



Chemistry of Platina(IV)cyclobutanes derived from acenaphthalene, 1,4-epoxy-1,4-dihydronaphthalene, benzonorbornene, and substituted and unsubstituted, norbornenes, and norbornadienes

by Rex A Moats

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

Montana State University

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Abstract:

Platina(IV)Cyclobutanes derived from acenaphthalene, 1,4-epoxy-1,4,-dihydronaphthalene, benzonorbornene, and substituted and unsubstituted norbornenes and norbornadienes were synthesized from the cyclopropanes derivatives of these compounds by the insertion of platinum(II) into the cyclopropane ring. Two major reaction types were studied, the ring expansion of the hydroxymethyl substituted platinacyclobutanes to platina(IV)cyclopentanes and the reaction of the platina(IV)cyclobutanes with diazocompounds.

The kinetics of platinum(II) insertion were studied for the systems derived from norbornadiene and norbornene in tetrahydrofuran. A mechanism based on the kinetic data was proposed.

One particularly water soluble complex derived from norbornadiene-1,2-dimethyldicarboxylate was studied in Salmonella systems for its ability to damage DNA.

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NORBORNENES, AND NORBORNADIENES**

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Rex A. Moats

**A thesis submitted in partial fulfillment
of the requirements for the degree**

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in

Chemistry

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Bozeman, Montana**

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APPROVAL

of a thesis submitted by

Rex Anthony Moats

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

5/17/90
Date

R. P. W. Jennings
Chairperson, Graduate Committee

Approved for the Major Department

5/17/90
Date

Edwin H. Abbott
Head, Major Department

Approved for the College of Graduate Studies

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Henry S. Parsons
Graduate Dean

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ABSTRACT

Platina(IV)cyclobutanes derived from acenaphthalene, 1,4-epoxy-1,4,-dihydronaphthalene, benzonorbornene, and substituted and unsubstituted norbornenes and norbornadienes were synthesized from the cyclopropanes derivatives of these compounds by the insertion of platinum(II) into the cyclopropane ring. Two major reaction types were studied, the ring expansion of the hydroxymethyl substituted platinacyclobutanes to platina(IV)cyclopentanes and the reaction of the platina(IV)cyclobutanes with diazocompounds.

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INTRODUCTION

General

In 1989 a headline in the *Scientist* read, "Organometallics tops a list as Hottest Chemistry Field".¹ The article, based on research activities from the past year, noted that not only were the publications in the area of organometallics itself increasing but also its ties to other areas of chemistry were becoming stronger. This last fact was also recognized by Crabtree in his book *The Organometallic Chemistry of the Transition Metals* he states "...organometallic chemistry has strong links to organic chemistry and is beginning to form strong ties with biochemistry".² All indications seem to be that study of organometallic compounds will continue to grow.

An important subdivision of organometallic chemistry in which research activity is heavy is that of organotransition metal chemistry. Collman, Hegedus, Norton and Finke in the introduction to their book *Principles and Application of Organotransition Metal Chemistry* state that within six years (1981-1989, the span between the first and second editions of their book) "the chemistry of organotransition metal complexes has continued to experience explosive growth in novel substances, new reactions, surprising mechanisms and further application to both organic synthesis and industrial processes."³ Organotransition metal chemistry is concerned with complexes

containing transition metals directly bonded through either a sigma bond or π -bond to an organic group. This definition limits the subject area by eliminating from its scope the chemistry of pure coordination compounds except as starting materials.

Within the chemistry of organotransition metals lies the chemistry of a number of different elements ranging from those of group IVa- Ib, the titanium triad to the copper triad. This thesis will be concerned generally with organoplatinum complexes, and more specifically with complexes containing platinacyclobutanes or platinum complexes that result directly from the reactions of platinacyclobutanes.

Platinum olefin complexes

Platinum olefin π -complexes may not seem to be related to the chemistry of platinacyclobutanes. However they are actually related in two ways. First the major pathway used for the synthesis of platinacyclobutanes is the insertion of platinum(II) into cyclopropanes. This pathway will be discussed in detail later in the introduction. Cyclopropanes have sp^2 character similar to olefin complexes; thus, the bonding concepts described here for platinum olefin π -complexes will be analogous to the initial interaction of platinum with cyclopropanes and have applications to the bonding in platinacyclobutane complexes. Second, and of significance to the discussion of kinetics in the introduction and in the discussion section, Ziese's dimer is used

for the insertion of platinum into cyclopropanes and is itself a platinum π -complex.

Ziese's preparation in 1830 of the platinum ethylene complex $K_2[PtCl_3C_2H_4]$ was the first synthesis of an organotransition metal complex and marked both the beginning of the study of transition metals and π -complexes and the beginning of organotransition metal chemistry. Since this initial synthesis a large number of platinum(II) olefin complexes have been synthesized and characterized.⁴ These complexes exist as dimeric halogen bridged complexes $[Pt(C_2H_4)XL_2]_2$, as salts of olefins containing cations $M^+[Pt(C_2H_4)X_3]^-$, or anions $Pt[(C_2H_4)XL_2]^+A^-$ or as neutral mononuclear species $[Pt(C_2H_4)X_2L_2]$. In these complexes X may be a halogen, alkoxide or hydride and L is a neutral ligand and C_2H_4 is an olefin.⁵ Each of the complexes described above contains formally Pt (II). Olefin complexes containing platinum(0) and platinum(IV) have also been prepared and will be discussed at other points throughout the introduction.

The models describing the bonding between the metal and the coordinated olefin are important because it is through these theories that understanding of the true structure of these complexes may be gained. This knowledge in turn helps us to predict the outcome of new reactions and better understand the chemistry of well established reactions which in turn allows us to refine our bonding models. The discussion of these models will help the reader understand the chemistry covered in this thesis. In

the models to be discussed the ligand will be ethylene and the metal platinum. However, it is important to realize that these models can be generalized to represent other metals and other ligands which are capable of backbonding. The coordinated ethylene in these complexes is described as π -bound. However it is usually understood that this bond is composed of two components, sigma and π . One author suggests that we call this a synergistic bond,⁶ suggesting that this would be more descriptive of its true nature. Formation of this bond requires the following conditions:

Metal-- must have an orbital, containing electrons, of the correct symmetry and energy to donate these electrons to the organic moiety and must have empty orbitals of the appropriate symmetry to accept electrons from the organic moiety.

Organic moiety --must have electrons available for donation and an empty orbital of appropriate symmetry and energy (the π^* orbital) to accept electrons from the metal. This arrangement is depicted in Figure 1.⁷

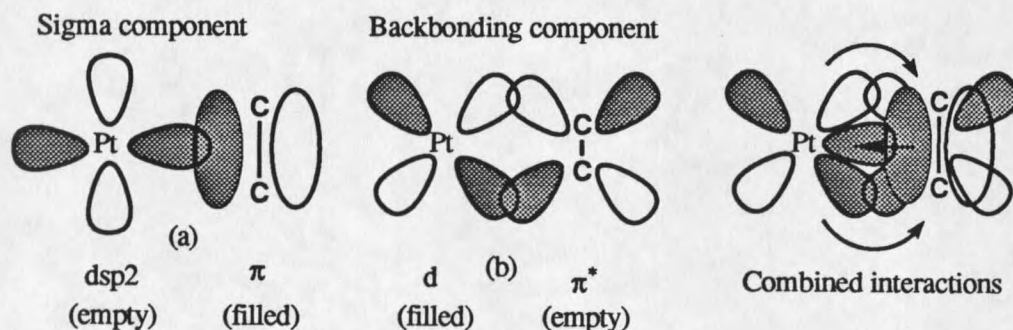


Figure 1. Backbonding and sigma bonding components of a platinum olefin π bond.

The donation of electrons by the olefin to an empty d_{sp^2} orbital on the platinum is referred to as the sigma component, Figure 1(a). The donation of electrons from a filled d orbital of the metal into the π^* orbital of the olefin is referred to as the backbonding component, Figure 1(b).⁸ Note that the olefin lies perpendicular to the ligand plane in these complexes (Figure 2).

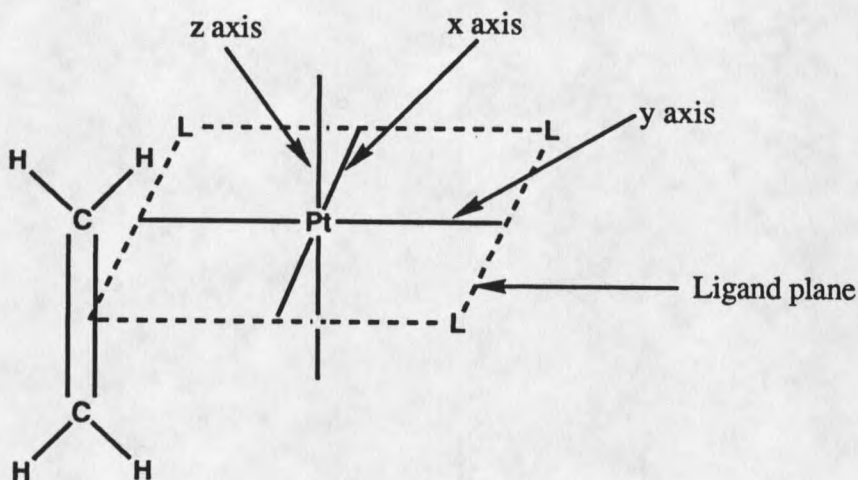


Figure 2. Perpendicular orientation of the olefin to the ligand plane.

One immediately recognizes that the two components of this π -bonding can be affected either positively or negatively, in terms of stronger to weaker bonding, by the exact nature of the metal or of the olefin. If the only component of the π -bonding is that of backbonding then the platinacyclopropane structure given in Figure 3b is the best representation of the bonding. If the only component is that of the sigma or dative component, a true σ -bond is formed (Figure 3a).⁹

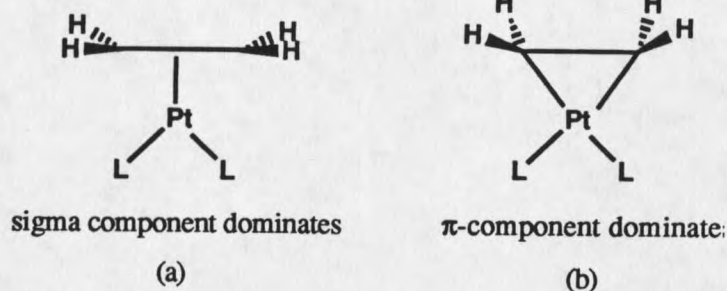


Figure 3. Bonding extremes of π -olefin complexes.

A newer bonding model, which is probably more nearly correct in specific detail, is that developed through computational methods and symmetry arguments as shown in Figure 4. In both of these representations the sigma bond in the ethylene unit is not involved; this represents a significant over-simplification. Diagrams in Figure 4 show the predicted interactions of the $2p_z$ ($2p\pi$) orbitals of the carbon atoms and the metal orbitals of suitable symmetry. The energy arguments discussed earlier of course also hold true here in that orbitals of the ethylene units and metal must lie close enough for sufficient mixing to allow bonding and antibonding interactions.¹⁰

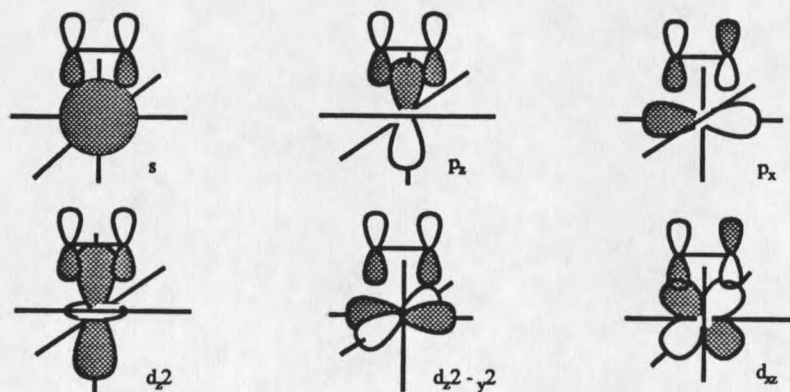


Figure 4. Molecular orbital picture of π -bonding of platinum and an olefin.

Generally the ability of a metal to donate electrons in a backbonding fashion follows its formal oxidation state. The lower the formal positive oxidation state the higher the electron density on the metal. The higher the electron density on the metal the better it can backbond. Conversely, the higher the oxidation state the lower the electron density and the poorer the ability of the metal to backbond. This is strongly influenced by ligands and is not always predictable.¹¹

Figure 5 depicts six π -type complexes of platinum (0,II,IV) covering a wide range of backbonding. Structure 1 represents a typical platinum(0) π -olefin complex¹²; whereas, structure 3 depicts a typical platinum(II) π -complex¹³. Structure 5 is the only known example of a platinum(IV) π -complex¹⁴. Structure 3¹⁵ is an example of a typical platinum(II) complex which should be contrasted and compared to structure 4¹⁶ and structure 6¹⁷. Both structures 2 and 6 are platinacyclopropanes as evidenced by the large upfield shift in both their ^1H and ^{13}C olefinic signals as well as the large platinum carbon coupling constant reported for compound 6. Structure 4 is a platinum (II); whereas, structure 6 is platinum (IV). Structure 6 is the only known platina(IV)cyclopropane. A comparison of structure 4 and structure 6 reveals that the only difference is that structure 4 has triphenylphosphine for a ligand where structure 6 has acetonitrile. This simple change in ligand greatly affected the bonding. Structure 2 is a platina(II)cyclopropane reported by

Stang. It is included here to demonstrate another example of the chemical shift range of platinacyclopropanes, Table 1.¹⁴

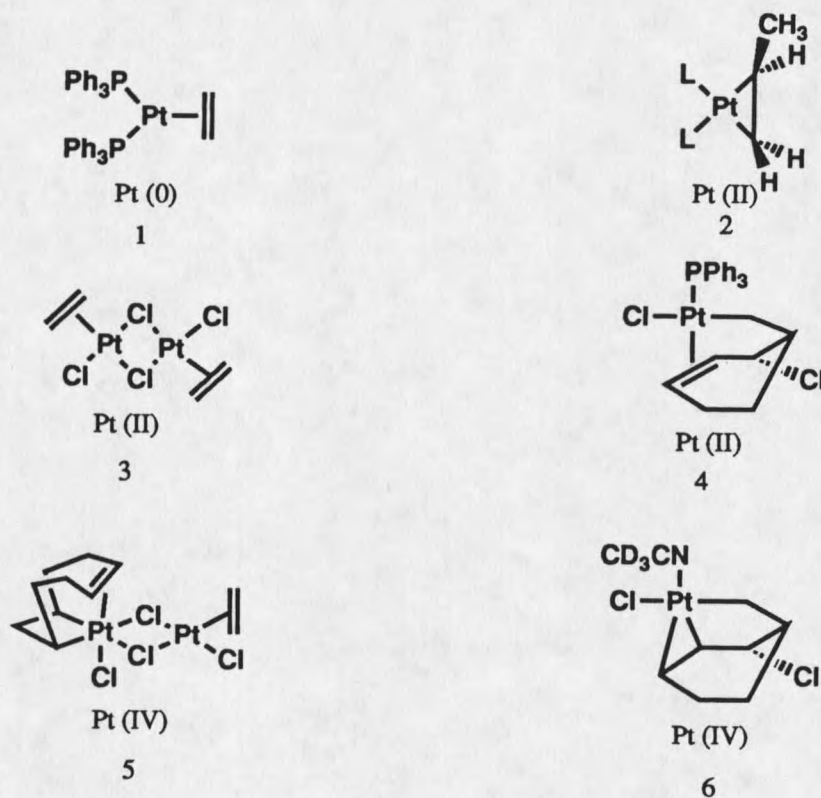


Figure 5. Examples of π -olefin complexes covering the extremes of π -bonding.

Table 1. NMR data for the olefinic region of compounds 2,3,4,6.

Cmd #	^{13}C ppm	^1H	Coupling Pt-C Range	Ref
2	64.6,42.3	3.0,2.1	Not reported	14
3	69	4.7	105-115	13
4	105,110	5.8,6.4	95-105	15
6	80,79	4.0,4.4	230-250	17

In summary, platinum π -complexes can exist with Pt (0, II, or IV). Platinum(0) will by definition never exist as a platinacyclopropane. Platinum(II) exhibits a range of platinum olefin bonding and many examples exist in the literature. The study of platinum(IV) olefin complexes represents a unique situation at this point. As indicated in Figure 5, at least two examples of platina(II)cyclopropanes exist but only one example of a platinum(IV) π -olefin complex exists. Considering the argument that platinum(IV) should have less electron density with which to backbond to the olefin than platinum (II), it is not surprising that few of these complexes exist. Considering the magnitude of the backbonding present in the platina(IV)cyclopropanes, it is surprising that they exist at all. This author suspects that the widely used model for π -bonding breaks down in these cases and that a more detailed orbital analysis such as that in Figure 4 is needed to explain the bonding in platina(IV)cyclopropane complexes.

Platinacyclobutanes: mechanistic, synthetic, and
chemotherapeutic perspectives

Platinacyclobutanes are the unifying theme of this thesis. Metallacyclobutane complexes are of mechanistic interest in that they have been proposed as intermediates in at least three major types of reactions: π -allyl formation, olefin metathesis, and olefin polymerization. Recently, the work of Nielsen, Ekeland, Waddington, and Jennings ^{18,19,20,21,22,23} has shown that these

complexes can be prepared in high yields and are thermally stable at room temperature. Furthermore they can be converted in high yields to other compounds, thus establishing these complexes as synthetic intermediates in their own right.

Organometallic platinum(IV) complexes have not been considered in the past to be interesting from a chemotherapeutic viewpoint because no organometallic platinum(IV) complex has shown activity in any bioassay. However platinum(II) complexes, the oldest of which is cis platinum, have activity in many cancer cell screens and are in fact commonly used chemotherapeutic agents. Later in this thesis the use of these complexes from a chemotherapeutic aspect will be explored. Each of these three areas will be developed in more detail in the following sections.

Mechanistic analogies

In the formation of π -allylic complexes from cyclopropanes, metallacyclobutanes are proposed intermediates. The metal inserts into the cyclopropane to form a metallacyclobutane (Figure 6). Next the metal abstracts a proton from the β -position and a metal hydride π -allyl is formed.²⁴

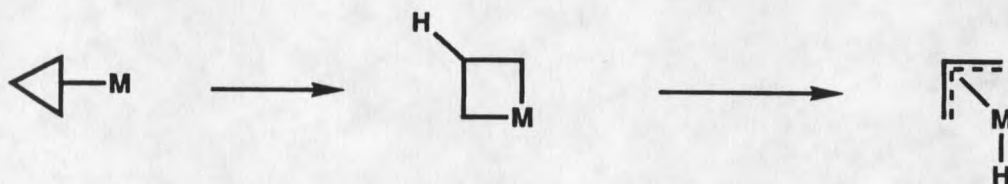


Figure 6. Pathway of π -allyl formation from a metallacyclobutane.

In classical olefin metathesis reactions, metallacyclobutanes are the proposed intermediates. The general form of the olefin metathesis reaction is as shown in Figure 7. One half of each olefin, an alkylidene unit, can become attached to either alkylidene unit of the other olefin. (It should be noted that olefin metathesis involving olefins with more than one substituent is rare but not unknown.) From Figure 7 it can be seen that an initial pair of olefins containing four different alkylidene units can produce 20 combinations of different units when isomerization of the olefin is taken into account. Of course most practical olefin metathesis reactions avoid forming such horrendous mixtures of olefins.²⁵

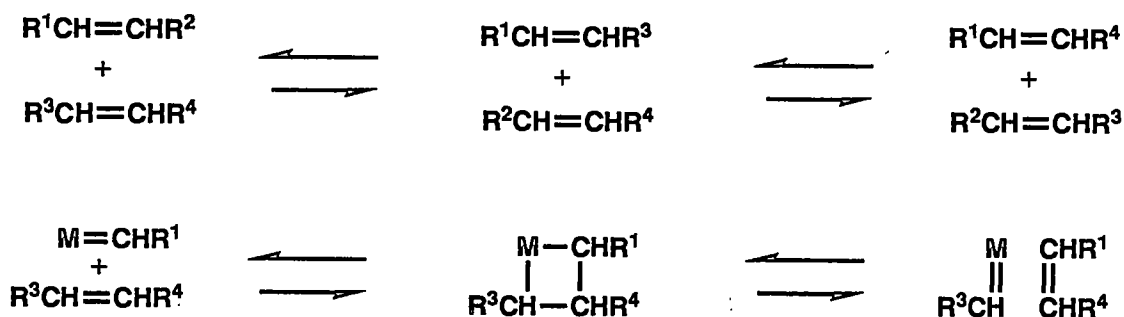


Figure 7. One mechanism of olefin metathesis.

Naturally, one wonders exactly what is the mechanism for this reaction. The active catalysts for metathesis in homogeneous systems are carbene complexes which also contain π -donor ligands and usually involve molybdenum, tungsten, or ruthenium. The Chauvin mechanism of olefin metathesis is given in Figure 7. Here it is seen that a metallacyclobutane is an important intermediate. The reaction

begins with the formation of a metallacyclobutane. Fragmentation of the first metallacyclobutane yields a new olefin and a new carbene complex which can go on to react with a different olefin.²⁶

In metal-catalyzed olefin polymerization, the carbon-carbon bond-forming chain propagation step involves, according to the mechanism of Green, the steps depicted in Figure 8.²⁷

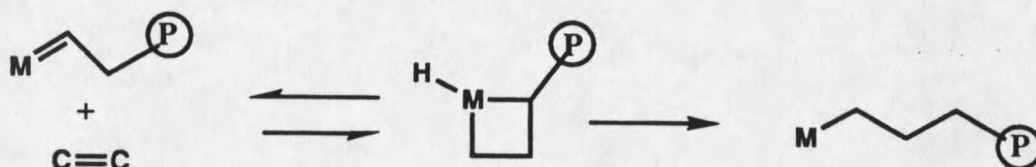


Figure 8 . Mechanism of olefin polymerization.

In Green's mechanism, a metal carbene species interacts with the next olefin to be added to the polymer to form a metallacyclobutane hydride species. This species reductively eliminates the hydride and the substituted carbon bond to form a species containing the metal on the end which can subsequently remove a hydride to form a new carbene species which begins the cycle anew. It should be noted that there exists another mechanism as proposed by Cossee which may describe the chain mechanisms more correctly in a number of cases. However since it does not contain a metallacyclobutane²⁸ it will not be discussed here.

The chemistry of platinacyclobutanes is of relevance to any reactions in which metallacyclobutanes are proposed

intermediates such as three reaction types just discussed. The fact that platinacyclobutanes exist supports these mechanisms in which the intermediates themselves have never been observed directly. By studying the chemistry of platinacyclobutanes it is hoped to gain information about these proposed intermediates. This information can help in the management of the outcome of subsequent reactions. Conversely, as new information is gained about these mechanisms, the information can be used to help guide the development of new synthetic reactions involving the same metals or other metals similar to those used in these more established reactions.

Synthetic potential

Platinacyclobutanes can be viewed as analogs of common intermediates whose reactivity should insure that new reactions can be developed which produce new products. If we consider the reaction profile for the three reaction types mentioned in the previous section, the proposed metallacyclobutane intermediates can be looked upon as either occurring at the top of the energy surface where they are representative of the transition state or existing in an energy well and are thus true intermediates. Both possibilities are depicted in Figure 9. In either case, the platinacyclobutanes described in this thesis can be viewed as trapped intermediates. Using these trapped species as reactants, one would expect that new reaction conditions could be developed in which these complexes would undergo organic

transformations to new and useful molecules as depicted diagrammatically in the bottom portion of Figure 9. This contention is supported by the fact that many platinacyclobutane species have been prepared in high yield and some have been shown to undergo interesting organic transformations under certain reaction conditions. To date these conditions include ring expansion procedures, stereospecific carbon-carbon bond forming reactions as well as others.^{18,19,20,21,22,23} Examples are discussed in section titled Chemistry of Platinacyclobutanes.

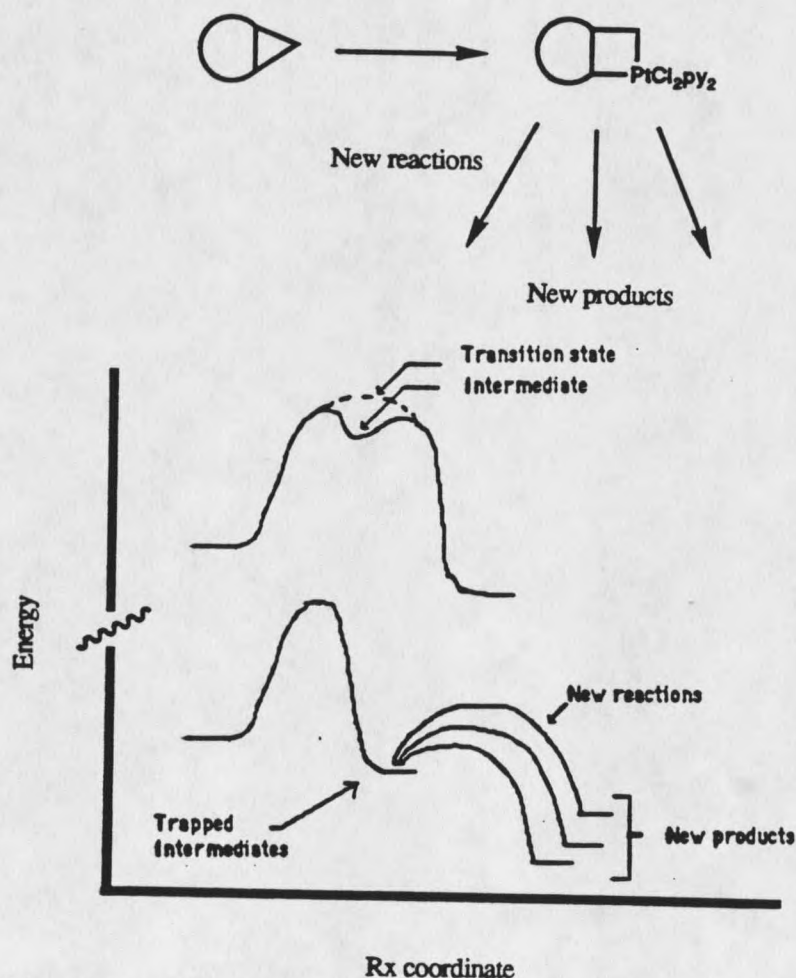
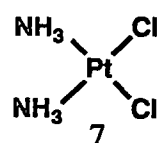


Figure 9. Idealized diagrams of reactions of platinacyclobutanes.

Chemotherapeutic value

At the time this author began his work there were no uses of organometallic platinacyclobutanes for chemotherapeutic purposes mentioned in the literature. Although some complexes had been screened for activity none were found to be reasonably active.²⁹

The platinum(II) complex cis platinum, also called Cisplatin or cis-dichloro-cis-diaminoplatinum (II), Figure 10, alluded to in the introduction to this section, is an entirely different case. Cisplatin first went into clinical trials in 1971 and approval was from the Food and Drug Administration in 1979 for use in the United States.³⁰ Since then it has become a common chemotherapeutic agent against a variety of cancers including those of head, neck, ovary, testes, and bladder. Cis platinum is often used in combination with other drugs and has been shown to be synergistic with methotrexate, 5-fluorouracil, etoposide, binblastine, bleomycin, and adriamycin. These compounds represent a wide range of mechanisms of action. Adriamycin and bleomycin are microbial antibiotics which intercalate into the DNA. Bleomycin is known to promote single strand cleavage. 5-Fluorouracil is a pyrimidine analogue which inhibits nucleotide synthesis. Methotrexate is a folic acid analogue which competitively inhibits mammalian dihydrofolate reductase an enzyme at the start of the biosynthetic pathway leading to TMP.^{31,32,33,34,35,36}



Cis platinum

Figure 10. The structure of cis platinum.

The mechanism of action of cis platinum has been a widely studied subject and much data is available, so much in fact, that the detailed mechanism will not be addressed here. However later in this thesis the mechanism of platinum(II) chemotherapeutic activity as compared to platinum(IV) will be discussed.

Synthesis of platina(IV)cyclobutanes.

Originally, the reaction of cyclopropane with hexachloroplatinic(IV) acid in acetic anhydride, Figure 11, produced the first documented platinacyclobutane complex which upon reaction with 2 equivalents of pyridine, yielded $\text{PtCl}_2(\text{C}_3\text{H}_6)\text{py}_2$.³⁷ This method cannot be used to prepare substituted platinacyclobutanes (Figure 11).³⁸

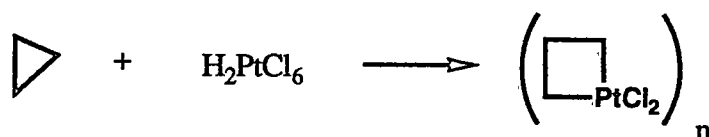


Figure 11. Insertion of platinum into cyclopropanes using H_2PtCl_6 .

The most practical method for the preparation of platina(IV)cyclobutanes is that first detailed by McQuillin in which Ziese's dimer is the platinum source (Figure 12).³⁸

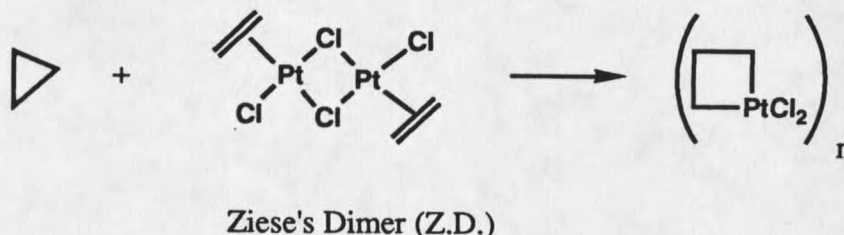


Figure 12. Insertion of platinum into cyclopropanes using Z.D.

The solvent of choice for these reactions is usually diethyl ether. However THF, methylene chloride, and methanol have also been used; interestingly, Z.D. is more soluble in these solvents than in diethyl ether. THF was used by Puddephatt in his kinetic studies because both reactants and products were soluble in low but sufficient concentrations for the studies, unlike diethyl ether or chloroform.

When the complexes are prepared in diethyl ether a precipitate is initially formed which has been termed the initially precipitated complex (I.P.C.), Figure 13. These I.P.C.'s are only sparingly soluble in any solvent with which they do not react. Thus they have been difficult to characterize. It is now believed based on mass spectrometry and x-ray powder diffraction data that they are tetrameric complexes as shown in Figure 13.⁴¹ It should be noted that symmetrical organic groups can adopt either of two orientations to the cube as depicted in Figure 13.

This fact takes on more significance when one begins to take into account steric factors in I.P.C. formation in complexes containing larger organic moieties.

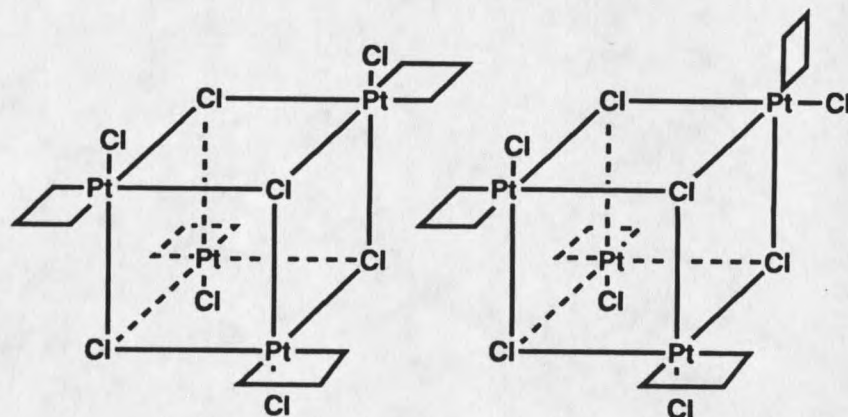


Figure 13. Possible structures of the tetrameric I.P.C.

As mentioned previously, upon treatment with pyridine and many other coordinating ligands, the monomeric complex is formed. These monomeric complexes are easily isolated and are soluble in many common solvents including chloroform, acetonitrile, and pyridine as well as others. X-ray crystal structure data has shown that the monomeric structures are an octahedral complex with the organic moiety trans to the pyridine ligands in this case and the chlorines are trans to one another as shown in Figure 14.^{42,43,44}

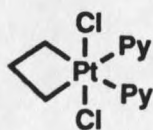


Figure 14. The octahedral arrangement of the monomeric platinum(IV)cyclobutanes.

Tables 2, 3, and 4 show examples of previously prepared and well characterized platinacyclo(IV)butanes representing complexes of unsubstituted, mono-, di- and tri-substituted simple cyclopropanes, respectively. Platinacyclobutanes have also been made from more complex species such as (X.1.0.) systems and unsubstituted and substituted norbornyl moieties. However, these complexes will not be discussed here but will be discussed fully under the section titled Chemistry of Platinacyclobutanes.

Table 2. Platinacyclobutanes of the form: $[\text{PtX}_2(\text{CH}_2\text{CH}_2\text{CH}_2)\text{L}_2]$

X	L	m.p.	Ref.
Cl	C ₅ H ₅ N	140-145	42
Cl	1/2(bipy)	340-355d	42
		230-240d	41
Cl	1/2(1,4 dioxane)	110-125	41
Cl	NH ₃	130d	45
Cl	1/2(phen)	224d	46
Br	C ₅ H ₅ N	140d	41
Br	NH ₃	105-110	45

d Decompositon point

Table 3. Platinacyclobutanes of the form: $\text{PtCl}_2(\text{C}_3\text{H}_5\text{R})\text{L}_2$

R^a	L	m.p.($^\circ\text{C}$)	Ref
2-Me	$\text{C}_2\text{H}_5\text{N}$	112	47,48
2-Me	4-Me $\text{C}_5\text{H}_4\text{N}$	147d	48
2-Me	3-Me $\text{C}_5\text{H}_4\text{N}$	120	48
2-Me	1/2(phen)	302d	48
2-ET	$\text{C}_5\text{H}_5\text{N}$	--	49
2-iPr	$\text{C}_5\text{H}_5\text{N}$	--	49
2-Bu	$\text{C}_5\text{H}_5\text{N}$	132d	47
2-hexyl	$\text{C}_5\text{H}_5\text{N}$	125	40,51,52
2-PhCh ₂	$\text{C}_5\text{H}_5\text{N}$	111	40,51,52
2-Ph	$\text{C}_5\text{H}_5\text{N}$	130d	40,51,52
1-Ph	$\text{C}_5\text{H}_5\text{N}$	130	50
2-Ph	1/2(tmed)	172	50
1-Ph	1/2(tmed)	129	50
2-Ph	1/2(bipy)	235d	50
1-Ph	1/2(bipy)	229d	50
1-(4-Me C_2H_4)	$\text{C}_5\text{H}_5\text{N}$	107	40,51,52
2-(2-NO ₂ C_6H_4)	$\text{C}_5\text{H}_5\text{N}$	220d	40,51,52
2-(2-Me C_6H_4)	$\text{C}_5\text{H}_5\text{N}$	128d	50
2-(4-Me C_6H_4)	$\text{C}_5\text{H}_5\text{N}$	135d	50

^a Prefix 1 or 2 indicates R on carbon alpha or beta to platinum respectively. Where mixtures of isomers are present only the dominant isomer is listed.

^d decomposition point.

Table 4. Platinacyclobutanes of the form: $\text{PtCl}_2(\text{C}_3\text{H}_4\text{RR}')\text{L}_2$

R, R'	L	m.p.(oC)	ref
2, 2-Me ₂	C ₅ H ₅ N	--	49,47,48
2, 2-Me ₂	1/2(bipy)	125d	48
2, 2-Me ₂	1/2(phen)	175d	48
trans-1,2-Me ₂	C ₅ H ₅ N	133d	49,47,48
trans-1,2-Me ₂	1/2(phen)	252d	48
trans 1-Me,2-Ph ^a	C ₅ H ₅ N	122d	47,48
trans-1,2-Ph ₂ ^b	C ₅ H ₅ N	116	40,51,52
trans-1,2-Ph ₂ ^b	4- ^t BuC ₅ H ₅ N	--	47
trans-1,3-(4-MeC ₆ H ₄) ₂ ^c	C ₅ H ₅ N	--	47
trans-1,3-(4-MeC ₆ H ₄) ₂ ^c	4- ^t BuC ₅ H ₅ N	--	47

Analysis of Walsh orbital interactions of cyclopropanes with the frontier molecular orbitals on platinum.

Walsh orbitals are commonly used for the orbitals of cyclopropane. The Walsh orbitals X₁, X₂, and X₃ depicted by Hoffmann are shown in Figure 15.⁴⁴ X₁ and X₂ are degenerate. (The low-lying sigma orbital was taken from the original Walsh paper.⁴⁵) According to Hoffmann, as the C₂-C₃ bond distance increases the orbital energies change as shown. Eventually X₂ and X₃ cross in energy.

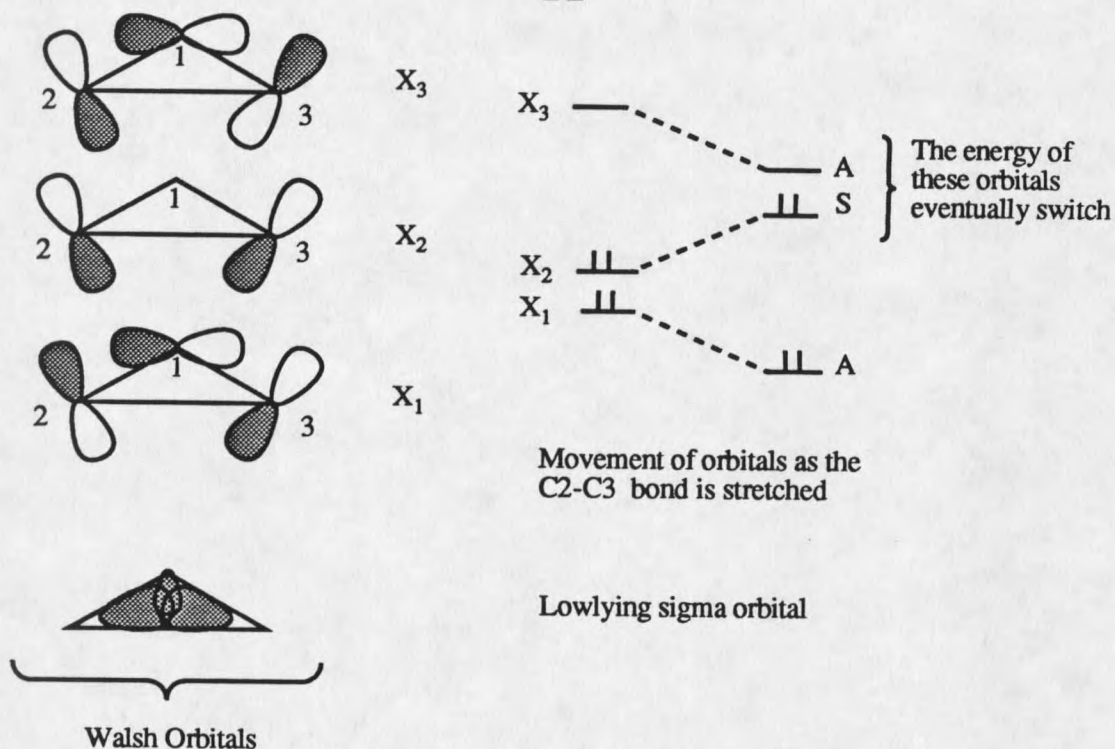
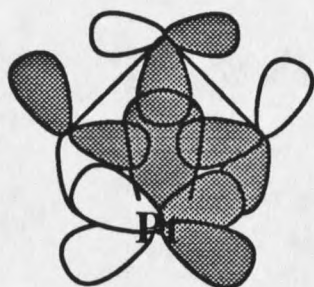


Figure 15. Walsh orbitals and the effect of stretching the C2-C3 bond.

As noted by McQuillin and Powell, these Walsh orbitals may not be applicable to platinum cyclopropane interactions in a significant way if the cyclopropane orbitals continually rehybridize as the insertion proceeds. On the other hand, if one considers the insertion event to be analogous to the bonding in metal π -olefin complexes as shown in Figure 1, one could rationalize that the sigma component is formed mainly by the platinum interaction with the low-lying sigma orbital.⁵⁵ The π -backbonding component occurs between X_3 and the platinum d orbital as depicted in Figure 16. Note that this picture implies an edge on bonding mode which Puddephatt has deemed the "edge complex".

Even though this McQuillen-Powell suggestion lacks quantitative calculations for support, several facts do support this idea. First, it has similarities to the dihydrogen insertion mechanism which is suggested to go through an early transition state thus indicating that the MO's of the cyclopropane as pictured may be the important ones. Second, the observed exchange of cyclopropanes in platinacyclobutanes parallels the exchange of olefins in similar complexes. However in the crystal structures of platinacyclobutanes, the platinum-C2 distance is too large to suggest bonding.



Sigma bonding component composed of low-lying sigma cyclopropane orbital and platinum dsp^2 -orbital.

π -component composed of a platinum d-orbital and X_3 cyclopropane orbital as shown in Figure 15.

Figure 16. McQuillin and Powell's suggestion for the orbital overlap in platinum cyclopropane interactions.

To date the exact mechanism of platinacyclobutane formation has not been delineated. However, the kinetics studies of the next section are pertinent to this discussion.

Kinetics studies of the insertion of platinum into
arylcyclopropanes

Kinetics studies have shown the insertion of platinum(II) into cyclopropane to be first order in both platinum and cyclopropane; thus, the reaction is second order overall. Figures 17 and 18 show two possible pathways proposed by Puddephatt with the edge complexes shown in brackets. The essential difference between these two mechanisms is that in the mechanism in Figure 17, the complexation of the cyclopropane is the rate determining step whereas in the mechanism in Figure 18, the insertion of platinum into the cyclopropane ring is the rate determining step.⁵⁶

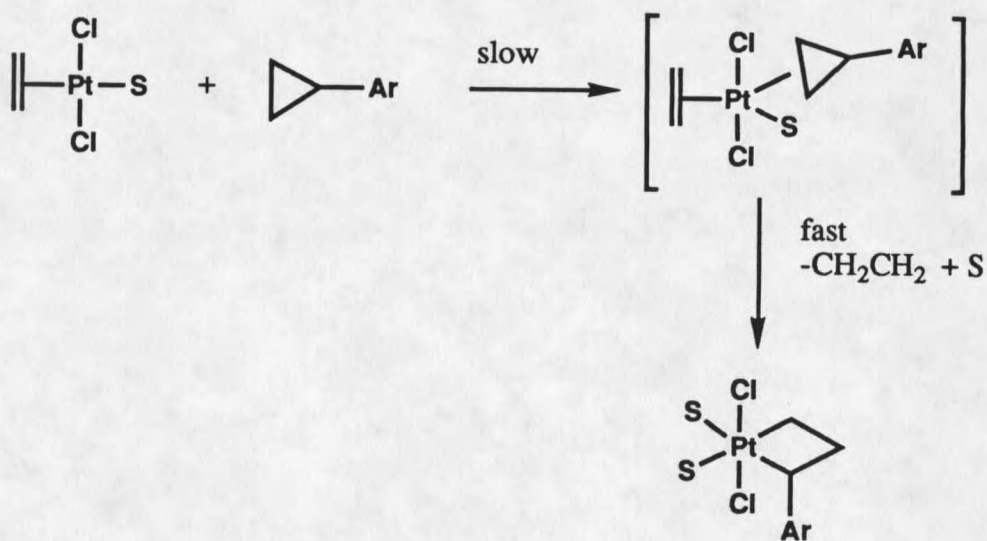


Figure 17. One possible mechanism of platinum insertion into arylcyclopropanes.

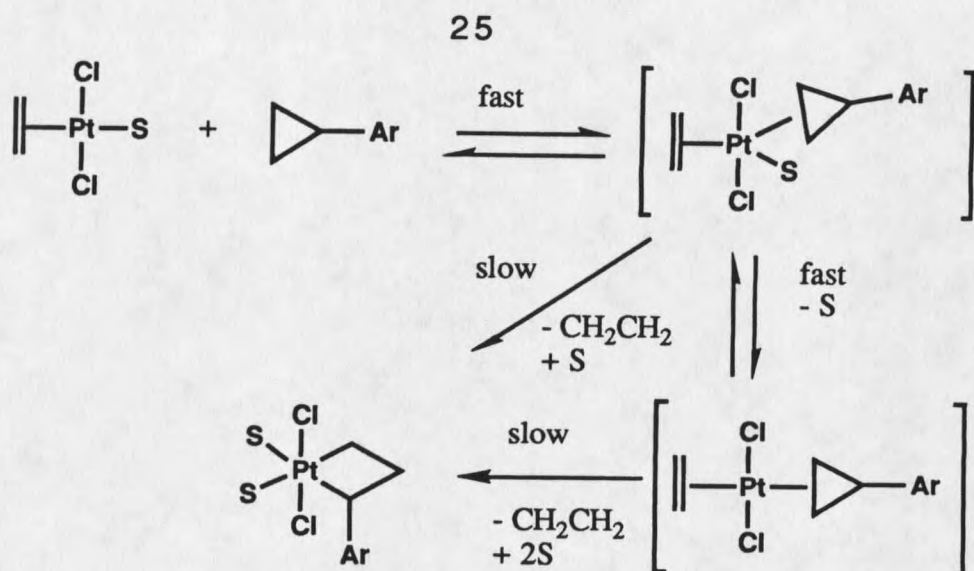


Figure 18. A proposed mechanism of insertion of platinum into arylcyclopropanes.

Studies have shown that varying the electron donating or electron withdrawing nature of the group attached to the cyclopropane markedly affects the rate of insertion. The quantitative data was taken on the exchange of cyclopropanes with platinacyclobutane itself. The proposed mechanism of this reaction is shown in Figure 19.⁵⁶ Electron withdrawing substituents slow the reaction and, in fact with even more strongly withdrawing groups, eventually no product formation is observed.³⁸ The fact that insertion products are not observed could be due to two factors. Either the platinum insertion product is not stable or insertion essentially does not occur at all in the length of time the reactions are run because of retardation of the rate. Note that the length of time that these reactions can be run is limited by the stability of Zeise's Dimer (Z.D.) in the solvent used (author's note).

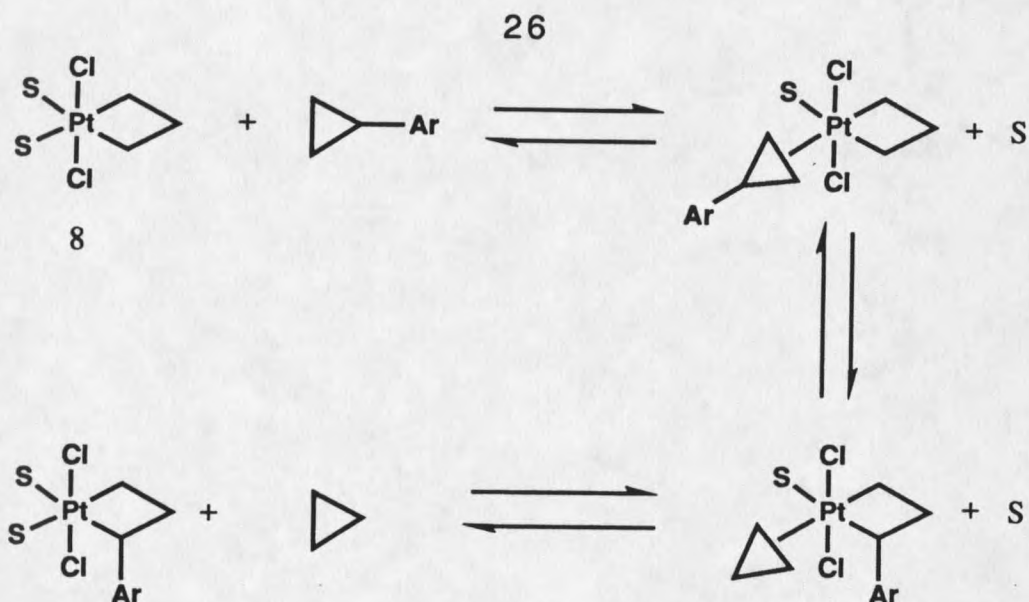


Figure 19. Exchange of cyclopropanes used to measure kinetics.

Platinum(II) is viewed as an electrophilic reagent attacking the electron density of the cyclopropane ring. Electron donating groups transfer ring electron density into the cyclopropane and, as expected, enhance the rate of insertion of the metal into the cyclopropane. The insertion reaction is stereospecific. That the configuration of groups is maintained when the platinum inserts into cyclopropane is judged by the production of the starting material upon reductive elimination.³⁸ This fact has been used to rule out nucleophilic-type reactions which would lead to an ionic intermediate with free rotation about a C-C bond with concomitant loss of stereochemistry such as that shown in Figure 20. The rates of insertion have been shown to increase in more polar solvents suggesting some polarity in the intermediates. However, the rate enhancement may be the result of simple ligand chemistry and solvation effects.⁵⁶

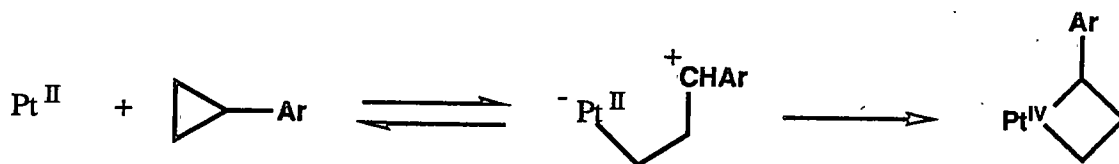


Figure 20. Mechanism of platinum insertion into cyclopropanes involving a zwitterionic intermediate.

