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Competition Between Concerted and Biradical Diels-Alder Reactions

A thesis presented

by

Jacques Jean-Benoit Mallet

to

The Department of Chemistry

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

May, 1972

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To Jeannette

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Acknowledgment

I wish to express my profound gratitude to Professor Paul D. Bartlett for the role he played in the investigation to be described. His advice and guidance were invaluable. Among his gifts is also the ability to inspire a student to do better, a desire born of his example, his patience and confidence in the student.

I also wish to acknowledge my indebtedness and to express my thanks to the members of the Department of Chemistry, particularly the occupants of the third floor of Converse who made my stay in Cambridge so profitable and enjoyable

Professors Jean-Marie Lehn and Lionel Salem for having kindly agreed to be on my thesis committee

David Lang for the photographic and artistic work

Thomas Ormond for having proofread sections of this thesis

Dr. Xavier Chapuisat for his assistance, kind friendship and provocative discussions about chemistry

And above all I am very grateful to my wife for her constant encouragement.

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TABLE OF CONTENTS

CHAPTER I. Introduction 1

I-1. Concerted 2 + 4 Cycloaddition Reactions . . . 5

I-2. Biradical 2 + 2 Cycloaddition Reactions . . . 15

I-3. Competition Between 2 + 2 and 2 + 4 Cycloaddition Reactions. 23

CHAPTER II. Results and Discussion 32

II-1. Introduction 32

II-2. Cycloaddition of 1, 1-Dichloro-2, 2-Difluoroethylene and trans, trans-2, 4-Hexadiene. . 32

II-3. Cycloaddition of 1, 1-Dichloro-2, 2-Difluoroethylene and cis, trans-2, 4-Hexadiene . . . 50

II-4. Photosensitized Cycloaddition of 1, 1-Dichloro-2, 2-Difluoroethylene and 2, 4-Hexadiene 53

II-5. Scale Model Study of a Biradical Diels-Alder Reaction. 55

II-6. Cycloaddition of cis- and trans-1, 2-Dichloro-1, 2-Difluoroethylene 60

A. Butadiene. 60

B. trans, trans-2, 4-Hexadiene 72

II-7. Discussion. 86

II-8. Conclusion 92

CHAPTER III. Experimental. 94

APPENDIX NMR and IR Spectra 113

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CHAPTER I

INTRODUCTION

The family of organic reactions known as cycloadditions was drawn into the mainstream of chemical research by the extensive work of Otto Diels and Kurt Alder.[1] The remarkable versatility of these reactions has served the synthetic chemist with a valuable tool and the intricacies of their mechanisms have fascinated the physical organic chemist. Few developments, in this century have stimulated more chemical research or speculation.[2,3]

Interest in the detailed course of cycloaddition during the last three decades has centered around the question of simultaneous versus sequential bond formation. As in many other fields the mechanistic interpretation of these reactions has lagged behind the accumulation of experimental data and it was not until 1965 that the plethora of facts was successfully unified. In that year, Woodward and Hoffman propounded their fundamental theory[4] of conservation of orbital symmetry, firmly based upon the principles of quantum mechanics and group theory, which tied together for the first time information pertaining not only to cycloadditions but also to many related reactions. So

---

[1] O. Diels and K. Alder, Liebigs Ann, Chem. 98, 460 (1928).

[2] R. Huisgen, R. Grashey, and J. Sauer in S. Patai: The chemistry of Alkenes. Interscience, New York, 1964, page 739.

[3] A. Wassermann, "Diels Alder Reactions," Elsevier, New York, (1965).

[4] R. B. Woodward and R. Hoffman, J. Am. Chem. Soc., 87, 395, 2046, 2511, 4388, 4389 (1965).

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consistent has been the theory with newly uncovered facts[5] that it has already achieved acceptance as an established principle of chemistry.[6]

To present the principle of conservation of orbital symmetry in detail here would be redundant in view of its recent comprehensive definition by the authors.[7] Rather I should like to limit consideration to conclusions gained from the principle, particularly those shedding light on the question of simultaneous versus sequential bond formation. Figure 1, in which the relative energy inputs for different modes of reactions of a simple alkene and a simple diene are plotted against the "reaction co-ordinate," will serve that purpose.[8]

As shown, a diene is more stable in the S-trans conformation but it is only by acquiring its S-cis conformation that it will be able to react with the alkene through the low-lying transition state proper to the concerted 2 + 4 cycloaddition.[9] A two-step reaction, which can in addition give rise to a four membered ring, requires a higher energy of activation and appears therefore less likely.

---

[5]For example, J. S. Berson, Accounts Chem. Res. 1, 152 (1968); R. Huisgen, W. Scheer and H. Huber, J. Am. Chem. Soc. 89, 1753 (1967); G. H. Whitman and M. Wright, Chem. Commun., 1967, 294.

[6]For example, Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller, and A. Eschenmoser, Angew. Chem. Internat. Edit. 8, 343 (1969).

[7]R. B. Woodward and R. Hoffman, Angew. Chem. Internat. Edit. 8, 781 (1969).

[8]P. D. Bartlett, Quart. Rev. 24, 473 (1970).

[9]We will not consider here the concerted $\pi_S^2 + \pi_A^2$ mechanism which for normal olefin would present insurmountable difficulties due to steric hindrance factors. See reference 7.

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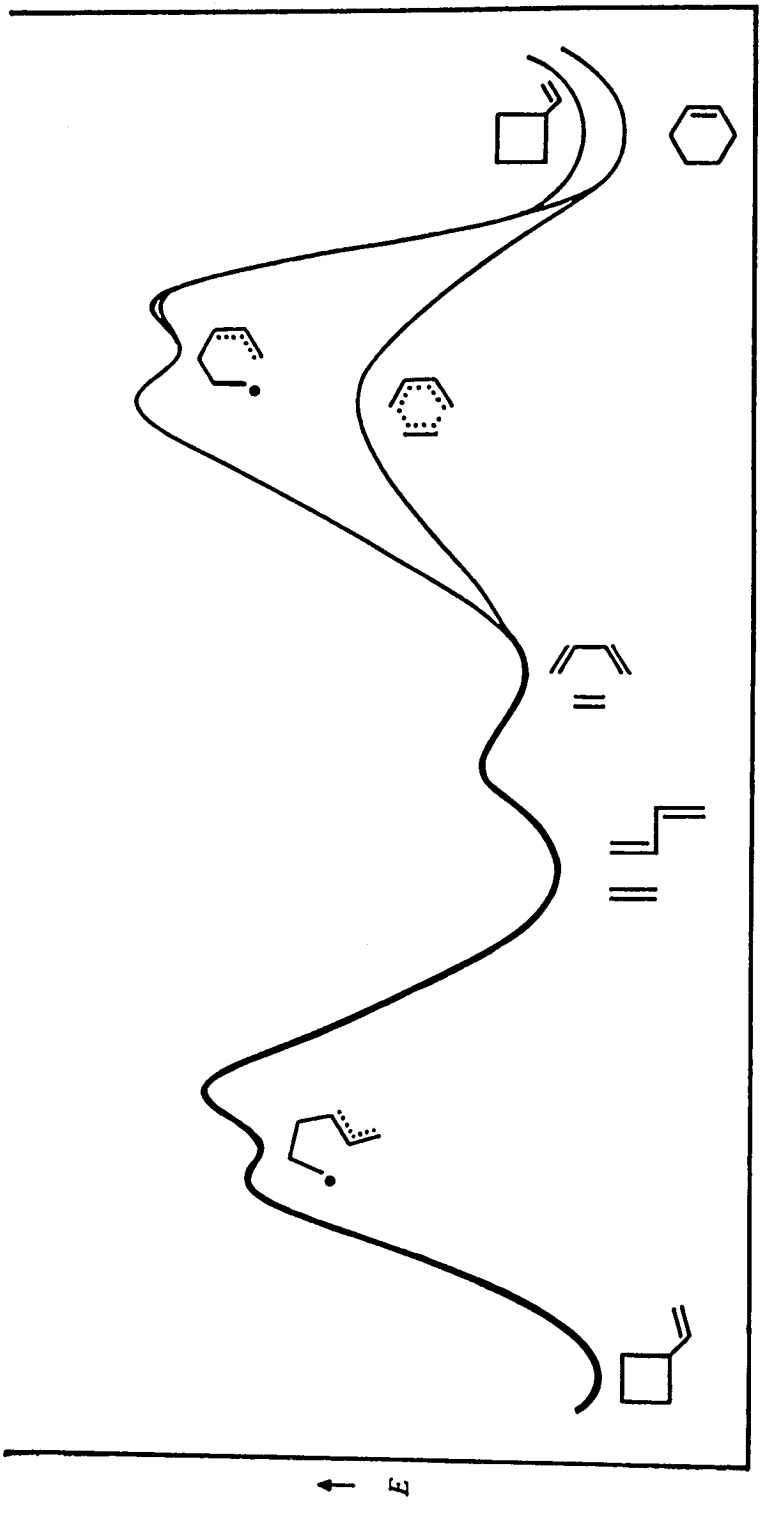

Figure 1 (8)

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Nevertheless, if by any means the transition state of the two-step cycloaddition becomes lower than the one of its competing Diels-Alder cycloaddition, we may expect to obtain four membered ring products from the reaction. This is the case of fluoroalkenes which exhibit dimerization and 1,2 addition with dienes.[10]

Thermodynamical studies show that fluoroalkenes are much less stable than other alkenes, and this destabilization is held responsible for the biradical behavior.[11]

Although formation of cyclobutanes is the rule with fluoroalkenes, in some instances 2 + 4 cycloadditions do occur and it has not been unambiguously established what mechanism is operating. This lack of information constituted the impetus for this thesis.

In considering how to approach that problem it appears germane to point out and discuss the salient features attendant upon both Diels-Alder and biradical mechanisms.[12]

---

[10] J. D. Roberts and C. M. Sharts, Organic Reactions, 12,1 (1962) P. D. Bartlett, Science, 159, 833 (1968).

[11] R. C. Wheland, Ph. D. Thesis, Harvard University, 1970.

[12] The cycloadditions we will be dealing with are not solvent dependent; therefore the two-step dipolar mechanism is not relevant to our work and will not be presented here. For a discussion on cycloaddition via Dipolar Ion see reference 8 page 475.

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PART I. Concerted 2 + 4 cycloaddition reactions.

Reviews dealing with particular aspects of this reaction such as synthesis,[13a] stereochemistry,[13b] substituents effects,[13c] mechanism,[13d] retro-addition,[13e] M. O. Theory,[13f] are available. Consequently we shall only emphasize those aspects which we feel have some bearing on the question of concerted versus sequential bond formation.

If a synchronous formation of the bonds occurs between the two components in a one step reaction, the configuration of the substituents in the dienophile and in the diene should be preserved. As illustrated in the case of the isomeric β-cyano-acrylates, cis and trans dienophiles react with dienes to give 1, 1 adducts in which the cis and trans arrangement is retained.[14]

Similarly the principle applies to the diene components.[13b] For example, trans 1, 4 diphenylbutadiene cycloadds maleic anhydride to give the adduct 3 in which the two phenyl groups are cis to each other.[15]

---

[13](a) J. Sauer, Angew. Chem. Internat. Ed. Eng., 5, 211 (1966).
(b) J. C. Martin and R. K. Hill, Chem. Rev., 61, 537 (1961).
(c) Y. A. Titov, Russian Chem. Review, English Translation, 31, 267 (1962).
(d) J. Sauer, Angew. Chem. Internat. Ed. Eng., 6, 16 (1967).
(e) H. Kwart and K. King, Chem. Rev., 68, 415 (1968).
(f) A. Streitwiesser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, 1961, p. 432.
(g) M. Dewar, 'The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, Inc., 1969, p. 316, 428.

[14]J. Sauer, H. Wiest and A. Mielert, Chem. Ber., 97, 3183 (1964).

[15]K. Alder and M. Schumacher, Liebigs Ann. Chem. 571, 87 (1951).

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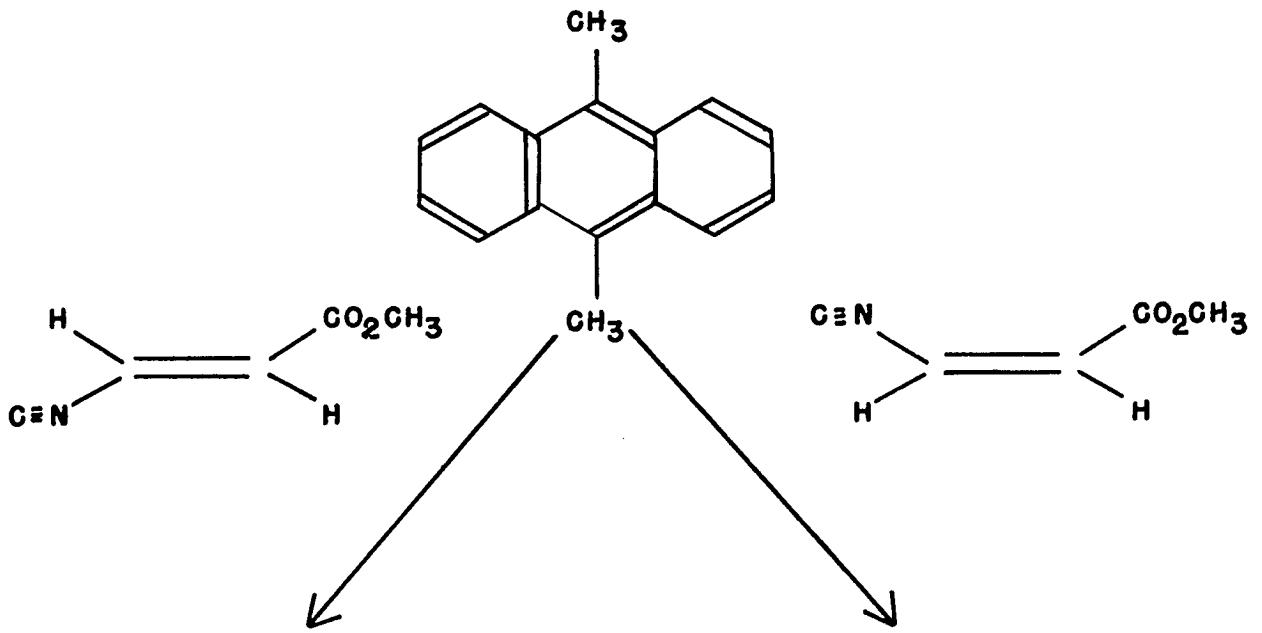

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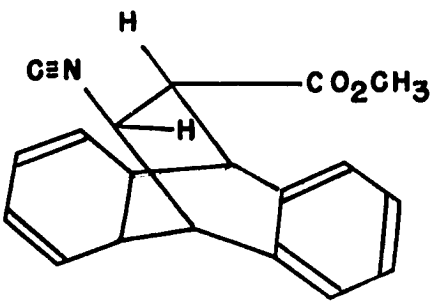

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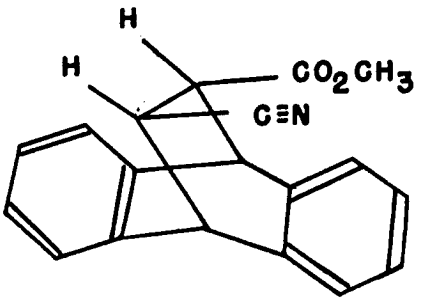

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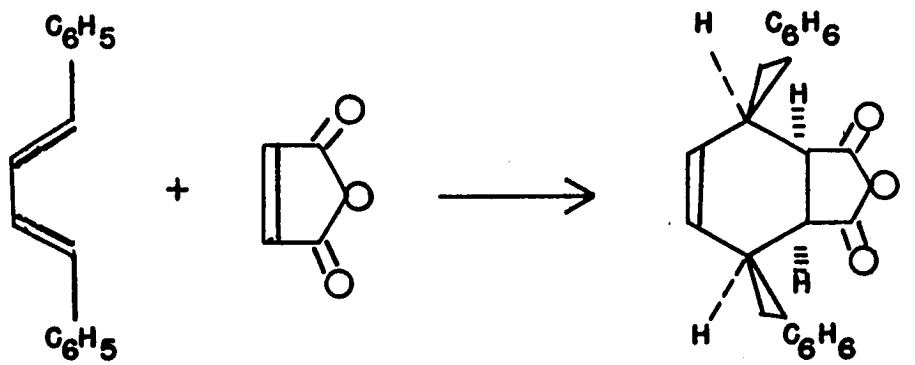

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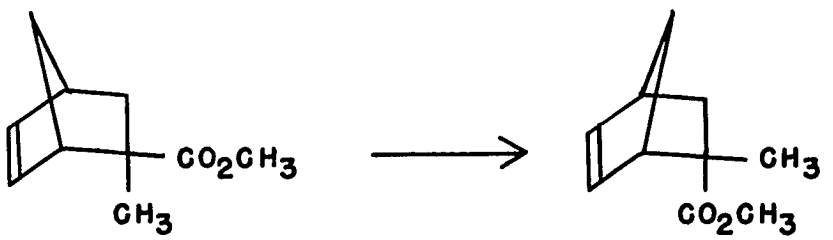
Further the fact that the isomerisation of 4 to 5,[16] 6 to 7[17] and 8 to 9,[18] all go by complete dissociation and recombination is entirely in consonnance with the concerted nature of the formation or breaking (principle of microscopic reversibility) of the bonds between the two components.



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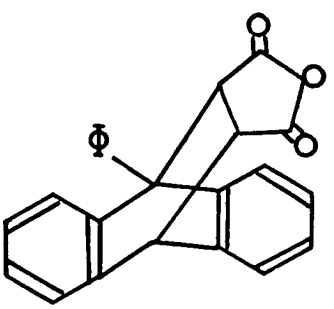

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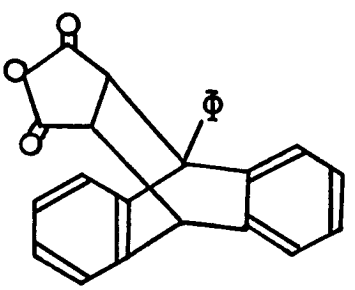

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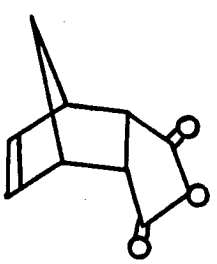

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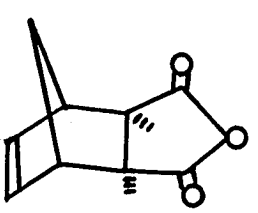

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A cycloaddition can still be concerted even though there might be considerable asymmetry in the rate at which the different newly formed bonds are established. Such a reasoning was put forward by Woodward and Katz in 1959.[19] They suggested the possibility that a second low energy barrier will be involved in some specific cases and not in others. More recently, Salem, using his intermolecular orbital theory of interaction between conjugated systems[20] supported this hypothesis.[21]

Should there be inequality in the rates of bond formation, one may then expect the transition state to have a partially polar and/or radical character.[22]

The intervention of dipolar species is ruled out according to studies concerning solvent effects.[23] For example the rate of cyclopentadiene dimerization increases threefold on going from benzene to

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[16](a) J. A. Berson and A. Remanick, J. Am. Chem. Soc. 83, 4947 (1961).
(b) J. A. Berson, A. Remanick and W. A. Mueller, ibid., 82, 5501(1960)

[17]J. A. Berson and W. A. Mueller, ibid., 83, 4940 (1961).

[18]C. Ganter, U. Scheidegger, and J. D. Robert, ibid., 87, 2771 (1965).

[19]R. B. Woodward and T. J. Katz, Tetrahedron, 5, 70 (1959).

[20]L. Salem, J. Am. Chem. Soc., 90, 543 (1968).

[21]L. Salem, ibid., 90, 553 (1968).

[22]In singlet system, unlike triplet system, partial homolytic and partial polar character can coexist. For a discussion of the electronic properties of diradicals see: L. Salem and C. Rowland, Angew. Chem. Internat. Ed. Eng., 11, 92 (1972).

[23](a) H. Kaufmann and A. Wassermann, J. Chem. Soc. 78, 2101 (1956).
(b) A. Wasserman, J. Am. Chem. Soc., 870 (1939).
(c) M. Ahmad and J. Hamer, J. Org. Chem., 31, 2831 (1966).

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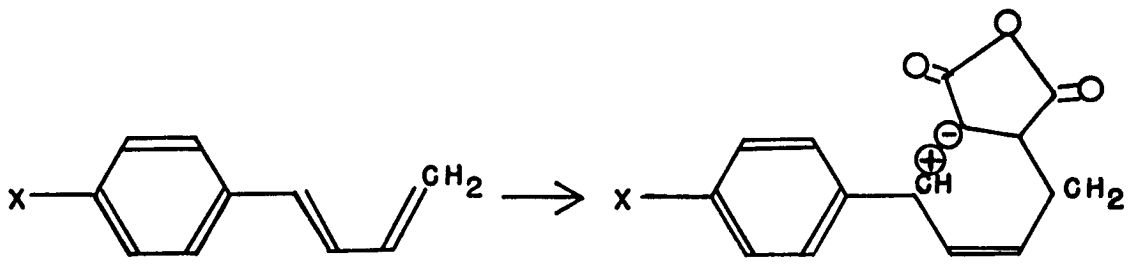
ethanol,[23a] and the rate of addition of cyclopentadiene to benzoquinone increases ten fold on going from n-hexane to ethanol.[23b] In fact there is little variation in rate between vapor and solution phases indicating that the dipolar contribution requiring solvation is minimal.[24]

This is consistent with the study of the effects of substituents on the dienes and on the dienophiles on the rate of the reaction. These



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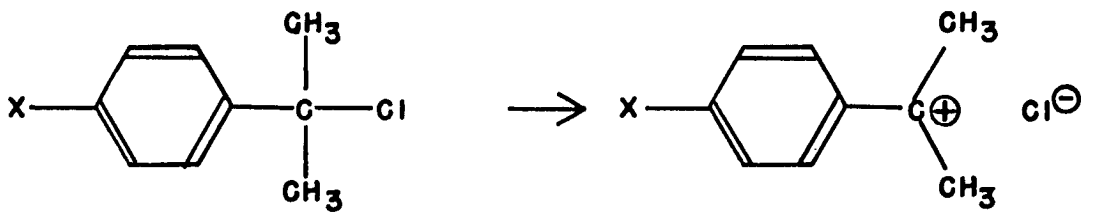

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[23](d) P. Brown and R. C. Cookson, Tetrehedron, 21, 1977 (1965).
(e) M. J. S. Dewar and R. Scott Pyron, J. Am. Chem. Soc. 92, 3098 (1970).

[24](a) Wassermann, J. Am. Chem. Soc., 1028 (1936).
(b) Wassermann, Trans. Faraday Soc., 34, 128 (1938).

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effects are much too small for a rate determining transition state that corresponds closely to a zwitterion intermediate. Thus replacement of CH_3O by NO_2 in the reaction of p-substituted 1-phenyl-butadienes 10 with maleic anhydride, only decreases the rate by a factor of 10.[25] On the other hand, the rate of solvolysis of p-substituted α,α-dimethybenzyl chlorides 12 to give the ion pair decreases to 7.6×10^{-8} of the original value when the p-NO_2 compound is used instead of the p-CH_3O.[26] Quantitative treatment using the Hammett equation corroborates these findings. ρ values are always low which is in good accord with very small partial charge development in the transition state.[27] Nevertheless, in some instances the use of σ^+ fits best the results as in the case of the addition of acylated dienes or dienophiles[27f] on the other hand, σ^- is more appropriate in the reactions of tetraphenyl cyclopentadienone with esters of substituted phenyl propiolic acid.[27b] Those facts are not bewildering when one recalls that the purely free radical decomposition of substituted t-butyl phenylperacetates shows a $\rho\sigma^+$ ($\rho = 1.20$) correlation with a 40 fold rate difference between p-MeO and p-NO_2.

---

[25] E. J. Dewitt, C. T. Lester, and G. A. Ropp, J. Am. Chem. Soc., 78, 2101 (1956).

[26] H. C. Brown and Y. Okamoto, J. Am. Chem. Soc., 72, 1913 (1957).

[27] (a) I. Benghiat and E. I. Becker, J. Org. Chem., 23, 885 (1958).
(b) D. N. Mathews and E. I. Becker, J. Org. Chem., 31, 1135 (1966).
(c) G. Kresze, J. Firl, H. Zimmer and U. Wollnik, Tetrehedron, 20, 1605 (1964).
(d) J. Hamer, M. Ahmad and R. E. Holiday, J. Org. Chem., 28, 3034 (1963).
(e) M. Ahmad and J. Hamer, ibid., 31, 2829, 2831 (1966).
(f) Y. Ohamoto and H. C. Brown, J. Org. Chem., 22, 485 (1957).

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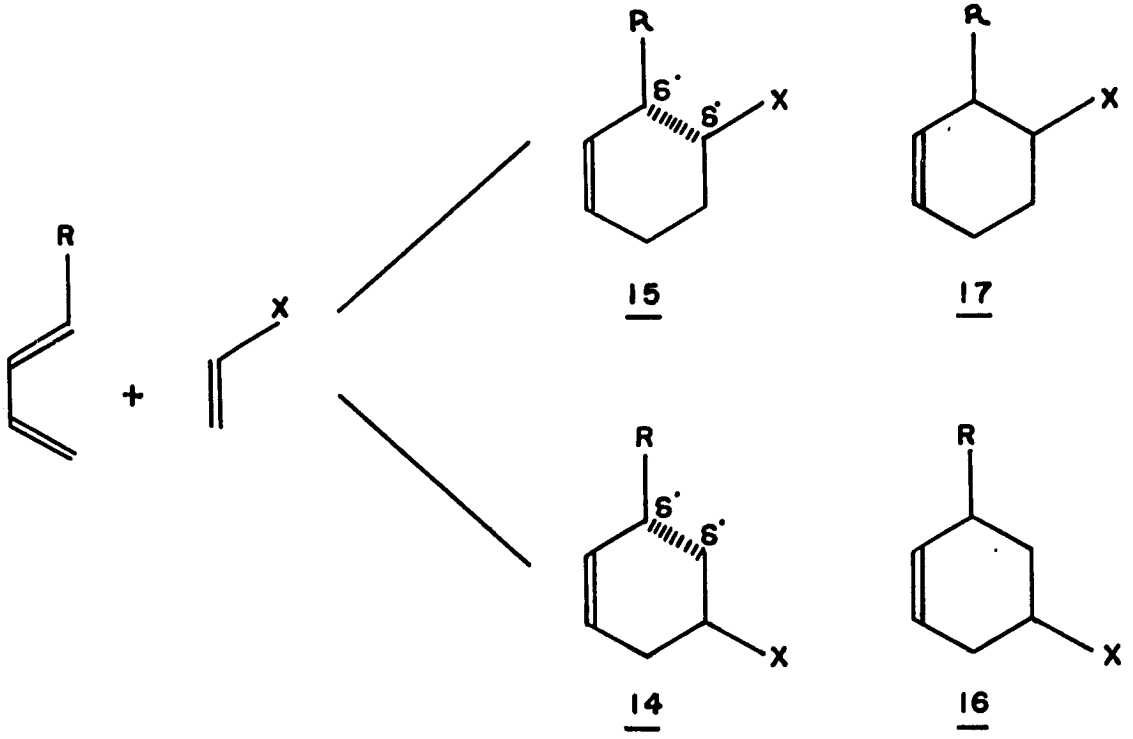
Clearly the above cogent examples militate against the development of a partial polar character in the transition state of the Diels-Alder reactions. On the other hand, the development of a partial homolytic character[28] agrees with experimental evidence. First, radical processes show no solvent effect and are independent of the polarity of the reactants. Further the homolytic concept can accommodate the structural directivity in cycloadditions. For example, let us consider the condensation of 1-substituted dienes with unsymmetric dienophiles. Two intermediates 14 and 15 can be envisaged. The latter, a bisecondary biradical-like intermediate, is more stable than



[28]Perhaps, the designation "Quasi-homolytic" would be better. A homolytic transition state can have some zwitterionic character which could account for the aforementioned facts.

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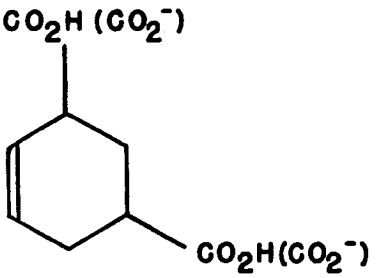
the former which is a "primary, secondary biradical" - like intermediate. Consequently 17 should be formed preferentially as it is actually observed. These orienting forces are nevertheless relatively weak as is clearly shown by the influence of steric factors or Coulomb repulsion. As a case in point the anion of trans-butadiene-1-carboxylic acid and acrylic acid give equal amounts of 18 and 19 whereas the free carboxylic acid gave only 19.[13d] In addition, it should be pointed out, that through the language of Molecular Orbital theory, one can also regard these regioselectivities within the concerted mechanism.[13f,g]



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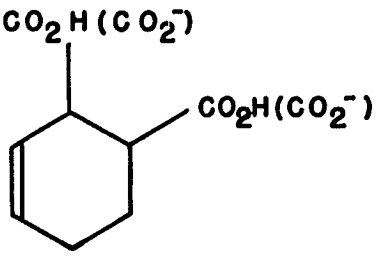

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Finally substituents have a great effect on reaction rates. It was recognized earlier, that the reaction rate of Diels-Alder reactions has increased by electron donating substituents (e.g., $N(CH_3)_2$, OCH_3, CH_3) in the diene and by electron attracting substituents ($C\equiv N$, CO_2CH_3, CHO, NO_2) in the dienophile. Those facts, supplemented by the transient color formation often observed during cycloadditions led Woodward to propose in 1942 that the first step in the Diels-Alder reaction is the formation of a polar aggregate.[29] These

[29] R. B. Woodward, J. Am. Chem. Soc., 64, 3058 (1942).

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characteristics are still cited as evidence that the reaction may go through a charge transfer complex.[30]

Konovalov corroborated this scheme by showing the existence of a linear relationship between the ionization potentials of a series of polynuclear hydrocarbons and the log of their reaction rates with maleic anhydride.[31]

The idea of electron transfer is also in agreement with the striking fact that electron poor dienes react preferentially with electron rich dienophiles.[32] These cycloadditions are known as Diels-Alder reactions with inverse electron demand.

On the other hand, the fact that cis-1-substituted dienes do not form Diels-Alder adducts with tetracyanoethylene but do form charge transfer complexes as readily as dienes that form adducts, is unexplained.

More recently Woodward and Hoffmann,[33] from a consideration of symmetry elements and an extended Huckel calculation, have shown

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[30](a) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry", Holden-Day, San Francisco, 1964, pp. 177, 178.
(b) E. M. Kosower, "Progress in Physical Organic Chemistry", Vol. 3, Ed. S. G. Cohen, Interscience Publishers, New York, 1965, p. 81.

[31]A. I. Konovalov and V. D. Kiselev, Zh. Org. Chem., 2, 142 (1966).

[32](a) M. G. Romanelli and E. I. Becker, J. Org. Chem., 27, 662 (1962).
(b) H. Bluestone, R. Bimber, R. Berkey and Z. Mandel, J. Org. Chem., 26, 346 (1961).
(c) R. E. Blanks, A. C. Harrison, R. N. Haszeldine and K. G. Orrel, Chem Commun 1965, 41.
(d) J. Sauer and H. Wiest, Angew. Chem., 74, 353 (1962).

[33]R. Hoffmann and R. B. Woodward, J. Am. Chem. Soc., 87, 2046 (1965).

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that there is some charge transfer contribution in the transition state. However it is not quite clear why the solvent has so little effect on the rate of reaction.

