ends are no longer equivalent, rotation could be conceived at either end. Rotation about the single bond will be easy, while that about the central bond of the delocalized system should be notably hindered. Ring closure from either situation now requires that one positive entity act as a nucleophile with respect to the other, leading to a ring with severe localization of the double positive charge. This must be the rate determining step, and should be

followed by a rapid decomposition into products. The drawbacks to this mechanism are obvious, and it seems to offend chemical good sense to accept this as a very likely possibility.

The amine protonation route is outlined below with the rate determining step involving an electrocyclic ring closure. Protonation



is shown for the cis form, and since protonation fixes the double bonds rotation to the S-cis conformation can be expected to occur readily. The electrocyclic reaction can then occur, though it must be less favorable thermodynamically than the reactions of the uncharged base because it localizes the positive charge of the immonium ion. Otherwise the reaction does not seem intuitively unreasonable.

Either of these mechanisms corresponds to the general form

$$S_tH^+ \overset{K_1}{\rightleftharpoons} ScH^+$$

$$S_cH^+ + H^+ \overset{K_2}{\rightleftharpoons} S_CH_2{}^{++}$$

$$S_CH_2{}^{++} \overset{rds}{\underset{k_3}{\rightarrow}} DHPH_2{}^{++}$$

$$DNPH_2{}^{++} \overset{fast}{\underset{k_4}{\rightarrow}} \text{products}$$

S_tH^+ = 42 trans form

S_cH^+ = 42 cis form

DHP = dihydropyridine form

The rate for the reaction scheme is equal to $K_1k_2k_3[SH^+][H^+]$, and the process corresponds to a rapid protonation equilibrium followed by a rate determining step in which the proton is not removed. The rate would be first order in acid concentration only if the protonation equilibrium was proportional to the acid concentration. In solutions of the type used here it is more likely that protonation is a function of H_+ rather than $[H^+]$. Since the H_+ function is not tabulated for acetic acid-sulfuric acid, the H_o function was tested. A correspondence between H_o and H_+ has frequently been observed[80]. While the relation was not exactly linear, the best fit was observed for H_o. The fact that a slope of -0.62 was obtained rather than 1.0 is not very surprising since plots of log k vs. $-H_o$ generally give lines with slopes other than 1.0[80], and we do not wish to read any mechanistic significance into this.

At this point it should be stressed that no mechanism can be considered as effectively established. However, we feel that the amine protonation-electrocyclic route is more satisfactory. Assuming this mechanism then, it permits comparison with the rate of the uncharged base reaction. These are shown here with the comparable rate equations. At ca. 1 M sulfuric acid the rate in acid solution is faster than the maximum rate for the uncharged base. The K_1's in the two equations are the same, representing the <u>trans</u> $\rightleftharpoons$ <u>cis</u>

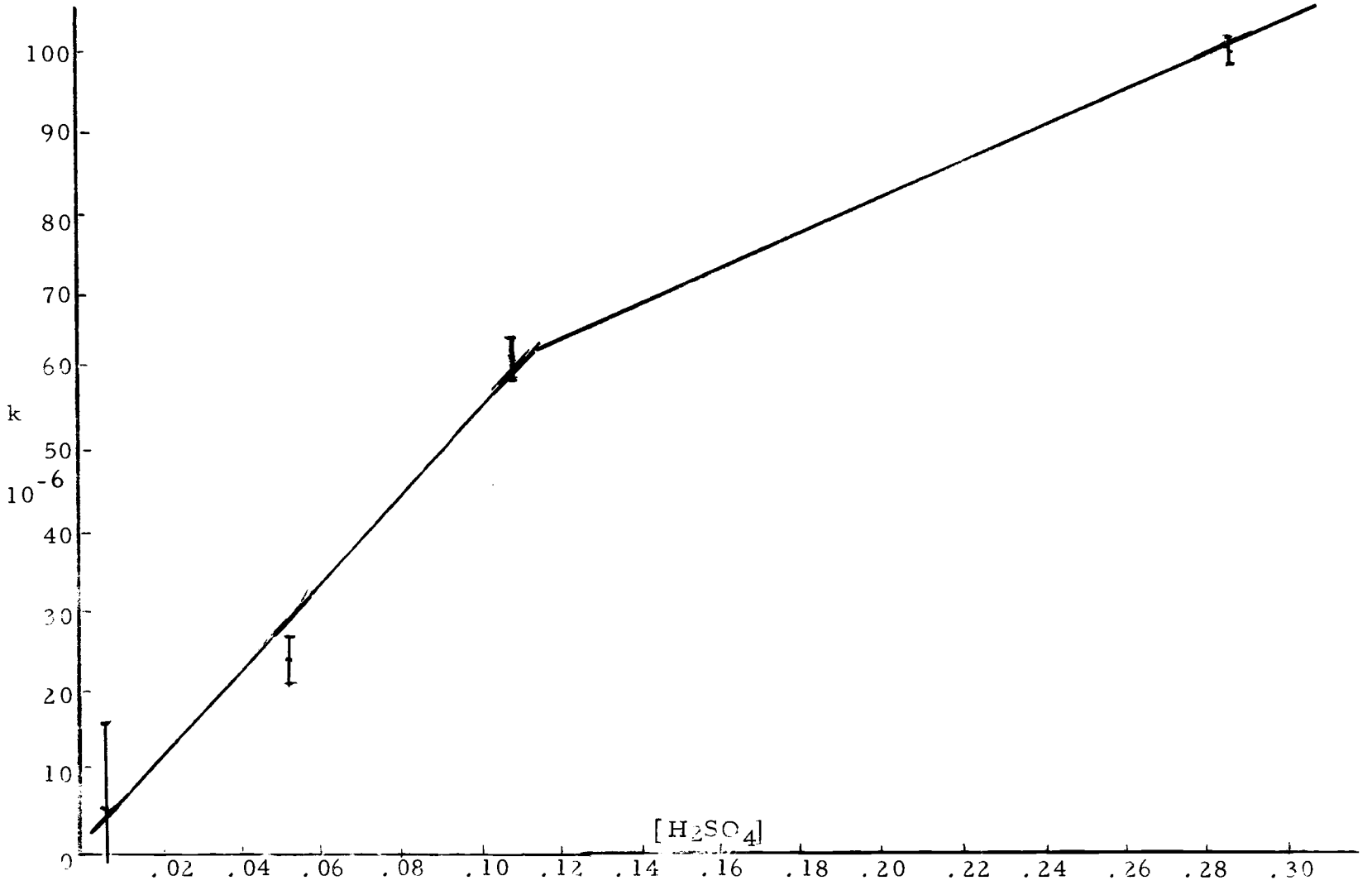


Figure 12. Plot of concentration of H_2SO_4 vs. k at 40°C.

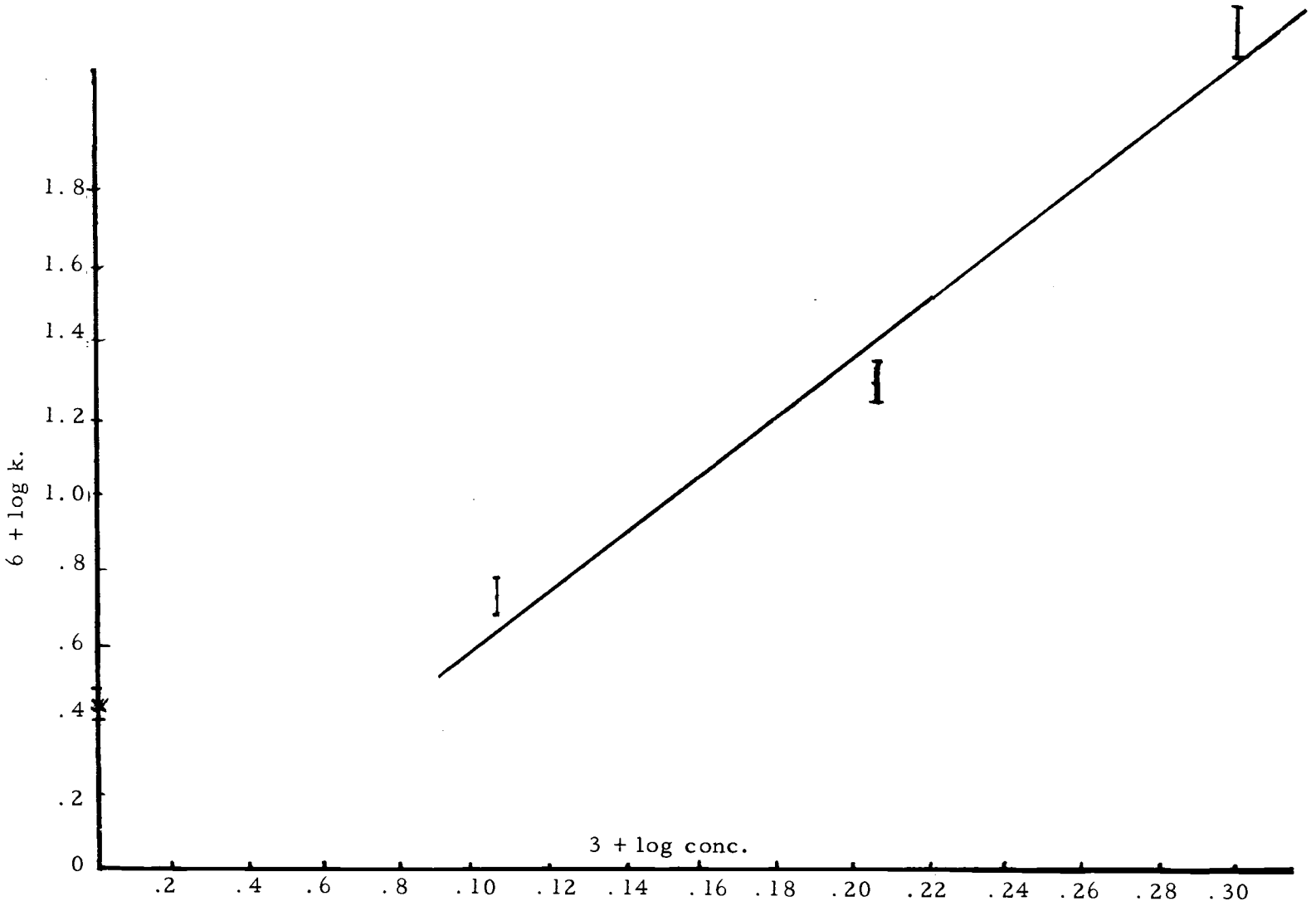


Figure 13. Plot of log conc. of p-toluene sulfonic acid vs. log k at 40°C.

