To the graduate council:

I am submitting herewith a thesis written by Cyril V. Thompson entitled "The Stereochemistry of the S_N2' Reaction of Ethylamine with 3-Chloro-1-butene." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

Ronald M. Magid, Major Professor

We have read this thesis
and recommend its acceptance:

Clifton Woods

Accepted for the council:

The Graduate School

THE STEREOCHEMISTRY OF THE S_N2' REACTION OF ETHYLAMINE WITH 3-CHLORO-1-BUTENE

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Cyril V. Thompson

August 1985

DEDICATION

This thesis is dedicated to the author's wife, Wanda, who provided both material and spiritual support during the development of this thesis and the research on which it is based.

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The author is very appreciative to his parents for their positive influences and encouragement which made attainment of this goal possible.

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ABSTRACT

Allylic compounds are known to react via nucleophilic substitution in which the double bond is displaced to another position in the compound (allylic rearrangement by the S_N2' reaction). Theoretical and experimental work on the mechanism of this reaction is ambiguous and often contradictory. The reaction of optically active 3-chloro-1-butene-1-d (α-methylallyl chloride) with the primary amine, ethylamine, proceeds by an S_N2' pathway that is stereoselectively syn. The allylic amine which results from the S_N2' reaction of the above is first reduced by treatment with diimide and then ethylated using ethyl iodide. The optical rotation of the reduced, alkylated amine is then compared to that of a sample of the optically pure amine. This comparison shows that the reaction proceeds with syn stereoselectivity.

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CHAPTER I

INTRODUCTION

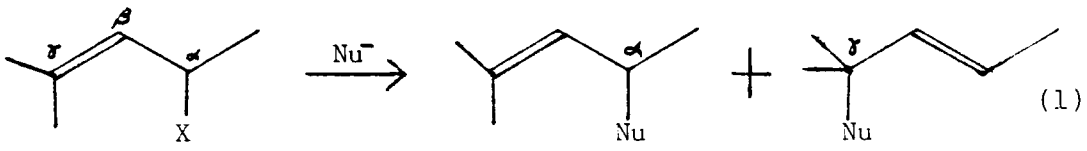
A. Proem

The substitution reactions of allylic compounds have been the subject of investigation by both synthetic and theoretical chemists for several decades. Because the double bond of these compounds activates the functional group, substitution occurs more easily than would be the case if the compound were saturated. This proclivity for reaction involves allylic systems in many naturally occurring compounds which are formed via enzyme catalysis. Synthetic chemists utilize allylic substitution reactions in the formation of some of these compounds, such as steroids and prostaglandins.

The interest of theoretical chemists in substitution reactions involving rearrangement is directed at the mechanism of rearrangement and the corresponding stereochemistry which can be predicted using calculations based on the type of nucleophile and allylic substrate.

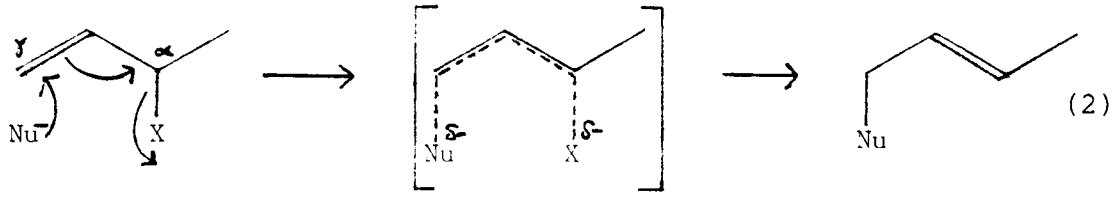
B. Historical Background

As early as the 1920s, it was well-established that allylic halides, reacting by a process of nucleophilic substitution (or solvolysis), yielded two products, allylic isomers, which resulted from attack by nucleophile on either the alpha (α) or the gamma (γ) carbon of the allylic system (Equation 1).



(1)

In the latter half of the 1930s, Bergmann,[1] Hughes,[2] and Winstein[3] all independently proposed a mechanistic theory in which nucleophilic attack at the γ-carbon of the allylic system would result in a π-electron shift with concerted loss of the halide anion, yielding the "abnormal" allylic substitution product (Equation 2). This mechanism is represented by the symbol S_N2' (substitution, nucleophilic, bimolecular, allylic rearrangement).



(2)

DeWolfe and Young[4] have proposed three conditions which must be satisfied before a reaction can be considered as following the S_N2' pathway:

1. The rate of the reaction must be proportional to the concentration of both the nucleophile and the allylic compound.

2. The reaction must yield abnormal substitution product in isolable amounts.

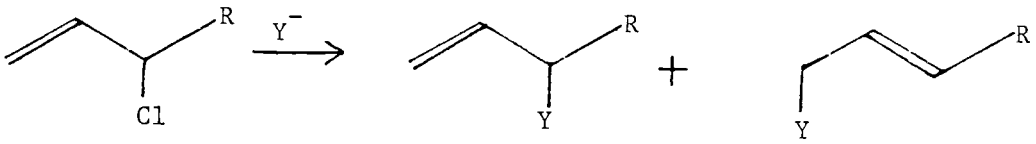
3. It must be demonstrated that neither the starting material nor the normal substitution product undergoes rearrangement under the conditions of the reaction.

The search for examples of the S_N2' reaction during the 1930s and the 1940s was generally unsuccessful. In 1930, Meisenheimer and Link[5] had reported abnormal product in a series of allylic substitution reactions quite similar to those which form the basis for this thesis, but they did not conduct the kinetic determinations which would have established the mechanism as S_N2'.

As a result of the aforementioned lack of success in finding verifiable S_N2' reactions, Catchpole, Hughes, and Ingold[6] concluded in 1948 that the available theoretical considerations and experimental data precluded the possibility of discovering an authentic example of the S_N2' reaction. Their reasoning was that the π electrons of the allylic system shield the γ-carbon from nucleophilic

attack; thus, the S_N2' could never compete with the more facile S_N2 mechanism.

Less than a year later, Young and co-workers[7] reported the first valid example of an S_N2' reaction. In the reactions of diethyl sodiomalonate with α-methyl and α-ethylallyl chloride, the yields of S_N2' product were 10 and 23%, respectively (Equation 3). Moreover, the reaction with α-ethylallyl chloride also fulfilled the requirements of second-order kinetics and non-rearrangement of either the allylic reactant or the S_N2 product under the conditions of the reaction.

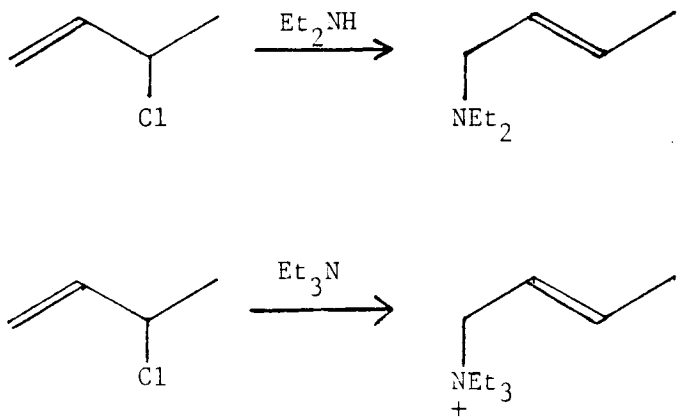


(3)

R= CH_3, C_2H_5 Y= $CH(CO_2Et)_2$

Reports of other examples of the S_N2' reaction soon followed. British researchers, including Hughes, contributed several of the early papers on the subject.[8] In 1951, Young et al.[9] reported the results of the reactions of α-methylallyl chloride with diethyl- and triethylamine. Both amines reacted with the chloride to give exclusively abnormal product (Equation 4). Based on the kinetic data, lack of reactant isomerization, and product stability, the diethylamine reaction was determined to have proceeded by an S_N2' mechanism. However, the strenuous conditions and

length of time required for the triethylamine reaction caused considerable (50%) rearrangement of the allylic chloride and decomposition of the quaternary ammonium salt product, so the mechanism of reaction could not be established with certainty. A comparison of reaction rates showed that the diethylamine reaction was much faster than that of triethylamine. This acceleration was attributed to a transition state in which nucleophilic push by nitrogen is accompanied by electrophilic pull by hydrogen.

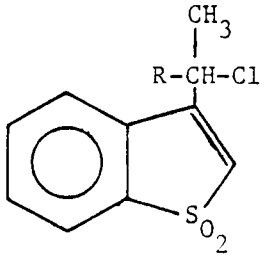


(4)

Because of the possibility of such hydrogen bonding, Ingold[10] classified the reaction as S_Ni' rather than S_N2'.

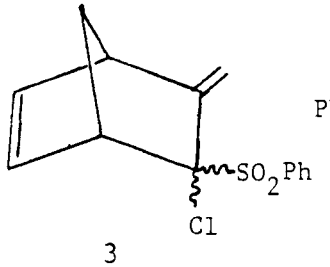
However, DeWolfe and Young[4] have noted that hydrogen bonding is a weak interaction compared to the covalent bonds being formed and broken in the intermediates of S_Ni' reactions. Thus, the difference between calling this process a modified S_N2' or a borderline S_Ni' is largely dependent on one's theoretical preferences. Relevant to this discussion is the report by Dittmer and Marcantonio[11] in which they found no deuterium kinetic isotope effect for the reactions of α-methylallyl chloride with Et_2ND and $Ph(CH_3)ND$. Their conclusion that hydrogen bonding is not important in the S_N2' transition state appears to refute Ingold's S_Ni' theory.

In another controversy over the nature of the S_N2' reaction, Bordwell[12] has questioned the concept of the S_N2' as a concerted mechanism. He has based his arguments on his studies of a series of reactions of four allylic halosulfone systems. The sulfone group is electron-withdrawing and should inhibit a carbonium ion reaction while activating the γ-carbon of the double bond to nucleophilic attack. With a combination of this effect and those of the halide and phenyl substituents, the compounds used provide allylic systems with electron withdrawal at the α- (Compound 3), the γ- (Compound 4), and the β- and γ- (Compounds 1 and 2) carbons, for comparison of S_N2' reactions.