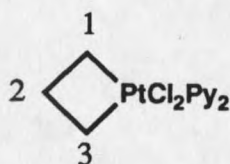
Structure determination of platina(IV)cyclobutanes and related complexes

As is usually the case for organic compounds, a variety of techniques are used for structural determination including ^1H and ^{13}C NMR spectroscopy, infrared spectroscopy, x-ray crystallography as well as others.

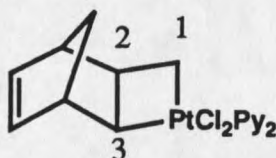
X-ray crystallographic data is available for a wide variety of complexes including some which are directly analogous to compounds discussed later in this thesis. Since the first x-ray crystal structure of the platina(IV)cyclobutane $\text{Pt}(\text{C}_3\text{H}_6)\text{Cl}_2\text{Py}_2$ was reported in 1971, a number of others have been reported.^{57,58,61} Data from a sampling of these structures is reported in Table 5. The bond distances (Table 8) C1-C2 and C2-C3 in these complexes are longer than the analogous bonds in the parent cyclopropanes. This difference, however, is not surprising since the analogous difference of 1.542 angstroms in the cyclopropane compared to 1.56 angstroms in the cyclobutane is of about the same magnitude. The distances between C1 and C3 in all of these complexes are too large to suggest any bonding interaction. These platinacycles all show some puckering in the ring ranging from 0-30 degrees in the solid

state.⁶⁰ The pucker may be due to crystal packing forces and is assumed to differ in solution.

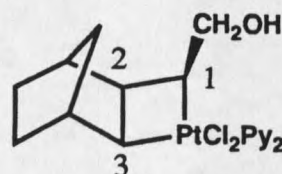
Table 5. X-ray crystallographic data for complexes 9, 10, and 11.



9



10



11

Angles (°)	Complex 9	Complex 10	Complex 11
Pt C1 C2	99(4)	94.7(10)	96.7(16)
C1 C2 C3	101(4)	97.3(11)	97.2(16)
C2 C3 Pt	84(3)	95.7(10)	94.6(10)
C3 Pt C1	74(2)	70.0(6)	69.8(6)
Cl1 Pt Cl2		176.6(1)	177.4(3)
N1 Pt N2	89(1)	87.3(4)	90.0(8)
C3 Pt N1		169.1(5)	167.7(5)
C1 Pt N2		171.3(5)	170.6(8)
Distances (Å)			
Pt C1	2.04(5)	2.057(14)	2.0011(22)
Pt C3	2.19(5)	2.093(14)	2.097(4)
Pt Cl1	2.29(1)	2.323(3)	2.307(7)
Pt Cl2	2.29(2)	2.327(3)	2.325(8)
Pt N1	2.25(3)	2.237(10)	2.213(16)
Pt N2	2.11(3)	2.237(10)	2.202(18)
Reference	42	58	21

Infrared spectroscopy also may be used to indicate platinacyclobutane formation because, as can be seen in Table 6, many new absorbances appear due to the breaking of the

symmetry of the cyclopropane ring upon opening.⁶¹ The infrared data for the I.P.C. is also given for comparative purposes. It is interesting that the infrared spectrum for the I.P.C. has a number of additional peaks compared to the monomer.

Table 6. Infrared data for selected molecules.

Bands due to the			
C ₃ H ₆ unit	[Pt(C ₃ H ₆)Cl ₂] ₄	Pt(C ₂ H ₆)Cl ₂ L ₂	C ₃ H ₆
C-H	3025	2992	3103
	2954	2938	
	2948	2917	
CH ₂ deformation	1414	1437	1442
CH ₂ wag	1255	1238	
	1237		
CH ₂ twist	1165	1217	
ring deformation	1149	1134	
	1125	1087	
CH ₂ rock	1087	1038	1029
	1022		
ring deformation	981	980	
CH ₂ rock	948	976	869
	890	892	
	663		
ring deformation	563		
(mainly Pt-c)			

The NMR spectroscopy of the monomeric complexes is probably the most practical tool for structure determination of platinacyclobutanes. Proton NMR spectroscopy to date has been less useful than carbon NMR spectroscopy because the chemical

shifts of the carbon resonances follow a more predictable pattern than do those of protons. The Pt- ^{13}C coupling gives evidence that platinum is present in the molecule and the magnitude of this coupling helps in determining the position of the metal. The $^2\text{J}_{\text{Pt-H}}$ coupling constants range from 70 to 110 Hz, $^3\text{J}_{\text{Pt-H}}$ range from 0 to 50 Hz and $^4\text{J}_{\text{Pt-H}}$ range from 0-10 Hz. However, the chemical shifts of protons in these molecules often overlap and geminal protons, especially those attached ^2J to the platinum, can have rather different and unpredictable chemical shifts.

In ^{13}C NMR spectroscopy the patterns are much more predictable with the ^1J carbons always being upfield of the analogous carbons in the cyclobutanes or parent cyclopropanes ²⁰. Furthermore, the platinum satellites are often readily distinguishable from other peaks with $^1\text{J}_{\text{Pt-C}}$ ranging from 300-470 Hz and $^2\text{J}_{\text{Pt-C}}$ ranging from 80 to 130Hz. Platinum to carbon coupling constants for substituent carbons are typically on the order of 0-60hz. Four-membered and five-membered ring systems, in the case of the norbornyl derived platinacycles, are readily distinguished by the chemical shift as well as the size of $^1\text{J}_{\text{Pt-C}}$ coupling constants as shown in Table 7.

Table 7. Chemical shift range and $^1\text{J}_{\text{Pt-C1}}$ coupling constants*.

Ring size	Pt-C1 coupling(Hz)	Chem. shift range	Reference
4	300-425	10-(-20) ppm	18,19,20
5	530-600	15-45 ppm	18,19,20

* The platinacycles must be of the form $(\text{C}_n\text{H}_n\text{X}_n)\text{PtCl}_2\text{Py}_2$

As noted above, platinum coupling is seen in these complexes due to the platinum-195 isotope. With a spin 1/2 it is correspondingly NMR active and couples to any other NMR active nuclei including ^1H , ^{13}C , ^{15}N and ^{31}P . Platinum coupled peaks appear as triplets because the center resonance, comprising 66.3% of the area, is attached to the nonNMR active isotope and the remaining satellites appear equidistant upfield and downfield from the center resonance, each comprising one half of 33.7% or 16.9% of the total peak.³⁸ The separation of these satellites represents the size of the platinum coupling to the NMR active platinum 195 isotope. Because of the reasonable sensitivity of the platinum nucleus and its fast relaxation time it can be observed with signal-noise ratios similar to those of carbon in comparable time periods.

The chemical shifts of the platinum-195 resonances cover a range of approximately 13000 ppm.⁶² Resonances for platinum(II) with its higher electron density occur upfield of those of the more deshielded platinum(IV)'s. Thus, platinum NMR spectroscopy can give one an indication of the oxidation state of the platinum. Because of its sensitivity to electronic differences in the molecule it can also indicate that two different but very similar platinum complexes are present when the ^1H or ^{13}C NMR spectroscopy might not reveal this.

A unique property of platinacyclobutanes: the Puddephatt rearrangement

Contrary to the general opinion at the time that platinum inserted into the least substituted bond of the cyclopropane, it was shown by Puddephatt that in fact it actually inserted at the most substituted bond and rearranged, at least in the case of phenylcyclopropane. This rearrangement hence has been called the Puddephatt rearrangement. In the reaction of Zeise's dimer with phenylcyclopropane, Puddephatt characterized a mixture of two isomeric platinacyclobutanes ^{69,63} Figure 21.

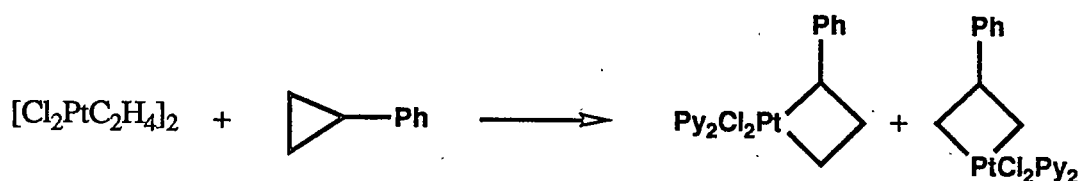


Figure 21. Mixture of alpha and beta phenyl isomers.

The alpha phenyl isomer was shown to predominate in shorter term reaction; whereas, as time passed the beta-phenyl isomer would grow to predominate. Deuterium substitution studies showed that the result of the rearrangement was a skeletal one and not a phenyl migration from one carbon to the other.³⁸

Furthermore, crossover products were not observed when the cyclopropane was reacted with unlabeled cyclopropane indicating that the reaction was intramolecular. In another experiment, radioactive chloride ion in the form of potassium

chloride was added, but no radioactivity was incorporated. Thus exchange of the chlorines was not occurring. The reductive elimination products of the platinacycles, trans and cis bipyridyl platinum dichloride, would not react with phenylcyclopropane. This indicated that the reaction was not a series of reductive eliminations and oxidative additions which eventually led to the equilibrium mixture.³⁸

The isomerization slowed down in the presence of excess pyridine and was completely halted by bidentate ligands. Labeled pyridine was incorporated into the products indicating ligand exchange which is characteristic of transition metal chemistry of this type.³⁸

As mentioned earlier, the stereochemistry about the cyclopropane ring was maintained. Labeling experiments using cis-phenyl-deuterocyclopropane depicted in Figure 22 showed, as would be expected, that the stereochemistry of a labeled platinacyclobutane was maintained in the complex and in the parent cyclopropane after reductive elimination. For clarity of explanation and continuity of the figures all the mechanistic proposals which follow will also be depicted using the cis phenyl-deutero compound although of course it was not used originally in the proposed mechanisms.³⁸

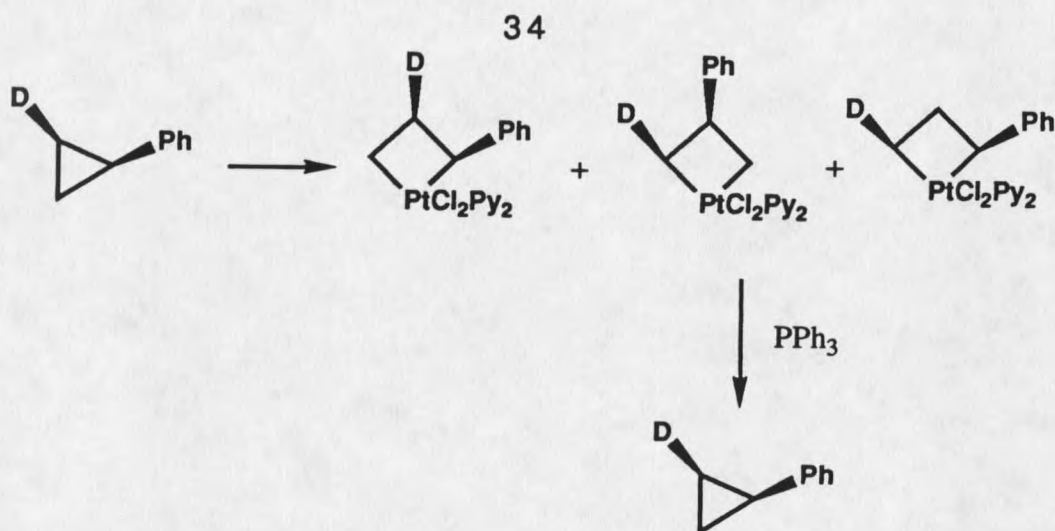


Figure 22. Deuterium labeling experiment with phenylplatinacyclobutane.

Based on what was known at the time, several mechanisms were proposed. Casey proposed the mechanism displayed in Figure 23.⁶⁵ A 2+2 cycloreversion of the platinacyclobutane similar to the mechanism of olefin metathesis was proposed. The metal carbene olefin complex in the middle of the figure has the olefin and ligands perpendicular to one another. A disrotatory 180 degree rotation about the platinum alpha carbon bond followed by ring closure would result in the observed isomerization.

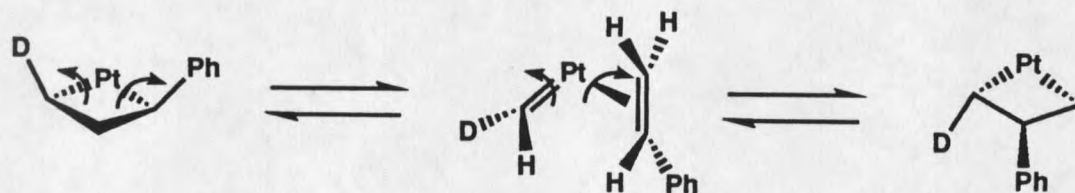


Figure 23. 2+2 Cycloreversion mechanism proposed by Casey.

Several pieces of information make this mechanism unlikely but not necessarily incorrect. Olefin metathesis often results in cis-trans isomerization because the olefin itself is isomerized. This would result in the loss of stereochemistry which is not observed. Since olefin exchange is known to occur in these systems, if this mechanism was correct one would expect to find that added olefin is incorporated into the product and that is not the case.³⁸

In another possible mechanism, the formation of an edge complex is invoked. This mechanism is similar to the reductive elimination \ oxidative addition mechanism ruled out by the fact that the reductive elimination products do not reinsert in an oxidative addition step. However, if the platinum is essentially trapped in an edge bound complex as shown Figure 24, the platinum could move around the edge and reinsert before being trapped as the observed reductive elimination product.⁶¹ This mechanism was ruled out by Hoffmann because no exchange of cyclopropane was observed during isomerization and the edge complex binding energy was approximately 10 kcal too small, in his opinion to prevent exchanges.⁶⁶



Figure 24. Proposed mechanism of Puddephatt rearrangement.

Puddephatt proposed a mechanism wherein the intermediate was one in which all the carbons of the cyclopropane ring (Figure 25) are bound to the platinum via a nonclassical delocalization of electrons.⁶⁷ The platinum can be envisioned as coming out of the one position to obtain a position above the cyclopropane ring as contrasted to being in the plane of the cyclopropyl carbons as required by the edge mechanism, Figure 22. In this position the stereochemistry at the carbons would be maintained.

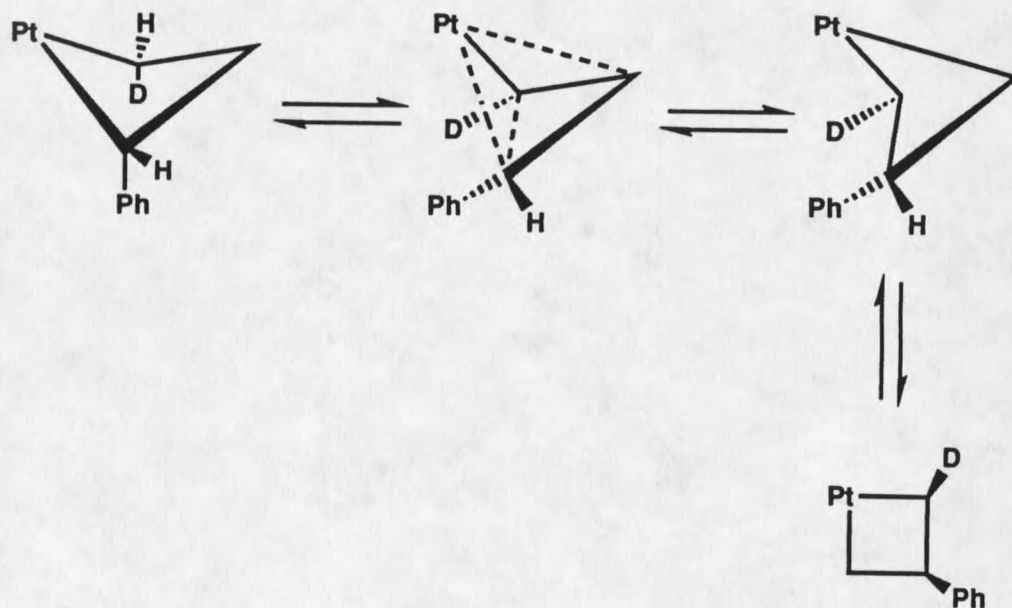


Figure 25. Concerted mechanism of Puddephatt rearrangement.

Hoffmann modeled, using extended Hückel calculations, an intermediate in which the one ligand was lost, as Puddephatt also suggested, leaving a five coordinate square pyramidal structure. This structure is isolobal with cyclobutyl cation. The calculated intermediates gave the two structures shown in Figure

26. Unfortunately, the Y-shaped intermediate was the lowest in energy. However, Hoffmann ruled it out as the species which existed longest because its existence would imply loss of stereochemistry. Rather he favored the T-shaped intermediate as the relevant intermediate stating that the platinacyclobutane could rearrange by way of the Y-shaped intermediate.⁶⁶

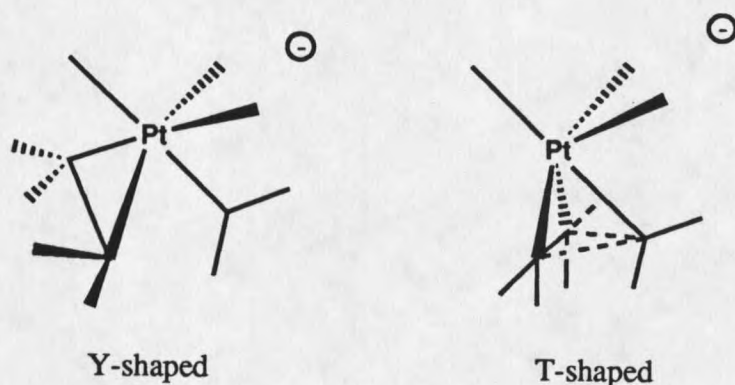


Figure 26. Intermediates in the Puddephatt rearrangement as proposed by Hoffmann.

Hoffmann's mechanism and the mechanism first proposed by Puddephatt (and later modified by Casey) differ only slightly. Puddephatt's mechanism does not clearly indicate the presence of intermediates and can be taken as being concerted. Hoffmann clearly postulates the presence of intermediates. Hoffmann's mechanism, because of its computational nature, attempts to be quantitative whereas Puddephatt's is qualitative. Hoffmann's mechanism is probably best seen as support for and clarification of the details of Puddephatt's original proposal.

Chemistry of platinacyclobutanes

The chemistry of platinacyclobutanes can be grouped according to the initiating step of the reaction, for example pyrolysis, light-induced homolytic bond cleavage (photolysis), charged ligand dissociation aided by very polar solvents, or neutral ligand dissociation. The scope of this discussion will be limited to the chemistry of monomeric complexes which is known or assumed to be initiated by neutral ligand dissociation. All reactions which involve the production of new or different platinum-carbon bonds discussed in this thesis are of this type.

Decomposition pathways

Decomposition of platinacyclobutanes involving initial ligand dissociation occurs by three major mechanisms: reductive elimination of the parent cyclopropane, rearrangement to form an olefin or a π -allyl, and rearrangement to form an ylide.

Reductive elimination of the parent cyclopropane can be precipitated thermally or by introduction of a soft ligand: triphenyl phosphine, alkenes, CO, KCN, and DMSO.^{52,68,69,70,71} As might be anticipated these ligands must successfully compete for a ligand site in order to induce reductive elimination. As alluded to previously, the elimination is believed to be concerted and to result in the retention of stereochemistry around the ring.

Decomposition leading to olefinic products usually results in the production of the least-substituted olefin. If cis and trans

olefins can be produced, cis usually predominates. The first example was reported by Cashman and Brown ⁷², Figure 27.

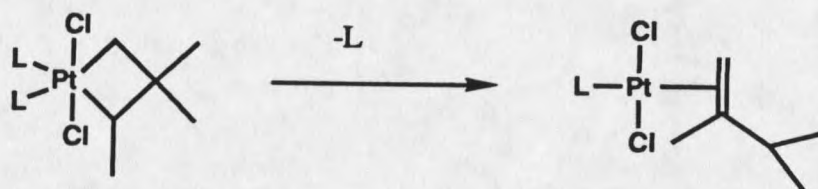


Figure 27. Decomposition of platinacyclobutanes.

In this paper, the authors proposed the following two possible mechanisms. A number of complexes other than the ones shown here have since been reported. ^{72,73,74,75,41}.

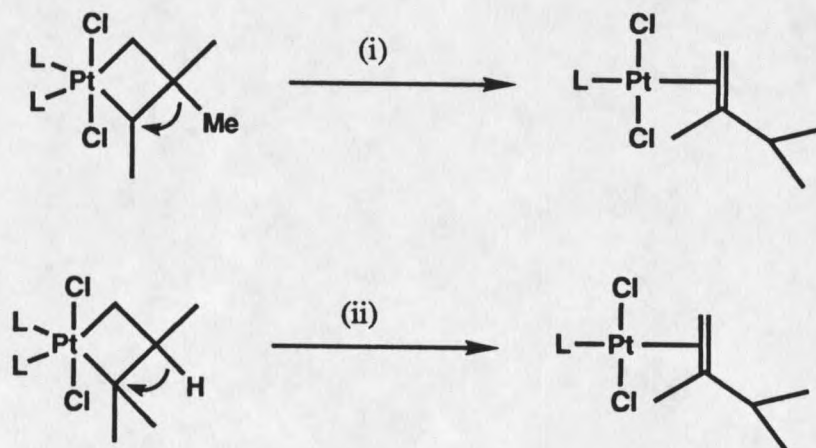


Figure 28. Two possible mechanisms of the decomposition of platinacyclobutanes to produce olefins.

A selective deuterium labeling experiment by Johnson and Cheng provided evidence that mechanism (ii), involving isomerization of the platinacyclobutane by a 1,2 hydride shift, is

correct. The H shift is believed to occur by β -elimination followed by reductive elimination. Next β -elimination of a ring hydrogen rather than a hydrogen from an alpha methyl group lead to the olefin complex.. A dipolar mechanism is possible but, given the general rarity of such mechanisms, seems less likely.⁷⁶

η^3 -Allyl complexes have been proposed as intermediates in the formation of the alkene products shown in Figures 27 and 28. The mechanism of formation would be as shown in Figure 29. Whether the η^3 -allyl or the η^2 -alkene complex is formed depends on the particular platinacyclobutane complex with which one begins.^{46,77}

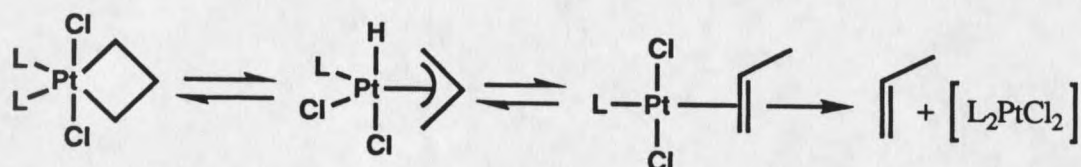


Figure 29. Decompositions of platinacyclobutane to an alkene with a η^3 -allyl as an intermediate.

Rearrangement to form an ylide involving ligand loss has been shown to proceed through the mechanism proposed in Figure 30.⁷⁸

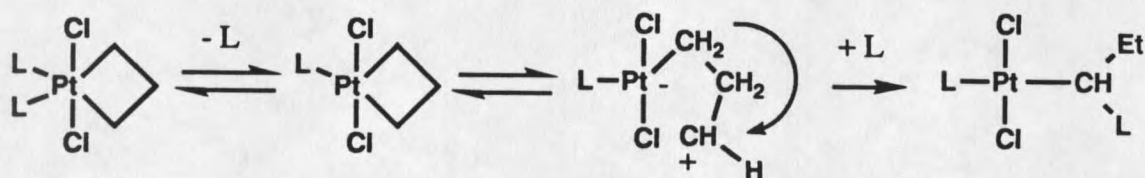


Figure 30. Decomposition of platinacyclobutanes leading to an ylide.

Note that the ylide can be produced more efficiently by the reaction of platinum(II) with diazoalkanes, Figure 31.⁷⁹ However, this reaction most likely does not go through a platinacyclobutane.

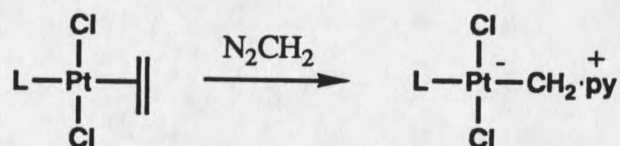


Figure 31. A more facile and higher yielding pathway to the ylide.

Ring expansion pathways

Two ring expansion pathways exist which are germane to this thesis. First the tetrameric platinacycle, compound 10, which is derived from norbornadiene, undergoes, when dissolved in DMSO, an interesting ring expansion reaction in high yield, Figure 32.⁸⁰ The mechanism of this ring expansion has been thoroughly investigated.⁸¹

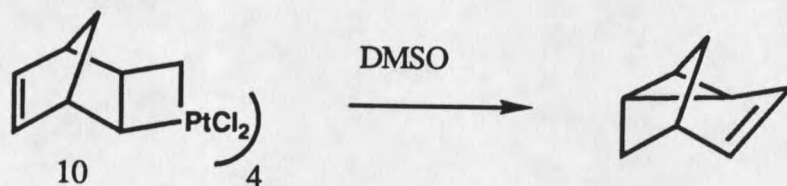


Figure 32. An interesting rearrangement of platinacyclobutanes.

The second ring expansion was devised by Burton and Puddephatt based on the cyclobutyl carbinol cation analogy. This involved the solvolysis reaction of 2-hydroxymethyl-TMS-platinacyclobutanes as shown in Figure 33.^{82,83}

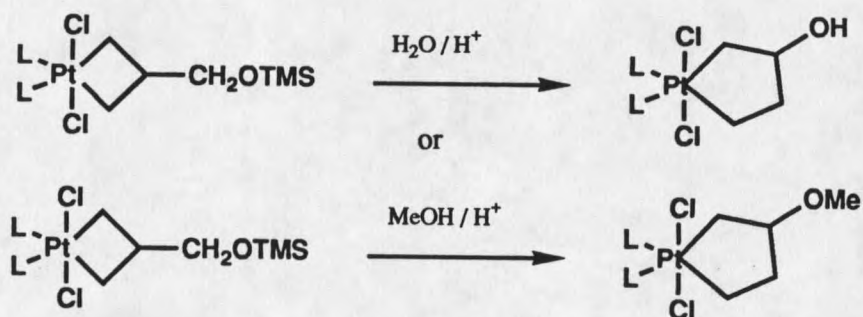


Figure 33. Ring expansion of Puddephatt and Burton using solvolysis conditions.

The cyclobutyl carbocation reasoning was also applied by Jennings and Neilsen to the stereospecific ring expansion of hydroxymethyl-platinacyclobutanes, compounds 11 and 13 respectively, to platinacyclopentanes as detailed in Figure 34.^{20,21,22}

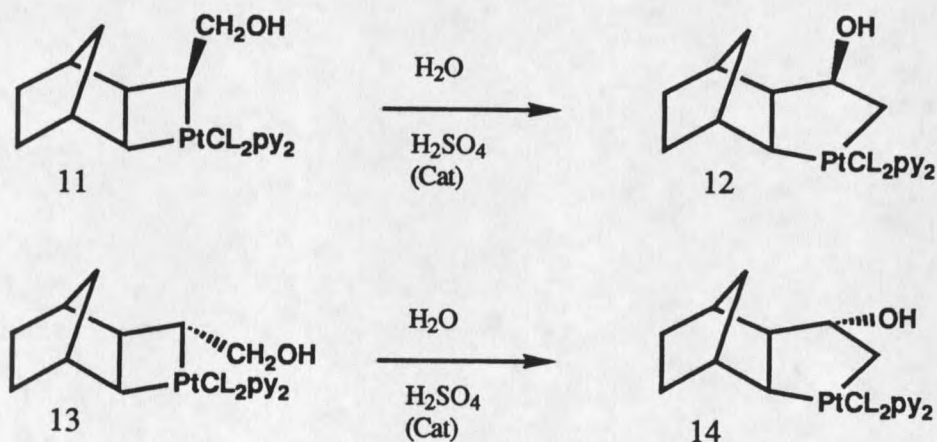


Figure 34. Stereospecific ring expansion of 1,2,3-trisubstituted-platinacyclobutanes to platinacyclopentanes.

A series of these compounds was made by using a series of different nucleophiles as shown in Figure 35.^{20,21,22} Although only the syn isomer, compound 11, is depicted in Figure 35, the anti isomer was also shown to undergo the same stereospecific reactions.

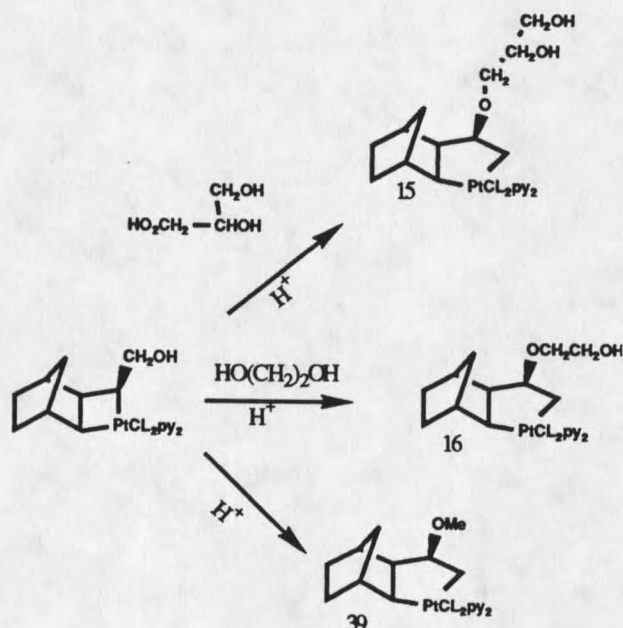


Figure 35. Ring expansion of platinacyclobutanes using a series of oxygen nucleophiles.

In a similar reaction, the anti and syn aldehydes, 17 and 18, which were derived from the oxidation of the respective hydroxymethyl compounds, also gave ring expansion products, compounds 19 and 20, Figure 36. The stereochemistry of compound 19 was not assigned unambiguously. However, that of compound 20 was known from x-ray crystallography. Thus by analogy, compound 19 probably has the stereochemistry shown.

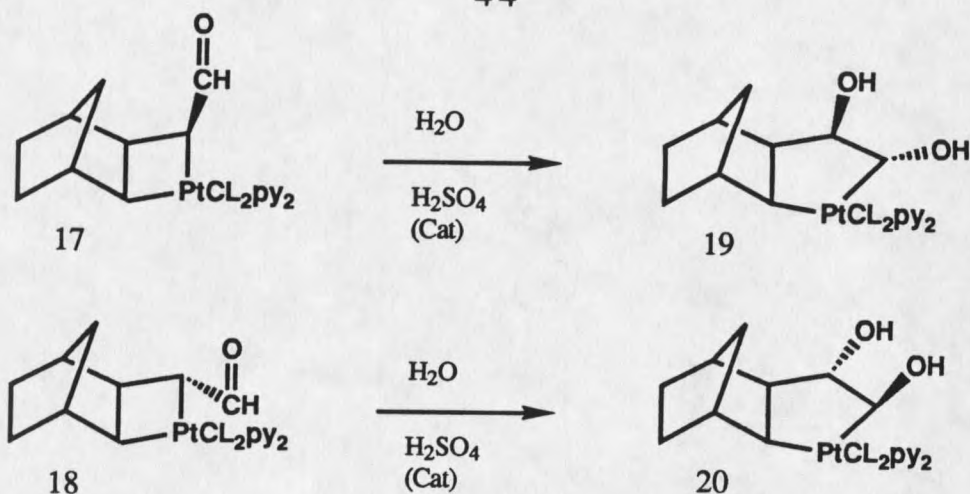


Figure 36. Ring expansion of platinacyclobutanes to dihydroxyplatinacyclopentanes.

Compounds 11,13,17,18,19, and 20 mentioned above were characterized by ¹H and ¹³C NMR spectroscopy and x-ray crystallography with all ¹³C peaks being specifically assigned. Not all the ¹H resonances were assigned specifically because of the unpredictable nature of the chemical shifts and the fact that most of the resonances are not well resolved at low field.²⁰

Reaction of platinacyclobutanes with diazocompounds.

It was shown by Ekeland and Jennings that the reaction of 1,2-cis-disubstituted platinacyclobutanes with diazomethane produced 1,3-cis-divinylcyclopentanes, Figure 37.⁸⁰

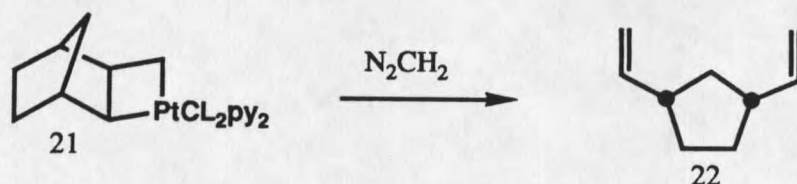


Figure 37. Reaction of platinacyclobutanes with diazomethane.

Using this precedent, Nielsen and Jennings expanded their 1,3-trisubstituted-platinacyclobutanes to 1,3-divinyl cyclopentanes with diazomethane.^{20,21} As can be seen in Figure 38, the syn platinacyclobutane produced a divinyl olefin with a cis configuration in the double bond originating from carbons contained in the platinacycle. Likewise the anti platinacycle, compound 13, produced a trans olefin at this position. These stereospecific results encouraged the study of similar systems as detailed later in this thesis.

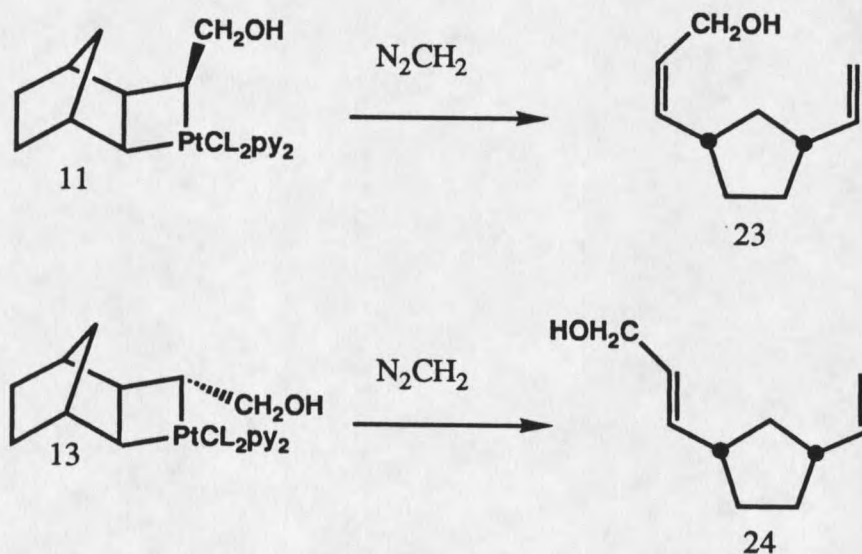


Figure 38. Production of 1,3-cis-divinylcyclopentanes from the hydroxymethylplatinacyclobutanes.

The chemistry of platinacyclopentanes themselves has been partially studied and is interesting; however, in the interest of brevity it will not be discussed in this text.

Chemistry of platinacyclobutanes derived from (X.1.0.) systems.

Parsons and Jennings synthesized platinacycles from the (X.1.0.) systems shown in Figure 39.⁸³ However these species were not particularly stable .

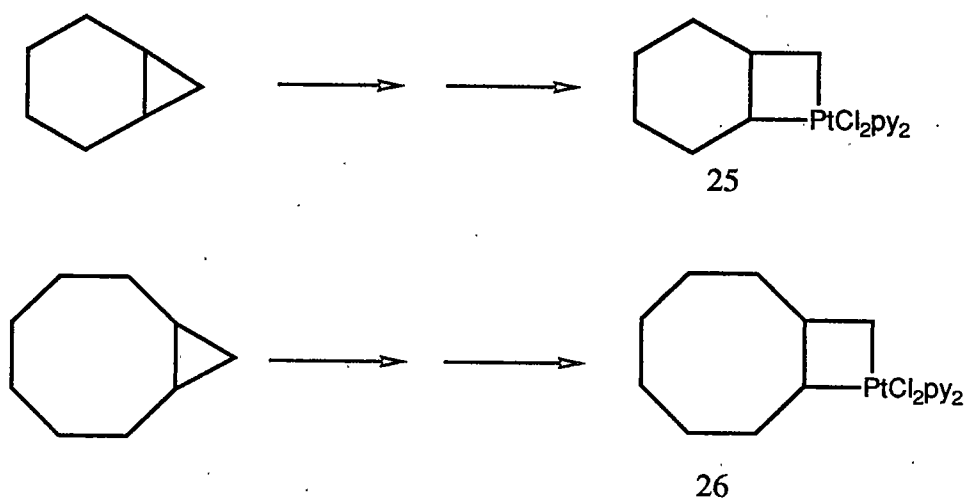


Figure 39. Platinacyclobutanes derived from (X.1.0.).

Hoberg and Jennings, simultaneously with the work described in this thesis, synthesized the analogous (X.1.0.) systems with an alpha double bond and upon the introduction of platinum (II), obtained the platinum olefin complexes of the type shown below (Figure 40). Subsequently, considerable chemistry was developed from these systems. These studies do lend a great deal to the understanding of the platinum carbon bond but are not directly relevant to the chemistry discussed later in this thesis and will not be discussed in detail.⁸¹

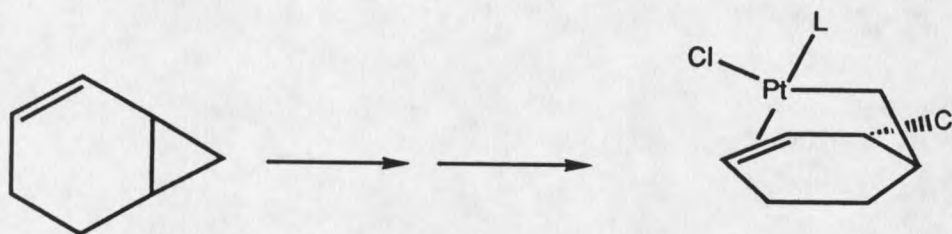


Figure 40. Pathway leading to new chemistry of (X.1.0.) systems.

The use of mmp2 calculations

Clark in his book on computational chemistry for the organic chemist notes how easy and how useful it can be for the organic chemist to use molecular energy minimization.⁸⁴ Mm2 calculations have been used extensively throughout this thesis for molecular mechanical minimizations of metal complexes. A commercially available program called Pcmode⁸⁵ was used unless otherwise noted. Pcmode, while not specifically parameterized for platinum, was designed by its authors to perform calculations on metal complexes. Since no other program capable of doing calculations on these complexes without added parameterization was readily accessible, Pcmode was the logical choice.

Because this thesis is not centered around these calculations, they will not be compared or contrasted to results obtained using other energy minimization programs. However, the results of many calculations were used to predict geometries of the complexes and in some cases even relative energies. The geometries were used to obtain bond angles and distances. When

these results are easily checked against other data, qualitative comparisons will be made.

For comparison purposes, Appendix A will contain a survey of most of the complexes which were energy minimized . The name of the compound, the file name, the geometry, and the calculated energies will be included. Furthermore, because the file formats generated by this program are compatible with MNDO, MOPAC, MMX, and MM2 formats, the data will be left in storage to facilitate additional calculations should the impetus develop.

RESULTS AND DISCUSSION

Detailed ^1H and ^{13}C NMR spectroscopic analysis of a group of platinacyclobutanes derived from norbornene and norbornadiene.

This chapter will perform three functions. First, it will contain spectral data for three new platinacyclobutanes juxtaposed to the data for four well established structures for the purpose of justification of structural assignments in the new compounds. Second, it will contain new ^1H data on the well established systems as well as for the newly synthesized compounds. Finally, it will contain a discussion of what this new ^1H data can tell us about the electron donating or electron withdrawing nature of the platinum nucleus in these systems.

A number of platinacyclobutanes derived from norbornyl systems have been well characterized by ^1H NMR spectroscopy, ^{13}C NMR spectroscopy and x-ray crystallography. However, at the time these structures were published due both to the limitations of the available NMR spectroscopic techniques in terms of pulse sequences and field strength and to the complexity introduced by the platinum nucleus, complete ^1H assignments were impossible to make and thus were not reported. Several reasons now exist to assign all of the ^1H resonances of these complexes. One of course is to make the ^1H spectrum a useful tool for identifying or distinguishing similar complexes. Another is to gain information about the electronic environment at or near the centers attached to platinum, thus getting a qualitative picture of the effect of

having platinum present in these molecules. This information may be used to predict some of the chemical properties of the centers attached to platinum.

Specifically, we would like to know if we can classify the center attached to the platinum as either electron rich or electron deficient. This can be done at least in part by judging whether the resonance of the center of interest is deshielded or shielded by the platinum atom attached to it. Deshielding often corresponds to electron withdrawing groups being attached either directly or one bond away whereas, shielding often corresponds to electron donation. Puddephatt considered this concept important in his now well established review article on platinacyclobutanes as he asked the question can the platinum be classified as either an electron withdrawing or an electron donating group using NMR spectroscopy as a probe.

At this time it should be pointed out that only the ^1H chemical shifts and coupling constants can be discussed in this context. The interpretation on ^1H chemical shift values in terms of whether or not they are attached to a carbon bearing electron withdrawing groups or electron donating groups is a reasonably straight forward correlation. ^{13}C chemical shifts however contain diamagnetic as well as paramagnetic components and correlation of their chemical shift values with substituent effects is highly complex. Although this rules out using ^{13}C spectra for identification of the electron donating or withdrawing character of the platinum based on ^{13}C chemical shifts, a

comparison of chemical shifts values and coupling constants remains useful for structural determinations.

In this section are reported the detailed ^1H assignments for a seven platinacyclobutanes. Platinacyclobutanes 21, 10, 11, 13, (Figure 48) were previously synthesized by others. Platinacyclobutanes 27, 28, 29 (Figure 48) will be reported here for the first time and the reader will be reminded of this fact by a reference stating this thesis. Their synthetic and chemical reactivity will be reported later. The NMR spectra for the newly synthesized compounds could have been reported in later sections however, their ^1H spectra were helpful in confirming the ^1H assignments of the previously synthesized compounds. In addition it was convenient to juxtapose the data in this section for comparison purposes and structural arguments involving spectral similarities.

As a starting point for the proton assignments for the platinacyclobutanes derived from norbornyl systems, the data for the previously synthesized and well characterized compound 21 (Figure 41) was compiled.¹⁹ A detailed explanation of the technique used for the structure assignments in this compound will follow. This explanation is meant to serve as an example of the methods used for all seven compounds. The structure of compound 21 was known by x-ray analysis and the carbon assignments had been made using the platinum coupling constants and, where possible, proton carbon selective enhancement experiments for a guide.¹⁹ However as mentioned previously, the

complete proton assignments were impossible to make both because of limited resolution in the proton spectrum and because of the unavailability of 2-dimensional NMR spectroscopic techniques at the time. Compound 21 was synthesized and further experiments were conducted in order to assign all the proton resonances.

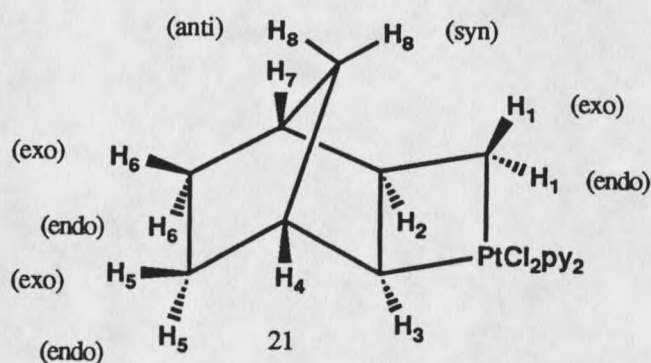


Figure 41. Proton numbering for compound 21.

As can be seen in the 500 MHz proton spectrum for compound 21, Figure 42, all the protons on the norbornyl moiety fall between 1 and 3 ppm. At 250 MHz each of these peaks would be twice as wide; although, they would be centered at the same chemical shift. Figure 43 shows a blowup of the region between .8 and 3.0 ppm of the 500 MHz data. All the spectra from this point on will have been taken at 500 MHz. The proton signals are well resolved except for a resonance integrating for two protons at 2.76 ppm. Figure 44 shows the proton carbon correlation experiment (XHcorr) performed to show which carbon peaks correspond to which protons. From this data each proton

resonance was assigned to the carbon to which it was bonded as labeled in Figure 43. However the proton pairs: 5 exo , 5 endo ; 6 exo, 6 endo; 1 anti and 1 syn, needed additional experiments and reasoning to distinguish. Note 8 syn and 8 anti had previously been distinguished by the presence of w-coupling between 8 anti and proton 3.¹⁹

Proton 4 according to mmp2 models would have dihedral angles (according to the Karplus equation) with protons 5 exo and 5 endo such that only the coupling to 5 exo would be of any size. Figure 45 shows the one dimensional decoupling experiment in which proton 4 was selectively decoupled revealing its small but easily distinguishable coupling to the proton at 1.36. The proton at 1.36 is thus the proton 5 exo. This was believed to be the case from COSY experiments but careful 1-dimensional decoupling showed the coupling much more conclusively. Proton 6 exo was assigned by comparing its coupling pattern to 5 exo as well as from selective decoupling of proton 7 which is not as obvious as that from 4 to 5 exo.

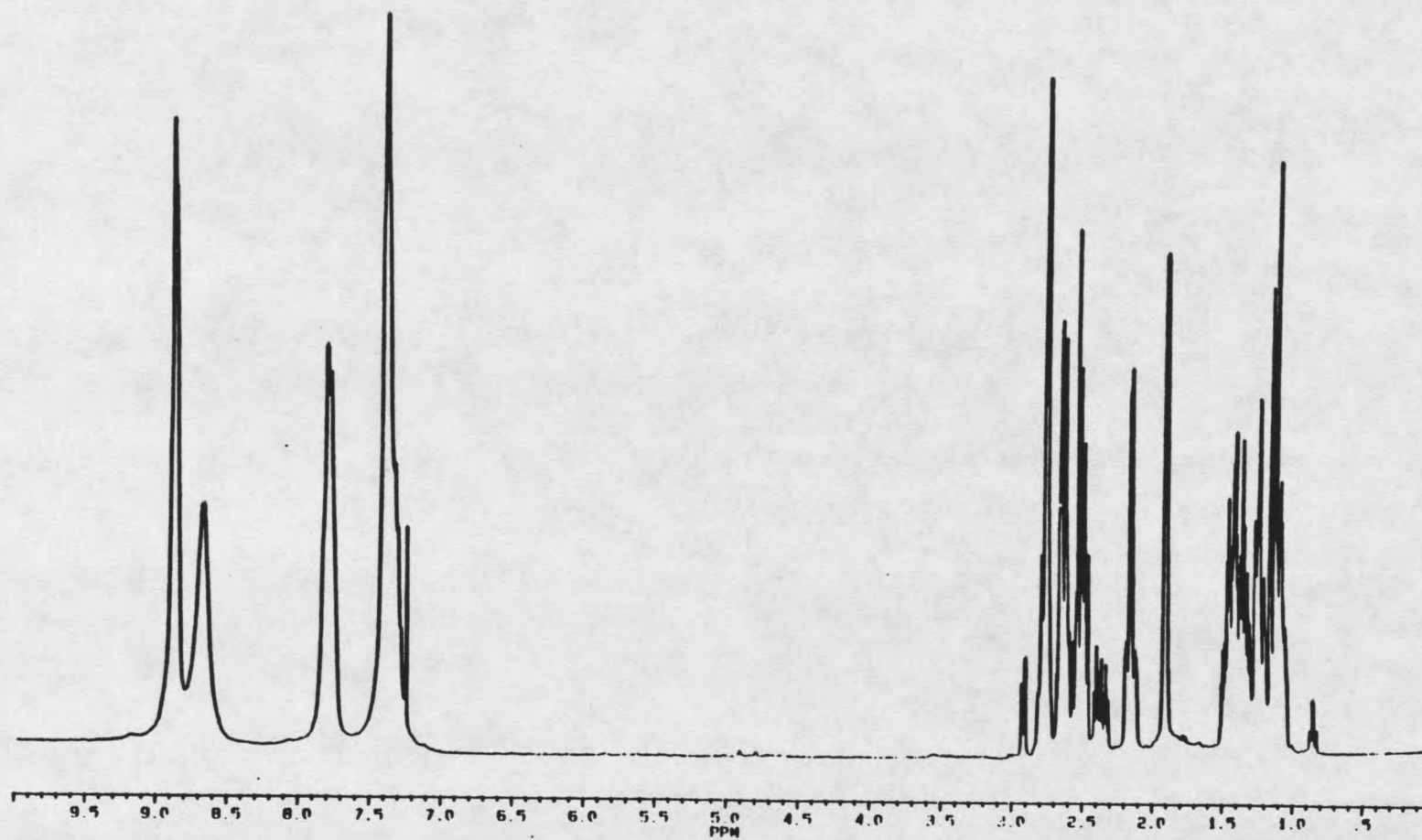


Figure 42. ^1H spectrum of compound 21.