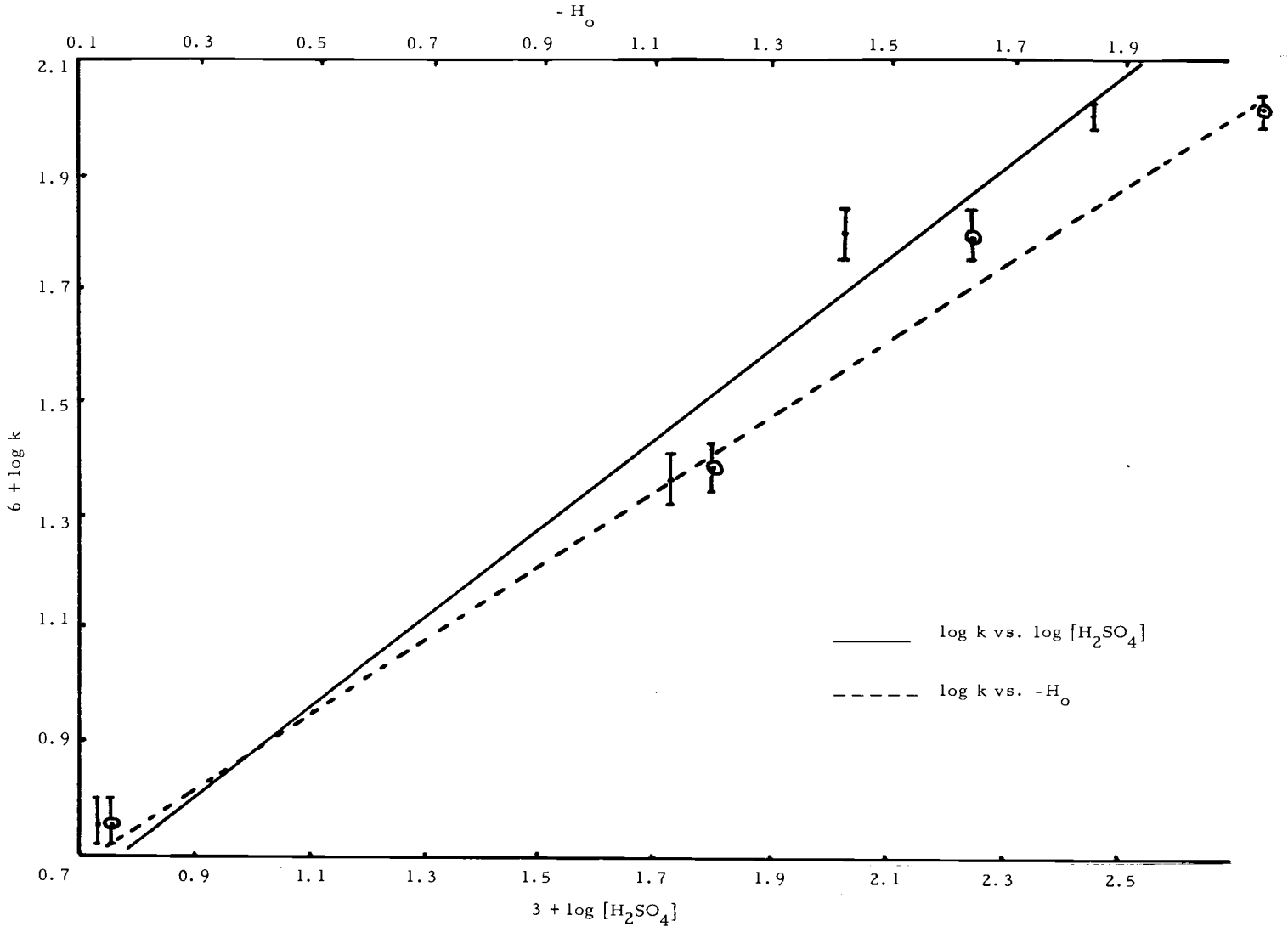
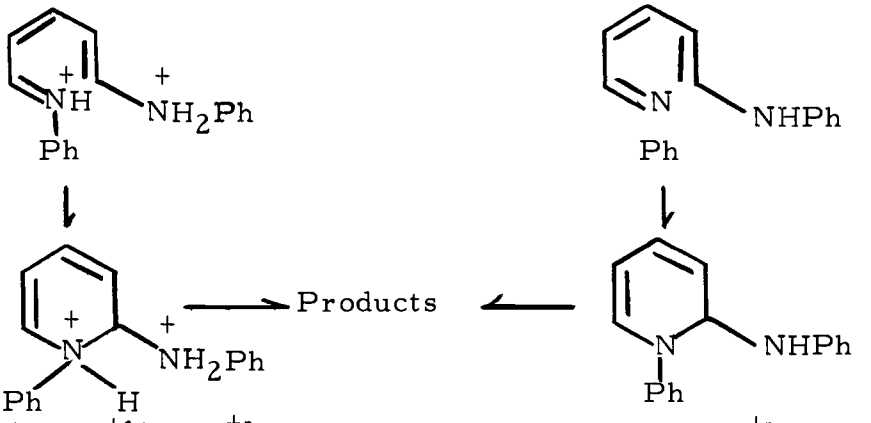


Figure 14. Plot of log k vs. log [H_2SO_4] and - H_o



equilibrium. The extra term in the acid reaction $K_2[H^+]$ must be small since even in 60% sulfuric acid we could find no spectral evidence for a doubly charged species. Consequently k_3 must be larger than k'_3. As a result one could conclude that the electrocyclic reactions of trienes having heteroatoms in a terminal position are of increased rate as compared to cis-hexatriene because of the inherent electronegativity of the heteroatom, and that the unshared pair of electrons on the heteroatom plays no role.

Reaction of 5-Anilino-N-Phenyl-2,4-pentadienylideniminium Chloride (42) in TFA

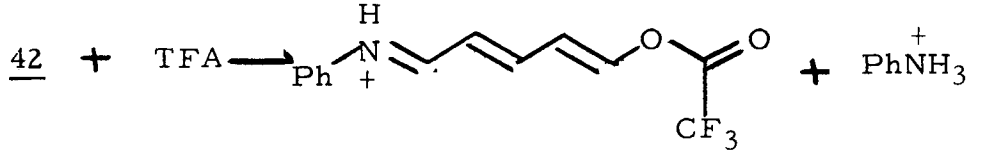
The behavior of 42 in TFA would be expected to be similar to its action in acetic-sulfuric acid mixtures of comparable acidity. In some respects this appears to be true -- that is, it undergoes ring closure to give the same products, and the rate followed by disappearance of the visible band at 461 nm is first order in 42 and is about as fast as expected, i.e., 2.03×10^{-4} sec^{-1} at 40°. There

occurs, however, one very puzzling and yet intriguing phenomenon in this medium. The nmr spectrum of 42 in TFA is normal, if observed shortly after dissolution at low temperature. Repeated observation over a period of time shows that the nmr spectrum undergoes a rather rapid series of changes eventually giving rise to a spectrum which matches band for band that of a 1:1 mixture of N-phenylpyridinium ion and aniline. The amazing part of this observation is that the changes occur with a rough rate constant of 1.5×10^{-4} sec^{-1} at 0^{o} or 2.6×10^{-4} sec^{-1} at 5.5^{o}! Thus the rate for what appears to be the same reaction is 9.22×10^{-5} sec^{-1} at 30^{o} when measured by visible spectroscopy, but is about 2.6×10^{-4} sec^{-1} at 5.5^{o} when followed by nmr!

This puzzling result is rendered yet more mysterious, though perhaps more palatable mentally by two further observations. First it is noted that when the initial rapid reaction appears to be complete by the nmr test, the nmr spectrum is not sharp, the bands are broader than normal and these slowly sharpen up until, at that time when reaction is complete to the visible spectral test, they match exactly, both band for band and in degree of resolution, the spectrum of a 1:1 mixture of N-phenylpyridinium ion and aniline. Finally the nmr spectral sample is originally deep red which becomes deep brown after the nmr first stage is complete. This deep brown color then slowly fades, even though the sample is stored in the dark until

reaction has completed its second phase. The final solution in the nmr tube is light yellow.

The data lead one to postulate that 42 reacts rapidly to lose one molecule of aniline giving some intermediate which retains the long wavelength visible band, but whose protons have chemical shifts similar to these of the pyridinium ring protons of N-phenylpyridinium ion. We considered the replacement of one aniline by TFA as a

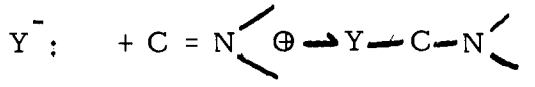


possible reaction, though the nmr spectrum of this ion would resemble that of N-phenylpyridinium ion only by some rare coincidence. However, we were not able to develop convincing evidence for the presence of such an intermediate. Infrared studies could be equally well interpreted as suggesting the presence of TFA in the solid product isolated after a brief reaction period. Consequently the problem remains without a solution.