1 R=H

2 R=CH_3



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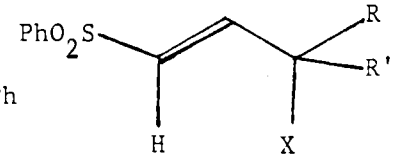
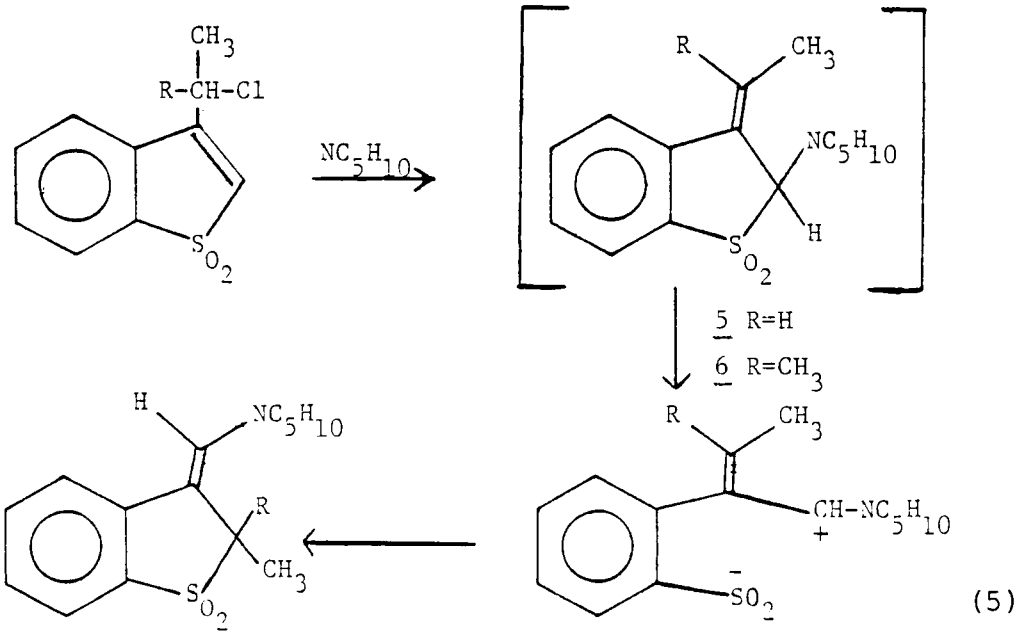


4

R,R'=H,CH_3

Compounds 1 and 2 reacted with piperidine by an S_N2' process, but the intermediate products 5 and 6 underwent a ring-opening/ring-closing rearrangement (Equation 5) which prohibited resolution of the mechanism.[13] Fortunately, the reactions of Compound 2 with N_3^-, CN^-, PhS^-, and $PhSO_2^-$ yielded S_N2' prcducts which were more stable and didn't rearrange.[14]

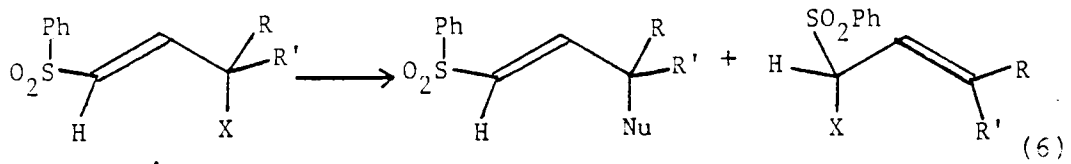


5 R=H

6 R=CH_3

(5)

Compound 3 should have been inhibited to both S_N1 and S_N2 reactions, with S_N2' nucleophilic attack being accelerated because of the inductive effect of the sulfone group on the double bond. Contrary to expectations, Compound 3 was found to be resistant to any mode of attack by any nucleophile.[15] Finally, Compound 4 , in reaction with a large variety of nucleophiles, gave only double bond isomerization or products resulting from an S_N2 mechanism (Equation 6). No S_N2' product was found in spite of the logical expectation that Compound 4 would be relatively



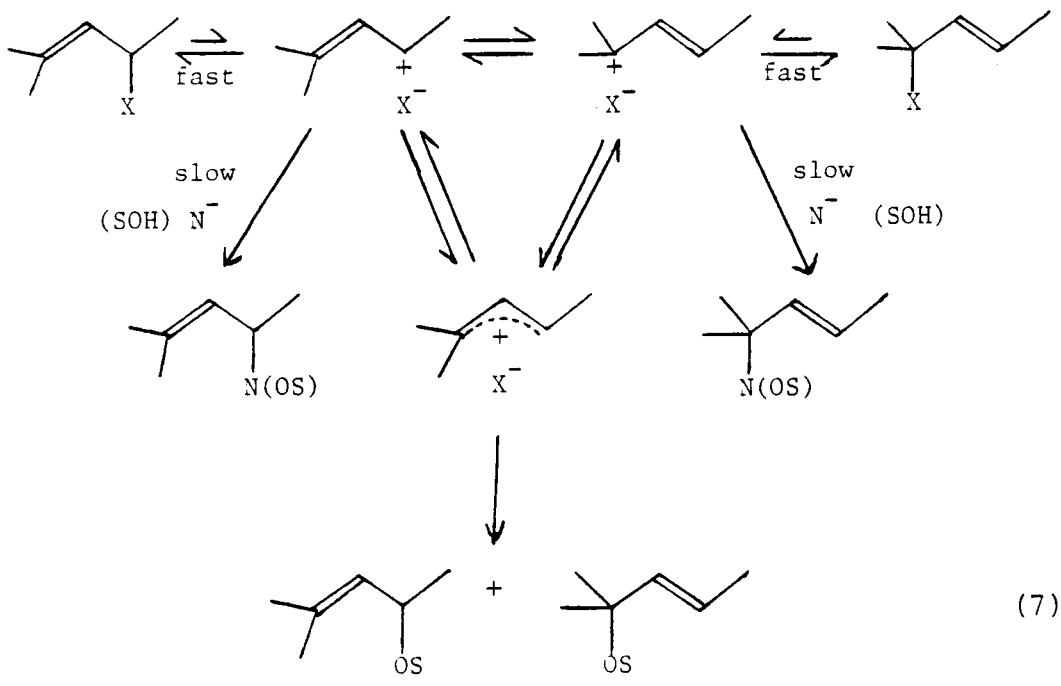
4
R,R'=H,CH_3

(6)

susceptible to S_N2' nucleophilic attack.[15,16] Bordwell's opinion, based on these results, is that the concerted S_N2' mechanism is probably fictitious, and the Sneen[17] ion-pair mechanism is a better explanation of the formation of rearranged product. Cromwell and co-workers[18] have used similar studies in which a carbonyl group activated the allylic system to come to essentially the same conclusion.

Sneen and his co-workers[19] have studied the solvolysis of various allylic systems (with substituents ranging from methyl to phenyl) in the presence of added nucleophiles.

The results of these reactions are interpreted as denoting an ion-pair mechanism. This process begins with the rapid formation of a physically discrete ion pair with the leaving group closely associated with the carbon from which it came. This intimate ion pair can isomerize to another allylic intimate ion pair, it can undergo nucleophilic substitution at the original carbon, or it can become a solvent separated ion pair. The variety of products and their relative percentages are attributable to competition between ion pair isomerization and nucleophilic attack (Equation 7).



(7)

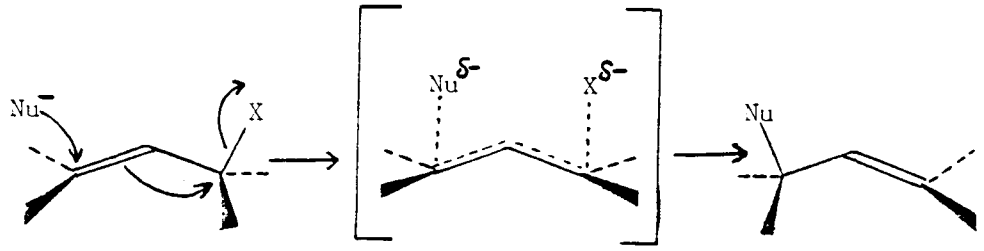
A concerted S_N2' mechanism is "intellectually unreasonable" to Sneen because it requires "unprovoked nucleophilic attack at the γ-position of the allylic system."[19c] But ion pair formation in an allylic system induces electron deficiency at the γ-carbon and thereby provides a driving force for the S_N2' reaction.

McLennan,[20] who favors a concerted mechanism, has responded to Sneen's preference for an ion-pair mechanism by re-examining Sneen's data. He contends that the nucleophilic salt parameter used by Sneen is adjustable, and by a judicious choice of the parameter (b), one may correlate the experimental data with the mechanistic model of one's choice. He also points out that in the alleged formation of an allylic ion pair, the nucleophile would have to act as a spectator to ionization, an unrealistic expectation. He concludes that the ion pairs postulated by Sneen must be "more intimate than intimate," or in actuality, "polarized R-X molecules."[20] Georgoulis and Ville,[21] in carrying out various S_N2 and S_N2' reactions, found that the optical purity of the S_N2 products was the same as the optical purity of the reactants, that S_N2 reactions proceeded with total inversion of configuration, and that the reactants exhibited no allylic interconversion. These results tend to support McLennan's conclusions about the validity of the classical S_N2 and S_N2' reactions.

C. Stereochemistry

While the concerted S_N2' mechanism versus the ion pair S_Ni' may be a hotly debated subject for many years to come, the stereochemistry of the various S_N2' reactions is more easily ascertained.

Winstein (as quoted by Young[4,22]) was first in proposing a **syn** relationship between entering and leaving groups. His reasoning was that the entering nucleophile would so displace the π electrons as to allow them to attack the back-side of the carbon bearing the leaving group (Equation 8). Syn attack is certainly necessary if hydrogen bonding is an important feature of the transition state.



(8)

Fukui and Fujimoto,[23] pioneers in theoretical calculations for the S_N2' mechanism, used frontier molecular orbital (MO) theory in a treatment of σ-π interactions in the reaction to predict **syn** attack of the nucleophile. Drenth[24] and Jefford *et al.*[25] have also

postulated syn attack by nucleophile using Hückel MO theory.

Based on an orbital symmetry analysis supported by ab initio and semiempirical MO calculations, Yates et al.[26] have concluded that neutral nucleophiles will attack syn, and charged nucleophiles will attack anti to the leaving group in the S_N2' reaction.

Liotta and Burgess,[27] from a molecular orbital analysis of the major $\sigma - \pi$ interactions in rigid allylic systems, have proposed syn attack for monointeractive nucleophiles and competitive syn/anti stereochemistry for diinteractive nucleophiles in the S_N2'.

Stohrer[28] used semiempirical and ab initio calculations as a basis for his consideration of the S_N2' reaction with an emphasis on the role of the β-carbon in the mechanism. His reasoning was that this carbon acquires somewhat of a negative charge in the transition state. Because it is non-planar in a syn mechanism, its hybridization is somewhere between sp^2 and sp^3, and this better accomodates the negative charge than the planar sp^2 hybridization in an anti mechanism can. Also, the larger lobe of the p-orbital on the β-carbon must "change sides" in an anti mechanism, this being an unfavorable inversion not required in the syn process. So a "poor" leaving group favors syn stereochemistry by allowing the negative charge at the β-carbon to build, and a "good" leaving group

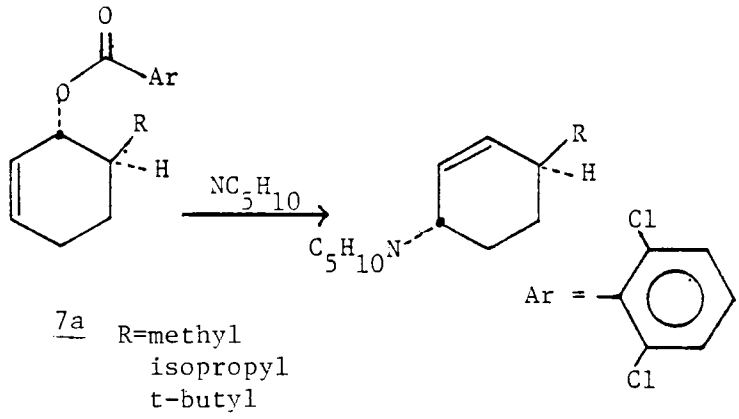
favors anti stereochemistry for the opposite reasons.

Matthieu and Rassat[29] have used an extension of the Woodward-Hoffmann rules to predict syn stereochemistry for the S_N2', while Anh[30] has approached the mechanism of the reaction with a method analogous to the Woodward-Hoffmann treatment of sigmatropic reactions. Using this approach, Anh postulates anti attack with synchronous bond-breaking and bond-making in the transition state. However, if bond-breaking occurs slightly before bond formation, although the reaction is still concerted, nucleophilic attack will be syn.

Houk et al.[31] have used ab initio calculations to show that the trans bending of alkenes and the anti-periplanar relationship of the developing lone pair and the leaving group lead to overall syn S_N2' attack in a synchronous reaction. Attraction and repulsion between the nucleophile and leaving group are of no consequence. They propose that syn attack is favored by strong nucleophiles, poor leaving groups, and low solvent polarity. Also, the syn preference should be independent of the charge on either nucleophile or leaving group.