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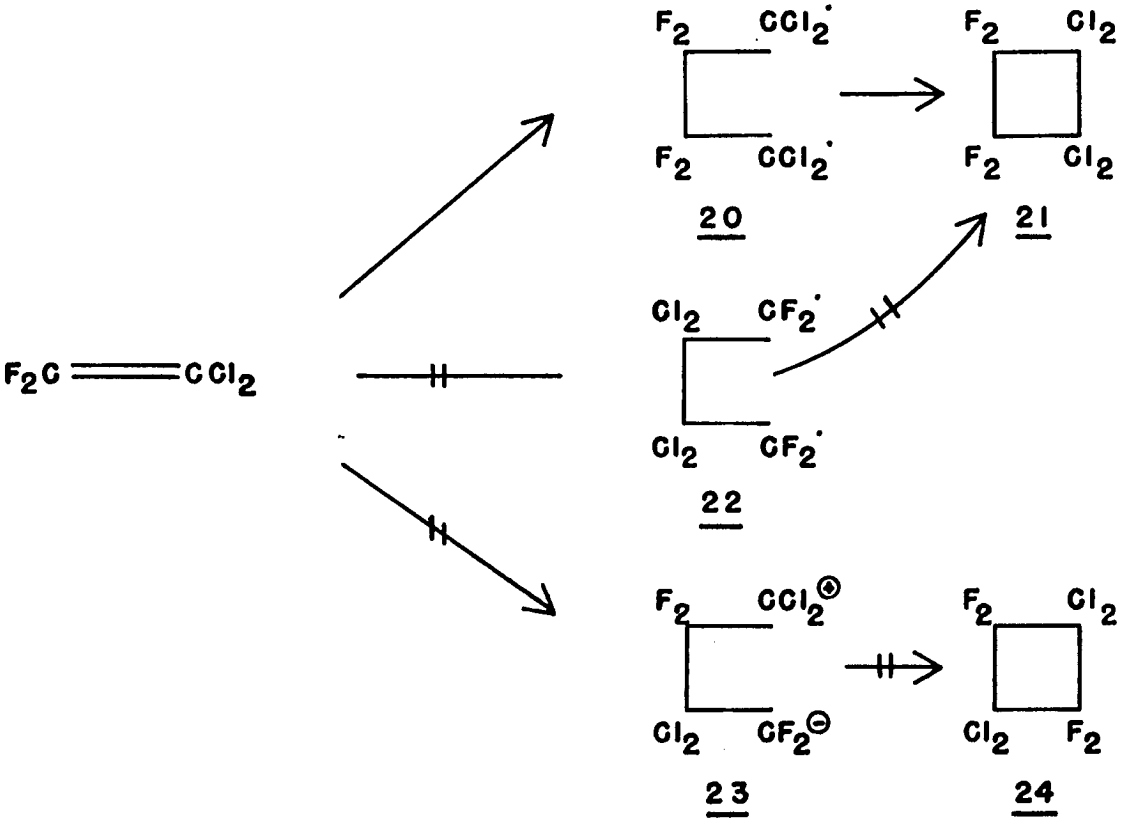
PART II. Biradical 2 + 2 cycloaddition reactions

At one limit, the lack of symmetry in the bond formation can be such as to give rise to biradical behavior. In this case the Woodward Hoffmann rules no longer apply and the formation of cyclobutane is then allowed.

As expected, the products arise from the most stable biradical. For example, 1, 1-dichloro-2, 2-difluoroethylene (hereafter called 1122) and chlorotrifluoroethylene dimerize by second order kinetics[34]



[34](a) B. Atkinson and M. Stedmann, J. Chem Soc., 512, (1962).
(b) J. R. Lacher, G. W. Thompkin and J. D. Park, J. Am. Chem. Soc., 74, 1693 (1962).

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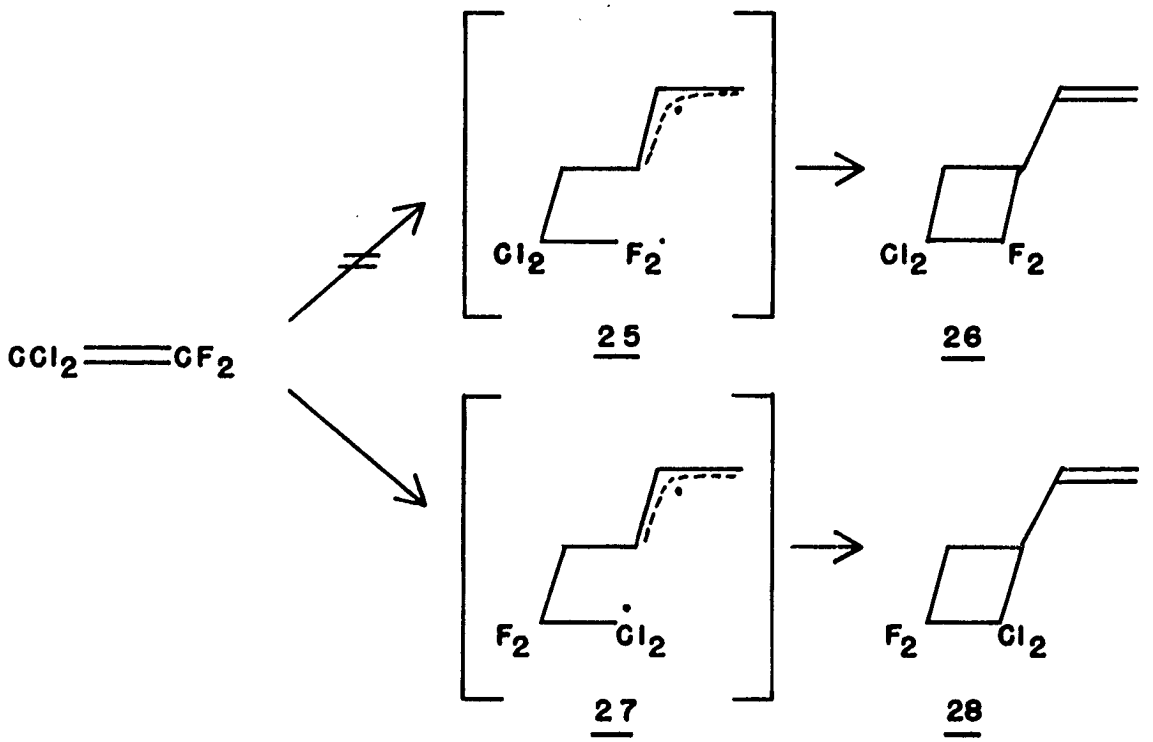
through an intermediate of type 20 rather than 22 since chlorine stabilizes a radical center roughly 4 kcal/mole more than does fluorine through the agency of its d orbitals.[35] In contrast, if a dipolar mechanism were operating, we should expect the formation of the head to tail dimer.

Recourse to the biradical theory also accounts well for the 1122 addition to butadiene where the biradical intermediate 27 is stabilized by a double bond and two chlorines. In that case Swenton studied the effect of the solvent on the rate of reaction and found only a three-fold



[35](a) Walling, "Free Radical in Solution", John Wiley and Sons, Inc., New York, 1957.
(b) F. W. Stacey and J. F. Harris, Jr., Org. Reactions, 13, 150 (1953).

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increase on going from methanol to nitromethane or hexane.[36] This behavior is in sharp contrast with the dipolar (2 + 2) addition observed with cyanoethylenes. As a case in point, the rate of cycloaddition of TCNE to p-methoxystyrene increases to 10^5 times on going from cyclohexane to nitromethane.[37]

Another compelling evidence of the presence of distinct biradical intermediate in fluoroalkene cycloaddition is inferred from the decisive experiment of Bartlett and coworkers where they allowed 1122 to react with the three isomers of 2-4 hexadiene.[38] For example, the addition of the trans, trans-2,4-hexadiene to 1122 gives rise to an initial biradical intermediate 29 that can either close to 30 or else rotate to a new biradical intermediate 31 before subsequent closure to 32. Similar results are obtained with the cis-trans- or cis-cis-2,4-hexadienes.

This loss of stereospecificity is also observed in the biradical addition of alkene to strained olefins as illustrated in the reaction of bicyclopentane and maleonitrile.[39]

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[36] J. S. Swenton, unpublished results.

[37] B. D. Kramer, Ph. D. Thesis, Harvard University, 1968.

[38] L. K. Montgomery, K. Schueller and P. D. Bartlett, J. Am. Chem. Soc., 86, 622 (1964).

[39] P. G. Gassmann, K. T. Mansfield and T. J. Murphy, J. Am. Chem. Soc., 91, 1684 (1969).

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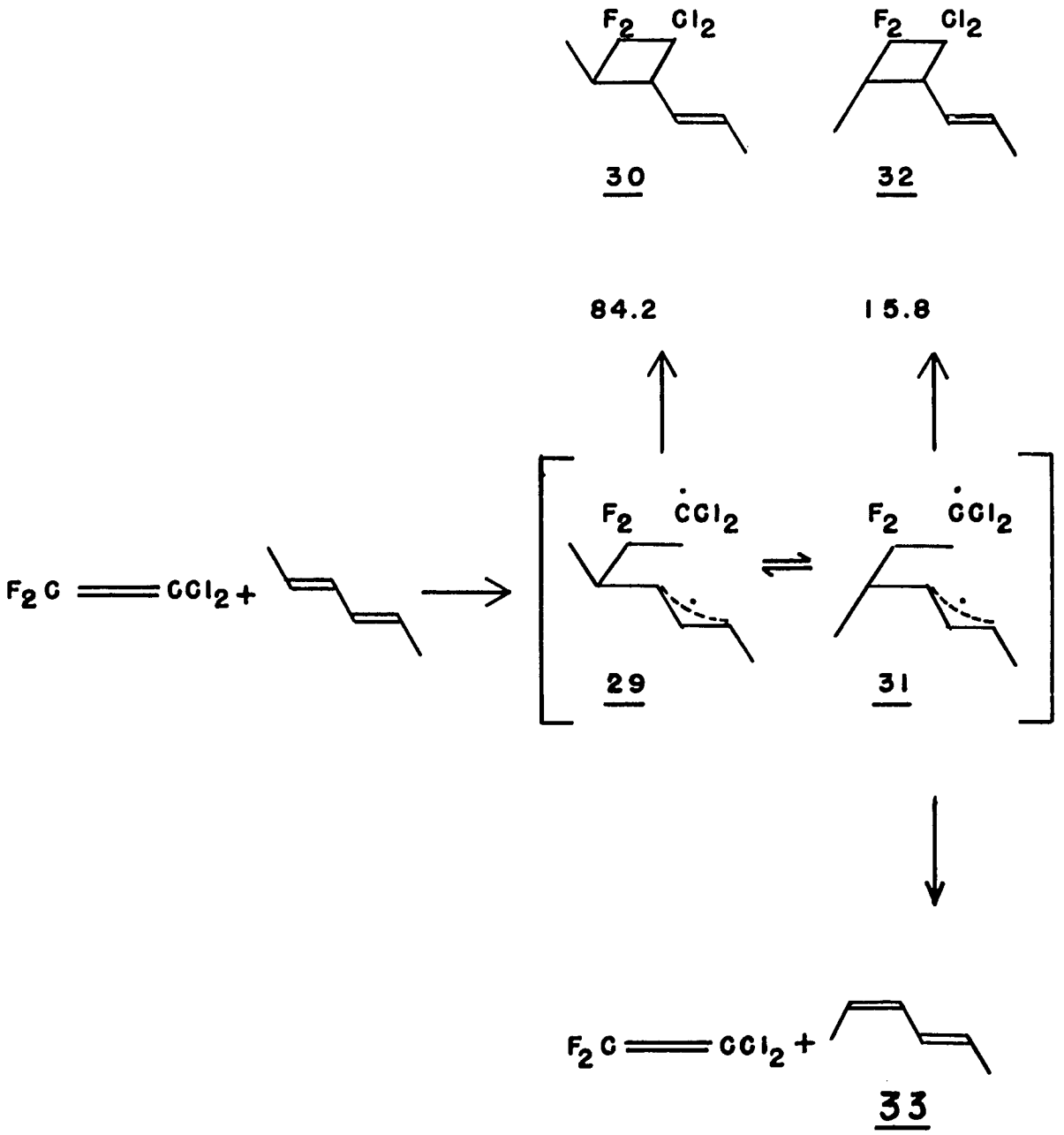

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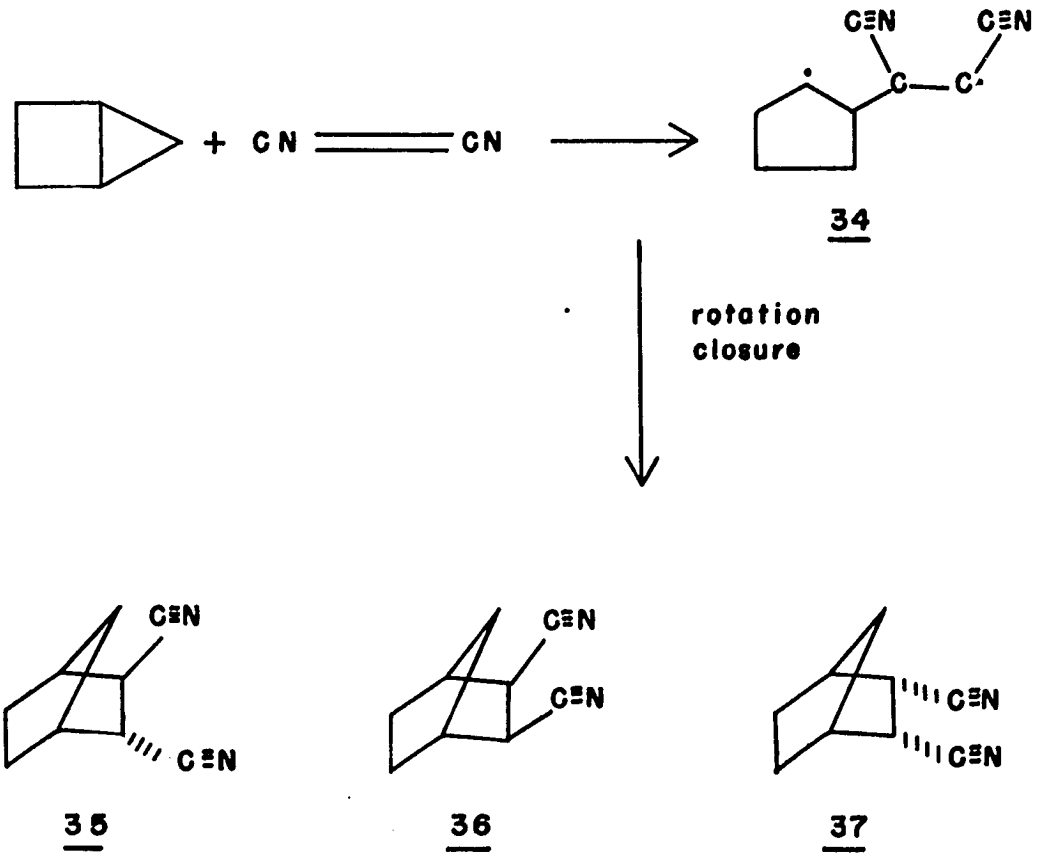
Also consistent with the mechanism at hand is the observation that biradical 31 undergoes β-scission to isomerized 2,4 hexadiene 33 with a cis double bond in place of the original trans.[40] A similar



[40] P. D. Bartlett, C. J. Dempster, L. K. Montgomery, K. E. Schueller and G. E. H. Wallbillich, J. Am. Chem. Soc., 91, 405 (1969)

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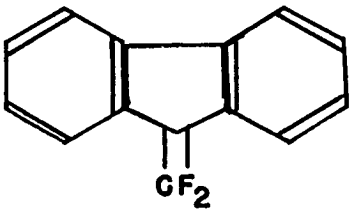
phenomenon has been encountered in the cycloaddition of 1122 to all three isomers of 1,4-dichlorobutadiene,[41] but not in the cycloaddition of tetrafluoroethylene to trans, trans-2,4-hexadiene, presumably as the result of the extreme C = C destabilization in tetrafluoroethylene.[40] Difluoromethylenefluorene 38 forms no addition products with trans,-trans-2,4-hexadiene, but after heating for forty two hours at 125° the starting material is 33% isomerized to cis,trans-2,4-hexadiene.



38

Apparently the diene adds to 38 to form a biradical intermediate in which rotation about the bond undergoing addition can take place. The fluorene group must hinder ring closure, so the intermediate reverts to partially isomerized starting materials.[42]

Thus far we have set forth criteria in support of the biradical mechanism such as orientation in products, absence of major solvent effects and loss of configuration in the products and in the recovered diene. Let us look now into the effect of substituents on the reaction and compare them with the concerted 2-4 cycloaddition.

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[41] P. D. Bartlett and G. E. H. Wallibich, J. Am. Chem. Soc., 91, 409 (1969).

[42] P. D. Bartlett and A. Wingrove, unpublished results.

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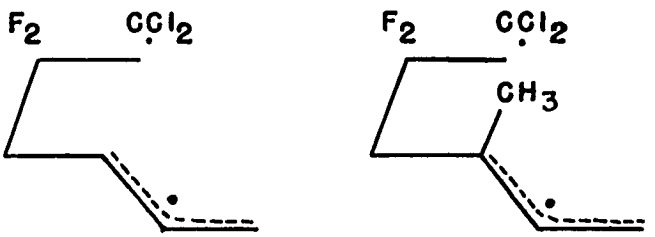
We have seen that chlorine can orient a cycloaddition due to its ability to stabilize free radicals; so can the methyl group through hyperconjugation. The stabilization of the biradical intermediate brings about the increase in the rate of cycloaddition. For example (see Table I), the addition of 1122 to butadiene is slower than its 1,2 addition to isoprene because 39 is less stable than 40.[43]



39 40

On the other hand, when a methyl group or a chlorine atom is so located that the intermediate in cycloaddition has no radical character at the position of substitution both substituents appear to have a depressive effect upon 1,2 addition with 1122. Furthermore, that depressing effect is not balanced by the presence of a methyl group at a site where it can stabilize the biradical intermediate as illustrated by the case of 2-4 hexadienes. This behavior is substantiated by recent findings[44] that tetrafluoroethylene adds, by way of a biradical, to ethylene ten times as fast as 2-butene. These results contrast sharply with the

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[43] P. D. Bartlett and L. K. Montgomery, J. Am. Chem. Soc., 86, 628 (1964).

[44] K. Hummel and S. Elliot, unpublished results.

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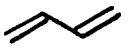
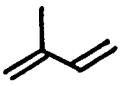
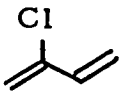
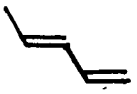
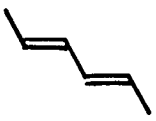
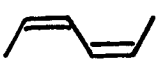
2-4 concerted mechanism in which the presence of methyl at the reactive center causes acceleration.[43]

Table I: Relative Rates of Cycloaddition[43]

Diene	1,2-	3,4-	cis	trans	Maleic anhydride (Diels-Alder reacn.) Craig 25°	Sauer
	1	1			1	1
	2.3	0.42			2.9	2.25
	1.2	0.30			0.14	0.10
	[0.053]	2.3			very small	
	[0.028]	1.65			4.8	3.3
	0.113	0.113				
				0.046		
			[0.087]	[0.064]		
			[0.12]			

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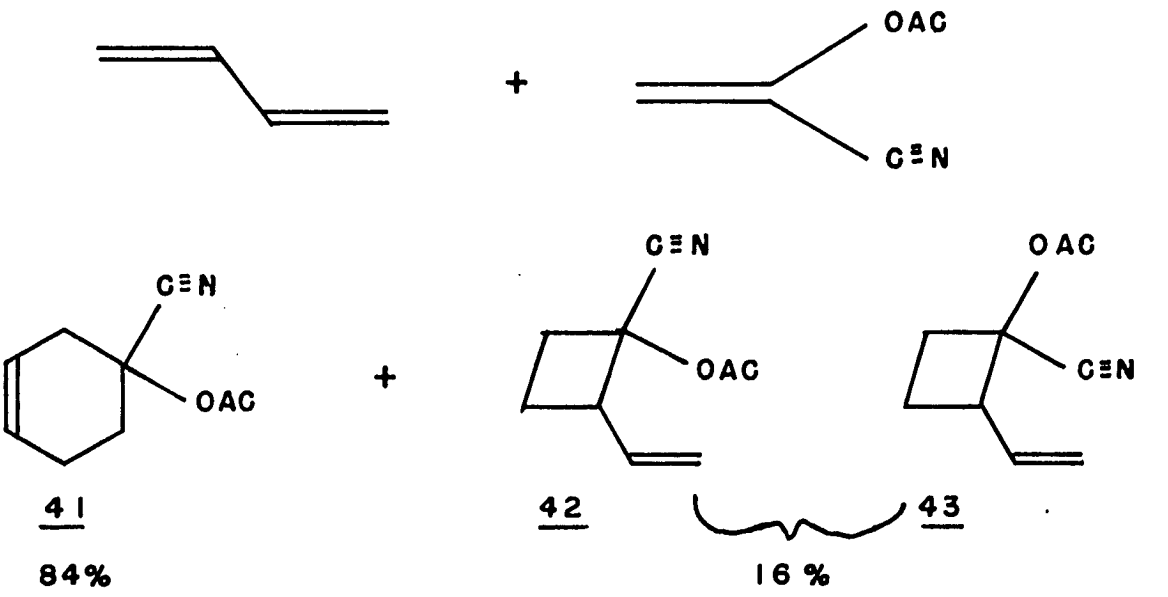
PART III Competition between (2 + 2) and (2 + 4) cycloaddition reactions

Most of the dienophiles can be classified in two groups according to their ability to lead to 2+2 or 2+4 additions. However, there are reagents of weak preference leading to the uncommon result of mixed 1,2 and 1, 4 cycloaddition products. In such a situation, the problem comes to the fore of whether the Diels-Alder product is formed concertedly or is resulting from a branching of a biradical stepwise mechanism. In the ensuing discussion we will illustrate how one can make use of the features inherent in either concerted or biradical pathway in drawing conclusions as to which mechanism is operating.

One versatile reagent appears to be α- acetoxyacrylonitrile which has been found by Little to yield 41, 42 and 43 upon reaction with butadiene.[45]



[45] J. C. Little, J. Am. Chem. Soc., 87, 4020 (1965).

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The dependence of the reaction rate on solvent polarity is so small as to exclude a common dipolar ion intermediate for the two modes of addition in the above reaction. Moreover the relative rates do not vary appreciably over the temperature range (65^{o}) nor is there a large effect of either solvent or temperature on the isomer ratio.

On the ground that distinctly different mechanisms would show markedly different dependence on solvent and temperature, Little propounded a common mechanism for the 1,2 and 1,4 addition involving a single intermediate with apparent allylic bonding at the site where the eventual ring closure was to be effected. (fig.2.)

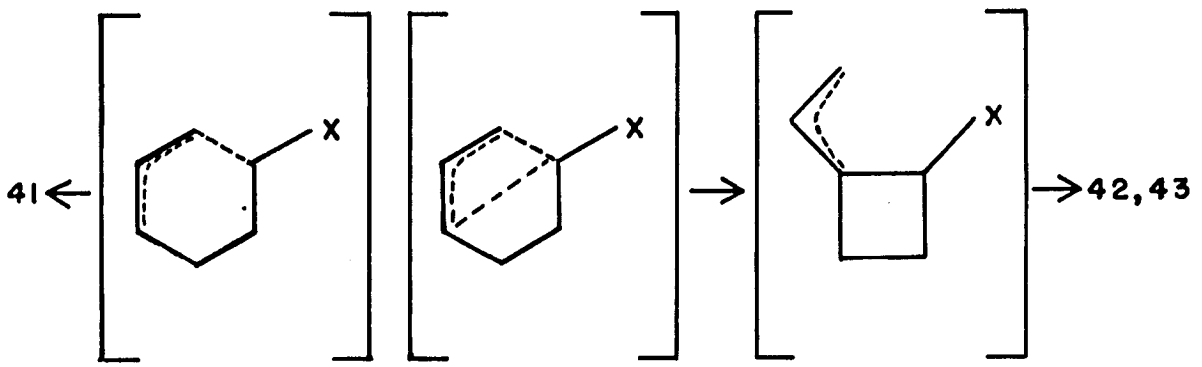

Figure 2.

In light of the theory developed by Woodward and Hoffmann, Little's contention is now untenable. The 1,2 product must be regarded as having originated by way of a biradical. Bartlett and Schueller[46]

[46] P. D. Bartlett and K. E. Schueller, ibid., 90, 6077 (1968).

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set forth to test the mechanism pertaining to the Diels-Alder adduct by testing the reaction of α-acetoxyacrylonitrile with trans, trans-2,4-hexadiene as the simplest homolog of butadiene that possesses configuration at both double bonds.

In contrast to the case of butadiene, they found only 0.4% of mixed cyclobutanes in addition to the 36:64 mixture of the two stereoisomers of 4-cyano-4acetoxy-cis-3,6-dimethylcyclohexene; no trans compound could be detected. Referring to the stereospecific course of the 1-4 cycloaddition, the authors advocated a concerted mechanism for the Diels-Alder adduct and extended their results to the butadiene case.

Bartlett and Schueller's contention is strengthened by the fact that the proportion of 1,2 cycloadduct is about 40-50 times less with hexadiene than with butadiene. This is due, as we discussed previously, to an acceleration of the Diels-Alder mechanism by the two methyl groups which, on the other hand, decelerate the biradical process. If the 1,4 cycloadduct had originated through the biradical process, the proportion of the 1,2 cycloadducts would have been nearly the same in the two cases.

The case of α-acetoxyacrylonitrile is rather special. Nevertheless, one can force a strongly 1,4 adding reagent to give partly 1,2 addition. This occurs, for example, when cisoid formation of the diene is sterically prohibited[47] or when the Diels-Alder product would

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[47] C. A. Stewart, Jr., J. Am. Chem. Soc., 84, 117 (1962).

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have been antiaromatic.[48] Conversely one can help a strongly 1,2 adding reagent like fluoroolefines to give some 1,4 cycloadducts by forcing the diene to have a cis geometry.

On that ground Bartlett et al.[49] reasoned that substituents larger than methyl would, by hindering the transoid conformation of dienes, stimulate the strongly 1,2 adding reagent to yield some 1,4 cycloadducts.

Table 2 shows the composition of the cycloadducts of 1122

2 substituents	% of prodt. of addn at 1,4	Rel. Diels-Alder rate[50]
Ethyl	5	6,1
n-Propyl	4	-
Isobutyl	16	11.6
t-Butyl	45	29
Neopentyl	10	51
Phenyl	12	-

Table II.

Thermal Cycloaddition of 1122 to 2-substituted 1,3 dienes at 80°

obtained from six 2-substituted butadienes. The results substantiated the authors' expectations and prompted them to reconsider the case of

[48] A. T. Blomguist and Y. C. Meinwald, J. Am. Chem. Soc., 79, 5316 (1957); 81, 667 (1959).

[49] P. D. Bartlett, G. E. H. Wallbillich, A. S. Wingrove, J. S. Swenton, L. K. Montgomery and B. D. Kramer, J. Am. Chem. Soc., 90,2049(1968).

[50] Reaction with maleic anhydride[50], [(k butadiene) = 1.0].

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isoprene which led to the detection of 1.6% of the 1,4 adducts. Although gratifying, these figures afford no compelling evidence as to which mechanism is responsible for the Diels-Alder adducts.

First of all, a similar effect has been reported by D. Craig et al.[51] to be operating in the concerted Diels-Alder reaction of maleic anhydride. However (Table II and Fig. 3) it is striking that the neopentyl group which is almost twice as effective as the t-butyl in enhancing the rate of the Diels-Alder reaction yields less than one fourth as much as 1,4 addition of 1122 as with t-butyl.

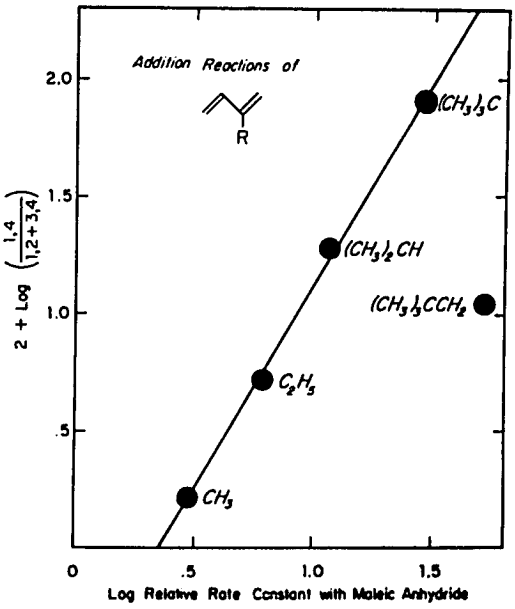

Figure 3.

Different effects of 2-neopentyl group on 1,4 addition by maleic anhydride and 1122.

[51] D. Craig, J. J. Shipman and R. B. Fowler, J. Am. Chem. Soc., 83, 2885 (1961).

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There are indications pertaining to the biradical mechanism that attack on a transoid diene is at least as easy as on the cisoid;[43] hence the radical mechanism cannot lead to a ratio of 1,4 to 1,2 addition in excess of the ratio of cisoid to transoid diene in the conformational equilibrium. In the present two cases this condition is satisfied and so no way of distinguishing between the two mechanisms is available in this way. This behavior is in sharp contrast with the case of α-acetoxyacrylonitrile and butadiene where 86% of 1,4 adduct is obtained although the fraction of the diene in the cisoid form is only about 6%.

Here emerges a very interesting point. Should the 1,4 adduct be originated through a biradical pathway, it is fair to think that its temperature dependent amount will be governed by the cisoid-transoid conformational distribution of the diene alone. In the case of a concerted process such a situation would only be fortuituous although not impossible.

The availability of the thermodynamic data concerning the conformational equilibrium of butadiene[52] and the fact that isoprene yields 1.6% of 1,4 adducts conferred on the reinvestigation of the cycloaddition of 1122 to butadiene a particular interest.

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[52] J. G. Aston, G. Szasz, H. W. Woolley and F. G. Brickwedde, J. Chem. Phys., 14, 67 (1946).

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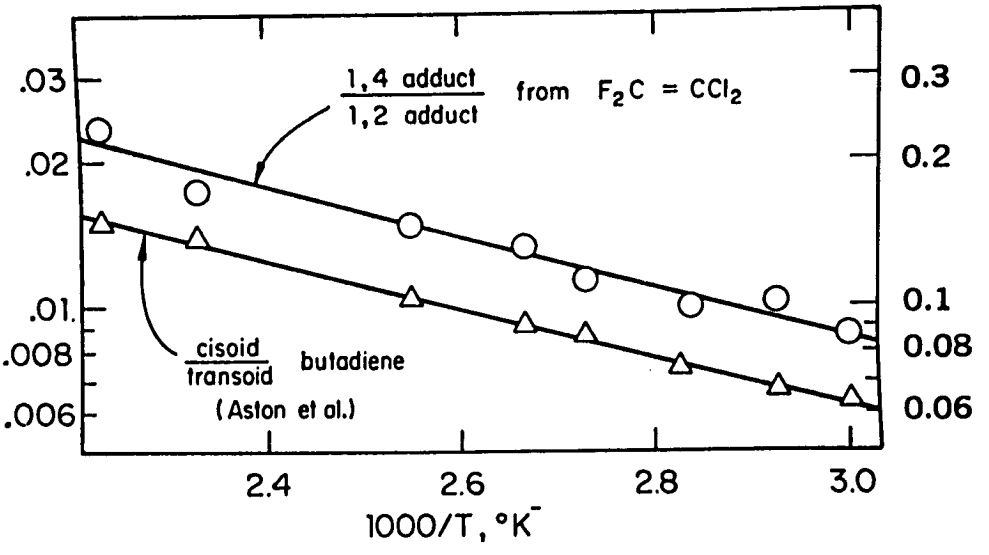

Figure 4.

Temperature dependence of product (left hand scale) and diene conformation (right hand scale) for cycloaddition of 1122 butadiene.

The results obtained by Swenton and Bartlett[53] can be summarized in Figure 4 where we can observe that the amounts of Diels-Alder adduct represent an essentially constant fraction of the cisoid butadiene over the temperature range investigated.