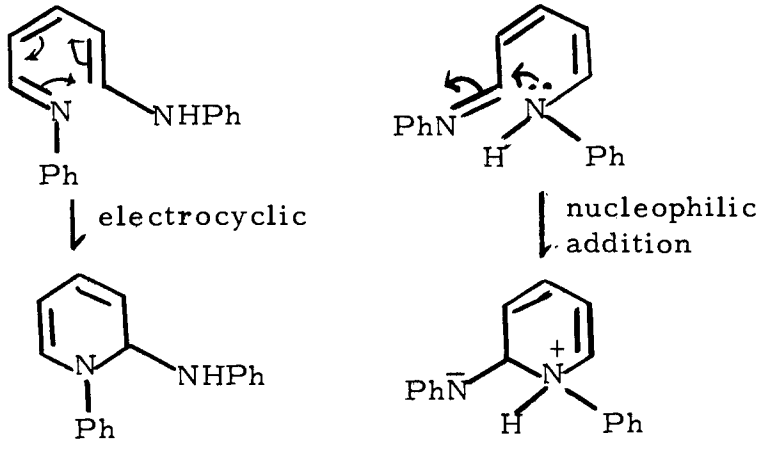
Reaction of 5-Methylamino-N-(2,4-dinitrophenyl)-2,4-pentadienylideniminium Chloride (93) in DMSO

In view of the very common occurrence of nucleophilic addition to immonium ions, it may seem rather surprising that the ring

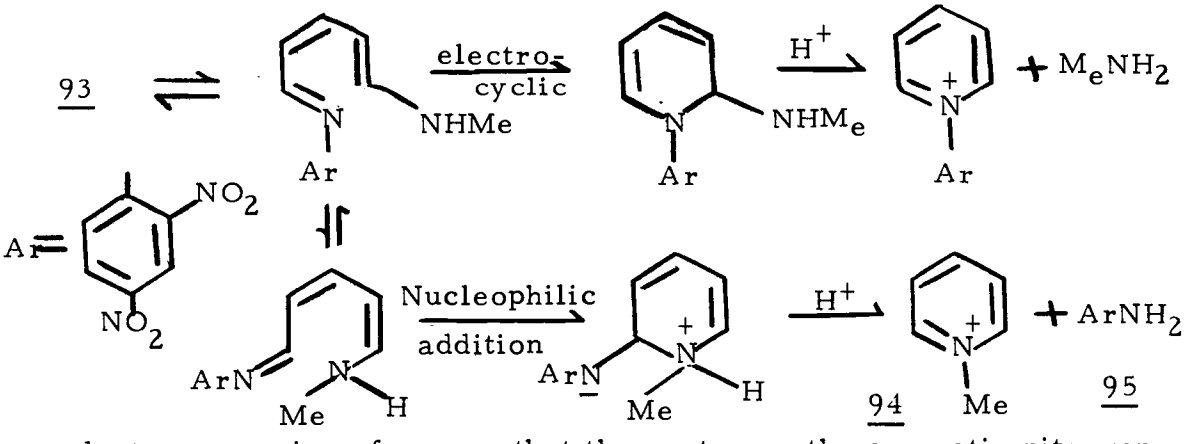
closure reaction of 42 is an electrocyclic process rather than a



nucleophilic addition. In fact nucleophile addition is unfavorable because it requires both a double cis form of the reactant and develops



a charge separation. Despite the disadvantages of that process, we felt it might be possible to study an example of that reaction by using 93 as a substrate. In this case the two routes lead to different

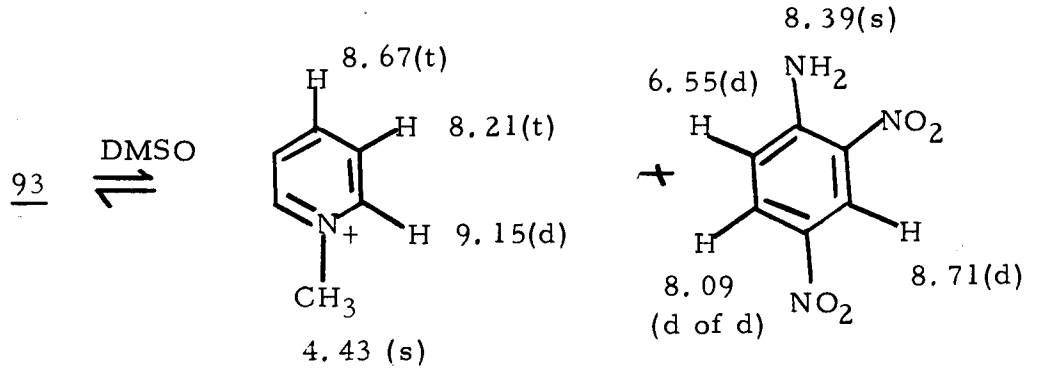


products, assuming of course that the proton on the aromatic nitrogen is lost, and the nucleophilic addition route is more favorable because the dinitrophenyl group can stabilize the developing negative charge

and the aliphatic nitrogen is a better nucleophile.

Preliminary studies by Shahidi in this laboratory[83] revealed that the reaction of 93 in basic methanol gave N-methylpyridinium chloride (94) and 2,4-dinitroaniline (95), together with a small amount of 2,4-dinitroanisole. In weakly acid methanol, the main product became 2,4-dinitroanisole. The reaction was found to be pH sensitive and in strongly acidic media, no reaction occurred. Dr. Paik[84] studied the ring closure of 93 in TFA. The reaction is first order in 93 with a rate constant of 8.3×10^{-6} sec^{-1} at 55°. Product studies revealed that N-methylpyridinium chloride (94) and 2,4-dinitroaniline (95) were formed in a 1:1 ratio.

Because of the formation of 2,4-dinitroanisole, as a result of a side reaction in methanol, DMSO was used as the solvent for the study of the ring closure reactions of 93. It was shown by product isolation studies that reaction of 93 in DMSO leads to the formation of 94 and 95 in a 1:1 ratio. The kinetics of this reaction were measured and the results are presented in Table 8. The rate can be followed by the disappearance of either the visible band at 455 nm or at 400 nm. Both bands appear when 93 is dissolved in DMSO. The reaction is cleanly first order and leads to no side reactions.

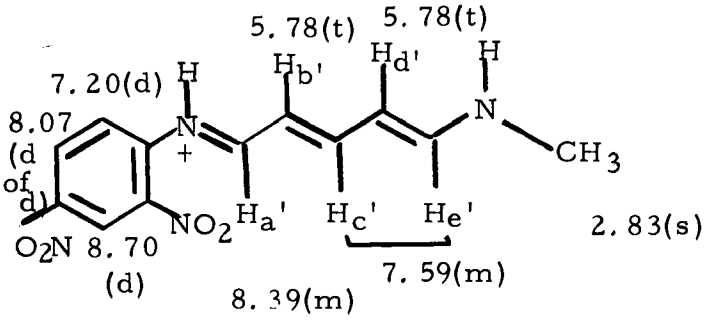


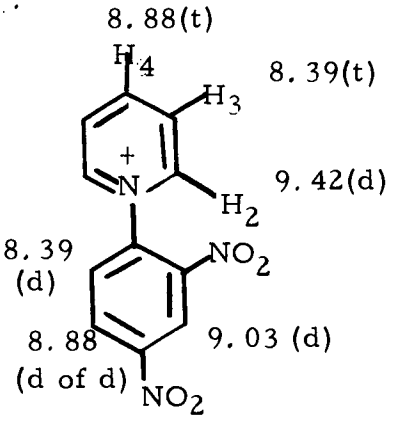
94 95

The nmr spectrum of 94 contains a singlet at 4.43 δ (3H, methyl H's), a triplet at 8.21 (2H, H_3 and H_5 of Py, J ≃ 7 Hz), a triplet at 8.67 (1H, H_4 of py, J ≃ 7 Hz), and a doublet at 9.15 (2H, H_2 and H_6 of Py, J ≃ 6 Hz). It is identical with that of N-methylpyridinium iodide prepared by the reaction of pyridine with methyl iodide. The nmr spectrum of 2,4-dinitroaniline in DMSO-d_6 has a doublet at 6.55 (o-H, J ≃ 10 Hz), a doublet of doublets at 8.09 (1H, J ≃ 2, 10 Hz, m-H), a doublet at 8.71 (1H, J ≃ 2 Hz, m-H) and a broad peak at 8.38.

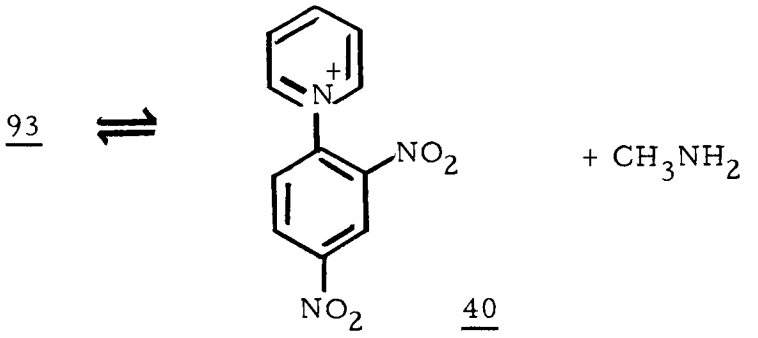
Initial attempts to assign the structure of 93 in DMSO-d_6 revealed a complicated spectrum with a total of 11 bands. Careful examination revealed, however, that a number of bands in the spectrum matched these of 2,4-dinitrophenylpyridinium ion (40). The remainder of the spectrum can reasonably be assigned to 93. The spectrum of 93 (DMSO-d_6) δ, is composed of a singlet at 2.83 (3H, N-methyl H's), a near triplet at 5.78 (H_b' and H_d', J≃12 Hz), a

doublet at 7.20 (1H, o-H, J≃10 Hz), a multiplet at 7.59 (2H, tentatively assigned as H_c' and H_e' even though there is no clear cut proof of this assignment), a doublet of doublets at 8.07 (m-H, J≃10, 2 Hz), a doublet at 8.70 (m-H, J≃2 Hz), a multiplet at 8.39 (4H, H_a' along with H_3, H_5, and o-H of 40. The remainder of the spectrum which is attributable to 40 includes a triplet overlapping a doublet at 8.88 (2H, H_4 and m-H of 40), a doublet at 9.03 (m-H, J≃2 Hz) and a doublet at 9.42 (H_2 and H_6 of 40, J≃6 Hz). The spectrum corresponds roughly a 1:1 mixture of 93 and 40.