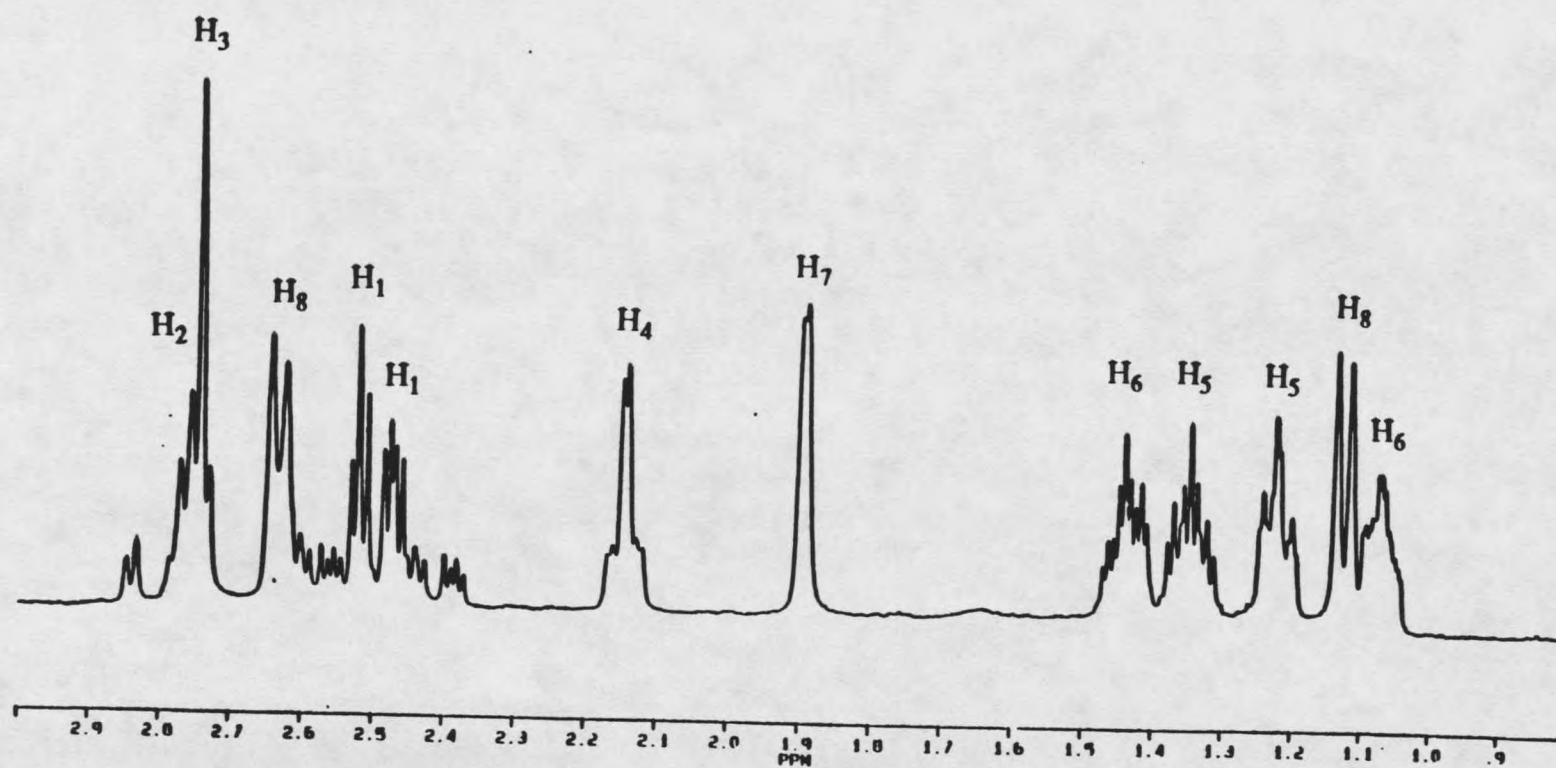


Figure 43. Compound 21 ^1H spectrum expansion 3.0-.8 ppm.

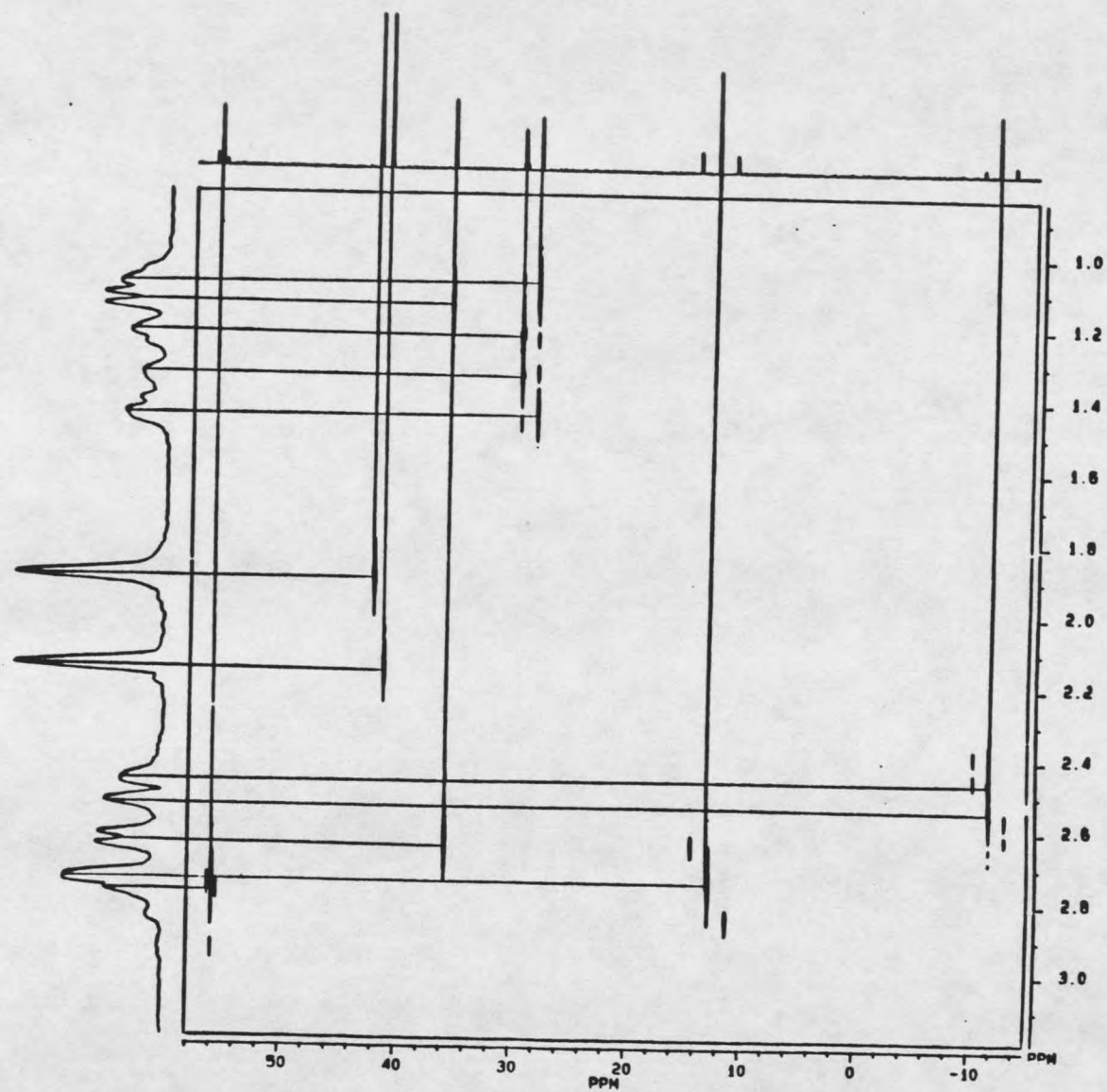


Figure 44. XHcorr experiment for compound 21.

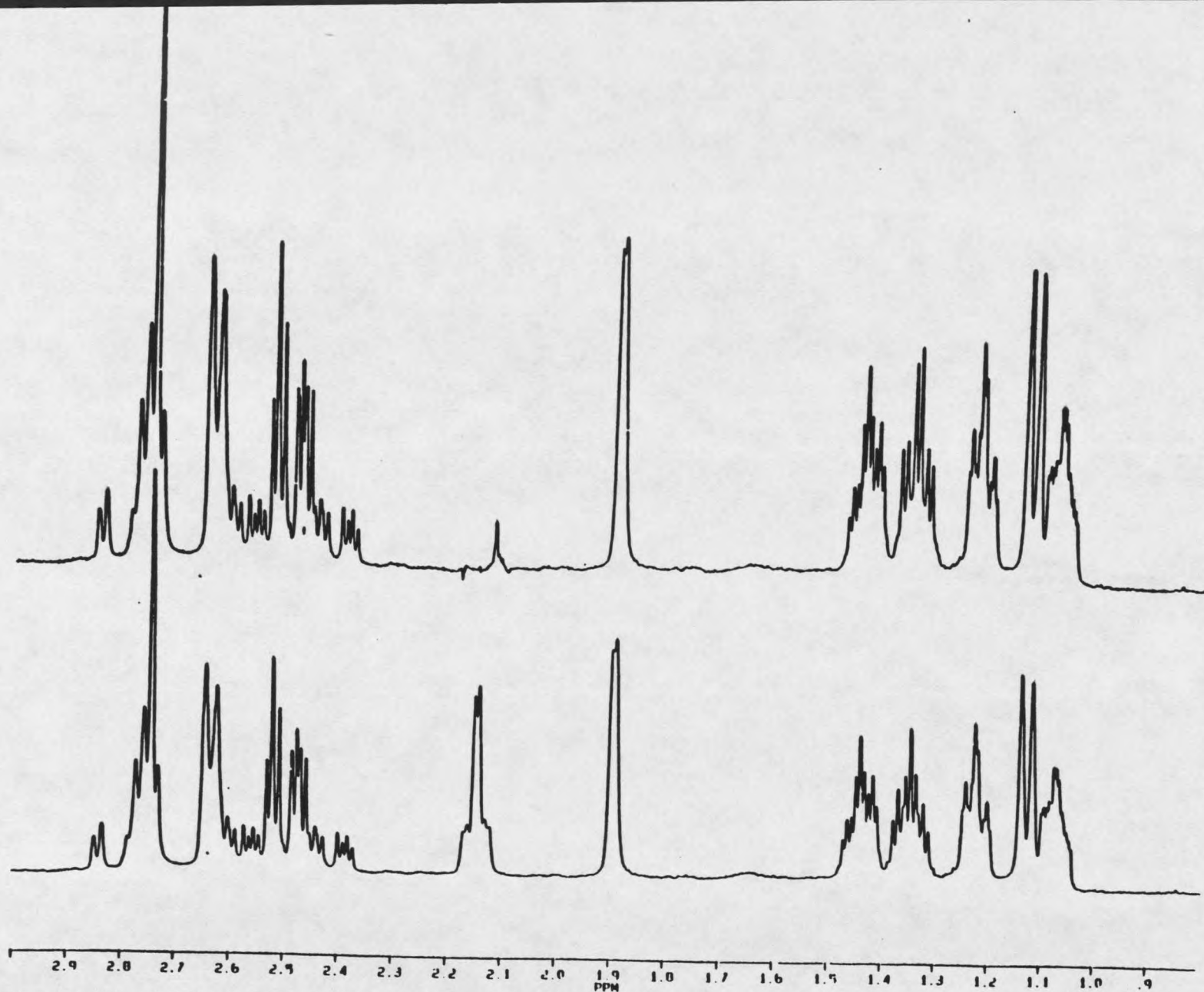


Figure 45. 1-Dimensional decoupling of proton 4 in compound 21.

The assignment for 1 syn and 1 anti was made by judging that 1 anti's coupling to proton 2 (dihedral angle of 8 degrees) would be larger than 1 syn's (dihedral angle of 143 degrees), based on the angles derived from the mm2 models. This however is a difficult system. It represents an ABM system where the geminal AB chemical shift difference is approaching their J value thus eroding the first order character of the spectrum. And the platinum satellites overlap with the resonances. Not to mention the fact that decoupling attempts in this system were of no use which is not surprising since the resonances are separated by only about 20 hertz. However it is easy to see that 1 anti and 1 syn should be coupled only to each other and 2; thus, the proton containing the larger total coupling (total coupling equals the geminal coupling plus coupling to proton 2) of the two total couplings would be the one that is cis to proton 2. The total coupling to the resonance at 2.52 is 11 Hertz and to the resonance at 2.48 is 14 Hertz (Figure 46) Thus the proton resonating at 2.48 was assigned 1 anti. Further from comparison of the measured coupling it could be ascertained that the geminal coupling is on the order of 6-7 Hertz. The size of the coupling between proton 2 and proton 1 in compound 28 was constant with size of the coupling for proton 2 and 1 endo as assigned in compound 24. The complete ^1H assignments for compound 21 are shown in Figure 47.

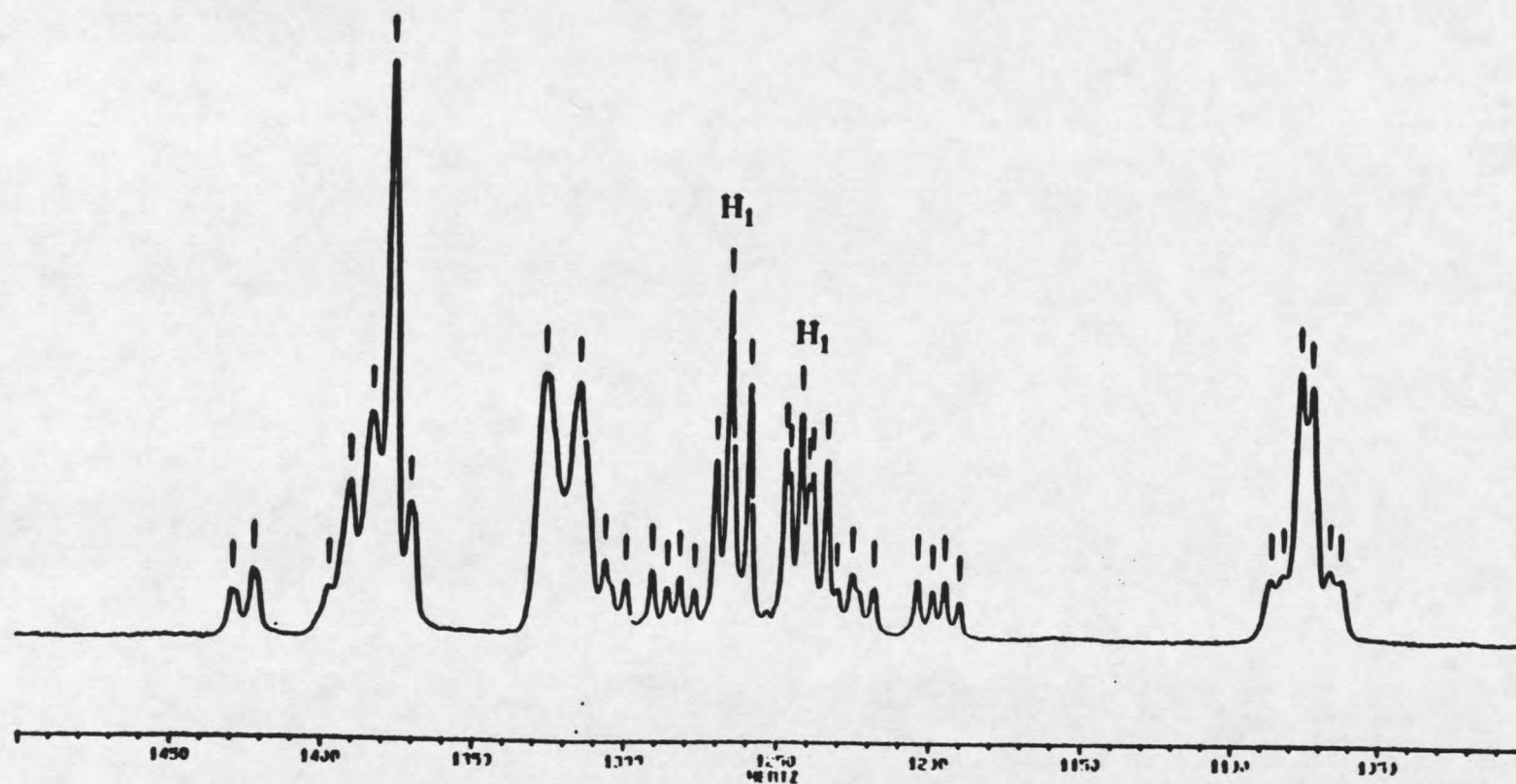


Figure 46. Expansion plot showing coupling in proton 1 exo and 1 endo.

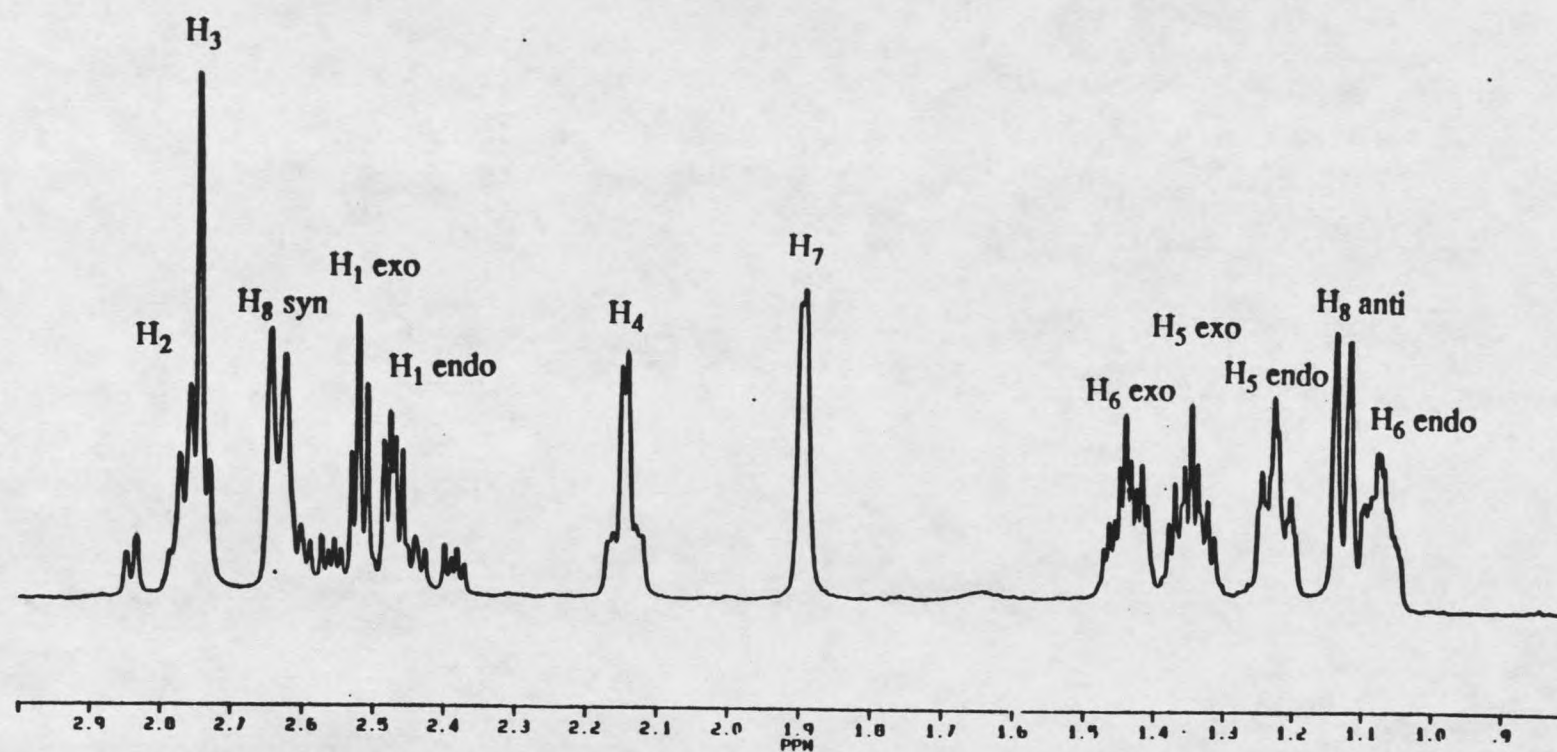


Figure 47. Complete ^1H assignments for compound 21.

Using the new information learned about compound 21, past structural data, and the information gained by performing cpd, dept, cosy, XHcorr, noesy, 1-dimensional decoupling, and 1 dimensional noe difference experiments where needed, the complete ^1H and ^{13}C assignments all the compounds shown in Figure 49 were made.

Compound 10, and 11 have been previously prepared and exact ^{13}C assignments had been made. However exact ^1H peak assignments had not been previously assigned and thus these assignments are the responsibility of this author. The synthesis of compounds 27, 28, and 29 had not been accomplished previously and is described later in this thesis. The ^1H and ^{13}C resonances will be detailed here so that they may juxtaposed to more established data for comparison purposes. Comparison of this data will show that these compounds are indeed of the structure shown in Figure 48.

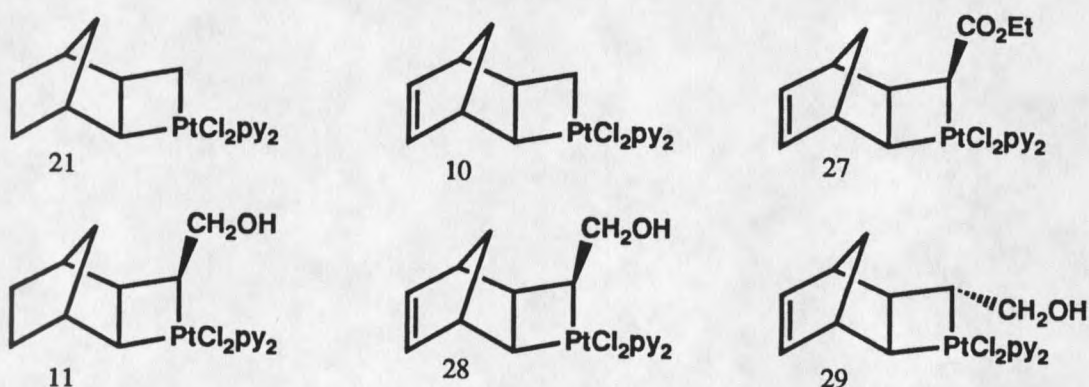


Figure 48. The compounds for which detailed carbon and proton data is provided in Tables 8,9,10, and 11.

Figure 49 shows the numbering scheme used in the tables that follow.

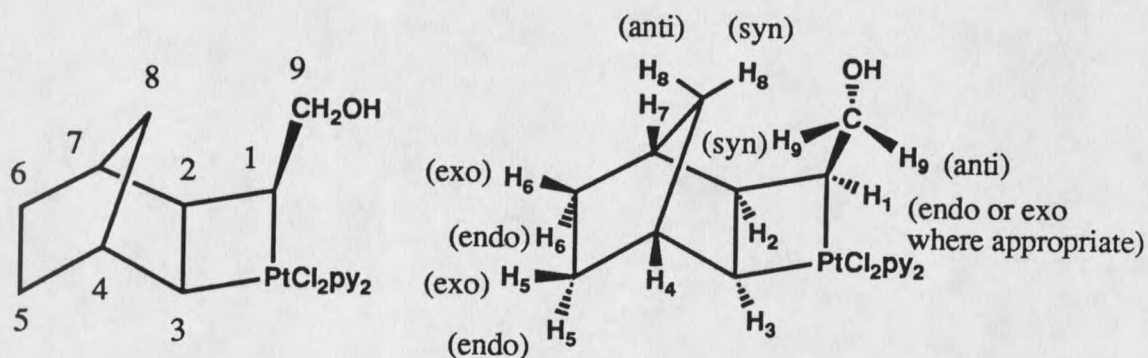


Figure 49. Numbering scheme used in Tables 8, 9, 10, and 11.

The following tables are a compilation of all the ^1H and ^{13}C assignments for the compounds shown in Figure 49. In addition the ^{13}C data is included for compound 13, the antihydroxymethyl analog of compound 11, in Table 8. Directly following the tables in Figure 51 is the cosy for compound 28 and directly following this cosy is the XHcorr experiments for compounds 28, 29, and 30 in Figures, 52, 53, 54, 55, and 56. Figures 51, 52, 53, 54, 55, and 56 are provided as examples of some of the 2-dimensional experiments used to compile the data in the tables and are not meant as the sole sources of information in themselves, although the reader with good eyes can pick out the resonances reported in the tables.

Table 8. ^{13}C assignments for 21, 11, and 13.

Compound# Carbon #	21 ppm (J Pt)	11	13
1	-12.1 (352)	6.36 (370)	4.05 (370)
2	55.6 (95)	56.7 (98)	59 (98)
3	12.4 (351)	13.0 (394)	14.4 (398)
4	40.9 (<10)	40.1 (10)	41.3 (28)
5	29.3 (44)	28.6 (41)	29.2 (41)
6	27.9	28.9	27.4
7	41.8 (24)	37.8 (10)	40.7 (<10)
8	35.4	37.5	35.6
9		63.7 (24)	67.0 (28)
m-py		125	
o-py		149.8	
p-py		138	
References	20	20	20

Table 9. ^{13}C assignments for compounds 10, 28, 29 and 27.

Compound#/ Carbon #	10 ppm (J-Pt)	28	29	27
1	-2.2 (371)	15.8 (394)	14.6 (392)	3.0 (406)
2	51.5 (83)	52.72 (86.1)	54.24 (81.3)	53.2 (87)
3	10.7 (403)	11.14 (405)	12.45 (404)	3.3 (394)
4	45.7 (<10)	45.04 (8.3)	45.63 (8.7)	45.8 (8.9)
5	134.9 (37)	134.9 (36)	135.91(34.7)	135.9(34.1)
6	136.3	150.78	153.58	139
7	46.9 (24)	43.62 (8.7)	156.62 (26)	45.6 (9.1)
8	44.4	46.94 (25)	45.07	47.6
9		63.66 (23.)	67.06 (24.1)	176.2(44.8)
O-CH ₂ -CH ₃				59.01
O-CH ₂ -CH ₃				13.9
m-py	126	126	126	125
o-py	151	151	153	150
p-py	139	139	139	138
References	20	This thesis	This thesis	This thesis

Table 10. ^1H assignments for 21, and 11.

Compound#	21	11
Proton #		
1 exo	2.51	
1 endo	2.47	3.55
2	2.77	2.89
3	2.74	2.70
4	2.14	2.36
5 exo	1.35	1.36
5 endo	1.22	1.19
6 exo	1.43	1.43
6 endo	1.08	1.00
7	1.9	2.17
8 anti	1.12	1.25
8 syn	2.63	2.81
9 syn		2.65
9 anti		3.68
o-py	8.9,8.15	8.9,8.7
p-py	7.8	7.8
m-py	7.4	7.35
References	This thesis	This thesis

Table 11. ^1H assignments for 10, 28, 29, and 27.

Compound# Proton#	10	28	29	27
1 exo	2.76			
1 endo	2.72	3.90	4.12	5.16
2	2.48	2.45	2.85	2.80
3	2.34	2.52	3.06	2.86
4	2.78	3.09	3.05	3.36
5	6.00	6.05	6.05	6.13
6	6.00	6.17	6.05	6.26
7	2.61	2.82	3.08	3.79
8 anti	1.30	1.4	1.5	1.74
8 syn	2.52	2.73	3.10	3.51
O-CH ₂ -CH ₃				3.82
O-CH ₂ -CH ₃				.59
9 syn		2.92		
9 anti		3.89		
o-py	8.6, 8.8	8.6, 8.9	8.7, 8.9	8.75, 8.85
p-py	7.80	7.77	7.80	7.80
m-py	7.40	7.35	7.38	7.45
References	This thesis	This thesis	This thesis	This thesis

From comparison of the compounds in Tables 11 and 12 one can see that all the complexes have 1J platinum carbon coupling in the now well established range for platinacyclobutanes with pyridine as a ligand, of 350-420 Hertz. These carbons always come in the upfield region between 15 ppm and -15 ppm and this is true of all the complexes in the table. One also notices the similarities of the coupling and chemical shift values of the carbon across the four membered ring from the platinum, carbon 2. Its chemical shift range is very small and usually has a platinum 2J coupling of 80 to 100 Hertz. Platinum coupling is also always seen to carbon 5 generally around 40 Hertz and carbon 7 generally around 10 Hertz. Platinum coupling to carbon 4 seems to be more unpredictable but is often present. Platinum coupling is so prevalent in these systems that carbon 6 can be picked out because it never has platinum coupling. The same is true of carbon 8.

Carbon 9, which represents the hydroxy bearing carbon or the carbonyl carbon in these systems, is easily picked out by the fact that it is downfield of the other carbons and has 2J platinum coupling of approximately 20 Hertz. Interestingly the coupling is bigger in the case where carbon 9 is a carbonyl (compound 27).

This author believes that the similarities in the spectra of these compounds due to their close structural similarity and due to the presence of the second spin active nucleus, platinum, is so prevalent that one can realistically determine the structure of

these complexes given only the ^{13}C chemical shift data (which includes the platinum satellites).

The similarities in the ^1H spectra are not as striking as those in the ^{13}C data but are still consistent with and correspond to those in the ^{13}C spectra. Using highfield NMR actually allows one to pick out recognizable patterns common to all these complexes. The protons 2J to platinum always have the largest platinum coupling 90-120 hertz. Proton 2 usually has ^3J platinum coupling of around 80 hertz. Proton 4 and Proton 7 are broad singlets with several small couplings to other protons. Proton 4 is always platinum coupled but usually is not resolved. Proton 7 does not exhibit coupling to platinum.

Protons 9 syn and 9 exo of course did not exist in our example compound, compound 21. The fact that they are not chemical shift equivalent is due to the lack of free rotation around the carbon 1 and carbon 9 bond. The hydroxymethyl group is not free to rotate because of unfavorable steric interaction between the pseudoaxial chlorine and the hydroxy group. Which proton resonances represented those of the hydroxymethyl group was easy to determine from the XHcorr experiment. However, which was over the ring (here deemed 9 syn) and which was not (9 anti) was determined with difference noe experiments. Proton 8 syn was indicated by mmp2 models to be close enough to 9 syn for a strong noe to develop between the two. Thus proton 8 in compound 29 was selectively irradiated and the resonance at 3.89

ppm showed an noe enhancement indicating that it was proton 9 anti.

Now let us turn our attention to the question of whether or not platinum can be classified as an electron withdrawing group in a qualitative sense based on ^1H data. Because protons 1 and 3 are connected to a carbon attached to platinum their chemical shift values should be indicative of whether platinum is acting as a electron donating or withdrawing group. The chemical shift values are 2.5 and 2.7 for protons 1 and 3 respectively. Cyclobutane itself has a chemical shift of 1.96 and compound 32 is reported in the older literature as having two broad resonances centered at 2.03 and 1.80.⁸⁷ If in the case of compound 32 it is assumed that the value at 2.03 is probably that of the protons on the four membered ring, we see that the platinum has caused a slight deshielding of the ^2J protons suggesting the platinum is probably slightly electron withdrawing.

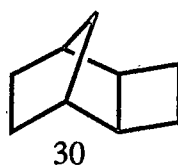


Figure 50 Structure of compound 30.

Another relevant comparison is the size of the geminal coupling between protons 1 anti and 1 syn of compound 24 and that of in compound 32. Unfortunately the data for the analogous protons in compound 32 is not available. If this data were known

the size of the geminal coupling would be smaller if the platinum was acting as an electron withdrawing group. A search of the literature for some naturally occurring cyclobutanes and their geminal coupling constants was fruitless. Several comparable cyclobutanes were found but the ^1H NMR data was not detailed enough to extract the desired information.

The geminal coupling in compound 21 is 6-7 Hertz. According to Jackman and Sternhill the geminal coupling of cyclobutanes ranges from 10-15 hertz with 12 hertz being considered typical.⁸⁷ The size of geminal coupling in general is reported as being the largest in systems in which the geminal protons are in hyperconjugation with electron deficient π -systems. Electron withdrawing groups attached directly to the carbon bearing the geminal protons are reported to lower the geminal coupling constant.⁸⁸ Because the geminal coupling in 21 is approximately 6 hertz lower than would be expected in the analogous compound 30, the platinum is probably acting as an electron withdrawing group.

When we combine this conclusion with the chemical shift information given above we can probably say that the platinum which is formally a platinum (IV) is probably slightly electron withdrawing. However it is not nearly as electron withdrawing as the carboethoxy substituent in compound 27 which shifts the proton (5.1 ppm) downfield by several ppm as compared to compound 21.

In conclusion it can be seen that compounds 27, 28, and 29 are indeed of the structure proposed in Figure 49. Secondly, all the ^1H NMR assignments for compounds 21, 11, 10, 28, 29, and 27 have been made with reasonable certainty. Thirdly, we can conclude that platinum behaves in these systems like a slightly electron withdrawing substituent. The tables found in this chapter will be useful for comparison to NMR data contained in the Experimental section for other similar proposed structures.

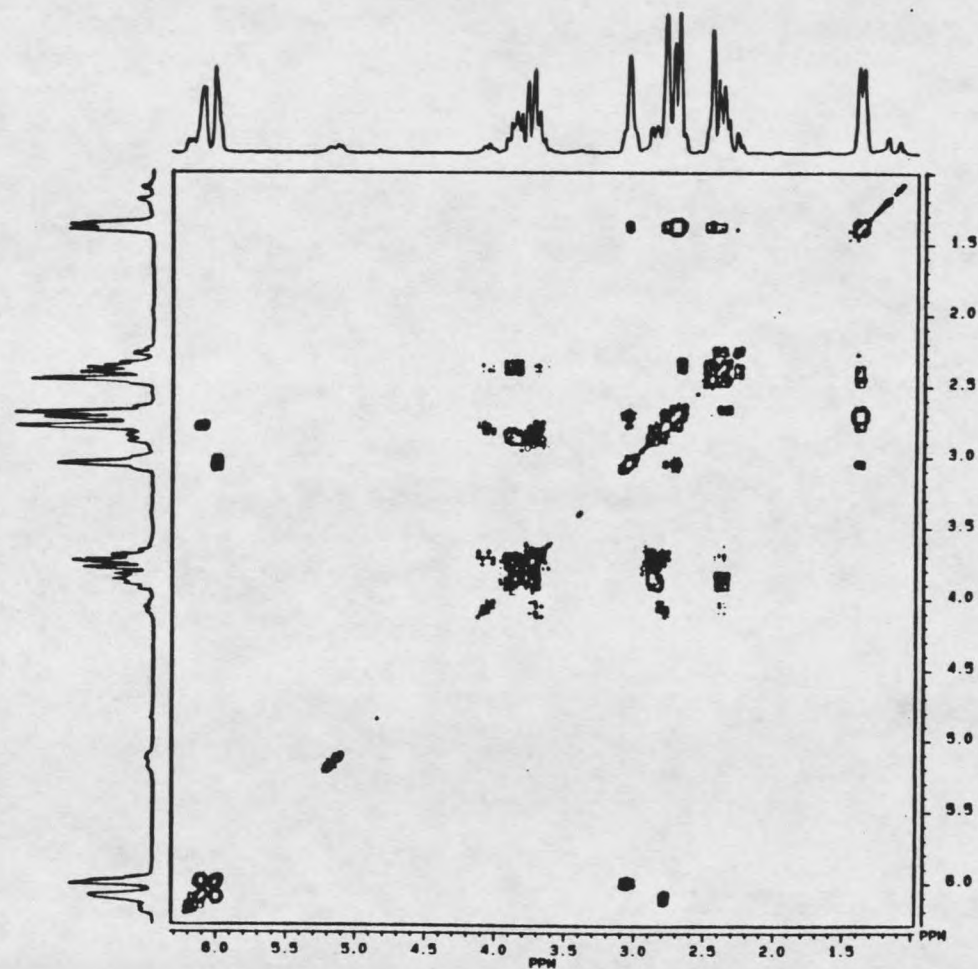


Figure 51. Cosy experiment for compound 28.

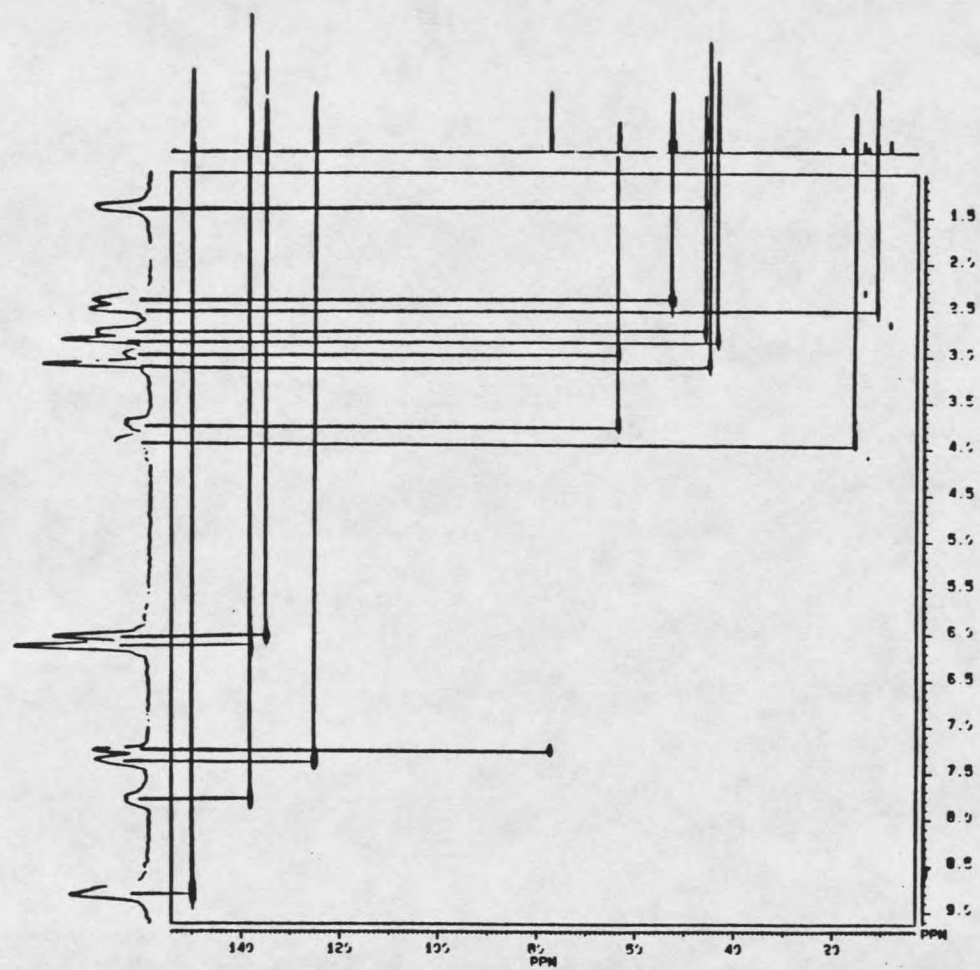


Figure 52. XHcorr experiment for compound 28.

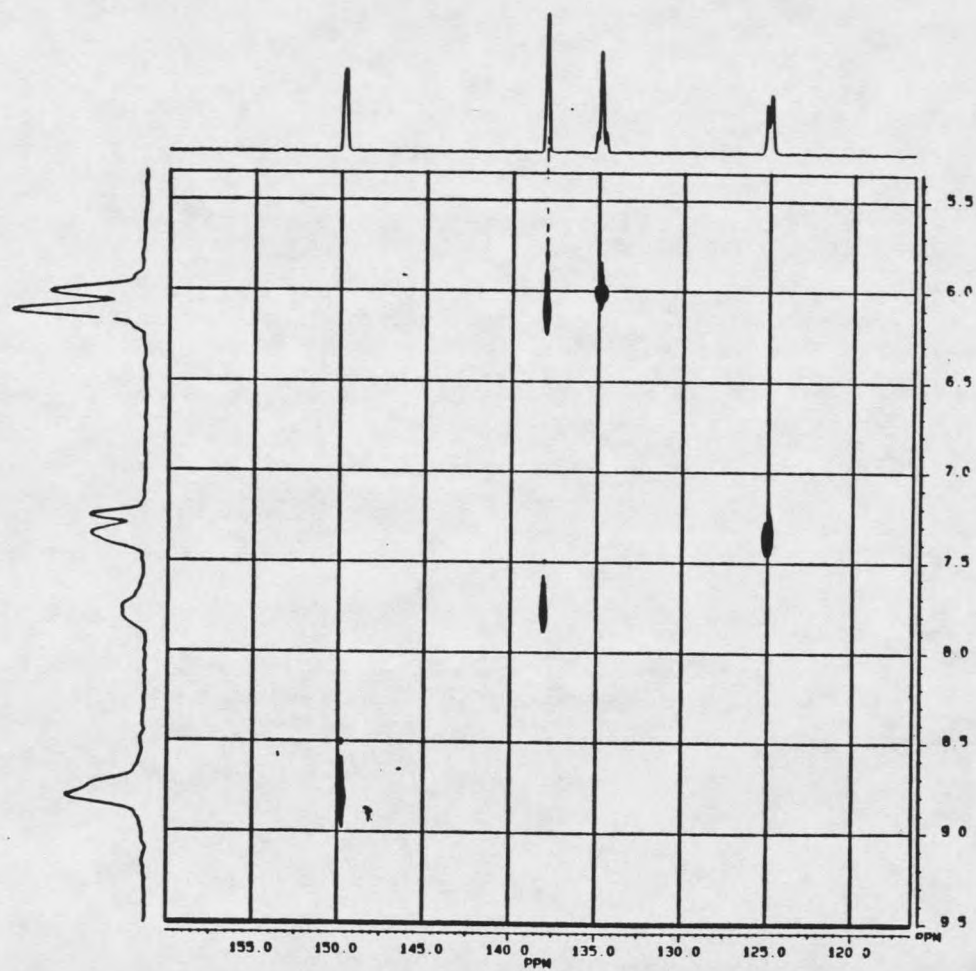


Figure 53. XHcorr experiment for compound 28 downfield region.

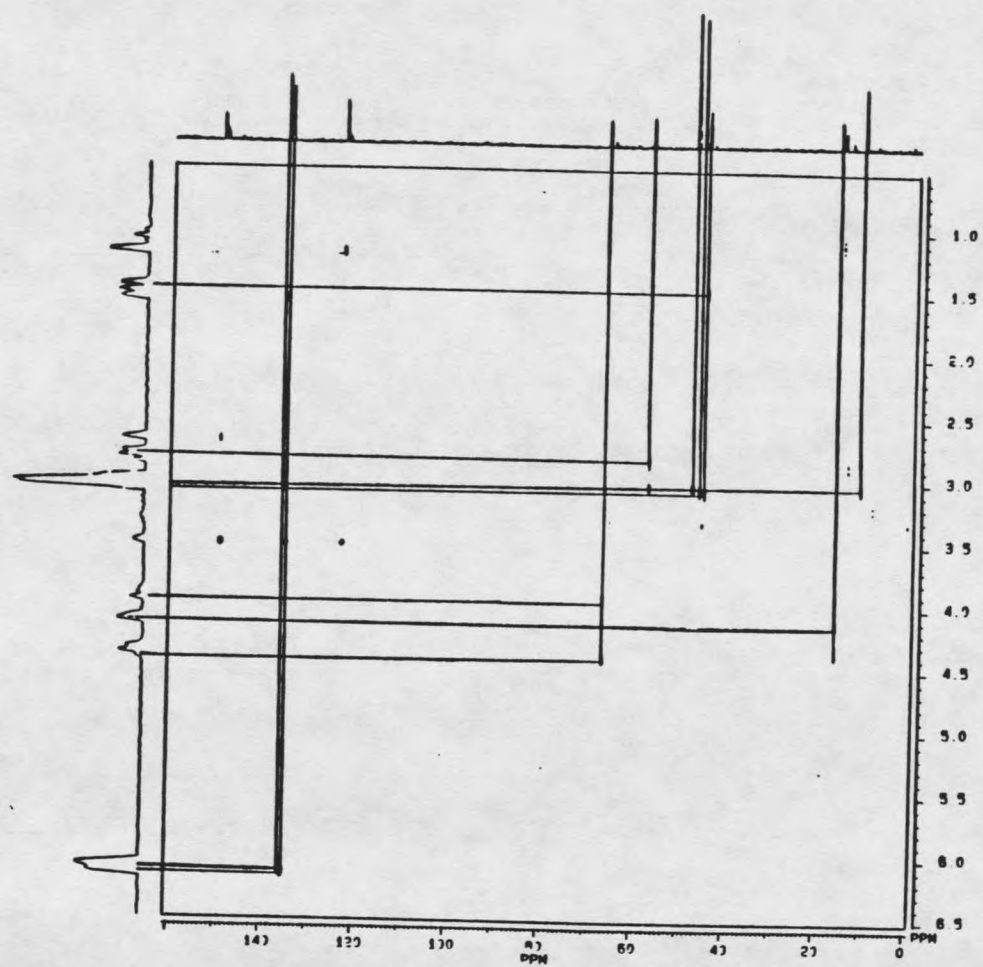


Figure 54. XHcorr experiment for compound 29.

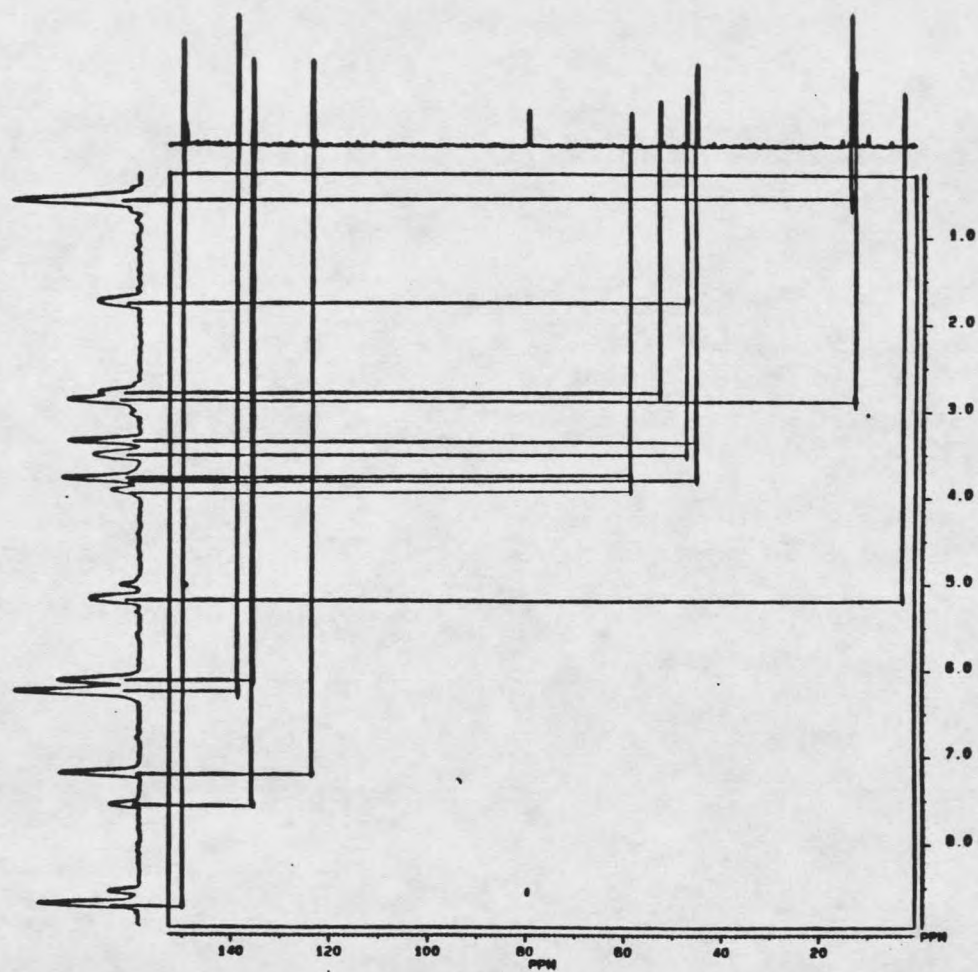


Figure 55. XHcorr experiment compound 27.