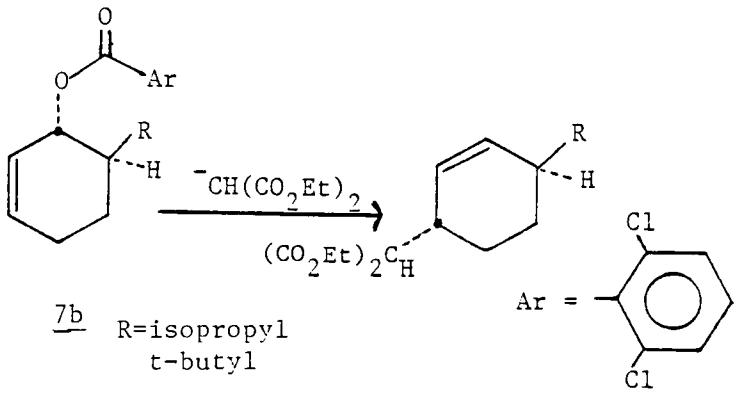
The volume of experimental research done on the stereochemistry of the S_N2' reaction is relatively small. Until the 1970s, the primary work done on the subject was that of Stork and White,[32] completed in the 1950s. They studied the S_N2' reactions of several allylic systems

(the 2,6-dichlorobenzoates of various 6-alkyl-2-cyclohexenols and of α-methylallyl alcohol) with piperidine and malonic ester ion. When Compound 7a was treated with piperidine, the only product was that produced by syn S_N2' attack of the nucleophile (Equation 9). When Compound 7b reacted with malonic ester ion, the product again was that of syn S_N2' nucleophilic attack (Equation 10).



7a R=methyl
isopropyl
t-butyl

(9)



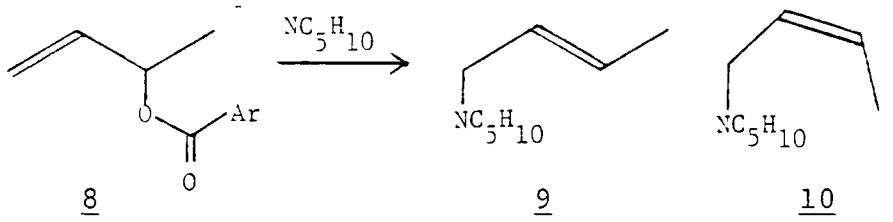
7b R=isopropyl
t-butyl

(10)

Although the S_N2' stereochemistry for the reactions of these esters proved to be syn, the relevance of these

results to any generalization about overall S_N2' stereochemistry is limited, because a conformational bias is inherent in the cyclohexenyl system. This bias, as thoroughly discussed by Magid,[33] results from a need for the leaving group to be quasi-axial for S_N2' attack to occur.

Stork and White[32] also examined the reaction of acyclic Compound 8 with piperidine. The reaction yielded a mixture of the trans and cis isomers 9 and 10 resulting from S_N2' nucleophilic attack (Equation 11). These pro-



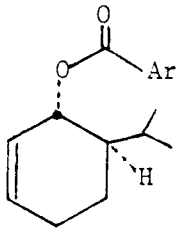
8 9 10 (11)

ducts were proposed as resulting from syn attack on two different conformations of the ester 8, although proof of syn attack was impossible without an optically active, isotopically labelled compound (as will be discussed shortly).

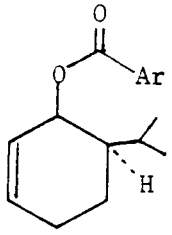
Concurrent with the stereochemical examination of the allylic esters was Stork and Clark's[34] investigation of the isomerizations of the α- and β-chlorocodides. When either of the chlorocodides was treated with lithium aluminum hydride (LAH), the product was that of S_N2' attack. Treatment of the chlorocodide isomers with

piperidine yielded products which were stereospecifically syn, but this fact is not indicative of a general preference in the S_N2' mechanism. It has been shown by Magid[33] that attack on the lower face of the double bond in the chlorocodides is somewhat hindered. The piperidine attacks in a syn S_N2' fashion, presumably because anti S_N2' and regular S_N2 mechanisms are sterically hindered.

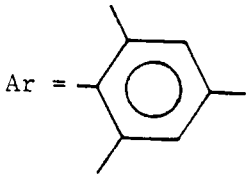
In a recent reproduction of the earlier work with cyclohexenyl systems, Stork and Kreft[35] have confirmed the accuracy of the original results for the cyclic ester and have investigated reactions of the same system with other nucleophiles in various solvents. When ester 11 reacted with propanethiolate, the major product was that resulting from S_N2 displacement. The S_N2' product was formed largely by a syn process. There were, however, varying amounts of product from anti attack also present. The respective amounts of syn to anti product ranged from approximately 9:1 (propanethiolate in butanol solvent) to approximately 2:1 (propanethiolate in hexamethylphosphoramide). When ester 12 was refluxed with sodium propanethiolate in butanol, the S_N2' product was only 35% syn. With the lithium salt of propanethiol, ester 12 reacted to give essentially equal amounts of syn and anti product.



11

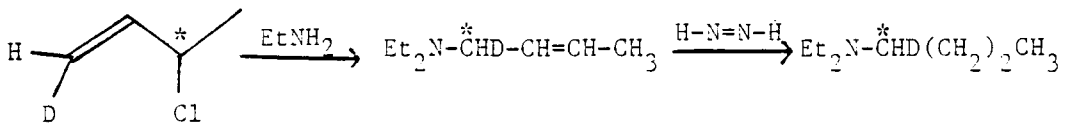


12



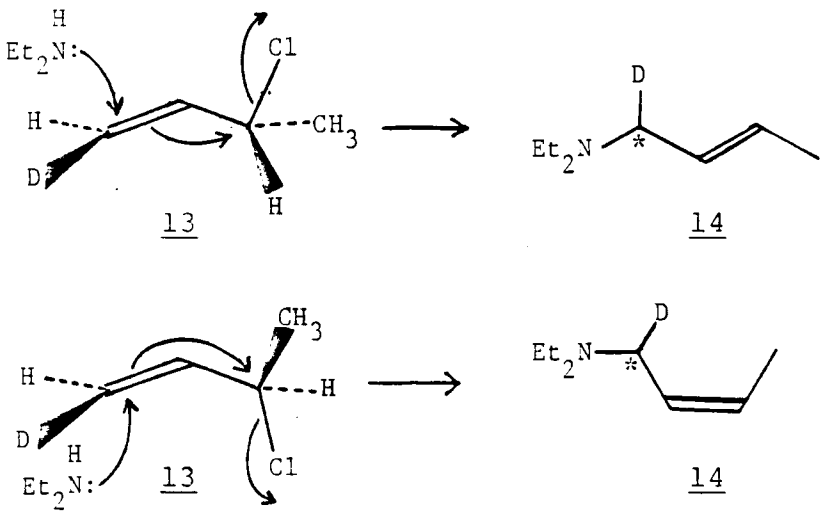
Overton and Dobbie[36] have also reinvestigated the earlier work done by Stork and White[32] and have verified its authenticity. Both Stork[35] and Overton[36] have expressed reservations about the conformational bias inherent in the cyclohexenyl allylic systems and its possible effect on the reaction stereochemistry.

To avoid the possibility of such conformational bias, Magid and Fruchey[37] used the optically active, deuteriated, acyclic, allylic chloride 13 in their study of the stereochemistry of the S_N2' reaction. Treatment of 13 with diethylamine yielded a mixture of S_N2' and S_N2 products in the ratio of 99:1. The S_N2' products, a 95:5 mixture of trans to cis amine 14, were reduced to Compound 15 (Equation 11). Comparison of 15 with an independently



13 14 15 (12)

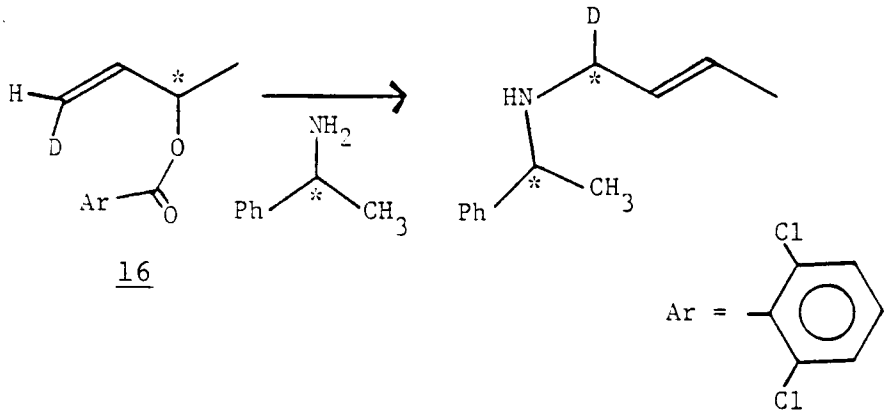
synthesized standard indicated that the S_N2' reaction proceeded with at least 96% syn stereospecificity. When Compound 13 reacted with either dimethylamine or piperidine, the S_N2' products were formed with a syn stereospecificity of at least 95-99%. As was mentioned previously in Stork and White's[32] acyclic case, the cis and trans isomers of 14 were assumed to have been produced by the same mechanism with the nucleophile attacking two different conformations of the chloride 13 (Equation 12). The experimental data proved this assumption to be true.



(12a)

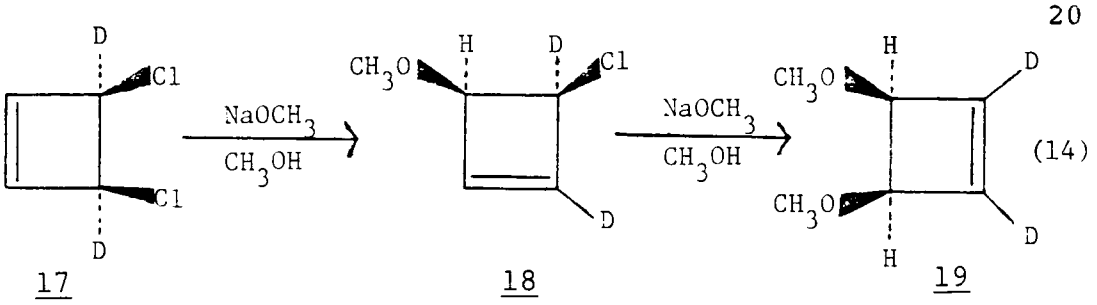
Using a system very similar to that employed by Magid and Fruchey, Overton and Oritani[38] treated Compound 16 with (R)- or (S)- α-methylbenzylamine. Eighty percent of the product was that resulting from S_N2' nucleophilic attack. Of this 80%, 60-65% was from syn attack (Equation 13). With this preference for syn attack of only approximately

1.4 to 1.8, Overton calculated the difference in energies of activation (E_a) for syn and anti attack to be 0.5 kcal/mol or less, in favor of syn. He reasons that the difference in preference for syn attack between this work and Magid's[37] is the more effective hydrogen bonding between the amines and the allylic chloride 13, although it appears that Dittmer and Marcantonio[11] negated this possibility with their earlier work.