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[53] J. S. Swenton and P. D. Bartlett, J. Am. Chem. Soc., 90, 2056 (1968).

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If the temperature study had shown a large difference between the response of the 1,4 addition and that of the conformational equilibrium, it might have constituted evidence for independent mechanisms of the two modes of cycloaddition. Such evidence is lacking; nevertheless the indications in favor of the formation of the Diels-Alder adduct through a biradical process were persuasive enough to make it desirable to fully establish the origin of the 1,4 adduct. We set forth to solve that problem by looking at the cycloaddition of 1122 to a butadiene having geometrical configuration such as trans, trans-2,4-hexadiene. The results of this study will be the subject of the ensuing chapters.

In only one other case has the mechanism of the 1,4 addition of a fluoroalkene been elucidated.[54] Wheland and Bartlett followed the stereochemistry of the thermal addition of 1,2-dichloro-1,2-difluoroethylene to cyclopentadiene and concluded that the 1,2 adducts are indeed formed by a biradical mechanism whereas the 1,4 are simultaneously formed by a concerted mechanism. Cyclopentadiene, in addition to being a cis fixed diene, has a very short distance between the ends of the conjugated system (2.44 Å). These attributes, although they should facilitate a 1,4 biradical mechanism, confer on cyclopentadiene a remarkable ability to enter into Diels-Alder concerted processes.

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[54] P. Wheland and P. D. Bartlett, J. Am. Chem. Soc., 92, 3822 (1970).

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Finally, it is germane to discuss an entirely different approach to the problem of 2 + 2 and 2 + 4 cycloaddition.[55] This approach stems from the assumption that photosensitized cycloaddition will give essentially the same product distribution as the singlet biradical intermediate responsible for thermal (2 + 2) addition. Then the excess of 1, 4 adducts on thermal addition over those on photosensitized addition can be accounted for only by an additional competing process: concerted Diels-Alder cycloaddition.

Certain pitfalls are nevertheless attendant upon that reasoning. First of all it must be emphasized that the closure to a six membered ring depends upon the biradical having a cisoid conformation. Hammond and coworkers[56] have shown that the cisoid and transoid conformation of butadiene require different amounts of transferred energy for excitation to the triplet state. Therefore a sensitizer which will preferably excite the cisoid diene is more prone to give the 1-4 cycloaddition and will not mimic as well the thermal singlet biradical behavior as a sensitizer equally able to excite both conformations. It must also be kept in mind that singlet and triplet biradicals may not be entirely comparable, for example, as far as the degrees of internal rotation and reversion to alkene[54] are concerned.

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[55] P. D. Bartlett, Quart. Rev., 24, 473 (1970).

[56] R. S. Liu, N. J. Turro and G. S. Hammond, J. Am. Chem. Soc., 87, 3406 (1965).

[57] P. D. Bartlett and N. A. Porter, J. Am. Chem. Soc., 90, 5317 (1968).

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CHAPTER II

RESULTS AND DISCUSSION

I) Introduction

In the preceeding chapter we have directed our attention to the established properties of concerted and biradical cycloadditions. In the course of our presentation we have indicated that trans, trans-2,4-hexadiene should be a good candidate for the reaction with 1122 with regard to the problem we had set forth to solve. Trans, trans-2,4-hexadiene with its geometrical configuration will allow us to determine whether the cycloaddition is concerted or biradical. In addition to the 1,2-adduct, the latter mechanism should lead to a mixture of cis- and trans-4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene while the former should yield only the cis isomer.

II) Cycloaddition of 1122 and trans, trans-2,4-hexadiene

Following the method of Bartlett et al.,[38] we allowed trans, trans-2,4-hexadiene to react with 1122 at 100°. In addition to the 1,2-adducts already identified, a careful vapor phase chromatographic study revealed the presence of a small peak, the area of which was less than one percent of the total area.

The substance corresponding to this small peak was collected by preparative vapor phase chromatography using a Carbowax column. Spectral evidence conclusively established that we were dealing with cis- and/or trans-4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene.

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The mass spectrum showed a parent peak at 214 equal to the calculated value for $C_8H_{10}Cl_2F_2$. The observed ratio of m, m + 2, m + 4 was 56.3:36.7:7 (calculated 57.4:36.7:5.9). The principal peaks and their intensities were 179(100), 143(59), 123(16), 104(31), 82(45). This fragmentation corresponds to the loss of Cl, loss of Cl and HCl, loss of Cl, HCl, and HF, loss of Cl, HCl, HF, and F, and loss of 2,4-hexadiene.

^1H nmr studies showed the presence of olefinic and allylic hydrogens in the ratio of 2:2 which is what is to be expected for a 1,4-adduct and clearly eliminates the possibility of a 1,2-adduct. The olefinic absorption occurs at τ = 4.56 and the allylic hydrogens yield a complex pattern at τ = 6.75 - 7.25. At higher field the 60 Mc spectrum (Figure 5) exhibits eight lines interpreted as a pair of doublet of doublets centered at τ = 8.67 (J = 7 and 2 Hz) and τ = 8.73 (J = 7.5 and 1.5 Hz). This conclusion was confirmed by the 100 Mc spectrum; in this instance some peaks have accidentally merged, but the coupling constants are conserved. The two secondary methyl groups of either of the two 1,4-adducts fit this description perfectly. The additional secondary coupling can be attributed to long-range interaction with the fluorines.[58]

^{19}F nmr spectroscopy substantiates our assignment. The spectrum exhibits an AB quartet with a coupling constant of 243 cycles

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[58] For a discussion of long-range coupling in fluorinated compounds see: N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", p. 123.

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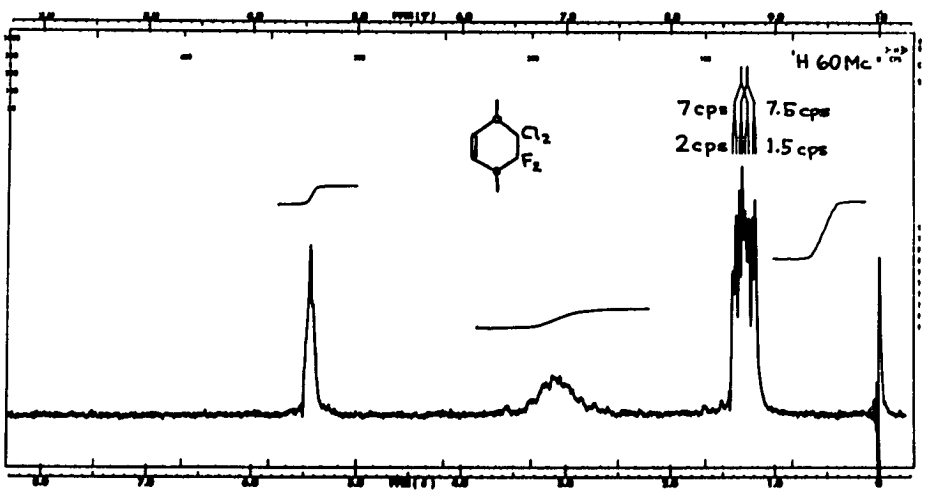

Figure 5. 60 Mc ^{1}H nmr spectrum of cis-4, 4-dichloro-5, 5-difluoro-3, 6-dimethylcyclohexene.

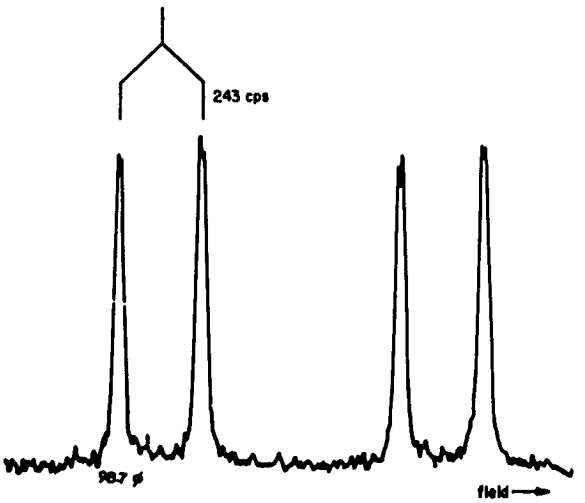

Figure 6. 94.1 Mc ^{19}F nmr spectrum of cis-4, 4-dichloro-5, 5-difluoro-3, 6-dimethylcyclohexene.

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(Figure 6) which falls into the reported range of 230 - 250 cycles for six-membered rings.[59] Further, we could infer that we had collected only one isomer, for had we had a mixture of cis- and trans-1,4-cycloadducts, two AB quartets would have been observed owing to the ability of fluorine to show appreciable chemical differences even when two isomers differ only by conformational subtleties.

The establishment of the configuration of the collected 1,4-cycloadduct was done chemically as outlined in Scheme 1.

Independent synthesis of cis-1-chloro-2-fluoro-3,6-dimethylcyclohexene: The best way to insure the stereochemistry of this compound was by making use of a Diels-Alder reaction for which the stereochemistry has been well established.

Ethyl-3,3-dichloro-2-fluoroacrylate 44 which was first synthesized by D.C. England served our purpose.[60] Its reaction with trans, trans-2,4-hexadiene for two days at 180°C yielded a 1.7:1 mixture of isomers 45 and 46. No 1,2-adduct could be detected, as expected, due to the great enhancement of the dienophilic character of 44 compared to 1122, conferred by the ester group.[61]

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[59] R.E. Lack, C. Ganter and J.D. Roberts, J. Am. Chem. Soc., 90, 7001 (1968). Geminal fluorine-fluorine coupling in four-membered rings is smaller, (~185 cps), for example see: J.B. Lambert and J.D. Roberts, J. Am. Chem. Soc., 87, 3884 (1965).

[60] D.C. England, R.V. Lindsey, Jr., and L.R. Melby, J. Am. Chem. Soc., 80, 6442 (1958).

[61] See reference 13d, p5.

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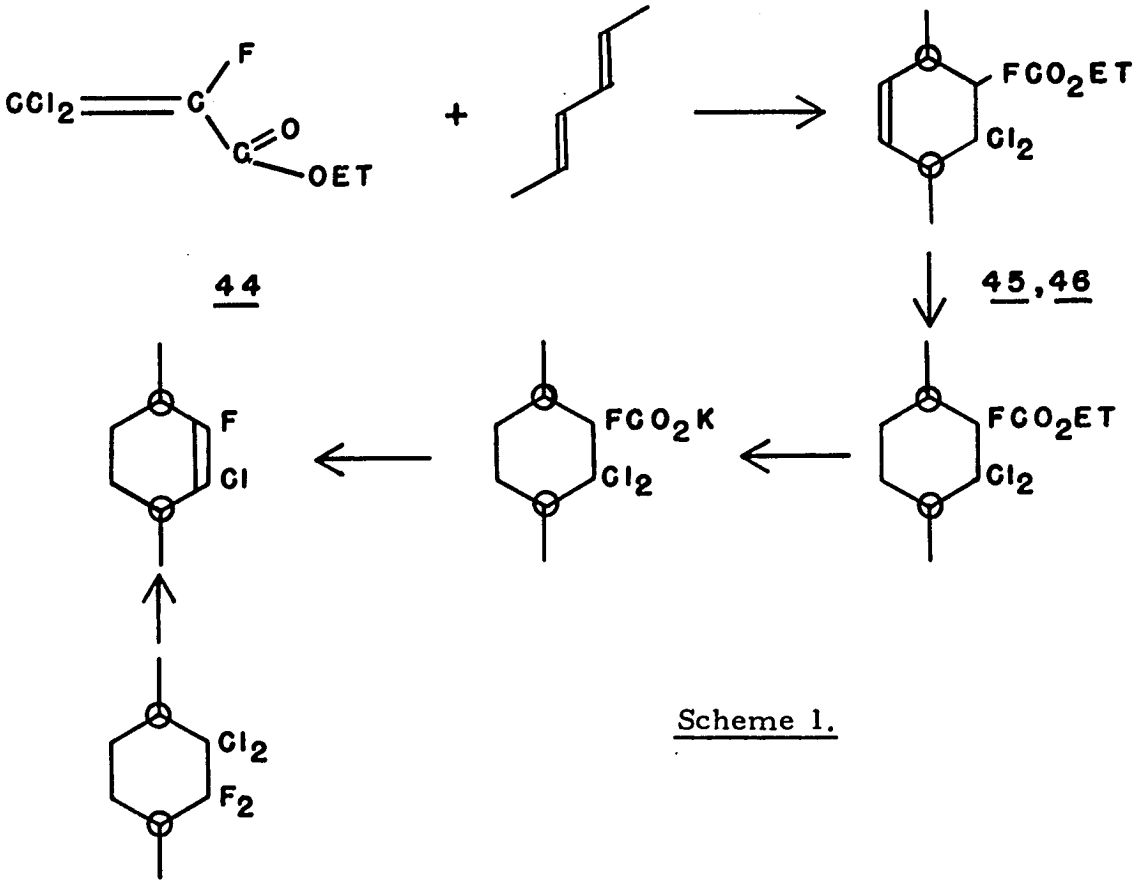
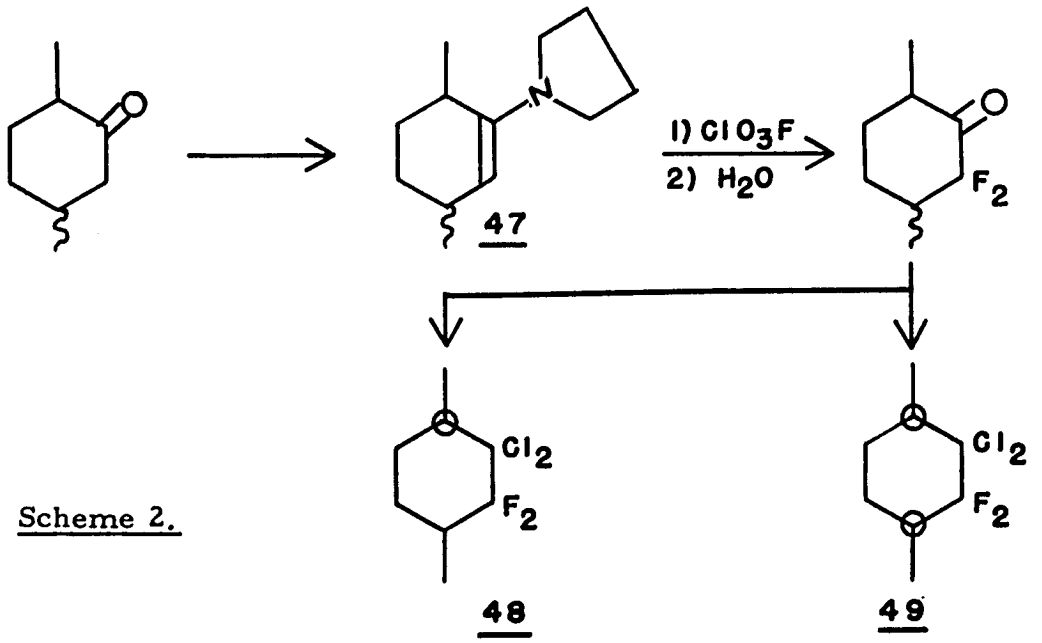


Scheme 1.



Scheme 2.

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The mixture of the two isomers was hydrogenated and hydrolyzed by potassium hydroxide dissolved in ethanol. A white precipitate formed which upon thermolysis at 170°C gave a colorless liquid, the analytical vapor phase chromatography of which exhibits only one peak.

The mass spectrum shows a parent peak at 162 equal to the calculated value of $C_8H_{12}ClF$. The observed ratio of m, m + 2, was 73.9:26.1 (calculated 75.8:24.2). The principal peaks and their intensities were 147(37), 127(100), 111(73), 107(18). These fragmentations correspond to the loss of CH_3, loss of Cl, loss of HCl and CH_3 and loss of Cl and HF.

The nmr spectrum showed the presence of vinylic and allylic hydrogens in the expected ratio of 1:1. The two methyl groups appeared as a pair of doublets. The ir exhibits a strong band at 1700 cm^{-1} whose position and intensity are quite characteristic of the fluoroalkenes.[62]

Referring to the stereospecificity of the Diels-Alder reaction[63] which could not be destroyed during the successive operations we concluded that we were dealing with cis-1-chloro-2-fluoro-3,6-dimethylcyclohexene.

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[62] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, New York, 1957, p. 42.

[63] This statement may seem at first out of place in a thesis where we will evidence some non-stereospecific Diels-Alder reaction. Nevertheless, it must be kept in mind that we will be dealing with a branching of a biradical reaction leading mostly to 1,2-adducts. As we will see later, the concertedness of a 1,4-cycloaddition increases with the decrease of the 1,2-addition process and, in the case at hand, the sheer fact of obtaining only Diels-Alder products suffice to confirm our statement.

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Dehalogenation of cis-1,1-dichloro-2,2-difluoro-3,6-dimethyl cyclohexane: The dehalogenation was carried out by using chromium salt. Considerable work pertaining to the dehalogenation of alkyl halide and vicinal dihalide including fluorine has been done using this method.[64]

25 mg. of isolated 1,4-cycloadduct was hydrogenated and stirred with Zn dust, $Cr_2(SO_4)_3$, water and dimethyl formamide in a sealed tube under nitrogen at about 110°C. In addition to the solvent, preparative vapor phase chromatography using a 20% Carbowax column gave only one peak corresponding to a compound whose ir and nmr spectra match with that of cis-1-chloro-2-fluoro-3,6-dimethylcyclohexene.

We have so far established that the thermal cycloaddition of 1122 and trans, trans-2,4-hexadiene gives a small amount of cis-4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene. On the basis of this it would have been premature to conclude that this compound was formed via a concerted path without having fully established that there was no trans counterpart in the products. At this point, it became mandatory to synthesize the trans isomer or one of its degradation products. The synthesis which did not need to be stereospecific is pictured in Scheme 2.

The synthesis of the gem difluoro ketones was carried out by bubbling a stream of perchlorylfluoride through an ether solution of the

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[64](a) J.R. Hanson and E. Premuzic, Angew. Chem. Internat. Ed. Eng. 7, 247 (1968).
(b) D.M. Singleton and J.K. Kochi, J. Am. Chem. Soc., 89, 6547 (1967).
(c) J.K. Kochi and D.M. Singleton, J. Am. Chem. Soc., 90, 1582 (1968).

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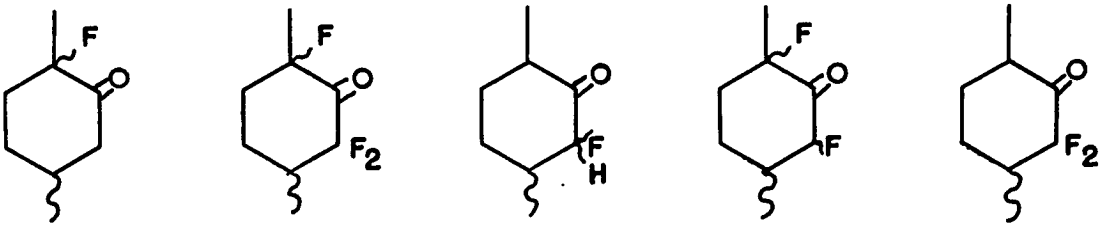
enamime 47 at 0°C. A mixture of mono-, di-, and trifluoro ketones was obtained and separated by preparative vpc. The number and position of the fluorines was easily determined by mass spectrometry and nmr.



a b c d e

-Compounds a and b were identified by the large coupling constant of their deshielded methyl groups adjacent to the fluorine (τ = 8.6 ; J = 24 cycles).

-Compound c had a characteristically very large geminal hydrogen fluorine coupling constant of 50 cycles.

-Compound d shared characteristics of both compounds a and c.

-Finally, compound e shared none of these aforementioned features.

The chlorination was carried out by vigorously stirring, at room temperature, a mixture of the two gem-difluoro ketones and phosphorus pentachloride in a phosphous trichloride solution. Vpc was used to follow the reaction. Three new substances were formed and isolated. The major one was a monochlorinated compound probably resulting

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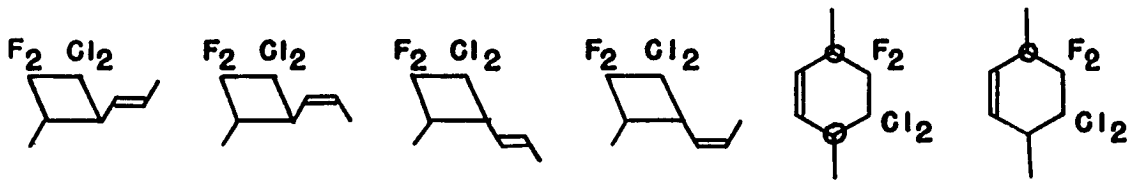
from the chlorination of the enol while accumulated evidence indicated the two others were substances 48 and 49. First, one had an ir and a mass spectrum which matched those of the hydrogenated cis-1,4-adduct of 1122 and trans, trans-2,4-hexadiene. Further, the two compounds had very similar mass spectra (the only difference lying in the intensity of the peaks) and also, as shown in Figure 7, their nmr spectra bore close resemblance; we could then conclude that the two substances were very similar and that they could differ only in the orientation of the methyl groups.

After having synthesized the cis and trans-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexanes, we were in a position to investigate fully the 1,4-cycloaddition behavior of the thermal addition of the 2,4-hexadienes. Although, we are presently concentrating on the trans, trans-2,4-hexadiene case, for convenience, we will now report results pertaining also to the cis, trans and cis, cis-2,4-hexadienes.

We investigated the thermal reaction at four different temperatures using an oil bath which allowed us to maintain the temperature within $\pm$ 0.01°C. The composition with respect to the cycloadducts numbered below is shown in Tables III - VI.



50 51 52 53 54 55

[65]

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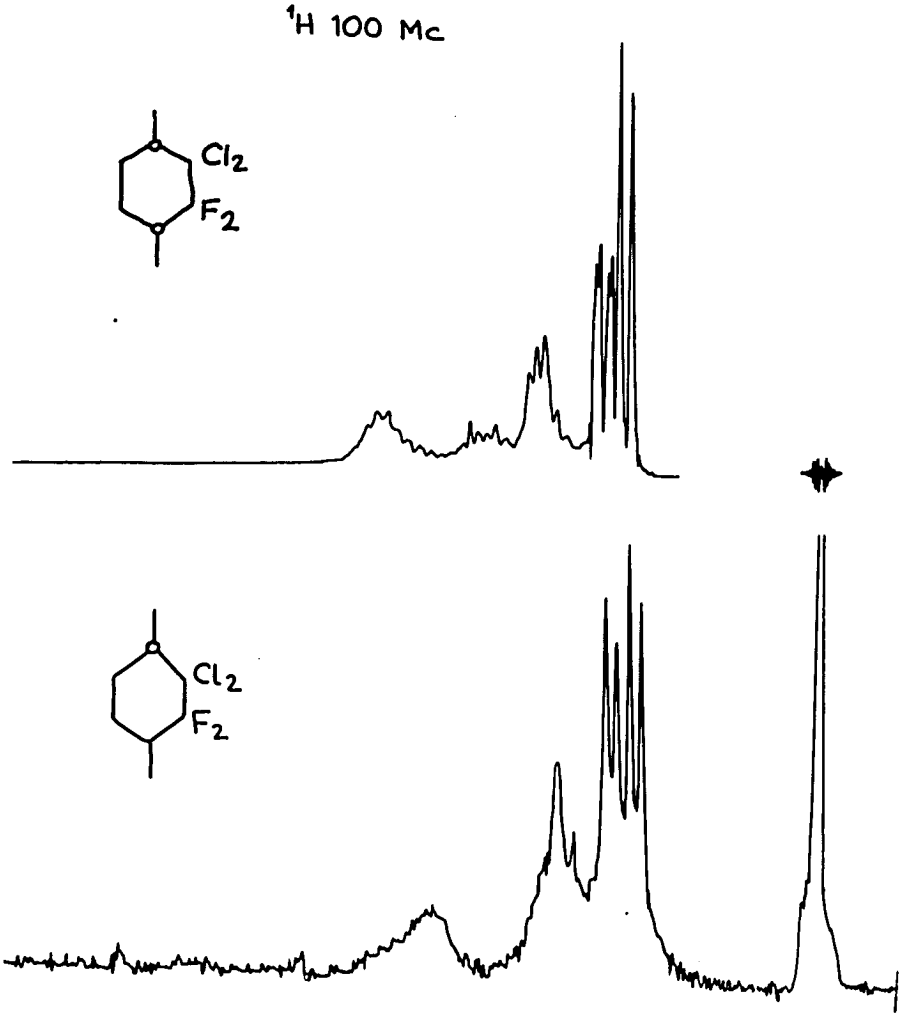

Figure 7. (a) 100 Mc ^{1}H nmr spectrum of cis-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane. (b) 100 Mc ^{1}H nmr spectrum of trans-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane. The spectrum was obtained by means of a Fourier transformation.

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Table III: Cycloaddition of 2,4-hexadienes and 1122 at 79.5°

	50	51	52	53	54	55
trans-trans	82.9	<.1	16.4	<.05	.46	~.003
	83.1	<.1	16.6	<.05	.46	~.004
cis-trans	47.2	33.3	13.7	5.8	.07	~.015
	46.3	33.2	14.7	5.8	.08	~.014
cis-cis	<1	76.0	<.2	22.8		
	<1	76.6	<.2	22.1		

Table IV: Cycloaddition of 2,4-hexadienes and 1122 at 99.5°

	50	51	52	53	54	55
trans-trans	80.5	1.80	16.9	.22	.64	~.005
	80.7	1.86	16.6	.25	.61	~.006
cis-trans	44.6	33.6	15.2	6.5	.115	~.015
	45.6	32.2	15.3	7.0	.116	~.016
cis-cis	2.4	75.0	.76	21.8		
	2.2	74.5	.80	22.5		

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Table V: Cycloaddition of 2,4-hexadienes and 1122 at 120.12°

	50	51	52	53	54	55
trans-trans	77.2	4.1	17.1	.80	.80	~.01
	78.8	3.4	16.2	.78	.79	~.009
cis-trans	46.7	31.3	15.5	6.3	.17	~.015
	47.7	29.6	16.0	6.5	.18	~.016
cis-cis	5.5	70.5	1.9	22.1		
	6.0	70.4	2.1	21.5		

Table VI: Cycloaddition of 2,4-hexadienes and 1122 at 153.25°

	50	51	52	53	54	55
trans-trans	76	4.8	17.3	.80	1.10	~.020
	75.4	4.5	17.1	.82	1.12	~.015
cis-trans	45.3	30.3	16.8	6.9	.22	~.020
	45.4	31.2	16.4	6.8	.20	~.023
cis-cis	6.1	66.4	2.1	25.4		

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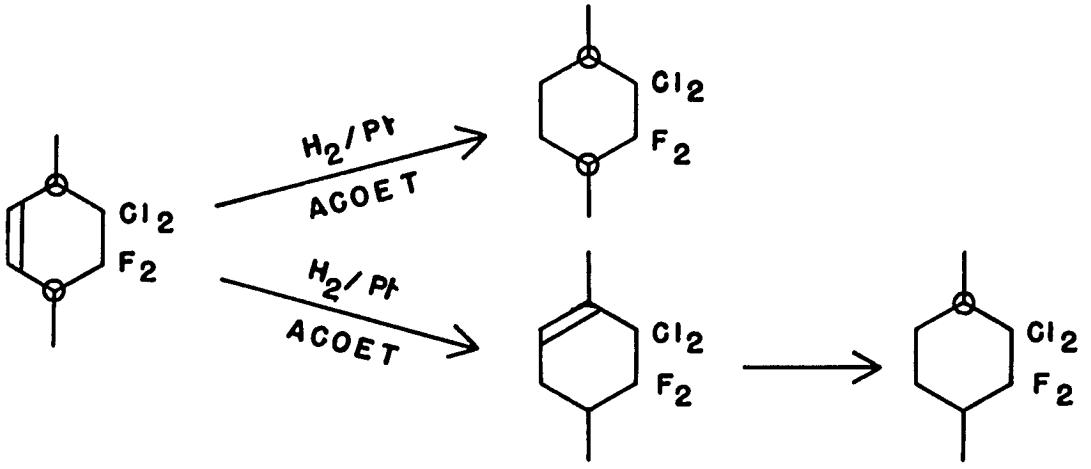
The dienes used analyzed as follows:

trans, trans-2,4-hexadiene	(99.7% t-t, 0.3% c-t, 0% c-c)
cis, trans-2,4-hexadiene	(0.4% t-t, 99.6% c-t, 0% c-c)
cis, cis-2,4-hexadiene	(0.3% t-t, 1.4% c-t, 98.3% c-c)

Clearly Tables III-VI show that the Diels-Alder addition of 1122 and trans, trans-2,4-hexadiene yielded mostly the cis adduct (>99%). Furthermore, the origin of the trans cycloadduct is questionable. It can be argued that the trans compound arose from the cis during the hydrogenation step according to the scheme below.



Such a process has been demonstrated by K. Schueller in the case of cis-3,6-dimethylcyclohexene where she reported 9.7% isomerization during the hydrogenation process using acetic acid as the solvent.[66]

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[65]The percentages assigned to the compounds 54 and 55 have been obtained by analyzing the hydrogenated mixtures.

[66]K. Schueller thesis, Harvard University, 1966, page 43.

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Nevertheless, in our case, we do not believe that such a process occurred because the hydrogenation of trisubstituted double bonds do not take place in non-acidic solvents. Furthermore, the use of acetic acid did not change our results.

At this point, on stereochemical grounds alone it would be tempting to conclude that the 1,4-cycloaddition of trans, trans-2,4-hexadiene and 1122 is concerted. On the other hand, the interpretation of our result in light of those reported in the case of butadiene would lend support to the biradical mechanism. As we have discussed in the preceding chapter[67] the methyl groups of trans, trans-2,4-hexadiene should accelerate the concerted process while decelerating the biradical one. Consequently a concerted mechanism should have led to an increase of 1,4-adduct on going from butadiene to trans, trans-2,4-hexadiene; on the contrary, we have a very slight decrease.

Our reasoning based upon the acceleration of the concerted process by the methyl group has been inferred from cycloaddition run with maleic anhydride and it can, of course, be argued that 1122 and maleic anhydride behave quite differently in their concerted fashion. Nevertheless, with all poor dienophiles investigated so far, which have led to a mixture of 1,2 and 1,4-cycloadducts, one has always observed an increase of the ratio of 1,4 against 1,2 adduct on going from butadiene to trans, trans-2,4-hexadiene. For example, in the case of ethylene the ratio went from 5×10^3 to ∞[68], and from 5.3 to 250 for α-acetoxyacrylonitrile.[46]

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[67] See page 21.

[68] P. D. Bartlett and K. E. Schueller, J. Am. Chem. Soc., 90, 6071 (1968).

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This inconsistency restrained us from drawing a conclusion at this point and led us to further our investigation. First, let us examine the relation between the 1,2 versus the 1,4 addition and the temperature.

B) Temperature dependence of 1,2 vs. 1,4 addition

A cursory examination of Tables III - VI reveals an increase in the amount of 1,4-cycloadduct with temperature. Such behavior is to be expected if the Diels-Alder process is of a biradical type but, on the other hand, a concerted pathway cannot be ruled out on these gounds. Hoping for more information, we undertook a more quantitative investigation.

Before proceeding to our study we should note that in accord with the reported observation,[40] at temperatures higher than 80° the cycloaddition of trans, trans-2,4-hexadiene and 1122 led to an appreciable formation of compounds 51 and 53. These substances arise from the cis, trans-2,4-hexadiene formed in the cycloaddition due to the reversibility of the biradical mechanism. (The isomerization into the cis, cis-diene which requires two such processes, is minimal, and can therefore be neglected. Consequently a correction must be made for the percentage of 54 obtained at a given temperature.

The amount of 51 or 53 found in the trans, trans-2,4-hexadiene cycloaddition is indicative of how much cis, trans diene was involved in the reaction and permitted us to make our correction. As a case in point let us consider the study at 153.25° C.