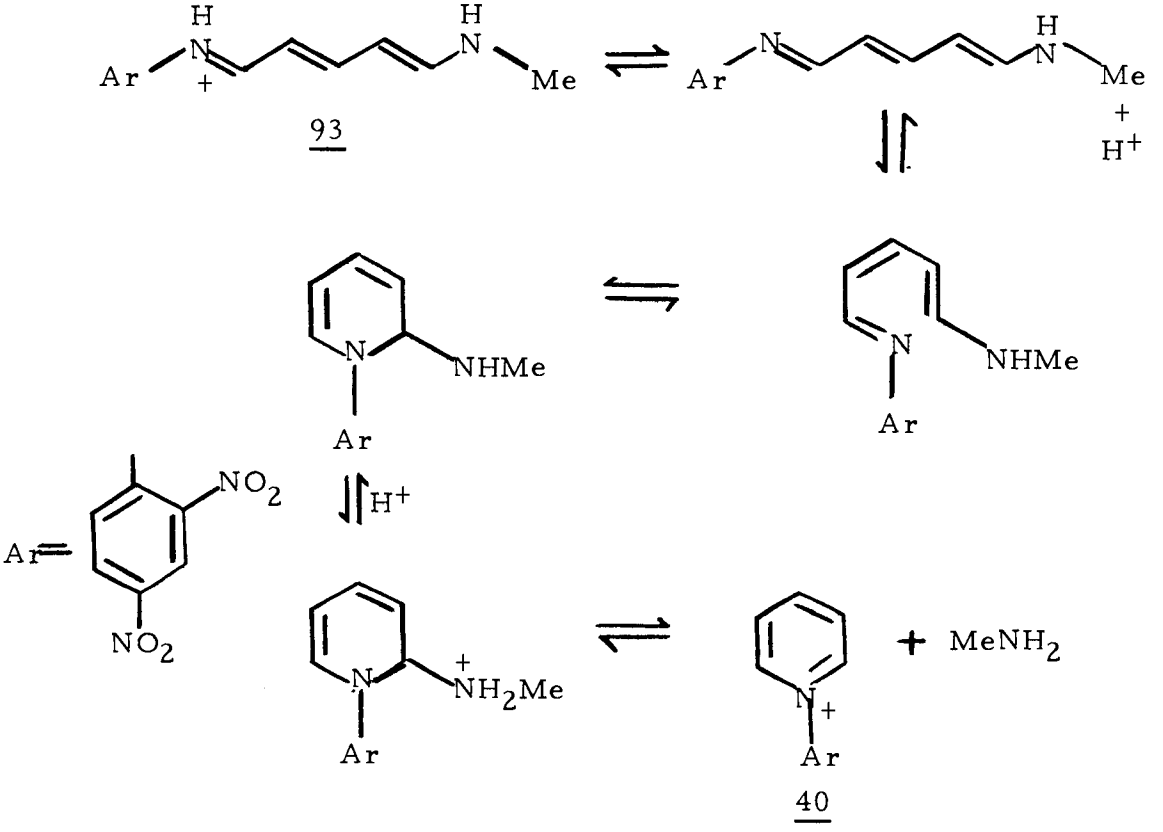


This spectrum appears immediately upon solution of an apparently pure sample of 93 in DMSO-d_6. Purity of the sample was established by melting point. Naturally this points to a very rapid reversal of the reaction which forms 93, and an equilibrium must result. The work of Dr. Paik[84], which showed that the spectrum of 93 in TFA included no bands of the dinitrophenylpyridinium ion, indicates effectively that 93 must lose a proton before reverting to the



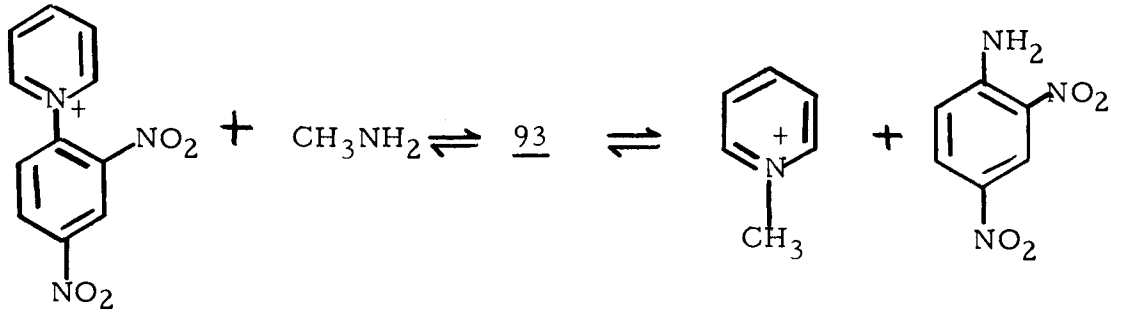
93 40 + CH_3NH_2

dinitrophenylpyridinium ion. Thus in strongly acidic solution the first equilibrium produces so little uncharged base that the reversal to



dinitrophenylpyridinium ion and methylamine is too slow to complete with other reactions, i.e., the decomposition to N-methylpyridinium ion and dinitroaniline.

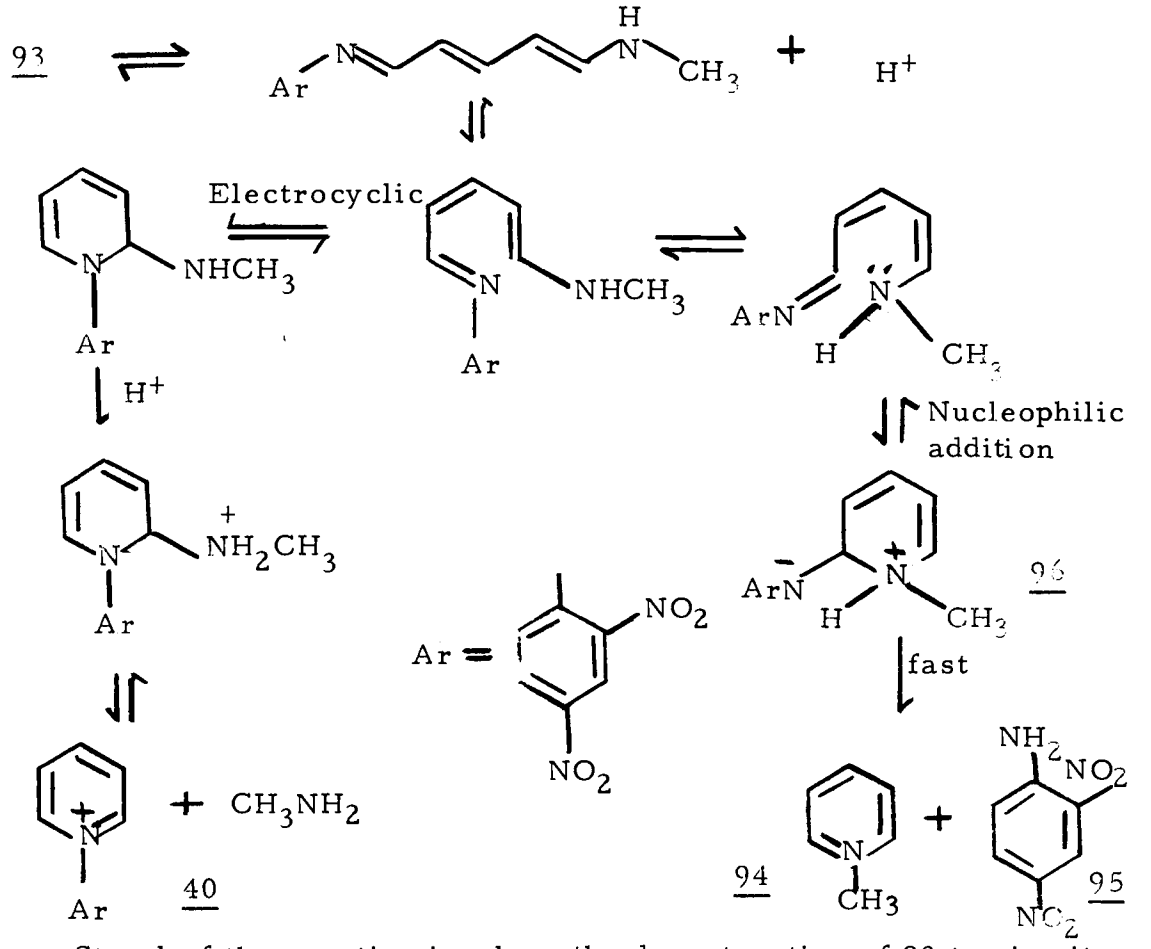
This fast equilibrium between 93 and 40 plus methylamine was established by treating a mixture of 1.42×10^{-4} mole of 40 and 1.25×10^{-4} mole of TFA in DMSO with a solution of methylamine in DMSO. The reaction was followed by nmr. Addition of just enough methylamine solution (1.25×10^{-4} mole) to neutralize the TFA caused the yellow solution to turn bright red. Examination of the nmr spectrum reveals the presence of a small amount of 93. Addition of a second portion (1.25×10^{-4} mole) of methylamine gave a solution whose nmr spectrum indicated the presence of 93 and 40 in a 1:1 ratio. Heating this sample at 70° for 20 hrs. resulted in the formation of 94 and 95 in a 1:1 ratio.



40 94 95

The rate of reaction of 93 to give N-methylpyridinium chloride and 2,4-dinitroaniline in DMSO is shown in Table 8. Both 93 and its free base form are present in the solution as is indicated by uv maxima at 455 and 400 nm. The rate can be followed by the disappearance of either species. It is about ten times slower than 42 in DMSO. Since the rapid equilibrium between 93 and 40 plus

methylamine has already been established, the overall reaction of 93 in DMSO can be summarized as follows:



Step 1 of the reaction involves the deprotonation of 93 to give its free base, which apparently can be converted rapidly to the mono-cis isomer. This intermediate can be cyclized via an electrocyclic process to the dihydropyridinium intermediate, and subsequently to 40 and methylamine. On the other hand, conversion of the mono-cis intermediate to the di-cis can give the reaction products 94 and 95 via an internal nucleophilic addition process. Experimentally, the rate for the conversion of 93 in DMSO to 94 and 95 is slower than the

formation of 40 and methylamine. Formation of 93 and 40 is observed by nmr spectroscopy as soon as 93 is dissolved in DMSO-d_6 at room temperature. Subsequently formation of 94 and 95 occurs at a much slower rate.