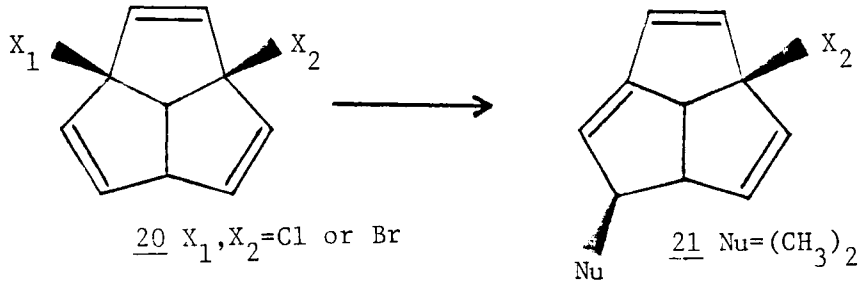
(13)

A clear, unbiased example of an S_N2' stereochemical determination using a cyclic system is that done by Kirmse et al.[39] The deuteriated cis-3,4-dichlorocyclobutene 17 was treated with sodium methoxide in methanol to give the syn S_N2' product 18. Subsequent treatment of 18 with methoxide ion in methanol gave the deuteriated cis-3,4-dimethoxycyclobutene 19, also formed by a syn S_N2' mechanism (Equation 14). Noteworthy in this reaction scheme is the syn stereospecificity and the preference for S_N2', as opposed to S_N2, substitution.



17 18 19 (14)

Butenschön and de Meijere[40] have also examined S_N2' substitution on a cyclic system and have reported results similar to Kirmse's. When the dihaloquinacene 20 was treated with dimethylamine, piperidine, or morpholine, the reaction yielded syn S_N2' product 21. Dibromoquinacene 22 reacted with dimethylamine and piperidine under mild conditions to give 23 (Equation 15). Under more strenuous conditions, 22 reacted with two equivalents of amine to produce 23a by a double substitution (Equation 16). The fact that all these reactions proceed with syn S_N2' stereospecificity may be attributed to the considerable steric hindrance to anti S_N2' substitution present in the molecule. This steric hindrance prevents application of these results to a resolution of the debate over S_N2' stereochemical preferences.



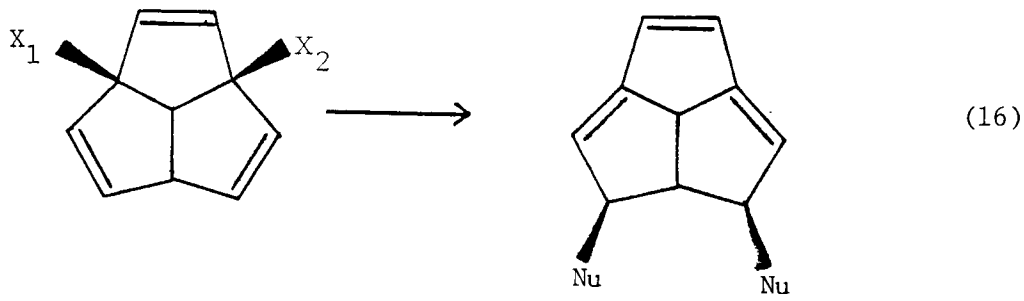
(15)

20 X_1, X_2=Cl or Br

22 X_1, X_2=Br

21 Nu=$(CH_3)_2N$, $(CH_2)_5N$, $(CH_2)_4NO$

23 Nu=$(CH_3)_2N$, $(CH_2)_5N$,

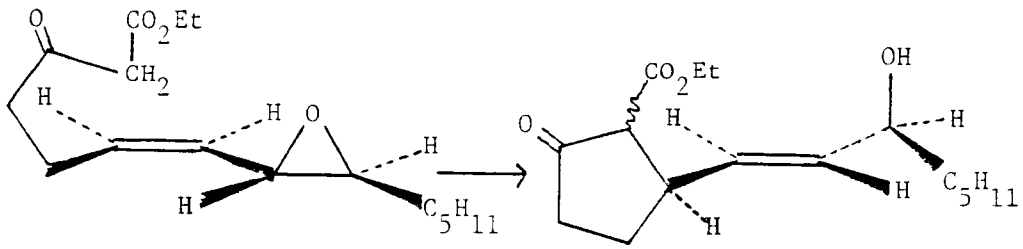


(16)

22 X_1, X_2=Br

23a Nu=$(CH_3)_2N$, $(CH_2)_5N$

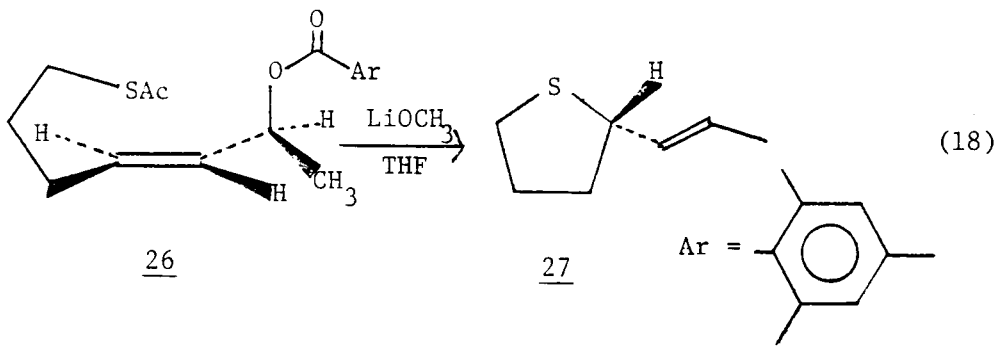
Several of the researchers interested in the stereochemistry of the S_N2' reaction have utilized systems which undergo an intramolecular S_N2' or S_{CN}' (substitution, cyclization, nucleophilic, allylic rearrangement) reaction. Martel *et al.*[41] were the first to make use of such a reaction in their synthesis of the prostaglandin nucleus. Treatment of ketoester 24 with pyrrolidine followed by sodium amide and then water, resulted in the formation of Compound 25 via a syn S_{CN}' process (Equation 17).



(17)

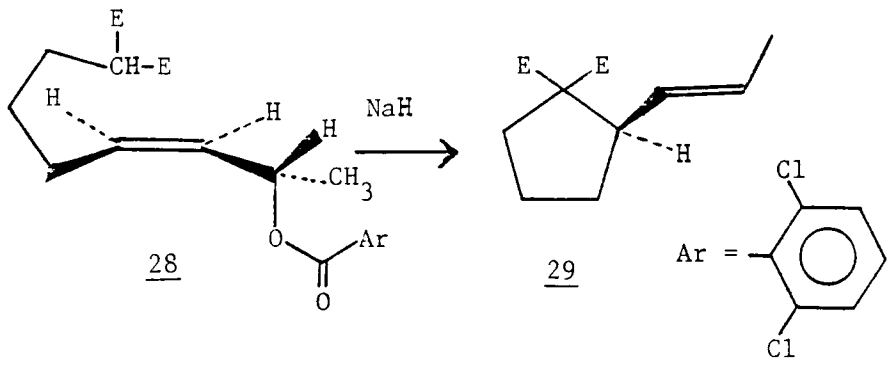
24 25

Stork and Kreft[42] have also used cyclization reactions to investigate the stereochemistry of the S_N2' process. Formation of the thiolate anion of optically active Compound 26 and its subsequent cyclization under a variety of basic conditions, yielded the substituted tetrahydrothiophene 27 (Equation 18) which was shown, based on its optical rotation, to have been formed largely and quite possibly entirely by an anti S_{cN}' mechanism. Based on these data, Stork concluded that the stereochemistry of such reactions may be markedly affected by the nature of the entering and leaving groups.



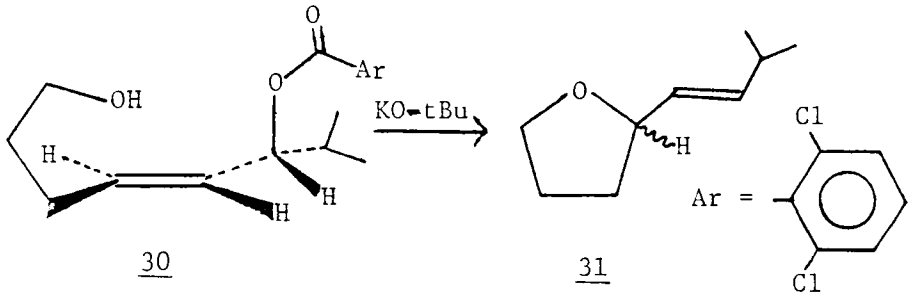
26 27 (18)

In a variation of the same system, Stork and Schoofs[43] studied the cyclization stereochemistry of Compound 28 in which the nucleophile is a carbanion. When 28 was treated with sodium hydride, it yielded substituted cyclopentane 29 (Equation 19) which was shown as resulting from anti S_{cN}' reaction by examination of its optical activity.



(19)

Stork and Poirier,[44] in a study using the S_{CN}' reaction with an alkoxide ion nucleophile, found that optically active ester 30, when refluxed with potassium tert-butoxide in 2,2,2-trifluoroethanol, cyclized cleanly to the 2-alkenylfuran 31 which was almost completely a racemic mixture (Equation 20). When the alkoxide nucleo-

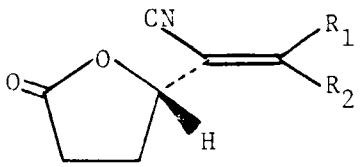


(20)

phile was replaced by a methoxyamine group, cyclization again gave a largely racemic product. However, that small amount of the pyrrolidine product which was not racemized

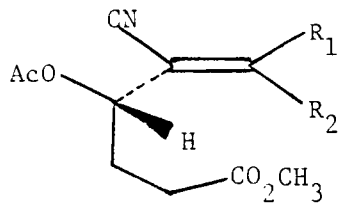
proved to have been formed by anti attack of the nucleophile.

In a reverse of the cyclization reactions done by Stork[42,43,44] and Martel,[41] Denmark and Eschenmoser[45] have studied S_N2' stereochemistry using a ring-opening reaction. trans-Lactone 32 gave primarily **syn** S_N2' product when treated with malonic ester (91% yield) and methoxyamine (96% yield). cis-Lactone 33 gave predominantly **syn** S_N2' product when treated with malonic ester but with only 28% stereoselectivity. When trans-acetoxy ester 34 reacted with malonic ester, the product was formed with 40% anti stereoselectivity. cis-Acetoxy ester 35 gave 51% anti stereoselectively formed product when treated with malonic ester. Reaction of trans-acetoxy ester 34 with methoxyamine yielded product with 84% **syn** stereoselectivity. Sulfur nucleophiles, in reactions with Compounds 32,33,34, and 35, gave products by largely non-stereoselective mechanisms.