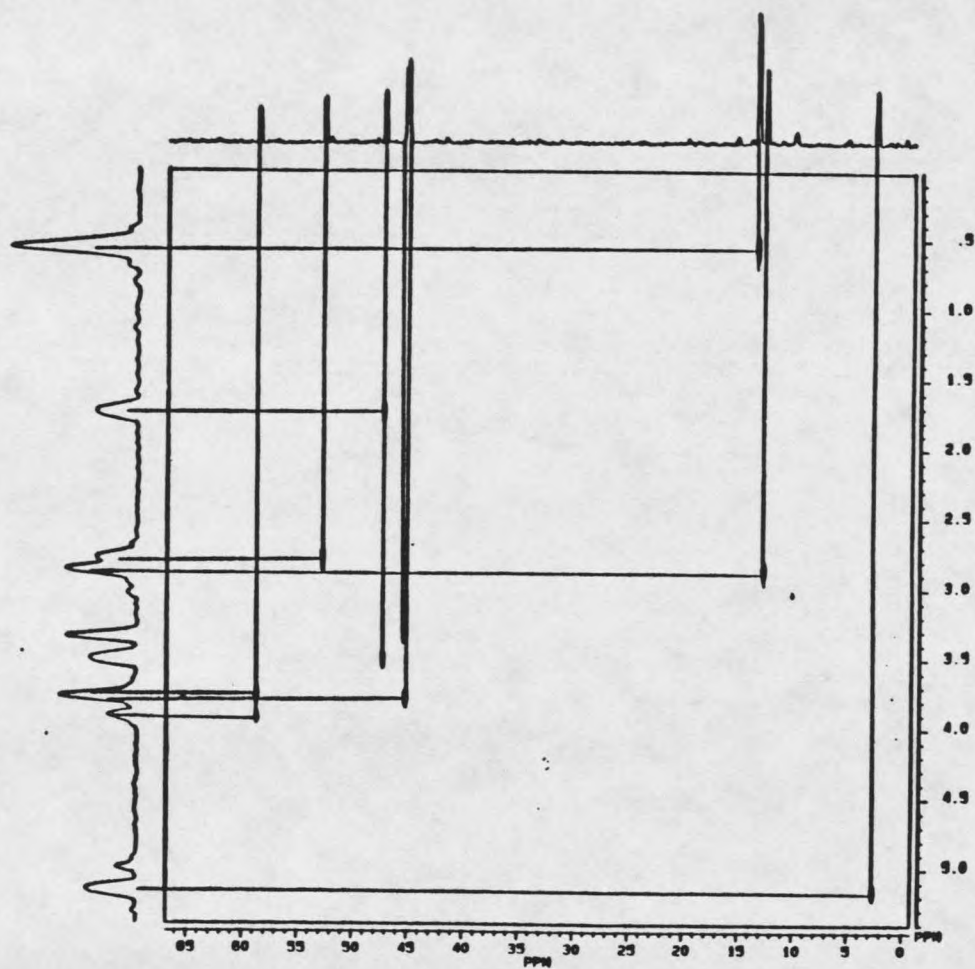


Figure 56. XHcorr experiment compound 27 upfield region.

Synthesis and chemistry of platinacyclobutanes derived from norbornadiene

Because of the extensive chemistry that was shown to be applicable to compounds 11 and 13 as partially summarized in Figure 57 and discussed in more detail in the introduction, it was desirable to see if these interesting and productive reactions could be extended to the analogous compounds derived from norbornadiene. These compounds would be analogous to compounds 11 and 13 with the introduction of a double bond between C5-C6. The introduction of the double bond also represented the addition of functionality upon which latter transformations could be carried out.

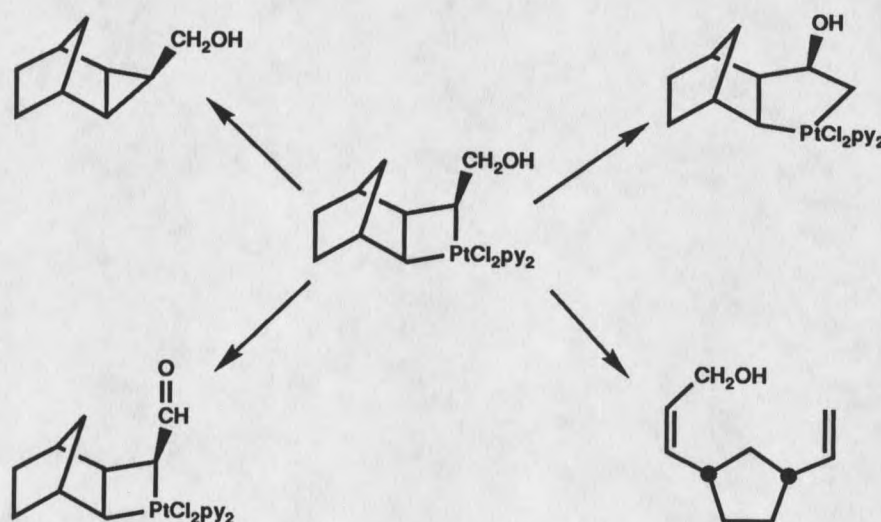
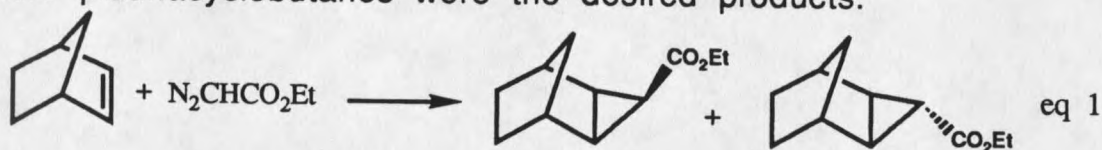


Figure 57. Organic transformation of compounds 11 and 13.

Synthesis of compounds 31, 32, 33, 34, 35, 36, 27, 28 and 29

The hydroxymethyl compounds derived from norbornene were prepared from the cyclopropanation of norbornene with ethyl diazoacetate with rhodium acetate as the catalyst according to the method of Doyle. The resulting exo epimeric esters shown in equation 1 were then reduced with excess LAH to the epimeric alcohols in reasonable but not high yields. These epimeric alcohols next were converted to the platinacyclobutanes. This methodology, when applied to norbornadiene, produced a mixture of four products: both pairs of exo and endo epimeric esters. A method around this problem had to be devised since ultimately pure platinacyclobutanes were the desired products.



A comparative study using the three different cyclopropanation catalysts rhodium acetate, palladium chloride, and palladium acetate was carried out. To a mixture of one equivalent of the norbornadiene and the catalyst in ether was slowly added dropwise one equivalent of the ethyl diazoacetate. The catalyst was filtered and the ether carefully removed under low vacuum. The products were the four expected monoesters plus small amounts of the dicyclopropanated products and maleate and fumarate esters. The ratio of products and extent of reaction was measured by NMR and the yield was judged by weight of the mixture. The product ratios are shown in Table 12. Only one

equivalent of ethyl diazoacetate was used in these reactions because of the need to minimize the production of dicyclopropanated products. As can be seen in Table 12, the difference in the catalyst in terms of the amount of exo products versus the amount of endo products is quite extensive with palladium acetate being the catalyst of choice. Under these conditions the yield from this catalyst was also lower. Silica gel chromatography of the products afforded pure 31 and 32.

Table 12. Cyclopropanation of norbornadiene with ethyl diazoacetate.

						
31	32	33	34			
Ratios of products						
		32	31	33	34	
	+ N ₂ CHCO ₂ Et	$\xrightarrow{[\text{Rh}(\text{O}_2\text{CCH}_3)_2]_2}$	55	22	17	6
		$\xrightarrow{\text{PdCl}_2}$	47	51	<1	<1
		$\xrightarrow{\text{Pd}(\text{O}_2\text{CCH}_3)_2}$	60	38	<1	<1

When the presence of dicyclopropanated products was not a concern yields of the exo alcohols (compounds 35 and 36, Figure 54) could be maximized at 40 percent by adding 2.5 equivalents of

ethyl diazoacetate instead of the one equivalent used in the above study. The presence of the dicyclopropanated products poses no problem if the alcohols are the desired isolated products because the mono alcohols can be separated from the diols by silica gel chromatography, Figure 58. When only the monocyclopropanated esters were desired, 1 equivalent of ethyl diazoacetate was added, because the esters are not as easily separated.

The crude reaction mixture, labeled products in Figure 58, after the removal of the ether was submitted to the reducing conditions. The reaction was quenched and the alcohols extracted from the water and aluminium salts with repeated extractions of ether. The ether was dried with potassium thiosulfate. Rotoevaporation of the ether then yielded the desired alcohols. Compounds 35 and 36 could be isolated by silica gel chromatography, Figure 58.

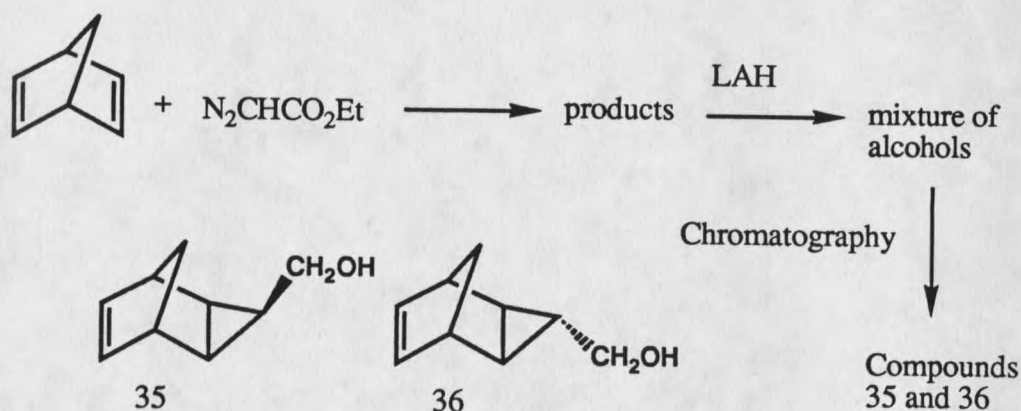
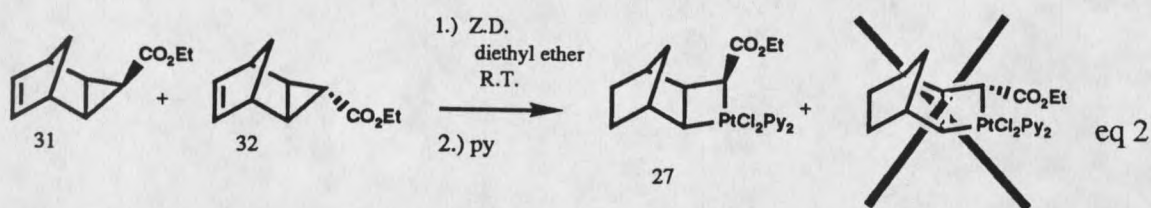


Figure 58. Synthesis and isolation of compounds 35 and 36.

Synthesis of platinacyclobutanes derived from norbornadiene

The present literature claims that platinum will not insert into cyclopropanes with strongly electron withdrawing groups such as carboxycyclic acid groups, attached directly to the ring.³⁸ In fact cyclopropanecarboxylic acid will not insert platinum under any known conditions. This author, on the outside chance that compounds 31 and 32 might insert platinum despite the fact that they fit in this class of compounds, attempted the insertion reaction. The standard reaction conditions for the insertion of platinum(II) into cyclopropanes was used. To a mixture of the epimeric esters in ether was added one equivalent of Z.D. and the reaction was let stir for 8 hours, equation 2.



Against the literature precedent,³⁸ compound 27 was produced. No platinacyclobutane resulting from the insertion of platinum into compound 32 was observed. (For the characterization of compound 27 see Tables 8, 9, 10, and 11.) When reactions were done in which one equivalent of compound 31 was added the yield was 95%. Isolated compound 32 was reacted with Z.D. over extended periods and no insertion product was observed. The reason for this selectivity will be discussed later.

Compounds 35 and 36 both inserted platinum into the cyclopropane to form the platinacyclobutanes. Figure 59 depicts the methodology used to produce compounds 28 and 29 selectively from a mixture of 35 and 36.

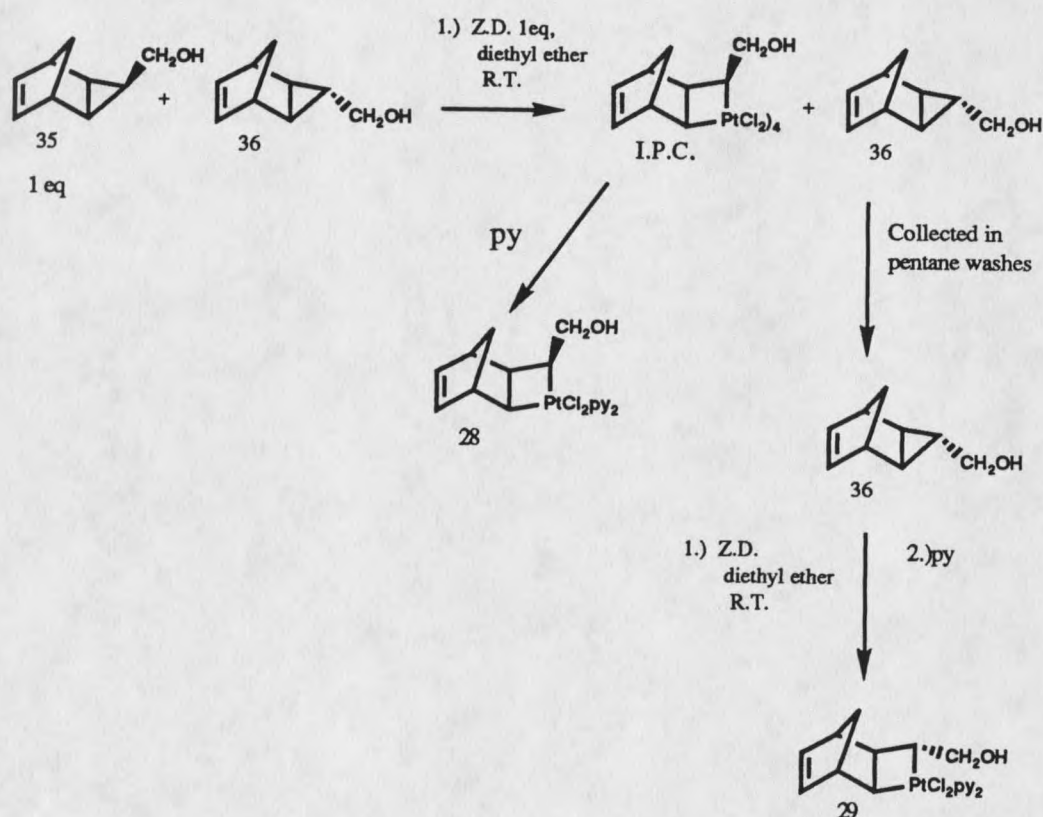
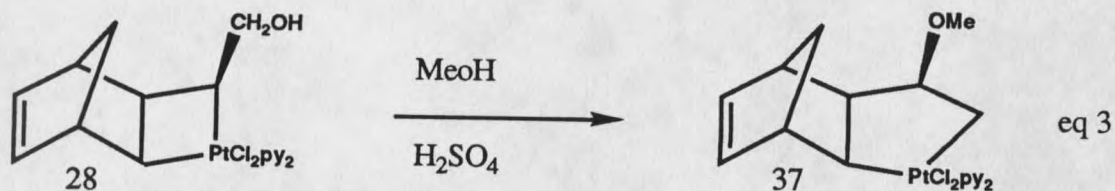


Figure 59. Synthesis of compounds 28 and 29.

Ring expansion of compounds 28 and 29 to platinacyclopentanes

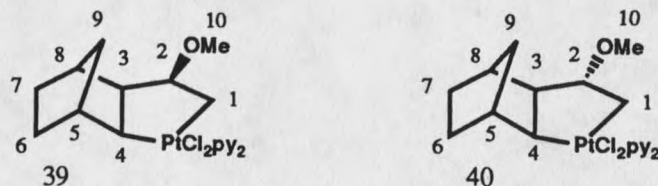
Compounds 28 and 29 were stereospecifically ring expanded to the platinacyclopentanes compounds 37 and 38, respectively. To compound 28 in methanol was added a catalytic amount of H_2SO_4 and the mixture was allowed to stir producing compound 37 after workup, equation 3.



The same procedure was used with compound 31 producing compound 38 after workup, equation 4.

Table 13 contains ^{13}C NMR spectroscopy data for compounds 37 and 38 as compared to that for compounds 39 and 40

Table 13. ^{13}C data for compounds 37, 38, 39, and 40.



Cpd#/ ^{13}C #	37/ppm(J-Pt)	38	39	40
1	20.33 (548)	19.5 (536)	21.2 (546)	21.9 (544)
2	82.20 (44)	87.7(23)	82.9 (56)	86.6 (59)
3	45.32 (27)	47.8(<10)	52.5	56.4
4	36.1	32.3(517)	41.8(530)	36.6(523)
5	49.01	47.4	44.2	39.8
6	136.7	137.2	29.3(32)	32.2
7	139.0	136	30.8	28.2
8	45.92	44.8	37.3	43
9	42.49	46.2	36.8	36.4
10	57.3	56.6	57.1	57.6
o-py	151,149	150,149.3	NR	NR
m-py	125,125.1	125,125.2	NR	NR
p-py	138,138.3	138,138.3	NR	NR
References	This thesis	This thesis	20	20

NR = Not reported.

Contrasted to the parent platinacyclobutane the platinacyclopentanes can be seen to have larger platinum carbon coupling constants for carbons 1 and 4. The 1J platinum to carbon coupling constant usually ranges from 400-600 hertz. The carbons connected to platinum are not shifted as far upfield in the platinacyclopentanes as they are in the parent platinacyclobutanes. The chemical shifts differences in compounds 37 and 38 compared to those of 39 and 40 are those expected for the introduction of a double bond. The stereochemistry in the case of compounds 39 and 40 was established by x-ray crystallography.²⁰ The stereochemistry in 37 and 38 is based on the observation that, in the synthesis of compounds 39 and 40, the relative orientation of the bridge and the hydroxymethyl translated into the analogous stereochemistry in the platinacyclopentanes. Thus, the stereochemistry should be that shown. Additional evidence for this stereochemistry comes from the similarities in ^{13}C chemical shift data.

Mechanism of ring expansion.

The mechanism of ring expansion of compounds 39 and 40 has been proposed.²¹ It is compatible with the results of ring expansion for these compounds as is shown in Figures 60 and 61. This author has shown to be the case that the stereochemistry of the hydroxymethyl moiety is as shown by NMR spectroscopy and mm2 calculations. The ring expansion begins with protonation of the hydroxy group, then bond migration leading to the olefin

complexes indicated. The stereochemistry of the hydroxymethyl group in the syn and anti compounds must lead to different intermediates since they lead to different products. In the case of the syn substituted platinacycles, the olefin is held up toward the bridge. When the nucleophile attacks the olefinic face opposite the platinum atom, the newly forming carbon platinum bond swings down rotating the nucleophile up, giving the observed stereochemistry, Figure 60. It is possible but not likely that the carbocation shown is formed but, if it is, it either reacts quickly to form the olefinic complex or forms a tight ion pair.

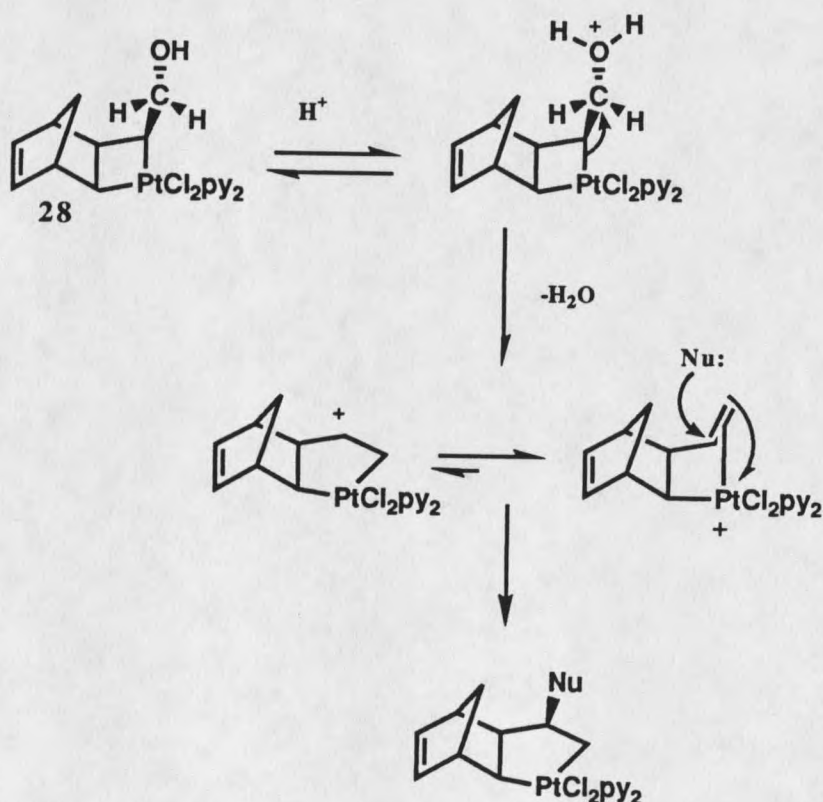


Figure 60. Ring expansion mechanism of syn hydroxymethylplatinacyclobutane.

The ring expansion of compound 29 proceeds by an analogous mechanism. However in this case when the new platinum carbon bond forms the carbon rotates up causing the nucleophile to swing down. This motion results in the formation of the epimeric product.

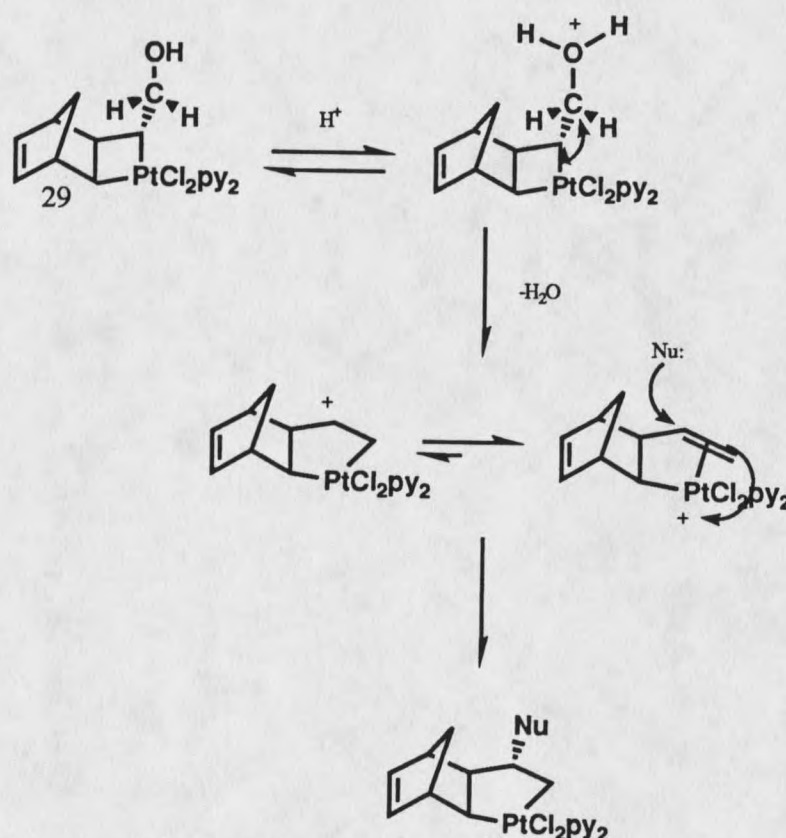
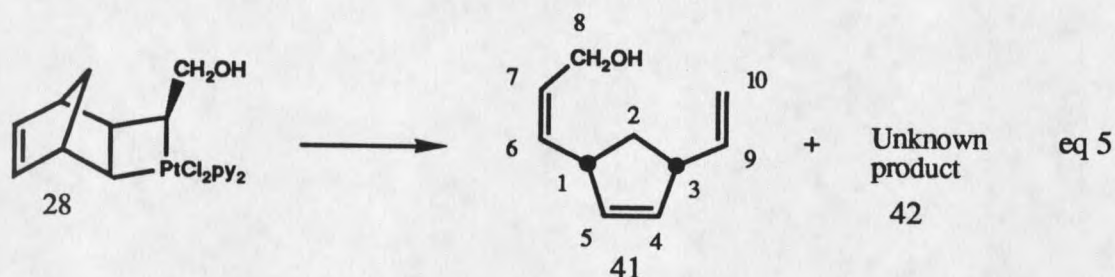


Figure 61. Mechanism of ring expansion for anti hydroxymethylplatinacyclobutane.

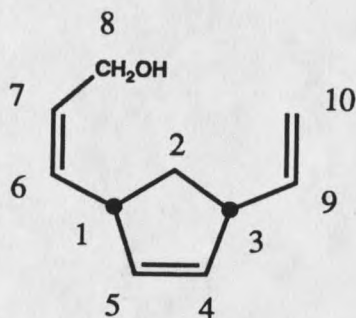
Reaction of compound 28 with diazoalkanes

Diazoalkanes have been shown to react with compounds 11 and 13 to produce cis-1,3-divinylcyclopentanes (see introduction). Following this precedent, diazomethane gas was bubbled into a

chloroform solution of compound 28. The products could be analyzed directly in the NMR spectrometer by doing the reaction in deuteriochloroform or, if desired, the organic products could be isolated by reducing the volume of chloroform and precipitating out the platinum compounds. The supernatant containing the organic products was filtered. Pentane washes extracted any organic products remaining with the platinum species. The combined supernatant and pentane washes contained the organics. The products were shown to be those in equation 5.



The complete ^1H and ^{13}C assignments for compound 41 is given in Table 14. The ^3J coupling constant of 11 hertz for the hydroxymethyl bearing olefin is consistent with cis stereochemistry.²¹ Concerning Table 14 while the proton assignments were made with extensive 1-dimensional decoupling experiments in which it was possible to obtain all connectivities, the ^{13}C assignments were not made with XHcorr experiments but were assigned using chemical shift logic and other information. Thus, their reliability is not certain.

Table 14. ^1H and ^{13}C data for compound 41.

Atom number	^1H	^{13}C
1	3.59	49.6
2 cis to 1	2.34	38.5
trans to 1	1.28	
3	3.28	43.8
4	5.53	134.6
5	5.67	134.3
6	5.38	142.2
7	5.53	136.9
8	4.2	58.7
9	5.77	127.7
10 cis to 9	4.92	113.28
10 trans to 9	5.01	

The unknown product, compound 42, was the subject of an intensive structural characterization attempt but a conclusive result was never obtained. The carbon data for the compound is given in Table 15. The two large coupling constants strongly

suggest a platinacyclic ring larger than 4 members. A reaction with ^{13}C labeled diazomethane revealed that the carbon that came from the diazomethane was one of the carbons with a large 1J carbon platinum coupling constant. The ^{13}C NMR spectrum was carefully examined for coupling that should be present in any resonance that was directly attached to the enriched ^{13}C . None was apparent. Diazomethane is known to insert into platinum chlorine bond or to form ylides.³⁸ If either had occurred in this case, the carbon originating from the diazomethane would have a large platinum coupling constant but would not be coupled to any other resonance. That is observed. Because only one other carbon show 1J platinum carbon coupling and the rest of the ^{13}C spectra indicated that the norbornyl framework was still intact, this meant that the oxygen atom was attached to the platinum. The ^1H NMR spectrum corroborated this contention. Based on this data two possible structures were proposed, Figure 62.

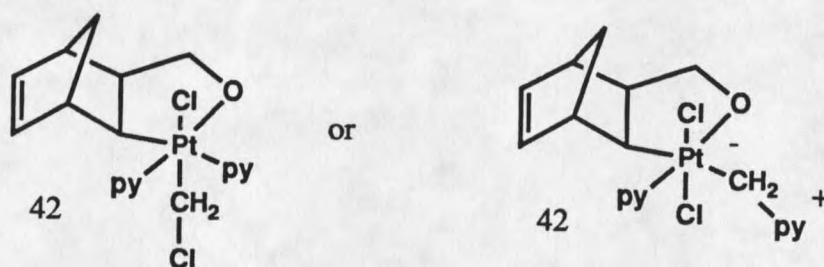


Figure 62. Proposed structures for compound 42.

Table 15. ^{13}C data for compound 42.

^{13}C ppm	$J_{\text{Pt-C}}$	Methylene
29.7		x
31.3	15	x
41.9		
43.0		
45.4		
46.0		x
52.1	587	
64.3	571	x ^{13}C labelled
135.9		
136.8		

Mechanism of diazomethane reaction

Several mechanisms have been proposed for the reaction of diazocompounds with the platinacyclobutanes. The mechanisms are shown diagrammatically in Figures 63 and 64.²¹ Both mechanisms begin with the loss of the pyridine ligand. In the first mechanism, Figure 63, the diazomethane attaches to the platinum and generates a platinum carbene which goes on to form a platinacyclopropane species which reductively eliminates the divinyl product. In the second mechanism, Figure 64, the chlorine migrates cis to the remaining pyridine and the diazomethane

attaches cis to the R group. A bond migration from the platinacyclobutane ring to the diazocompound produces a platinacyclopentane which decomposes to the divinyl product.

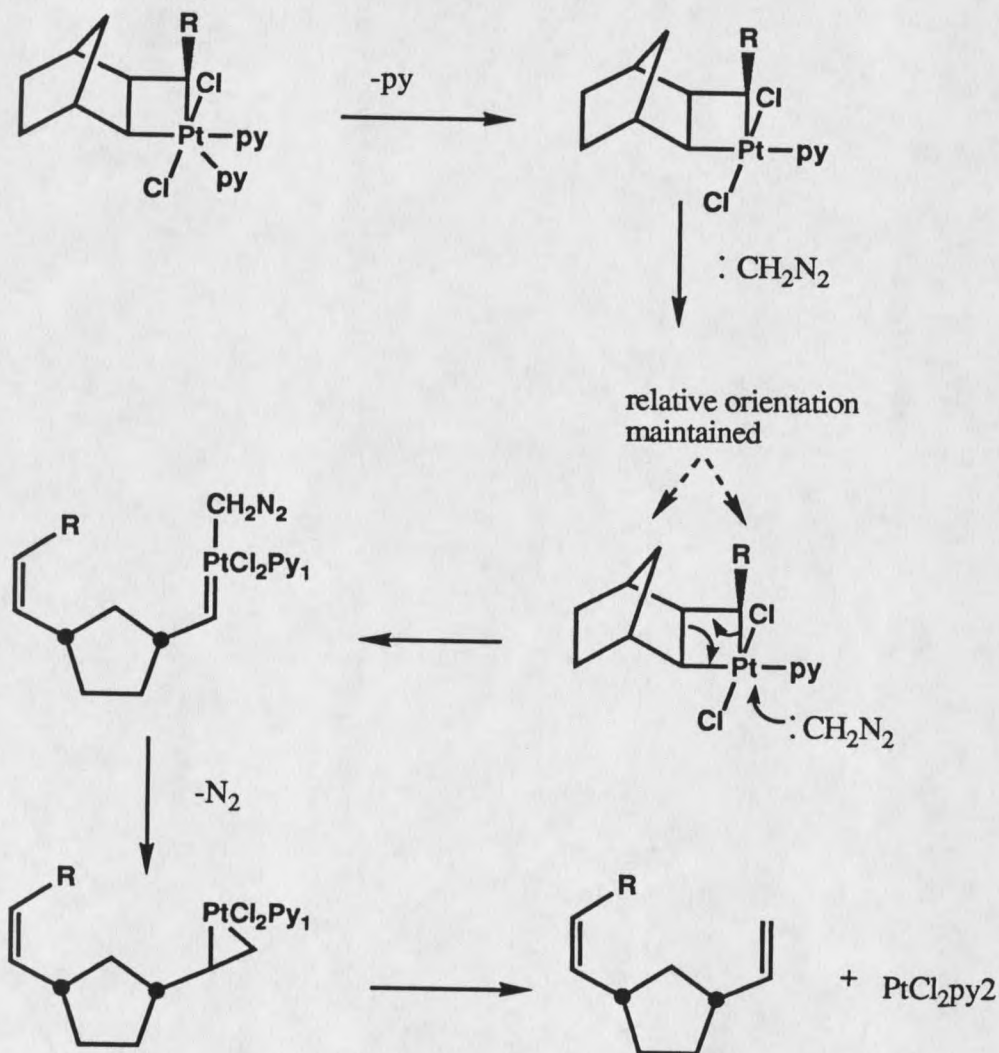


Figure 63. A proposed mechanism for divinyl product formation.

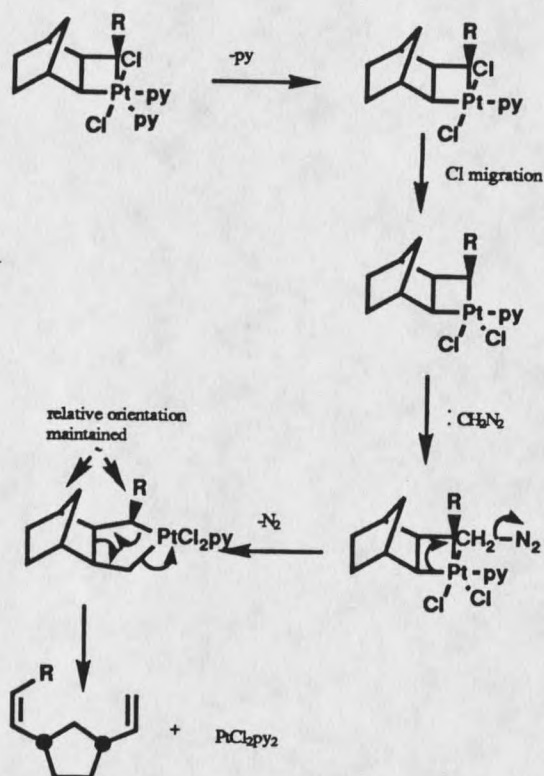


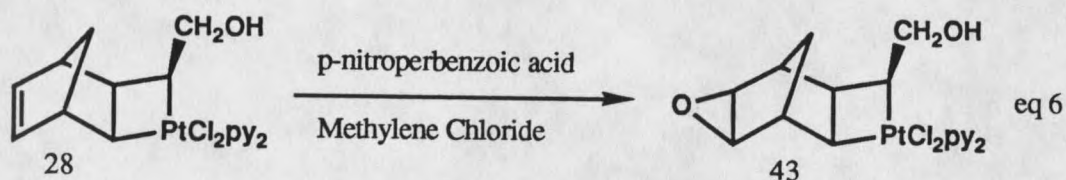
Figure 64. A proposed mechanism of divinyl product formation.

Epoxidation of compound 28.

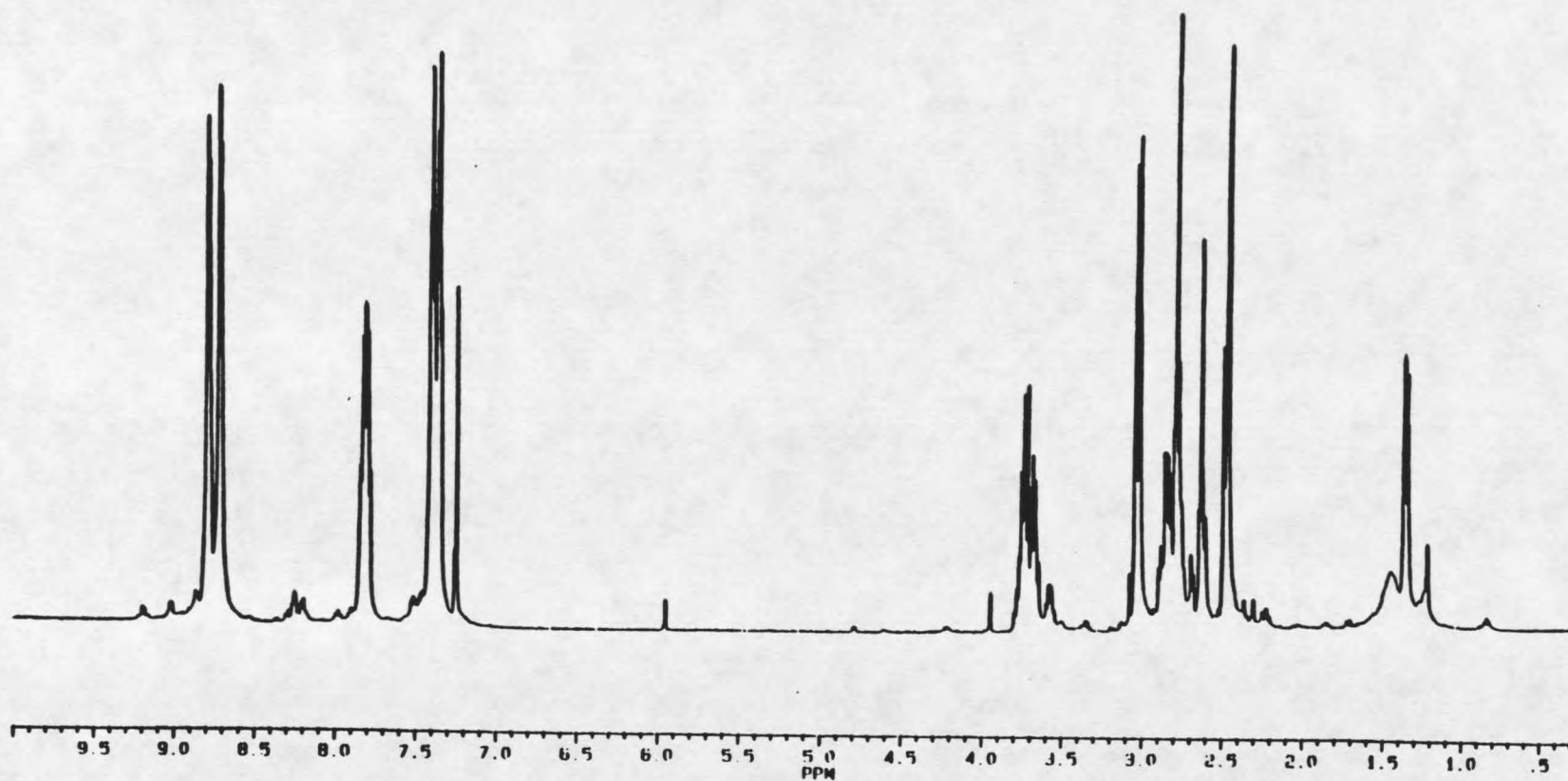
Platinacyclobutanes in general are not very stable compounds. Those of the norbornyl system and simple cyclopropanes seem to be uniquely stable. Thus, it is always of interest to see what type of reaction conditions the platinacyclobutane ring will go through and remain intact. Of course these reaction conditions have a purpose and that is to carry out an organic transformation on the complex.

Compound 28 was reacted with p-nitroperbenzoic acid in the hope of obtaining the epoxide shown as, compound 43, equation 6. This epoxide would be of interest in that it could be used in

further syntheses, such as the production of a diol, which was desired for cancer bioassays. Formation of the epoxide would also show that the platinacyclobutane ring could survive these oxidation conditions. Compound 28 in deuteromethylene chloride was reacted with the perbenzoic acid. The reaction proceeded to completion in less than 5 minutes and was shown to be quantitative by NMR spectroscopy. Methylene chloride was used because the acid by-product is not soluble. The reaction was also done biphasic with the second layer being water buffer. However this later was shown not to be necessary. The epoxide complex was recovered by extracting the methylene chloride with water to remove any excess peracid or p-nitrobenzoic acid. The epoxide yield was repeatedly greater than 90%. Careful water extraction is the key to good yields.



It is somewhat surprising that neither compound 28 nor 43 ring expanded under these conditions because p-nitrobenzoic acid, the byproduct of this reaction, is fairly acidic. The conclusion is that the nature of the acid in the ring expansion reactions may make a difference. In other words, H_2SO_4 may be catalyzing the ring expansion reactions in more ways than just acting as a proton source. Figures 65 and 66 contain the ^1H and ^{13}C NMR spectra for compound 43.



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Figure 65. ^1H spectrum for compound 43.

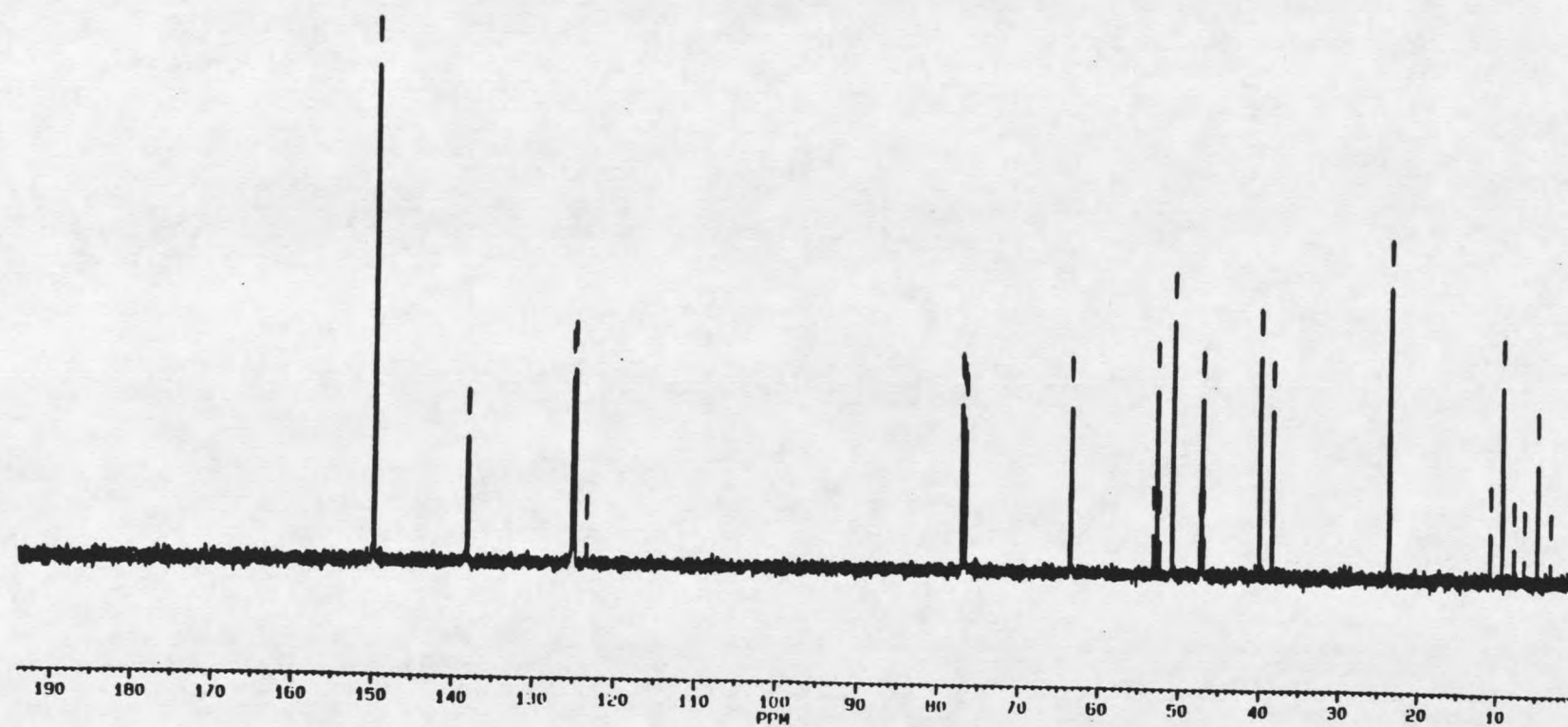
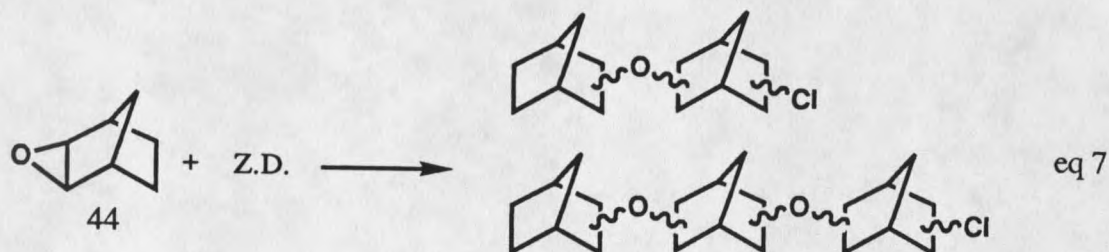


Figure 66. ^{13}C spectrum for compound 43.

Reaction of norbornyl epoxide with Z.D.

As both an attempt to synthesize a four membered ring platinacycle containing oxygen and as a test for the compatibility of Z.D. and epoxide rings, norbornyl epoxide was stirred in ether with Z.D. under stoichiometric conditions, equation 7. The ^1H and ^{13}C data indicated that the norbornyl framework was still intact but a complex series of similar resonances appeared. The mass spectral data indicated that the mixture was actually composed of dimers and trimers of norbornyl epoxide with a chlorine being incorporated regularly in the case of the stoichiometric reaction. A reaction with only a catalytic amount of platinum gave similar results with less chlorine incorporation. Because the reaction produced such a complex mixture further characterization of the products was not attempted.



The two main pieces of information to be gained from this reaction are that Z.D. reacts with epoxides very quickly to produce products other than platinacycles. This of course most likely rules out the prospect of inserting platinum into cyclopropanes in the presence of epoxide functionality.

Platinacyclobutanes derived from
1,4-epoxy-1,4-dihydronaphthalene

As mentioned previously, platinacyclobutanes which are derived from the norbornyl moiety are reasonably stable and can be used as intermediates upon which organic transformations can be carried out. Contrasted to this are the platinacyclobutanes derived from (X.1.0) systems, compounds 25 and 26, which are stable only in neat pyridine.¹⁶ A logical pathway between these two systems would be a system which had the norbornyl topology (assuming that this was the most important factor in the stability of the norbornyl systems) and could be converted to a six membered ring. A system containing a heteroatom at the bridge instead of the methylene unit would still contain, within a small margin of error the norbornyl topology. Knowing from past examples of platinacyclobutane formation that the reactions were compatible with oxygen functionality, the choice of oxygen as the heteroatom to replace the methylene unit was made because these systems were easily synthesized and the opening of the oxygen ring would produce a substituted 6-membered ring system, Figure 67. 7-Oxabenzonorbornene was readily available and routes to other similar systems were known. Thus the preparation of platinacyclobutanes derived from 7-oxabenzonorbornene was attempted. Simultaneously for comparison purposes the

preparation of platinacyclobutanes from the analogous system with a methylene bridge, benzonorbornene, was attempted.

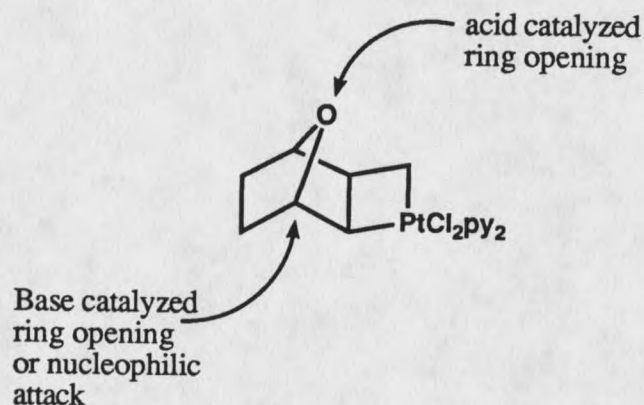
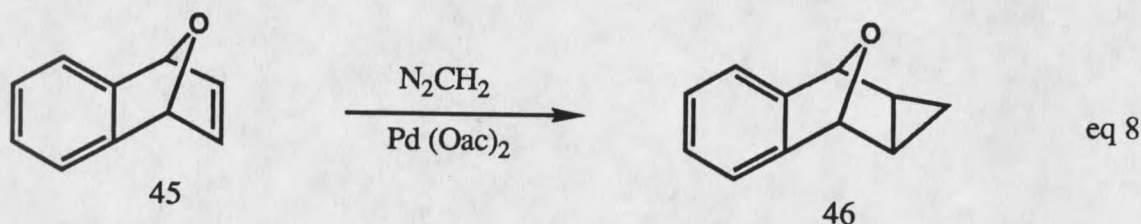


Figure 67. Ring opening of oxygen bridged platinacyclobutanes.

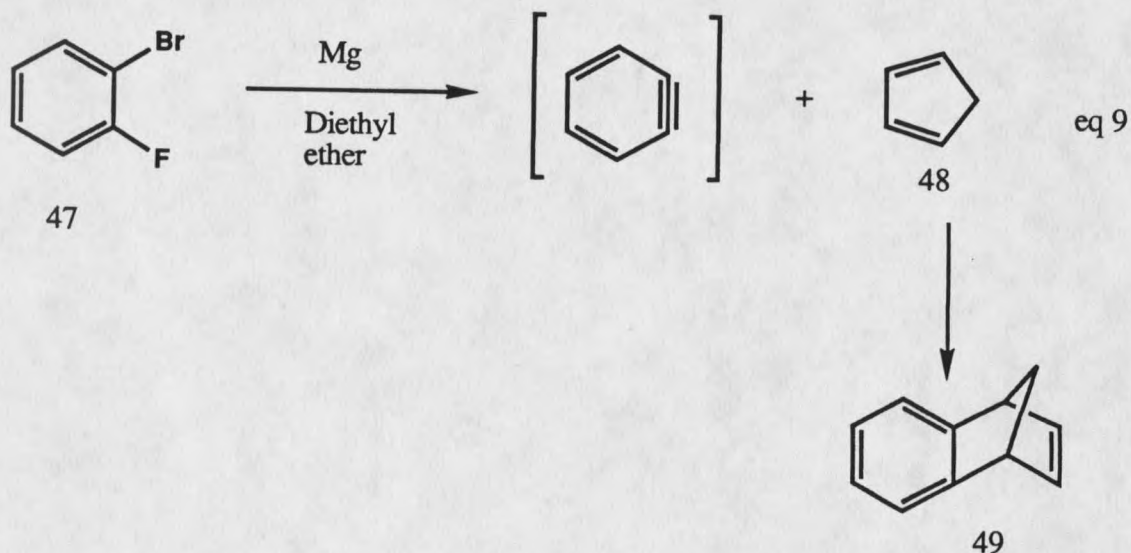
Synthesis of the cyclopropanes derived from 7-oxabenzonorbornene and benzonorbornene

7-Oxabenzonorbornene, compound 45, was cyclopropanated to produce compound 46 in quantitative yield, equation 8. Benzonorbornene was also prepared, equation 9, and cyclopropanated, equation 10.

