Study of the Stereochemical and Reactivity Phenomena of the Addition Reaction of 8-Membered Cyclic Nitrone by NMR Spectroscopy

by

Said Salman Al-Jaroudi

A Thesis Presented to the

FACULTY OF THE COLLEGE OF GRADUATE STUDIES

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
Requirements for the Degree of

MASTER OF SCIENCE

In

CHEMISTRY

May, 1996

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DHAHRAN 31261, SAUDI ARABIA

COLLEGE OF GRADUATE STUDIES

This thesis, written by

Said Salman Al-Jaroudi

under the direction of his Thesis Advisor and approved by his Thesis Committee, has been presented to and accepted by the Dean of College of Graduate Studies, in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN CHEMISTRY.

Thesis Committee

Chairman (Dr. H. Perzanowski)

Member (Dr. Sk. Asrof Ali)

Member (Dr. M. I. M. Wazeer)

Chairman, Department of Chemistry

Dean, College of Graduate Studies

Date 26.6.96

بسم الله الرحمن الرحيم

اللهم صل على محمد وآله الطيبين

الطاهرين وعلى صحبه المنتجبين

TO MY FAMILY

ACKNOWLEDGMENTS

First and foremost thanks to Allah, Lord of the universe, who gave me strength, patience and ability to accomplish this research. My blessings and greetings be upon prophet Mohammed, his posterity, and his companions.

My appreciation and acknowledgment are due to the King Fahd University of Petroleum and Minerals for financial support of this thesis.

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Finally, a word of appreciation goes to my family and friends for their morale support and encouragement.

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خلاصة الأطروحة

اسـم الـطـالب : سعيد سلمان الجارودي

عنـوان الدراسة : دراسة ظاهرة السلوك الكيميائي المجسم و سرعة التفاعل لتفاعلات الإضافة لنيترون حلقي ثماني الأطراف بواسطة مطياقية الطنين النووي المغنطيسي

حقل التخصص : الكيمياء

تاريـخ الشهـادة: ذو الحجة ١٤١٦ هـ (مايو ١٩٩٦ م)

لقد تمت بنجاح دراسة الإضافة الحلقية ثنائية القطب (١ر٣) لعدة الكينيات من أحادية وثنائية التعويض مـع ٣، ٤، ٥، ٦، ٧–بنتهيدرو–٢ هيدروجين–أوندكين ١–أو كسيد. وقد اعتمدت المدارات الجزئيـة الأماميـة في تفسـير الدرجـة العالية الملحوظة لتحكم الاتجاه الكيميائي الموضعي"regiochemical" في هـذه التفـاعلات، في حـين تم تفسـير انتقائيـة التجسيم "stereoselectivity" بالنظر إلى العوامل الفراغية والتفاعلات المدارية الثانوية.

إن ثوابت سرعة تفاعل الإضافة الحلقية للنيترون الحلقي ثماني الأطراف مع ميثل أكريلت و ميثل ميثاكريلت قـد عينت بواسطة الطنين النووي المغناطيسي للبروتون "^{1}H NMR" في درجات حراريـة مختلفـة. وقـد أخـذت في الاعتبـار عدة عوامل لتفسير الاختلاف في سرعة تفاعلات الإضافة مثل الإجهاد الالتوائي "torsional strain"، وإجهـاد انحنـاء زاوية الرابطة، والعوامل الفراغية (من قبيل تنافر عدم الترابط) في حالة التحول.

تفاعل غاز الإثيلين مع عدة نيترونات حلقية مختلفة الأطراف مكننا ولأول مـرة مـن تحضـير نواتـج أوليـة ثنائيـة الحلقة ذات ٥–٥، ٦–٥، ٧–٥، و٨–٥ الأطراف الخالية من أي تعويض.