32 R_1=CH_2Ph, R_2=H

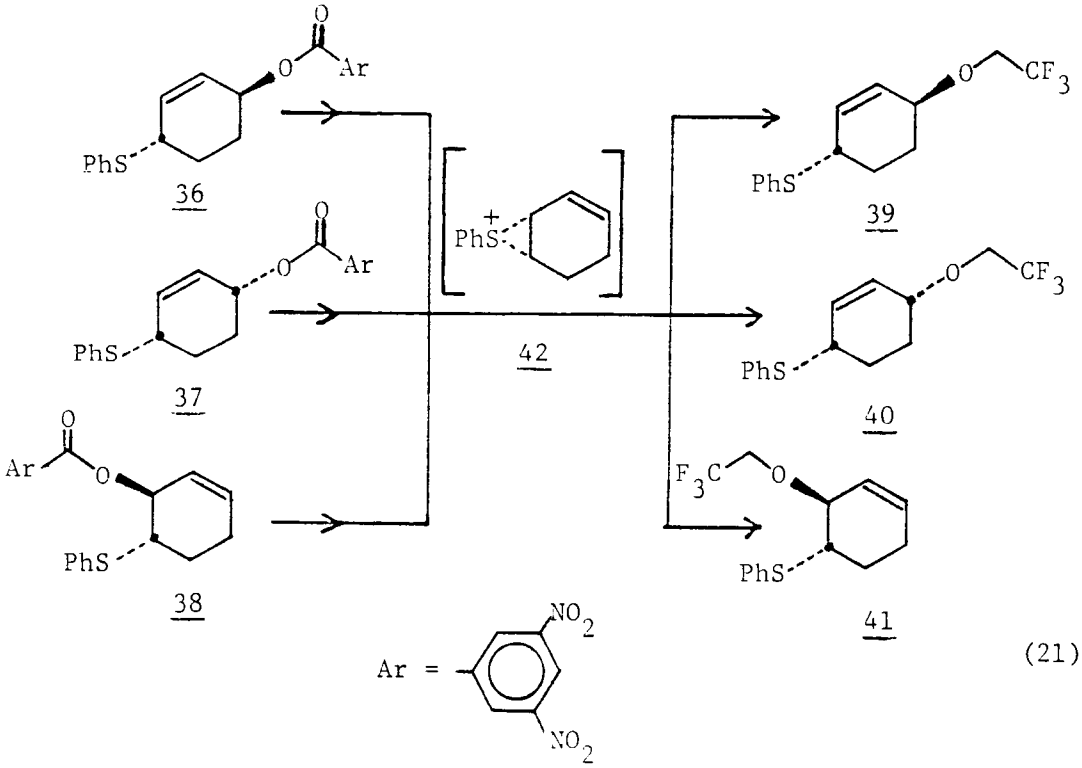
33 R_1=H, R_2=CH_2Ph



34 R_1=CH_2Ph, R_2=H

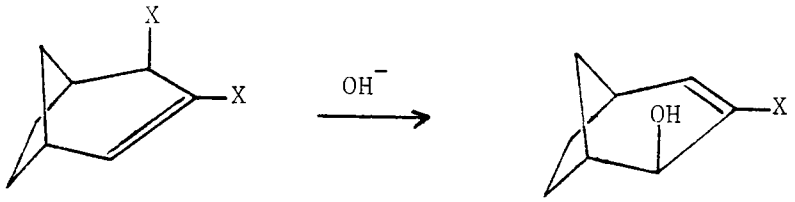
35 R_1=H, R_2=CH_2Ph

Uebel et al.,[46] in their study of S_N2' stereochemistry, used a cyclohexenyl system as did Stork, but their particular substituents produced some very different results. Compounds 36, 37, and 38 each underwent solvolysis in 2,2,2-trifluoroethanol, and each yielded the three products 39, 40, and 41. Since each isomeric reactant gave the same products in approximately 1:1:5 ratios for 39, 40, and 41 respectively, a common intermediate for the solvolysis was indicated. This intermediate is believed to be the episulfonium ion 42 which undergoes either S_N2' or S_N2 attack by solvent (Equation 21). Uebel has concluded from these data that when the leaving group is the leading element in the reaction, S_N2' reactions aren't too stereospecific nor are they very facile.



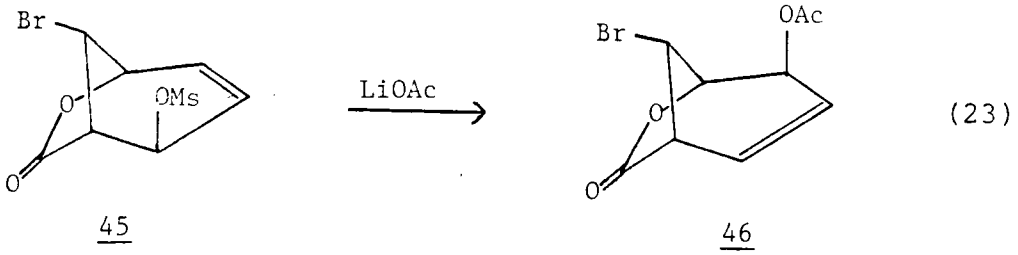
(21)

In yet another variation of Stork's[32] work, Maskill and Wilson[47] have examined the hydrolysis of exo-3,4-dichlorobicyclo[3.2.1]oct-2-ene 43 and its dibromo analogue. The S_N2' reaction which yields the hydrolysis product 44 is stereospecifically **syn** (Equation 22). It has been noted[48] that the system favors exo attack by about four kcal/mol, and it is probably this bias which is responsible for the observed stereochemistry.

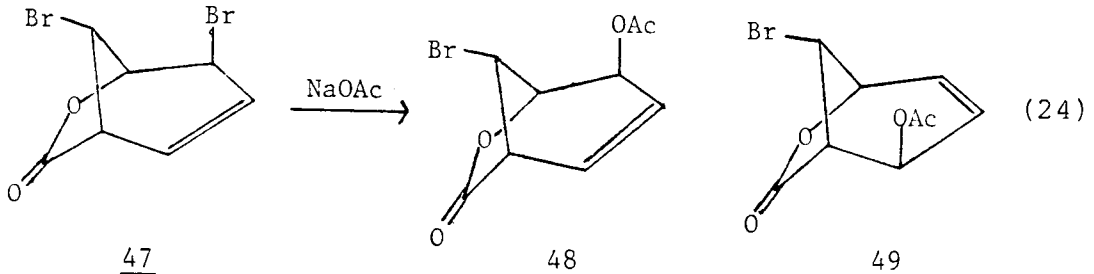


43 44 (22)

Ganem et al.,[49] in earlier work, treated mesylate 45, a bicyclic system similar to that used by Maskill and Wilson, with lithium acetate to form the **syn** S_N2' acetate 46 (Equation 23). However, when the related bromide 47 was treated with sodium acetate, a mixture of compounds 48 (note retention of configuration here) and 49 were obtained (Equation 24), indicating that either the reactants were rearranging to form the allylic isomers, or the reaction was proceeding by an ion-pair mechanism. Also worthy of notice is the fact that nucleophilic attack occurs only on the exo side of the bicyclic systems as was found by Maskill and Wilson.

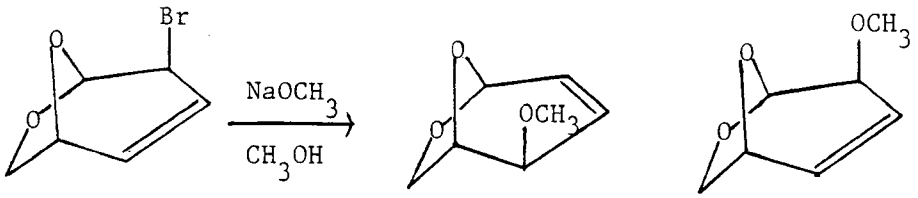


45 46 (23)



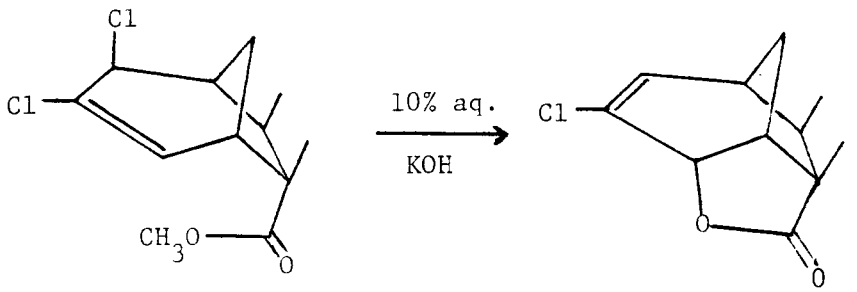
47 48 49 (24)

Brown et al.,[50] in earlier work paralleling Ganem's, treated bromide 50 with sodium methoxide in methanol and recovered 51 and 52 in a 2:1 ratio (Equation 25). The facts that no product from anti S_N2' attack was formed and that Compound 52 was formed with retention of configuration are further confirmations of the likelihood of reactant rearrangement or an ion-pair mechanism in the substitution reactions of this kind of bicyclic system.



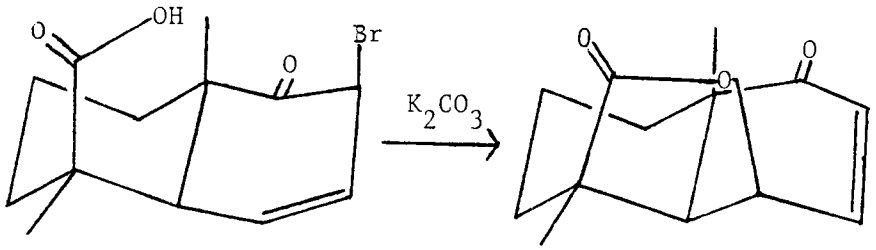
50 51 52 (25)

In the only example of anti S_{CN}' nucleophilic attack using a bicyclic system like those previously mentioned, Schomberg and Landry[51] refluxed Compound 53 in 10% aqueous potassium hydroxide to yield the tricyclic lactone 54 (Equation 26). This reaction has no choice but to proceed by an anti mechanism.



53 54 (26)

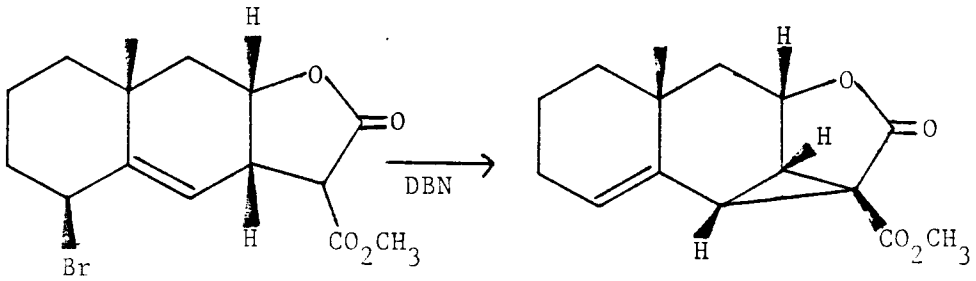
A similar reaction using carboxylate anion as the nucleophile is that reported by Welch et al.[52] in which the bicyclic carboxylic acid 55 was treated with potassium carbonate to facilitate syn S_{CN}' attack by nucleophile, yielding lactone 56 (Equation 27). As with the Schomberg example, there is only one stereochemical path for the reaction to follow.



(27)

55 56

Another example of an S_{CN}' reaction which is structurally restricted is found in the work done by Schultz et al.[53] When compound 57 was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the resulting conjugate base cyclized by an anti mechanism to form the lactone ester 58 (Equation 28).

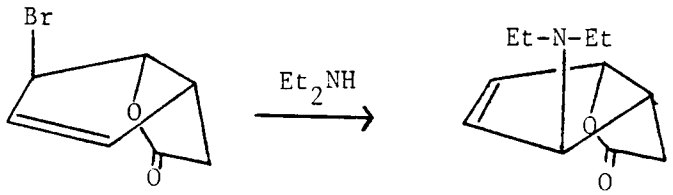


(28)

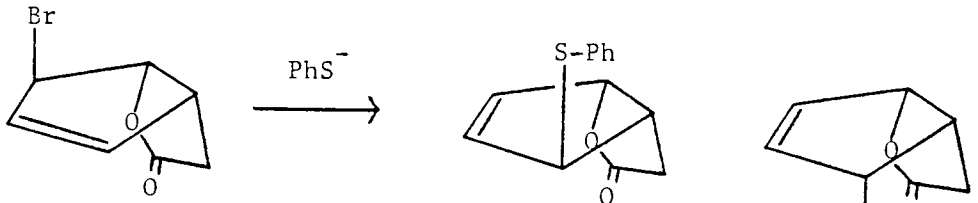
57 58

Chapleo et al.[54] have investigated the stereochemistry of the S_N2' reaction in several bicyclic systems. Bromolactone 59, in reaction with diethylamine, yielded Compound 60 by a syn S_N2' mechanism (Equation 29). Reaction of Compound 59 with thiophenoxide ion gave S_N2' products

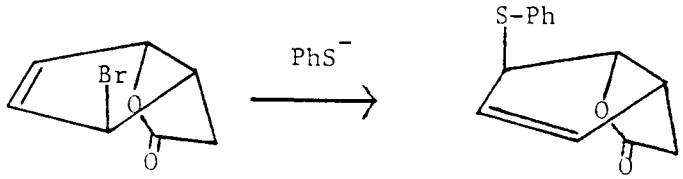
61 and 62 in a 95:5 **syn** to anti ratio (Equation 30). When bromolactone 59a was treated with thiophenoxide ion, the reaction was stereospecifically **syn**, yielding Compound 63 (Equation 31). Haloacetate 64 also reacted by a **syn** S_N2' stereospecific process with thiophenoxide ion to give Compound 65 (Equation 32). However, the relevance of these results to a resolution of the question about stereochemical preferences of the S_N2' mechanism is small, because the side of the molecule on which anti attack would occur is sterically hindered.