One might expect the nucleophilic addition step to be more favorable than the electrocyclic reaction since the dinitrophenyl group can stabilize the developing negative charge of intermediate 96. However, the conversion of the mono-cis to the less favorable di-cis isomer must also be taken into account. The present evidence does not establish what the mechanism for the formation of 94 and 95 really is. More work will be required before a final conclusion can be reached.

Table 4. Rates of ring closure of 42 in TFA/DMSO at 40°.

[TFA] (M)	k (sec.$^{-1}$)
--	2.31×10^{-4}
0.3	3.90×10^{-6}
0.6	4.00×10^{-6}
1.25	4.40×10^{-6}
2.00	4.80×10^{-6}

Table 5. Rates of ring closure of 42 in TFA.

Temperature	k (sec.$^{-1}$)
30°	9.22×10^{-5}
40°	2.03×10^{-4}

Table 6. Rates of ring closure of 42 in H_2SO_4/HOAc at 40°.

[H_2SO_4] (M)	k (sec.$^{-1}$)
--	2.47×10^{-5}
0.00534	5.75×10^{-6}
0.0534	2.37×10^{-5}
0.107	6.23×10^{-5}
0.287	1.01×10^{-4}

Table 7. Rates of ring closure of 42 in p-toluenesulfonic acid/HOAc at 40°.

[p-toluenesulfonic acid] (M)	k (sec.$^{-1}$)
0.001	2.69×10^{-6}
0.0117	5.19×10^{-6}
0.117	2.04×10^{-5}
1.00	1.69×10^{-3}

Table 8. Rates of ring closure of 93 in DMSO at 40°.

Wavelength	k (sec.$^{-1}$)
455 nm	2.27×10^{-5}
400 nm	2.23×10^{-5}

Table 9. Effects of acetic anhydride and water on the ring closure of 42 in 0.1069 M of H_2SO_4/HOAc at 40°.

Reagents	Amount (wt. %)	k (sec.$^{-1}$)
--	--	6.23×10^{-5}
Acetic anhydride	0.065	4.40×10^{-5}
Acetic anhydride	0.175	3.84×10^{-5}
Acetic anhydride	1.0	1.02×10^{-3}
Water	0.066	4.17×10^{-5}
Water	0.168	4.10×10^{-5}
Water	1.0	1.1×10^{-5}

EXPERIMENTAL

Part I. Cope Rearrangement of 2-Aryl-1, 5-hexadienes: Rates and Mechanism

All nmr spectra were obtained using a Varian HA-100 nuclear magnetic spectrometer. The infrared spectra were recorded on a Beckman IR 8 instrument, and a Cary 15 was used to determine all ultraviolet spectra.

Preparation of Allylacetophenone

1-Phenyl-4-penten-1-one (67a)— This compound was prepared according to the procedure of G. Vavon and J. Conia[85]. To a well stirred solution of 60.0 g (0.5 mole) of freshly distilled acetophenone and 66.0 g (0.55 mole) of allyl bromide in 200 ml reagent grade toluene, was added dropwise 275 ml of 1.8 N sodium t-amylate. During the addition, the solution was cooled in an ice bath, and after the addition had been completed the solution was refluxed for two hrs. The reaction mixture was washed with distilled water and extracted with ether. The combined ether layers were dried (anhydrous $CaCl_2$) and the solvents were removed in vacuo. The residue was distilled with a 45-cm spinning-band column to give 37.8 g (34.8% of 1-phenyl-4-penten-1-one, b.p. 108.2-108.8°C. (5 mm); [Lit.[86] b.p. 140 C. (9 mm)]; ir (neat), 1680, 1640, 912, 745 and 690 cm^{-1} [identical to

the one reported by A. Padwa et al.[86]; nmr (CCl_4) δ, 7.82 (m, 2H, aromatic), 7.32 (m, 3 H, aromatic), 2.90 (t, 2 H, J≃ 7 Hz, $-CH_2-$), 2.42 (m, 2 H, $-CH_2-$, 5.78 (m, 1 H -CH=), 4.92 (m, 2H, $=CH_2$) [identical with the published spectrum[87]].

Preparation of Substituted Allylacetophenones

All substituted allylacetophenones were prepared according to the procedure of G. Vavon and J. Conia[85], through the reaction of the appropriate acetophones with allyl bromide as in the synthesis of 1-phenyl-4-penten-1-one.

1-(p-Bromophenyl)-4-penten-1-one (67-f). Reaction of 59.7 g (0.30 mole) of p-bromoacetophenone with 39.6 g (0.33 mole) of allyl bromide and 150 ml of 2.0 N sodium t-amylate in 120 ml of reagent grade toluene gave, after the usual work up and distillation, 24% of 1-(p-bromophenyl)-4-penten-1-one, white solid, m.p. 36°C; b.p. 68-70°C. (0.002 mm); ir (CCl_4): 916, 1640, 1680 cm^{-1}; uv max. (95% ethanol) 254 nm (ε = 16700); nmr (CCl_4) δ 2.43 (m, 2H, $-CH_2-$), 2.93 (t, 2H, J≃ 7 Hz, $-CH_2-$), 4.99 (m, 2H, $=CH_2$), 5.83 (m, 1H, -CH=), 7.51 (d, 2H, J≃ 8 Hz, aromatic), 7.75 (d, 2H, aromatic). Anal. Calc'd for $C_{11}H_{11}BrO$: C, 60.78; H, 5.53. Found: C, 60.62; H, 5.50.

1-(p-Chlorophenyl)-4-penten-1-one (67-d). A mixture of 77.3 g (0.50 mole) of p-chloroacetophenone and 67.0 g (0.55 mole) of allyl

bromide was treated with 250 ml of 1.95 N sodium t-amylate to give, after distillation, 30% of 1-(p-chlorophenyl)-4-penten-1-one, b.p. 80-82°C. (0.07 mm); ir: 733, 760, 776, 795, 816, 838, 912, 1640, 1680 cm^{-1}; uv max (95% ethanol) 250 nm (ϵ = 19900); nmr (CCl_4) δ 2.43 (m, 2H, $-CH_2-$), 2.94 (t, 2H, J≏7 Hz), $-CH_2-$), 4.98 (m, 2H, $=CH_2$), 5.83 (m, 1H, -CH=), 7.34 (d, 2H, J≏8 Hz), aromatic), 7.82 (d, 2H, J≏8 Hz, aromatic). Anal. Calc'd for $C_{11}H_{11}Cl$): C, 67.87; H, 5.69. Found: C, 67.97; H, 5.69.

1-(p-tolyl)-4-penten-1-one (67-b). Addition of 256 ml of 1.95 N sodium t-amylate to a solution of 67.1 g (0.50 mole) of p-methylacetophenone and 66.0 g (0.55 mole) of allyl bromide in toluene gave 13.3 g (15.3%) of 1-(p-tolyl)-4-penten-1-one, b.p. 62.5°C (0.02 mm); ir (neat) 780, 806, 825, 912, 1640, 1680 cm^{-1}; uv max (95% ethanol) 242 nm (ϵ = 9580); nmr (CCl_4) δ, 2.36 (s, 3H, $-CH_3$), 2.42 (m, 2H, $-CH_2-$), 2.92 (t, 2H, J≏7 Hz, $-CH_2-$), 4.98 (m, 2H, $=CH_2$), 5.82 (m, 1H, -CH=), 7.16 (d, 2H, J≏8 Hz, aromatic), 7.76 (d, 2H, J≏8 Hz, aromatic). Anal. Calc'd for $C_{12}H_{14}$: C, 82.94; H, 8.27. Found: C, 82.89; H, 8.46.

1-(p-Anisyl)-4-penten-1-one (67-c). A solution containing 75 g (0.50 mole) of p-methoxyacetophenone and 66 g (0.55 mole) of allyl bromide was allowed to react with 265 ml of 1.95 N sodium t-amylate. After the usual work up, distillation gave 30% of 1-(p-anisyl)-4-penten-1-one, b.p. 106°C (0.5 mm); ir (neat) 838, 912, 1030, 1210, 1258,

1640, 1675 cm^{-1}; uv max (95% ethanol) 272 nm (ϵ = 16250); nmr (CCl_4) δ 2.40 (m, 2H, $-CH_2-$), 2.88 (t, 2H, J = 7.0 Hz, $-CH_2-$), 3.80 (s, 3H, $-OCH_3$), 4.98 (m, 2H, $=CH_2$), 5.78 (m, 1H, -CH=), 6.80 (d, 2H, J = 8 Hz, aromatic), 7.80 (d, 2H, J = 8.0 Hz, aromatic). Anal. Cal'd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.07; H, 7.41.

2-Methyl-1-phenyl-4-penten-1-one (70). Reaction of 67 g (0.50 mole) of propiophenone with 66.0 g of allyl bromide (0.55 mole) and 250 ml of 2.04 N sodium t-amylate gave 79% of 2-methyl-1-phenyl-4-penten-1-one, b.p. 73-74°C. (0.15 mm), ir (neat) 703, 792, 914, 1640, 1680 cm^{-1}; uv max (95% ethanol) 242 nm (ϵ = 9860); nmr (CCl_4) δ 1.16 (d, 3H, J = 6 Hz, $-CH_3$), 2.16 (m, 1H, $-CH_2-$), 2.51 (m, 1H, $-CH_2-$), 3.41 (m, 1H, -CH-), 4.98 (m, 2H, $=CH_2$), 5.72 (m, 1H, -CH=), 7.40 (m, 3H, aromatic), 7.86 (m, 2H, aromatic). Anal. Calc'd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.68; H, 8.00.

Deuteration of Ketones

Ketones were deuterated following the method of V. J. Shiner et al.[88]. Deuterium Oxide-d_2 (99.8% D) of Stohler Isotope Chemicals was used as the reagent. In all cases, nmr spectra showed the complete disappearance of the methylene triplet at 2.90 δ and the replacement of the methylene multiplet at 2.42 δ by a doublet, (J = 6.0 Hz). All allylacetophenones were deuterated according to the

following sample procedure.