كما تضمنت الدراسة تحديـد قيـم حـاجز انقـلاب النيـتروجين "nitrogen inversion" في نواتـج تفـاعلات الإضافة الحلقية للنيترون الحلقي ثماني الأطراف وذلك بواسطة التحليل الدقيق لشكل النطـاق "band shape" لطيـاف الطنين النووي المغنطيسي للـبروتون والكربـون، وكـانت قيـم حـاجز إنقـلاب النيـتروجين تـتراوح بـين ٥ر٥٣–٤ر٥٧ كيلـو جول/مول. أن المتشكل الرئيس كان دائما ثنائي الجانب "trans conformer" وهـو في حالـة اتـزان مـع المتشـكل ذي أحادي الجانب "cis conformer" بواسطة الانقلاب البطيء للنيتروجين.

درجة الماجستير في العلوم

جامعة الملك فهد للبترول والمعادن

الظهران، المملكة العربية السعودية

مايو ١٩٩٦ م

THESIS ABSTRACT

Name of Student : Said Salman Al-Jaroudi
Title of Study : Study of Stereochemical and Reactivity Phenomena of Addition of 8-Membered Cyclic Nitrone by NMR Spectroscopy
Major Field : Chemistry
Date of Degree : May, 1996

A study of the regio- and stereo-chemical behavior of the 1, 3-dipolar cycloaddition of 3, 4, 5, 6, 7-pentahydro-2H-undecane 1-oxide with a series of mono- and di-substituted alkenes has been achieved. The high degree of both regiochemical and stereochemical control observed in these reactions has been explained in terms of steric factors and secondary orbital interaction in the transition states. Significant secondary orbital interactions are observed in the addition reaction of alkenes having conjugated methoxycarbonyl substituents or having oxygen at allylic position.

Rate constants for the cycloaddition of 3, 4, 5, 6, 7-pentahydro-2H-undecane 1-oxide to methyl acrylate and methyl methacrylate have been determined at different temperatures by ^{1}H NMR spectroscopy. The activation parameters indicate the concerted nature of the reaction. Differences in the rates of cycloadditions have been explained in terms of combination of various factors such as torsional strain, bond angle bending strain and steric factors (non-bonded repulsion) in the transition state.

The reaction of ethylene with 5, 6, 7, and 8-membered nitrones led us to prepare for the first time the very important parent 5-5, 6-5, 7-5, and 8-5 fused ring systems and determine their nitrogen inversion barriers.

The nitrogen inversion barrier in the 8-membered nitrone cycloaddition products has been determined by detailed band shape analysis of proton and carbon NMR spectra and were in the range of 53.5 to 57.4 kJ/mol. The major isomer is shown to be the trans isomer which is in equilibrium with the minor isomer (cis conformer) by a relatively slow nitrogen inversion.

Master of Science Degree
King Fahd University of Petroleum and Minerals
Dhahran, Saudi Arabia
May, 1996

CHAPTER 1

INTRODUCTION

The use of 1,3-dipolar cycloaddition of nitrones in organic synthesis has developed quite rapidly in recent years.[27b] Constructing the isoxazolidine ring can be accomplished by this type of reaction, which is indeed the best template and also efficient in incorporating multiple stereocenters in a single step. Among a plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemicals. This was possible largely owing to the brilliant efforts of Huisgen,[27, 22] LeBel[21] and Tufariello[27] who explored systematically the inter- and intra-molecular 1,3-dipolar cycloaddition. The nitrone cycloadditions have culminated in the synthesis of several interesting alkaloidal and non-alkaloidal natural prouducts.[24a] While, the regiochemical aspects of nitrone cycloadditions have been explored in detail, the progress in the study of stereochemical details has been hampered in most cases as a result of the difficulties associated with unambiguous assignment of adduct configurations.[28, 35]

The regio-, stereochemical and reactivity features associated with 1,3-dipolar cycloaddition reactions of cyclic nitrones with a series of mono- and di-substituted alkenes have been explored in some detail.