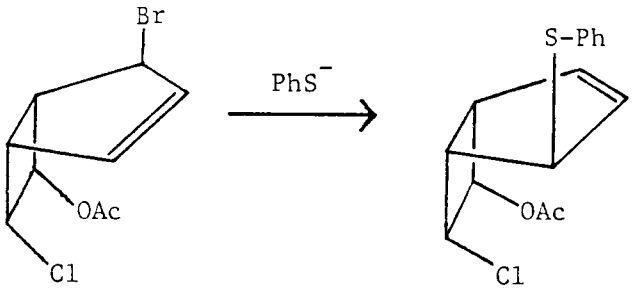
59 60 (29)



59 61 62 (30)



59a 63 (31)



64 65 (32)

CHAPTER II

EXPERIMENTAL SECTION

A. General Considerations

All reactions involving an optically active, deuteriated compound were first run with racemic, undeuteriated material to determine optimum reaction conditions and gas-liquid partition chromatography (glpc) retention times and peak separations.

A Nicolet NT-200 instrument was used for both the ^{1}H and ^{13}C NMR spectra. Tetramethylsilane (TMS) was the internal standard for all samples, and chemical shifts were recorded in δ units, ppm downfield from TMS.

Optical rotations were determined with a Rudolph MP7A41 photoelectric polarimeter.

A Varian Aerograph model 920 gas chromatograph coupled with a Sargent-Welch model SRG recorder, was used for all preparative glpc work. The helium flow rate was 40 mL/min. Columns were constructed from 0.375 in. aluminum tubing with Chromosorb W-AW (45-60 mesh) as a solid support.

Columns were:

Column A--12 ft, 15% Carbowax 20M;

Column B--12 ft, 20% Carbowax 20M/5% KOH.

Analytical glpc work was carried out on a Hewlett-Packard Model 5750 gas chromatograph equipped with a Leeds and Northrup Speedomax XL601 recorder. The flow rate for helium as a carrier gas was 65 mL/min. A Series 200 Disc Integrator was used to determine the relative peak areas, based on the assumption of equal molar responses. Columns were of .125 in. stainless steel tubing with Chromosorb W-AW (80-100 mesh) as the solid support.

Analytical columns were:

Column C--10 ft, 10% Carbowax 20M;

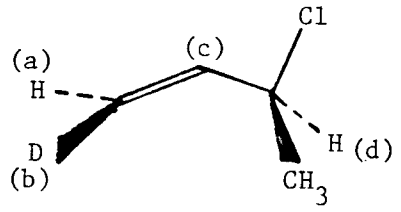
Column D--10 ft, 15% Carbowax 20M/2.5% KOH.

B. Reactions

1. Preparation of (S)-(+)-3-Chloro-(Z)-1-butene-1-d (67)

According to the procedure of Magid and Fruchey,[37] (R)-(-)-3-buten-2-ol-(Z)-4-d (66)[55] (4.972 g, 0.068 mol) was combined with hexachloroacetone (70 mL, 122 g, 0.5 mol) in a flask equipped with a magnetic stirrer. The solution was cooled to 0°C and triphenylphosphine (19.724 g, 0.075 mol) was added in small portions over a 40-minute period. After addition was complete, the mixture was warmed to room temperature. Flash distillation at 4.0 mm Hg into a reciever cooled with dry ice/acetone yielded ca. 5.5 mL of a clear solution which was purified by preparative glpc (Column A) to give pure (S)-(+)-3-chloro-(Z)-1-butene-1-d (67)

(3.400 g, 0.037 mol), α_D^{29} +35.47 ± 0.01° (neat, l=0.1), yield = 54.4%: ^{1}H NMR ($CDCl_3$) (a) δ 5.09 (dd, 1 H, J_{a-c} = 10.16 Hz, J_{a-d} = 0.81 Hz), (c) δ 5.95 (ddt, 1 H, J_{c-a} = 10.10 Hz, J_{c-d} = 7.38 Hz, J_{c-Deu} = 2.61 Hz), (d) δ 4.53 (m, 1 H, J_{d-c} = 7.38 Hz, J_{d-a} = 0.81 Hz, J_{d-e} = 6.65 Hz), (e) δ 1.60 (d, 3 H, J_{e-d} = 6.65 Hz).

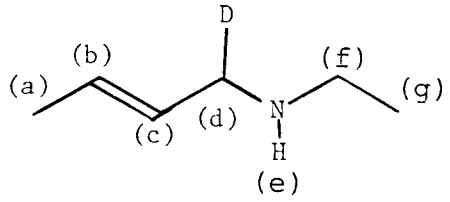


67

2. Reaction of (S)-(+)-67 with Ethylamine

A pressure bottle equipped with a magnetic stirrer was charged with ethylamine (40 mL, 27 g, 0.6 mol), ether (25 mL), and (S)-(+)-67 (1.959 g, 0.021 mol), α_D^{29} +35.47 ± 0.01° (neat, l=0.1). The contents were allowed to stir for 9 days at room temperature and then were cooled, and neutralized with excess 10 N KOH. The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (4x20 mL). The combined organic phases were dried over KOH pellets, and most of the ether was removed by distillation. Purification of the residue by preparative glpc (Column B) yielded N-ethyl-1-aminobut-2-ene-1-d (68) (0.737 g, 0.007 mol), which was estimated to be a 95:5

mixture of the E and Z isomers by ^{1}H NMR, and N-ethyl-3-aminobut-1-ene-(Z)-1-d (69) (0.603 g, 0.006 mol) for a combined yield of 62%: Amine 68, ^{1}H NMR ($CDCl_3$) (a) δ 1.7 (m, 3 H), (b and c) δ 5.6 (m, 2 H), (d) δ 3.20 (m, 1 H), (e) δ 1.90 (br s, 1 H), (f) δ 2.65 (q, 2 H, J_{f-g} = 7.15 Hz), (g) δ 1.12 (t, 3 H, J_{g-f} = 7.15 Hz); Amine 69, ^{1}H NMR ($CDCl_3$) (a) δ 5.01 (dd, 1 H, J_{a-c} = 10.21 Hz, J_{a-d} = 0.63 Hz), (c) δ 5.67 (ddt, 1 H, J_{c-a} = 10.21 Hz, J_{c-d} = 7.65 Hz, J_{c-Deu} = 0.63 Hz), (d) δ 3.19 (m, 1 H, J_{d-c} = 7.65 Hz, J_{d-e} = 6.51 Hz, J_{d-a} = 0.63 Hz), (e) δ 1.16 (d, 3 H, J_{e-d} = 6.51 Hz), (f) δ 1.36 (br s, 1 H), (g) δ 2.65 (dq, 1 H, $J_{g-g'}$ = 11.35 Hz, J_{g-h} = 7.16 Hz), (g') δ 2.56 (dq, 1 H, $J_{g'-g}$ = 11.35 Hz), (h) δ 1.10 (t, 3 H, J_{h-g} = 7.16 Hz).



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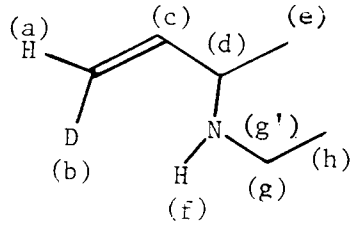
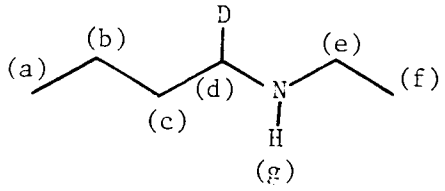


69

3. Diimide Reduction of Amine 68

Amine 68 (0.660 g, 0.006 mol) was combined with water (40 mL), p-toluenesulfonylhydrazide (PTSH) (17.673 g, 0.094 mol), and KOH (1.00 g, 0.02 mol) in a flask equipped with a magnetic stirrer. KOH (9.60 g, 0.19 mol) in water (35 mL) was added dropwise with stirring over 3 hours at

room temperature. After addition was complete, the solution was allowed to stir at room temperature for 16 h. The solution was then heated to 80 °C for 2 days. After cooling, the solution was extracted with ether (4x20 mL), the combined extracts were dried over KOH pellets, and most of the ether was removed by distillation. Preparative glpc purification of the residue yielded N-ethyl-1-aminobutane-1-d (70) (0.404 g, 0.004 mol) for a yield of 61%: ^{1}H NMR ($CDCl_3$) (a) δ 0.92 (br t, 3 H, J_{a-b} = 7.1 Hz), (b) δ 1.4 (m, 2 H), (c) δ 1.5 (m, 2 H), (d) δ 2.60 (tt, 1 H, J_{d-c} = 7.17 Hz, J_{d-Deu} = 1.63 Hz), (e) δ 2.66 (q, 2 H, J_{e-f} = 7.15 Hz), (f) δ 1.12 (t, 3 H, J_{f-e} = 7.15 Hz), (g) δ 1.76 (br s, 1 H).

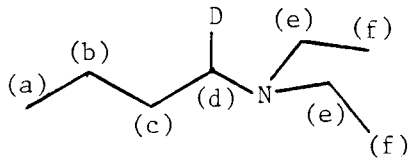


70

4. Ethylation of Amine 70

Into a flask equipped with a reflux condenser and a magnetic stirrer were placed sulfolane (4 mL) and Amine 70 (0.404 g, 0.004 mol). The temperature of the solution was elevated to 50 °C, and ethyl iodide (0.686 g, 0.004 mol) was added dropwise over a period of 1 h during which the temperature rose to 75 °C. After addition was complete, the

mixture was heated at 90°C for 5 h and was then allowed to cool to room temperature. Neutralization of the mixture with KOH pellets yielded a clear, yellow liquid which was purified by preparative glpc to yield N,N-diethyl-1-amino-butane-1-d (71) (0.052 g, 0.0004 mol), $[\alpha]_D^{29}$ -3.46 ± 0.38°, (0.026 g/mL, ether, l=0.1), $[\alpha]_{365}^{29}$ -13.85 ± 0.38°, (0.026 g/mL, ether, l=0.1), for a yield of 10%: ^{1}H NMR ($CDCl_3$) (a) δ 0.92 (br t, 3 H, J_{a-b} = 7.12 Hz), (b and c) δ 1.3 (m, 4 H), (d) δ 2.38 (tt, 1 H, J_{d-c} = 7.56 Hz, J_{d-Deu} = 1.80 Hz), (e) δ 2.52 (q, 4 H, J_{e-f} = 7.12 Hz), (f) δ 1.02 (t, 6H, J_{f-e} = 7.15 Hz); ^{13}C NMR ($CDCl_3$) (a) δ 14.01 (s, 1 C), (b) δ 20.76 (s, 1 C), (c) δ 28.78 (s, 1 C), (d) δ 52.11 (t, 1 C), (e) δ 46.71 (s, 2 c), (f) δ 11.51 (s, 2 c).