1-Phenyl-4-penten-1-one-2-d_2 (68-a). A 2.0 g (0.0125 mole, 0.0250 g-atom of exchangeable H) sample of 1-phenyl-4-penten-1-one and 0.6 g of dry redistilled triethylamine were dissolved in 20 ml of purified dioxane. To this, 2.0 g (0.100 mole, 0.200 g-atom exchangeable H) of deuterium oxide was added. The mixture was gently refluxed for 17 hrs. The water was removed as the dioxane azeotrope (b.p. 87-88°C) and an additional 2 ml of dioxane was collected at 101°C. A new mixture of deuterium oxide, triethylamine and 20 ml of dioxane was added and the process was repeated. This procedure was run a third time. Distillation under reduced pressure gave 90% of 1-phenyl-4-penten-1-one-2-d_2. The nmr spectrum was identical with that of the parent allylacetophenone except for the disappearance of the $-CH_2-$ triplet at 2.90 δ and the replacement of the $-CH_2-$ multiplet at 2.42 δ by a doublet (J = 6.0 Hz).

2-Phenyl-1,5-hexadiene-3-d_2 (69-a). To a solution containing 0.0125 mole of phenyllithium[89] in a mixture of 50 ml of benzene and 30 ml of ether was added 4.46 g (0.0125 mole) of solid methyltriphenylphosphonium bromide[90]. The mixture was stirred at room temperature for five hrs., after which 2.0 g (0.0125 mole) of 1-phenyl-4-penten-1-one-2-d_2 in 10 ml of benzene was added dropwise. The mixture was refluxed for 12 hrs. at 40°C. It was then cooled to room temperature and 0.5 g of deuterium oxide in 100 ml of pentane

was added to quench the reaction. The pentane solution was decanted and dried (anhydrous $MgSO_4$). After the solvent had been removed in vacuo, gas chromatographic analysis indicated that the product contained 60% of 2-phenyl-1,5-hexadiene-3-d_2. A 15 ft. x 1/4 in. column of 5% FFAP on Chromosorb G was used both for analytical and preparative work. IR (neat) 695, 763, 778, 910, 1000, 1450, 1625, 2110, 2210, 2930 cm^{-1}; nmr (CCl_4) δ 2.15 (d, 2H, J≐6 Hz, $-CH_2-$), 4.99 (m, 4H, two sets of $=CH_2$), 5.73 (m, 1H, -CH=), 7.23 (m, 5H, aromatic).

Preparation of Other Deuterated, Substituted Hexadienes

All other deuterated substituted hexadienes were prepared according to the above general procedure from the appropriate deuterated allylacetophenones. NMR spectra of these deuterated compounds are identical to the non-deuterated ones, prepared separately for elemental analysis, except the disappearance of the $-CH_2-$ triplet at around 2.50 δ and the replacement of the methylene multiplet by a doublet at 2.15 δ (J = 6.0 Hz).

Preparation of Other Substituted Hexadienes

Other substituted hexadienes were prepared for elemental analysis by the same general procedure from the various allylacetophenones.

2-(p-Bromophenyl)-1,5-hexadiene (69-f'). Reaction of 0.0088 mole of phenyllithium and 0.0088 mole of triphenylmethylphosphonium bromide with 0.0073 mole of 1-(p-bromophenyl)-4-penten-1-one in 20 ml of anhydrous ether and 35 ml of dry benzene gave, after the usual work up, a 65% yield of 2-(p-bromophenyl)-1,5-hexadiene as indicated by gas chromatography. A 6 ft. x 1/4 in. column of 5% DEGS on Chromosorb G was used both for analytical and preparative work. Ir (neat) 830, 910, 1640 cm^{-1}; uv max (95% ethanol) 247 mm (ϵ = 15800); nmr (CCl_4) δ 2.16 (m, 2H, $-CH_2-$), 2.52 (t, 2H, J = 7.0 Hz, $-CH_2-$), 5.00 (m, 4H, $=CH_2$), 5.72 (m, 1H, -CH=), 7.18 (d, 2H, J = 8.0 Hz, aromatic), 7.38 (d, 2H, J = 8.0 Hz, aromatic). Anal. Calc'd for $C_{12}H_{13}Br$: C, 60.78; H, 5.53. Found: C, 60.82; H, 5.50.

2-(p-Chlorophenyl)-1,5-hexadiene (69-d'). Reaction of 0.012 mole of phenyllithium and 0.012 mole of triphenylmethylphosphonium bromide with 0.01 mole of 1-(p-chlorophenyl)-4-penten-1-one according to the general procedure gave 68% of 2-(p-chlorophenyl)-1,5-hexadiene, ir (CCl_4) 892, 910, 1640 cm^{-1}; uv max (95% ethanol) 246 nm (ϵ=10,400); nmr (CCl_4)δ, 2.15 (m, 2H, $-CH_2-$), 2.51 (t, 2H, $-CH_2-$), 5.01 (m, 4H, $=CH_2$), 5.73 (m, 1H, -CH=), 6.97 (s, 4H, aromatic). Anal. Calc'd for $C_{12}H_{13}Cl$: C, 74.80; H, 6.80. Found: C, 74.63; H, 6.85.

2-(p-Tolyl)-1,5-hexadiene (69-b'). Reaction of 0.015 mole of phenyllithium and 0.015 mole triphenylmethylphosphonium bromide

with 0.0126 mole of 1-(p-tolyl)-4-pentenlone gave a 72% yield of 2-(p-tolyl)-1,5-hexadiene, ir (neat) 822, 892, 914, 1680 cm^{-1}; uv max (95% ethanol) 243 nm (ϵ = 11080); nmr (CCl_4) δ, 2.29 (s, 3H, $-CH_3$), 2.20 (m, 2H, $-CH_2-$), 2.49 (t, 2H, J = 7.0 Hz, $-CH_2-$), 4.93 (m, 4H, $=CH_2$), 5.70 (m, 1H, -CH=), 6.99 (d, 2H, J = 8.0 Hz, aromatic), 7.17 (d, 2H, J = 8.0 Hz, aromatic). Anal. Calc'd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.79; H, 9.30.

2-(p-Anisyl)-1,5-hexadiene (69-c'). A mixture of 0.0075 mole of phenyllithium and 0.0075 mole of triphenylmethylphosphonium bromide was allowed to react with 0.0063 mole of 1-(p-anisyl)-4-penten-1-one to give, after the usual work up, 65% of 2-(p-anisyl)-1,5-hexadiene, ir (neat) 832, 890, 910, 1032, 1248, 1640 cm^{-1} uv max (95% ethanol) 272 nm (ϵ = 16200); nmr (CCl_4)δ 2.15 (m, 2H, $-CH_2-$), 2.49 (t, 2H, J = 7.0 Hz, $-CH_2-$), 3.73 (s, 3H, $-OCH_3$), 4.93 (m, 4H, $=CH_2$), 5.75 (m, 1H, -CH=), 6.71 (d, 2H, J = 8.0 Hz, aromatic), 7.21 (d, 2H, J = 8.0 Hz). Anal. Calc'd for $C_{13}H_{16}O$: C, 82.94; H, 8.27. Found: C, 82.89; H, 8.46.

3-Methyl-2-phenyl-1,5-hexadiene (69e). Reaction of 0.0175 mole of phenyllithium and 0.0175 mole of triphenylmethylphosphonium bromide with 2-methyl-1-phenyl-4-penten-1-one gave a 76% yield of 3-methyl-2-phenyl-1,5-hexadiene. ir (CCl_4) 890, 910, 1640 cm^{-1}; uv max (95% ethanol) 233 (ϵ = 10100); nmr (CCl_4) δ 1.10 (d, 3H, J = 6.0 Hz, $-CH_3$), 2.12 (m, 2H, $-CH_2-$), 2.71 (m, 1H, -CH-), 4.98

(m, 4H, $=CH_2$), 5.69 (m, 1H, -CH=C-), 7.18 (s, 5H, aromatic). Anal. Calc'd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.45; H, 9.20.

β-Methylallyl Phenyl Ether (71). This compound was prepared according to the procedure of Q. R. Bartz et al.[91]. A solution of 49.5 g (0.55 mole) of methallyl chloride, 75.9 g of anhydrous potassium carbonate (0.55 mole) and 47.0 g of phenol in 95 ml of acetone was heated to reflux for 14 hrs. The reaction mixture was cooled, 300 ml of water was added and the aqueous layer separated and extracted with 150 ml of petroleum ether. The extract and the water insoluble layer were combined and washed with 10% aqueous sodium hydroxide, and then with water. The petroleum ether solution was dried (anhydrous $MgSO_4$) and the product was isolated by distillation, b.p. 39.5°C (0.2 mm); [Lit.[91] b.p. 70°C (8.0 mm)]; yield 40.2 g (49%); nmr (CCl_4) δ, 1.77 (s, 3H, $-CH_3$, 4.31 (s, 2H, $-CH_2-$), 4.89 apparent s, 1H, $=CH_2$), 5.03 (apparent s, 1H, $=CH_2$), 6.78 (m, 3H, aromatic), 7.11 (m, 2H, aromatic); ir (neat) 690, 750, 1015, 1030, 1060, 1450, 1650 cm^{-1}.

Kinetic Studies

Via nmr. Solutions containing 5% of the substrate in cyclohexane-d_{12} (99.5% D, Stohler Isotopes) with a trace of diphenylamine added as stabilizer were placed in ampules, degassed by repeated

freeze-thaw cycles and sealed under reduced pressure. The ampules were of Pyrex and were prepared by washing with an alkaline detergent, rinsed with dilute ammonium hydroxide and dried at 110° for 24 hrs. The ampules were heated in a thermostatted bath at 164° for specified times. As the tubes were removed reaction was quenched by cooling, the tubes were opened and the contents transferred to nmr tubes for analysis. Progress of the reaction was followed by noting the decrease in number of vinyl protons and increase in the number of methylene protons. A_o values were obtained prior to reaction and A_∞ values were derived after reaction times of 12-14 hrs.