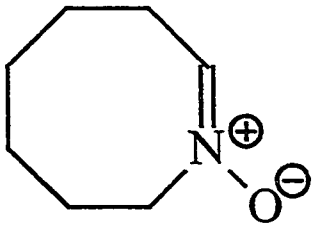
The frontier orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena of 1,3-dipolar cycloadditions. According to Sustmann's classification, the nitrone cycloaddition is a type (II) process, where both HOMO (nitrone), LUMO (alkene) and LUMO (nitrone), HOMO (alkene) interactions contribute to the stabilization of the transition state. Both electron-rich and electron-deficient alkenes undergo addition faster than normal alkenes

In light of the importance of the eight membered nitrone, our objectives in this study were to undertake:

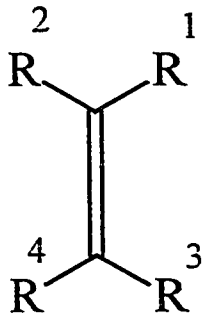
(i) a systematic study of the regio- and stereochemical details of the nitrone (I) to several mono- and di-substituted alkenes (II).

(ii) a kinetic study of the additions of the nitro (I) to several alkenes (II).

(iii) a study of nitrogen inversion in substituted 1-oxa-11-azabicyclo [6,3,0]undecane, the resultant cycloaddition products(III).



(I)



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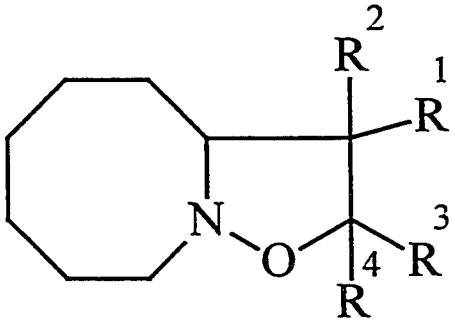


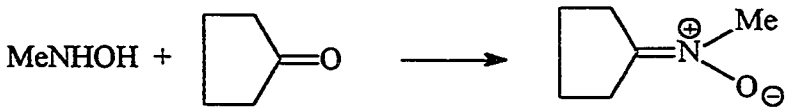
(III)

CHAPTER 2

THE CHEMISTRY OF NITRONES

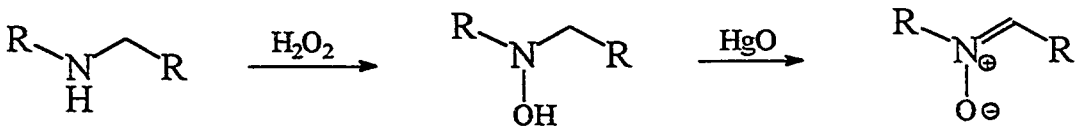
2.1 SYNTHESES OF NITRONES

Preparatory aspects of nitrone synthesis have been reviewed in detail.[1-6] The general method of preparation of nitrone is the condensation of aldehydes or ketones with hydroxylamines. Thus, cyclopentanone (**2**) reacts with N-methylhydroxylamine (**1**) at -10°C to give the corresponding nitrone (**3**).[7]



(1) (2) (3)

The conversion of secondary amines (**4**), (**5**) and (**10**) to the corresponding hydroxylamines (**6**), (**7**), and (**11**) has been performed by a variety of oxidants, the most notable being hydrogen peroxide.[8] Oxidation of hydroxylamines (**6**) and (**7**) in presence of mercuric oxide affords the corresponding nitrones (**8**) and (**9**).



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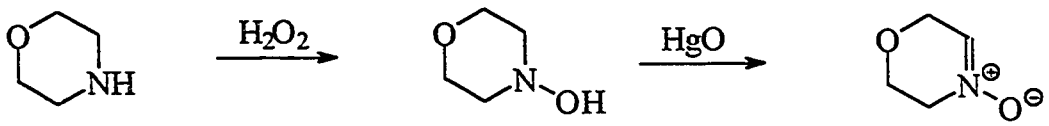
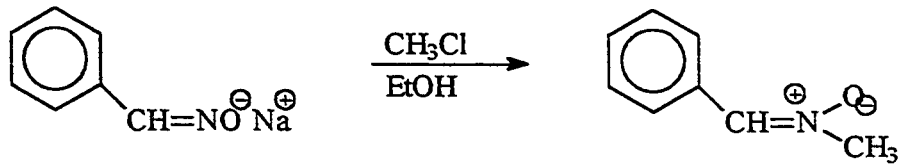