The reaction with trans, trans-2,4-hexadiene yielded 4.8% of 51. Considering that the cis-trans counterpart gave 31% of 51 we could

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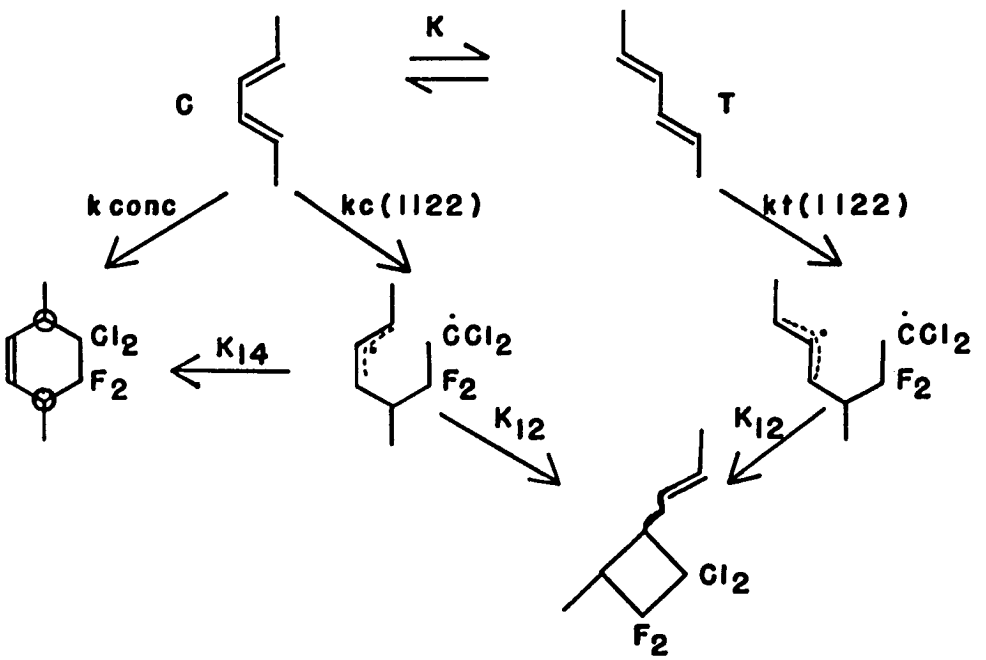
infer that the cis, trans-2,4-hexadiene was responsible for $\frac{4.8}{31}$ or 15.5% of the so called "cycloaddition of trans, trans-2,4-hexadiene and 1122." Using compound 53 we obtained a percentage of 11.9. We then took the average of these two values ($\simeq$ 14%) which led to a corrected value for 54 equal to 1.11 × 100 : 86 = 1.29%. (We have neglected the fact that the cis, trans-2,4-hexadiene was also giving some 54.)

By the same token we arrived at the following results:

%cis-1,4-adduct	temperature
.46	79.5
.65	99.5
.91	120.12
1.29	153.25

We are now in a position to return to our subject matter and scheme 3 will serve as the foundation for our discussion.



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If we regard the conformational equilibrium as mobile and each subsequent step as irreversible, we arrive at the following equation for the relative rates of formation of 1,2 and 1,4 adducts as a function of the rate constant K = C/T.

$$\frac{V_{12}}{V_{14}} = \frac{k_{12} + \frac{kt}{kcK}(k_{12} + k_{14})}{k_{14} + \frac{kconc}{kc}(k_{12} + k_{14})} \qquad (1)$$

This equation is quite unwieldy and we will limit our discussion to the two extreme cases.

1) Kconc = 0 leads to:

$$\frac{V_{12}}{V_{14}} = \frac{k_{12}}{k_{14}} + \frac{kt}{kcK}\left(1 + \frac{k_{12}}{k_{14}}\right) \qquad (2)$$

which is identical to the one arrived at by Swenton and Bartlett.[52]

2) $K_{14} = 0$ leads to:

$$\frac{V_{12}}{V_{14}} = \frac{kc}{Kconc} + \frac{kt}{kconK} \qquad (3)$$

As in the butadiene case it is reasonable to assume that k_{12} and k_{14} which refer to radical couplings will have similar and very low activation energy while kt and kc which refer to very similar processes might have identical coefficients. Consequently, equation (2) can be written:

$$\frac{V_{12}}{V_{14}} = a + \frac{b}{K} \qquad K = ae^{\frac{-\Delta H}{T}}$$

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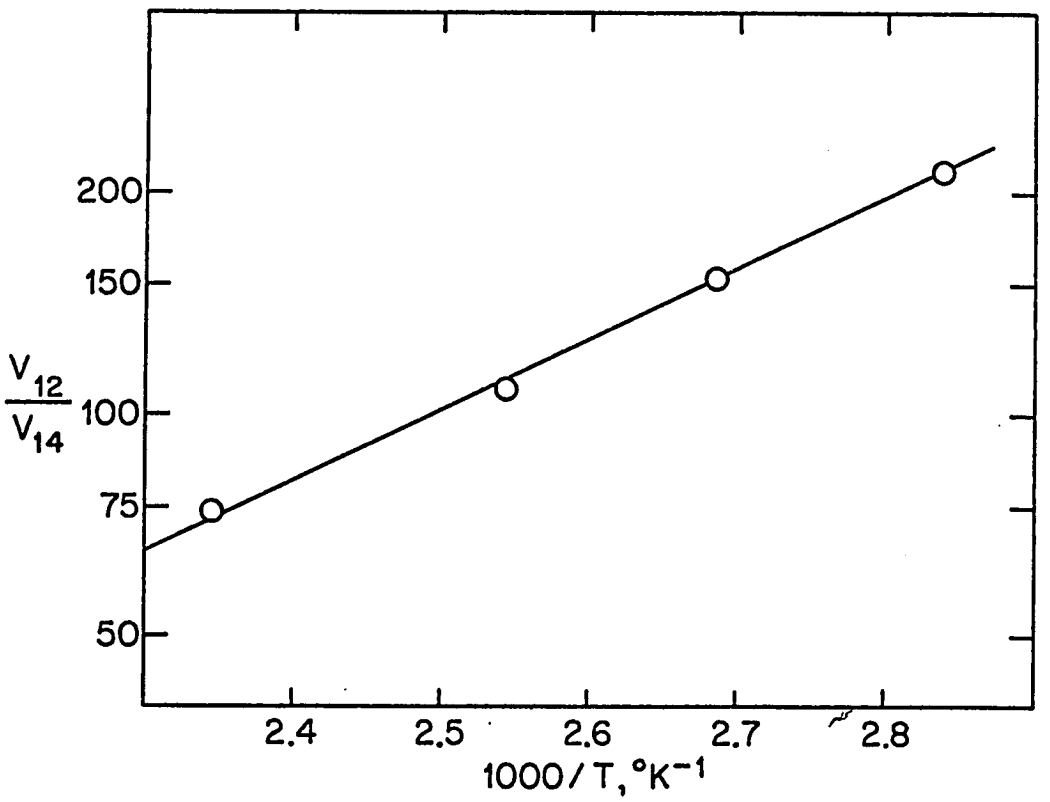

Figure 8. Temperature Dependence of cis 1,4 Addition for cycloaddition of 1,1-dichloro-2,2-difluoroethylene to trans, trans-2,4-hexadiene.

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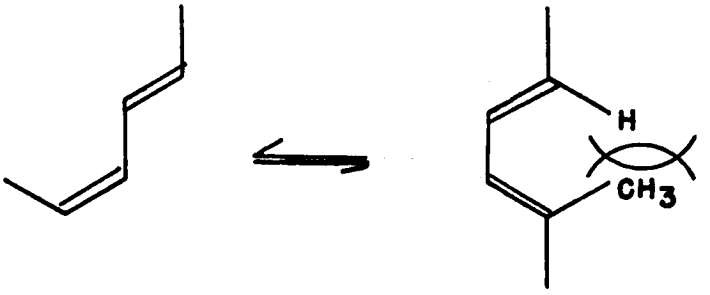
Unfortunately, contrary to the case of butadiene the conformational equilibrium K is not available for trans, trans-2,4-hexadiene but we can, nevertheless, notice that the logarithmic curve representing V_{12}/V_{14} against the temperature fits a straight line with a positive slope which is consistent with a biradical mechanism. (Figure 8.)

For $k_{14} = 0$ the obtaining of a straight line would require very similar coefficients for kc and kconc. This could happen to be the case by sheer chance, and consequently this study, although informative, did not provide us with any compelling evidence as to which mechanism was operating. Clearly, the straightforward means of approaching the problem we set out to answer did not lead us to any conclusion and it became apparent that we would have to broaden the scope of our investigation through comparative studies. First we investigated the cycloaddition of 1122 and a closely related diene.

III Cycloaddition of cis, trans-2,4-hexadiene and 1122

Due to nonbonding interactions between a hydrogen and a methyl group in the cisoid conformation, cis, trans-2,4-hexadiene exists mostly in its transoid conformation.



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As a result this diene does not react readily in its role as a Diels-Alder partner. For example, maleic anhydride which is one of the most powerful dienophiles known, reacts at room temperature with trans, trans-2, 4-hexadiene but does not react with the cis-trans counterpart below 80°. Weaker dienophiles like ethylene completely fail to react with cis, trans-2, 4-hexadiene.[69] Such a handicap should also apply to the biradical 1, 4-cycloaddition and there was little hope that we would find any 1, 4 adduct with this diene.

Nevertheless, using the same experimental conditions as in the case of the trans, trans-2, 4-hexadiene we did observe 1, 4-cycloadducts (see Tables III - VI). Furthermore, the process is nonstereospecific and the less stable cis isomer is predominant. The amounts of 1, 4 adducts are small but represent a fairly high percentage of what was obtained with trans, trans-2, 4-hexadiene.

Before this interesting example could be discussed it was essential that we establish that the cis-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane could not be entirely accounted for by the trans, trans-2, 4-hexadiene obtained during the reversible biradical cycloaddition.

At first sight this possibility appeared very improbable. Even at 79. 50° C where the isomerization was almost nil, (at least as inferred from the trans, trans and cis, cis diene cases) we did have a sizable amount of cis-1, 4 adduct.

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[69] P. D. Bartlett and K. E. Schueller, J. Am. Chem. Soc., 90, 6071 (1968).

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Calculation aimed at finding a probable value for this isomerization process would have been intricate and would have involved too many approximations. Fortunately, we were able to circumvent that problem experimentally.

The cycloadditions reported in Tables III - VI were run with an excess of 1122. Under such conditions most of the cis, trans-2, 4-hexadiene reacted with 1122 and the recovered diene sharply bore the mark of the isomerization process. For example, considering the run at 120°, it analyzed as follows: trans, trans: 34. 6%, cis, trans: 62%, cis, cis: 3. 4%. On the other hand, should we use an excess of cis, trans -2, 4-hexadiene, little of it would react, and the percentage of isomerized dienes would be kept so low as to allow us to neglect their participation in the cycloaddition process.

Accordingly we allowed 1122 to react with a tenfold excess of cis, trans-2, 4-hexadiene at 120° and the recovered diene analyzed as: trans, trans: 1%, cis, trans: 98. 2%, cis, cis: 0. 8%. The percentage of 1, 4 cycloadducts were cis 0. 12%, trans 0. 038%. Clearly, the 1% of trans, trans diene could not account for the 0. 12% of cis-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane.

In fact, we have shown in the case at hand that there occurred a biradical Diels-Alder reaction. This example is rather special and this biradical behavior can be attributed to steric effects. The cisoid conformation of cis, trans-2, 4-hexadiene is certainly not planar in order to avoid interaction between a methyl and a hydrogen. Consequently, the concerted process is strongly impaired in two ways. First,

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the non planarity does not favor the interaction of the four atomic orbitals of the diene. Second, the repulsion prevents the two terminal atomic orbitals of the diene from being close enough to overlap with the p-orbitals of the dienophile. This last restriction which might be the most important does not intervene in the biradical process. Further, the interaction of the atomic orbitals of the diene might still be consequential enough to allow the allylic end of the biradical to know it can be allylic.

In light of the opposite stereochemical behavior of trans, trans and cis, trans-2, 4-hexadiene during their cycloaddition with 1122 we could have concluded that they skirt a line between the concerted and biradical mechanism. On the other hand, if in the case of the cis, trans a fraction of the cisoid biradical was able to close 1, 4 we did not understand why it should not have been so with the trans, trans diene. Further we shall have to account for the predominance of the less stable cis-1, 4 adduct in the cycloaddition of cis, trans-2, 4-hexadiene.

IV Photosensitized Cycloaddition of 2, 4-Hexadiene and 1122

We have previously indicated that, under certain restrictions, photosensitized cycloadditions can be used as a model for biradical cycloaddition. It was then of the greatest interest to us to study the reaction of 2, 4-hexadienes with 1122.

First of all, it must be remembered that we cannot consider specifically one isomer since the isomerization of the dienes occurs during the reaction.[70] Nevertheless, it is reasonable to assume that

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most of the 1,4-cycloadducts will originate from the trans, trans-2,4-hexadiene due to the unlikelihood of the cis, trans or cis, cis adopting the cisoid conformation.

A mixture of trans, trans-2,4-hexadiene, 1122 and β-acetonaphtone was irradiated using a 450W Hanovia lamp at 2°C for four days. The reaction led mostly to 2,4-hexadiene dimers and the cross-cycloadducts analyzed as follows:

50	51	52	53	54	55
46.3	30.7	11.8	10.8	0.38	0.02

As in the thermal addition, we notice a large preponderance of the cis-1,4-cycloadduct. The ratio of trans to cis-1,4-adduct in the photochemical reaction is higher than in the case of the thermal addition. It falls short, however, of our expectation that the more stable trans 4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene would be formed preferentially. This experiment did not clearly eliminate the biradical mechanism. Therefore, no mechanistic conclusion could be drawn from our investigation of the 1,4-cycloaddition of trans, trans-2,4-hexadiene and 1122. Both mechanisms, concerted and biradical found their advocates and we could not make a judgment. A reconsideration of the problem imposed itself if we were to make further advances.

We were then led to question our starting hypothesis and specifically the question of the stereoequilibration of the two methyl groups during the supposed biradical cycloaddition.

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[70] J. Saltiel, L. Metts and M. Wrighton, J. Am. Chem. Soc., 91, 5684 (1969).

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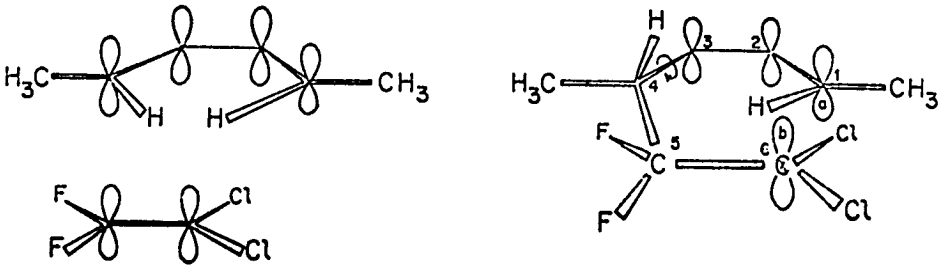
V Scale Model Study of a Biradical Diels-Alder Reaction

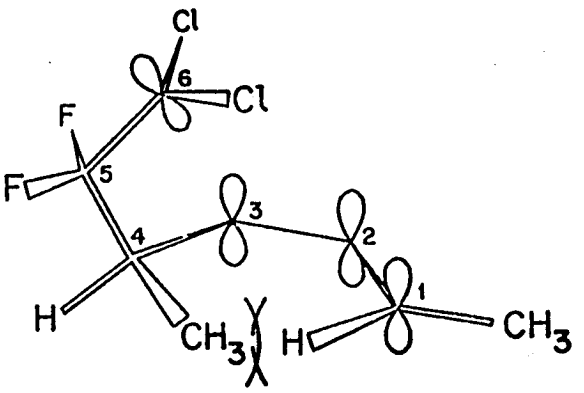
Let us consider the biradical cycloaddition of trans, trans-2, 4-hexadiene and 1122. In the first step, as in a concerted process, the 1122 must lie in a plane parallel or nearly parallel to the flat 2, 4-hexadiene in order for the two p-orbitals to fully overlap.



Once the intermediate biradical is formed interaction between lobes a and b gives rise to cis-4, 4-dichloro-5, 5-difluoro-3, 6-dimethyl-cyclohexene.

In order for the isomerization to occur two processes can be involved.

First, we can envision a clockwise rotation around the bond 3-4. In doing so we go through the intermediate pictured below in which a



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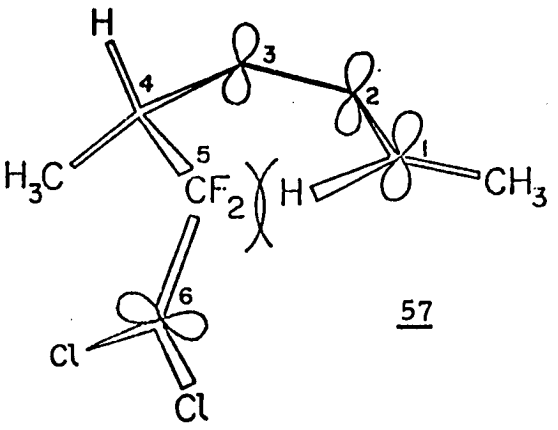
methyl group and a hydrogen are forced into close proximity. A scale model of this system confirms the hydrogen methyl interaction which reminds us of the difficulty which cis, trans-2,4-hexadiene has in assuming cisoid conformation. In other words, along the path of clockwise rotation we impose another energy barrier.

Second, we can have a counterclockwise rotation also around bond 3-4 which leads to a similar situation.



57

Clearly, on steric grounds, the isomerization process appears very unfavorable compared to four membered ring formation or cis-1,4-cycloaddition. Such an opinion, although it does not constitute a proof, would allow one to account for a stereospecific 1,4 biradical Diels-Alder reaction. Photochemically, we did get a meaningful amount of trans-1,4 adduct (5% compared to the cis). This lower selectivity can be attributed to the triplet state of the biradical which has a longer lifetime and can use the energy released during its conversion to singlet to overcome the barrier due to steric inconveniences.

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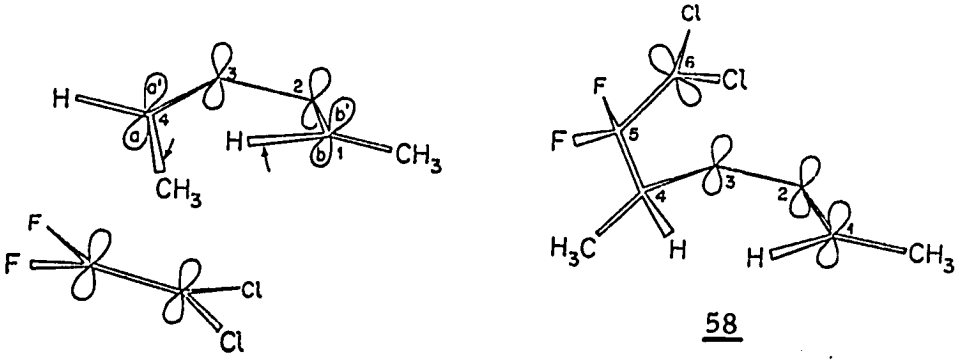
Further, looking at the problem in these terms would allow us to explain the occurrence of the cis-1,4-adduct in the cycloaddition of cis,trans-2,4-hexadiene and 1122.

The cisoid conformation of the cis, trans diene is certainly not planar. In the cycloaddition process the interfering hydrogen and methyl will tend to move away from each other. If we envision an



58

attack at lobe a, followed by or concommitant with clockwise rotation around bond 3-4 we will have complete steric release; the intermediate 58 contrarily to 56 or 57 will be free from steric hindrance and cis-4,4-dichloro-5,5-difluoro-1,6-dimethylcyclohexene will be formed.

The trans compound can be obtained from attack at lobe a'. Such a process also allows a relief of steric hindrance, but lobe a' is pointing toward carbon atom 1 and is less accessible than lobe a which might explain the preponderance of the cis adduct. Further, in such a process the transition state of the formation of the trans-dimethyl-cyclohexene has a pseudo-axial methyl where that for the cis -dimethyl-

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cyclohexene has a pseudo-equatorial methyl.

Attack at either lobe b or b' appears very unfavorable to yielding 1,4 cycloadducts because they do not allow the removal of the methyl from the plane defined by the 2,4-hexadiene.

Finally, we applied our reasoning to the known isomerization process pertaining to the 1,2 biradical cycloaddition and found these processes perfectly feasible.

Such reasoning may be very attractive, but did not allow us to decide which mechanism was operating in the Diels-Alder reaction of trans, trans-2,4-hexadiene and 1122. Nevertheless, these reflections provided us an insight which was of significant consequence for our further progress both in understanding and in practice.

It appears that, in the biradical intermediate, no hindrance prevents rotation around the bond linking $-CF_2$ and CCl_2 radical. Consequently the use of a dienophile with a stereochemical identification appealed to us.

Accordingly, we turned our attention to cis and trans-1,2-dichloro-1,2-difluoroethylene (1212) as vehicles to test our hypothesis. On the one hand 1212 has inherent tendencies to enter biradical processes: like 1122 it is destabilized compared to ethylene (though only by 5 kcal.). On the other hand, the potential CClF radical is less stable than its CCl_2 counterpart by 4 kcal.[71] This confers on 1212 a greater dienophilic character than 1122 as reflected by its addition to cyclopentadiene

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[71] C. Walling, Free Radicals in Solution, John Wiley and Sons, New York, 1957.

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which yields 6% of 1,2 adduct compared to 16% in the case of 1122. Further, using pure cis and trans-1212, the 1,4-cycloaddition with cyclopentadiene was shown to be stereospecific.

This particular point deserves comment. If we assume that 1,4-cycloaddition of 1122 and butadiene proceeds by a branching of the biradical mechanism we will recall that only about a seventh of the cisoid biradicals closed 1,4. Of course, this ratio should vary with cases, but it is legitimate to believe that since the 1212 cyclopentadiene cycloaddition gave less than 6% of 1,2 adduct, there was little chance to observe any loss of configuration in the Diels-Alder adducts by using cis and trans-1212 which were 99% and 96% pure respectively.

In view of the above consideration, by using trans, trans-2,4-hexadiene, or better butadiene, which are less inclined than cyclopentadiene to enter concerted Diels-Alder process, it was reasonable to hope that the biradical process would be consequential enough to allow us to evidence 1,4 biradical cycloaddition. The next part of this chapter will comment on this study.

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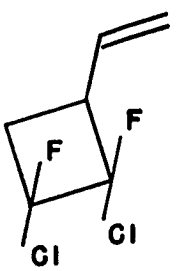
VI Cycloaddition of cis - and trans-1,2-dichloro-1,2-difluoroethylene

A) Butadiene

First we ran the cycloaddition on a 46/54 mixture of purified cis - and trans -1212 at 190°C for 24 hours. Vpc analysis on a 1/8 inch tcp column showed two sets of peaks (Figure 9a) with quite different retention times. By analogy with the 1122 studies, it was likely that these two sets corresponded to the 1,2- and 1,4-adducts. The first group consisted of three poorly resolved peaks. Upon hydrogenation a better separation was obtained and, as expected, four peaks could be observed (Figure 9b). We did not attempt their isolation, which would have required a good deal of trial and error work as suggested by the fact that among more than ten different columns used, only one gave some separation. Further, although of some interest, the configuration of the 1,2-adducts were not directly relevant to our problem. At that point, our goal was to insure that we were dealing only with compounds 59 - 62.



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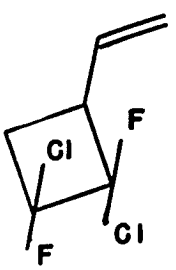
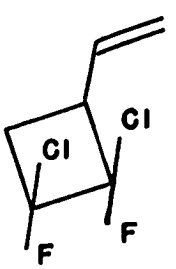


60



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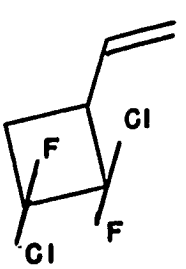

62

We first made sure that the retention time of our four hydrogenated adducts did not match those of the hydrogenated dimers of butadiene.

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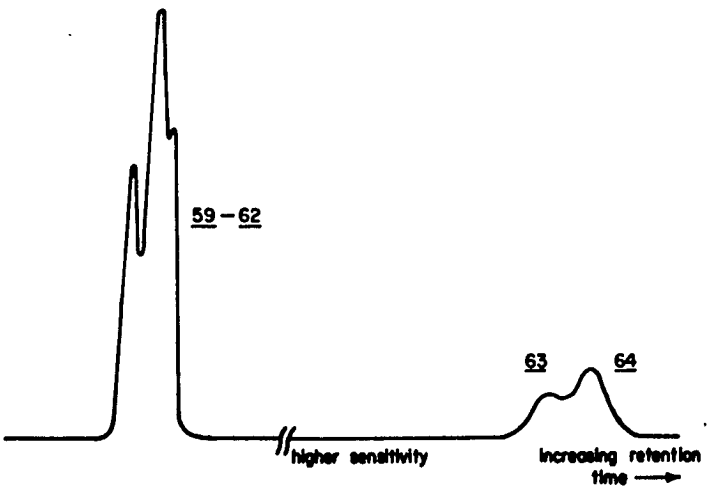

Figure 9a. TCP vpc traces of the cycloadducts of 1212 and butadiene.

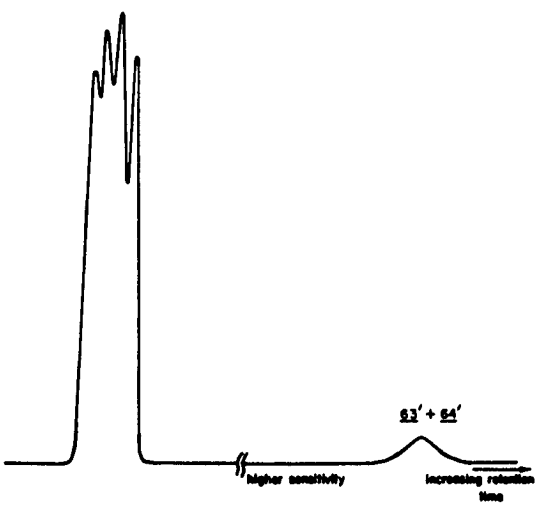

Figure 9b. TCP vpc traces of the hydrogenated cycloadducts of 1212 and butadiene.

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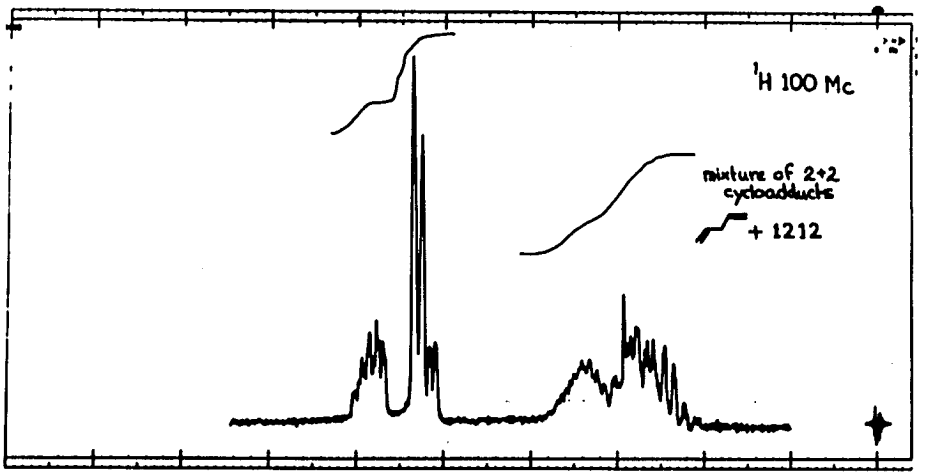

Figure 10a. 100 Mc ^{1}H nmr spectrum of the mixture of 1, 2 cycloadducts of 1212 and butadiene.

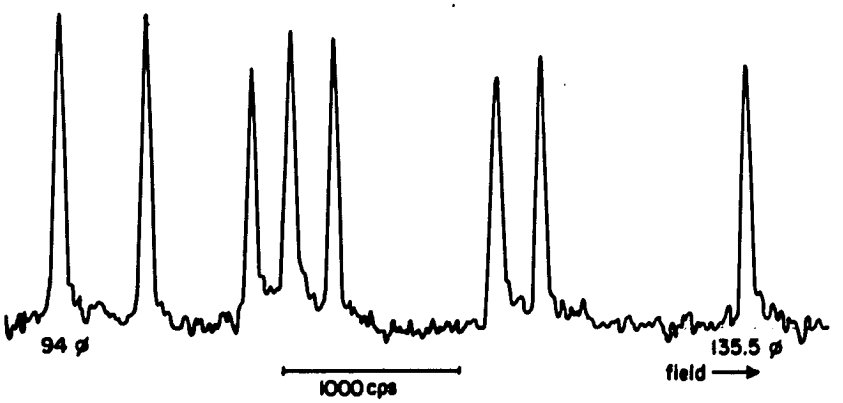

Figure 10b. 94.1 Mc ^{19}F nmr spectrum of the hydrogenated mixture of 1, 2 cycloadducts of 1212 and butadiene.

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The mass spectrum showed a parent peak at 186, equal to the calculated value for $C_6H_6Cl_2F_2$. The observed ratio for m, m + 2, m + 4 was 58:35.8:6.2 (calculated 57.4:36.7:5.9).

The elemental analysis of the hydrogenated mixture gave the following percentages: C:38.13%, H:4.33%, Cl:36.96%, F:20.58% (calculated C:38.12%, H:4.27%, Cl:20.10%, F:37.51%).

The nmr spectrum indicated the presence of ethylenic hydrogens which accounted for half of the total number of hydrogens. (Figure 10a)

Finally the fast ^{19}F nmr sweep of the hydrogenated mixture at room temperature exhibited eight peaks attributable to the two different fluorines of each of the four 1,2-cycloadducts (Figure 10b). (The 1,4-adducts have two equivalent fluorines.)

Clearly, the above observations served our purpose in allowing us to conclude that the first set of peaks observed in the chromatogram (Figure 9) did correspond to compounds 59-62.

We then turned our attention to the second set, comprising two poorly resolved peaks. Unfortunately, preparative vpc was not successful here either, indicating that we were probably dealing with very closely related compounds.

The mass spectrum of the mixture showed a parent peak at 186, equal to the calculated value for $C_6H_6Cl_2F_2$. The observed ratio of m, m + 2, m + 4 was 56:37:7 (calculated 57.4:36.7:5.9). The principal peaks and their intensities were 151(14), 115(100), 95(16), 75(11), 54(8). The prevalent fragmentation corresponded to the loss of Cl, loss of Cl and HCl, loss of Cl, HCl and HF, loss of Cl, HCl and 2HF and loss of butadiene.

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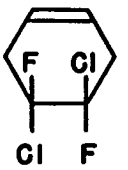
The nmr spectrum showed the presence of ethylenic and allylic hydrogens in the expected ratio of 1:2 which clearly eliminated the possibility of 1,2-cycloadducts (Figure 11a).

At that point there were good reasons to believe the two peaks observed in the chromatogram corresponded to a mixture of cis- and trans-4,5-difluoro-4,5-dichlorocyclohexenes 63 and 64.

63



64

The ^{19}F nmr spectrum at room temperature corroborated our view. The spectrum of the hydrogenated mixture (Figure 11b) exhibited two peaks in a ratio of 1.6:1 attributable to the fluorines of each of the 1,4-adducts respectively. Further, this ratio compared well with the ratio of the two somewhat overlapping peaks of the chromatogram estimated at 1.56:1.

Beyond that, the presence of fluorine in these molecules provided an excellent solution to a subtle and potentially formidable problem of particular importance to us, namely, differentiating between the cis- and trans-1,4-cycloadducts without isolating them.