Via glc. Solutions containing 5% of 3-methyl-2-phenyl-1,5-hexadiene and a crystal of diphenylamine in reagent grade cyclohexane were sealed in ampules and heated as described above. A 300 ul sample was removed from each tube in turn and was mixed with 50 ul of a 10% solution of biphenyl in cyclohexane. The combined solution was analyzed using a 6 ft. x 1/4 in. column of 5% DEGS on Chromosorb G at 150°. Peak areas were calculated by triangulation and the results were expressed as ratios of the observed peaks relative to those of the biphenyl.

Solutions containing 2% by weight of β-methallyl phenyl ether in either nitrobenzene or diphenyl ether were sealed in ampules as above. They were heated at 185° in a thermostatted bath and the contents were analyzed by glc using the 5% DEGS column. Peak areas

were obtained by digital integration, and the rate was calculated from the disappearance of the reactant.

Product Studies

3-Phenyl-2,6-heptadiene (73). A sample 98 mg, of pure 3-methyl-2-phenyl-1,5-hexadiene, collected by preparative gas chromatography at 135°C from a 6 ft. x 1/4 in. column of 5% DEGS, was sealed in an ampoule with 3 ml of reagent grade cyclohexane and a trace of diphenylamine. The reaction was allowed to run for 40 hrs. at 190°C. The product was collected by preparative gas chromatography using the 5% DEGS column at 125°C; ir (CCl_4) 910, 1440, 1640 cm^{-1}; uv max (95% ethanol) 240 nm (ϵ = 10700); nmr (CCl_4) δ 1.80 (d, 3H, J = 6 Hz, $-CH_3$), 2.06 (m, 2H, $-CH_2-$), 2.56 (t, 2H, J = 7.0 Hz, $-CH_2-$), 4.92 (m, 2H, $=CH_2$), 5.74 (q overlapping m, 2 H, $=CH-CH_3$ and $-CH=$), 7.20 (s, 5H, aromatic). Anal. Calc'd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.52; H, 9.35.

o-(β-methylallyl)phenol (97). A solution of 0.4 g of β-methylallyl phenyl ether in 20 g of freshly distilled reagent grade nitrobenzene was heated at 185°C for 17 hrs. The reaction mixture was allowed to cool to room temperature and was extracted with 10% sodium hydroxide. The aqueous portion was then saturated with CO_2 and extracted twice with 50 ml of ether. The ether extracts were combined and dried (anhydrous Na_2CO_3). Solvent was removed in vacuo,

and the o-(β-methylallyl)phenol was collected by preparative gas chromatography using the 5% DEGS column at 150°C; nmr (CCl_4) δ 1.71 (s, 3H, $-CH_3$), 3.31 (s, 2H, $-CH_2-$), 4.87 (m, 3H, vinyl $=CH_2$ and phenolic OH), 6.59-7.13 (m, 4H, aromatic); ir (neat) 760, 890, 1090, 1170, 1216, 1260, 1640, 3480 cm^{-1}, identical to the spectral data reported by A. T. Schulgin and A. W. Baker[92].

Part II. Formation of N-Phenyl and N-Methyl Pyridinium Salts from 1,7-Diaza-1,3,5-Heptatrienes

Source of Materials

5-Anilino-N-Phenyl-2,4-pentadienylidenimium Chloride (42). All of the experiments using 42 were carried out with material prepared by Dr. I. K. Shahidi according to the procedure of Zincke[42]. The product was purified by recrystallization from methanol and was dried in vacuo, m.p. 146-147° [liter.[42] m.p. 142-143°]; nmr (DMSO-d_6) δ, 6.54 (t, 2H, J≏12 Hz), 7.40 (m, 2H), 7.53 (two sharp peaks, 8H), 7.95 (t, 1H, J≏12 Hz), 8.67 (d, 2H, J≏12 Hz); nmr (TFA at -10°) δ, 6.18 (t, 2H, J≏12 Hz), 7.17 (m, 10H), 7.56 (t, 1H, J≏12 Hz), 7.87 (d, 2H, J≏12 Hz).

5-Methylamino-N-(2,4-dinitrophenyl)-2,4-pentadienylidenimine Chloride (93). One sample of 93 was used for all work on this substance. This sample was prepared by Dr. C. Paik according to the directions of Zincke[42]. Material obtained by acidifying a reaction

mixture containing 2, 4-dinitrophenylpyridinium chloride and 40% aqueous methylamine with methanolic hydrogen chloride was washed repeatedly with ether and dried in vacuo, m. p. 122° [liter.[42] m. p. 120°]. This compound could not be recrystallized successfully. nmr (DMSO-d_6) δ , 2. 83 (s, 3H), 5. 78 (near t, 2H, J≃12 Hz), 7. 20 (d, 1H, J≃10 Hz), 7. 59 (m, 2H), 8. 07 (d of d, 1H, J≃10 Hz and J≃2 Hz), 8. 70 (d, 1H, J≃2 Hz), 8. 39 (m, 4H), 8. 88 (m, 2H), 9. 03 (d, 1H, J≃2 Hz), 9. 42 (d, 2H, J≃6 Hz); nmr (TFA) δ, 3. 24 (d, 1. 25H, J≃6 Hz), 3. 34 (d, 1. 75H, J≃6 Hz), 6. 43 (m, 2H), 7. 35 to 7. 87 (m, 3H), 8. 02 (m, 1H), 8. 35 (d, J≃9 Hz), 9. 02 (s, 1H), 9. 25 (broad s, 1H).

2, 4-Dinitrophenylpyridinium Chloride (40). This compound was prepared from 2, 4-dinitrochlorobenzene and pyridine according to the procedure of Zincke[42]. The light yellow solid was purified by recrystallization from methanol and dried in vacuo, m. p. 204° [liter.[42] m. p. 212°]; nmr (DMSO-d_6) δ , 8. 35 (t, 2H, J≃6 Hz), 8. 45 (d, 1H, J≃9 Hz), 8. 86 (d of d with overlapping t, 3H, J≃9 Hz, 2 Hz), 9. 45 (d, 2H, J≃ 6 Hz).

Anhydrous Acetic Acid. Acetic acid was dried and purified according to the procedure of Eichelberger and La Mer[77]. One liter of reagent grade acetic acid was refluxed for 12 hrs. with 20 g of chromium trioxide. This acid was distilled using two ft. modified Hempel column, b. p. 117°. This was then refluxed for 5 hrs. with

39 g of triacetylborate, prepared according to the direction of Pectet and Gellznoff[93] by warming to 60° a mixture of powdered boric acid and acetic anhydride (in the ratio of one to five parts by weight).* Distillation gave acetic acid, m.p. 16.5°. Repeated recrystallization gave anhydrous acetic acid, m.p. 16.6° [liter.[94] m.p. 16.5965°].

Sulfuric Acid. Sulfuric acid was prepared by bubling sulfur trioxide (generated by heating 30% fuming sulfuric acid (Allied Chemical) at 170°) through reagent grade sulfuric acid (Du Pont) for several hours. Water was then added cautiously to this concentrated acid until its f.p. was 10.4° [liter.[96] f.p. 10.4° for 100% sulfuric acid].

p-Toluenesulfonic Acid. p-Toluenesulfonic acid (Eastman) was dehydrated in vacuo over phosphorus pentoxide for ten hrs. at 56°. The anhydrous acid is light purple in color.

Dimethylsulfoxide. Practical grade dimethylsulfoxide (Matheson, Coleman and Bell) was purified and dried according to the procedure of Johnson[95]. The solvent was dried over Molecular Sieves 4A, then over Barium oxide, and was fractionally distilled, b.p. 58-59° (28 mm). The center cut (60%) was used for all kinetic runs and product isolation studies.

Sulfuric Acid-d_2. Sulfur trioxide (from heating 30% fuming sulfuric acid at 170°) was bubbled through 30 ml. of deuterium oxide

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*Reaction becomes violent when heating is above 65°C.

(Stohlers Isotope Chemicals, 99.8%) until nmr spectroscopy indicated the sulfuric acid was at least 99% deuterated. Titration indicated the concentration to be 95%.

Kinetic Studies

Rate studies were carried out either in a thermostatted bath held to $\pm$ 0.2°C or directly in a Cary 15 spectrophotometer equipped with a thermostatted cell holder and cell compartment. The temperature in the latter case was found to be constant to $\pm$ 0.1°C. Rates were followed by the disappearance of the intense peak or peaks in the visible region, either directly or using aliquots removed via syringe from the reaction solution at appropriate intervals. Rate constants were calculated from the expression $\log (A_o - A_\infty)/A - A_\infty) = kt$. In all cases good first order kinetics were observed and rates were followed to at least two half lives. In those cases where water was found to influence the rate, all solutions were made up in a dry box. Results are shown in Tables 4-9.

Product Studies

Reaction of 42 in DMSO-d_6. A solution containing 20 mg of 42 in 2 ml DMSO-d_6 was sealed in an nmr tube and heated at 70° for 24 hrs. The nmr spectrum of the solution at that time showed the following resonances (δ), 8.44 (t, 2H, J$\simeq$7 Hz), 8.90 (t, 1H, J$\simeq$7 Hz),

9.46 (d, 2H, J≏7 Hz), 7.94 (m, 5H), 7.10 (t, 2H), 6.64 (m, 3H), 5.16 (broad m, ∼2H). The spectrum is matched by that of 1:1 mixture of N-phenylpyridinium chloride and aniline in DMSO-d_6.

Reaction of 93 in DMSO-d_6. A solution of 30 mg of 93 in 3 ml of DMSO-d_6 sealed in an nmr tube was heated at 40° for 41 hrs. NMR examination revealed only partial reaction, so the sample was heated at 70° for six hrs. The nmr spectrum then consists of (δ), 4.46 (S, 3H), 7.35 (d, 1H, J≏10 Hz), 8.22 (m, 3H), 8.66 (m, 3H), 8.88 (d 1H, J≏2 Hz), 9.19 (d, 2H, J≏6 Hz). The spectrum is duplicated by that of a 1:1 mixture of N-methylpyridinium chloride and 2,4-dinitroaniline.