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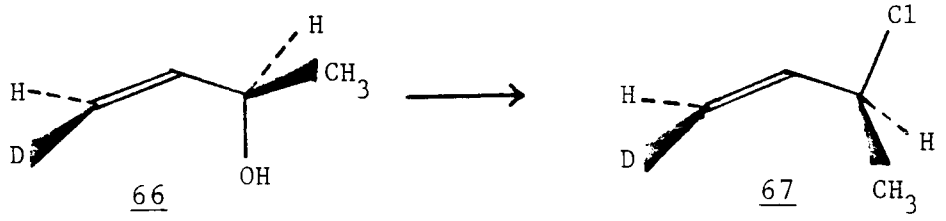
CHAPTER III

RESULTS AND DISCUSSION

The determination of the stereochemical preference of the S_N2' reactions of primary amines methyl- and ethylamine began with the synthesis of the allylic substrate (S)-(+)-3-chloro-1-butene-(Z)-1-d (67) from (R)-(-)-3-buten-2-ol-(Z)-4-d (66)[55] according to the procedure of Magid and Fruchey.[37]

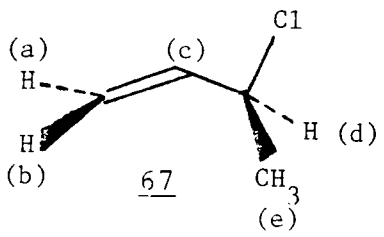
Reaction of (R)-(-)-66, α_D^{29} -19.93 ± 0.01° (neat, l= 0.1), 72.2% optically pure,[56] with triphenylphosphine in hexachloroacetone and subsequent flash distillation and purification gave (S)-(+)-67, α_D^{29} +35.47 ± 0.01° (neat, l=0.1), 58.1% optically pure[57] (Equation 33). The loss of

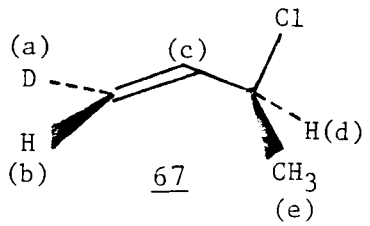


(33)

optical activity in the chlorination is atypical of the reaction as reported by Magid and Fruchey,[37] and there is no obvious explanation for the loss. One possible rationale is a variation in rate of addition of triphenylphosphine, which would increase the temperature of the reaction substantially, contributing to racemization. A similar

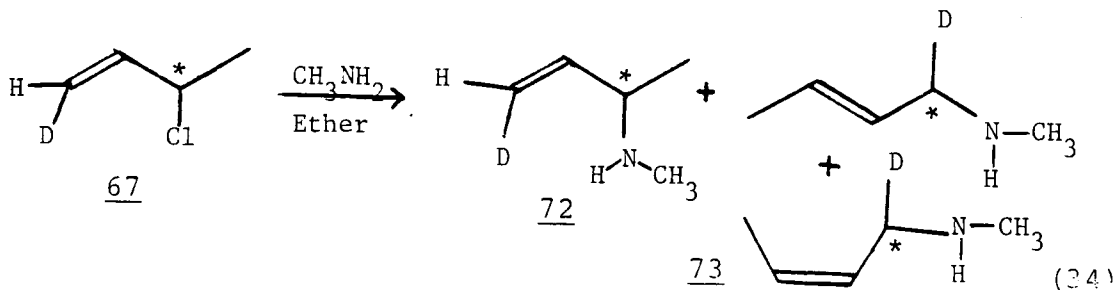
loss of optical activity was observed in a corresponding chlorination performed by Charles Bass.[58] The ^{1}H NMR spectrum showed that 1.2% of Chloride 67 was undeuteriated and 0.4% was deuteriated trans. These percentages are based on an analysis of the portion of the 200 MHz spectrum corresponding to the terminal vinyl hydrogens. The main signal is centered at 1018.2 Hz and is a doublet of doublets split by the (c) hydrogen (J = 10.2 Hz) and the (d) hydrogen (J = 0.8 Hz). At 1051.6 Hz are what appear to be a doublet of triplets but are actually a doublet of doublets of doublets. This is the signal of the (b) hydrogen on the undeuteriated compound split by the (c) hydrogen (J = 17.0 Hz) and the (a) and (d) hydrogens (J = 1.0 Hz). The inside peaks of the latter pairs of doublets overlap to form the center peak of the false triplet. These peaks and their frequencies correspond exactly to those of the (b) hydrogen in the 200 MHz spectrum of commercially available 3-chloro-1-butene. At 1048.8 Hz is a doublet of doublets which forms the signal for the (b) hydrogen on the trans deuteriated compound, the signal of this proton being split by the (c) hydrogen (J = 17.0 Hz) and the (d) hydrogen (J = 1.0 Hz).





Integration of the signals for these terminal vinyl hydrogens and comparison of the relative integration values gave the results mentioned above. However a rising base-line in the integration and the relatively small sizes of the peaks integrated lowers the reliability of these numbers.

S_N2' reaction of methylamine with Chloride 67 in diethyl ether proceeded in a pressure bottle for 10 days. After the contents were cooled, neutralized, and extracted, analytical glpc showed that the products were a 60:40 ratio of N-methyl-3-aminobut-1-ene-(Z)-1-d (72) (formed by S_N2 reaction) and the E and Z S_N2' products N-methyl-1-amino-but-2-ene-1-d (73) (Equation 34). The ^1H NMR spectrum of Amine 73 showed the Z isomer as being between 1 and 5% of



total, based on an analysis of small peaks upfield from the signal for the methyl group on the nitrogen.

The fact that Amine 72 was the major product is attributable to the lack of steric hindrance due to only one methyl group on the amine nucleophile as opposed to dimethylamine which yielded S_N2 and S_N2' products in a 1:99 ratio. Unlike the results reported by Magid and Fruchey,[37] i.e. no Z isomer in the S_N2' product, the methylamine

reaction yielded between 1 and 5% of the S_N2' Z isomer. Magid and Fruchey reported ca. 5% of the Z isomer in the S_N2' product from the diethylamine reaction. This appears to be a more typical result. The earlier (Fruchey) analytical glpc work done on the dimethylamine product employed an SE-30 column, and this allows for the possibility that a small amount of the Z isomer was hidden by the tailing of the E isomer. The analytical glpc work done on the methylamine products employed a 15% Carbowax/2.5% KOH column which reduced such tailing and allowed the Z isomer to be seen as a small peak in the tail of the E isomer peak. Also, the ^1H NMR instrument used by Magid and Fruchey for the dimethylamine-produced compounds utilized 60 MHz as opposed to the 200 MHz on which the spectra for this research were run. The limits of these methods of analysis may have prevented observation of the Z isomer, if formed, by Magid and Fruchey.

Because the only primary standard available for determination of the syn or anti preference in the S_N2' attack of methylamine (by comparison of optical activities) is optically active N,N-dimethyl-1-aminobutane-1-d, two more steps in the synthetic chain were necessitated-- addition of a methyl group to the nitrogen in Amine 73 and reduction of the double bond.

Alkylation of Amine 73 was carried out using the Eschweiler-Clarke method.[59] Minor variations in the

procedure included cooling the amine in the reaction flask in an ice bath and subsequent addition (dropwise) of formic acid and then formaldehyde. After addition was complete, the reaction flask was placed in a 90°C oil bath. Vigorous CO_2 generation, characteristic of the reaction, began after 4-5 minutes, and the oil bath was removed until gas generation subsided. The oil bath was then replaced, and the solution was refluxed for ca. 20 hours. After neutralization and extraction, preparative glpc of the ether-product solution yielded N,N-dimethyl-1-aminobut-2-ene-1-d (74).

The final step in the synthesis was the reduction of the double bond in Amine 74 with diimide. Diimide was generated in the presence of Amine 74 by treating p-toluenesulfonylhydrazide (PTSH) with KOH in water. The reactants are generally combined simultaneously and heated to reflux.[37] Modifications of this procedure which included a slow addition of aqueous base at room temperature, reaction at room temperature for 8-10 hours, and finally, a gradual heating of the solution to reflux (ca. 100°C), increased the percentage of reduced compound from 75% to 100% and allowed a reduction in the molar excess of PTSH from 25 to 10 in practice runs with optically inactive, unlabelled amine. However, in the reaction with Amine 74, so little of the desired product was recovered that it was unmeasurable, either by weight or by optical activity. Possibilities for the loss include co-distillation of the amine through the

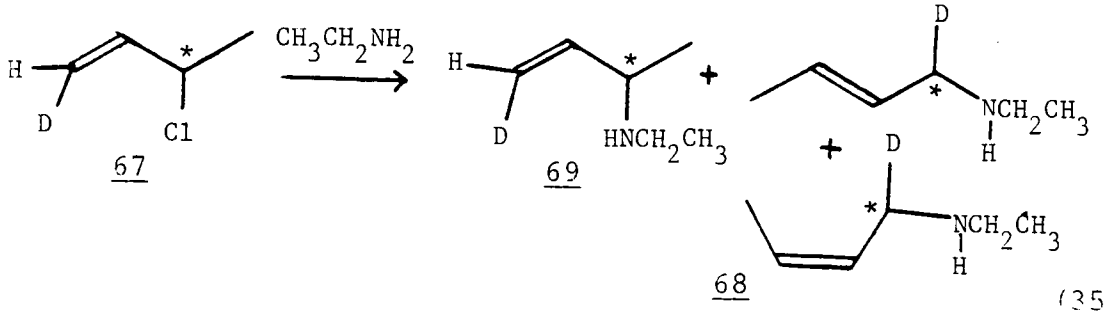
condensing column and/or evaporation from the pressure-equalizing dropping funnel connected to the reaction vessel (although the funnel was stoppered and no escape should have been possible).

Because the final product had been lost in this synthesis, no determination of the stereochemistry of the S_N2' reaction of methylamine with Chloride 67 was possible.

In anticipation of studying the stereochemistry of the S_N2 reaction of methylamine with Chloride 67, commercially available (R)-(-)-2-aminobutane α_D^{29} -5.25 ± 0.01° (neat, l=0.1), 92.1% optically pure,[60] was methylated using the previously outlined method to yield (R)-(-)-N,N-dimethyl-2-aminobutane (75), $[\alpha]_D^{29}$ -24.43 ± 0.23° (ether, l=0.1), $[\alpha]_{365}^{29}$ -58.14 ± 0.23° (ether, l=0.1). The corrected values for 100% optically pure Amine 75 are $[\alpha]_D^{29}$ -26.56° ± 0.25° and $[\alpha]_{365}^{29}$ -63.13 ± 0.25°.

The methylation of Amine 72 proceeded typically to yield N,N-dimethyl-3-aminobut-1-ene-(Z)-1-d (76) which was reduced by reaction with diimide as has previously been outlined. This reaction was run concurrently with the reduction of Amine 74 and met the same fate of loss of product. If anything, the loss was more complete in this reaction, as the familiar amine odor was absent from the reaction vessel and solution. Therefore, no stereochemical study was possible in the S_N2 reaction, either.

In the study of the S_N2' reaction of ethylamine with Chloride 67, the reactants were combined with ether in a pressure bottle and stirred for 9 days. This reaction yielded a 45:55 ratio of the S_N2 and S_N2' products N-ethyl--3-aminobut-1-ene-(Z)-1-d (69) and N-ethyl-1-aminobut-2-ene-1-d (68) in both its E and Z isomeric forms in a ratio of approximately 95:5, respectively (Equation 35). Percentages of the E and Z isomers are based on analytical glpc and ^1H NMR which shows a small triplet representing the methyl protons of the ethyl group on the nitrogen shifted slightly downfield and a small quartet representing the methylene protons of the ethyl group on the nitrogen, also shifted slightly downfield.