Our reasoning was based on the ^{19}F nmr spectrum of the hydrogenated mixture[73] at -100° which is displayed in Figure 12. In the

[73] We hydrogenated the adducts because with cyclohexenes the temperature at which spectra cease changing is much lower than with the corresponding saturated compounds.

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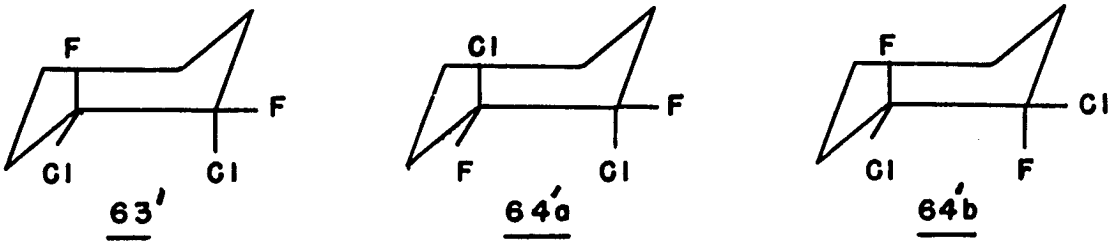
process of lowering the temperature the two absorptions displayed in Figure 11b persisted to about -30°. They then coalesced into a quite broad peak. At about -60° the shapes of the lines began to resemble those found in Figure 12. Finally no change was observed when the temperature was lowered below -100°, indicating that the spectrum represented a mixture of locked conformers and isomers.

A special note on conformational analysis is perhaps not out of place at this point. Studies of monochlorocyclohexanes using ^{1}H[74] or ^{19}F[75] nmr indicate the presence of about 20-30% of the conformer with the axial position contrary to the situation with alkyl groups. Accordingly we expected that the hydrogenated trans-adduct would give rise to two conformers 64'a and 64'b. On the other hand, only one conformation can be envisaged for the cis- counterpart.



We have then four different kinds of fluorine which are in perfect consonnance with the display of four peaks in the spectrum in Figure 12. Their assignments were made on the basis of the coupling constants

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[74] L. W. Reeves and R. O. Strømme, Can. J. Chem., 38, 1241 (1960).

[75] S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nugarajom and J. D. Roberts, J. Am. Chem. Soc., 89, 88 (1967).

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of the fluorines with the neighboring protons. We assumed that a relationship similar to the Karplus relationship between dihedral angle and coupling constant for vicinal protons is also valid for vicinal proton fluorine coupling as suggested by studies on difluoro cyclobutane.[76]

In order of increasing field we attributed the first absorption to 64'a. The sharpness of the peak is in accord with the equatorial nature of the fluorines as also found by Roberts in the gem difluorinated cyclohexane.[73] Then we have a doublet with a J value of 20 cps. This figure corresponds to the F-F coupling constant of 21.5 cps reported in the gauche rotamers of the meso isomer of CFClBr-CFClBr which led us to attribute this doublet to the equatorial fluorine of 63'.[77]

The third absorption assigned to 64'b appears also as a doublet with a large J value of 38 cps typical of a trans F-H coupling constant. Bovey et al.[78] have reported a similar value of 43.5 cps in the case of the axial conformer of fluorocyclohexane. Finally, the quartet corresponds to a doublet of doublets with respective coupling constants of 20 cps and 42 cps. The axial fluorine of 63' which couples strongly with both the equatorial counterpart and the axial vicinal hydrogen corresponds perfectly to that description.

We should remark in passing that the resonance peaks for the equatorial fluorines came at lower field than those for the axial

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[76] J. B. Lambert and J. D. Roberts, J. Am. Chem. Soc., 87, 3891 (1965).

[77] D. S. Thompson, R. A. Newmark and C. H. Sederholm, J. Chem. Phys., 37, 411 (1962).

[78] F. A. Bovey, E. W. Anderson, F. P. Hood and R. L. Kornegay, J. Chem. Phys., 40, 3099 (1964).

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fluorines, as was also the case with the difluorocyclohexanes studied by Roberts et al.[75]

The integration of each peak, still in order of increasing field, gave a ratio of 21.3:23.8:54:24. In perfect accord with our assignment the second and fourth peaks had within experimental error, the same area. Furthermore, the ratio of the first plus the third over the second plus the fourth was 1.58, which compared well with 1.6:1, ratio of the two peaks exhibited at room temperature. We also recall that this value corresponds to the ratio of the peaks observed in the chromatogram.

Beyond any doubt, the evidence presented was persuasive enough to permit us to assign, in order of increasing retention time, the two overlapping peaks of the chromatogram (Figure 9a) to compounds 63 and 64.

In summary, then we were able to continue our work upon a completely assured basis and study the cycloaddition with pure cis- and trans-1212.

The cis- and trans-1212 were separated from each other by preparative column chromotography according to the technology developed by R.C. Wheland.[79] Although very effective, the separation is very tedious and only small amounts of pure cis- or trans-1212 (~ 150 mg) were used in each run. The cycloadditions using at least a fivefold excess of fluoroalkene were carried out at 180°-190°C, in

[79]R.C. Wheland, Ph.D. Thesis, Harvard University, 1970.

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small, heavy walled, pyrex tubes sealed under vacuum. The results of our investigation based on analytical vapor chromatography (Figure 13) are reported in Table VII.

%cis 1212 before reaction	%cis 1212 after reaction	%1-4 adducts	ratio of 63 : 64	
> 99	97.5	2.1	57.5	42.5
< 1	< 1	2.4	23.0	77.0
46	45	2.2	39.0	61.0

TABLE VII

Clearly, the figures in Table VII reveal a great loss of configuration in both 1,4-cycloadditions which cannot be accounted for by the 1% cis impurity in recovered trans-1212 and the 2.5% trans impurity in recovered cis-1212. In view of the theory developed on page 54 these results were most gratifying and constituted cogent proof that biradical Diels-Alder reactions did exist.

Before discussing the above data in greater detail, we would like to describe our investigation of the cycloaddition of 1212 with trans, trans-2,4-hexadiene.

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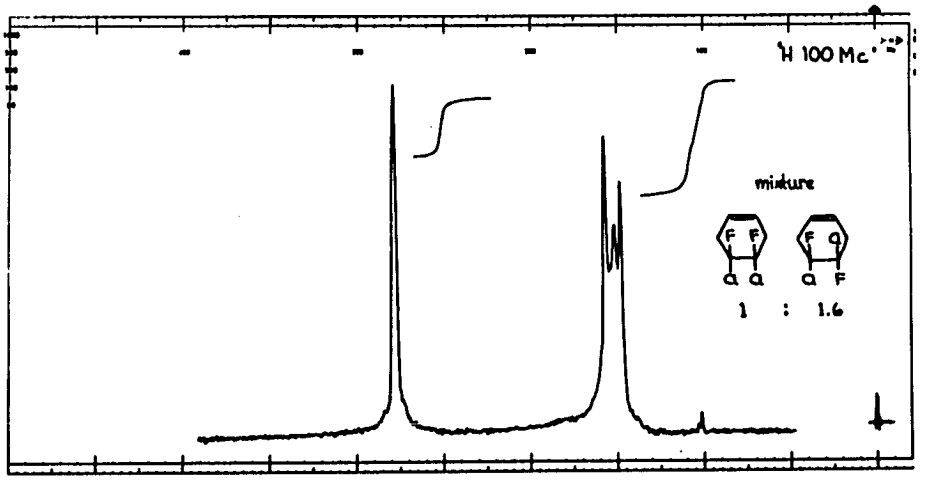

Figure 11a. 100 Mc ^{1}H nmr spectrum of a mixture of cis and trans-4, 5-dichloro-4, 5-difluorocyclohexenes.

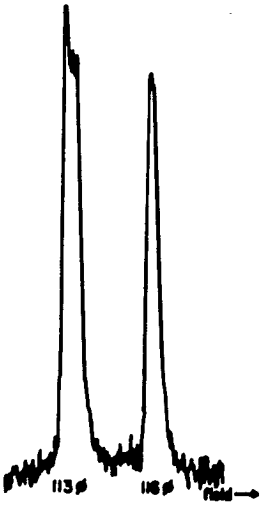

Figure 11b. 94.1 Mc ^{19}F nmr spectrum of a mixture of cis and trans-1, 2-dichloro-1, 2-difluorocyclohexanes at room temperature in CS_2.

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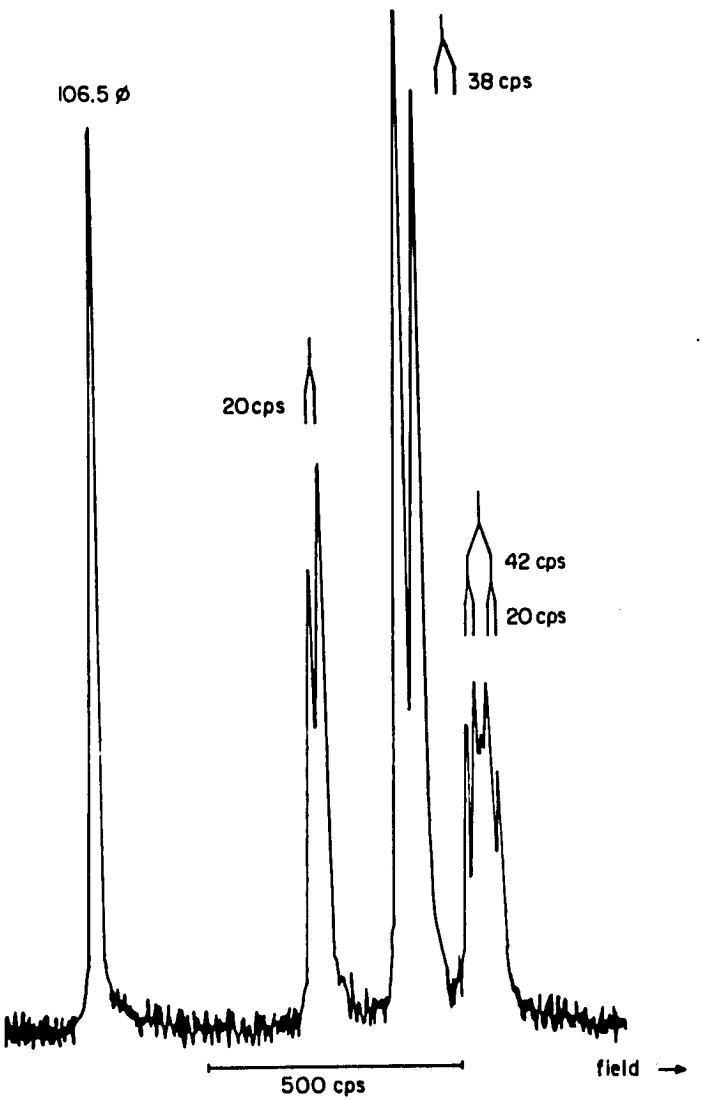

Figure 12. 94.1 Mc ^{19}F nmr spectrum of a mixture of cis and trans-1,2-dichloro-1,2-difluorocyclohexanes at -100° in CS_2.

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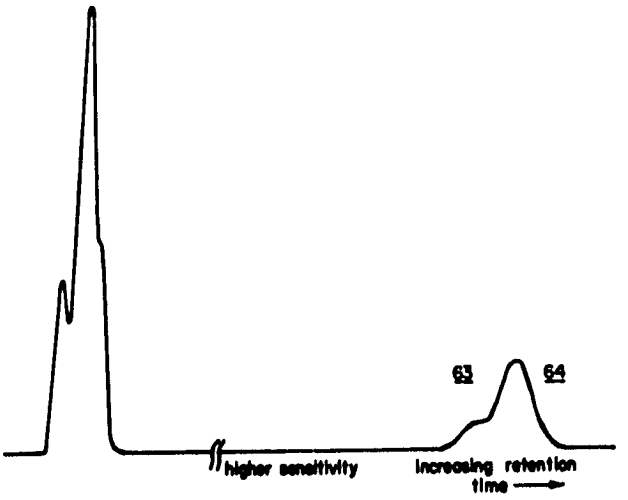
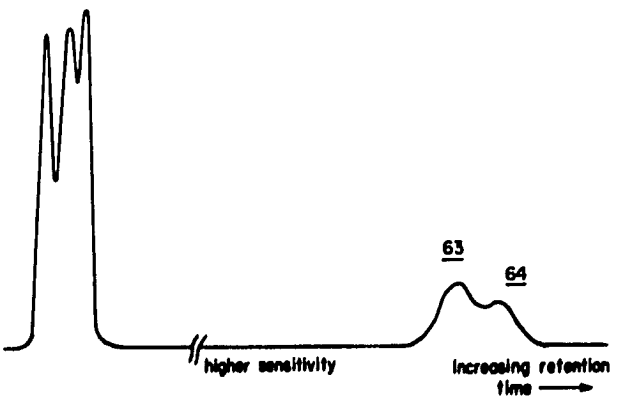


(a)



(b)

Figure 13. (a) TCP vpc traces of the cycloadducts of trans 1212 and butadiene. (b) TCP vpc traces of the cycloadducts of cis 1212 and butadiene.

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B Trans, trans-2,4-hexadiene

The conditions of the cycloaddition were similar to those used with butadiene. The vpc analysis of the reaction mixture also revealed two sets of peaks (Figure 15). The first comprised eight peaks; we did not attempt to isolate the corresponding compounds. They were not 2,4-hexadiene dimers and on the basis of the mass spectrum, the elemental analysis (C: 44.95%, H: 4.76%, Cl: 32.24%, F: 18.05%, calculated, C: 44.67%, H: 4.69%, Cl: 32.97%, F: 17.67%), and nmr spectrum of the mixture we believe they correspond to the eight possible 1,2 adducts of trans, trans-2,4-hexadiene and 1212.

Of greater interest to us was the second set of three peaks corresponding to at least three compounds A, B, and C which we were able to isolate. Their individual mass spectra showed a parent peak at 214, equal to the calculated value for $C_8H_{10}Cl_2F_2$. The observed ratio of m, m + 2, m + 4 substantiated the presence of two chlorine atoms. All three nmr spectra showed ethylenic and allylic protons in a ratio of 1:1 indicating we had isolated 1,4-cycloadducts of trans, trans-2,4-hexadiene and 1212. We were then left with the task of elucidating the configuration of the compounds at hand. Information gleaned from ^{1}H and ^{19}F nmr spectroscopy at room and low temperature permitted us to unravel this unwieldy problem.

To prepare the stage for our reasoning we shall draw the hydrogenated equivalent[73] of the six possible 1,4 adducts as well as their theoretically possible conformers.

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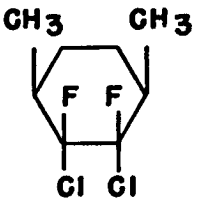
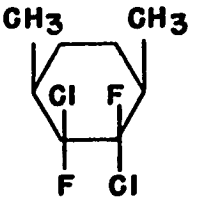


73'



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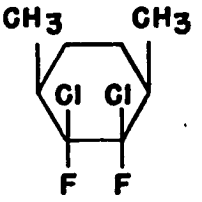
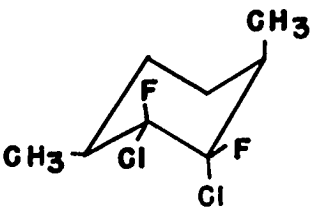
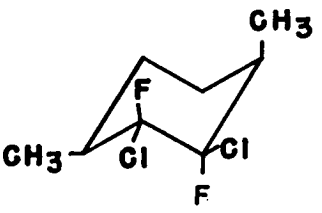
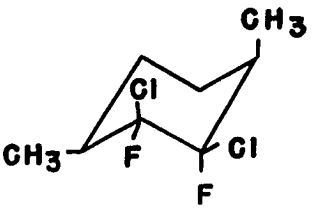


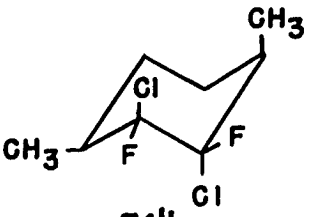
75'



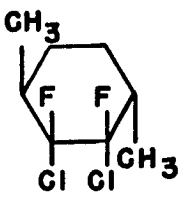


74'a

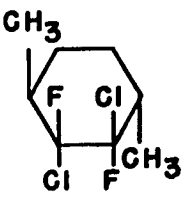




74'b



76'



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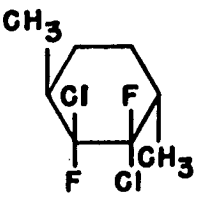
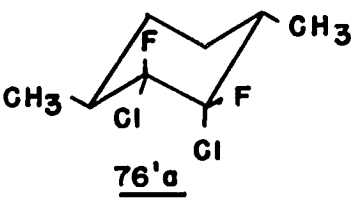
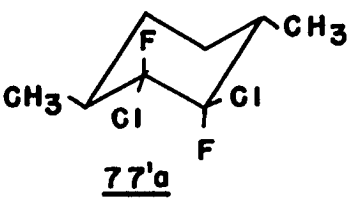


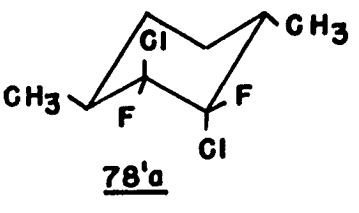
78'



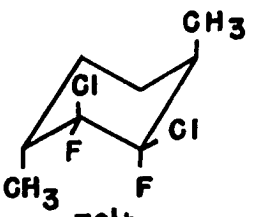
76'a



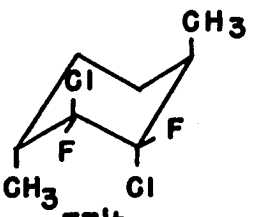
77'a



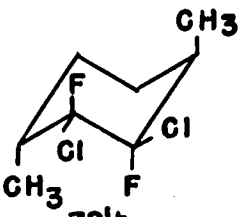
78'a



76'b



77'b



78'b

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Room temperature ^{1}H and ^{19}F nmr spectroscopy (Figures 16, 18, 19a and 21a) revealed that the hydrogenated adducts A' and C' both have equivalent methyl groups and fluorines. Four compounds, 73', 75', 77', and 78', fit this description. However, at -100° at which temperature the molecules are frozen, the ^{19}F spectra of A' and C' exhibited two absorptions of equal intensity (Figures 19b and 21b) which clearly eliminated compounds 77' and 78'. The former, due to the overwhelmingly disfavored conformer 77'b in which the two methyls and the two chlorines occupy axial positions, would have yielded only one absorption attributable to the two magnetically equivalent fluorines of 77'a. On the other hand, two absorptions of quite different intensities would have been observed for the 78'. The chlorine atoms are more prone than methyl groups to assume axial conformation and consequently conformer 78'a is expected to be preponderant over its counterpart 78'b. Finally the ^{19}F nmr spectra of 73' and 75', each of which in frozen conformation possesses two magnetically non equivalent fluorines, are expected to exhibit two absorptions of equal intensity. We therefore believe that substance A' and C' correspond to 73' and 75'.

Final identification can be inferred from the analysis of the ^{19}F nmr splitting pattern at -100°. First, to facilitate our presentation we should recall the discussion of the splitting pattern of both cis- and trans-1,2-dichloro-1,2difluorocyclohexanes at -100°. More precisely, we have seen that the presence of the two chlorines did not perturb the splitting pattern from the one observed by various researchers in the fluorinated cyclohexanes.[75,78] In the case at issue, in addition to the

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two chlorines we introduced two methyl groups which exercise strong diaxial non-bonding interaction with chlorine or fluorine. The molecules should flatten somewhat; dihedral angles will differ from their normal values and consequently the H-F coupling constants will be different from those observed with cis- and trans-1,2-dichloro-1,2-difluorocyclohexanes. Figure 14 in which is plotted the variation of the vicinal H-F couplings (using ethyl fluoride as a model) with dihedral angle ϕ, predicted by various methods,[80] will help us in rationalizing our experimental observations.

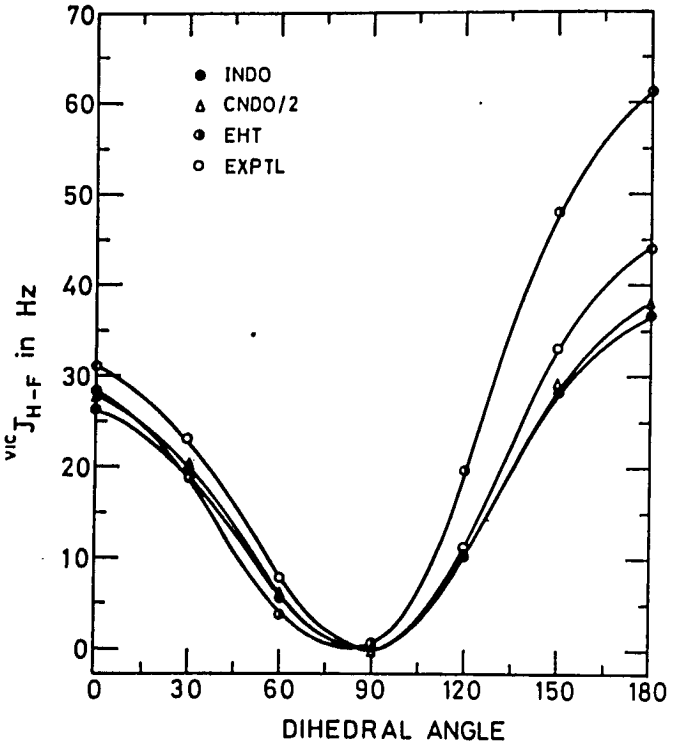

Figure 14. Variation of HF coupling with dihedral angle.

[80]Gopinathan, M. S., and Narasimhan, P. T., 1971, Molec. Phys., 21, 1141.

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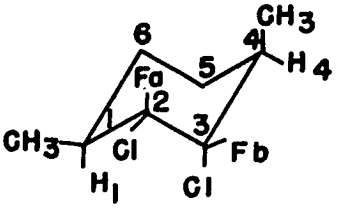
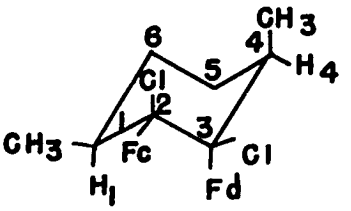
The spectra of both A' and C' exhibit a quartet and a doublet. Beyond any doubt, the doublets (J = 19.5 in A' and 18.5 cps in C') arise from the couplings between the two vicinal fluorines while the quartets are due to the fluorines which couple with their adjacent hydrogens in addition to coupling with their counterparts.



73'



75'

We attributed the quartet with J = 19.5 and 28 cps (spectrum of A') to the Fa of 73'. The diaxial nature of H and F favors their strong magnetic interaction. Nevertheless, the coupling constant (28 cps) is lower than that observed for the axial fluorines of 63' (38 cps). This fact can be explained in terms of the CH_3-F diaxial repulsion which decreases the dihedral angle between H_1-C_1 and C_2-Fa bonds, (henceforth to be called H_1-C_1-C_2-Fa). Concomitantly this interaction increases the Fb-C_3-C_4-H_4 dihedral angle which becomes larger than 60°; therefore, as is shown in Figure 19b, there is no appreciable magnetic interaction between Fb and H_4.

Considering now 75', the repulsion between Cl and CH_3 will decrease both dihedral angle H_1-C_1-C_2-Fc and Fd-C_3-C_4-H_4 from their normal value of 60° and it is not inconceivable that one of them

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(probably Fd-C_3-C_4-H_4) will be small enough (35-45°) to allow a coupling constant of 14.5 cps between H and F, as sown in the spectrum of C'.

Clearly the above evidence suggests that we assign to substances A' and C' the structures 73' and 75' respectively.

^{1}H nmr spectroscopy (Figures 16 and 18) at room temperature corroborates our assignments. The methyl groups of C' exhibit a doublet while the methyl groups of A' exhibit two sets of three peaks. In accord with all the reported observations we attributed this additional coupling to long range through space interaction with fluorine[81,58] which requires the methyl groups and the fluorine to be on the same side of the plane defined by the six membered ring skeleton. As expected only substance 73' meets this condition.

We are now left with the assignment of the structure of substance B'. The non-equivalence of the methyl groups and fluorines, as inferred from the room temperature ^{1}H and ^{19}F nmr spectra (Figures 17 and 20a) presented us with 74' and 76' as possible candidates.

Here again, low temperature ^{19}F nmr spectroscopy proved very useful. Figure 20a displays the spectrum at -100°. In sharp contrast with the other cases discussed so far, little change occurred during the lowering of the temperature, the major transformation being the appearance of two small peaks (~4%) indicated by two arrows. We had

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[81] The two methyls are then part of a potentially very complex $AA'X_3X'_3$ system which, to our knowledge has not been analysed yet.

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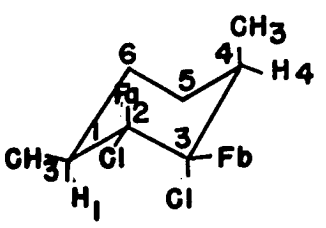
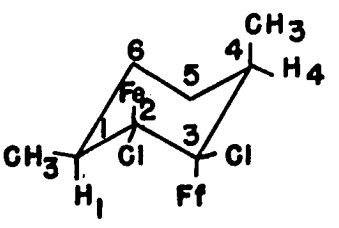
then two sets of two peaks which clearly indicated the presence of a mixture of two conformers. This feature alone allowed us to establish that we were dealing with substance 74'. We rejected 76' on the basis that this substance would have yielded only one conformer. A simplified model which takes into account only the fact that the two methyl groups are axial in 76'b without further considering the strong CH_3-Cl non-bonding interaction, reveals that 76'b has a higher energy level than its 76'a counterpart by 3.6 kcal,[82] which at -100° corresponds to the ratio 76'a : 76'b as $100 : >10^{-4}$. On the other hand, the difference in energy between 74'a and 74'b corresponds only to having two chlorines axial instead of two fluorines. In the case of the trans-1,2-dichloro-1,2-difluorocyclohexane at -100° we have seen that this fact alone led to a ratio of 21.3 : 54 in favor of the conformer with the two equatorial chlorines. In the case at hand, we have an additional CH_3-Cl non-bonding interaction which shifted the ratio 74'a : 74'b to 96 : 4.

The ^{19}F nmr splitting pattern of the two large peaks of B' at -100° (Figure 20b) reinforced our assignment. We attributed the upfield quartet to Fe. As a result of the CH_3-Fe non-bonding interaction



73'



74'a

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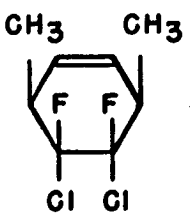
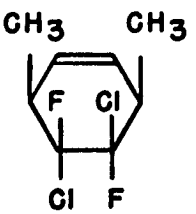
conformer 74'a should have a spacial arrangement similar to that of 73'. It was then most gratifying to find a H_1Fe coupling constant of 29 cps which compared well with the H_1Fa coupling constant of 28 cps observed in 73'. Finally the $Ff\text{-}H_4$ coupling constant of 12.5 cps was in accord with the lowering of the $Ff\text{-}C_3\text{-}C_4\text{-}H_4$ dihedral angle from its normal value of 60°.

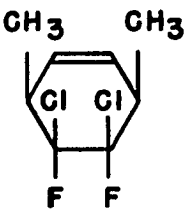
In summary, we have so far established that the three isolated 1,4-cycloadducts A, B, and C arising from the cycloaddition of trans, trans-2,4-hexadiene and a mixture of 1212 isomers correspond to structures 73, 74, and 75 respectively.



73



74



75

We should now notice that all three 1,4 cycloadducts isolated have their methyl groups cis to each other. In the present work, we have not ascertained that no 1,4 cycloadducts with trans methyl groups were present, which, for complete certainty, would require their independent synthesis. Nevertheless, should they exist, we feel confident that they would be present only in minute amounts. (On the order of 1% compared to the amount of 73, 74, and 75.) Based upon the experience

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[82] M. Hanack, Conformation Theory, page 72, Academic Press, New York, 1965.

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which we gained in the course of our work we believe that the retention times of the trans-1,4-cycloadducts would be very similar to those of the cis counterparts. A careful examination of the chromatogram in this region[83] revealed no additional peaks. Further, should there have been overlapping of the peaks, ^{19}F spectroscopy would have indicated it. Although there is little reason to question the non- (or nearly non-) occurrence of 1,4 cycloadducts with trans methyl groups, it is important to emphasize that no subsequent argument will be based upon this supposition.

Nevertheless, using pure cis and trans 1212 the above information permitted us to determine the stereochemical behavior of the dienophile in the Diels-Alder reaction of trans, trans-2,4-hexadiene and 1212.

The cycloadditions were carried out under conditions similar to those reported in the case of butadiene and the results of our investigation based on analytical vapor chromotography are reported in Table VIII.

TABLE VIII

%cis 1212 before reaction	%cis 1212 after reaction	%1-4 adducts	%73-75	%74	ratio $\frac{73+74}{75}$
> 99	> 99	16.8	15.4	1.36	91.9:8.1
< 1	< 1	19.4	0.97	18.4	5:95
46	45.5	16[84]	6.72	9.3	42:58

[83] Perhaps, at this point we should recall that the three isolated 1,4-cycloadducts had longer retention times than the 1,2 cycloadducts (Figure 15).

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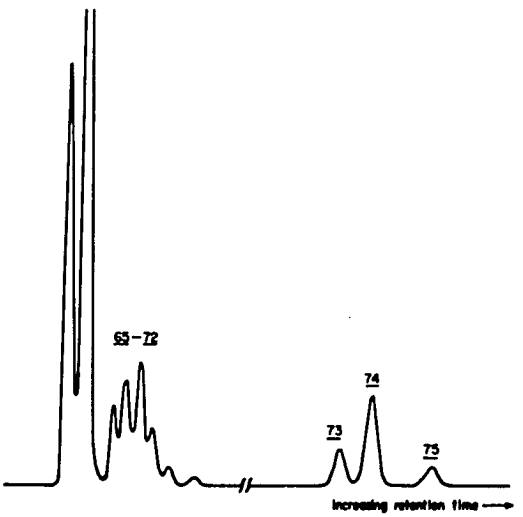

Figure 15. TCEP vpc traces of the cycloadducts of 1212 and trans, trans-2,4-hexadiene.

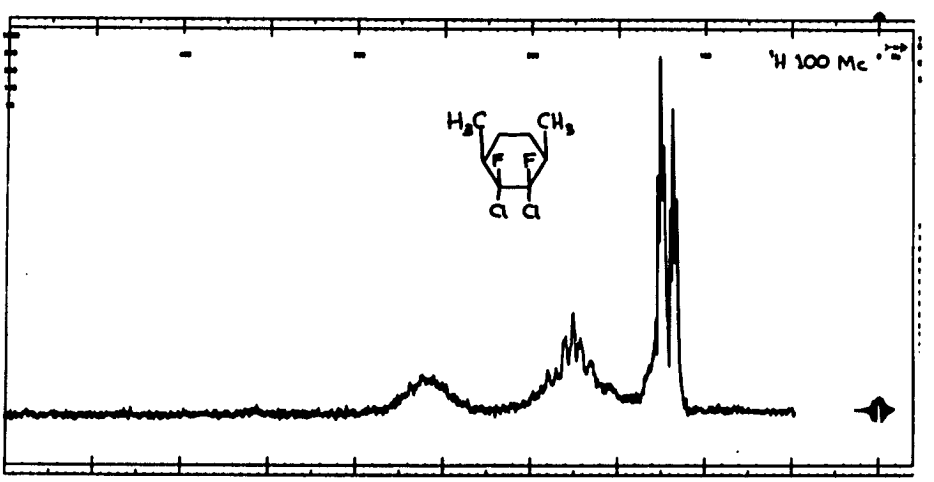

Figure 16. 100 Mc ^{1}H nmr spectrum of 73' (A') at room temperature.