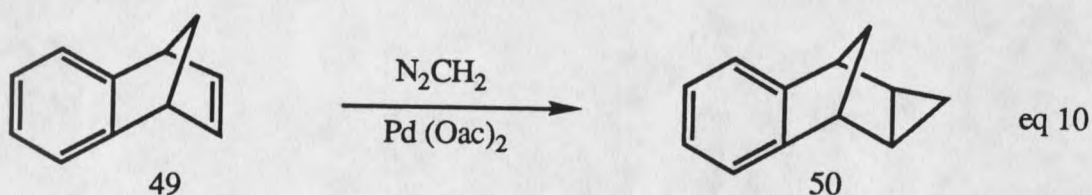


The methylene bridge analog of compound 45, compound 49, was not available but was synthesized via what is proposed to be a benzene intermediate according to reference⁸⁹ in approximately 70% yield. Bromofluorobenzene was reacted with magnesium

metal in ether and a ethereal solution of freshly cracked dicyclopentadiene was slowly introduced with heat as the catalyst. Compound 49 was isolated after silica gel chromatography.



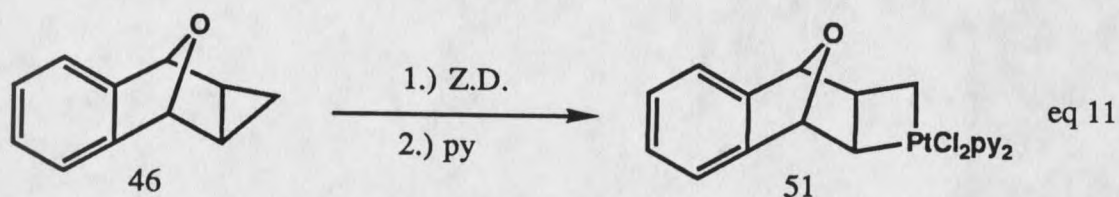
Compound 49 was cyclopropanated in quantitative yield with diazomethane using palladium acetate as the catalyst, equation 10.



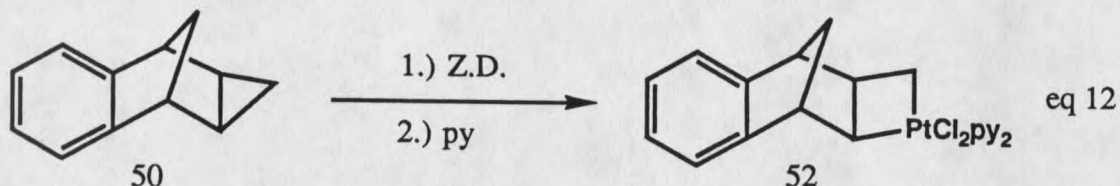
Synthesis of platinacyclobutanes derived from compounds 46 and 50.

To Z.D. in ether was added one equivalent of compound 46 and the mixture was allowed to stir for 8 hours. I.P.C. formation was observed as is usual for this reaction. However, the color of the

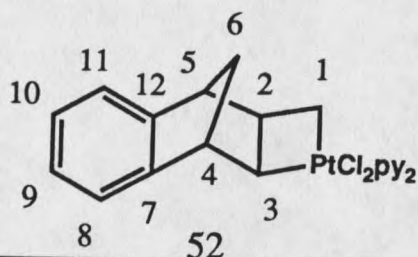
I.P.C. was not the yellow color as seen in those derived from norbornene but a brown color. The tetrameric complex was reacted with pyridine to form compound 51, equation 11.



Compound 50 also reacted with Z.D. and the monomeric complex of pyridine formed exactly as in the case of compound 51 above. The I.P.C. was a tan color and not nearly as dark as that formed from compound 46, equation 12.



The ^1H and ^{13}C data for compounds 51 and 52 are summarized in Table 16 and the individual spectrum are given in Figures 68 and 69, respectively. A saturated solution of compound 52 in chloroform was placed in a pentane diffusion chamber and x-ray quality crystals were grown. The ortep drawing is shown in Figure 70.

Table 16. ^{13}C data for compounds 51 and 52.

Cpd #/ ^{13}C ppm	51(JPt-C)	52(JPt-C)
1	-6.39(364)	-5.7(365)
2	52.36(96)	56.6(97)
3	5.37(440)	10.1(408)
4	80.7(16.1)	47.9(9)
5	82.5(23.5)	48.8(25)
6		45.9
8 or 11	118.2	120
8 or 11	119.5	121.1
9 or 10	125.9	125.5
9 or 10	126.3	147.7
7	144.2	147.7(37)
12	153.2	153.6
py-o	149.5,149.2	159.5
py-p	138.1,138	148.8
py-m	125.2,125.1	153.6

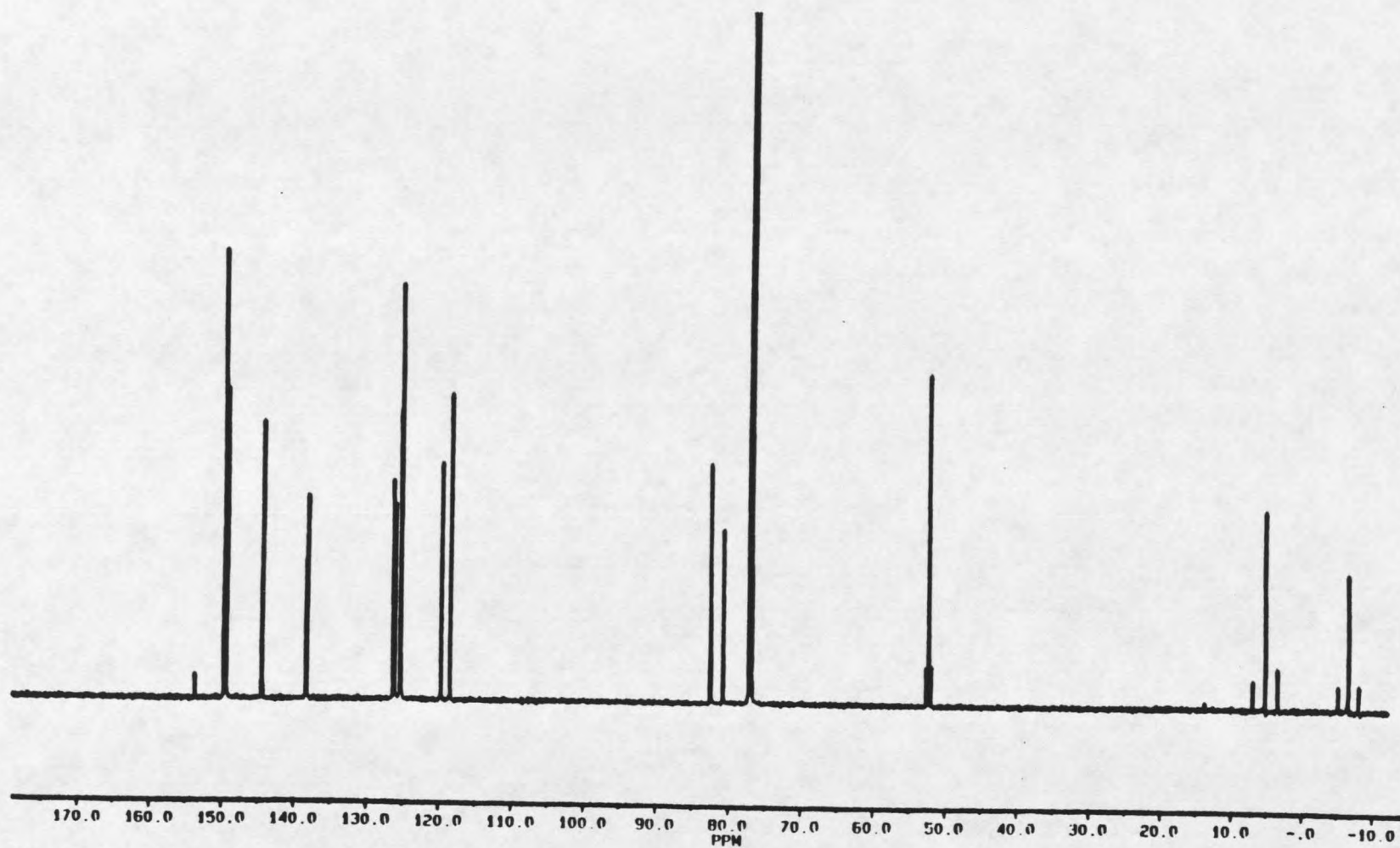


Figure 68. ^{13}C spectrum of compound 51.

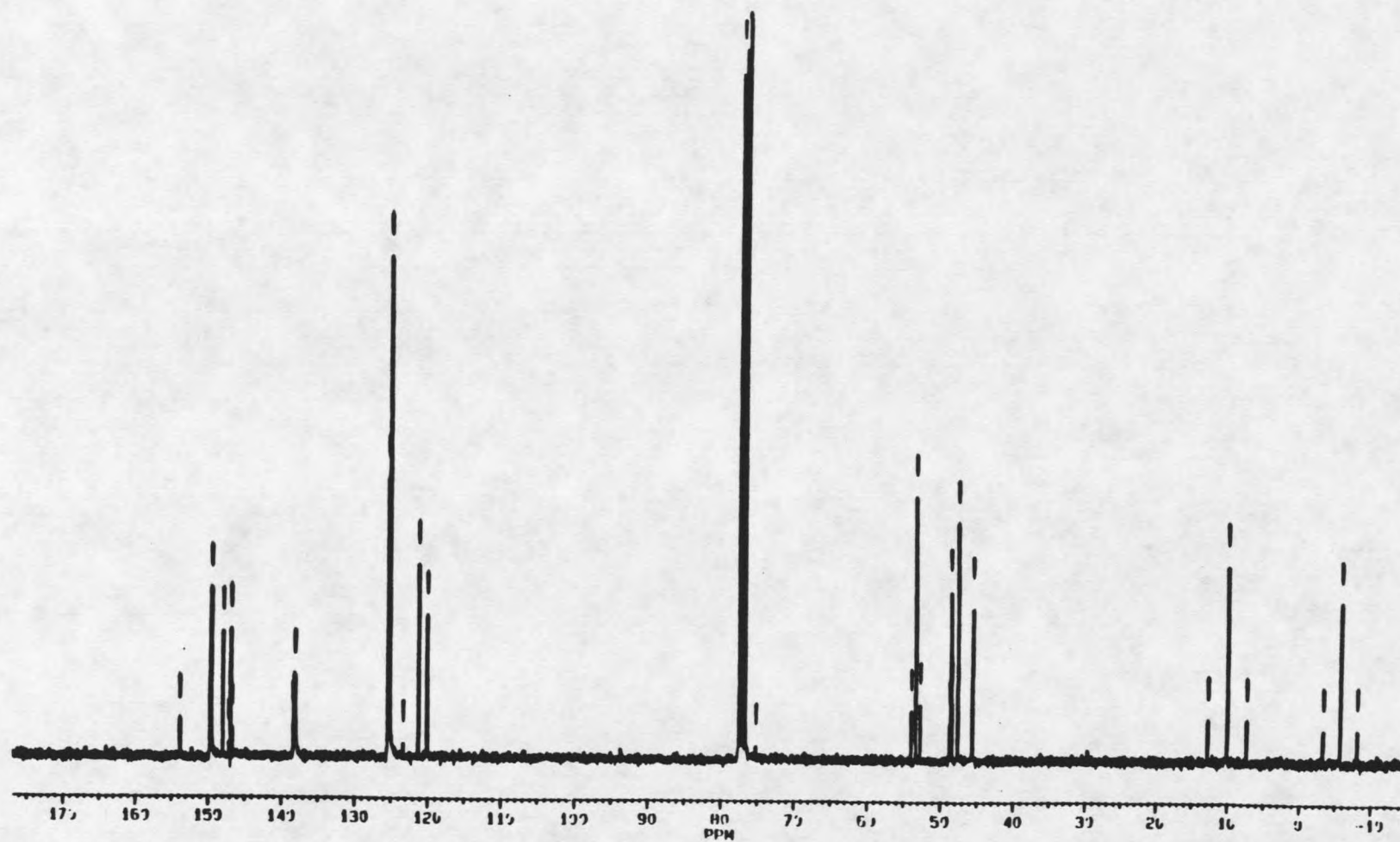
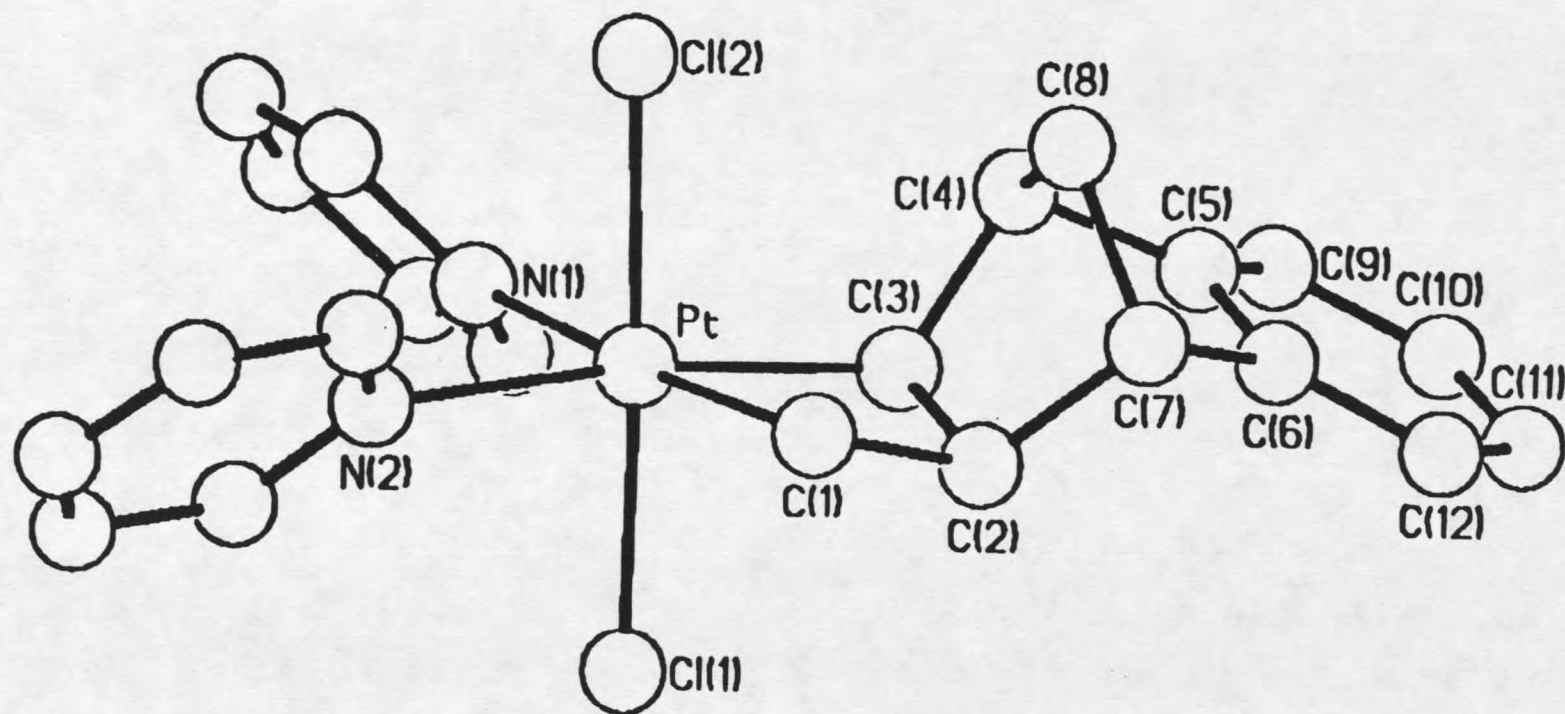


Figure 69. ^{13}C spectrum of compound 52.

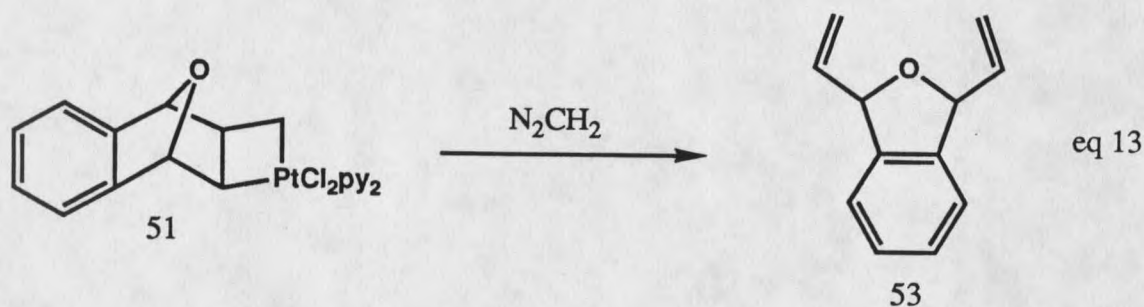


105

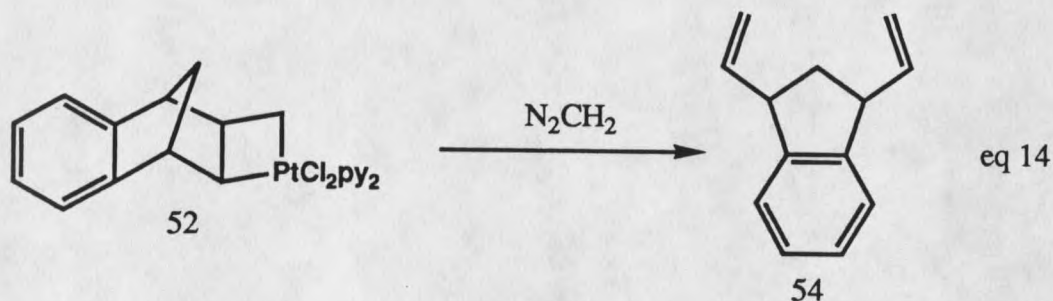
Figure 70. Ortep drawing for compound 51.

Reactions of compound 50 and 51 with diazomethane

To a solution of compound 51 in deuteriochloroform was bubbled in diazomethane gas with nitrogen gas as the carrier, equation 13. The reaction was analyzed by NMR spectroscopy. Judging by the characteristic olefinic peaks, product 53 was produced but no further purification was undertaken.



Compound 52 was reacted with diazomethane and analyzed for 54 exactly as described above for compound 51 and 53, equation 14. Proton data for these compounds are given in the experimental section.



To this point all reactions involving either the oxygen bridged compounds or the methylene bridged compounds had given virtually identical results. Certainly there were no differences that were not attributable to experimental variability. Thus, the

conclusion was reached that the oxygen bridge could replace the methylene bridge with no significant differences in the cyclopropanation reaction, the platinum insertion reaction or the reaction of the platinacyclobutanes with diazomethane. Since compounds derived from the 7-oxabenzonorbornene systems were the ones of most interest the companion study of the systems derived from the benzonorbornene systems was terminated.

Reaction of compound 54 with ethyl diazoacetate

The reaction of prochiral diazo compounds such as ethyl diazoacetate with compounds 11 and 13 had been shown to introduce a second olefin with functionality. It was originally hoped that additional stereochemistry might also be the result because of steric interaction with the hydroxymethyl group depending on the nature of the reaction mechanism. However, the second olefin was produced in approximately 1:1 E to Z ratio, Figure 71.

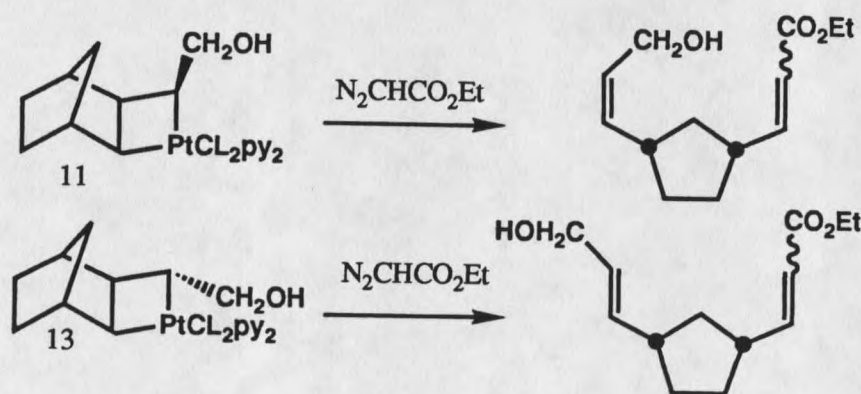
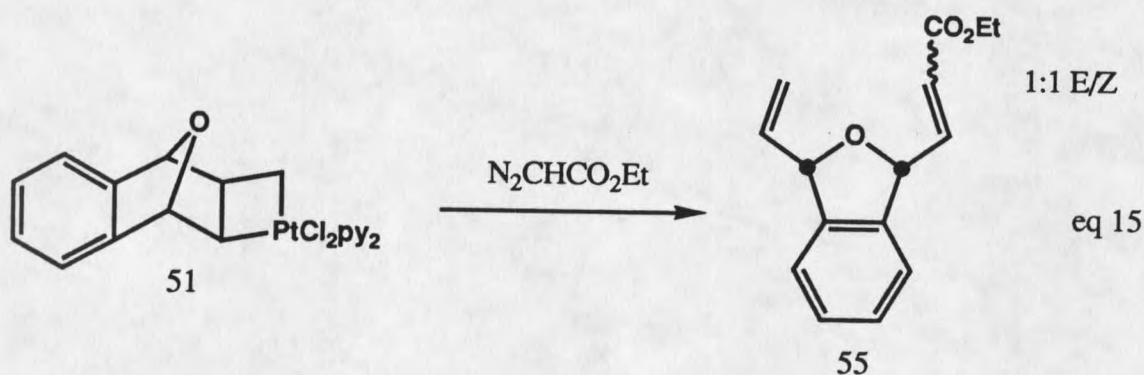


Figure 71. Reaction of ethyl diazoacetate with compounds 11 and 13.

Compound 51 was reacted with ethyldiazoacetate to test if the oxygen bridge had any influence on the outcome of the stereochemistry of the olefin containing the carboethoxy group. Again the stereochemistry was approximately 1:1 E to Z indicating that the oxygen bridge had no substantial effect on the outcome of the reaction, equation 15.



Synthesis and chemistry of syn and anti hydroxymethyl-7-oxabenzonorbornyl platinacyclobutanes.

Compound 45 was cyclopropanated by a modification of the method of Doyle, Figure 72.²⁰ In stark contrast to the accepted method of slow addition of ethyldiazoacetate to a solution of compound 45 and the catalyst, rapid addition of the ethyldiazoacetate gave the best results, 98% yield of the epimeric esters compounds 56 and 57. These esters are not soluble in ether and precipitate out of the ether solution and can be collected essentially pure by filtration. A large number of reducing agents and conditions were tried to produce compounds 58 and 59. However the best conditions were those originally tried: LAH in ether which gave a low yield 0-10% of the epimeric alcohols 58

and 58. Compound 57 was destroyed faster than compound 58 in the reduction process and thus only small amounts of compound 59 was produced.

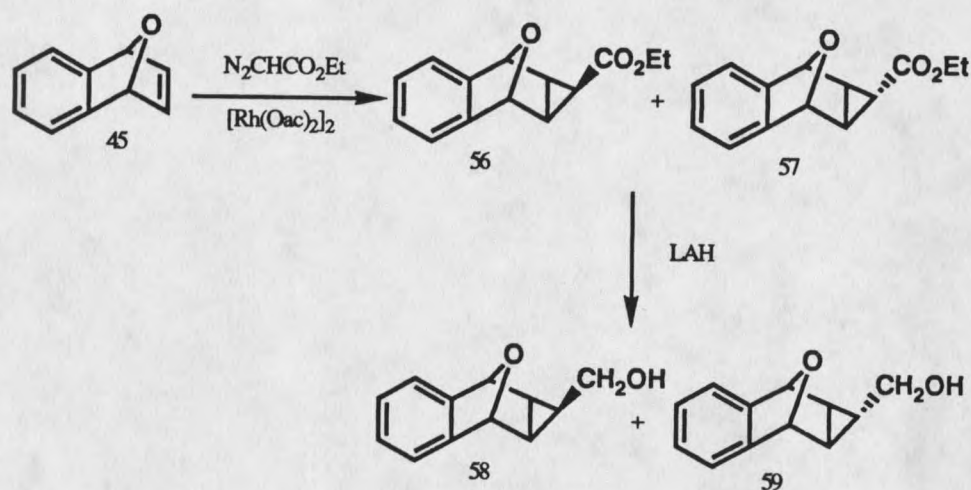


Figure 72. Synthesis of compound 58 and 59.

Compounds 58 and 59 were reacted with Z.D. to produce the platinacyclobutanes as shown in Figure 73. The methodology applied here is the same as was used for compounds 30 and 31.

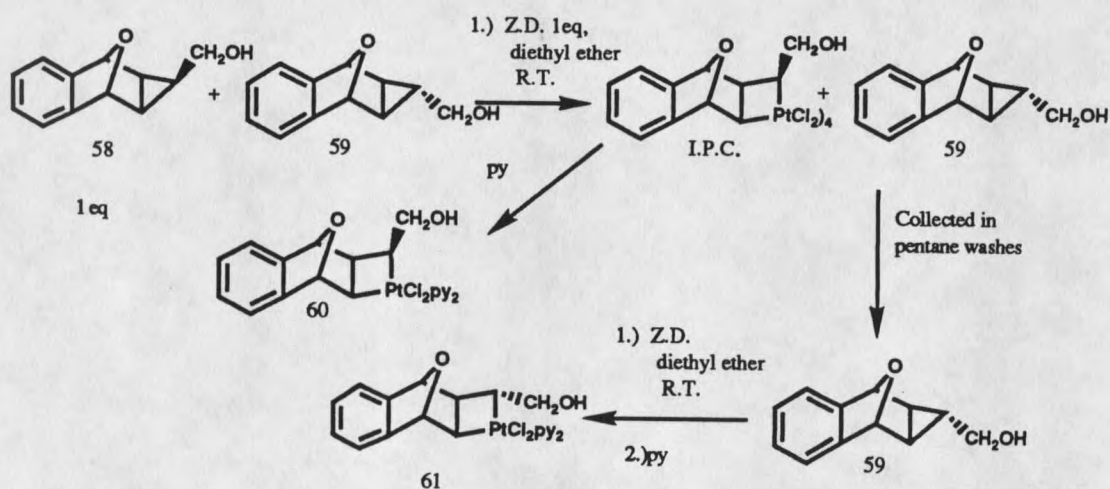
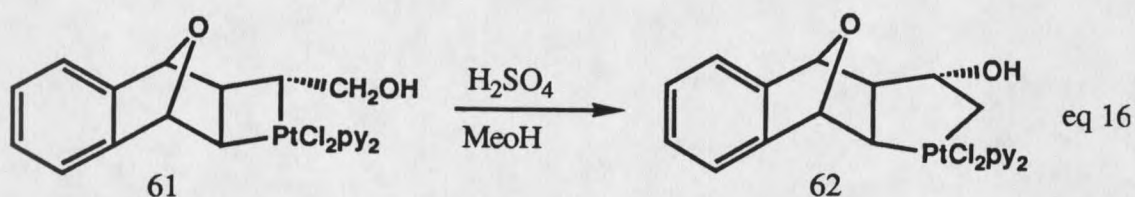


Figure 73. Synthesis of compounds 60 and 61.

The spectral data for the compounds in Figure 73 are given in the experimental section.

Ring expansion reaction of compound 61.

As mentioned above the yield of compound 58 was so low that the ring expansion reaction was done only on compound 61. Compound 61 ring expanded cleanly in methanol with a catalytic amount of H_2SO_4 to give compound 62, equation 16.



The structure of compound 62 was based on ^1H and ^{13}C NMR spectroscopy. The stereochemistry was based on the precedent that, in all ring expansions seen in this work as well as in that of Nielsen and Jennings, the anti platinacyclobutane yields the anti substituted platinacyclopentane (see experimental section).

Summary

Platinacyclobutanes can be prepared from both 7-oxabenzonorbornyl systems and benzonorbornyl systems with equal facility. Both compounds react with diazomethane to produce divinyl substituted systems. The stereospecific ring expansion reaction observed with other hydroxymethyl substituted platinacyclobutanes occurs in the 7-oxabenzonorbornyl system. However, the reduction of an ester functionality in the presence of the oxygen bridge leads to a drastically reduced yield. We can

conclude that the oxygen bridge does not make a significant difference compared to the methylene bridged systems as far as the formation of platinacyclobutanes and platinacyclopentanes is concerned. However the oxygen bridged molecules may be sensitive to reagents that the methylene bridged systems are not and this must be taken into consideration when planning synthetic strategies. The oxygen bridged systems have several useful characteristics. They can be converted into other systems by ring opening reactions. They can be synthesized from Diels-Alder reactions with furans and an appropriate dienophile. Many variously substituted furans are available in contrast to cyclopentadiene systems.

Synthesis, characterization, and chemistry of platinacyclobutanes derived from acenaphthalene.

The question has arisen "what is it that make the platinacyclobutanes derived from the norbornyl systems so stable compared to those of the (X.1.0) systems?" Further why do the platinacycles derived from the norbornyl systems seem to insert platinum in such high yields compared to the simple cyclopropanes? We thought that the first question could be addressed if we attempted to prepare platinacyclobutanes from a planar system that contained a five membered ring. When one looks at the topology of the norbornyl systems one sees that maybe it is the fact that the substituents on the cyclopropane ring are tied back that makes them stable. This led us to the idea that platinacycles prepared from acenaphthalene might also be stable.

In addition, there was another reason for attempting to make platinacycles from acenaphthalene. There are natural products which contain the naphthalic systems shown in Figure 74 and which had not been readily prepared from other routes. They can be synthesized from the product of the reaction of diazomethane and the platinacyclobutane derived from acenaphthalene.

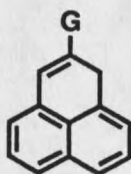
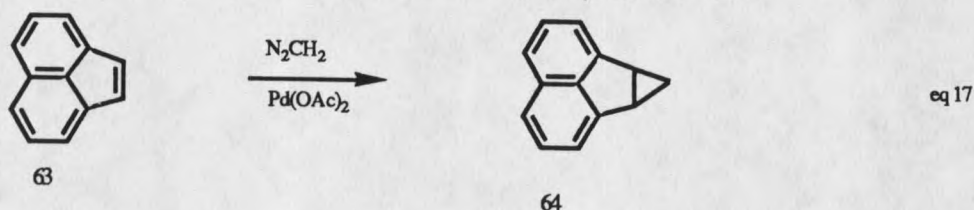


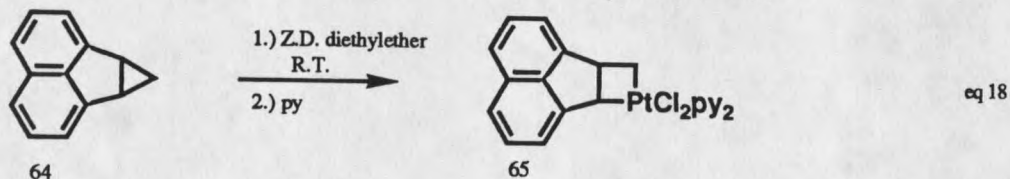
Figure 74. Potential synthetic targets.

Synthesis of platinacyclobutane derived from acenaphthalene.

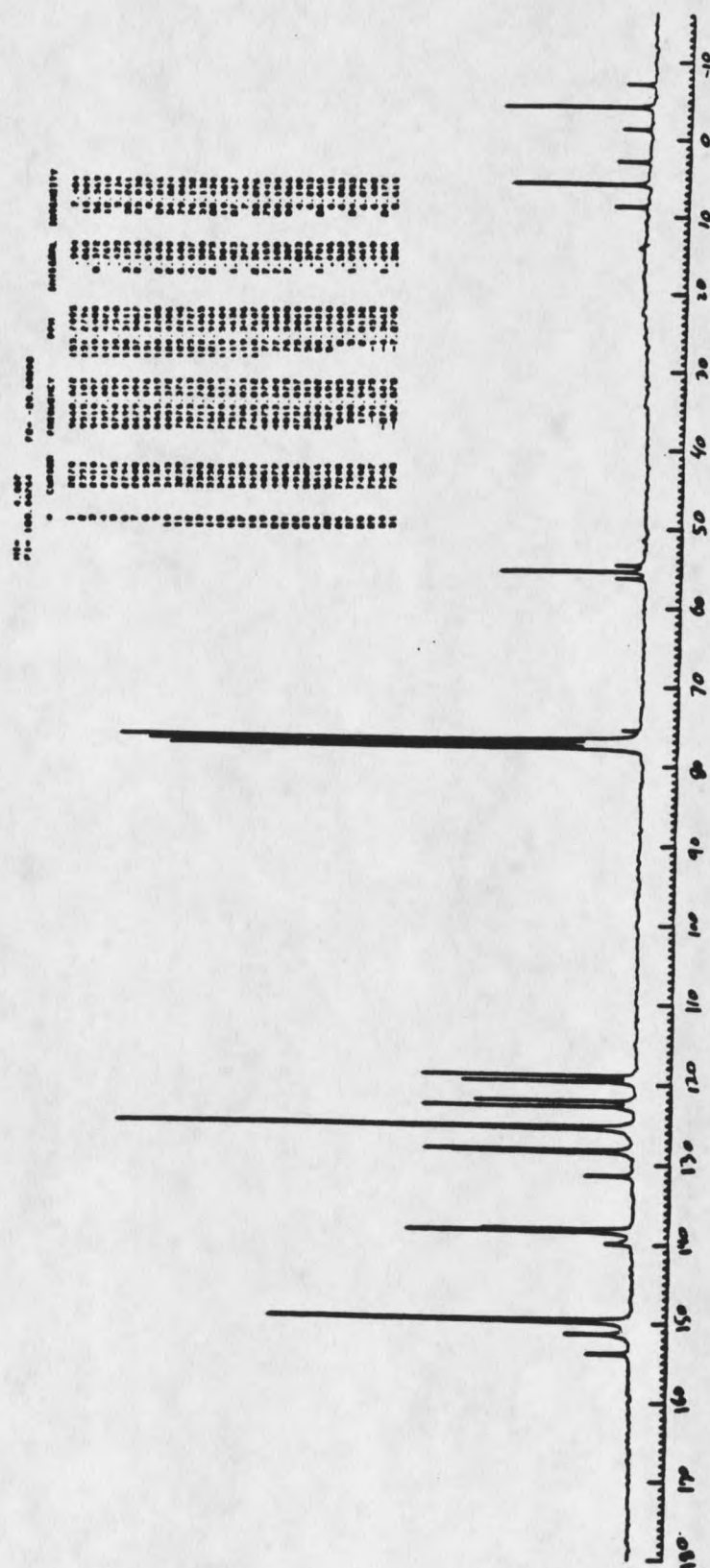
Acenaphthalene, compound 63, was cyclopropanated using diazomethane with palladium acetate, equation 17.



Compound 64 was isolated in quantitative yield after filtering the catalyst and removing the solvent under low vacuum. Platinum was next inserted into the cyclopropane compound 64 by stirring in ether in the presence of Z.D. equation 18.

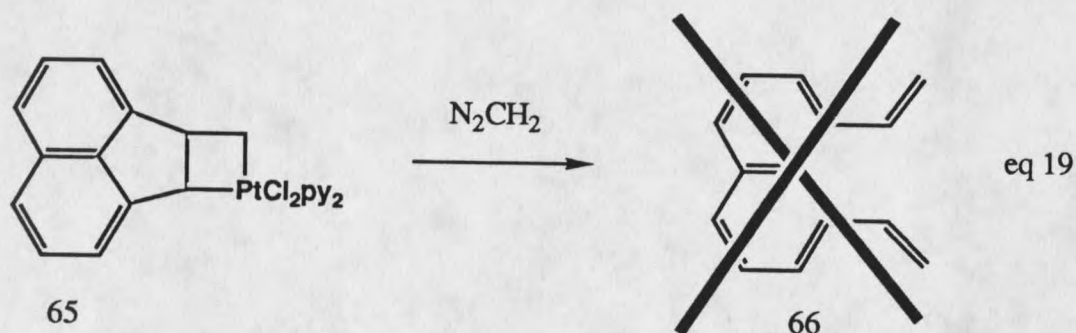


The ^{13}C data for compound 65 is shown in Figure 75.

Figure 75. ^{13}C spectrum compound 74.

Reaction of compound 65 with diazomethane

Into a chloroform solution of compound 65 was bubbled diazomethane with nitrogen gas as the carrier. The disappearance of starting material was noted. However divinyl product was not produced, equation 19. Instead some polymeric material was produced which was not fully characterized. After the fact, it is probably not surprising that when one aims to produce what is essentially a pair of styrene molecules joined together that polymeric material results.



An attempt was made to make the hydroxymethyl substituted platinacyclobutanes to see if these compounds might be better candidates for the production of the divinyl species. These compounds would also be of interest to see if the acenaphthalene system would undergo the ring expansion reaction seen in the introduction. The epimeric hydroxymethylcyclopropanes derived from acenaphthalene were synthesized as shown in Figure 76.

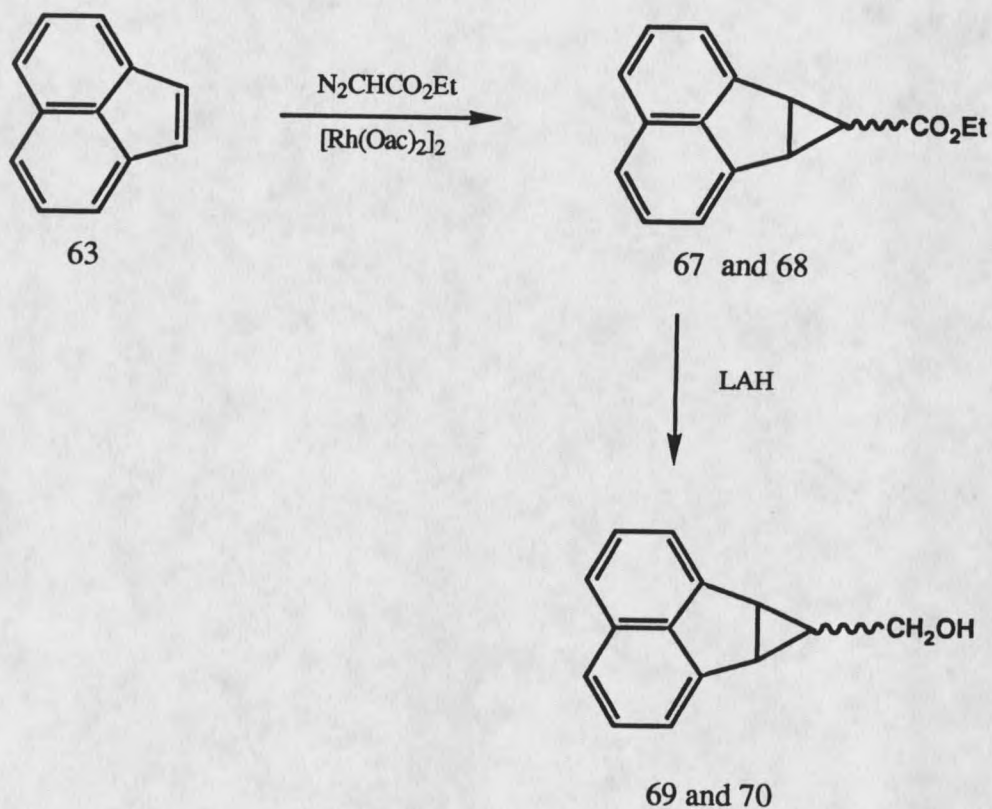
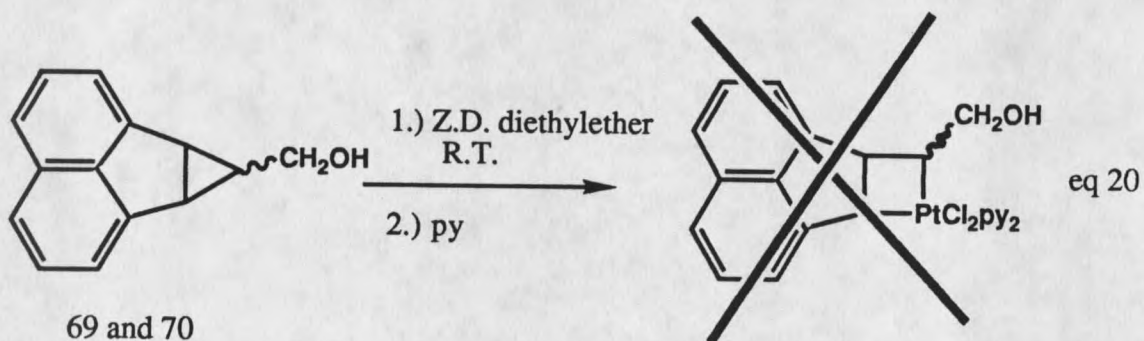


Figure 76. Synthesis of compounds 69 and 70.

A mixture of the epimeric alcohols 69 and 70 was reacted with Z.D. in ether; however, no insertion products were observed.

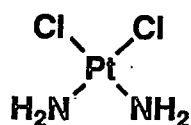


In conclusion, retrospectively, it was easy to see why the divinyl compound was not the expected product in the reaction of compound 65 with diazomethane. As mentioned previously the divinyl compound could have been made but only polymeric products could be isolated. It is not so easy to explain the fact that the epimeric mixtures of 69 and 70 would not insert platinum(II) when the analogous compounds derived from norbornene or norbornadiene do in good yield. The most logical conclusion is that the norbornyl cyclopropanes are more strained than this system.

Chemotherapeutic application of platinacyclobutanes

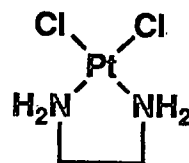
Introduction

As mentioned in the introduction, there exists a commonly used chemotherapeutic agent cis platinum, Figure 77. A slight variation on the theme of cis-dichlorodiamino platinum(II) is dichloroethylenediamine platinum(II), Figure 75. This compound was tested in several assays and exhibits less activity than cis platinum but nonetheless its activity is significant. Many structure activity studies have been done in which the ligand on the platinum, especially the amino groups had been varied in almost every conceivable way in an attempt to increase the activity of cis platinum. Some success has been achieved but little in terms of the effort involved in the studies (author's opinion). Thus a new approach was needed.



cis-dichloro-diaminoplatinum (II)

7



dichloroethylenediamine platinum (II)

71

Figure 77. Structure of compound 7 and 71.

Cis platinum has several side effects that make its use less desirable. These include nephrotoxicity, ototoxicity, and nausea. These problems are at least in part due to the compounds' low water solubility. The compound has to be given intravenously because it will not be absorbed in the gut. This lowers its bioavailability.

A platinum(IV) carrier complex of platinum(II) was envisioned that could reductively eliminate an active platinum(II) molecule like cis platinum, compound 7, or dichloroethylenediamine platinum (II), compound 71. Under the appropriate conditions, we might have a reasonable approach to solving some of the problems associated with the use of cis platinum. The platinum(IV) carrier molecule would need to have several important chemical characteristics. One, it would have to reductively eliminate the desired platinum(II) complex at the desired location and time. Two, the platinum(IV) carrier molecule itself could not be significantly toxic and probably would need to be much more water soluble than cis platinum to overcome cis

platinum side effects. Three, the reductive elimination would have to result in a platinum(II) with cis dichloro ligands.

Platinacyclobutanes seemed like an ideal candidate for such a system. The norbornyl framework would be used as the carrier molecule and could be modified to make the complex more water soluble, Figure 78. Ethylene diamine could be used as a ligand to guarantee the reductive elimination product would have the desired cis stereochemistry.

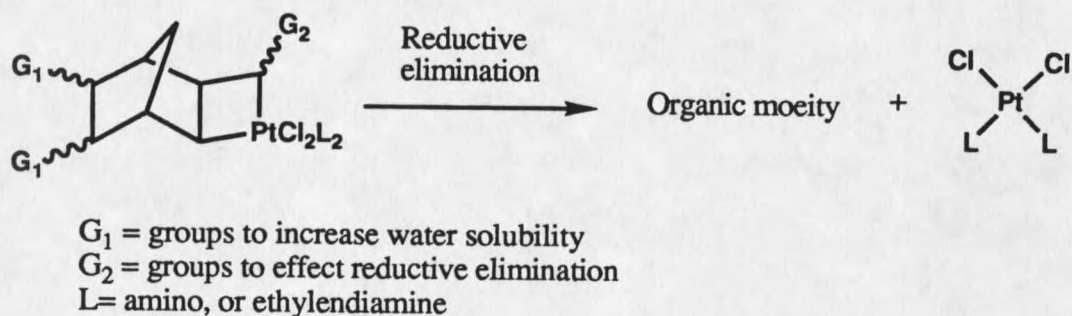
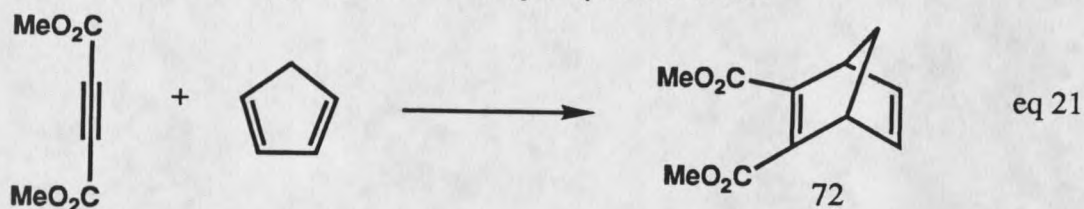


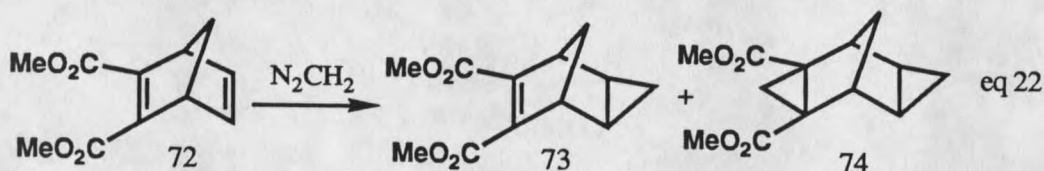
Figure 78. Idealized platinum(II) carrier molecule.

A key consideration in the design of this drug was and still is causing the reductive elimination where and when it is desired. For solid tumors of the skin topical application with ultraviolet light as the initiator would be possible. γ -Radiation during normal radiation treatments was another possibility. Heating the molecule to 50k might also work. Other possible methods include biological methods such as the body's natural heavy metal scavenging systems or detoxification pathways. The first step however was to synthesize a platinum(IV) molecule with the desired water solubility and test its toxicity.

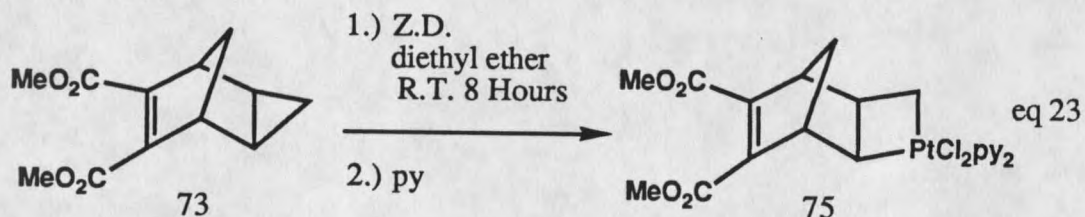
Compound 72 was synthesized according to equation 21. Dimethylacetylenedicarboxylate was condensed in a Diels-Alder reaction with freshly cracked dicyclopentadiene.



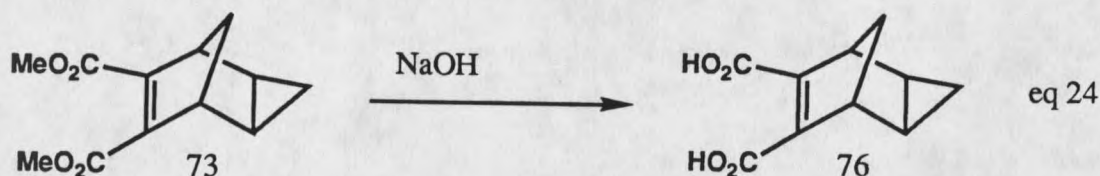
Compounds 73 and 74 were produced when 72 was cyclopropanated with diazomethane, equation 22. Compounds 73 and 74 could be readily separated by careful chromatography using pentane elution on silica gel (dry the silica gel completely).