(35)

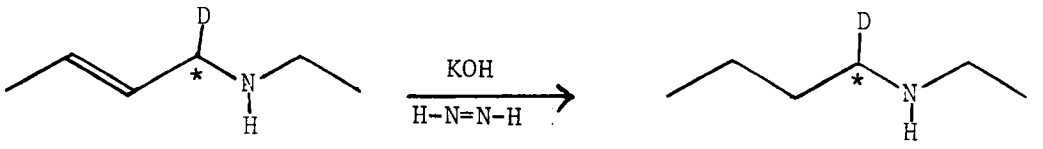
In their earlier work with diethylamine, Magid and Fruchey had found that reaction with optically active 3-chloro-1-butene-(Z)-1-d proceeded in a 99:1 ratio of S_N2' to S_N2 nucleophilic attack.[37] The relatively high percentage of S_N2 product in the ethylamine reaction is attributable to the lack of steric hindrance arising from having one less ethyl group on the amine, and in this respect is comparable to the previously mentioned methylamine reaction.

However, the slight increase in steric hindrance of the ethyl group on ethylamine over the methyl group on methylamine is seen in the respective ratios of S_N2 to S_N2' product, i.e. 45:55 and 60:40.

The ratio of E and Z isomers in the S_N2' product of the ethylamine reaction was comparable to that discussed in the methylamine reaction, and as has been mentioned before, to that reported by Magid and Fruchey in their diethylamine reaction.

To determine syn or anti preference in the S_N2' attack of ethylamine, it was necessary to convert Amine 68 into N,N-diethyl-1-aminobutane-1-d by reduction of the double bond and addition of an ethyl group to the nitrogen, so that its optical rotation and purity could be compared to those of (R)-(+)-N,N- diethyl-1-aminobutane-1-d synthesized by Magid and Fruchey.[37]

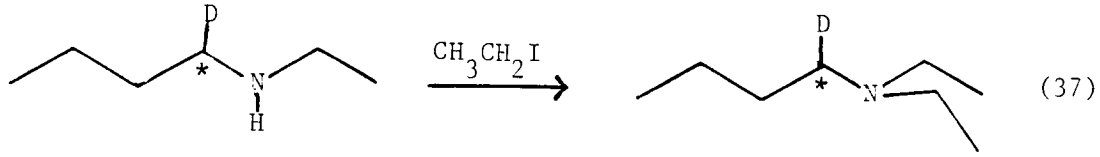
The reduction of Amine 68 was carried out first via the formation and reaction of diimide with the amine. Because this was the synthetic step in which the product had been lost in two previous syntheses, the reaction conditions were modified yet again in that the final temperature was not allowed to rise above 80°C. After reaction was complete, the solution was cooled and extracted, and preparative glpc of the product yielded N-ethyl-1-aminobutane-1-d (70) (Equation 36).



(36)

69 70

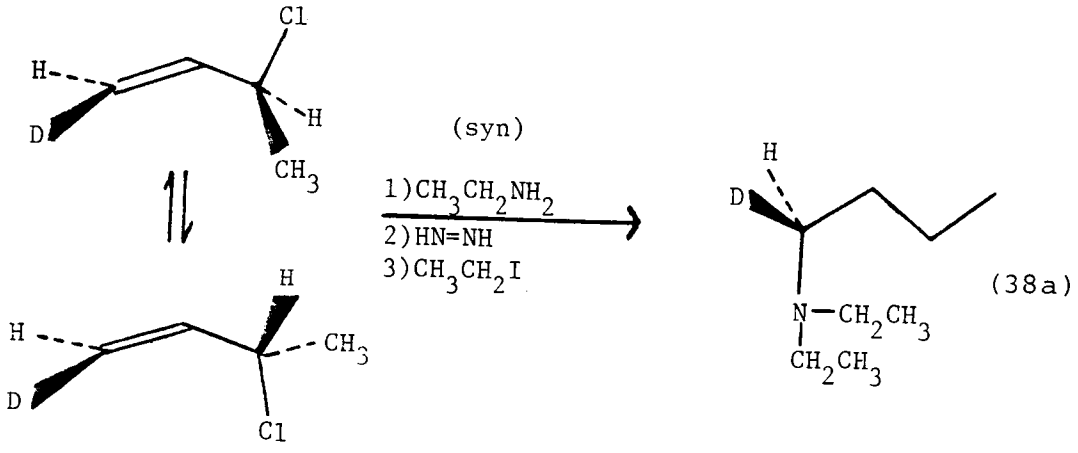
Amine 70 was then placed in sulfolane and heated to 50°C, and ethyl iodide was added dropwise to the solution over a 1-hour period. Sulfolane was chosen as the solvent in this reaction because of its high boiling point and the relative ease with which the amine could be separated from it. Other moderately polar solvents of lower boiling point and greater amine solubility, such as acetone, would have rendered the separation much more difficult. After the reaction was complete, the sulfolane-amine salt mixture was made basic with an excess of KOH pellets, and over a period of several hours, a clear, yellow liquid evolved which was almost pure alkylated amine. Further purification by preparative glpc yielded (S)-(-)-N,N-diethyl-1-aminobutane-1-d (71), $[\alpha]_D^{29}$ -3.46 ± 0.38°, (0.026 g/mL, ether, l=0.1), $[\alpha]_{365}^{29}$ -13.85 ± 0.38°, (0.026 g/mL, ether, l=0.1). (Equation 37).



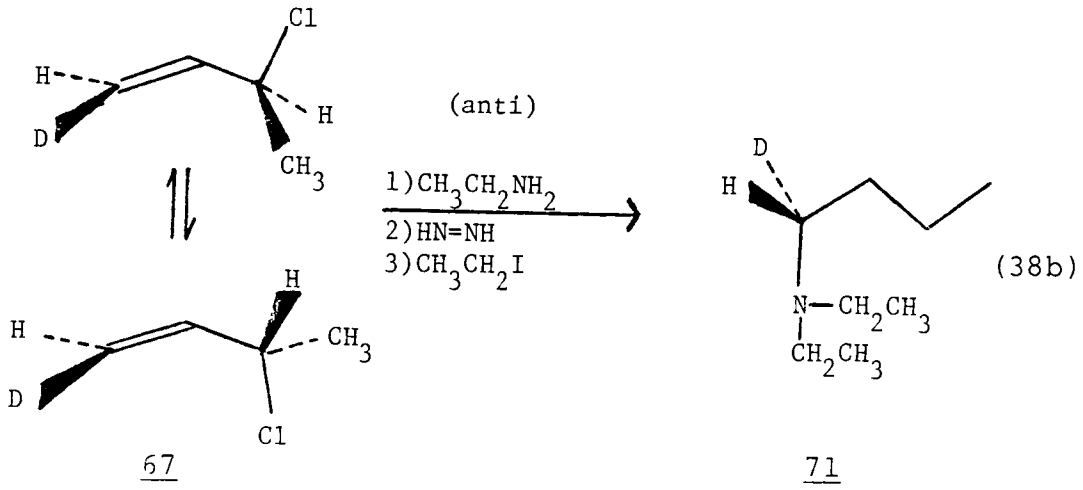
(37)

70 71

Because the reaction of Chloride 67 can occur from either of two chloride conformations, there are two possible S_N2' products-- E and Z isomers. We assume that both result from the same mechanism, i.e. either syn or anti nucleophilic attack (Equation 38). With a predominance of the E isomer, syn attack should ultimately yield a product with (S) configuration and (-) rotation, and anti attack should ultimately produce a product with (R) configuration and (+) rotation. As was reported, S_N2' attack produced a 95:5 ratio of E and Z isomers in the product, and the reduced, alkylated Amine 71 had an opposite rotation to that of Chloride 67. Therefore, the reaction had proceeded by the syn mechanism. For a quantitative



67 71



67 (38b) 71

assessment of the stereochemistry, the rotations of $[\alpha]_D^{29}$ -3.46 and $[\alpha]_{365}^{29}$ -13.85 have to be corrected for the optical purity of the starting chloride (58.1%), and for the undeuteriated (1.2%) and wrongly deuteriated (0.4%) portions of the same. Also, a correction has to be made for the E to Z ratio which, as a result of the opposite configurations and rotations, means that the optical purity of the amine was approximately 90% of the maximum possible if the reaction had produced only the E isomer. Using this formula-- (rotation ÷ 0.581 ÷ 0.9 ÷ 0.988 ÷ 0.992)-- the corrected rotations for Amine 71 are $[\alpha]_D^{29}$ -6.75 ± 0.73°, and $[\alpha]_{365}^{29}$ -27.02 ± 0.49°.

Comparison of these rotations with those of (R)- (+)- N,N-diethyl-1-aminobutane-1-d, $[\alpha]_D^{24}$ +5.66 ± 0.03°, $[\alpha]_{365}^{24}$ +19.14 ± 0.03°, 100% optically pure, which was synthesized by Magid and Fruchey,[37] gives numbers which indicate greater than 100% syn attack, or creation of optical

activity. The $[\alpha]_{\underline{D}}^{29}$ figure is 19% high and the $[\alpha]_{365}^{29}$, 41% high. The margin of error would encompass the 19% for the $[\alpha]_{\underline{D}}^{29}$ reading, as this translates into a reading error of 0.0015 on the polarimeter. There is no basis for this explanation for the $[\alpha]_{365}^{29}$ reading, as the error of 41% represents a difference in the original reading of 0.011. Other possible explanations are that Magid and Fruchey's original readings were done using a blank read on an empty cell or even a blank of the empty polarimeter chamber[61] (as opposed to the present work which utilized an ether blank).

As was mentioned earlier, Overton and Oritani[38] conducted experiments very similar to those in the previously outlined research (see Equation 35) with markedly different results. They attributed the syn stereospecificity in Magid and Fruchey's work to the more effective hydrogen bonding possible between the secondary amine and the chloride leaving group. However, the assumption that hydrogen bonding to a chloride leaving group is greater than to a benzoate leaving group, such as that used by Overton and Oritani, is suspect, and the work done by Dittmer and Marcantonio,[11] also mentioned earlier, apparently negates any hydrogen-bonding effect.

Another possible explanation for the discrepancy in stereoselection between Magid and Fruchey's and Overton and Oritani's work lies in the fact that benzoate is a better leaving group. This could result in a transition state

which more closely resembles an S_Ni' reaction and which could lead to a measure of racemization in the S_N2' product.

Overton and Oritani[38] used a primary amine and a benzoate leaving group in their work. The results of the research by Magid and this author show that the S_N2' reaction of a primary amine with an allylic chloride substrate is at least syn stereoselective if not syn stereospecific. The results of the doctoral research carried out by Charles Bass in which trimethylamine was used with optically active, deuterium labelled 3-chloro-1-butene showed that reaction to be largely syn, also. This agrees with Dittmer and Marcantonio's[11] work in ruling out hydrogen bonding as a necessary factor in the syn stereoselection of the S_N2' reaction. Therefore, the anomaly must lie in the use of different leaving groups.

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VITA

Cyril Vincent Thompson was born in Duluth, Georgia on December 2, 1959. He is the oldest of the four children of Mr. and Mrs. John P. Thompson Jr. He was graduated Rossville Comprehensive High School in June 1977. In August 1977, he entered Lee College at Cleveland, Tennessee and in August 1981 **received** a Bachelor of Science degree in Chemistry. He met Wanda Gail Hite while at Lee College and married her on August 23, 1980. In September 1981, he accepted a teaching assistantship at the University of Tennessee and began study toward a Master's degree. This degree was awarded in August 1985.

The author is presently employed as a Research Technician by the Health and Safety Research Division of the Oak Ridge National Laboratory, Oak Ridge, Tennessee.