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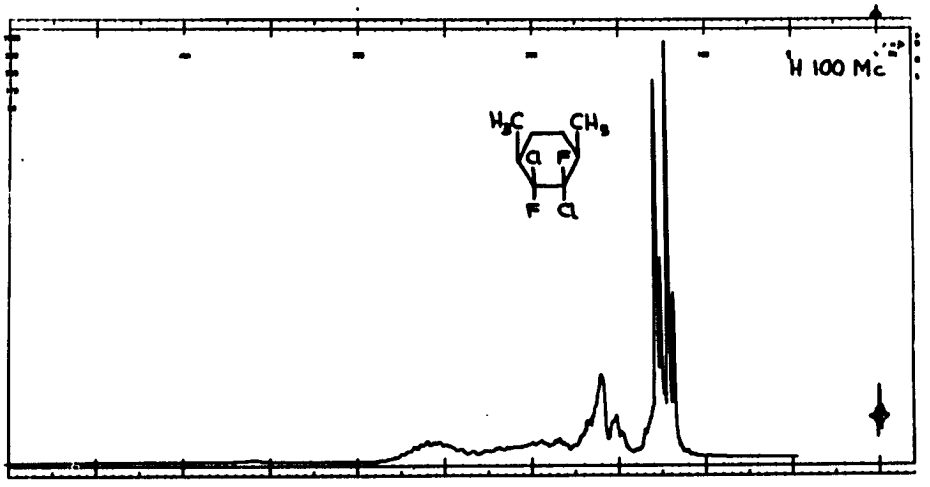

Figure 17. 100 Mc ^{1}H nmr spectrum of 74' (B') at room temperature.

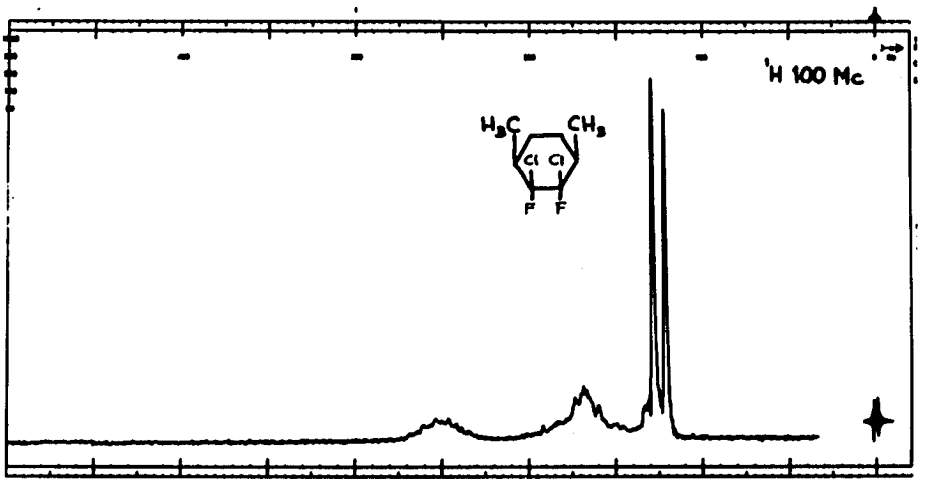

Figure 18. 100 Mc ^{1}H nmr spectrum of 75' (C') at room temperature.

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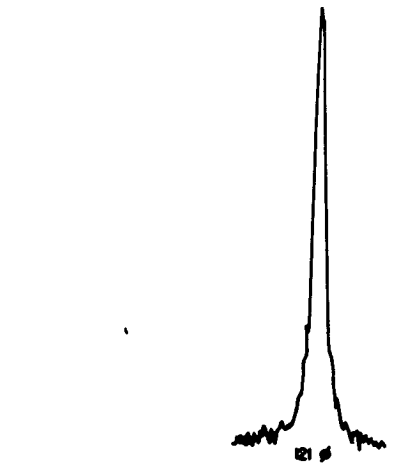
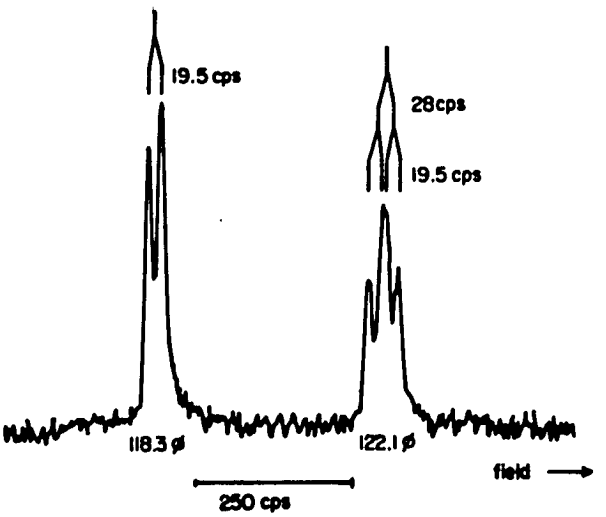


(a)



(b)

Figure 19. 91.4 Mc ^{19}F nmr spectra of 73' (A') in CS_2. (a) at room temperature, (b) at -100°.

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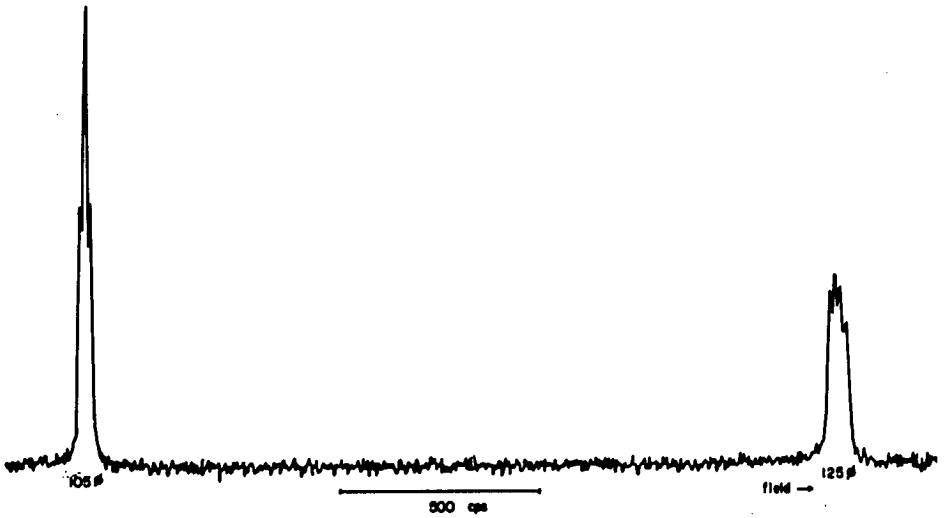
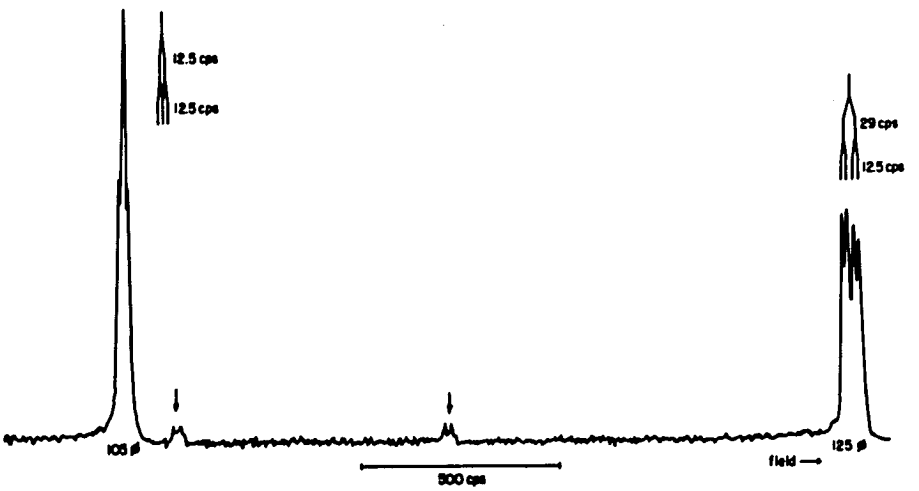


(a)



(b)

Figure 20. 94.1 Mc ^{19}F spectra of 74' (B') in CS_2. (a) at room temperature, (b) at -100°.

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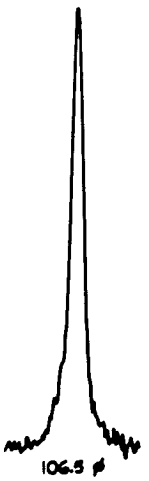
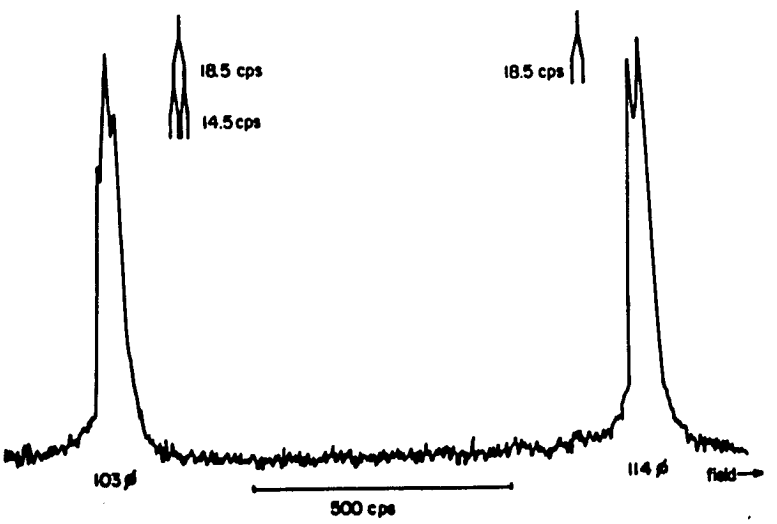


(a)



(b)

Figure 21. 94.1 Mc ^{19}F nmr spectra of 75' (C') in CS_2. (a) at room temperature, (b) at -100°.

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Here too, the data clearly indicate a loss of configuration of the dienophile which cannot be accounted for by the 1% cis impurity in the recovered trans 1212 and the 1% trans impurity in the recovered cis 1212. However, on going from butadiene to 2,4-hexadiene we notice a large increase in the amount of 1,4 adduct accompanied by an increase in stereospecificity.

We now have at hand a large body of information pertaining to the 1,4 cycloaddition of 1122 and 1212 with various dienes. The consideration of any one of the reactions in relation to the others should help us in drawing conclusions concerning their mechanisms and shed light on the competition between concerted and biradical Diels-Alder reactions.

VII Discussion

In discussing 1,4 cycloaddition mechanism the most convenient point of reference is provided by the Diels-Alder reactions of 1212, the stereo-chemical behavior of which has been fully established in three instances, namely, reactions with butadiene, trans, trans-2,4-hexadiene and cyclopentadiene.

In both the 1-4 cycloadditions with butadiene and trans, trans-2,4-hexadiene we observed a loss of configuration which could not be accounted for by the cis impurity in the recovered trans-1212 nor by

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[84] We would have expected this figure to lie between 16.8 and 19.4. We attribute this discrepancy to the fact that this run was not done simultaneously with the two others and the conditions of the reaction might have been somewhat different.

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the trans impurity in the cis-1212 (Table VII and VIII, page 68 and 85).[85] Beyond any doubt, these observations provide evidence that the biradical mechanism plays a role in the Diels-Alder reaction under consideration.

At this point, it is important to assert that these findings do not call into question the theory propounded by Woodward and Hoffmann. They do not even violate the famous "Rules"; on the contrary, our results bring more sophistication to the theory of concerted electrocyclic reactions by making inroads toward the discovery of its boundaries.

Looking at the problem in these terms, the first question to come to mind concerns the degree of biradical versus concerted behavior attendant upon a non-stereospecific Diels-Alder reaction. Of course, a straightforward answer could be given in the case of an identical product mixture from starting material of either configuration. However, the results pertaining to 2 + 2 biradical cycloaddition indicate there is little chance for this to occur. In most cases, researchers have observed a competition between rotation within the intermediate and the ring closure such that the products from each isomer show a net retention. Clearly, it appears that the assessment of the role played by the biradical and concerted process will vary among different cases and will rely on comparative studies and theoretical considerations.

---

[85] The data pertaining to the runs with the 46/54 mixture of cis and trans 1212 indicate that the rate of the cycloadditions with cis and trans 1212 are very similar. Therefore, the loss of configuration of one of the isomers cannot be accounted for by the much faster rate of its counterpart present in the reaction as an impurity.

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Once a reasonable value can be secured, for means of comparison, we will also compute the retention index PQ where P and Q are defined as follows:[86]

$$P = \frac{\text{retained product}}{\text{inverted product}} \text{ from cis starting material}$$

$$Q = \frac{\text{retained product}}{\text{inverted product}} \text{ from trans starting material}$$

In terms of these conventions, a stereospecific biradical reaction will have a PQ equal to infinity, and a cycloaddition proceeding over a freely rotating and eventually equilibrated biradical will have a PQ equal to one.

Let us now return to the case of butadiene and 1212. We observe at once(Figure VII, page 68) the significant loss of configuration experienced in both the cis-1212 (42.5%) and trans-1212 (23%) cycloaddition. Assuming that the process was entirely biradical, and using the above conventions, we computed a PQ of 4.5 which is smaller than those (5.6 and 11.5) obtained in a biradical 1,2-cycloaddition of 1212 and cyclopentadiene.[54] It is then very likely that the 1,4 cycloaddition of butadiene and 1212 is mostly of a biradical nature but it is not possible to assert that the concerted mechanism also does not intervene at all.

Considering now the reaction with trans, trans-2,4-hexadiene, we notice a large increase in the amount of 1,4 cycloadduct and an increase in stereospecificity. We believe that both these increases are due to the intervening of the concerted mechanism for the following

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[86] P. D. Bartlett, "Biradicals in Cycloaddition", 23rd IUPAC Congress, Pure Appl. Chem., 4, 281 (1971).

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reasons. First, on going from butadiene to trans, trans-2,4-hexadiene it is not expected that the transoid versus cisoid diene or the ratio 1,4 versus 1,2 ring closure will change drastically. Therefore, if the mechanism had been entirely biradical we would not have had an increase in the ratio 1,4 versus 1,2 cycloadducts. On the other hand, accumulated evidence indicates that the terminal trans substitution of the two methyl groups affects the rates of concerted 1,4 and stepwise additions in opposite directions and, consequently, the fraction of the 1,4 cycloadducts must increase on going from butadiene to hexadiene. As a case in point, a comparison between the 1,2 mode of addition of butadiene and trans, trans-2,4-hexadiene toward 1122 revealed that the butadiene is more reactive by a factor of 22. Further, trans, trans-2,4-hexadiene is more reactive than butadiene toward maleic anhydride by a factor of 11-12. We do not know whether these factors are as large in the case at issue but if they are, we will notice that much concerted behavior was not needed in the Diels-Alder reaction of butadiene and 1212 to yield 16-19% 1,4 cycloadduct in the case of trans, trans-2,4-hexadiene.

Second, the two methyl groups of the 2,4-hexadiene should not have a great influence, if any, on the PQ of the biradical 1,4 cycloaddition and, therefore, an increase in stereospecificity must indicate an increase in the role played by the concerted process.

Assuming that the P and Q are identical to those observed in butadiene we can compute an approximate value for the role played by the biradical mechanism. First, considering the cycloaddition with

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pure cis-1212 (Table VIII, page 80) we obtained 1.36% of the 1,4-cycloadduct with loss of halogen configuration. If we assume, as is the case with butadiene, that 42.5% of the 1,4 cycloadducts have lost their halogen configuration, we arrive at the following estimated percentage representing the role of the biradical mechanism:

$$1.36 \times \frac{100}{42.5} = 3.2\% \quad .$$

By the same token we can deduce that the cycloaddition with trans-1212 yields

$$0.97 \times \frac{100}{23} = 4.2\%$$

of 1,4 cycloadducts through a biradical pathway.

Finally, the reaction with cyclopentadiene yielded 94% and 97.3% 1,4 adducts with cis and trans 1212 respectively. No loss of configuration could be observed, indicating that the process was fully stereospecific (allowing for experimental error).

In summary, 1212 stands as a versatile dienophile which has allowed us to cover the total spectrum of biradical and concerted Diels-Alder reaction and, therefore, reveal their limits. We will note that in the cycloadditions discussed above, the response of the biradical and concerted pathways to substituent effects in the diene is in complete accord with previous studies. It should also be stressed that the concerted nature of a Diels-Alder reaction increases with the amount of 1,4 versus 1,2 cycloadducts in the reaction and, therefore, a cycloaddition yielding only 1,4 adducts is entirely concerted.[87] Finally,

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the above results should shed light on the mechanism of the Diels-Alder reaction of 1122 with butadiene and trans, trans-2,4-hexadiene.

First we will point out that the amount of 1,4 cycloadduct obtained with 1122 and cyclopentadiene[88] or trans, trans-2,4-hexadiene is lower than with either cis or trans 1212. Therefore, 1122 has a greater ability to enter biradical cycloaddition than 1212 which is attributed to the fact that one end of the intermediate biradical is stabilized by two chlorines instead of one in the case of 1212. Consequently, if the Diels-Alder reaction of 1212 and butadiene is biradical, we can infer that the Diels-Alder reaction of 1122 and butadiene is also biradical. Further, if the latter were concerted, we would expect, as in the case of 1212, that the amount of 1,4 cycloadducts would increase on going from butadiene to trans, trans-2,4-hexadiene, but this is not the case.

Considering now trans, trans-2,4-hexadiene, we have seen that in its reaction with 1212, the presence of the two methyl groups did not prevent the intermediate 1,4 biradical from yielding 1,4 cycloadducts, and by analogy, it should also be so when 1122 is used as the dienophile. As a matter of fact, we have observed such 1,4 ring closure in the cycloaddition with cis, trans-2,4-hexadiene. Clearly, all the evidence

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[87] Another way to express the matter is to say that the non concerted Diels-Alder reaction is due to a branching of the biradical mechanism which yields mostly 1,2 cycloadducts. Therefore, the absence of 1,2 cycloadducts implies that the cycloaddition is entirely concerted.

[88] P. D. Bartlett, L. K. Montgomery and B. Seidel, J. Am. Chem. Soc., 86, 616, (1964).

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available points to the fact that the Diels-Alder mechanism of trans, trans-2,4-hexadiene and 1122 is also biradical.

We have here, then, a very interesting example of a biradical cycloaddition which is stereospecific (or at least 99% stereospecific). We believe as was discussed above that this stereospecificity should be attributed to steric effects. The investigation of the cycloaddition of 1212 and trans, trans-2,4-hexadiene in which we believe that the diene does not isomerize (whereas the dienophile does) also lends support to our contention.

VIII Conclusion

In the present work we have shown that singlet 1,4 biradicals arising from the reaction between certain dienes and dienophiles have the ability to yield six membered ring adducts in addition to the four membered ones, proving then the existence of biradical Diels-Alder reactions. In some instances, as exemplified by the 1,4 cycloaddition of 1212 and trans, trans-2,4-hexadiene we have observed an interplay of both concerted and biradical mechanisms which reveals the limit of applicability of the well accepted view that Diels-Alder reactions are concerted.

The use of the above cycloaddition as a model can provide an insight into the amount of concertedness attendant upon a given Diels-Alder reaction in terms of various parameters inherent in the diene and the dienophile.[89]

In all cases known so far the intermediate biradical prefers closing 1,2 versus 1,4 and consequently a cycloaddition yielding only

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Diels-Alder products is likely to be entirely concerted.

Finally, a point of much importance concerns the discovery of a biradical Diels-Alder reaction which has an abnormally high stereospecificity attributed to steric effects. This observation stresses the important role that steric factors play in the interpretation of reaction mechanisms, a role which is frequently ignored. More precisely, when considering concerted versus biradical behavior it should be born in mind that the stereospecificity of a given reaction is a necessary condition for concertedness but stereospecificity does not always imply concertedness. Therefore, no conclusion as to which mechanism is operating can be drawn by considering stereospecificity alone.

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[89]We have discussed at length in the first chapter, the elements affecting the diene with respect to biradical or concerted behavior. In considering the dienophile, three factors influencing its biradical behavior are descernible (1) exothermicity of double bond opening, (2) accomodation of the odd electrons on the potential biradical and (3) ease of approach of the reactants in the formation of the initial new bond. See P. D. Bartlett and R. C. Wheland, J. Am. Che. Soc., 94, 2145 (1972).

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CHAPTER III

EXPERIMENTAL

Elemental analyses were performed by the Scandinavian Microanalytical Laboratories, Herlew, Denmark.

^{1}H nmr spectra were taken on either a Varian A-60 or HA-100. ^{19}F nmr spectra were taken in the HR mode on the Varian HA-100, and reported as Φ values.[90] Determination of the coupling constants and chemical shifts for the ^{19}F nmr spectra employed audio-frequency sideband modulation introduced by an internal oscillator. The ^{19}F coupling constants are generally reproducible to within $\pm$ 1 Hz. No attempt was made to run the ^{19}F nmr spectra at uniform concentration or to extrapolate chemical shifts to infinite dilution so that the reproducibility of the reported shifts may be somewhat poorer than the precision of $\pm$ 1Φ found when considering individual samples. A Varian Temperature Controller was used for variable temperature nmr experiments.

Infrared spectra were obtained by the use of a Perkin-Elmer Model 137-B Spectrometer.

Mass spectra were taken on an Associated Electrical Industries Ltd. Model MS 9 mass spectrometer.

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[90] Φ value: chemical shift of fluorine defined as parts per million upfield from the internal reference $CFCl_3$. G. Fillipovick and G. V. D. Tiers, J Phys. Chem., 63, 761 (1956).

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Vapor phase chromatograms were run with Hewlett-Packard F and M Models 700 and 7620 and Varian Aerograph Models 90-P. Peak areas were measured by a disk integrator and Hewlett-Packard digital integrator. If the base line drifted, more reproducible results were obtained by cutting out and weighing the paper to determine the area under the peak.

Table IX describes the various vapor phase chromatography columns utilized. The following notation has been used to describe the columns.

P: chromosorb P solid support.

W: chromosorb W solid support.

AW: acid washed solid support.

TCP: Tricresyl phosphate.

TCEP: 1,2,3, Tris (2 Cyano Ethoxy) Propane.

ODPN: oxydiproprionitrile.

2,4-Hexadienes

Trans,trans, trans,cis, and cis,cis-2,4-hexadienes were purchased from Columbia Organic Chemicals Co., Inc. Analysis was accomplished by using column G at room temperature. The composition of the three isomers has been reported on page 41.

Preparation and Isolation of cis-4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene

A mixture of 5 g. (0.061 mole) of trans,trans-2,4-hexadiene and 30 g. (0.227 mole) of 1,1-dichloro-2,2-difluoroethylene (hereafter called 1122), was heated at 125° in a thick-walled sealed tube. The unreacted hexadiene and 1122 were evaporated under

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TABLE IX

VPC CONDITIONS

Column	Liquid Phase	Solid Phase	Mesh	Length (ft.)	Outer Diameter (in.)	Chromatograph
A	20% Carbowax 20M	Chromosorb P	60/80	16	1/8	F&M 700
B	20% Carbowax 20M	Chromosorb W-AW	60/80	12	1/4	F&M 700
C	20% Carbowax 20M	Chromosorb W-AW	45/60	7	1/4	Autoprep 90-P
D	20% TCEP	Chromosorb P	60/80	30	1/8	F&M 7620
E	25% TCEP	Chromosorb P	60/80	10	1/4	Autoprep 90-P
F	20% TCP	Chromosorb W	60/80	30	1/8	F&M 7620
G	20% ββ' ODPN	Chromosorb P	60/80	17.5	1/8	F&M 7620
H	5% DMSO	Alumina	60/80	5	1/8	F&M 700
I	5% DMSO	Alumina	60/80	15	1/4	Autoprep 90-P

reduced pressure at room temperature. Distillation of the material gave 10 g. (76%) of adducts (estimated b. p. 64° at 40mm.).

Isolation of the cis-1,4 adduct (50 mg.) was achieved by preparative vpc using column C (column 130°, detector 170°, injector 160° and helium flow: 1cc/sec.). The 1,4 adduct (retention time 30 min.) was nicely separated from the 1,2 adducts which gave one enormous peak (retention time 10-20 min.).

Hydrogenation of cis-4,4-dichloro-5,5-difluoro-3,6-dimethylcyclohexene

In 2 ml. of ethyl acetate 40 mg. of cis-1,4 cycloadduct was dissolved. To this was added 0.006 g. of commercial platinium oxide catalyst. The catalyst was not hydrogenated before addition of the adduct. The mixture was hydrogenated at 27° and 1 atm. pressure. In 30 min. 5 ml of hydrogen was taken up and then the reaction stopped completely. (Theoretical hydrogen uptake: 22.4 X 0.04/214 X 300/273 = 4.6 ml.). The catalyst was removed by filtration.

Preparative vpc on column C yielded 35 mg. of cis-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexane. Both the ir and the nmr no longer showed olefinic absorptions.

Dehalogenation of cis-1,1-Dichloro-2,2-difluoro-3,6-dimethylcyclohexane

A mixture of 25 mg. of vpc collected cis-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexane 0.1 g. of Merck zinc dust, 0.1 g. of $Cr_2(SO_4)_3 . nH_2O$, 1 ml. of water, and 1 ml. of dimethyl formamide were stirred under nitrogen in a sealed thick-walled Pyrex tube

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containing a stirring bar. The tube was heated in a 95-110° oil bath for a day.

After cooling in dry ice-acetone, the tube was opened and its sides washed down with less than 1 ml. of pentane. The tube was warmed until the liquified contents could be vigorously shaken. Several milliliters of water were added after which the tube was again placed in dry ice-acetone. The pentane layer was decanted into a sample vial once the aqueous layer froze solid. The vial was refrigerated until such time as the vpc analysis could be run using column C (column 130°, detector 170°, injector 160° and helium flow 10 ml./10 sec.). There was obtained 12 mg. (64%) of dehalogenated product (retention time: 19 min.).

Synthesis of Ethyl-3, 3-dichloro-2-fluoroacrylate

50 g. of ethyl-3, 3-dichloro-2-fluoroacrylate was synthesized according to the method developed by D. C. England, R. V. Lindsey, Jr., and L. R. Melby, J. Am. Chem. Soc., 80, 6442 (1958).

Thermal Cycloaddition of Ethyl-3, 3-dichloro-2-fluoroacrylate to trans, trans-2, 4-Hexadiene

A mixture of 9 g. of ethyl-3, 3-dichloro-2-fluoroacrylate, (0.0517 mole) 3 g. of trans, trans-2, 4-hexadiene (0.0366 mole) and 10 ml. of benzene were sealed under vacuum in a heavy walled Pyrex tube. After heating for 3 days at 185°, the tube was opened and the contents distilled. There was obtained 3.5 g. of a colorless liquid (estimated b. p. 90° at 1mm). Vpc on column A at 200° (helium flow: 1 cc/sec.) showed two peaks in a ratio of 1.7:1 with respective retention times of 47 min. and 56 min. We believe that these two peaks

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correspond to the two stereoisomers 45 and 46.

We collected enough of each of the two substances using column B at 200° for mass spectrometry. Both spectra showed a parent peak at 256, equal to the calculated value for $C_{10}H_{15}O_2Cl_2F$. The ratio of m, m + 2, m + 4 was typical of dichlorinated substances.

The nmr and ir spectra of the mixture are consistent with the assigned structure. Further, the room temperature ^{19}F nmr of the mixture showed two absorptions whose areas were also in a ratio of 1.7:1 with respective ϕ values of 172 and 142.

Hydrogenation of the Ethyl-4,4-dichloro-5-fluoro-3,6-cis-dimethyl-cyclohexene-5-carboxylates.

In 20 ml. of ethylacetate, 3 g. of ethyl-4,4-dichloro-5-fluoro-3,6-cis-dimethyl-cyclohexene-5-carboxylates, (0.0117 mole) was dissolved. To this was added 0.04 g. of commercial platinum oxide catalyst. The mixture was hydrogenated at 27° and one atm. In 3 hours 300 ml. of hydrogen was taken up and then, the reaction stopped completely (theoretical uptake: 22.4 X 3/256 X 300/273 = 288 ml.). The catalyst was then removed by filtration and the solvent stripped off under reduced pressure. Distillation gave 2.1 g. of liquid (b.p. — 90° at 1mm.). The ir and the nmr no longer showed olefinic absorption.

Hydrolysis of the Ethyl-1,1-dichloro-2-fluoro-3,6-cis-dimethyl cyclohexane-2-carboxylates

2 g. (0.00775 mole) of the ethyl-1,1-dichloro-2-fluoro-3,6-cis-dimethylcyclohexane-1-carboxylate was added to 4 ml. of a 10% KOH ethanolic solution. The mixture was stirred for 24 hours at 60°. The

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potassium salt precipited. After filtration the residue was dried under vacuum to a constant weight of 1 g. (44%).

Decarboxylative Elimination of the Potassium chloride from Potassium 1, 1-dichloro-2-fluoro-3, 6-cis-dimethylcyclohexane-2-carboxylates

A microdistilling tube containing 0. 8 g. (0. 0027 mole) of the potassium 1, 1-dichloro-2-fluoro-3, 6-cis-dimethylcyclohexane-2-carboxilates was evacuated to 0. 1 mm. and the receiver was chilled with Dry Ice. The solid was heated at 180-190° for three hours. The material which distilled was 200-250 mg. of colorless liquid. Vpc of this material on column C (column 130°, detector 170°, injector 160° and helium flow 1 cc/sec.) gave only one peak (retention time: 19 min.). The ir and nmr of this material were superposable upon those of the hydrogenated and dehalogenated 1, 4 cycloadduct of trans, trans-2, 4-hexadiene and 1122.

cis- and trans-2, 5-Dimethylcyclohexanone

To a stirred mixture of 80 g. (2. 7 mole) of sodium dichromate and 65 g. (35. 3 ml., 0. 063 mole) of conc. sulfuric acid was added 50 g. (0. 40 mole) of 2, 5-dimethylcyclohexanol in three portions. After 3 min. the temperature rose to 68°. The reaction mixture was cooled in ice until the temperature fell to 55°. When the ice was removed the temperature continued to fall slowly. When it reached room temperature an equal volume of ether was added. The ether layer was separated and washed three times with 150 ml. of 5% sodium hydroxide. After drying over anhydrous sodium sulfate the ether was removed on a rotary evaporator and the residue was distilled. A colorless liquid, b. p. 76-77° (27 mm.) was obtained. Yield: 37.9 g. (77%).

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The infrared spectrum showed strong absorption at 5.83μ. The nmr spectrum in carbon tetrachloride showed a complex multiplet from 7.4 to 8.8τ (8H) and a pair of doublets for the methyl groups from 8.9 to 9.2τ (6H). Vpc analysis on column A at 110° showed two isomers to be present in the ratio 79:21 in order of increasing retention time.

N-(2,5-Dimethylcyclohex – 6 – enyl)-pyrrolidine

To a solution of 20 g. (.16 mole) of a mixture of the two isomers of 2,5-dimethylcyclohexanone in 120 ml. of benzene was added 26 g. (0.37 mole) of redistilled pyrrolidine. The reaction was refluxed and the water formed was collected in a Dean-Stark trap. After 12 hrs. no more water was formed and the reaction was stopped. The solvent was removed at reduced pressure and the residue distilled, b.p. 75° (2.5 mm.).

The ir exhibited a strong absorption 1660 cm^{-1} characteristic of the double bond stretching of enamines.

The nmr in benzene solution showed a multiplet centered at $\tau = 5.83$ corresponding to the vinyl hydrogen.

Synthesis of cis- and trans-2,2-Difluoro-3,6-dimethylcyclohexanone

Caution: Perchloryl fluoride is a stable compound quite safe to handle. It is however a powerful oxidizing agent and all mixtures with oxidizable substances should be considered potentially dangerous. No difficulties were encountered in handling perchloryl fluoride under the conditions of the present experiment. The details of handling and safety have been fully described: Booklet 1819, "Perchloryl Fluoride,"

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Pemsalt Chemical Corp., 3 Penn Center, Philadelphia 2, Penn.