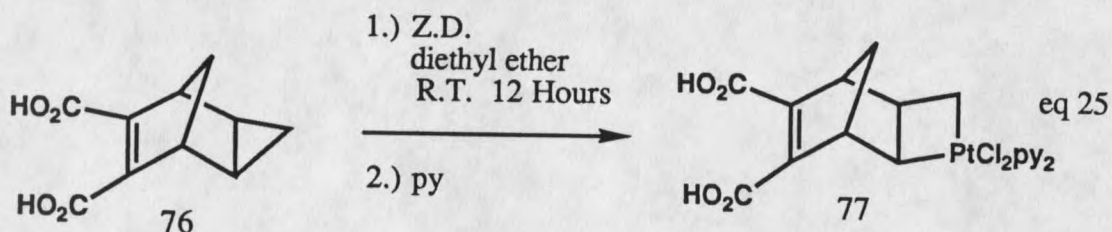
Compound 75 was synthesized according to equation 23. Thus, the platinum complex which still had the diacid functionality protected as the dimethyl ester was the first cyclopropane of the series into which platinum was inserted as a test to make sure platinum would insert into these systems, equation 23.



The lowest yielding step of this pathway is the hydrolysis of the dimethyl esters in compound 73 to produce the diacid analog, compound 76. The reaction takes strongly basic condition with yields being approximately 50%, equation 24.

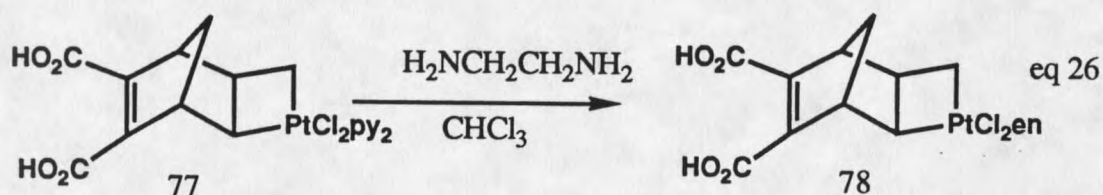


Platinum could be inserted into compound 76 but the reaction is sensitive to impurities such as the presence of the dicyclopropanated product. To a solution of 76 in ether was added Z.D. and stirred 12 hours at room temperature, equation 25. A fluffy yellow I.P.C. precipitated out of solution and upon ether removal, the solid was washed three times with pentane. A small amount of chloroform was added to which pyridine was next added to break-up the tetrameric complex forming the chloroform soluble monomer, compound 77. The complex 77 was triturated with pentane and washed again three times with pentane. The purity was high as could be checked by NMR spectroscopy.



Ethylenediamine can be added directly to the I.P.C. produced in equation 25 resulting in the production of compound 78. However, if this method is used it is difficult to purify 78

because it is not readily soluble in organic solvents other than DMSO. Thus, compound 78 was made and purified as shown. Ethylenediamine was then added to a chloroform solution of 77 and the complex 78 immediately precipitated out of solution, equation 26. Compound 78 was washed three times with pentane and triturated to remove pyridine.



Complex 78 was adequately water soluble for bioassays involving *Salmonella*. However, NMR spectroscopy was most easily achieved if a water solution was made slightly basic which increased the solubility of compound 78 immensely. The NMR spectroscopy could also be done on a solution of compound 78 in DMSO. The spectroscopic data for compound 78 is given in the experimental section.

The spectroscopic data given in the experimental section can be compared to that for the platinacyclobutanes shown in Tables 8, 9, 10, and 11. It contains all the characteristics generally found in platinacyclobutanes. The 1J platinum carbon coupling constants are in the range of 350 to 425 hertz. These carbons resonate upfield as is usually the case for platinacyclobutanes. The bridge carbon and the bridgehead carbons come in the correct chemical shift range. The ethylene diamine carbons are not chemical shift equivalent and appear around 40 ppm.

Salmonella bioassays of compound 78.

Bioassays using *Salmonella* containing plasmid pkm101 were performed according to the method of Ames.⁹⁰ These assays are reversion assays and are used to measure a compound's ability to damage DNA. When DNA damage occurs error prone repair results in mutant revertants which can live on the nutrient deficient media whereas the non-mutants cannot. Several controls are usually run in these experiments, for example, a background control to pick up spontaneous reversions and a control using compound 71 as a control to verify that the *Salmonella* are sensitive to a known mutagen.

Two different experiments were performed using two strains of bacteria, TA100 and TA102, hereafter referred to as strain 100 and 102. In the first type of experiment the bacteria were mixed in the top agar containing nutrient media. The compounds were placed on a disk which is located in the center of the plate. As the compound diffuses from the disk, a kill zone is created where the compound is above toxic levels. Where the compound is of sufficient concentrations to cause mutations a reversion zone is formed. Usually this test is not quantitative but can measure whether or not the compound is toxic as judged by the size of the kill zone. The presence of a reversion zone indicates that the compound is mutagenic.

Compound 78 when compared to cis platinum showed some toxicity in these assays, but the kill zone for 78, typically 4-5 mm, was less than that of cis-platinum, typically 6-7mm. It

should be remembered that this is also a measure of the compound's ability to diffuse out of the disk and into the media. A reversion zone for both compounds was noted especially in strain 100. If the compound was heated in boiling water the mutagenic activity was enhanced.

Because 78 exhibited some mutagenic activity, especially in strain 100, in these initial tests and was not extremely toxic to the cells, a second type of experiment which is quantitative was run. This experiment is performed by adding the compound directly to the mixture of the bacteria and the top agar containing nutrient deficient media. The number of cells on a plate can then be counted. Dose-response curves indicate that the compound is active. Background plates are also usually run. Figures 79 and 80 contain the data for an experiment in which compound 78, compound 78 which had been heated in boiling water for five minutes, and compound 78 which had been placed under a UV lamp for 120 minutes were tested in both strains 100 and 102. The x axis of these graphs is the number of microliters of a 0.01 molar solution added to the plates. The y-axis is the average value obtained from three replicates at each concentration.

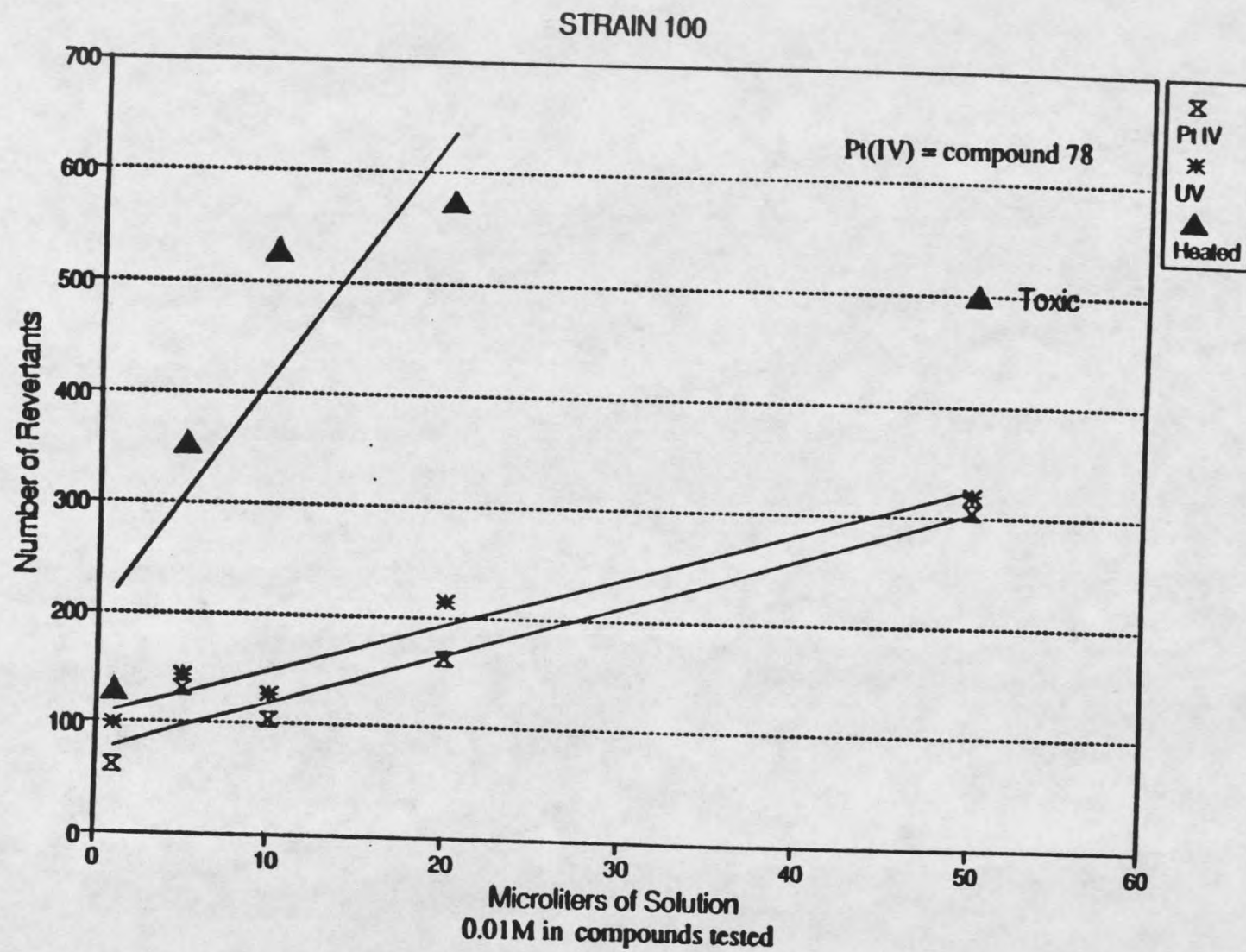


Figure 79. Bioassay result for strain 100.

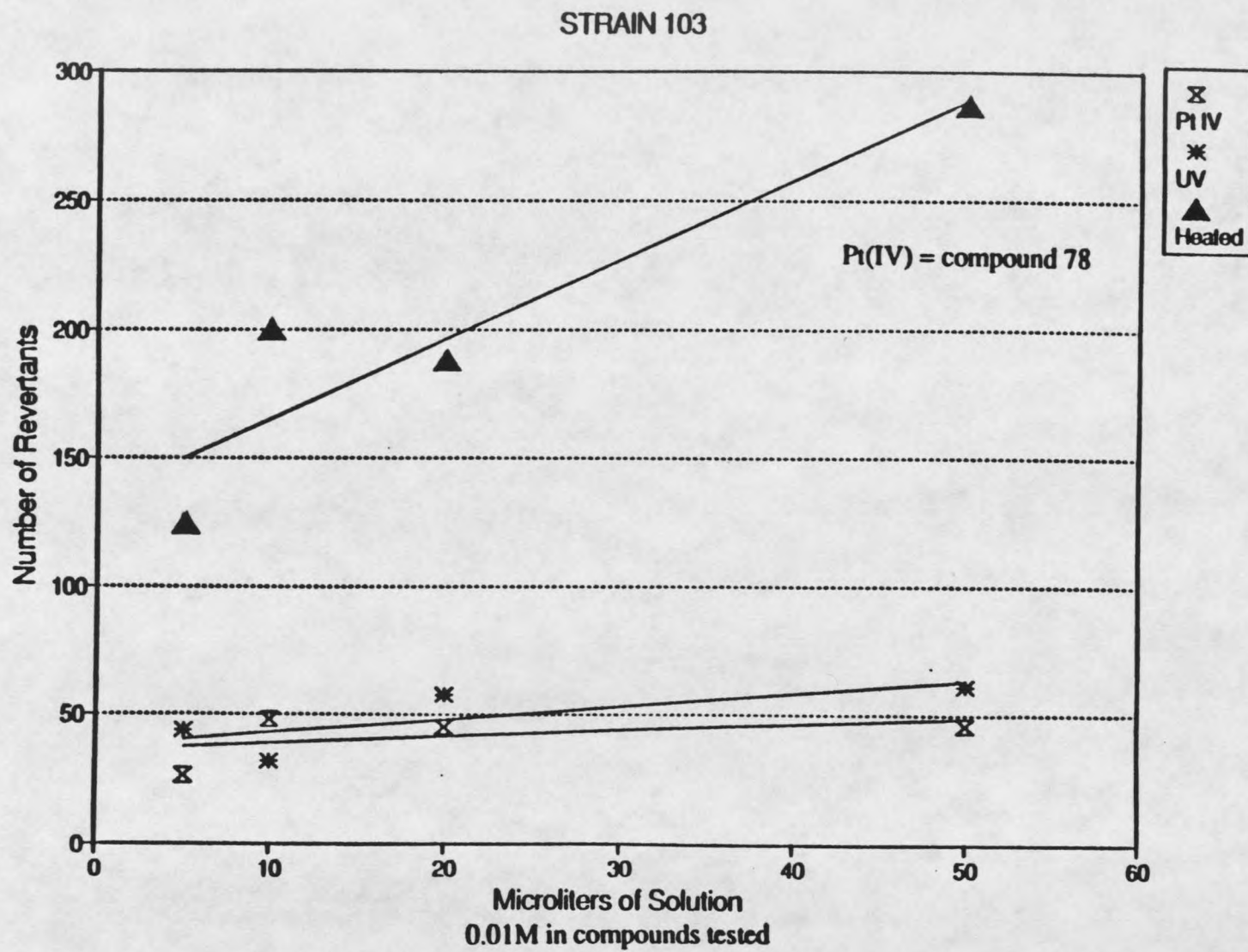


Figure 80. Bioassay results for strain 103.

As indicated by the data for strain 100, compound 78 showed a dose response indicating it was active. The sample treated with UV is probably not significantly more active than the untreated sample. The heated sample is clearly more active than the untreated sample. This indicates that the compound 78 is decomposing to a more active compound when heated. This compound could be compound 71. The results for strain 103 lead one to the same conclusion but the absolute numbers are definitely lower.

Another set of experiments were set up just as above except that the solutions were 0.007 molar solutions and compound 71 was also tested as a high control, Figures 81 and 82. Again for strain 100, the untreated compound 78 showed a dose response. Compound 78 which had been placed under the UV lamp was not significantly different from the untreated sample. The heated sample was much more active. However when compared to the compound 70, the heated sample is not as active. Strain 103 showed similar results but as had been seen above it was less sensitive in a quantitative sense.

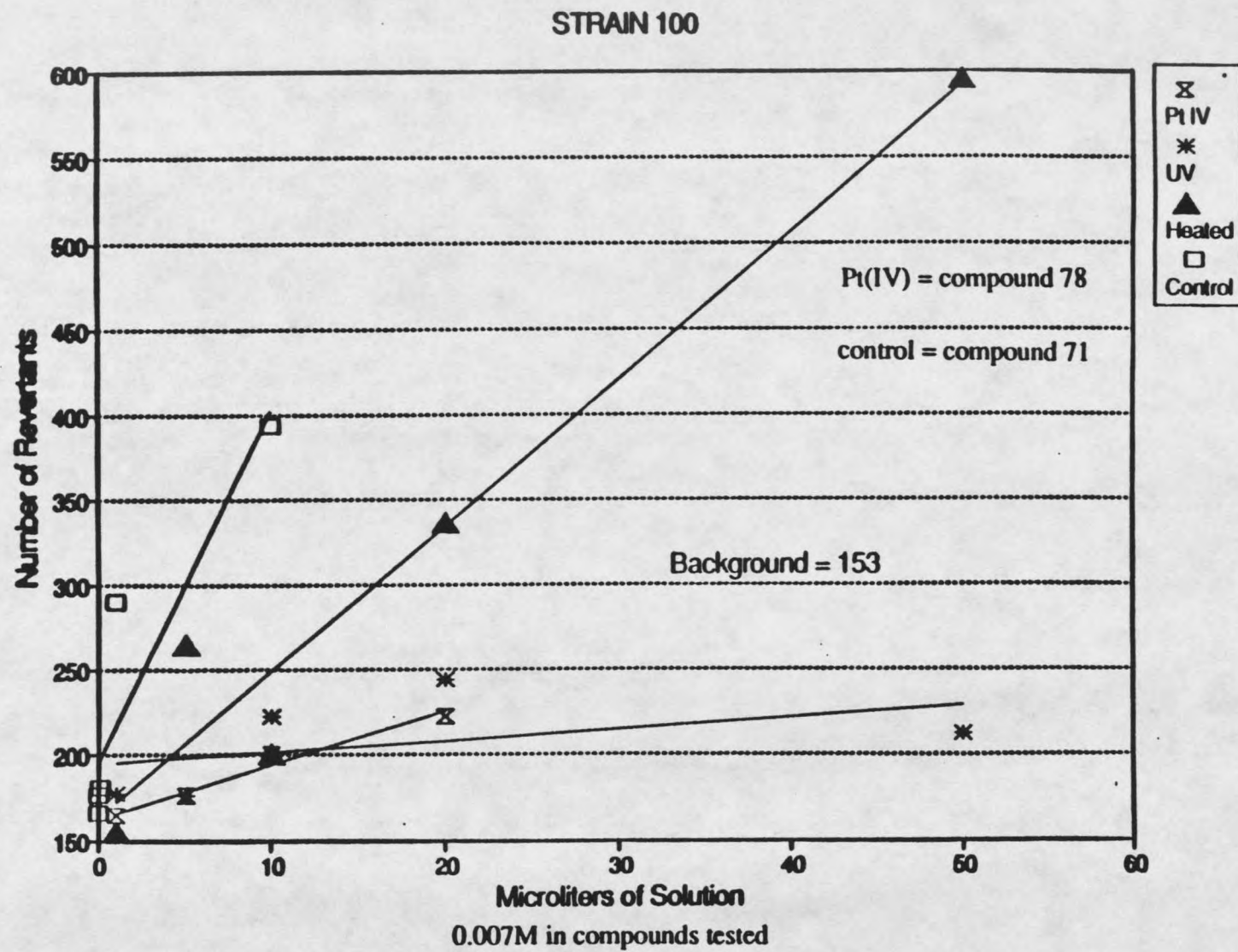


Figure 81. Bioassay results for strain 100.

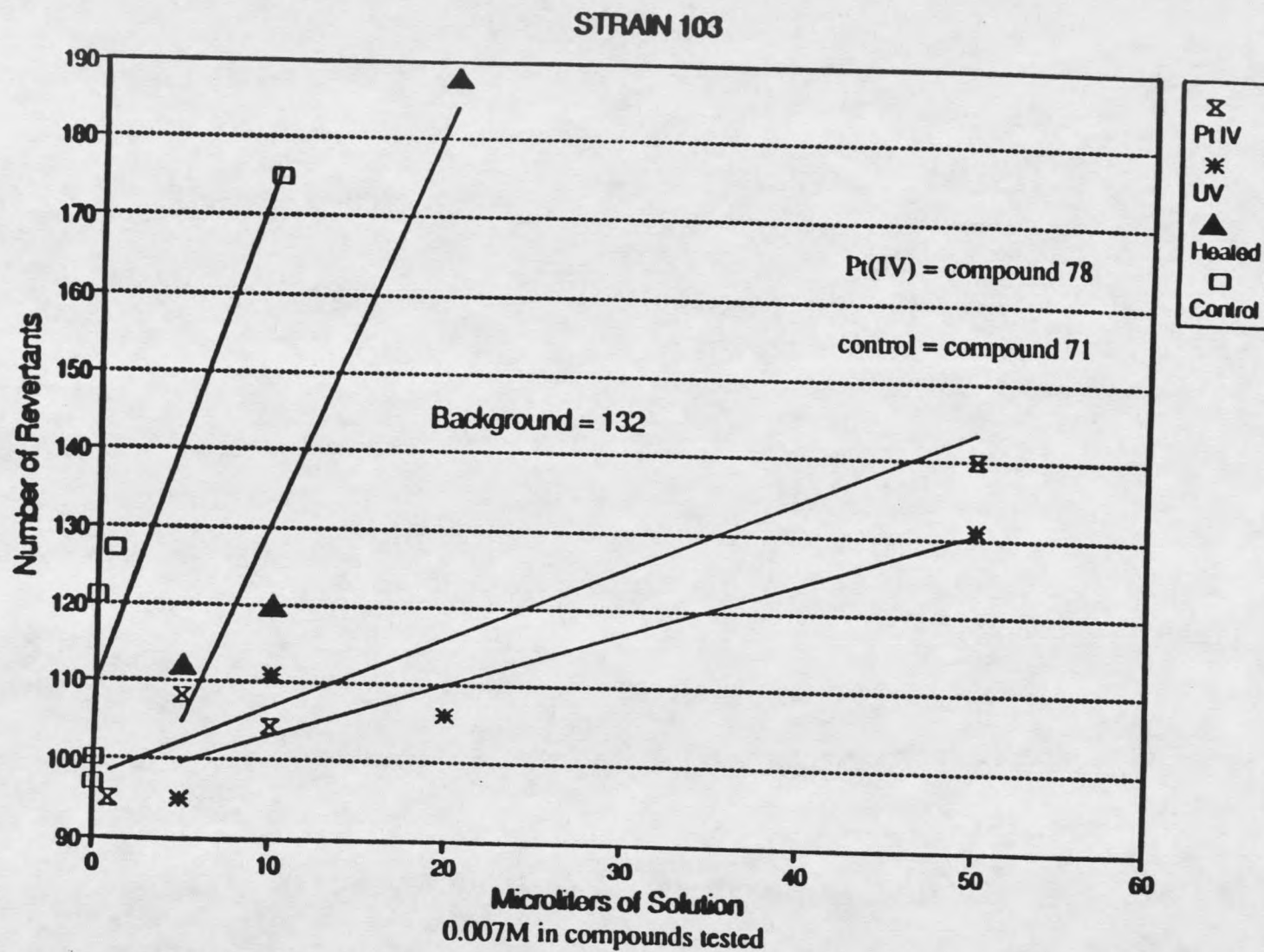


Figure 82. Biosay results for strain 103.

The data from these reversion assays indicated that while compound 78 was toxic to the cells to some extent, it was qualitatively no more toxic than cis platinum. The dose response behavior of untreated compound 78 indicated that either the compound itself was active or the decomposition of compound 78 is creating a platinum(II) species which is responsible for its activity. The level of activity of untreated compound 78 is certainly low. Clearly heating the sample caused it to become more active probably indicating the decomposition of 78 to produce a platinum(II) species. These results encouraged us to test 78 in mice because it was anticipated that it would be less toxic than cis platinum and might even be activated in vivo.

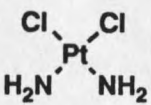
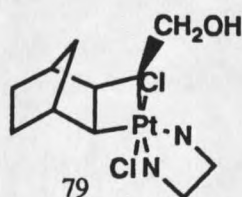
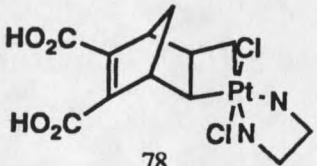
Other bioassay results on compound 78

At this point another graduate student, Wayne Edwards took over the bioassay of these compounds and the result reported here-in are from his masters thesis.⁹¹ Since compound 78 was not too toxic in the Salmonella studies it was subjected to mouse studies to see if it would be inert in this system. A toxicity study was done aimed at determining the dose of compound 79 which would kill 10% of the mice (LD₁₀). The LD₁₀ for cis platinum is 13 mg/kg; that for compound 78 is greater than 41 mg/kg but the exact value was not determined from the study. Histological studies were also done to determine if compound 78 had different toxicities than compound 7 at comparable dose levels. Its effect on the tissues studied was similar to compound 7. However the

major toxicity in mice and humans is nephrotoxicity where compound 78 was milder than compound 7. The kidney damage was noted as being repairable.⁹¹

Compound 78 was also compared to compound 7 in tissue culture assays in which the compound's ability to kill 100% of a cultured cancer cell population was measured. Compound 78 as well as other platinum(IV) platinacyclobutanes were tested. It was soon discovered that compound 78 was significantly active but compound 79 (see summary Table 17) was more active in these assays. However each was less active than compound 7. Table 17 contains a summary of the available information for compounds 7, 78, and 79.⁹¹

Table 17. Summary of bioassay data for 7,78, and 79.

			
	7	79	78
Solubility	1.0 mg/ml	1.0 mg/ml	10 mg/ml
Toxicity	13 mg/ml	NA	> 41 mg/Kg
Nephrotoxicity	severe	NA	moderate
Tissue culture			
LD ₅₀	15μM	28μM	145μM

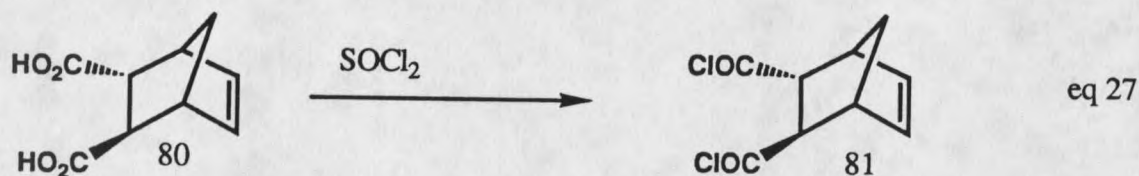
In summary, compound 78 showed significant activity in murine cancer cell lines, but another platinum(IV) compound 79 was the best of all compounds tested. The toxicity of compound 78 is lower than that of cis platinum. It remains to be seen if this fact can be generalized to all such complexes. Compound 78 and related compounds have an additional advantage over cis platinum in that their water solubility can probably be improved without decreasing their activity. Furthermore in vivo studies on implanted tumors in mice using compound 78 also indicated that the platinum(IV) had significant activity and that other tests using different compounds and different treatment procedures should be run.

Compounds designed to increase the water solubility of the platinum(IV) complexes

Because the neutral water solubility of compound 78 was not large enough to allow its disappearance to be monitored in experiments designed to follow its decomposition in the reductive elimination process, compounds with higher water solubility became the target of new synthetic attempts. Essentially new compounds composed of compound 78 or a closely related species with a sugar attached were designed.

Because of the ready availability of the starting compound 80, a scheme was developed to esterify a protected sugar (p-su), compound 83, onto 80 thereby eventually arriving at compound 84, Figure 83 Compound 80 was converted to acid chloride 81 by adding thionyl chloride with no proton scavenger. Excess thionyl

chloride and byproducts were removed under low vacuum to give clean product 81, eq 27. If pyridine was added as a proton scavenger unneeded cleanup steps were required.



To compound 81 in chloroform was added the protected sugar (p-su) yielding compound 82. Compound 82 was then cyclopropanated to yield 84.

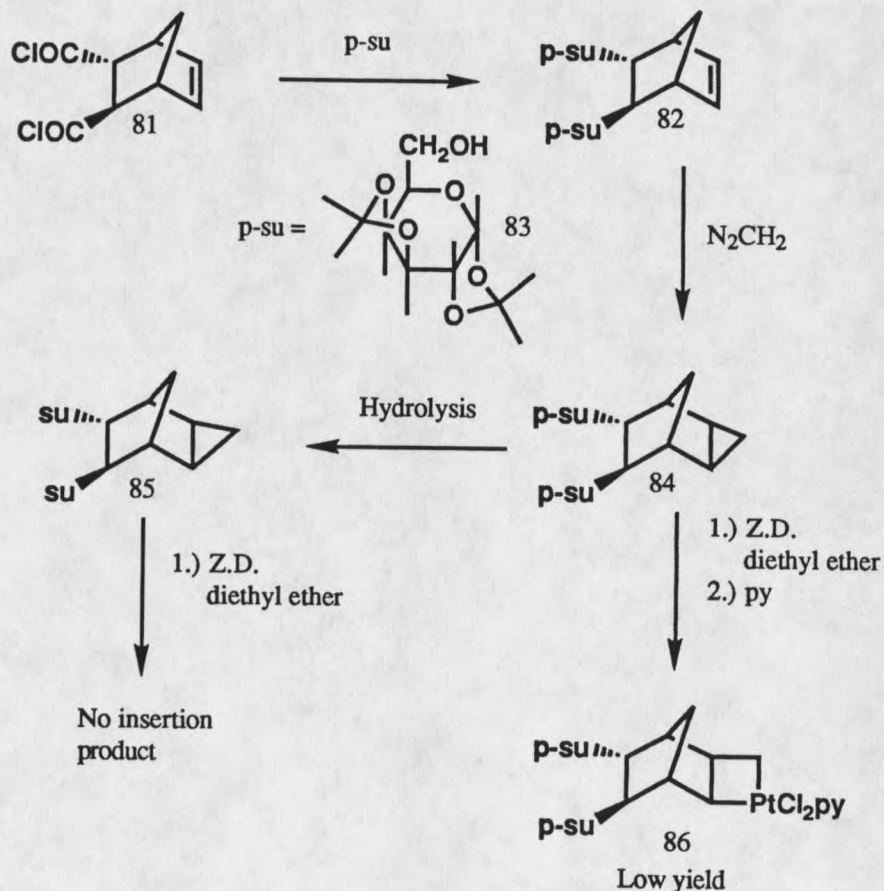


Figure 83. Synthetic scheme for the synthesis of compound 85 and 86.

Platinum would not insert into compound 85 under the usual conditions of diethyl ether at room temperature. Various other conditions and solvents were tried including tetrahydrofuran, chloroform, and methylene chloride to no avail.

All analytical data for the compounds in Figure 83 are included in the experimental section of this thesis.

The problem with the methodology outlined in Figure 83 was that the platinum would not insert into cyclopropane 84. It was reasoned that maybe a cyclopropane which was more likely to insert platinum was the answer. Since compound 76 had been shown to insert platinum in reasonable yield, the same methodology as used above was utilized to prepare the analogous compounds from 76, Figure 84. This time however the conditions which were used to hydrolyze the protecting group, 50% acetic acid in water, hydrolyzed the now activated sugar norbornyl ester linkage. Another approach was then selected. The platinum was inserted and protected by the ethylene diamine ligand, compound 89. Compound 89 was subjected to the hydrolysis conditions and yellow needles soon began to appear. These crystals were removed from the solution and compared by NMR spectroscopy with an authentic sample of compound 71. They were identical. Figure 84 summarizes these results.

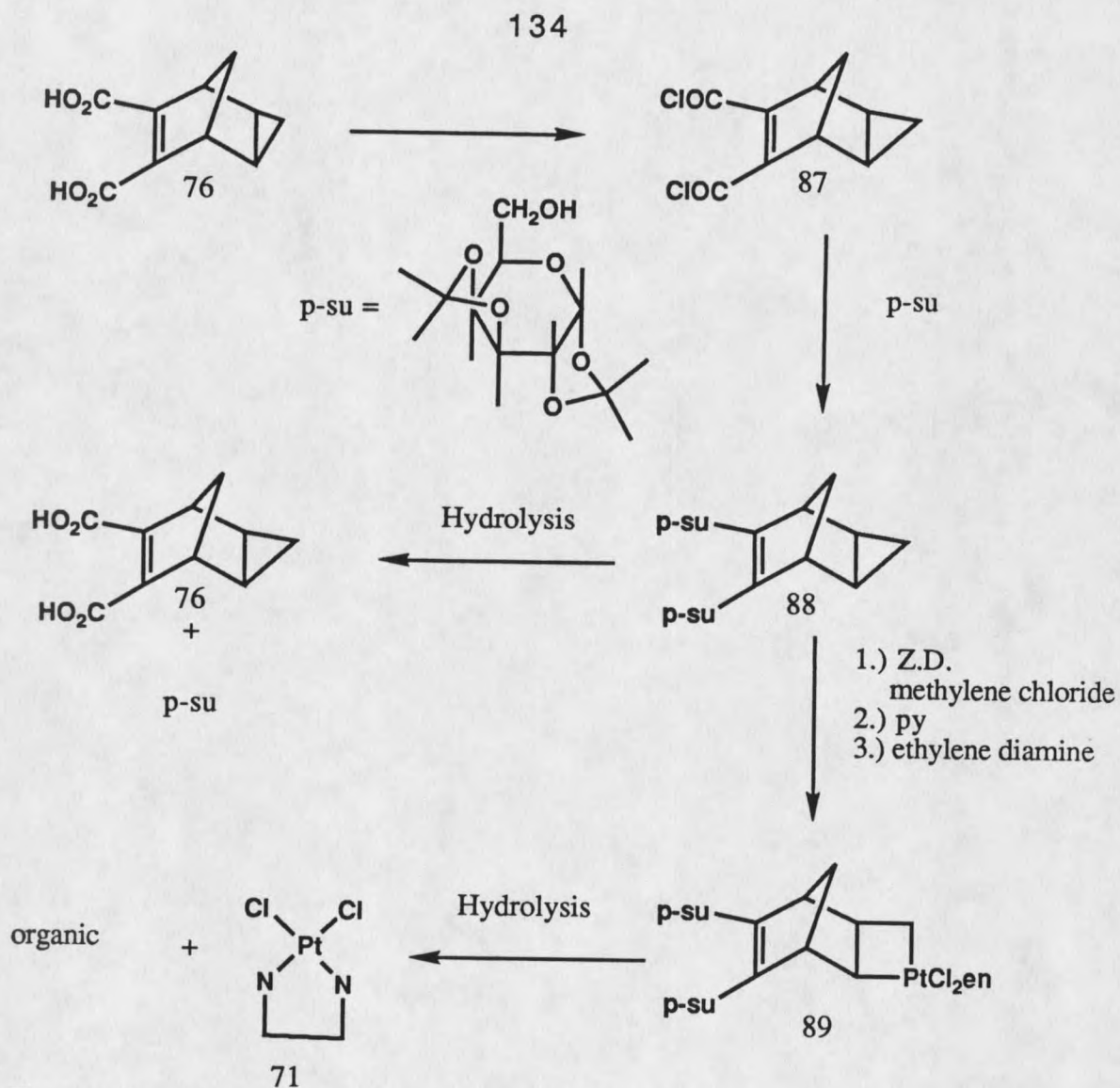


Figure 84. Reaction sequence designed to produce a water soluble platinum(IV) compound.

The desired product of these reactions was never reached. However if one designs a scheme in which the sugar is protected by groups which are more easily removed, the methodology used above could probably be used to achieve the desired compound. It should be noted that one attempt was made to esterify other sugars onto compound 83 without success. The protecting groups

were larger than those shown here and steric problems may have been the cause of the failure of this reaction. Future synthetic designs should keep these facts in mind.

Non-norbornyl water soluble compounds.

It was envisioned that a platinum(IV) compound which did not contain the norbornyl framework but instead was composed of a simple cyclopropane which could be attached to many different carrier molecules might be useful in the future. Compound 96 was designed with this in mind, Figure 85. A test of the methodology used in the last section was also utilized. Compound 91 was first reacted with Z.D. to make sure that platinum would insert into this homolog of cyclopropylcarboxylic acid because it will not insert into cyclopropylcarboxylic acid. Since product 96 was made utilizing the standard conditions of Z.D. in ether, the planned reaction sequence was carried out, Figure 85. Compound 93 was esterified to the protected sugar. Platinum inserted into compound 94 using Z.D., but in very low yields. This demonstrated that the methodology was feasible but further development was not pursued.

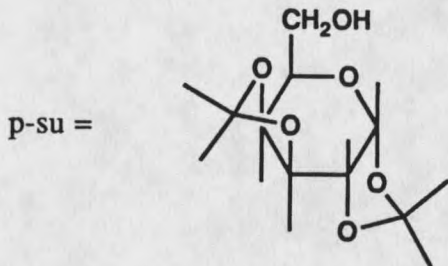


Figure 85. Synthetic scheme for compound 95.

Mechanism of insertion of platinum(II) into cyclopropanes derived from norbornene

To this point, the mechanism of selectivity of the insertion of platinum into the syn substituted cyclopropanes versus that of the anti substituted cyclopropanes had not been addressed. This selectivity is the origin of the first stereochemical product of a number of stereochemical results including the ring expansion reaction and the diazo reactions detailed previously. It is believed that the platinum approaches the cyclopropane edge on, deemed edge attack.

It was proposed by Neilsen that the origin of this selectivity was the fact that platinum did not attack the edge rigidly in plane. Thus, he could use the steric differences in the exo and endo faces to account for the selectivity of insertion. The anti substituted cyclopropane has both faces blocked creating a larger steric effect compared to the syn substituted cyclopropane which is blocked on only one face. While this explanation is plausible, it was felt that the kinetic selectivity was too high in relationship to the degree of steric differences in these two compounds, especially if the platinum insertion is completely in plane with the edge of the cyclopropane.

MM2 calculations were done on the anti and syn hydroxymethylcyclopropanes compounds 97 and 98, respectively shown in Figure 86. The results indicated that compound 97 was about 8 kcal in higher in energy than compound 98. As a check on

these calculations MNDO calculations were performed on the same molecules and the results were that 97 was 6 kcal higher in energy than 98. MM2 calculations were also done on the platinacyclobutanes 11 and 13 and the anti compound 13 was found to be approximately 1 kcal higher in energy than the syn compound.

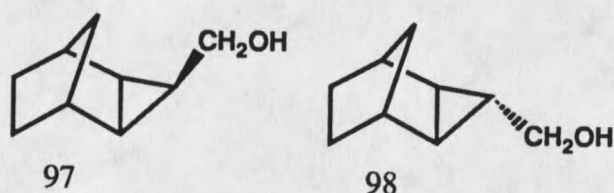


Figure 86. Structure of compounds 97 and 98.

If we assume that the transition states of the insertion of platinum into compounds 97 and 98 are of relatively equal energy which is a reasonable assumption for edge insertion, the $\Delta\Delta H^\ddagger$ would then be 4 kcal and this translates into a rate difference of 800 to 1.

There is another possibility and that is the apparent kinetic selectivity is actually a result of cyclopropane exchange and only represents the equilibrium between syn and anti complexes. The fact that the calculation indicated a small energy difference in compound 11 and 13 argues against this explanation, but does not rule it out. However this explanation can be and was empirically tested. The I.P.C. of the anti complex was placed into the original insertion conditions, diethyl ether at room temperature. To this solution was added excess compound 97 and let stir twice the length of time for the normal reaction. The results were

interesting. Compound 97 had indeed displaced some of compound 98 from the I.P.C. but only about thirty percent. This indicated that under the conditions of the reactions, exchange could occur but not enough to explain the total selectivity of syn over anti. Furthermore the exchange mechanism itself caused some never before seen decomposition products.

Some of the questions brought up here could be answered if the actual insertion rates could be measured. Thus, an attempt was made to measure these reaction rates by NMR spectroscopy.

Rate of platinum insertion into cyclopropane derived from norbornene and norbornadiene

The kinetic data on the rate of insertion of platinum(II) into cyclopropanes derived from norbornene and norbornadiene would be useful in four ways. First, data could be compared to that measured by Puddephatt for the simple cyclopropanes. This comparison would indicate whether or not mechanisms proposed in the case of the simple cyclopropanes would also be consistent for the insertion into norbornyl type systems. Second, the rates of insertion into the norbornyl systems could be compared within that group to delineate the effect of different substituents on insertion in the norbornyl compounds. Thirdly, the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values could be used to gain detailed information about the energetics of insertion. Fourth, since the kinetics were going to be followed by NMR if any intermediates were formed in appreciable amounts, they would be apparent in the NMR spectrum.

It was desirable to study the kinetics by NMR spectroscopy. The kinetics for the simple cyclopropanes had been done under pseudo first order conditions of approximately 50 equivalents of arylcyclopropanes at 0.0002M Z.D. or the exchange reaction of cyclopropane as outlined in Figures 17 and 18 in the introduction. The increase of absorbance between 280-350 nm in the U.V. spectrum was monitored. Such low concentrations and such high ratios of compound were not practical for studies using NMR spectroscopy. The sensitivity of the NMR experiment is too low to monitor compounds at such low concentrations and the relative sizes of the largest peaks versus the smallest peak is limited by the dynamic range. Different conditions had to be worked out for kinetics which were to be followed by NMR spectroscopy.

Compound 99 was reported by qualitative methods to insert platinum much faster than either compound 100 or 101 and 100 was reported to react faster than 101. Compound 99 was chosen as the model compound for which to develop the conditions for the kinetic studies of the compounds shown in Figure 87.

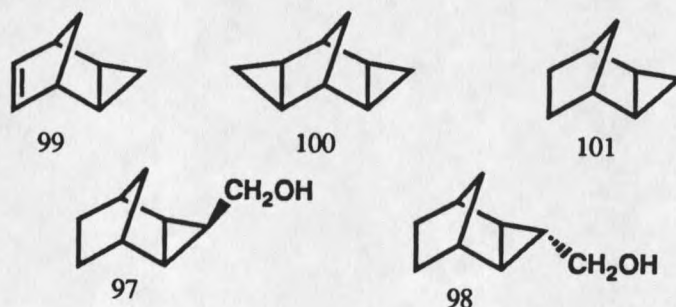


Figure 87. Compounds of interest for kinetics studies.

To a solution containing various concentrations of Z.D. in deuterio THF was added 1 equivalent of the compound 99. It was soon discovered at concentrations in the range of 0.1M that the reaction proceeded approximately half way by the time it was placed in the NMR spectrometer and the first scan was taken, approximately 80 seconds. But the reaction proceeded from this point on at a very slow rate. The concentration of Z.D. was lowered and the same behavior was noted except that the reaction went further to completion before the second rate took over.

At this point, a new approach had to be developed. Two routes were chosen. One was to switch to the exchange reaction that Puddephatt had used to study the kinetics and the other was to lower the concentration. These two approaches will be discussed separately.

Study of insertion of Pt(II) into compound 94 at low concentrations.

The concentrations at which the kinetics were to be studied were so low that 98% deuterated THF contained too much of the protio species and special 99.99% deuterated THF was purchased. This avoided the dynamic range problem caused by the protio species in the experiment. After many trial experiments, a concentration was found in which the rate was consistent throughout the reaction. At concentration of .0021M the reaction proceeded to 98%+ completion. The data plotted nicely second order. So a second order rate constant for compound 99 was obtained, Figure 88.

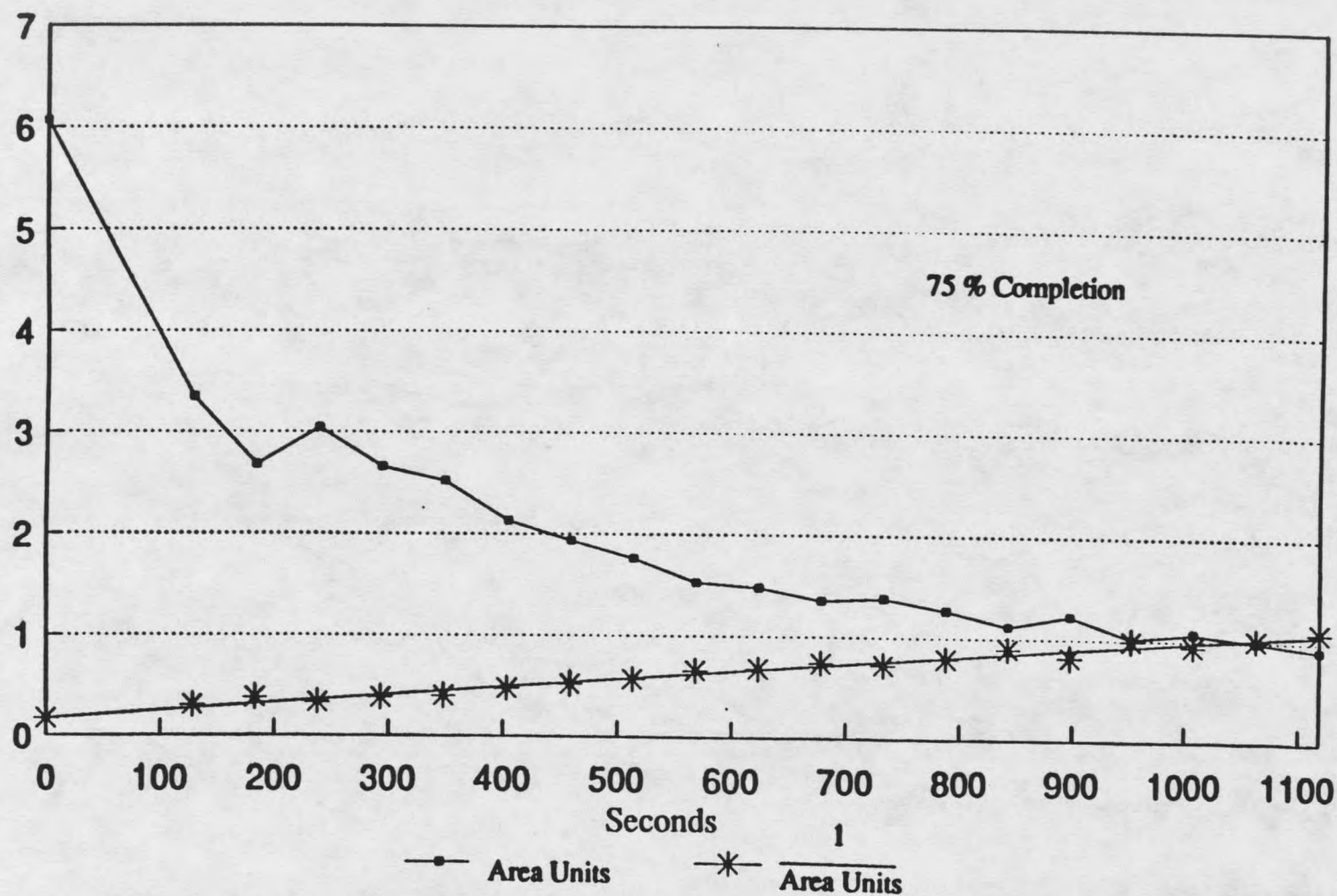


Figure 88. Kinetic experiment for reaction of 99 and Platinum(II) at low concentration.

One equivalent of Z.D. and one equivalent of compound 101 were allowed to react at room temperature. The reaction did not proceed at all. The ethylene peak on the platinum species broadened indicating exchange but no reaction occurred.

Two plausible explanations exist for the fact that the reaction of compound 99 proceeds to differing extents at differing concentrations and then slows down. The first is that the ethylene released in the reaction is inhibiting the reaction but in more than a first order reaction. The second is that platinum(IV) insertion product makes a dimeric species or interacts with the platinum(II) starting material in some way to inhibit the reaction. These two possibilities are given in Figure 89.

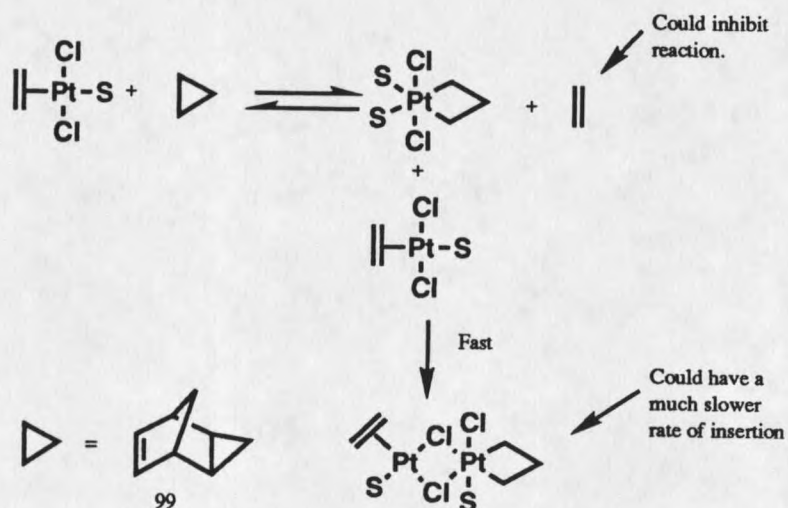


Figure 89. Explanation for results of kinetic studies using compound 99.

The explanation for why compound 101 did not insert platinum under the same condition as 99 could be explained by the fact that the cyclopropane could not displace the cyclopropane in the second step of the proposed mechanism, Figure 85.

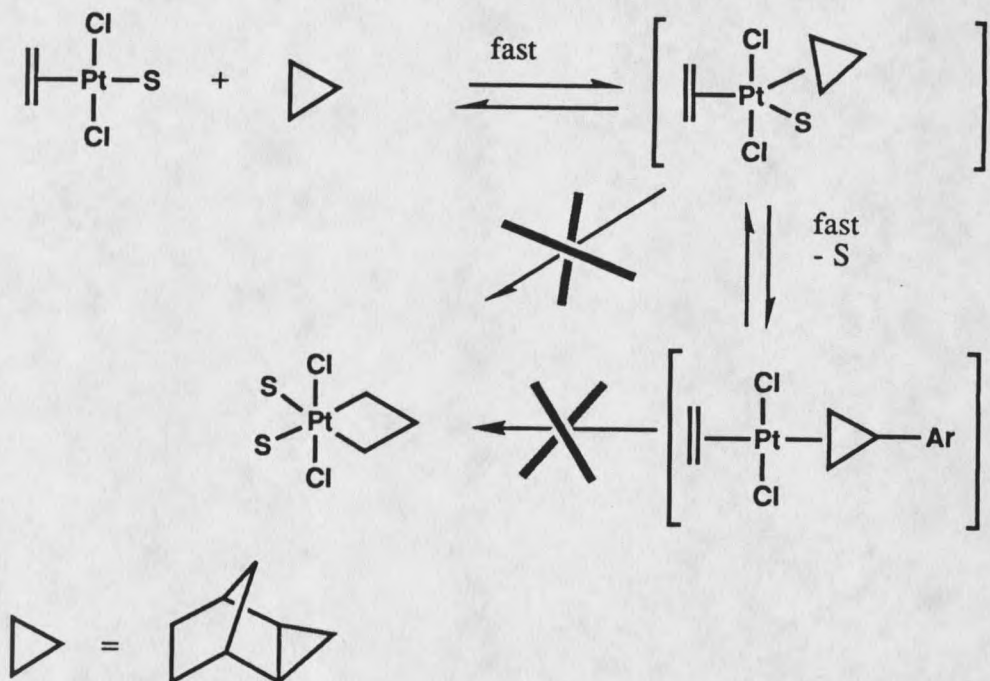


Figure 90. Expanation for why compound 101 did not insert platinum(II).