(5) (7) (9)

(10) (11)

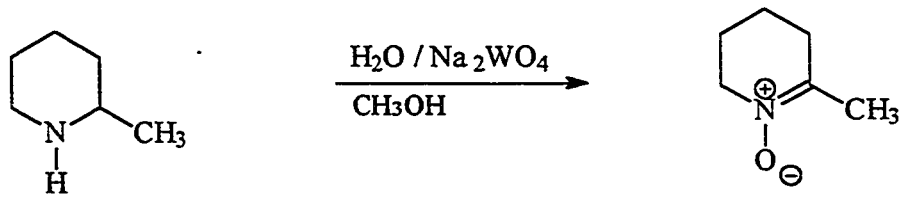
a, N = 1
b, N = 2
c, N = 3

A convenient synthetic method to α-phenyl-N-substituted nitrone (**13**) has been obtained by alkylation of anti-benzaldoxime (**12**)[10].



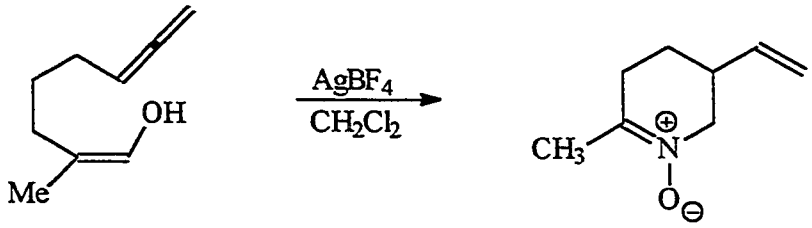
(12) (13)

Tungstate catalyzed oxidation of secondary amines (**14**) to give the corresponding nitrones (**15**) in good to moderate yield has been reported in the presence of sodium tungstate in either methanol or water at 0°C.[11]



(14) (15)

Regioselective synthesis of substituted heterocyclic nitrones may be achieved by the Ag+ promoted cyclization of allenic oximes.[12] Cyclic nitrones (**19**) are preferentially obtained by zinc catalyzed reduction of nitro-substituted carbonyl compounds (**18**).[13]



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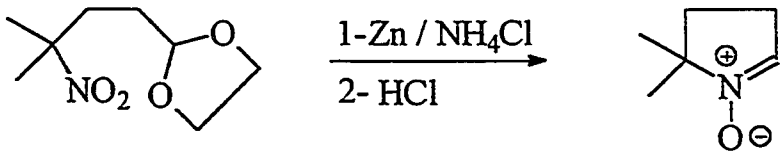
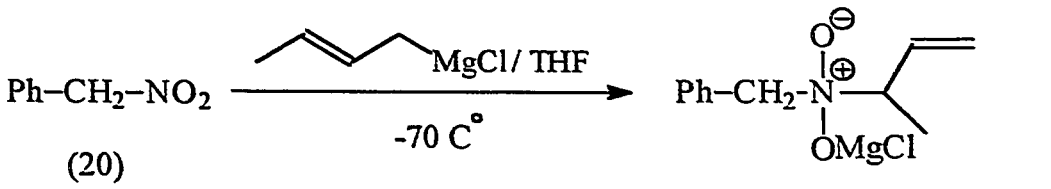
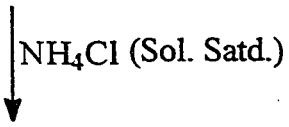
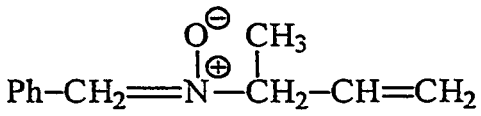


(18) (19)

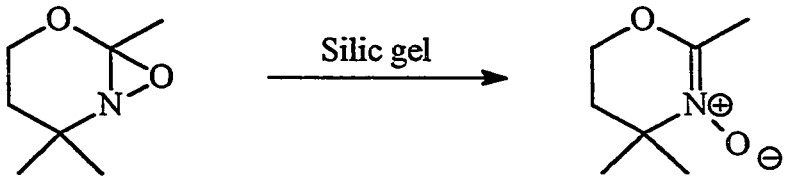

Ph–CH2–NO2
MgCl/ THF
-70 C°
Ph–CH2-N
OMgCl

(20)


NH4Cl (Sol. Satd.)