The reaction was conducted in a well-ventilated hood behind adequate safety shields. Further, the control of the reaction could be maintained without removing safety shields.

In a 2-l three-necked flask equipped with a gas inlet tube extending almost to the bottom of the flask, a thermometer and a magnetic stirring bar, is placed 5 g. of enamine (0.028 mole) and one liter of dry ether. The flask is cooled in an ice salt bath at -5 to -10° and a stream of perchloryl fluoride is bubbled through the solution with vigorous stirring over a period of approximately three minutes, at such rate that the temperature of the reaction mixture does not rise above zero degree. Stirring is continued for an additional 1 hour as the cooling bath melts. The solution is purged with nitrogen for 10 min. Then is added 200 ml. of a 10% HCl water solution and the mixture is stirred for 1 hour at room temperature before being placed in a 2-l separatory funnel. The aqueous layer is separated and then the ether layer is washed twice with 200 ml. of water and dried over anhydrous sodium sulfate. The solvent is removed on a rotary evaporator under reduced pressure. Distillation of the yellow mixture (70-85° at 25 mm.) afforded 3.2 g. of a colorless liquid.

A preparative vpc work-up on column E at 130°, followed by a mass spectrometry and an nmr study revealed the presence of mono, di and trifluorinated ketone as well as a small amount of starting material (~5%). The two desired gem difluoroketones (~25%) appeared as two overlaping peaks (retention times: 20 and 21.6 min.) directly

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following the trans and cis-2, 5-dimethylcyclohexanones (retention times: 16 and 18 min.).

By successive passings, we could isolate each of the two isomeric gem difluoroketones for analytical purposes. Both mass spectra showed a parent peak at 162, equal to the calculated value for $C_8H_{12}OF_2$. The ir showed strong carbonyl absorptions. Finally, the ^1H nmr indicated the geminal nature of the two fluorines (see Discussion, page 39).

For further treatment 180 mg. of the mixture of the two ketones was collected.

It should be noted that this fluorination reaction is very sensitive to reaction conditions. Below -30° only a mixture of 2-fluoro-3, 6-dimethylcyclohexanes is formed. If we isolate them, prepare their corresponding pyrrolidine enamines and run a fluorination reaction at -40° we only obtain a mixture of 2, 6-difluoro-3, 6-dimethylcyclohexanones.

The controlled monofluorination at temperature below -30° is attributed to the insolubility of the amonium salt formed which prevents further reaction. At higher temperatures, the white precipitate formed rapidly disolves, probably because of its decomposition into the fluorinated enamine and perchloric acid, allowing then the reaction to proceed further.

Synthesis of cis and trans-1, 1-Dichloro-2, 2-difluoro-3, 6-dimethylcyclohexanes.

180 mg. (0.0011 mole) of the mixture of cis and trans-2, 2-difluoro-

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3, 6-dimethylcyclohexanone was placed in 8 ml. of PCl_3 and 0. 6 g. (0. 029 mole) of PCl_5 was added. The mixture was stirred at room temperature for 8 days. It was then poured onto ice, a few ml. of CH_2Cl_2 was added, the solution extracted with $KHCO_3$ solution, dried over anhydrous magnesium sulfate and the CH_2Cl_2 was partially evaporated under reduced pressure.

Preparative vpc using column C at 120° allowed the isolation of a few mg. of cis-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane. Under these conditions the trans counterpart and the monochlorinated substance had the same retention time. Column E at 120° effected their separation in milligram quantities.

The mass spectrum of cis-1, 1-dichloro-2, 2-difluoro-3, 6-dimethylcyclohexane showed a parent peak at 216 equal to the calculated value of $C_8H_{12}Cl_2F_2$. The observed ratio of m, m + 2, m + 4 was 56. 2:36. 8:7 (calculated 57. 4:36. 7:5. 9). The principal peaks and their intensities were 181(17), 180(10), 161(18), 145(100), 125(42), 123(45), 104(48). This fragmentation corresponds to the loss of Cl, loss of HCl, loss of Cl and HF, loss of HCl and Cl, loss of Cl, HCl and HF, loss of Cl, HCl, HF and H_2 and loss of Cl, HCl, HF, F, and H_2.

The mass spectrum of the trans was very similar. The observed ratio of m, m + 2, m + 4 was 56. 8:36:7. The fragmentation was identical but the intensities were different: 181(14), 180(20), 161(15), 145(100), 125(25), 123(30), 104(40).

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Reaction of trans-trans-, trans-cis, and cis-cis-2,4 Hexadienes with 1122 at Various Temperatures

In a typical procedure a mixture of 2,4 hexadiene (0.5 g., 0.0061 mole) and 1122 (10 g., 0.0757 mole) was sealed under vacuum in a heavy-walled Pyrex tube. The tubes were heated for 24 hours in an oil bath, the temperature of which was maintained within ± 0.01°. The tubes were then opened, 1122 and any unreacted diene evaporated under reduced pressure and the residue trap-to-trap distilled under vacuum.

Analysis: The 1,2 adducts were analyzed directly on column D at 150°. The sequence of peaks was 48 (19.6 min.), 49 (20.4 min.), 50 (24.4 min.) and 51 (27.6 min.).

The 1,4 adducts were analyzed after hydrogenation of the reaction mixture. In a typical procedure 0.2 g. (0.0093 mole) of the cyclo-adducts were dissolved in 5 ml. of ethyl acetate. To this was added 15 mg. of platinium oxide. The mixture was hydrogenated at 27° and 1 atm pressure. After the theoretical amount of hydrogen (23 ml.) had been taken up, the reaction was stopped. The catalyst was filtered off and the solvent removed on a rotary evaporator. Column D was also used for the analysis of the cis and trans-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexanes. The sequence of the peaks was unknown compound (48 min.), trans (52.2 min.) and cis (59.5 min.).

The identification of the cis-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexane originating from the trans,trans-2,4-hexadiene has already been described. In the case of the trans,cis-2,4-hexadiene

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1 mg. of hydrogenated cis-1,4 adduct was isolated by preparative vpc on column C and was shown to have an ir spectrum which was superposable upon that of a sample of the authentic material.

The trans-1,1-dichloro-2,2-difluoro-3,6-dimethylcyclohexane was identified by comparison of its retention time with that of a sample of the authentic material using columns A, B and D.

The Hewlett-Packard F and M Model 7620 equipped with a flame ionization detector was used for the analysis. Integrations were performed with a digital integrator. The ratios of cis- over trans-1,4 adduct were checked by the triangulation method. The relative areas were not corrected for the flame sensitivity of the adducts because of the shortage of 1,4-adducts.

In each case 1 μl. of sample was injected. The conditions for all the runs were kept constant so that comparison of results are valid. The values were reproducible within 5%.

Photosensitized reaction of trans,trans-2,4-Hexadiene and 1122

A pyrex tube was charged with 1.5 g. (0.018 mole) of trans, trans-2,4 hexadiene, 25 g. (0.189 mole) of 1122 and 0.3 g. (0.00176 mole) of freshly redistilled 1-acetonaphtone. The tube was degassed by two freeze-thaw cycles and sealed under vacuum. A 450 watt Hanovia medium pressure mercury lamp was used for the irradiation (4 days). The tube was strapped to a pyrex well immersed in a water bath. The bath was kept at 2° by the use of a heat exchanger through which was passed cold methanol from a Lauda Kryomat Model TK30. Cold water was circulated through the pyrex well.

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The sample was then stripped of 1122 and the unreacted 2,4-hexadienes. Vpc analysis using column G revealed the composition of the unreacted dienes to be t-t, 74.2%; c-t, 21.7%; c-c, 4.1%.

Trap-to-trap distillation afforded 200 mg. of a colorless liquid comprising 2,4-hexadiene dimers and cross-cycloadducts. The analysis of the cycloadducts was performed in a manner similar to that for the thermal reactions. The adducts were identified by a comparison of the retention times with authentic materials on columns A and D.

Separation of cis-and trans-1212

Several approaches have been used to separate cis- and trans-1212.[91] The original paper reported separation by distillation.[91a] Tiers and Lauterbur, however, could not reproduce this separation.[91b] Craig and Evans obtained 99.6% trans-1212 and 95.1% cis-1212 by a tedious fractional melting procedure in conjunction with distillation. The best method available so far has been developed by R. Wheland using vpc. He found that rather volatile, highly polar liquid phases such as dimethyl sulfoxide, dimethylsulfone and dimethylformamide on 80-100 mesh Alcoa F-20 Chromatographic Alumina are particularly successful. A high proportion of liquid phase relative to solid support led to reduced retention times with loss of resolution whereas a low proportion of liquid phase led to extended retention times with blurring

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[91] (a) E.G. Locke, W.R. Brode and A.L. Henne, J. Am. Chem. Soc., 56, 1726 (1934).
(b) G.V.D. Tiers and P.C. Lauterbur, J. Chem. Phys., 36, 1110 (1962).
(c) N.C. Craig and D.A. Evans, J. Am. Chem. Soc., 87, 4223 (1965).
(d) D.E. Mann and E.K. Plyer, J. Chem. Phys., 26, 773 (1957).

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resolution. Thus roughly 5% by weight liquid phase is generally optimal. A liquid phase such as dimethylsulfoxide is sufficiently volatile so that the columns are not baked out but rather put into immediate use at 0-25°C.

A vpc analysis of 1212 obtained from Peninsular Chemresearch, Inc. revealed two major components with roughly 5-10% of a third component that has the retention time of 1122. This common impurity in 1212 is removed by refluxing with sodium ethoxide in ethanol. The purified 1212 is then collected preparatively using column I at room temperature. Comparison with published ir spectra distinguishes the two isomers, trans-1212 (retention time, 4 hours) eluting before cis-1212 (retention time, 4.5 hours). Analytical VPC with column H at 50° (flow 1 ml. /1 sec.) showed retention times of trans, 21 min.; cis, 24.5 min.

Addition of Butadiene to Mixed Isomers of 1212

A mixture of 1212 isomers (20 g., 0.1515 mole) of known composition (trans, 54%, cis, 46%) and butadiene (3 g., 0.0555 mole) was heated in a heavy-walled pyrex tube for 24 hours at 180-190°. Fractionation of the products through a microcolumn gave 6.3 g. (61%) of crude cycloadducts (estimated b.p. 147° at 761 mm.). Preparative vpc employing column C at 100° (helium flow 1 ml. /1 sec.) permitted separation of the 1,2-adducts (retention time, 12-24 min.) from the 1,4-adducts (retention time 52 min.). Analytical VPC using column F at 120° (Figure 9a) gave better separation and in particular, allowed discrimination between the two 1,4 adducts. The retention times of

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the five peaks were respectively, 34.5 min., 36.2 min., 37.5 min., 84.5 min., and 87 min. Identification of the adducts has been described in the second chapter.

Hydrogenation of the Cycloadducts of Butadiene to Mixed Isomers of 1212

In 40 ml. of ethyl acetate was dissolved 2 g. of distilled cycloadducts. To this was added 0.1 g. of commercial platimium oxide catalyst. The catalyst was not hydrogenated before addition of the adduct. The mixture was hydrogenated at 27° and one atm. pressure. In two hours 280 ml. of hydrogen was taken up and then the reaction stopped completely (theoretical hydrogen uptake 22400 X 2/186 X 300/273 = 265 ml.). The catalyst was removed by filtration, the solvent was stripped off under reduced pressure, and the residue was trap-to-trap distilled under vacuum.

Preparative vpc on column C at 120° allowed separation of the hydrogenated 1,2- and 1,4-adducts for spectroscopic analysis (ir, ^{1}H nmr and particularly ^{19}F nmr).

Thermal Cycloaddition of trans-1212 to Butadiene

1212 from which the contaminating 1122 had been removed was separated into cis and trans isomers with column I at room temperature. Analysis on column H at 50° indicated the purified trans-1212 to be in fact 99% trans-1212 with 1% cis impurity.

Roughly 0.15 g. of this 99% pure trans-1212 was bulb-to-bulb distilled into a small heavy-walled pyrex tube. To this was added roughly 10 mg. of butadiene. After sealing under vacuum the tube was heated in an oven at 180-190° for 24 hours, then cooled and opened.

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The colorless solution was vpc-analyzed as such without further treatment. Analysis of the recovered 1212 (column H at 50°) and of the cycloadducts (column F at 120°) has been reported in Table VII.

Thermal Cycloaddition of cis-1212 to Butadiene

Roughly 0.15 g. of 99% pure cis-1212 was bulb-to-bulb distilled into a small heavy-walled pyrex tube. To this was added roughly 10 mg. of butadiene. After sealing under vacuum the tube was heated in an oven (simultaneously with the trans-1212 butadiene run) at 180-190° for 24 hrs., then cooled and opened.

The colorless solution was vpc-analyzed as such without further treatment. Analysis of the recovered 1212 (column H at 50°) and of the cycloadducts (column F at 120°) has been reported in Table VII.

Addition of trans,trans-2,4-Hexadiene to Mixed Isomers of 1212

A mixture of 1212 isomers (15 g., 0.114 mole) of known composition (trans 54%, cis 46%) and trans,trans-2,4-hexadiene (3 g., 0.0366 mole) was heated in a heavy-walled pyrex tube for 24 hours at 180-190°. Fractionation of the reactants through a microcolumn gave 5 g. (64%) of crude cycloadducts (b.p. 73-74° at 15 mm.). Preparative vpc, employing column C at 110° (helium flow: 1 ml./sec.), permitted isolation of the 1,2-adducts as a whole (retention time 12-28 min.) and each of the 1,4-adducts (retention time 38 min., 44 min., and 47 min.). Analytical VPC was done on column D at 150°. The retention times were 1,2-adducts, 16-28 min.; and 1,4-adducts, 39 min., 42.5 min., and 47.5 min. Identification of the adducts has been described in the second chapter.

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Hydrogenation of Each of the 1,4 Cycloadducts of trans,trans-2,4-Hexadiene to Mixed Isomers of 1212

In a typical procedure, 40 mg. of each of the three 1,4-cycloadducts isolated by preparative vpc was dissolved in 2 ml. of ethyl acetate. To this was added 0.006 mg. of commercial platinium oxide catalyst. The catalyst was not hydrogenated before addition of the adduct. The mixture was hydrogenated at 27° and one atm. pressure. The catalyst was then removed by filtration, the solvent partly removed under reduced pressure and the hydrogenated adducts isolated by preparative vpc on column C at 135°. Roughly 30-35 ml. of substance was then obtained. The nmr no longer showed vinylic absorptions.

Thermal Cycloaddition of trans-1212 to trans,trans-2,4-Hexadiene

1212 from which the contaminating 1212 had been removed was separated into cis- and trans-isomers with column I at room temperature. Analysis on column H at 50° indicated the separated trans-1212 to be in fact 99% trans-1212 with 1% cis impurity.

Roughly 0.15 g. of this 99% pure trans-1212 was bulb-to-bulb distilled into a small heavy-walled pyrex tube. To this was added 10 μl. of trans,trans-2,4-hexadiene. After sealing under vacuum, the tube was heated in an oven at 180-190° for 24 hours, then cooled and opened.

The colorless solution was vpc-analyzed as such without further treatment. Analysis of the recovered 1212 (column H at 50°) and of the cycloadducts (column D at 150°) has been reported in Table VIII.

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Thermal Cycloaddition of cis-1212 to trans,trans-2,4-Hexadiene

Roughly 0.15 g. of 99% pure cis-1212 was bulb-to-bulb distilled into a small heavy-walled pyrex tube. To this was added 10 μl. of trans,trans-2,4-hexadiene. After sealing under vacuum, the tube was heated in an oven (simultaneously with the trans-1212 trans,trans-2,4-hexadiene run) at 180-190° for 24 hours, then cooled and opened.

The colorless solution was vpc-analyzed as such without further treatment. Analysis of the recovered 1212 (column H at 50°) and of the cycloadducts (column D at 150°) has been reported in Table VIII.

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APPENDIX

NMR AND IR SPECTRA

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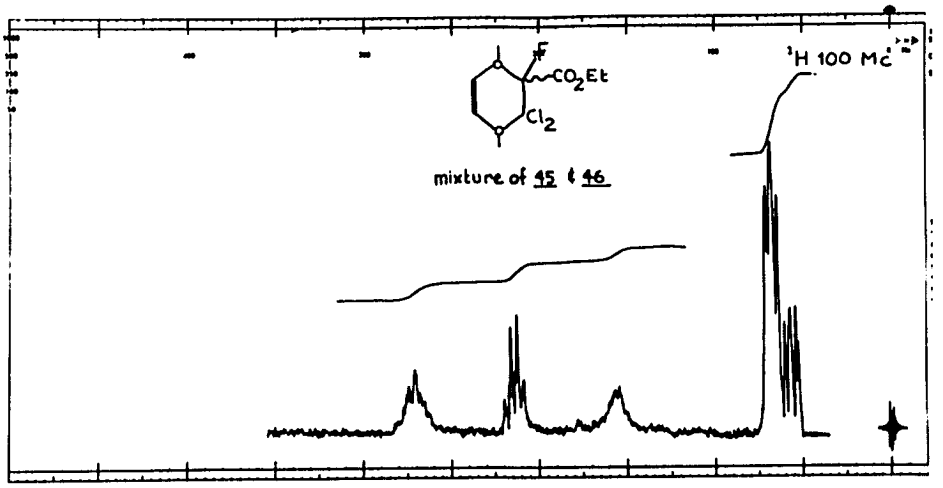

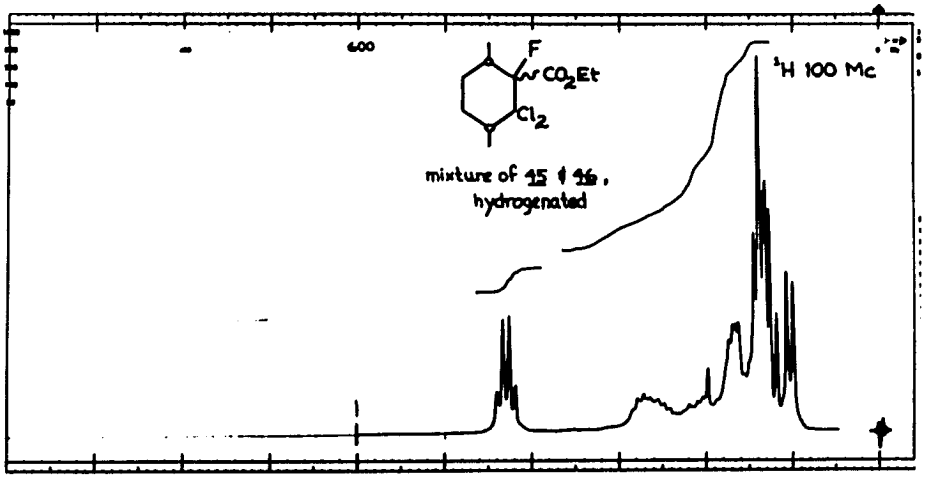

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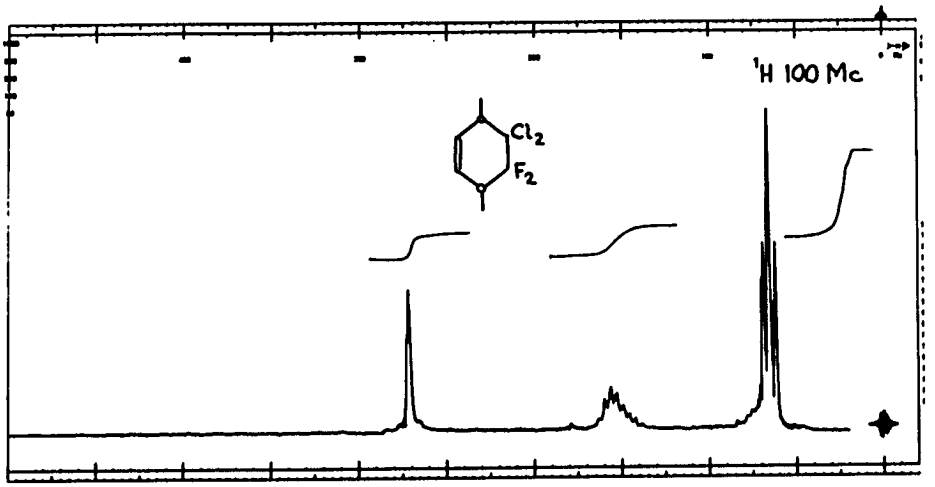

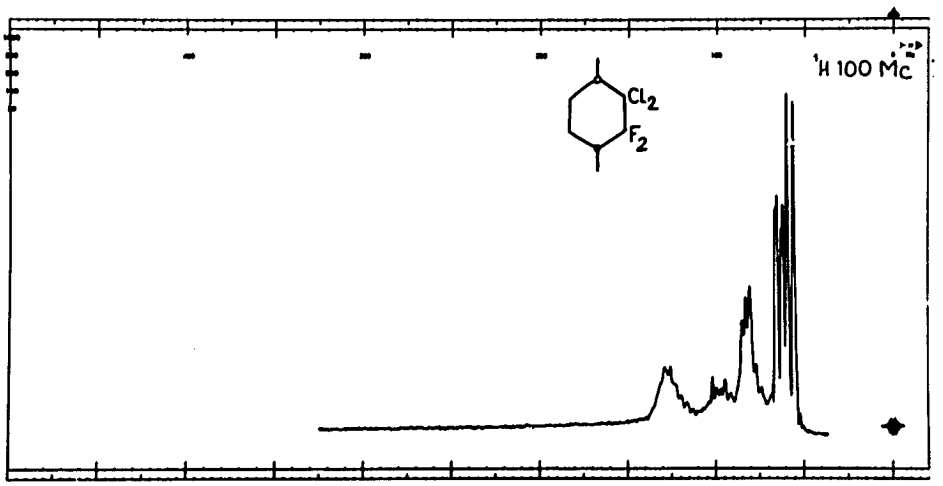

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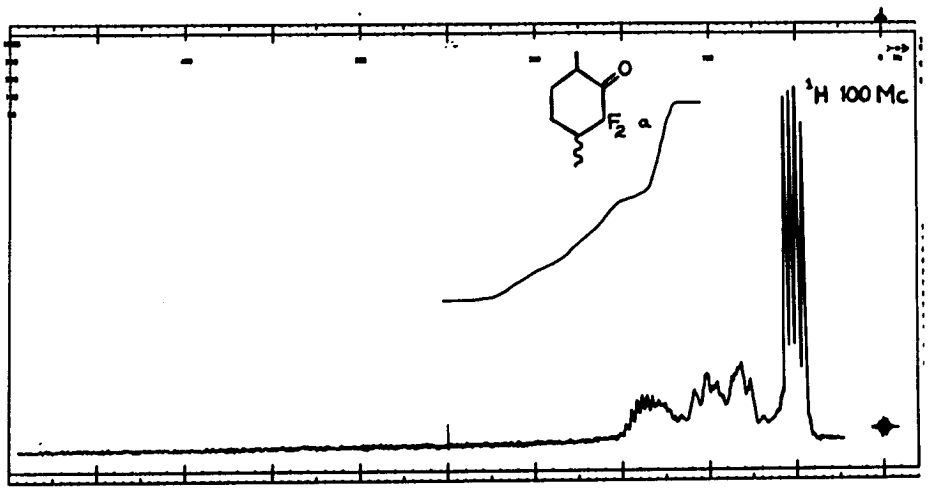

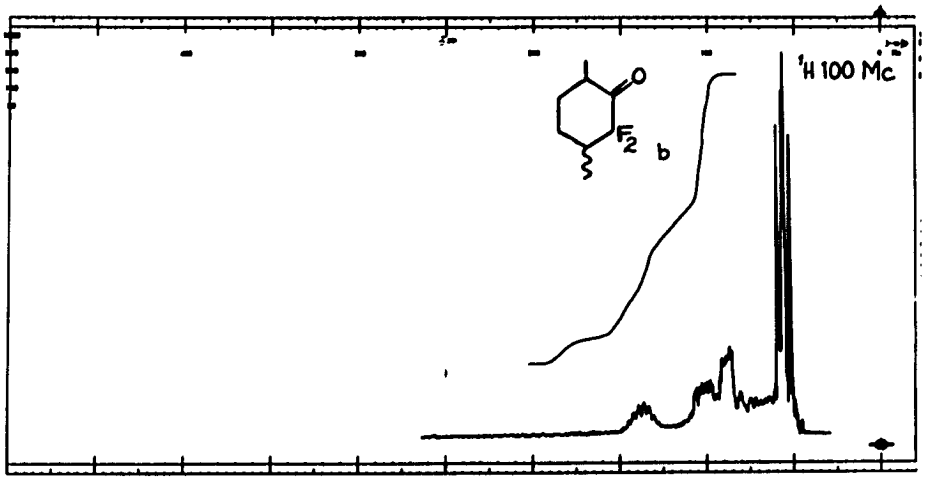

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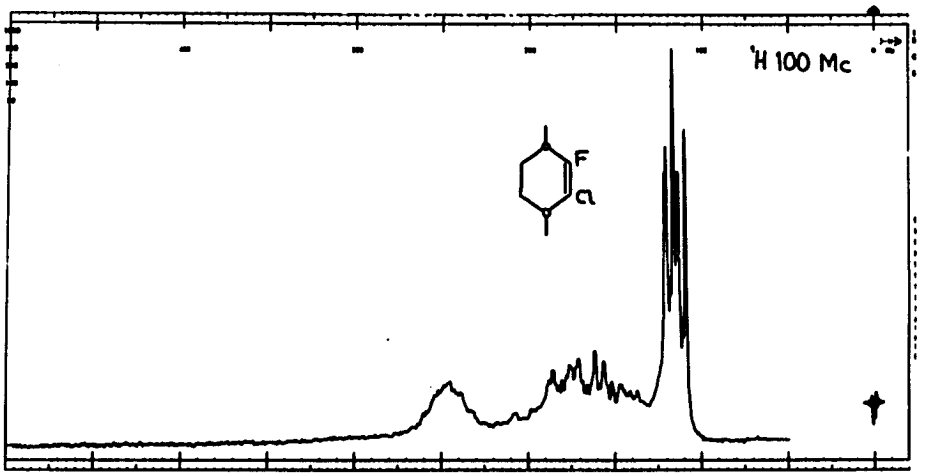

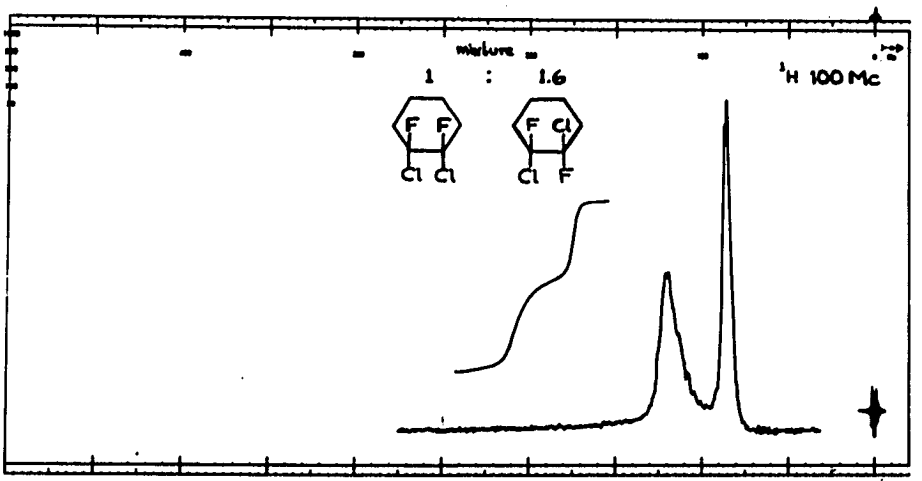

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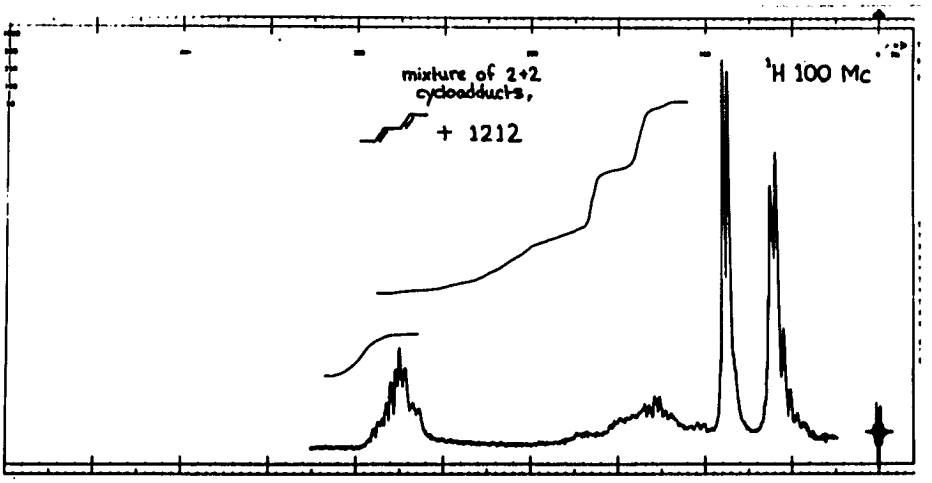

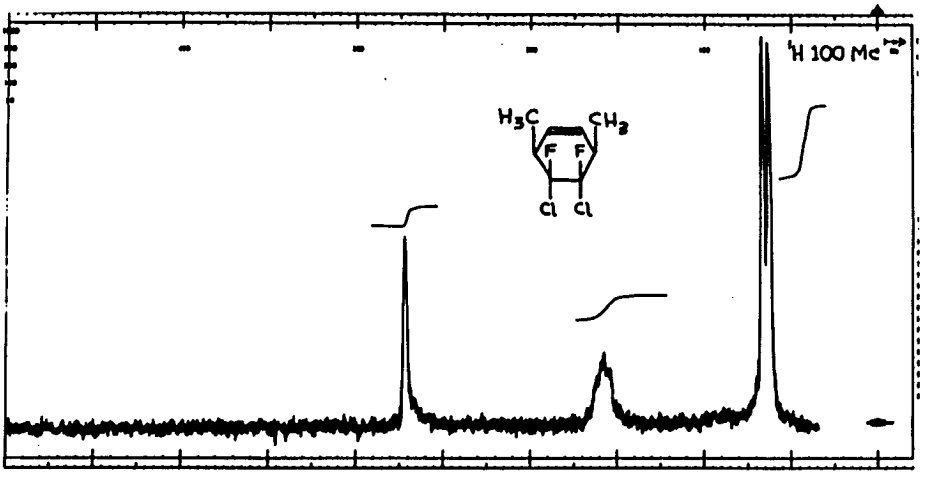

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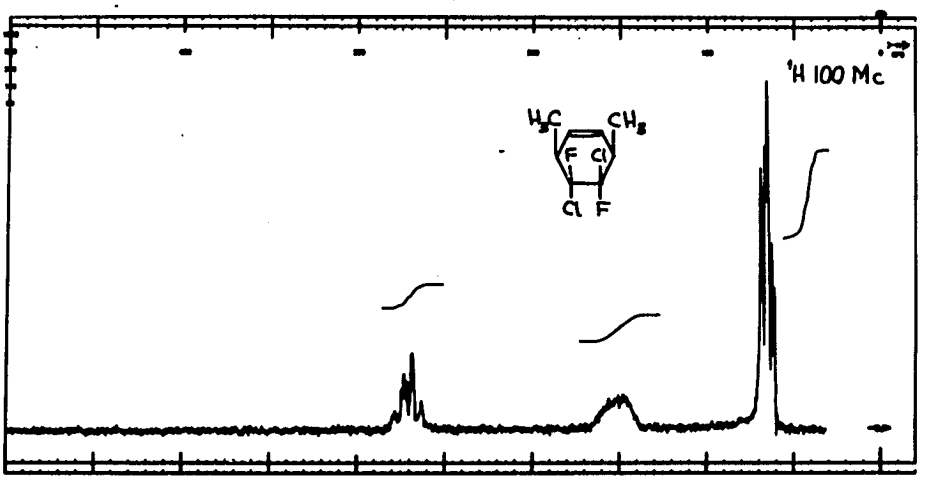