Study of the cyclopropane exchange reaction of platinacyclobutane with compound 99.

The exchange reaction of compound 99 with platinacyclobutane proceeded smoothly, Figure 91. However when the data was plotted it clearly fit first order assumptions much better than second order assumptions. In the interest of conserving on the amount of instrument time the experiment consumed a second reaction was done at higher initial concentration. Because the observed rate at this concentration

was higher a third experiment was run at different initial starting concentration. The data for these three concentrations is plotted in Figure 92.

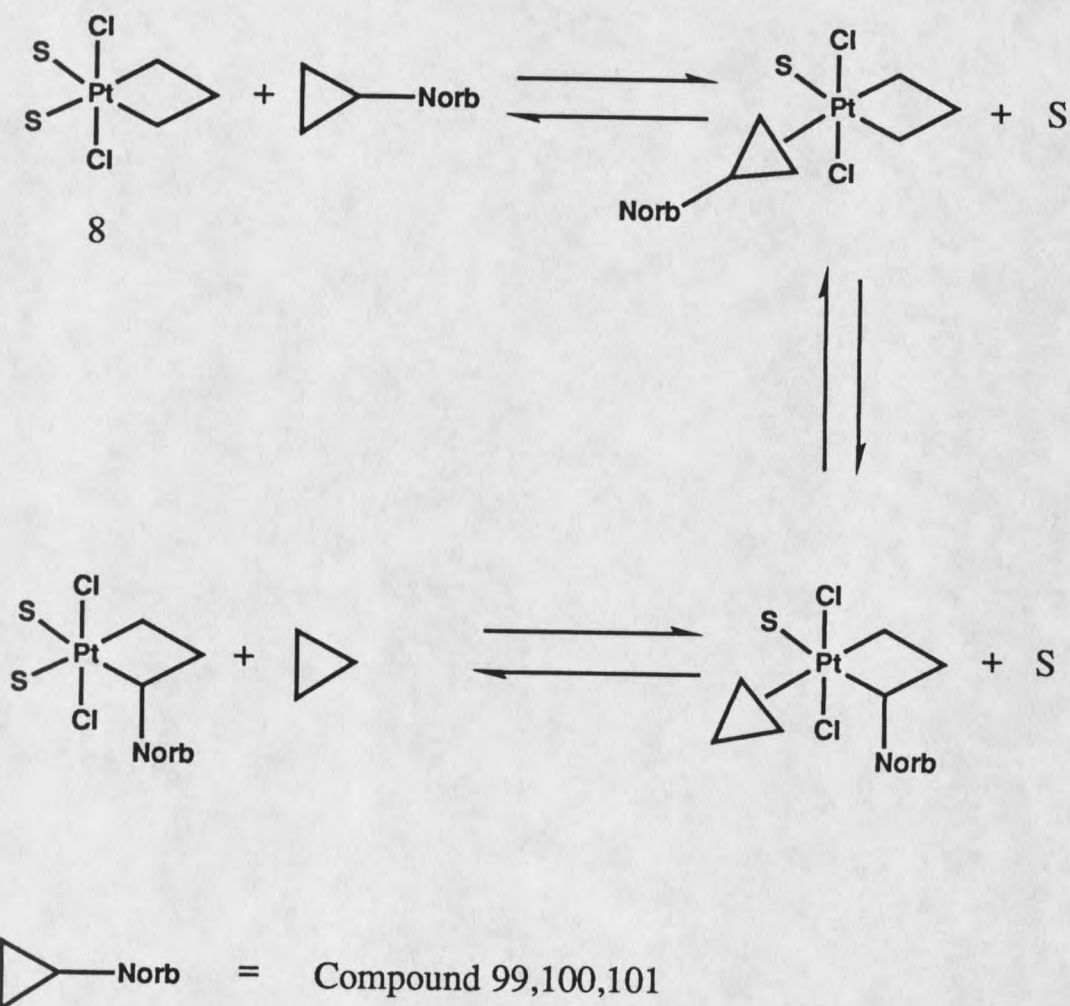


Figure 91. Exchange reaction used to measure kinetics.

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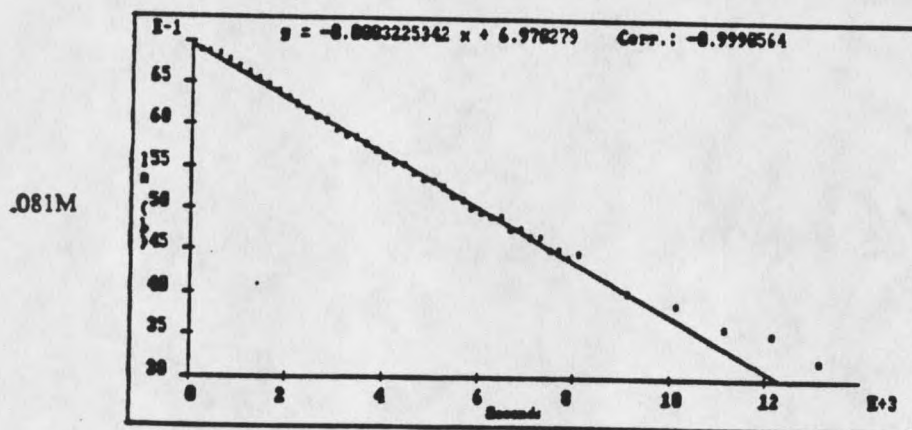
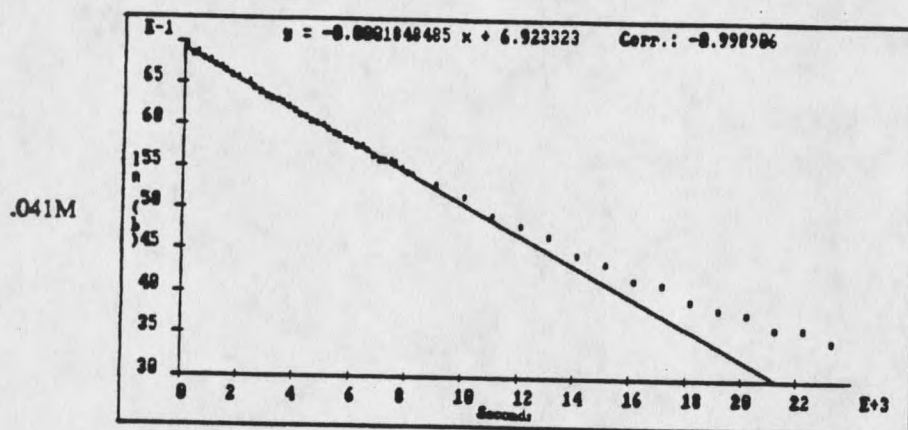
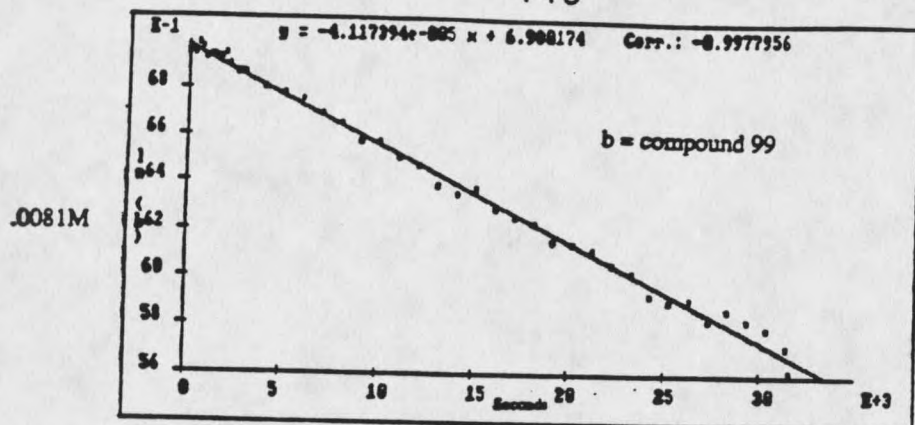


Figure 92. Plot of kinetic experiments for compound 99 at three concentrations.

To see if the rate was a function of the concentration of compound 99, 1 equivalent of platinum was reacted with 1, 2 and 4 equivalents of compound 99. Graphs of percent completion of the reaction for three different ratios of platinum to compound 94 were plotted versus time, Figure 93. The rate of reaction was dependent on the concentration of compound 99.

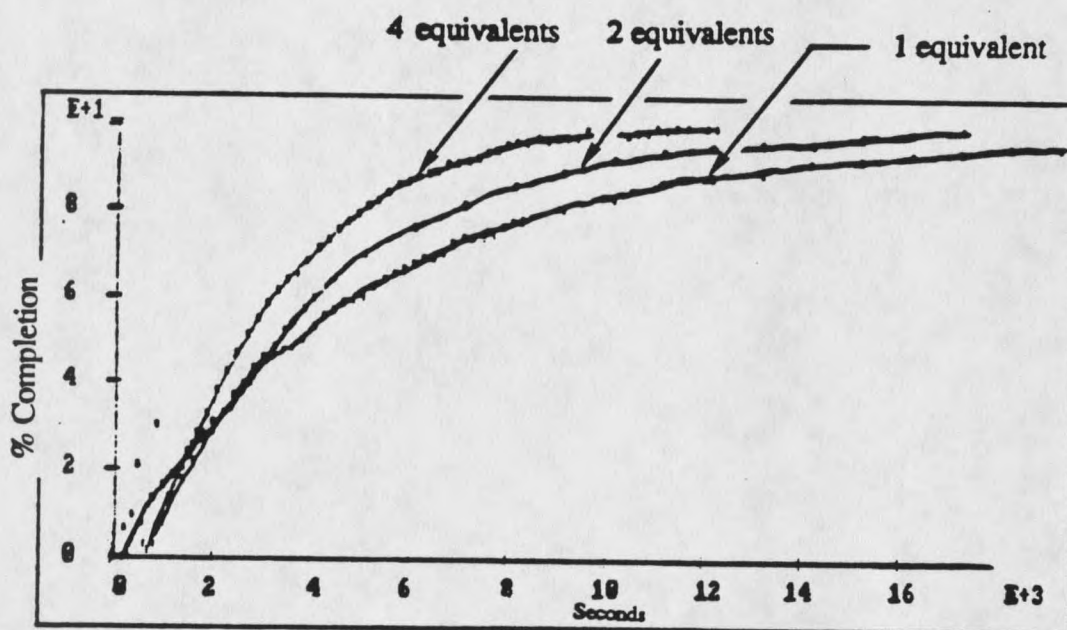


Figure 93. % completion plots for 1, 2, and 4 equivalents of 99.

An Eyring plot of the cyclopropane exchange reaction was done using data from first order reaction rates at 320K, 300K, and 280K., Figure 94. A fourth point was taken at 260K but the temperature control apparatus was discovered to have quit functioning during the run and the reaction was actually colder than programed; but the point was included for comparison

purposes only. The $\Delta H^\ddagger$ state is 21.0 kcal/mole and the $\Delta S^\ddagger$ is -3 cal/ mole K.

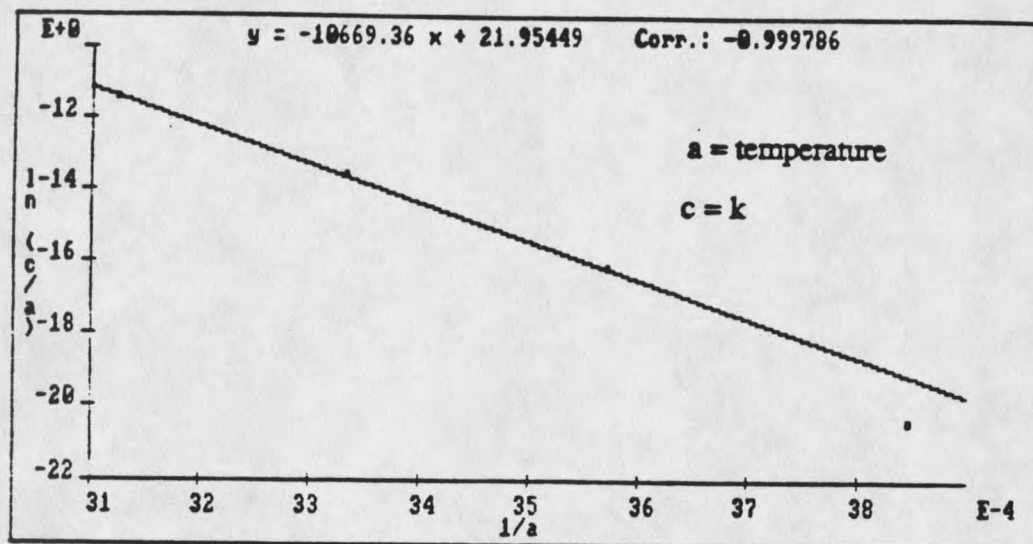


Figure 94. Eyring plot of temperature dependence of rate for 99.

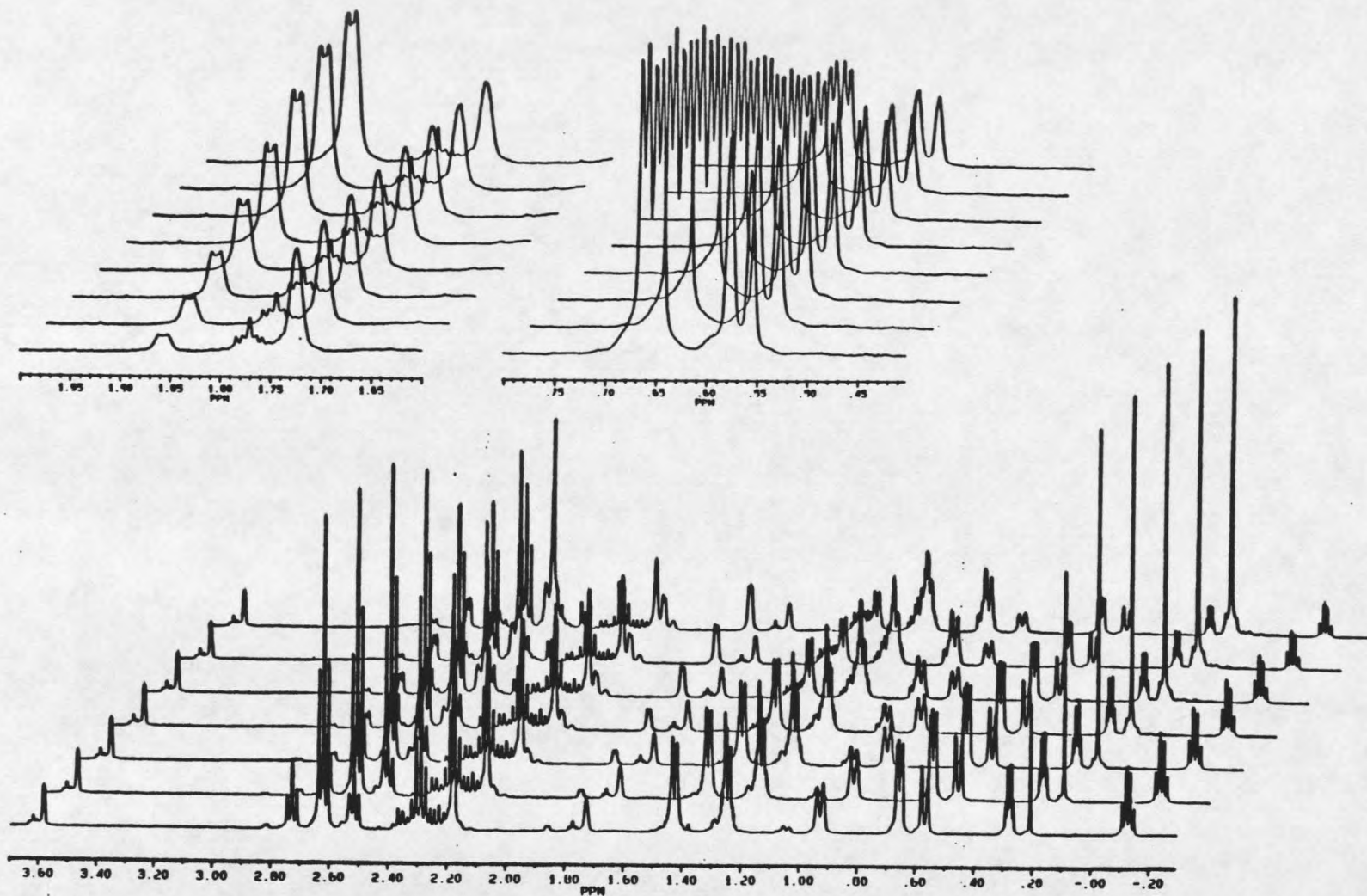
Note in the exchange experiments involving compound 99 that, although they plot first order at each initial concentration, they do not have the same k_{obs} . In fact K_{obs} is a function of both the initial concentration and the concentration of some platinum species. Table 18 gives the K_{obs} for the first order plots, and the K_{obs} divided by the initial concentration of starting species.

Table 18. Summary of kinetic runs for compound 94.

Init. Conc.	K_{obs}	$K_{\text{obs}}/\text{init. conc. (L}^2/\text{M}^2\text{s)}$
0.0081M	4.1×10^{-5}	5.1×10^{-3}
0.041M	1.8×10^{-4}	4.4×10^{-3}
0.081M	3.3×10^{-4}	4.1×10^{-3}
average		4.5×10^{-3}

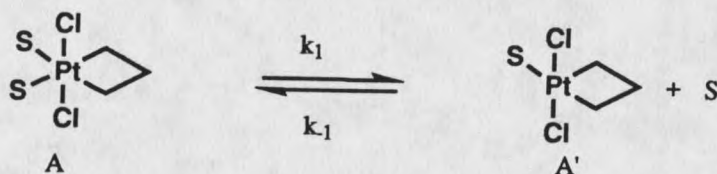
When the experiment was run for the exchange conditions using compounds 100 and 101 the data did not plot first order throughout the reaction. This is believed to be due to the back reaction occurring or could be due to the reaction shifting rate determining steps. The initial rate of the reaction was $2.1 \times 10^{-3} \text{ L}^2/\text{M}^2\text{s}$ for compound 101 and $3.6 \times 10^{-3} \text{ L}^2/\text{M}^2\text{s}$ for compound 100. A stacked plot of the NMR experiment for compound 101 is provided as an example, Figure 95.

Because data for compound 94 was first order for conditions in which 1 equivalent of each of the two reactants was added, in what must be a bimolecular reaction, it was concluded that one of the reacting species was in low concentration. Because the data from the % completion experiments with 1, 2, and 4 equivalents of compound 99 to 1 equivalent of platinum verses time indicated the reaction was dependent on the cyclopropane concentration but doubling the cyclopropane did not double the observed rate, it was concluded that compound 99 was not the limiting reactant responsible for the first order plots. Furthermore from a mechanistic point of view it is impossible to envision a mechanism in which the reaction depends only on the concentration of compound 94. Thus the limiting species must be a platinum species. The pseudo first order conditions are arrived at because the reactive platinum species is not the original solvated monomer and the reactive species is in low concentration compared to the concentration of compound 99. The data is consist with the kinetic model as given in Figure 96.



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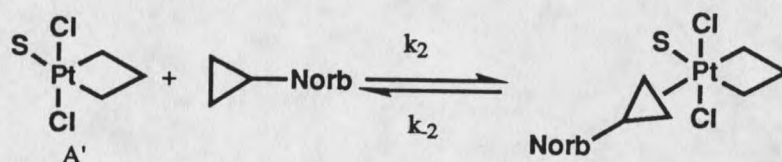
Figure 95. Stacked plot of NMR data of kinetics experiment for compound 101.



Assuming a fast equilibrium

$$[A'] = K_{eq} [A]$$

$$[S]$$



For compound 94 k_{-3} can be ignored but not for compound 95.

Ignoring k_{-3} and assuming k_3 is rate determining.

$$\text{rate} = k_3 [C]$$

Using steady state assumption

$$\frac{\partial C}{\partial t} = k_2 [A'] [B] - k_{-2} [C] - k_3 [C]$$

$$[C] = \frac{k_2 [A'] [B]}{k_{-2} + k_3}$$

low concentration

$$\text{rate} = \frac{k_2 k_3 [A'] [B]}{k_{-2} + k_3}$$

$$\text{rate} = k_{obs} [A]$$

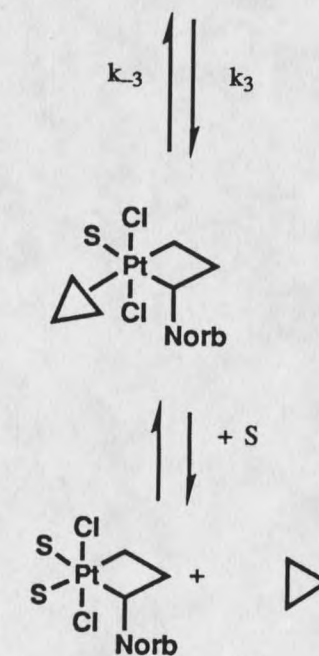


Figure 96. Mechanistic and kinetic model for the reactions of compound 99 with Z.D. in THF.

If k_3 is the rate determining step then one would expect the $\Delta S^\ddagger$ value to be around zero because in this step the no net ordering occurs. The $\Delta H^\ddagger$ value does not tell us much about this reaction.

A comparison of compound 92 and 93 in a kinetic experiment.

A kinetic experiment was done in which a mixture of compound 97 and 98 in a ratio of 2.4/1 were reacted with compound 8. No exchange product for compound 98 was observed. The reaction was followed to 35% of completion. The data for the rate of exchange of compound 92 was treated exactly as in the previous section and the value obtained was $2.1 \times 10^{-4} \text{ L}^2/\text{M}^2\text{s}$. Qualitatively a 2% change in the peak area for compound 98 could have been measured which means the reaction could have proceeded to 2% at most. Thus 97 reacts at least 30 times faster than 98.

EXPERIMENTAL SECTION

^1H NMR spectra were obtained on a Bruker AM500, AC300 or WM250-MHz instrument. Chemical shifts are reported in units of parts per million (ppm) (δ) downfield from tetramethylsilane (TMS). ^1H NMR shifts are relative to residual proteated solvent in: CDCl_3 - 7.24, THF-3.58, and pyridine-7.19. ^{13}C NMR spectra were recorded at 62.9, 75.5 or 125.8 MHz and chemical shifts are reported relative to the solvent resonance: CDCl_3 -77.0, THF-67.3, pyridine-123.5. CDCl_3 was used in all NMR spectroscopy unless otherwise noted. Most NMR experiments were performed in CDCl_3 and this was the solvent used unless otherwise stated.

Multiplicities in carbon spectra are referred to gated or dept experiments. All coupling constants reported are in Hertz. Mass spectral data were collected on a Varian MM-16 spectrometer. Infrared spectra were obtained on a Nicolet 5DX FT-IR spectrometer. X-ray data was collected on a Nicolet R3ME automated diffractometer and structure determinations and refinement calculation were carried out with SHELXTL software on Nicolet R3ME crystallographic system. Preparative GC collections were made with a Varian 3300 FID equipped with a 10" x 25" column packed with SE30 on Chromosorb w. Column chromatography was performed on silica gel. Diethyl ether was distilled from sodium and benzophenone, CHCl_3 was washed with

water 5 times, distilled from CaCl_2 and stored in the dark over 4Å molecular sieves for use in sensitive reactions. Pentane was distilled from LAH and C_6H_6 was distilled from CaH_2 unless otherwise stated.

All reactions were run under ambient air conditions and all products reported were stable to the air unless noted otherwise. Except where otherwise specified all solvents and reagents were purchased from commercial suppliers and used without further purification.

All cyclopropanation reactions with diazomethane were done according to Kottwitz⁹² with the following modification. Upon completion of the reaction the mixture was filtered to remove any solid $\text{Pd}(0)$ and the ether solution removed under vacuum. The compound was then chromatographed on a short silica gel column with pentane to remove any trace impurities and $\text{Pd}(0)$ which might not have been removed by the filtration step. Excess diazomethane was always used (5-10x) unless otherwise noted.

Diazomethane reactions with platinacyclobutanes were done according to Kottwitz⁹² except the carrier was N_2 instead of diethyl ether.

Cyclopropanations using ethyl diazoacetate were done using 1.5 -2.5 equivalents of ethyl diazoacetate according to the method of Doyle⁹³ except where otherwise noted.

Synthesis of compounds 31,32,33,34.

Into a solution of 15g of norbornadiene and 0.025g $\text{Pd}(\text{O}_2\text{CCH}_3)_2$ in diethyl ether (150 mls) was slowly added, over 2 hours, 2.5 equivalents of ethyl diazoacetate (46.5g) in 100 mls of diethyl ether. The solution was filtered to remove the palladium and the solvent removed under low vacuum. The products were dissolved in pentane, placed on a silica gel column and eluted off of silica with pentane in 70% yield based on norbornadiene. The solvent was removed giving a clear oil. Both 31 and 32 gave a m/e 178(m^+). The ^1H and ^{13}C spectra are given below.

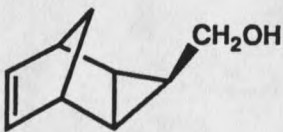
Table 19. ^1H and ^{13}C assignments for compounds 31 and 32.

C#	31		32	
	^1H	^{13}C	^1H	^{13}C
1	2.90	42.20	3.01	41.87
2	1.25	28.56	1.38	31.87
3	2.52	39.22	2.21	35.83
4	1.25	28.56	1.30	31.87
5	2.90	42.20	3.01	41.87
6	6.42	141.97	6.48	140.96
7	6.42	141.97	6.48	140.96
8 anti	0.98	40.27	0.89	40.27
8 syn	1.11		1.06	
9		171.95		171.6
CH_2	4.08	60.65	4.16	60.19
CH_3	1.29	14.05	1.38	14.24

The endo products can be recognized by the fact that their olefinic resonances come slightly upfield of compounds 31 and 32, at 5.75 and 5.6. Peaks between .89 and .5 are indicative of the dicyclopropanated products.

Reduction of 31 and 32. A solution of the epimeric esters 31 and 32 (0.5g, 0.028 mol) in 50 mls of diethyl ether was added dropwise to a stirred solution of LAH (4.25g, 112 mol) in 100 mls of diethyl ether in a three neck flask equipped with a condenser. The reaction was allowed to stir at room for 8 hours after which time basic H₂O was added slowly to the mixture to quench excess LAH. The alcohols 35 and 36 were extracted from the H₂O solution by repeated extractions (4x) with ether. The diethyl ether extracts were combined and the solvent removed under vacuum giving a light yellow oil consisting of 35 and 36 in a ratio of 40/60 in 60% yield; m/e (m⁺)136. The diethyl ether extracts were combined and the solvent removed under vacuum giving a light yellow oil consisting of 35 and 36 in 60% yield. m/e (m⁺) 136. ¹H and ¹³C data for compounds 35 and 36 are given in Table 20.

Table 20. ¹H and ¹³C data for compounds 35 and 36.

 35  36			
¹ H	¹³ C	¹ H	¹³ C
0.95	28.7	0.88	27.4
1.00	41.3	0.92	34.6
1.15	39.0	1.15	39.0
1.75	42.3	2.15	41.5
2.90	42.4	2.75	64.9
4.0	142.5	3.38	140.9
6.5		6.35	

Synthesis of platinacyclobutanes. The following description of the methodology used to insert platinum(II) into cyclopropanes will be used as the standard description for the insertion of platinum into all cyclopropanes in this thesis. Syntheses hereafter will be referred to this section. The only variables will be percent yields, time, and cyclopropanes reacted. Each variable will be reported under the appropriate compound number. Before reacting an epimeric mixture of substituted cyclopropanes such as 35 and 36, the exact ratio of the compounds was determined by integratable ^1H spectrum. One equivalent of the more reactive isomer was reacted with 1 equivalent of Z.D. The typical reaction sizes ran from the range of 100-200mg of Z.D. To a mixture of the cyclopropane(s) in diethyl ether was added the Z.D. at room temperature. A solid precipitate falls out of solution as the reaction proceeds (I.P.C.) After the designated time period, the ether is removed and the precipitate is washed and triturated with pentane. The pentane washings are either discarded or saved in the case when they contain additional cyclopropanes to be used in other reactions. A small volume (.5mls) of chloroform is then added to solid and 2.1 equivalents of pyridine added to the suspension. The monomeric platinum complexes dissolve in the chloroform. Removal of all but a small amount of the chloroform solvent under low vacuum is effected and trituration with pentane yields the desired product. Several pentane washes were usually effected to remove any excess

pyridine or other organics. For a typical example see synthesis of compound 27, below.

Synthesis of compound 27. The ratio of compound 32 to 31 was determined to be 1.23 to 1.00. To a solution of diethyl ether (5mls) and 2.32 (.14g) equivalents of the epimeric mixture of 31 and 32 was added 1 equivalent of Z.D.(.1g) and the solution allowed to react for 8 hours. The ether was removed under low vacuum and the resultant sticky solid was repeatedly triturated with 10 mls of pentane. The pentane was decanted and trituration repeated until a fluffy precipitate was obtained. The pentane washings were collected and the solvent removed under low vacuum yielding unreacted compound 32. Excess pentane was removed from the solid under low vacuum. Chloroform (1 ml) was added to the solid and 2.1 equivalents pyridine was added. The volume of the chloroform was reduced to the point of saturation and pentane was added precipitating out the monomeric product which was then repeatedly triturated with pentane to remove excess pyridine. The pentane was removed under low vacuum; the product, 31 was obtained in 88% yield. For structure determination see Tables 8, 9, 10, and 11.

Synthesis of compounds 28 and 29. See synthesis of platinacyclobutanes. See also p85-86 of text. Reactions were done on the .1g-.5g scale of Z.D. Reactions involving compound 28 were run for 4 hours and those involving 29 were run overnight. Compounds 28 and 29 were obtained in 93-97% yields; the structural assignments are given in Tables 8, 9, 10, and 11.

Synthesis of compounds 37 and 38. Either 0.1g of compound 28 or 29, depending on the desired product, 37 or 38, was added to 5 mls of a 60% V/V solution of acetone/methanol. Three drops of H_2SO_4 were added and the solution allowed to react for 12 hours at room temperature. The solvent was reduced under low vacuum and 5mls of H_2O and 5 mls of chloroform were added in a separatory funnel. The chloroform portion was washed twice with 5 mls H_2O . The volume of the chloroform was reduced to .5 mls and added to 10 mls of pentane. The resulting precipitate was repeatedly triturated with pentane and the excess pentane removed under low vacuum. Compound 37 was produced in 60% yield and 38 in 50% yield. See Table 13 for the ^{13}C NMR.

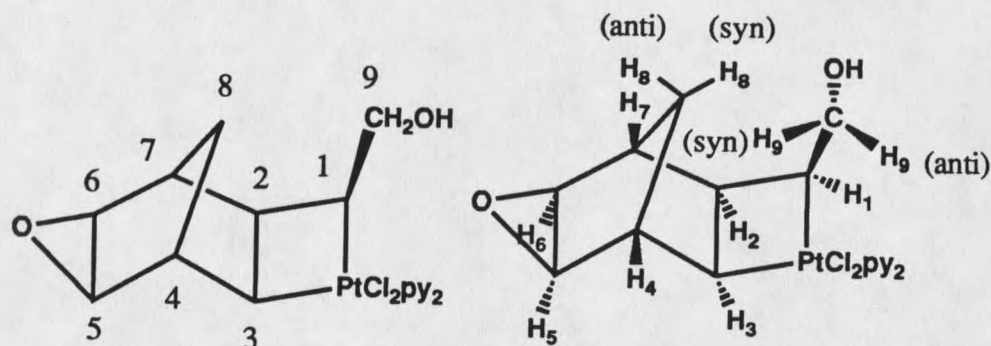
Synthesis of compounds 41 and 42. To a solution of platinum complex 17 (0.100g 0.18 mmol) in CDCl_3 (5mls) was bubbled diazomethane generated from a 30 fold excess of Diazald (N-methyl-N-nitroso-p-toluenesulfonamide, 0.861g, 5.4 mmol). Upon completion of the addition, the color of the solution was darker. A mixture of products 41 and 42 in a ratio of 50/50 were obtained in 50% yield. The ^1H and ^{13}C data for 41 is given in Table 14. The ^{13}C data for 42 is given in Table 15.

Compounds 41 and 42 were difficult to purify. If the chloroform solution was removed completely as possible without also removing compound 41 under low vacuum and the residue washed repeatedly with pentane, 41 and 42 could be extracted from the mixture but a certain amount of 42 remained with the residue. Compound 41 was slightly more soluble in pentane than

was 42 so repeated recrystallization steps could be used to separate 41 from 42.

In the reaction using ^{13}C labeled Diazald 1 equivalent of Diazald and 1 equivalent of 28 were reacted. A preponderance of starting material was the result. By using the methodology described above the 42 and 28 could be separated from 41. Compound 42 could be separated from 28 by virtue of the fact that 42 is slightly more soluble in a 1% chloroform/pentane solution. Repeated recrystallization steps using this solvent mixture yielded the ^{13}C labeled 42 in 5% yield.

Synthesis of compound 43. Compound 28 (0.1g) was reacted with 1.5 equivalents (0.049g) p-nitroperoxybenzoic acid (85% active) in (5mls) deuteromethylene chloride. The reaction proceeded to completion in less than 5 minutes and was shown to be quantitative by NMR spectroscopy. Methylene chloride is used because the acid by-product is not soluble. The solution was filtered to remove any solids. The reaction was also done biphasic with the second layer being buffered water. However this step is not necessary. The epoxide complex was recovered by extracting the solutions six times with H_2O (3mls) to remove any excess peracid or p-nitrobenzoic acid. The epoxide yield was 92%. Careful water extraction is the key to good yields. The ^1H and ^{13}C data are contained in Figure 63 and 64 and Table 21 below.

Table 21. ^1H and ^{13}C data for compound 43.

C#/H#	^1H	^{13}C (J _{Pt-C})
1	3.67	9.57 (379)
2	2.77	52.88(98.4)
3	2.79	5.12(420)
4	2.62	40.3(9.3)
5	3.04	47.26(53.1)
6	3.01	50.91
7	2.47	38.57(11)
8 syn	2.50	23.90
8 anti	1.35	
9 syn	2.85	63.55
9 anti	3.72	

Reaction of 44 with Z.D. Compound 44 (1 eq., 0.037g) was reacted with 0.1g Z.D. in diethyl ether (5mls) at room temperature for 2 hours. The ether was removed and the entire residue was analyzed by NMR spectroscopy in CDCl_3 . A picket fence of carbons appeared in the region were norbornyl carbons usually resonate. No platinum coupling appeared to be present, thus it was judged that no organometallic platinum complex had formed. The chloroform solution was added to pentane to precipitate the platinum species. The pentane was decanted off and the pentane

removed under low vacuum. The GC/MS revealed the presence of at least 30 different compounds. Many peaks had $m^+ + 2$ peaks indicating the incorporation of chlorine. Typically the highest mass peaks were those of the molecular ion of the dimers and trimers as described in the text or those of the dimers and trimers with the assumed loss of H_2O . Common observed highest masses were 110, 144, 146, 184, 254, 256, 238, 240, 254, and 256.

Synthesis of compound 46. Compound 45 was purchased from Aldrich and was cyclopropanated in quantitative yield as described earlier.⁹¹ Diazomethane was added until all starting material disappeared. m/e (m^+) 158, 1H 7.1dd, 7.28dd, 5.1s, 1.5dd, 1.2dd, .9dd.

Synthesis of compound 49 Compound 49 was synthesized according to the literature⁹⁴ in 60% yield which is good for these type reactions. The product was cleaned up by elution from silica gel with pentane. m/e (M^+) 142; 1H ; 7.2dd, 6.9dd, 6.8s, 3.8s, 2.1d, 2.2d.

Synthesis of compound 50. Compound 49 was cyclopropanated in quantitative yield as described earlier and purified by elution off silica gel with pentane. m/e (m^+) 156; 1H 7.18dd, 7.05dd, 3.2s, 1.5d, 1.48dd, 1.2d, 1.02dd, 0.8dd.

Synthesis of compounds 51 and 52. See synthesis of platinacyclobutanes. Compounds 46 and 50 (1.1 eq.) were reacted with 1 equivalent of Z.D. to insure complete use of the platinum source. Reaction yields were 90+%. ^{13}C data is given in Table 13.

Reaction of 51 with Diazomethane. Into a CDCl_3 solution of 51 was bubbled diazomethane until all starting materials had disappeared. The reactions were analyzed by NMR for the presence of compounds 53. The volume of the chloroform was reduced and pentane was added to precipitate the platinum species. The pentane washes were collected and the pentane removed under low vacuum. NMR and GC/MS analysis indicated that the reaction had yielded compounds 53 and the original cyclopropane in 57% and 25% yields respectively. Compound 53: m/e (m^+) 170, ^1H 7.29dd, 7.12dd, 5.60s, 5.44dd, 5.25dd, 5.90ddd.

Reaction of 52 with Diazomethane. Into a solution of 52 was bubbled diazomethane just as in compound 51 above. The solution was analyzed for compound 54. The ^1H data indicated that the divinyl product had been formed in 70% yield and the original cyclopropane in 30% yield. Characteristic peaks for the terminal vinyl groups were observed 5.15dd, 5.18dd, and 5.8ddd.

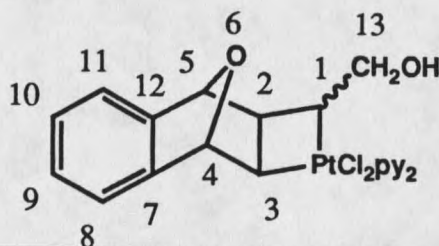
Reaction of 51 with Ethyldiazoacetate. Into a CHCl_3 (5mls) solution of 51 (0.100g) was slowly added ten equivalents of ethyldiazoacetate (0.196g). The reactions were analyzed by NMR for the presence of compounds 55 anti and 55 syn. The volume of the chloroform was reduced and pentane was added to precipitate the platinum species. The pentane washes were collected and the pentane removed under low vacuum. The products were eluted off silica with pentane. NMR and GC/MS analysis indicated that the reaction had yielded the compounds labeled 55 in 1 to 1 ratio, 80% isolated yield. Compound 55 E-isomer: m/e (m^+) 244, ^1H 7.4dd,

7.3dd, 5.6d, 5.9dd, 5.23dd, 5.42dd, 7.04dd(16 Hz, 5.7Hz), 6.18dd(16Hz, 6.2Hz), 5.74d. Z isomer m/e (M⁺) 244, ¹H 7.4dd, 7.3dd, 5.6d, 5.9dd, 5.23dd, 5.42dd, 6.24dd(11.4 Hz, 8Hz), 6.18dd(11.4 Hz, 5.9Hz), 6.744d.

Synthesis of compounds 58 and 59. Into a solution of compound 54 (10g,.069mol) in 250 mls of diethyl ether with rhodium(II) acetate dimer as catalyst (.025g) was added over a ten minute time period 2 equivalents of ethyl diazoacetate (16.9g) at room temperature. The 56 and 57 were not soluble in diethyl ether. After only a few minutes solid product crystallized out of solution and could be filtered and isolated in 98% yield. The ratio of 57 to 55 was 1.3 to 1.0. 56: m/e (m⁺) 230, 7.3d, 7.2d, 5.62s, 4.38d, 4.35(2H)q, 1.4 (totally obscured by methyl resonance at 1.4), 1.4(3H)t; 57 m/e (m⁺) 230, 7.3d, 7.2d, 5.48s, 3.72d, 4.35(2H)q, 4.35 (totally obscured by methylene resonance at 4.35), 1.4(3H)t. 56 and 57 were subjected to a variety of reducing agents, including viteride, selectride, NaBH₄, LiBH₄, and the esters were even hydrolyzed to the acid then converted via thionyl chloride to the acid chlorides as judged by IR and NMR spectroscopy. The acid chlorides were then reduced. None of these methodologies yielded any of the reduction products; instead a product with additional aromatic resonances was observed but never characterized. Compounds 56 and 57 could only be obtained in low yield 0-10% by the same methodology used for the synthesis of compounds 31 and 32. Attempts to shorten the reaction time or lower the equivalents of LAH only resulted in the

incomplete reduction of starting material. Furthermore compound 56 was selectively destroyed resulting in a final product ratio 59 to 58 of 2.5 to 1. 58: m/e (m^+) 188.2, ^1H 7.48dd, 7.2dd, 5.4s, 4.2d, 1.86m, 1.49d. 59: m/e (M^+) 188.2, ^1H 7.48dd, 7.2dd, 5.25s, 3.58d, 2.3m, 1.31d.

Table 22. ^{13}C data for compounds 60 and 61.



Compound #/ppm	60(J _{Pt-C})	61(J _{Pt-C})
1	12.3 (400)	11.2(396)
2	54.1(104)	55.8(104)
3	6.1(450)	7.9(458)
4	80.	81.1
5	81(20)	82.5(22)
6		
8 or 11	118.5	118.5
8 or 11	119.8	120.0
9 or 10	126.5	126.0
9 or 10	126.9	127.0
7	144.7(<20)	145.0(<20)
12	145.3	144.0
13	63.8(18)	66.8(20)
py-o	150	159, 149
py-m	126,126.1	126.5,127
py-p	138.8	138.5

Synthesis of compounds 60 and 61. See synthesis of platinumacyclobutanes. Compounds 60 and 61 were produced in 90+% yield. Table 22 above gives the ^{13}C data.

Synthesis of compounds 62. The methodology was the same as that used in the synthesis of 37 and 38. The yield was 53%. The compound was assigned the anti stereochemistry because to date in all ring expansion reactions involving the syn or anti hydroxymethyl platinacyclobutanes, it has been shown that the syn platinacyclobutane yields the syn platinacyclopentane and the anti platinacyclobutane yields the anti platinacyclopentane. The ^{13}C data for the platinacyclopentane ring is given here and is meant to be compared to the data in Table 13. $^{13}\text{C}(\text{JPt-C})$ C₁ 21.2(535.4), C₂ 86.3(51.3), C₃(52.2), C₄ 29.06 (576.2).

Synthesis of compounds 64. Compound 64 was synthesized from acenaphthalene purchased from Aldrich following the same cyclopropanation procedure described at the beginning of this section. The reaction could be followed by the disappearance of the olefinic peak and the appearance of the peaks for the cyclopropane protons. The yield was quantitative. m/e (m^+) 166, ^1H 7.32dd, 7.25dd, 7.23s, 2.9dd, 1.4ddd, 0.78dd.

Synthesis of compounds 65. See synthesis of platinacyclobutanes. The reaction was run for 4 hours with 1.1 equivalent of 64. The yield was 98%. Figure 73 contains the ^{13}C data.

Synthesis of compounds 69 and 70. The mixture of the epimeric esters was synthesized according to Doyle⁹³. The progress of the reaction could be followed by the disappearance of the olefinic proton peak and the appearance of cyclopropane protons. When the reaction was complete, the rhodium (II) acetate

dimer was filtered out of solution, the products were verified by GC/MS and the mixture subjected directly to the reduction procedure as described for compounds 31 and 32 above. The products from the reduction were purified by silica gel chromatography in 90% yield. 69: ^1H 7.51dd, 7.45d, 7.3dd, 3.15d, 2.86d, 1.9m 70: ^1H 7.46d, 7.44d, 7.3dd, 3.48d, 2.83d, 1.25m.

Insertion of Pt(II) into compounds 69 and 70. See synthesis of platinacyclobutanes. The presence of platinacyclobutane formation was noted in one ^{13}C spectrum but the data was not of good enough quality to claim that the platinacyclobutane had been observed. Furthermore which isomer it had chosen to insert into was completely unknown.

Synthesis of compounds 72 and 74.

Dimethylacetylenedicarboxylate was condensed in a Diels-Alder reaction with excess freshly cracked cyclopentadiene yielding as the only product 72 in quantitative yield. The excess cyclopentadiene was removed under low vacuum before it dimerized. 72: ^1H 6.9s, 3.9s, 3.8s(3H), 2.08d, 2.15d. ^{13}C 165, 152, 142, 72.5, 53, 51. Compound 72 was cyclopropanated as described earlier. The amount of a diazomethane (2 eq.) was limited to prevent the formation of large amount of dicyclopropanated product 74. Compounds 73 and 74 were produced in 60% and 10% yield respectively. Compounds 73 and 74 could be separated by silica gel chromatography using pentane. 73: ^1H 3.7 (3H), 3.1, 1.4, 1.25, 1.15, 1.05, 0.8.

Synthesis of compounds 75. See the synthesis of platinacyclobutanes. See synthesis of compound 78 for spectral data.

Synthesis of compounds 76. Compound 73 was added to 10% NaOH in H₂O. 73 is H₂O insoluble; however, the best results were obtained when the oil was stirred into the H₂O. This however was the lowest yielding step at 55%. The H₂O solution was acidified and the diacid extracted with diethyl ether. The ether was dried and removed under low vacuum. 76: ¹H (D₂O) 3.05d, 1.5dd, 1.1dd, 1.05d,.85d,.7d.

Synthesis of compounds 77 and 78. See the synthesis of platinacyclobutanes. Compound 77 was purified as described under the synthesis of platinacyclobutanes and the yield was 85%. The complex was redissolved in 1 ml of chloroform and 1 equivalent of ethylenediamine added. Complex 78 is only sparingly chloroform soluble. Pentane was added to the solution to precipitate 79. Compound 79 was washed three times with pentane. The ¹³C data for 75 and 78 in CHCl₃ and 79 in basic D₂O are given below, Table 23.

Table 23. ^{13}C data for compounds 75 and 78.

75 78			
Compound #/ppm	75($J_{\text{Pt-C}}$)	77($J_{\text{Pt-C}}$)	78($J_{\text{Pt-C}}$)
1	-3.8(387)	-3.7(366)	-5.54(345)
2	51.0	51.25(90)	51.6(87.4)
3	5.85(430)	5.8(422)	7.23(383)
4	49.5	49.54	48.9
5 or 6	143.1	(#5)142.9	144.0
5 or 6	143.5	143.8	143.8
7	50.5(20)	50.95	50.25(<10)
8	43.2	41.61	42.02
9 or 10	165.2	167.1	174.8
9 or 10	165.5	168.7	175.35
11	51.8		
12	51.8		
en			43.02, 42.8
py-o	150	149.8, 149.4	
py-m	125	126.2, 125.3	
py-p	138	138	

Synthesis of compound 81 and 82. To 5g of 80 was added in a round bottom flask 20 mls of freshly distilled thionyl chloride. The solution was let stir overnight and the excess thionyl chloride and byproducts were removed under low vacuum. Chloroform (20 mls) was added and removed under low vacuum. This step was repeated three times. ^1H NMR spectroscopy and IR indicated the presence of 81. The yield was essentially quantitative. ^1H 6.32d, 6.18d, 3.85d, 3.5s, 3.4s, 3.15d, ^{13}C 174.5, 173.1, 137.9, 135.2, 60,

59.2, 48.8, 47.5, 47. To a solution of 83 (.002mol, 0.5g) in 4 ml pyridine was added 81 (.001mol, 0.124g). The reaction turned a dark purple and purple crystals fell out of solution. The solution was stirred overnight. The crystals dissolved and the reaction turned a light tanish-purple. The pyridine was coevaporated with chloroform under low vacuum and the products purified by silica gel chromatography. The ^{13}C spectra indicated the presence of both peaks for the protected sugar with a slight shift in the hydroxyl bearing carbons and the presence of peaks for the diacid component; the carbonyls of compound 81 had shifted. IR indicated no presence of an acid.

Synthesis of compound 84. Compound 82 was cyclopropanated quantitatively as described at the beginning of this section. The product was chromatographed with silica gel. The desired product was judged to be present by the addition of cyclopropane protons at -.2 and .25. 84: ^{13}C (excluding the resonances for the protected sugar) It should be noted that the resonance of most of the norbornyl moiety were doubled including the carbonyls probably indicating two ways for the sugar to be bound. Only the middle of the resonance will be reported here. 174.5, 173.1, 51.0 , 49.0, 41.9, 39.9, 14.9, 11.8, 2.0

Synthesis of compound 85. A solution 60% acetic acid H_2O at reflux was used to cleave the isopropylidene protecting groups off of the sugars of 84. The reaction was run 24 hours. The solvents were removed under low vacuum. The resonances of the protecting groups had disappeared from the proton spectra (the methyls

resonate between 1.2 and 1.4 in the proton spectra and between 24 and 27 in the ^{13}C spectra). The norbornyl resonances were still present as reported in 84 but the sugar resonances indicated that sugar had epimerized and 85 was really a mixture of compounds. 1 equivalent of Z.D. was added to 85 in diethyl ether and the solution was stirred 12 hours. See synthesis of platinacyclobutanes. No insertion products were observed. Z.D. is more soluble in methylene chloride and the reaction was also run in this solvent at room temperature and at reflux, but again no insertion products were observed.