Ph–CH2=N–CH2–CH=CH2
CH3

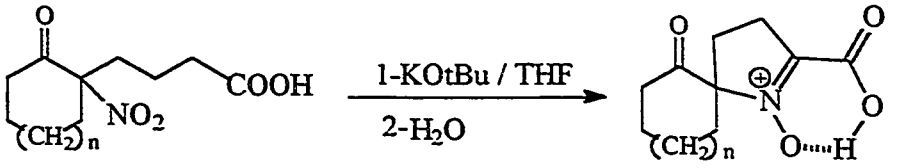
(21)


Silic gel

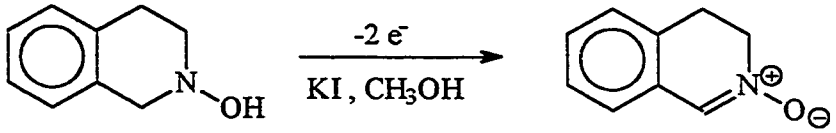
(22)

(23)

Formation of nitrone (**25**) has been achieved in the presence of K-*t*-BuO/THF from tertiary nitrones (**24**).[16] Facile preparation of cyclic (**27**) and acyclic nitrones has been achieved by electrochemical oxidation of N-hydroxy secondary amines (**26**) using a mediator such as halogen ions.[17]

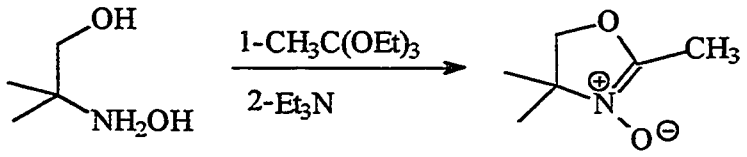


(24) (25)



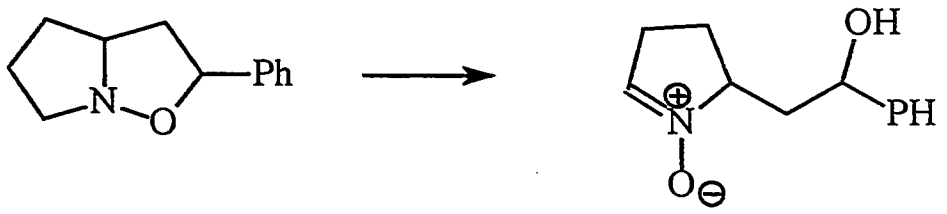
(26) (27)

Heterocyclic nitrone (**29**) is prepared in excellent yield by condensation of the hydroxylaminoalcohol (**28**) with triethyl orthoacetate in dichloromethane followed by neutralization of the nitrone salt.[18]



(28) (29)

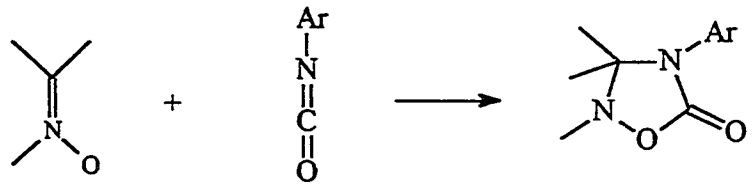
Regioselective preparation of the less substituted hydroxy nitrone (**31**) has been achieved by oxidation of isoxazolidine (**30**) with *o*-chloroperbenzoic acid in methylene chloride.[19]



(30) (31)

2.2 1,3 Dipolar Cycloaddition Reaction

The cycloaddition reactions of nitrones with alkenes were described nearly a century ago, involving the addition of an aryl isocyanate (**33**) with nitrone (**32**) to give the cycloadduct (**34**).[20] Pioneering investigations of intermolecular nitrone-alkene cycloaddition has been reported by LeBel and coworkers.[21] The vast panorama of 1,3-dipolar cycloaddition reactions, studied by Huisgen and his group, have helped nitrone functionality to etch an important position in the organic chemistry.[22] The development of the chemistry of 1,3-dipolar cycloaddition reactions, began in earnest in the late fifties.[23]