A solution of 200 mg of 93 in 25 ml of DMSO was heated at 70° for 48 hrs. The solvent was removed by evaporation at reduced pressure, and the dark brown residue was triturated with anhydrous ethyl acetate. The insoluble residue, 73 mg, was purified by the tlc on silica gel PF_{254} using ethanol/ethyl acetate (1:1) as eluant. A yellow solid, 50 mg; 68%; m.p. 107-108° [Lit.[51] m.p. 110-112°C]; nmr (δ, DMSO-d_6), 4.43 (s, 3H), 8.21 (t, 2H, J≏7 Hz) 8.67 (t, 1H, J≏7 Hz), 9.15 (d, 2H, J≏7 Hz) was obtained. The nmr spectrum was identical with that of an authentic sample of N-methylpyridinium iodide obtained from the reaction of pyridine and methyl iodide.

The ethyl acetate solution from above was evaporated giving 90 mg of a dark brown liquid. This was not purified further since its

nmr spectrum, (DMSO-d_6, δ) 6.55 (d, 1H, J≐10 Hz), 8.09 (d of d, 1H, J≐10, 2 Hz), 8.71 (d, 1H, J≐2 Hz), 8.39 (broad, 2H), was identical with that of an authentic sample of 2,4-dinitroaniline.

Reaction of 42 in Acetic Acid-d_1. A sample, 40 mg, of 42, was heated at 70° for ten hrs. in 5 ml of acetic acid-d_1 containing 52 mg of deuterosulfuric acid. The mixture was treated with 860 mg of sodium acetate and the precipitated sodium sulfate was removed by filtration. After the acetic acid had been evaporated in vacuo, the red brown residue was trituated with ether. The insoluble solid, 22 mg; 89%, exhibited an nmr spectrum (DMSO-d_6, δ) showing bands at 7.87 (2 peaks, 5H), 8.85 (s, 1H). 9.43 (s, 2H). Evaporation of the ether solution gave 13 mg (87%) of aniline, nmr (DMSO-d_6)δ, 6.66 (m, 3H), 7.10 (t, 2H).

N-Phenyl-3,5-diacetylpyridinium Chloride (98). A sample, 100 mg, of 42 in 10 ml of 0.1069 M sulfuric acid in acetic acid containing 1.0% of acetic anhydride was heated at 55° for ten hrs. To this was added 87 mg of sodium acetate, the precipitated sodium sulfate was removed and the solvent evaporated in vacuo. The residue was triturated with ether, and insoluble material was chromatographed (tlc) on silica gel PF 254 using ethanol/ethyl acetate (1:1) as eluant. Two fractions were obtained. The high R_f fraction was a white solid, m.p. 111°; nmr (DMSO-d_6) δ, 2.39 (s, 3H), 7.37 (t, 1H, J≐7 Hz), 7.65 (t, 2H, J≐7 Hz), 7.95 (d, 2H, J≐7 Hz), 10.25 (broad S, 1H)

whose nmr spectrum was identical with that of acetanilide.

The lower R_f fraction was a light brown solid, nmr (DMSO-d_6) δ, 8.06 (m, 3H), 8.24 (m, 2H), 9.16 (s, 1H), 9.24 (s, 2H), 9.38 (s, 1H); ir (KB_r), 1690, 1575, 1420, 820 and 755 cm^{-1}.

Proton Exchange in 42

With TFA-d_1. The nmr sample was prepared by dissolving 10 mg of 42 in ca. 1.5 ml of TFA-d_1 at -15°C. The spectrum was run at -12°C, 7.14 (m, 10H). 7.54 (s, 1H), 7.84 (s, 2H). The triplet at 6.18 in the nmr spectrum of 1 was completely absent. After the sample had been stored in the refrigerator for 24 hrs., the nmr spectrum was run again, 7.34 (s, 5H) 7.52 (m, 5H), 8.56 (s, 1H), 8.77 (s, 2H).

With DMSO-d_6 and TFA-d_1. A sample of 42 in DMSO-d_6 containing 20% TFA-d_1 was prepared at -10° and its nmr spectrum was monitored in the region near 6.54 at regular intervals at 24°C. Using the ten aromatic protons as an internal standard the rate of disappearance of the triplet at 6.54 was measured. The rate was first order with a rather rough k equal to 1.5×10^{-5} $sec.^{-1}$.

Proton Exchange in 93. A solution containing 300 mg of 93 in 5 ml of TFA-d_1 was stirred at 24° for 24 hrs. The solvent was evaporated under reduced pressure, and the residue was triturated repeatedly with dry ether. The insoluble red crystals were dried

in vacuo, nmr (TFA-d_1) δ, 7.49 (m, 1.5H), 7.69 (s, 1H), 7.81 (s, 0.5H), 7.99 and 8.04 (two s, 1H) 8.36 (d, 1H J≃9 Hz) and a doublet at 9.03 (d, J≃2 Hz). After ten days at 24° in TFA-d_1 the sample exhibited an identical nmr spectrum.

The crystals above were also studied in DMSO-d_6, 3.19 and 3.29 (two s, in 60:40 ratio, 3H), 7.54 (s, 0.6H), 7.73 (s, 0.4H), 7.83 (d of d, 1H, J≃10 Hz), 8.17 (d, 1H), 8.31, 8.37, 8.47 (three s, 2H), 8.78 (d, 1H, J≃2Hz). After the solution had been stored at 24° for 24 hrs. the spectrum showed 8.34 (d, 1H, J≃9 Hz), 8.86 (s overlapping d of d, 2H, J≃9, 2 Hz), 9.33 (s, 2H). This spectrum matches that of 2,4-dinitrophenyl-3,5-d_2-pyridinium chloride.

Time Dependent NMR Spectrum of 42. A sample of 42 in TFA was prepared at 0°. The nmr spectrum of the solution was run at 33° and showed 6.18 (t, weak signal, ca. 5% of normal), 7.17 (m), 7.33 (s), 7.52 (m), 7.87 (d, weak signal), 8.10 (t, J≃7 Hz), 8.58 (t, J≃7 Hz), 8.79 (approx. d, J≃6 Hz). After five hrs. at 24° the sample was again examined by nmr, 7.33 (s, 5H), 7.52 (m, 5H), 8.10 (t, 2H J≃7 Hz), 8.58 (t, 1H, J≃7 Hz), 8.79 (d and broad signal, 4H, J≃6 Hz). The uv max (TFA) was 480 nm at the five hr. After five days at 24° the sample was again examined in the nmr and the above spectrum was again noted except that the bands were much sharper and better resolved. The color of the nmr sample was initially red brown. It remained the same at five hrs., but after five

days the color was light yellow and the uv max. at 480 nm had disappeared.

A second sample of 42 in TFA prepared at 0° showed that the 6.18 triplet and the 7.87 doublet disappeared after ten mins. at 33°. A portion of the nmr sample was diluted then and the region from 320-720 nm was scanned. Absorbance at 480 nm only was observed.

A sample (8 mg) of 42 was dissolved at -15° in a mixture of 70 mg of TFA and 3 mg of anhydrous tetramethylammonium chloride. This sample was placed in the nmr probe at 0° and the spectrum was taken at intervals. The triplet (2H) at 6.18 disappeared at a first order rate ($k \triangleq 1.5 \times 10^{-4}$). A second run using sealed nmr tubes at 5.5° in a thermostatted bath and nmr examination at -10° gave the first order rate of 2.64×10^{-4} sec.$^{-1}$.

Attempted Trapping of Intermediate in Reaction of 42. A solution of 10 mg of 42 in 1 g of TFA was allowed to stand at 24° for 15 min. The solvent was evaporated under vacuum at -10°, and the dark red-brown solid was examined spectroscopically, nmr (DMSO-d_6) , 6.33 (t, $J \triangleq 12$ Hz), 7.41 (s), 7.69 (m overlapping broad s), 8.29 (t, 8.29 (t, $J \triangleq 6$ Hz), 8.55 (d, $J \triangleq 12$ Hz), 8.77 (t, $J \triangleq 7$ Hz), 9.32 (d, $J \triangleq 6$ Hz); ir (Nujol) 1780 [liter.[8] 1790-1830 for TFA].

Reaction of 2,4-Dinitrophenylpyridinium Chloride (40) with Methylamine. A solution containing 40.5 mg (1.42×10^{-4} mole) of 2,4-dinitrophenylpyridinium chloride (40) and 14.3 mg (1.25×10^{-4}

mole) of TFA in 1 ml of DMSO was mixed with 0.05 ml of 2.46 N (1.23×10^{-4} mole) of methylamine in DMSO. The original light yellow solution turned bright red and this solution was examined immediately by nmr. The spectrum indicates the presence of 2,4-dinitrophenylpyridinium chloride (40) along with a small amount of 93. Addition of a second portion (1.23×10^{-4} mole) of methylamine followed immediately by an nmr scan showed that the mixture contained approximately a 1:1 ratio of the 2,4-dinitrophenylpyridinium chloride (40) and 93. The spectrum is essentially identical with that of 93 in DMSO-d_6 after standing 24 hrs. at room temperature.

This sample was sealed in the nmr tube and was heated for 20 hrs. at 70°. NMR examination then indicates that the mixture contains N-methylpyridinium chloride (94), 2,4-dinitroaniline (95) and 2,4-dinitrophenylpyridinium chloride (40). Since the 9.45 band (2H) for 2,4-dinitrophenylpyridinium ion, and the 4.46 band (3H) for N-methylpyridinium ion do not overlap any other peaks in the spectrum integration indicated a 2:1 ratio of the methyl- to the 2,4-dinitrophenylpyridinium ions. Addition of one further portion (1.23×10^{-4} mole) of methylamine followed by heating at 70° for 48 hrs. gave two final products, nmr (DMSO) δ 7.32 (d, 1H), 8.29 (m, 3H), 8.72 (t, 1H), 8.87 (d, 1H), 9.17 (d, 2H), 4.47 (s overlapping broad s).

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