Synthesis of compound 86. To a solution of 84 in chloroform was added 1 equivalent of Z.D. (.1g) The solution was refluxed vigorously for 30 minutes. The reaction was worked up as under the section for synthesis of platinacyclobutanes. Platinum coupled ^{13}C resonances at -13.0 and 8.0 ppm indicated that platinacyclobutane formation had occurred but in low yield (10%). Peaks for starting material were also present. Compound 86 was not isolated.

Synthesis of compound 88. Compound 76 was available from the synthesis of 78. The acid chloride was formed exactly as described for compound 81 in quantitative yield. ^{13}C 163, 154.5, 48.0, 36.5, 23.2, 19.9. The protected sugar was added as described for compound 82. ^{13}C and ^1H spectra confirmed the product. When compound 88 was subjected to the conditions designed to remove the protecting groups (see compound 85), the silica gel chromatography step separated the protected sugar from the

norbornyl moiety indicating that cleavage of the ester bond had occurred.

Synthesis of compound 89. See the synthesis of platinacyclobutanes. After the normal workup of platinacyclobutanes the product was redissolved and 1 equivalent of ethylene diamine was added. The product was precipitated out of solution with pentane and washed 3 times with pentane. The ^{13}C spectra contained the peaks indicative of platinacyclobutanes of the norbornyl moiety: -14.2 (J_{Pt-C} 375) and 8.0 (J_{Pt-C} 416) and the ethylenediamine carbons at 43.0. When 89 was subjected to the conditions designed to remove the isopropylidene protecting groups (see compound 85) yellow crystals fell out of the solution. When these crystals were dissolved in DMSO and compared against the spectra of authentic 71 they proved to be identical.

Synthesis of compound 94. Compound 90 was reacted with the diazomethane with palladium as a catalyst as described at the beginning of this section. Compound 91 was purified by distillation. ^1H 3.68s(OMe), 2.15d, 1.0m, .5dd, .12dd. Compound 91 was hydrolyzed using 10% NaOH H_2O . The water was acidified and 92 extracted with ether. The ether was dried and removed under low vacuum. ^1H 12.3, 2.2d, 1.12m, 0.52dd, 1.1dd. 91 was reacted with thionyl chloride as described for 81 producing 93 in quantitative yield. ^1H 2.8d, 1.15m, .65dd, .22dd, 0 93 was reacted with 83 in pyridine as described for 82. After silica gel chromatography 94 was obtained in 50% yield. ^1H (Minus the resonances for the moiety due to 83) 2.2d, 1.05m, .55dd, 12dd.

Synthesis of compound 95. Compound 94 was reacted with Z.D. (see synthesis of platinacyclobutanes). The ^{13}C spectrum contained a peak upfield which is characteristic of platinacyclobutanes in particular that of compound 96, -7.4 and peaks at 39 and 42 compare to 96 below. The signal to noise however was not high enough to see the platinum satellites. The yield of the reaction was very low., 0-10%

Synthesis of compound 96 Compound 91 was reacted with Z.D.(see synthesis of platinacyclobutanes). After workup 96 was isolated in 88% yield. ^{13}C -7.64(J_{Pt-C} 349.2), 39.13(J_{Pt-C} 101.5) 42.02(J_{Pt-C} 50.2) 51.1, 173 and pyridine resonances at 125, 138, 150.

Kinetic experiments. All experiments were run in d_8 -THF using temperature control and the parameters were such that the spectra were integratable (a relaxation delay of 5 seconds). The platinum species was added to the d_8 -THF either as a solid or in the case of reactions done at low concentration from a freshly prepared solution of the platinum species in d_8 -THF. A spectrum of the starting compound was taken. Using a 1 or 10 μl syringe the compound whose rate of reaction was under investigation was injected onto the side of the NMR tube containing the platinum species and shaken by tipping upside down 5-7 times. Time zero was considered to be the point of initial mixing. Within 3 minutes of the initial mixing the first set of data was collected.

An automated program was written which wrote the files at given intervals. Another program was written which read these

files and automatically phased and integrated the peaks at preset p.p.m. ranges. The disappearance of the organic species as contrasted to the disappearance of the platinum species was followed.

Bioassays. Bioassay experiments were performed according to reference 90.

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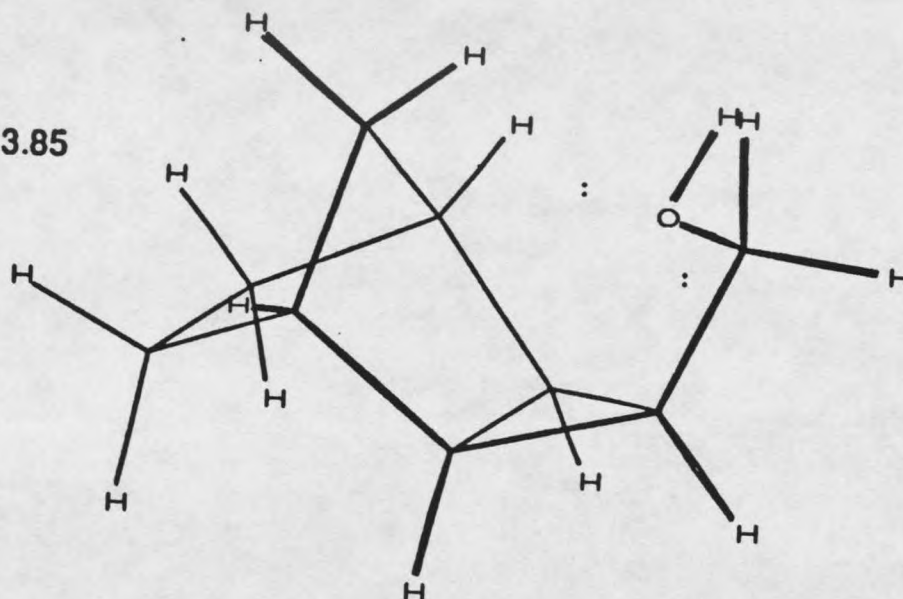
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APPENDICES

APPENDIX A

MM2 CALCULATIONS COMPOUNDS AND STRUCTURES
10, 11, 13, 21, 28, 29, 31,32, 51, 52, 97, 98, 102, 103

MNDO $H_{\text{form}} = -13.85$



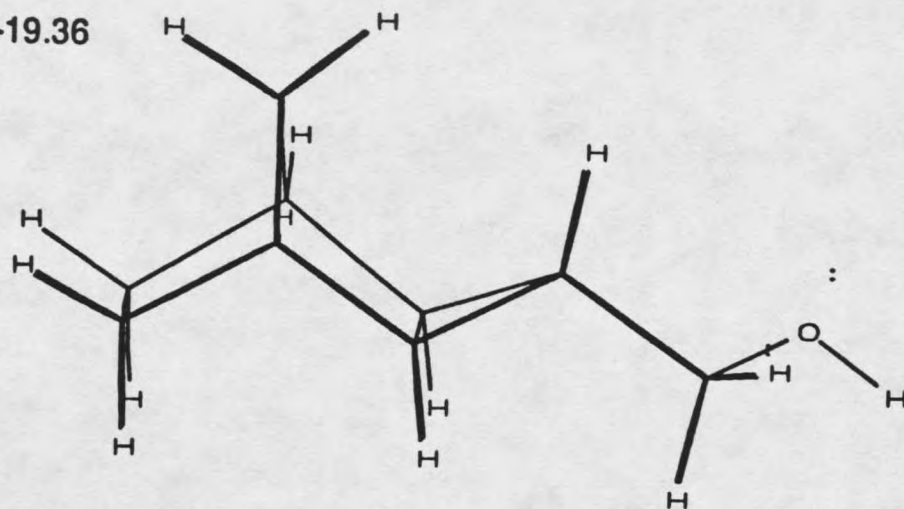
185

File = T2

STR	1.70	BEND	23.81	S-B	-1.06	TOR	14.63
VDW	5.43	DIP	.21	DIPOLE MOMENT		1.8750	
Heat of Formation		-18.615		Strain energy		55.942	

Figure 97. MM2 energy minimization, compound 97.

MNDO $H_{\text{form}} = -19.36$

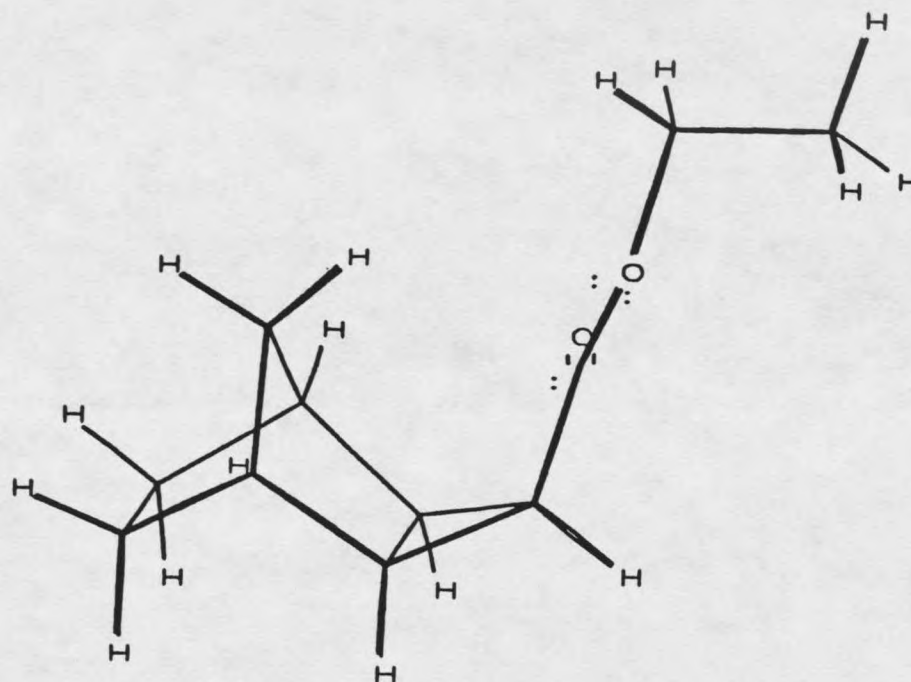


186

File = T1

STR	1.58	BEND	18.32	S-B	-1.20	TOR	12.93
VDW	4.72	DIP	.21	DIPOLE MOMENT	1.6156		
Heat of Formation	-26.758	Strain energy	47.799				

Figure 98. MM2 energy minimization, compound 98

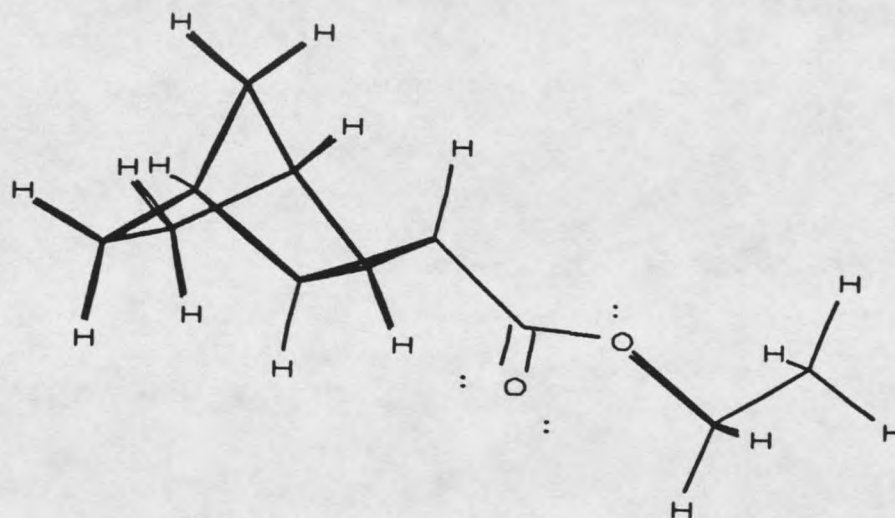


187

File = T13

STR	1.70	BEND	21.85	S-B	-1.07	TOR	12.27
VDW	5.15	DIP	.65	DIPOLE MOMENT	1.6367		
Heat of Formation	-64.056	Strain energy	51.778				

Figure 99. MM2 energy minimization, compound 102.

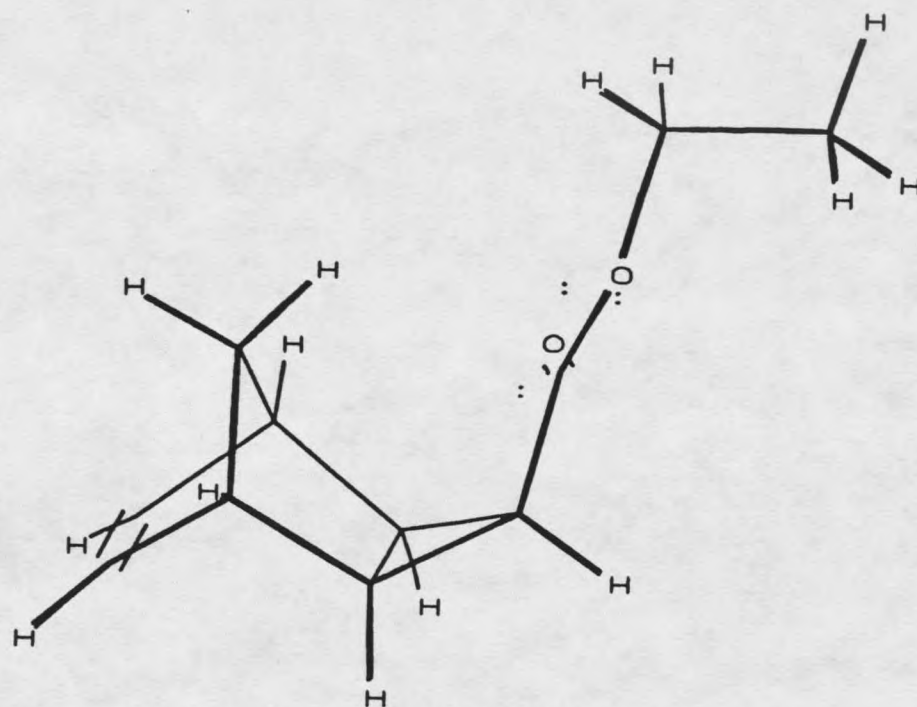


188

File = T9

STR	1.67	BEND	18.70	S-B	-1.18	TOR	11.94
VDW	5.27	DIP	.62	DIPOLE MOMENT		1.7619	
Heat of Formation		-67.581		Strain energy		48.253	

Figure 100. MM2 energy minimization, compound 103.

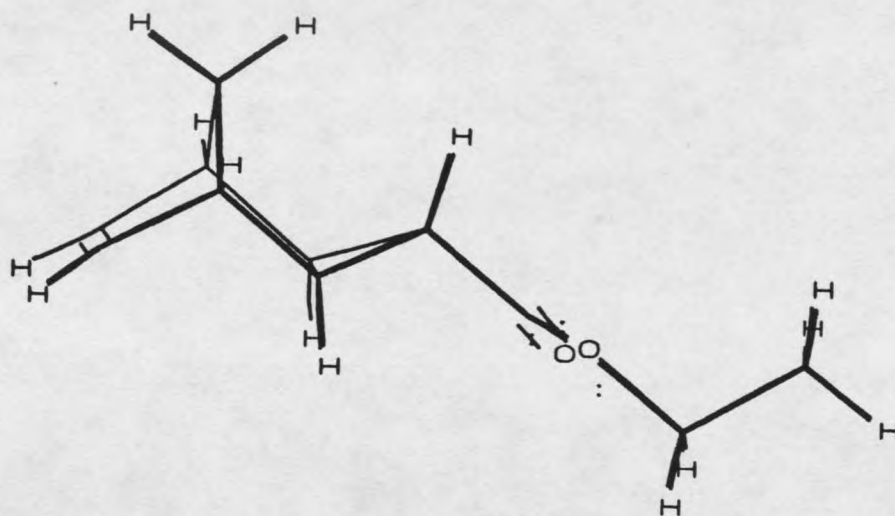


189

File = T14

STR	1.61	BEND	29.92	S-B	-1.25	TOR	8.98
VDW	4.95	DIP	.98	DIPOLE MOMENT		1.5716	
Heat of Formation		-29.800		Strain energy		58.252	

Figure 101. MM2 energy minimization, compound 31.

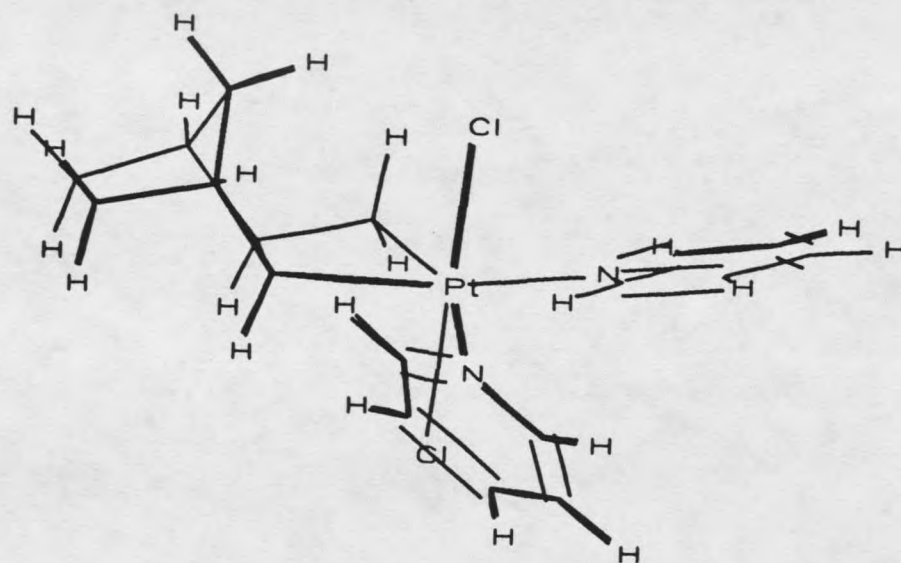


190

File = T10

STR	1.66	BEND	26.44	S-B	-1.39	TOR	8.81
VDW	5.17	DIP	.91	DIPOLE MOMENT		1.7556	
Heat of Formation	-33.388		Strain energy		54.664		

Figure 102. MM2 energy minimization, compound 32.

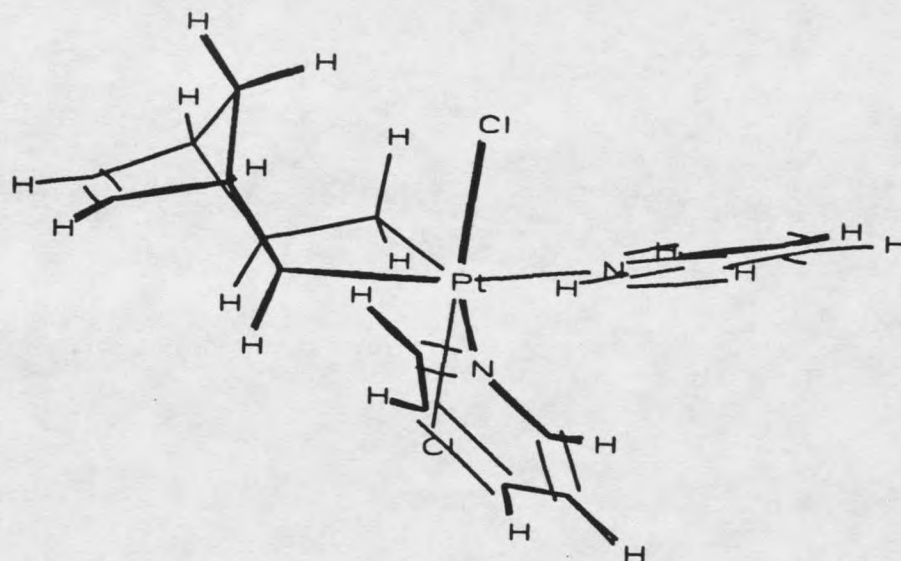


191

File = T8

STR	3.34	BEND	14.79	S-B	-.87	TOR	28.77
VDW	12.87	DIP	1.83	DIPOLE MOMENT		1.9357	
Heat of Formation		139.612		Strain energy		55.264	

Figure 103. MM2 energy minimization, compound 21.

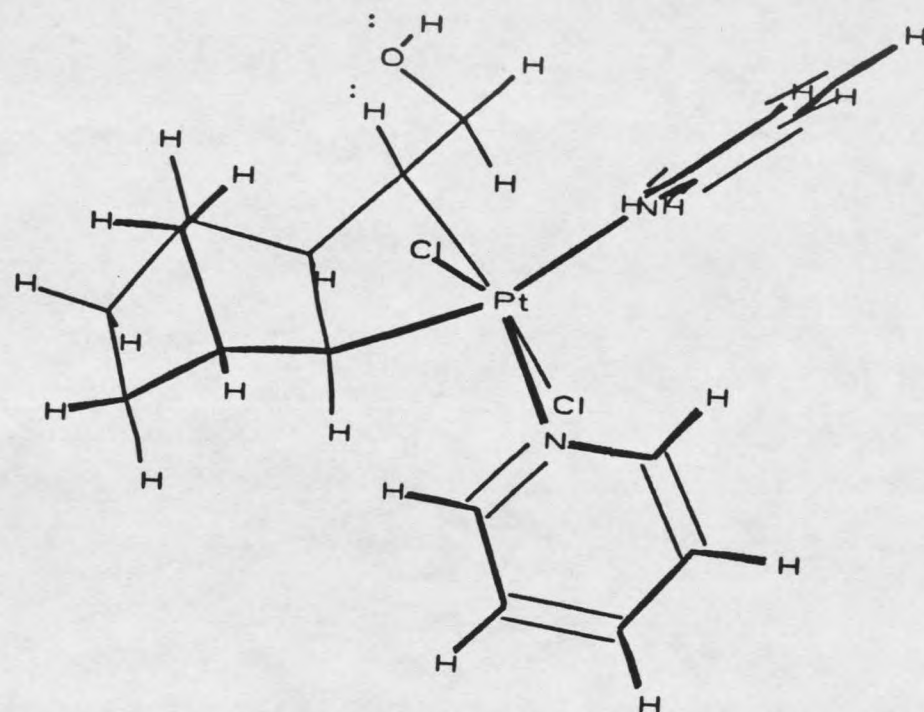


192

File = T12

STR	3.34	BEND	22.49	S-B	-1.10	TOR	24.05
VDW	12.76	DIP	2.14	DIPOLE MOMENT		2.1298	
Heat of Formation		172.182		Strain energy		60.052	

Figure 104. MM2 energy minimization, compound 10.

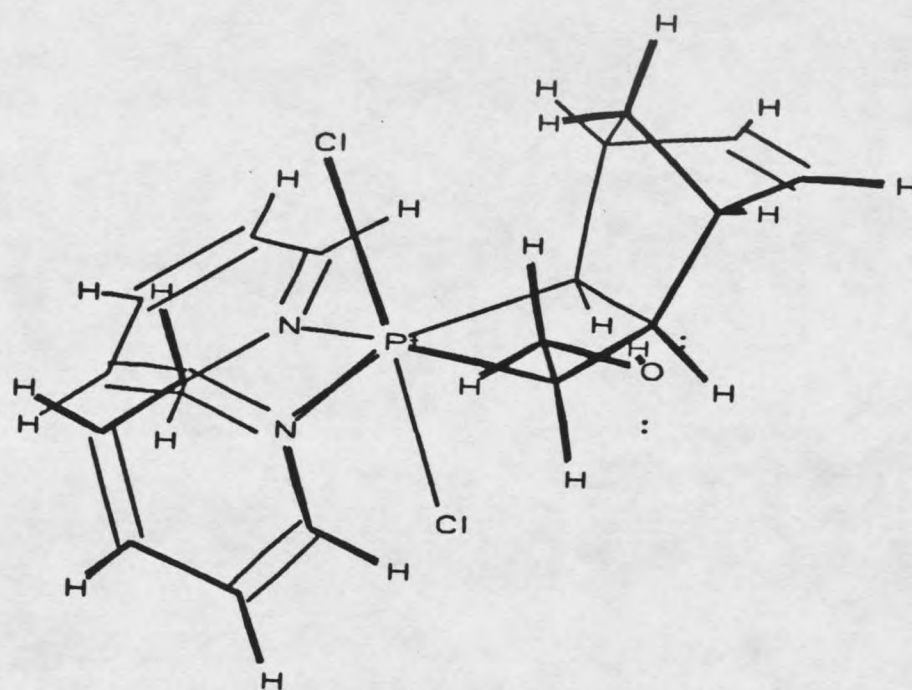


193

File = T15

STR	3.98	BEND	16.36	S-B	-.80	TOR	28.73
VDW	14.47	DIP	1.89	DIPOLE MOMENT	3.3984		
Heat of Formation	97.915	Strain energy	57.612				

Figure 105. MM2 energy minimization, compound 11.

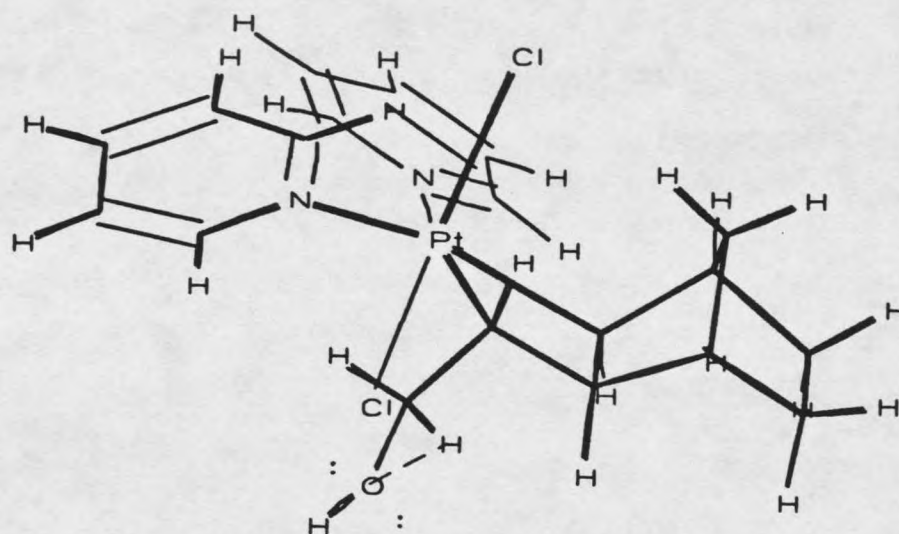


195

File = T7

STR	3.99	BEND	23.74	S-B	-.98	TOR	24.65
VDW	14.34	DIP	1.86	DIPOLE MOMENT		3.3453	
Heat of Formation		130.491	Strain energy		62.406		

Figure 107. MM2 energy minimization, compound 28.

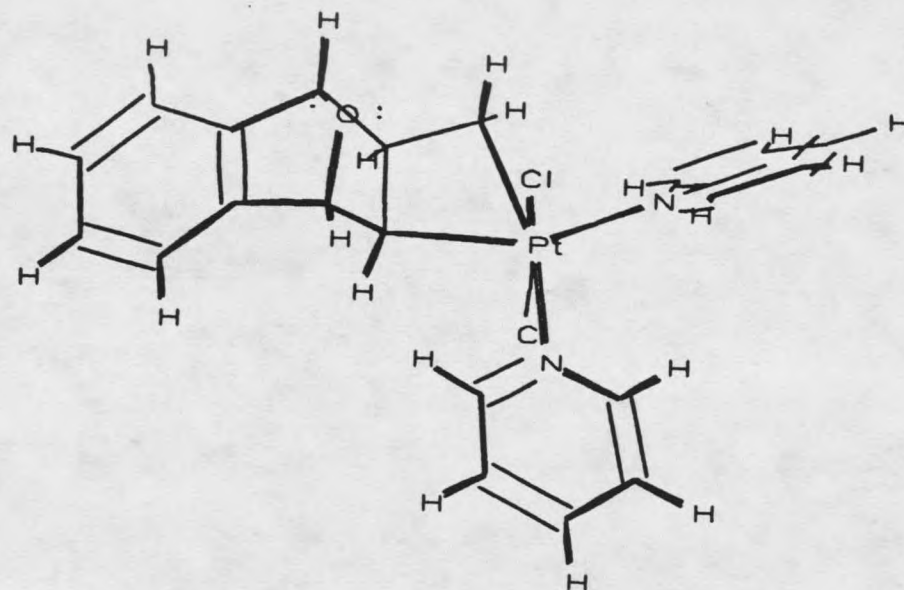


196

File = T4

STR	3.61	BEND	15.24	S-B	-.80	TOR	29.14
VDW	13.80	DIP	2.24	DIPOLE MOMENT		2.4852	
Heat of Formation		96.532		Strain energy		56.229	

Figure 108. MM2 energy minimization, compound 29.

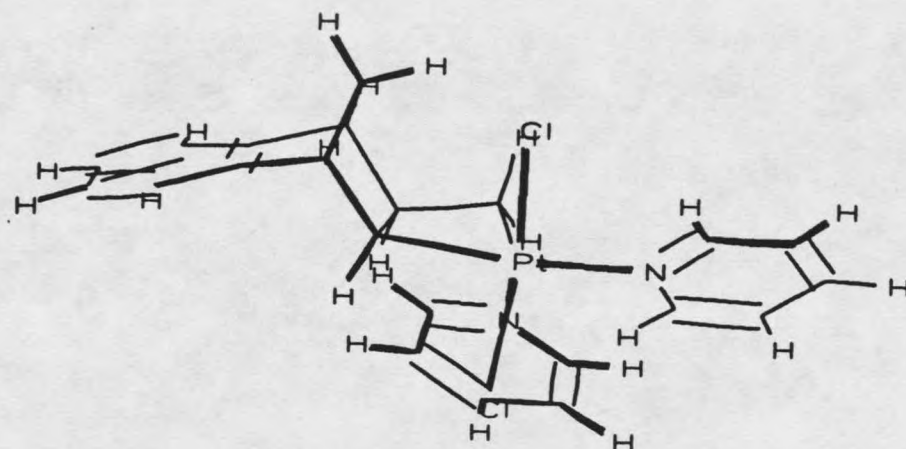


197

File = T11

STR	3.47	BEND	25.09	S-B	-.95	TOR	29.60
VDW	13.52	DIP	3.07	DIPOLE MOMENT		2.2039	
Heat of Formation		146.294		Strain energy		66.798	

Figure 109. MM2 energy minimization, compound 51.



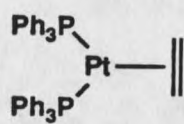
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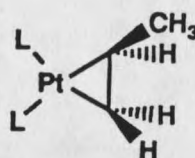
STR	3.64	BEND	23.32	S-B	-1.02	TOR	29.36
VDW	14.39	DIP	2.40	DIPOLE MOMENT	2.0312		
Heat of Formation	176.374	Strain energy	68.454				

Figure 110. MM2 energy minimization, compound 52.

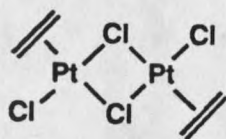
APPENDIX B
STRUCTURES



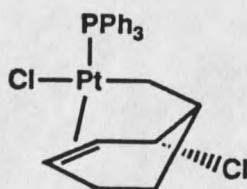
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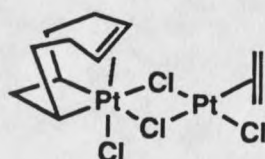
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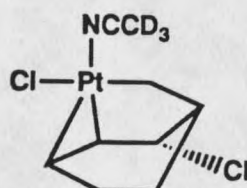
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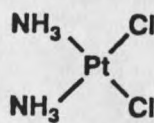
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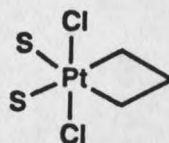
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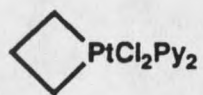
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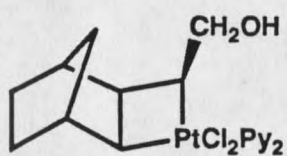
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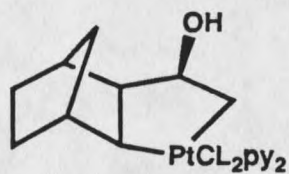
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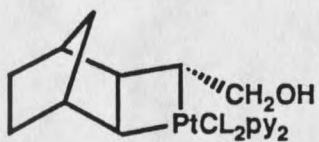
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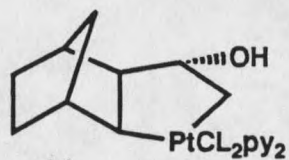
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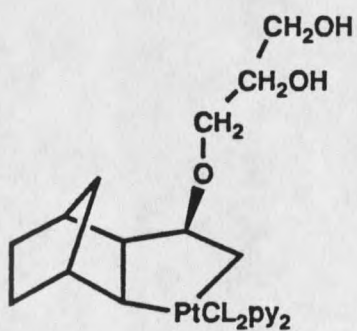
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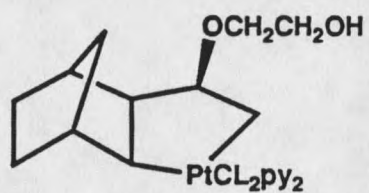
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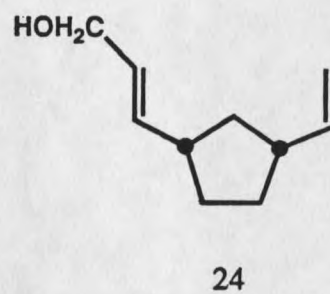
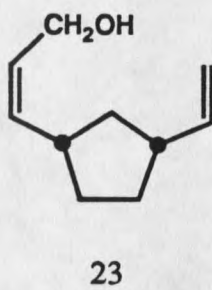
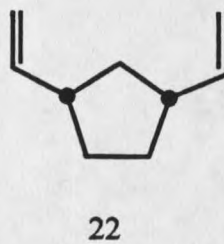
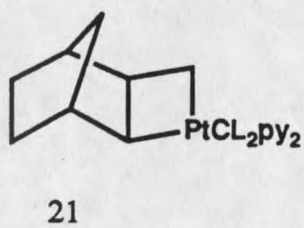
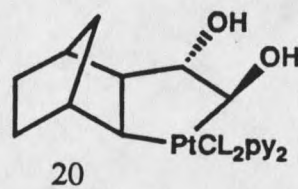
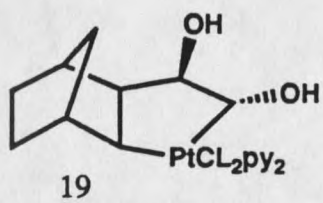
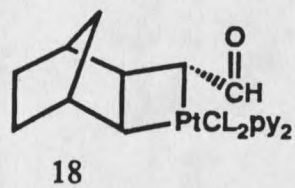
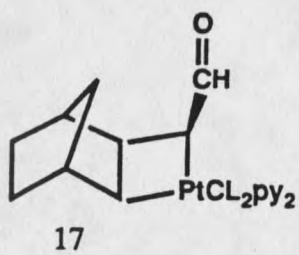
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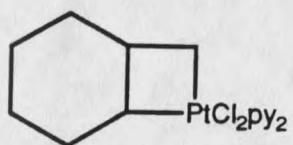


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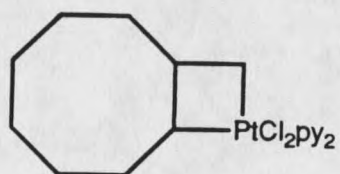


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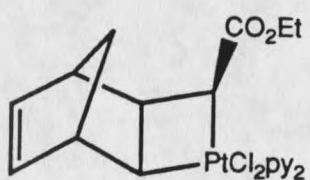




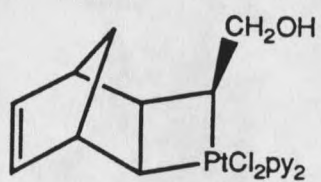
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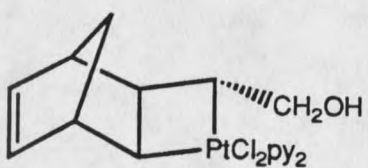
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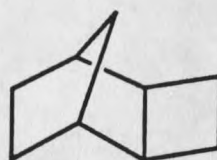
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28



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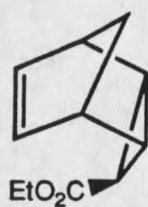
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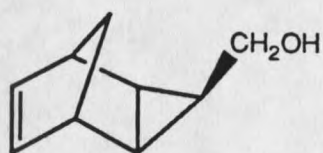
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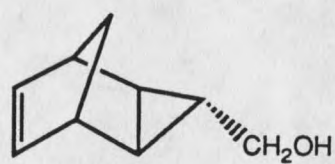
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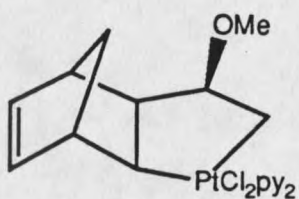
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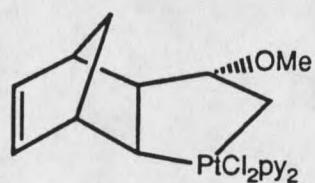
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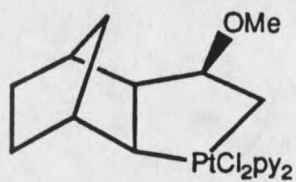
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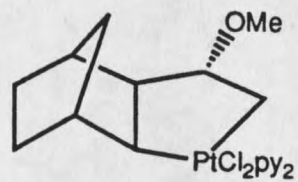
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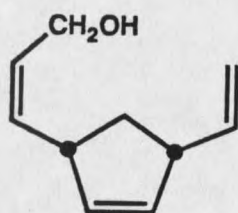
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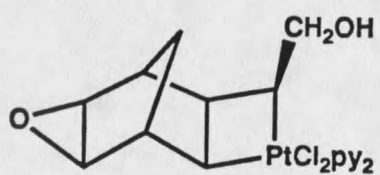
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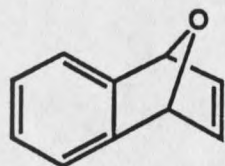
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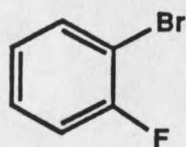
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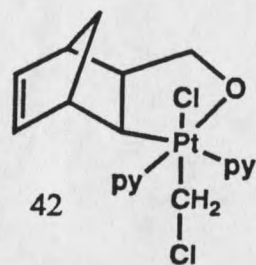
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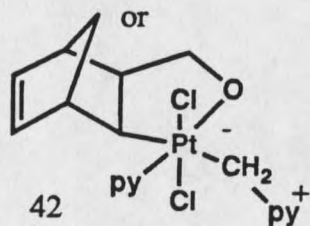
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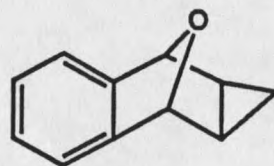
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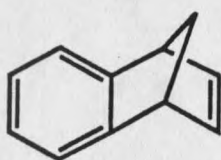
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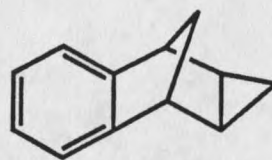
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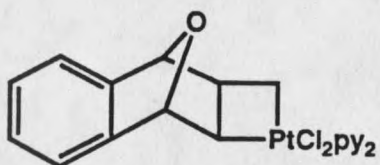
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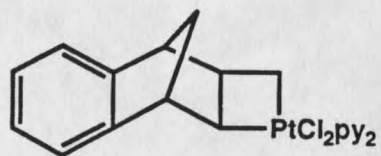
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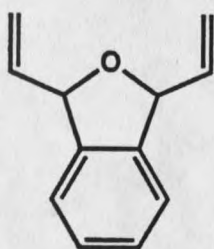
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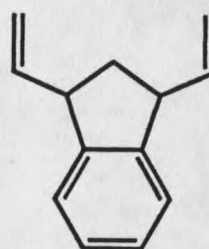
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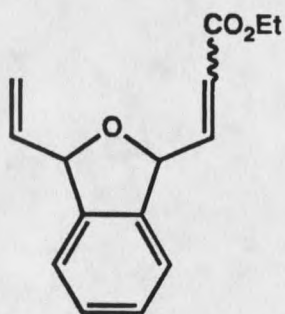
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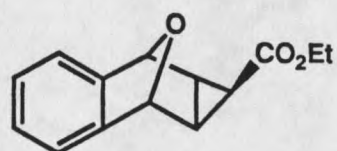
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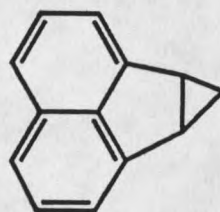
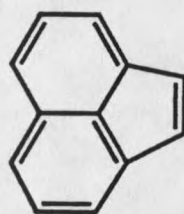
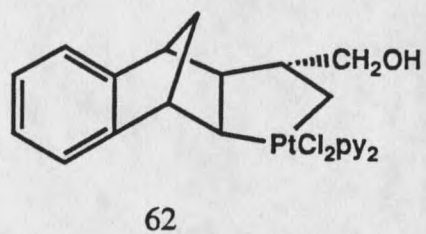
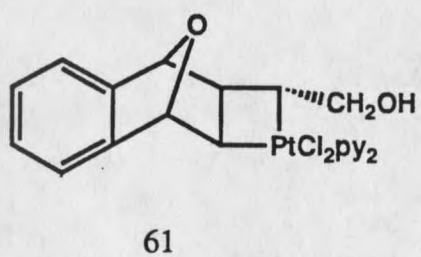
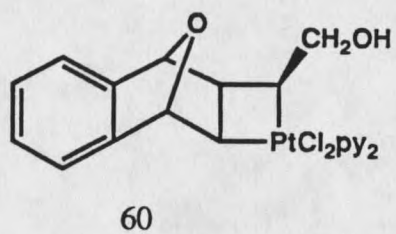
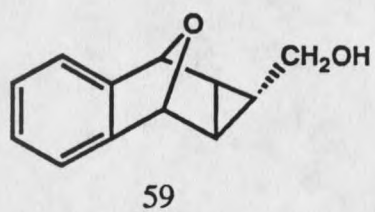
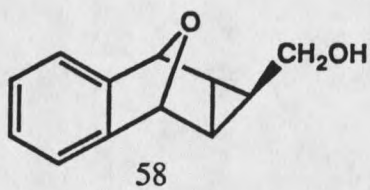
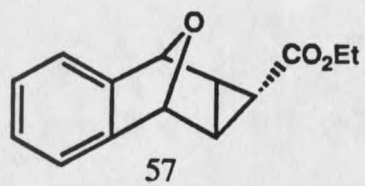
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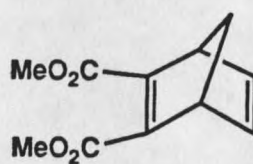
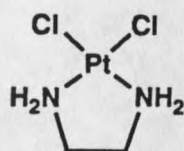
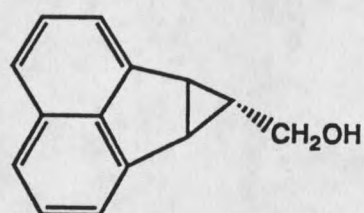
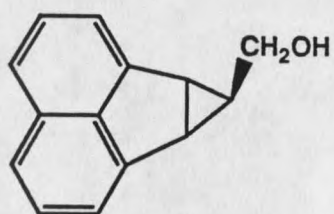
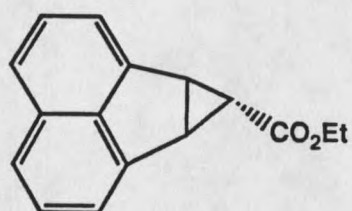
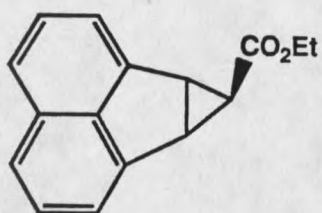
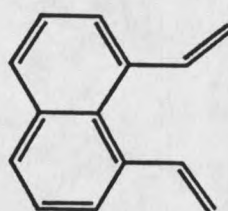
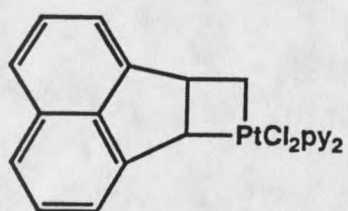
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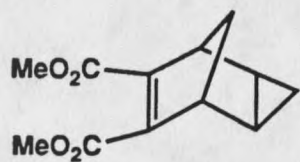


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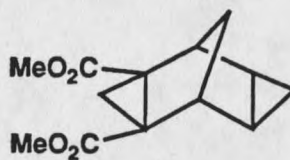


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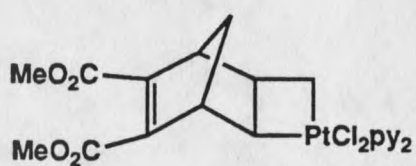




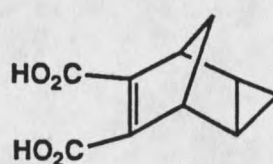
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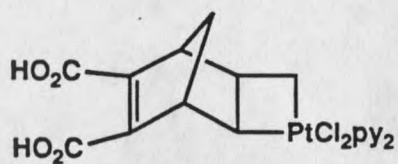
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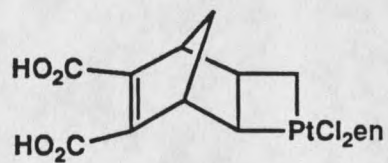
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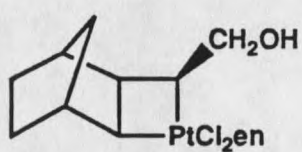
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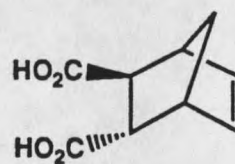
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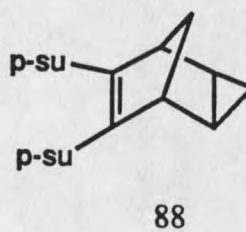
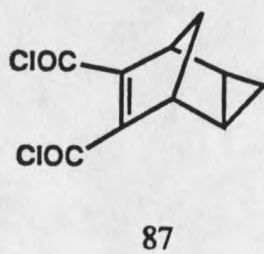
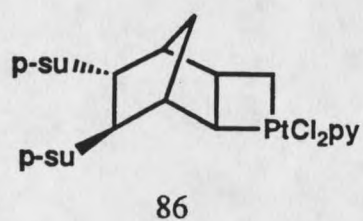
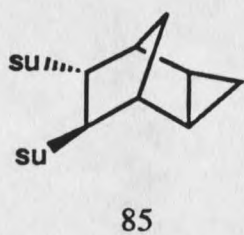
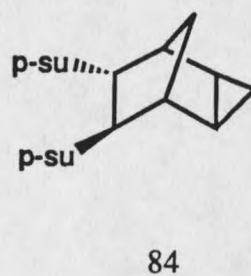
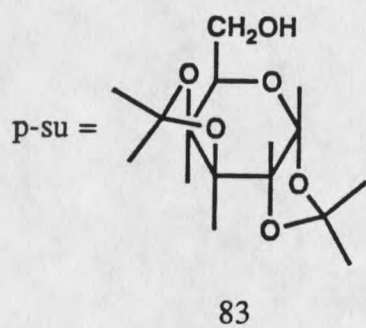
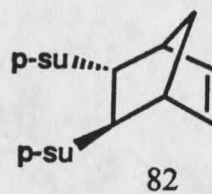
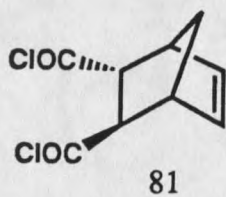
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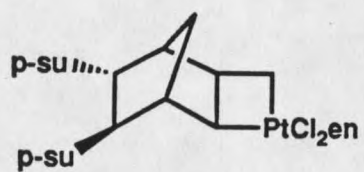


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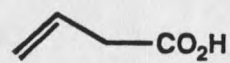


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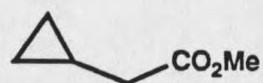




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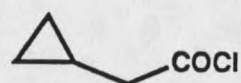
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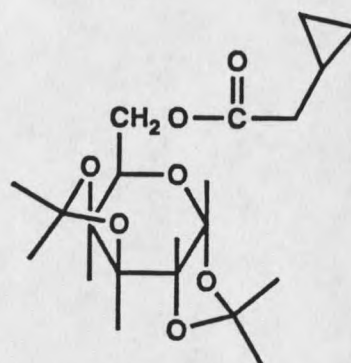
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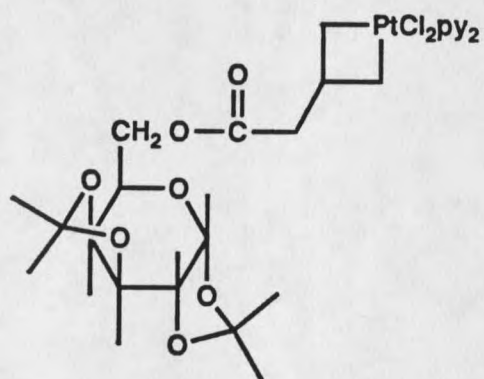
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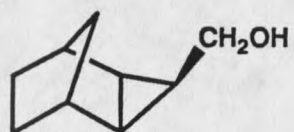
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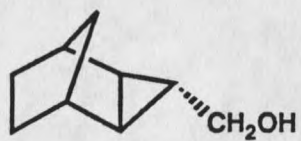
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