(32) (33) (34)

The presence of two heteroatoms within the isoxazolidine ring has made nitrone cycloaddition especially attractive for the synthesis of several natural products.[24] The 1,3-dipolar cycloaddition reaction of nitrone which has developed quite rapidly[25] is indeed the best chemical template for constructing isoxazolidine

rings in high yield and also efficient incorporation of multiple stereocenters in a single step.[26]

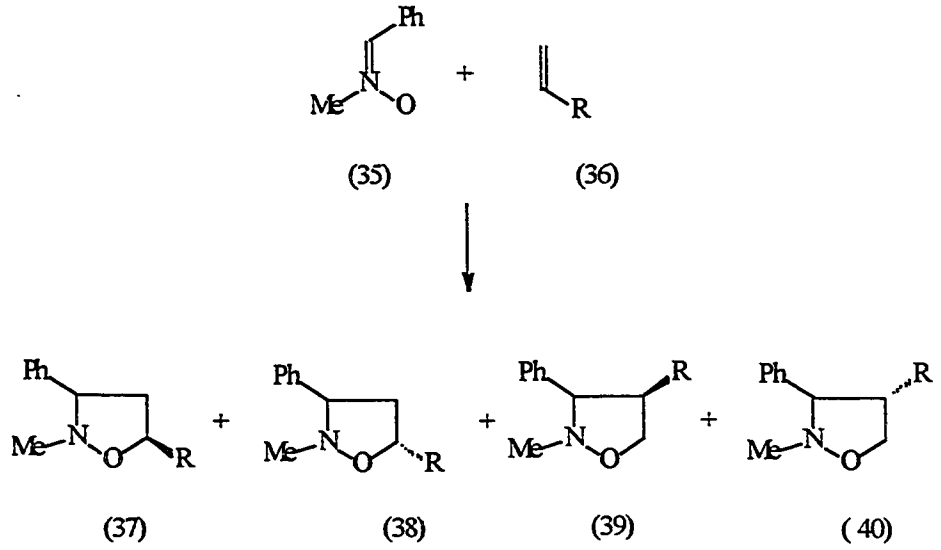
The degrees of variation of regio- and stereoselection in the 1,3-dipolar cycloaddition of both cyclic and acyclic nitrones with substituted alkenes depend on the electronic and steric effects of the substituents.[27,28] For example, with normal and electron-rich mono-and 1,1-disubstituted alkenes, the cycloadditions result in the regiospecific formation of cycloadducts, whereas, with electron withdrawing alkenes, usually a regioisomeric mixture of adducts are obtained and in some cases complete reversal in the regioselection is observed.[28,30]

2.2.1 Nitrone Cycloaddition with Monosubstituted Alkenes

It was believed that nitrone cycloaddition on to monosubstituted ethylenes proceeds in a unidirectional fashion, giving mainly 5-substituted isoxazolidines regardless of the alkene substituent.[22,31] However, more recent work suggests that alkenes bearing electron-withdrawing groups show an increasing tendency to afford the corresponding 4-substituted isoxazolidine, as the electron-withdrawing ability of the attached substituent increases.[32,33]

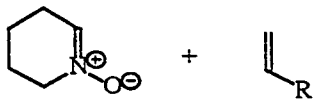
Nitrone (**35**) undergoes addition onto nonactived alkenes such as styrene (36a) to give a mixture of adducts (**37a**) and (**38a**) regiospecifically in (2:1) ratio respectively, in which, the nitrone carbon becoming bonded to the unsubstituted end

of the dipolarophile. While a complete reversal of the regioselection is observed with the addition of nitroethylene (**36c**), which is strongly deactivated alkene, to give a mixture of the adducts (**39c**) and (**40c**) in (2:1) ratio respectively.[34] On the other hand, the addition of methyl acrylate (**36b**), that is a moderate electron deficient alkene, affords a mixture of four possible cycloadducts.[35]