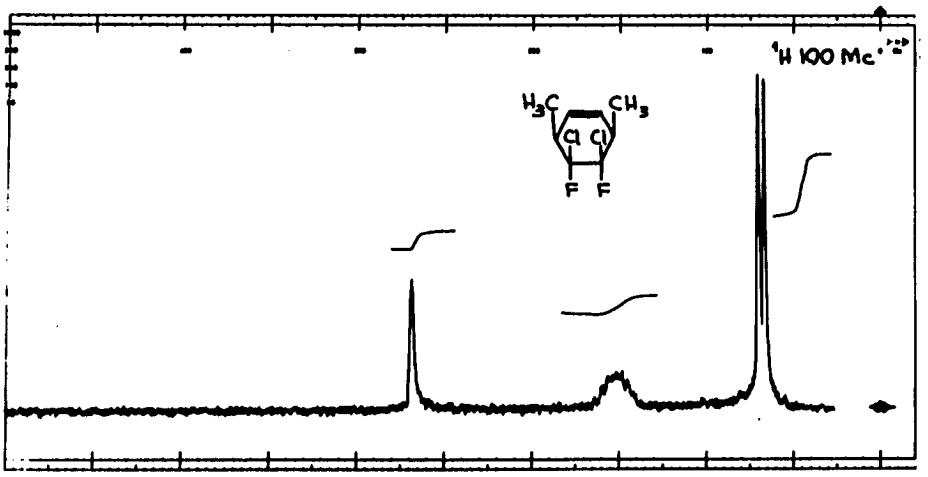

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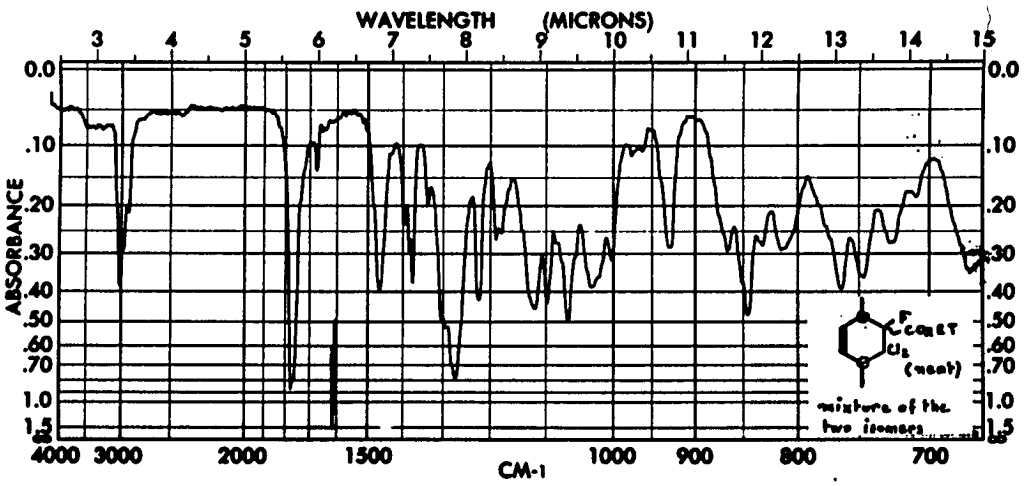

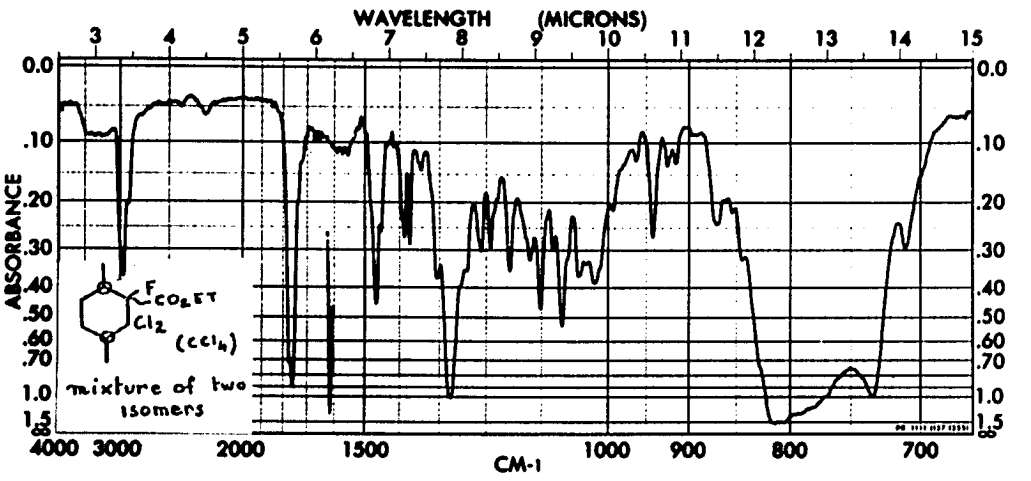

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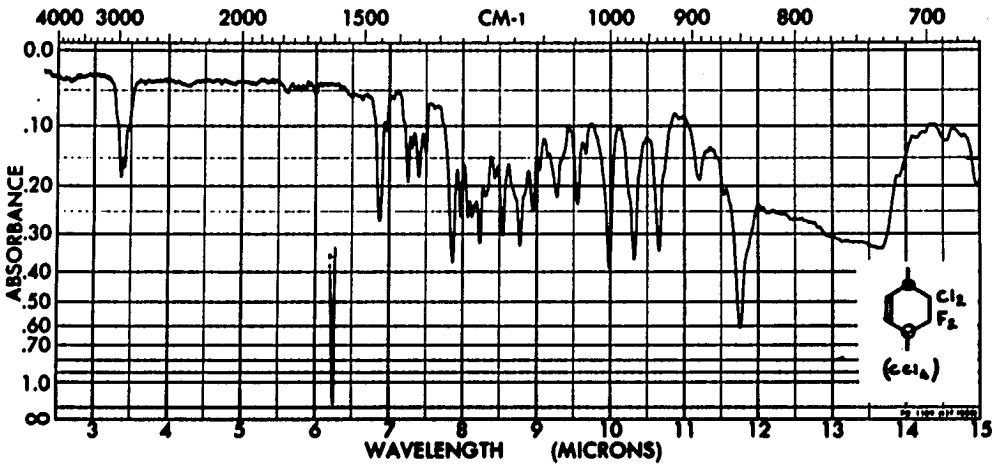

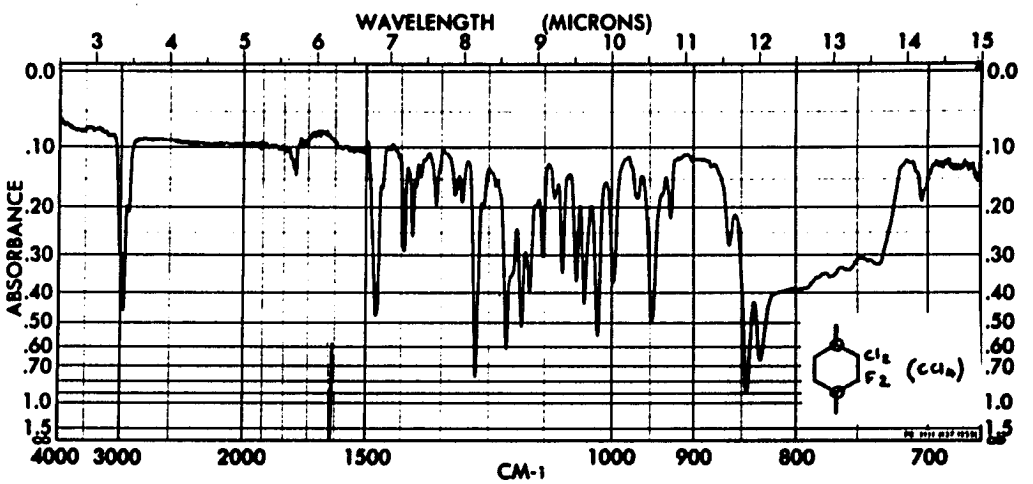

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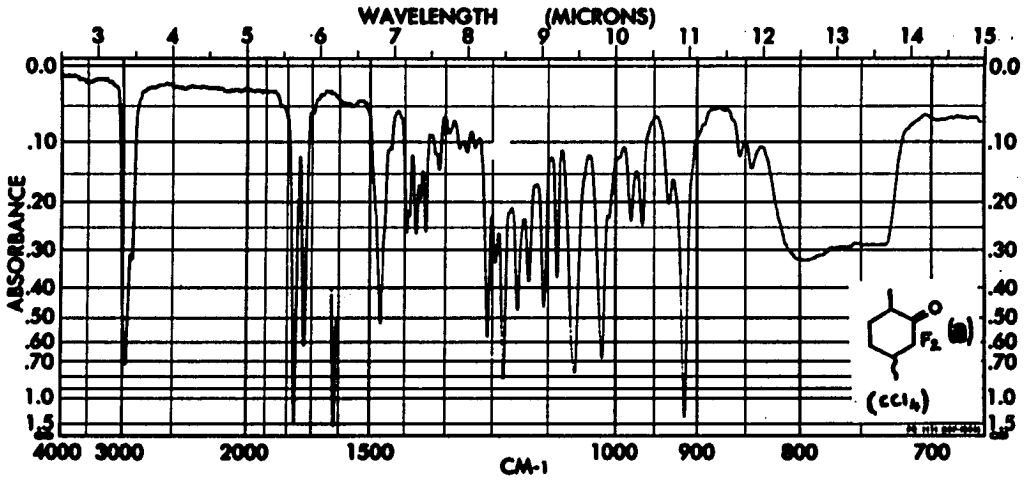

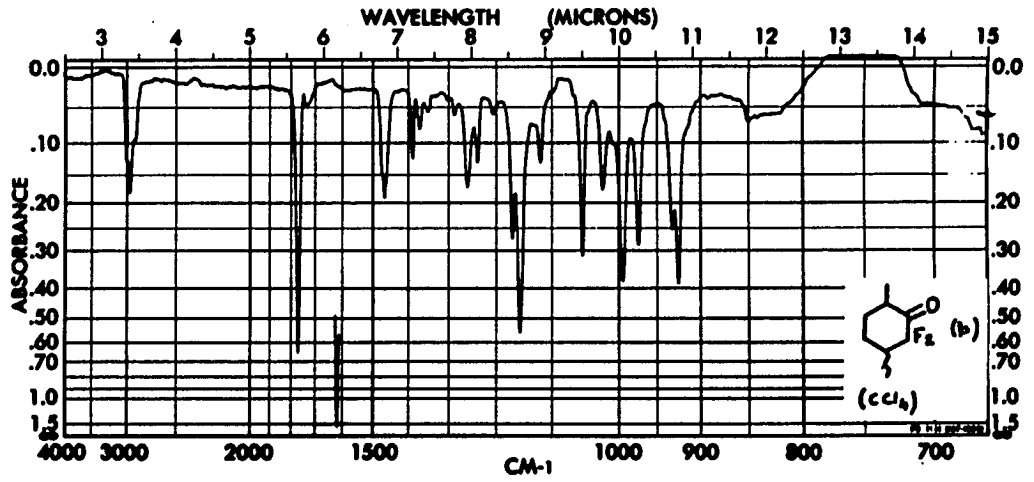

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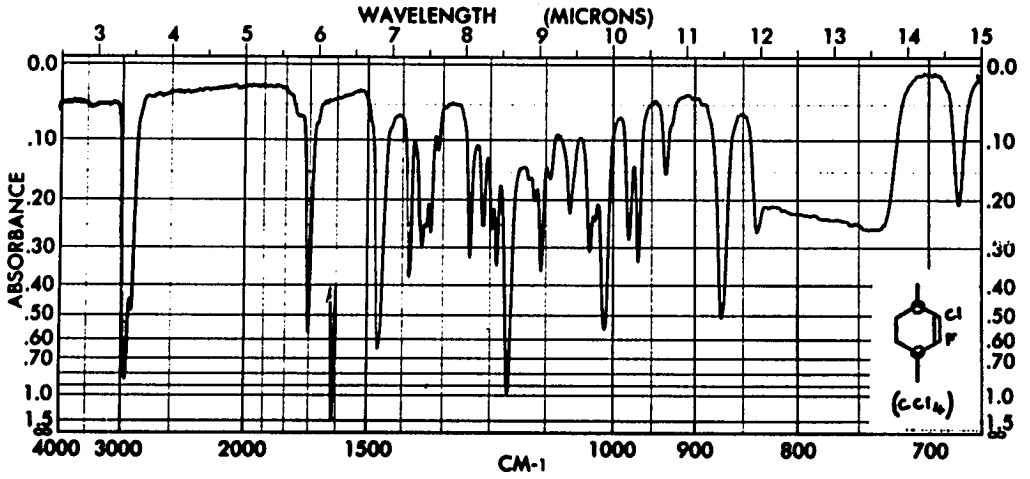

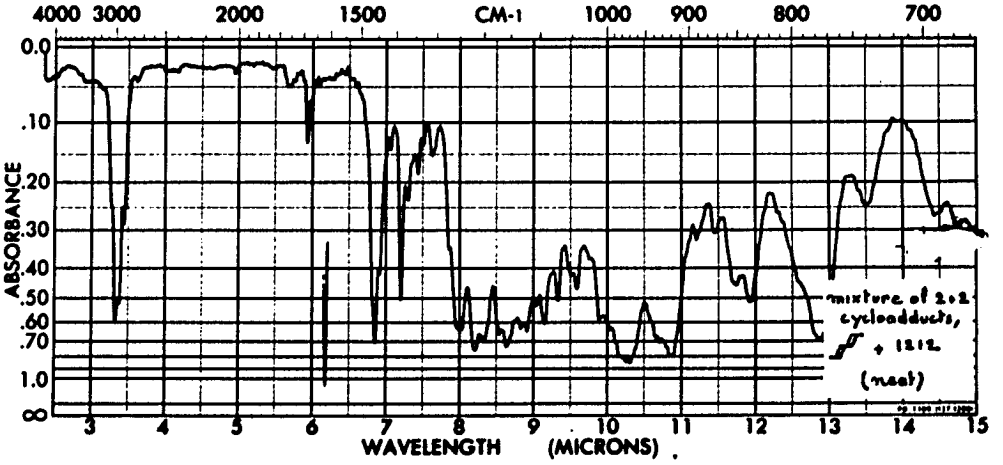

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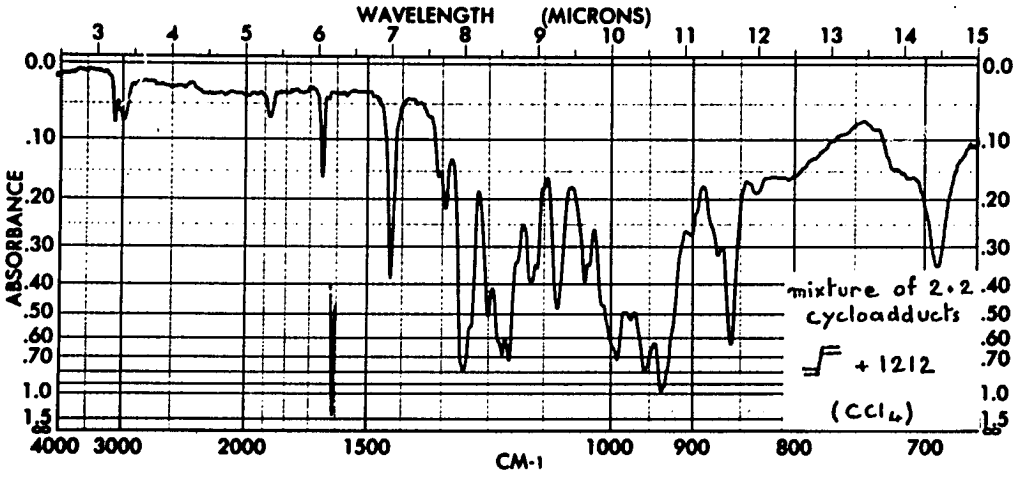

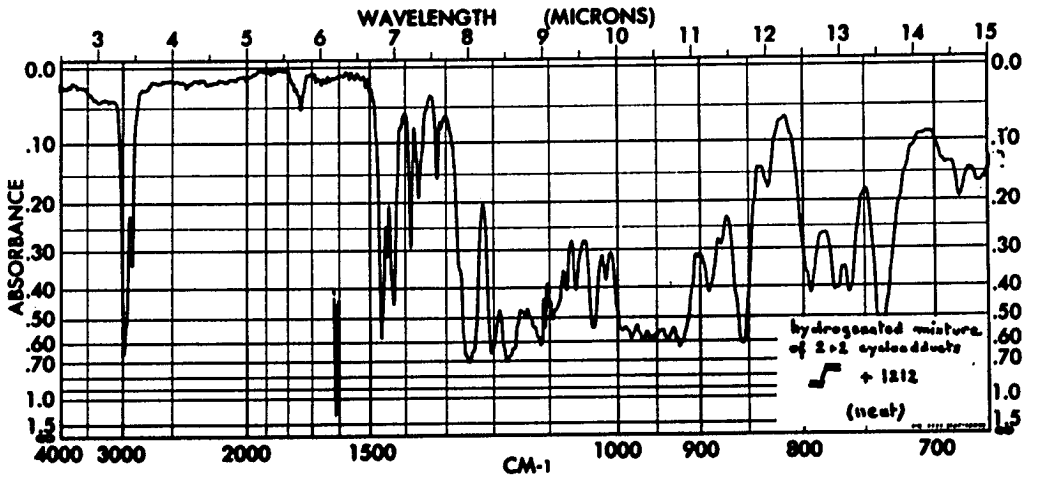

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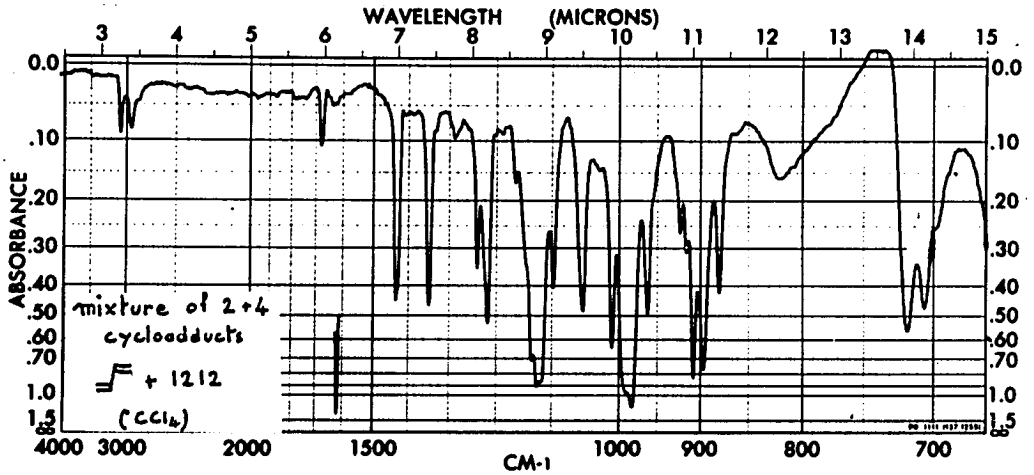

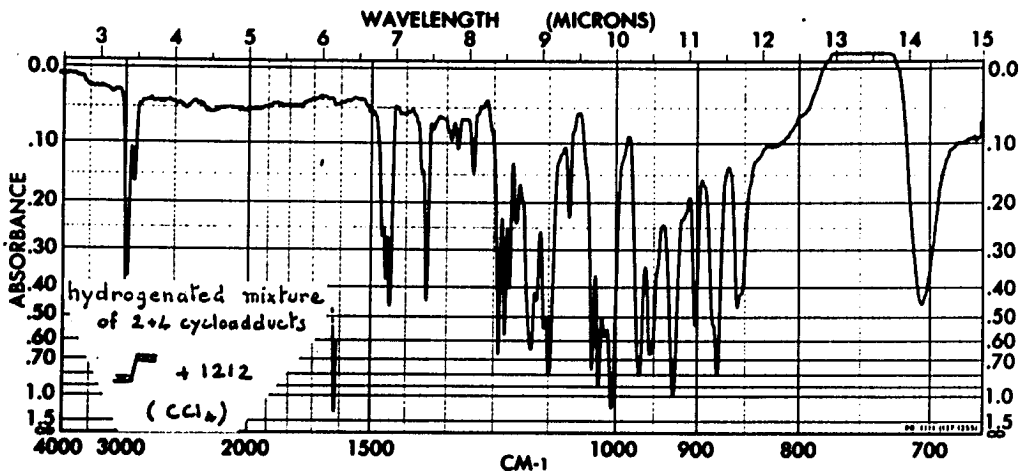

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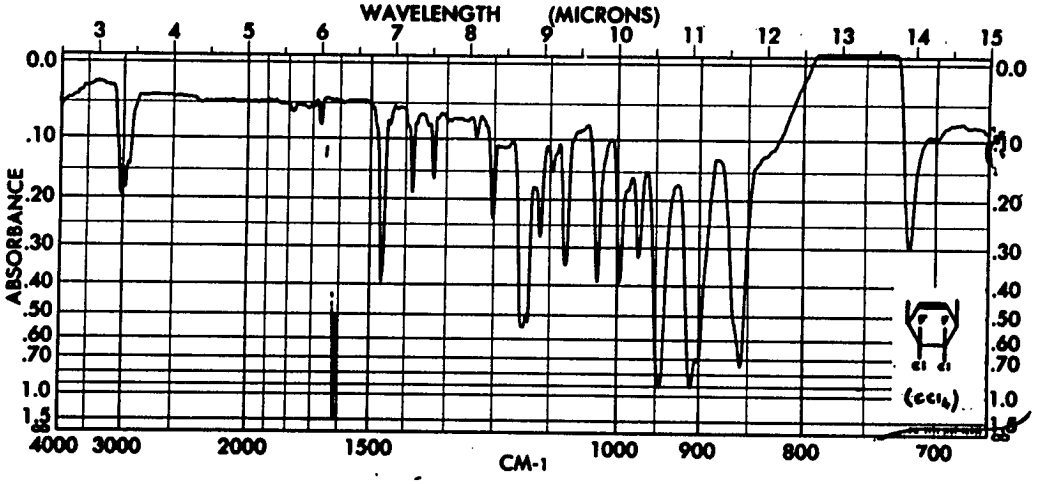

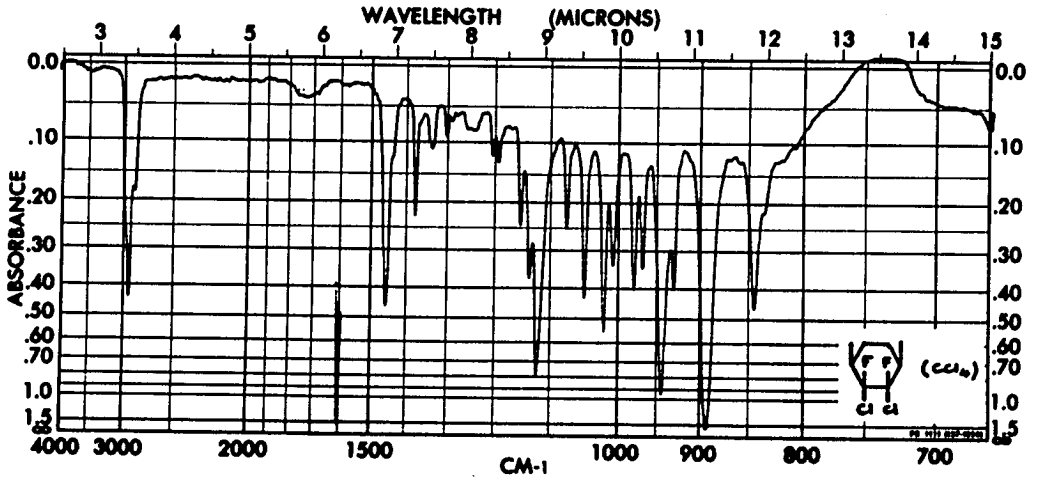

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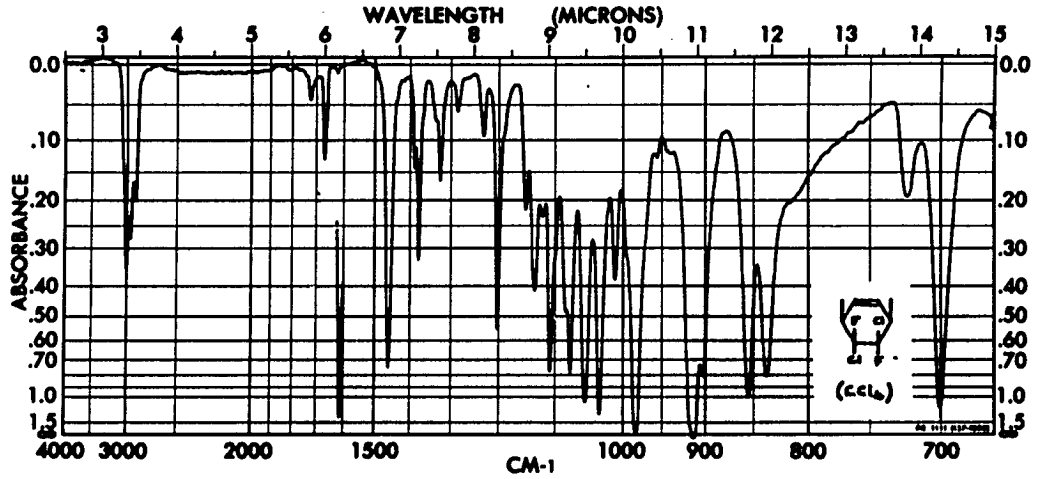

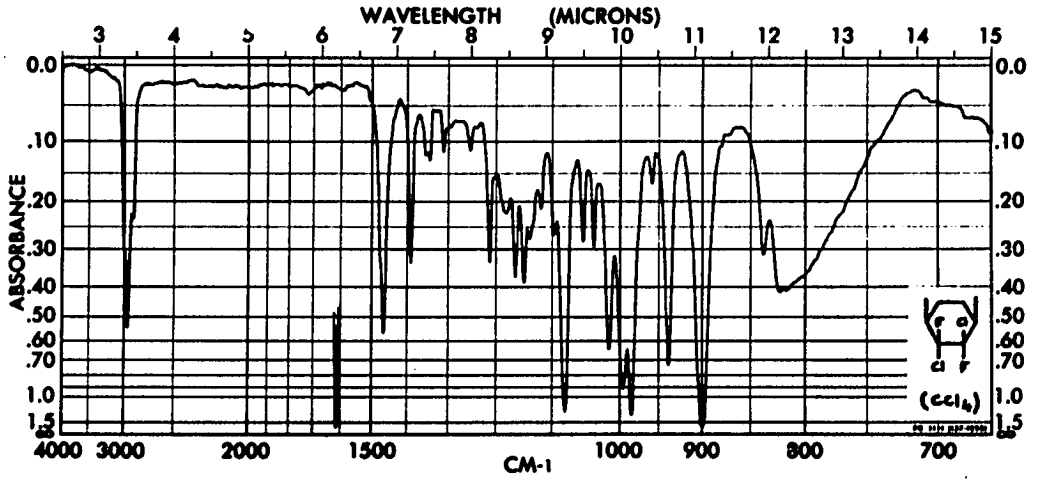

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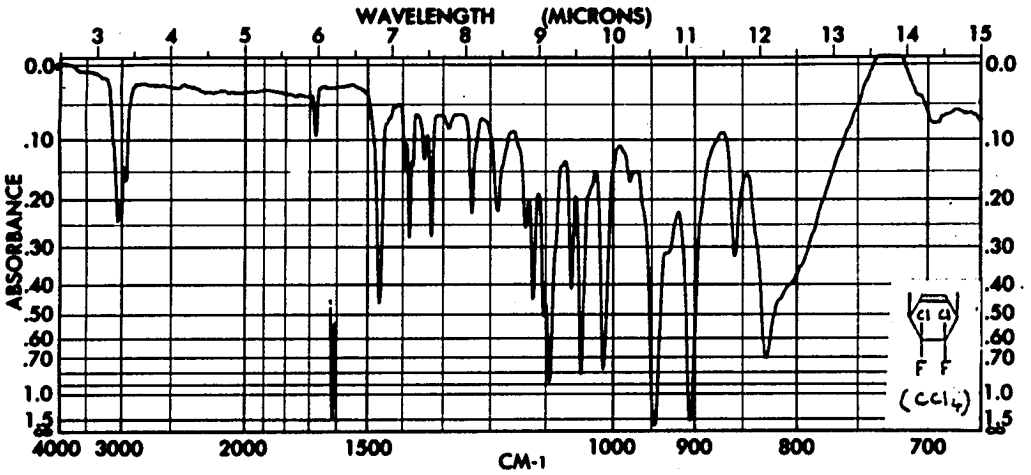

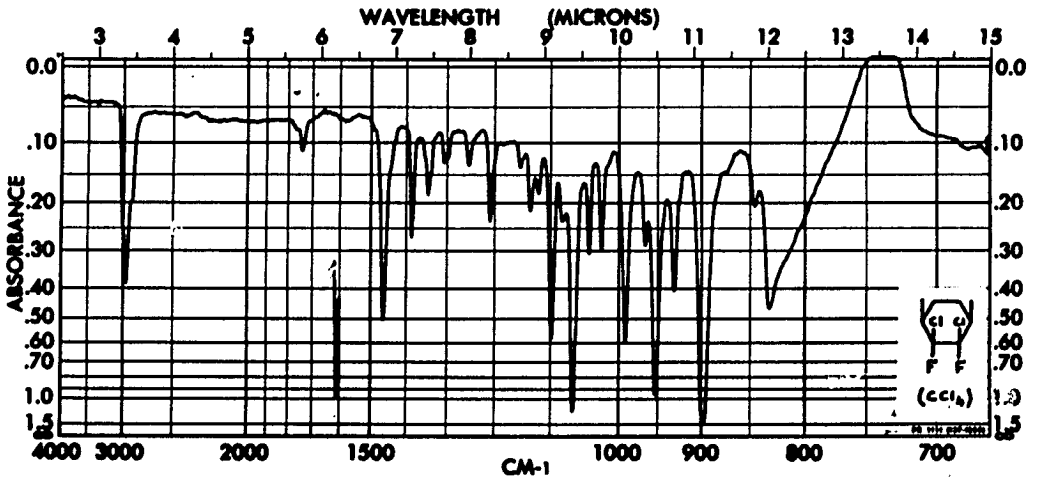

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COMPETITION BETWEEN CONCERTED AND BIRADICAL DIELS-ALDER REACTIONS

Professor P. D. Bartlett — Harvard University

Jacques J. Mallet — May, 1972

Summary

A reinvestigation of the thermal cycloaddition of $CCl_2=CF_2$ with 2,4-hexadienes revealed, in addition to the 1,2 adducts, the presence of small amounts of cis and trans 1,4 cycloadducts in a ratio of 99:1, respectively, using the trans, trans diene, and a ratio of 3:1 using the cis, trans diene. A large body of evidence points to the fact that the mechanism of the formation of these Diels-Alder adducts was of a biradical nature, and consequently, the composition of the cis and trans 1,4 adducts was kinetically controlled.

The thermal cycloaddition of butadiene and cis or trans ClFC=CFCl, in addition to yielding 1,2 cycloadducts gave respectively 2.1% and 2.4% 1,4 adducts with a loss of halogen configuration of 42.5% and 23%. Clearly then, the biradical pathway played a role in the Diels-Alder addition and most likely its role was largely preponderant over the concerted one.

On going from butadiene to trans, trans-2,4-hexadiene the cis and trans CClF=CClF gave respectively 16.8% and 19.4% 1,4 adducts with a loss of halogen configuration of 8.1% and 5%. We attribute this increase in both 1,4 adducts yield and stereospecificity to the intervening or large increase of the concerted pathway due to the two methyls which slow the biradical mechanism while accelerating the concerted one.

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