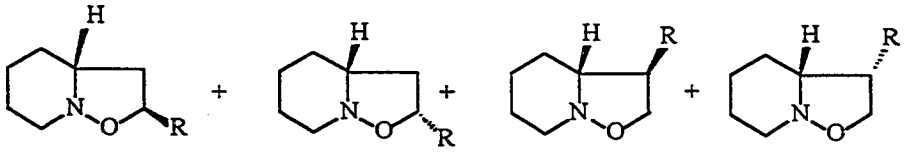


a, R=Ph	67	33	0	0
b, R=CO_2Me	77	4	15	4
c, R=NO_2	0	0	67	33

Addition of the nitrone (**41**) to propene gives a single regiospecific and stereoselective adduct (**100a**). Ethyl vinyl ether, which is an electron-rich alkene, undergoes cycloaddition with the same nitrone to afford stereoselectively the adducts (**43b**) and (**44b**) in a (93:7) ratio respectively. Whereas, a reversal of regiochemistry occurs with acrylaldehyde (**42c**) to give a mixture of isomers (**43c**), (**44c**), (**45c**), and (**46c**) in a ratio of 3:5:24:68, respectively.[28]



(41) (42)

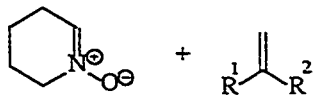


(43) (44) (45) (46)

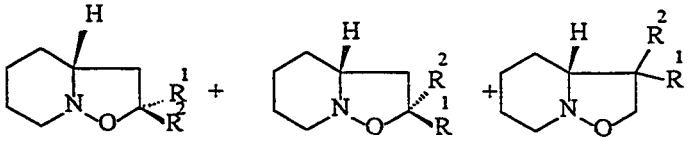
a, R=Me	100	0	0	0
b, R=OEt	93	7	0	0
c, R=CHO	3	5	24	68

2.2.2 Nitrone Cycloaddition with 1,1-Disubstituted Alkenes

Most of the 1,1-disubstituted ethylenes undergo cycloaddition with nitrones to afford 5,5-disubstituted isoxazolidines. Thus, the addition reaction of nitrone (**41**) with methyl methacrylate gives a mixture of adducts (**48a**) and (**49a**). The methacrylaldehyde undergoes stereoselective addition with the same nitrone to afford a single adduct (**48b**).[28] While, a complete reversal of regioselection is noted when methylene malonate undergoes cycloaddition with nitrone (**41**) to afford only the 4,4-isoxazolidine dicarboxylate (**50c**)[36] due to favorable frontier orbital interactions.



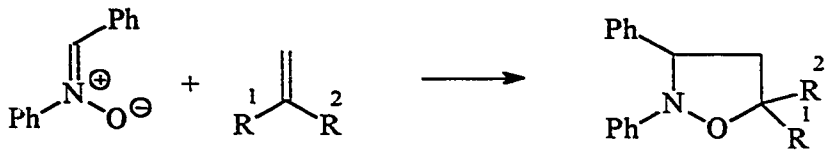
(41) (47)



(43) (44) (45)

a, $R^1 = CO_2Me$, $R^2 = Me$	54	42	0
b, $R^1 = CHO$, $R^2 = Me$	100	0	0
c, $R^1 = R^2 = CO_2Me$	0	0	100

The C-phenyl-N-phenyl-nitrone (**51**) reacts with electron-rich keteneacetal (**52a**) to give the adduct (**53a**) regiospecifically.[37] The 1-tert-butylthio-1-chanoethylene (**52b**),[38] 1-acetamido acrylate (**52c**)[39] and the enamine (**52d**)[40] all undergo cycloaddition in the same regiochemical sense to give the 2,2-disubstituted adducts (**53**) regiospecifically in each case.



(51) (52) (53)

a, $R^1 = R^2 = OEt$

b, $R^1 = CN$; $R^2 = S\text{-}t\text{-}Bu$

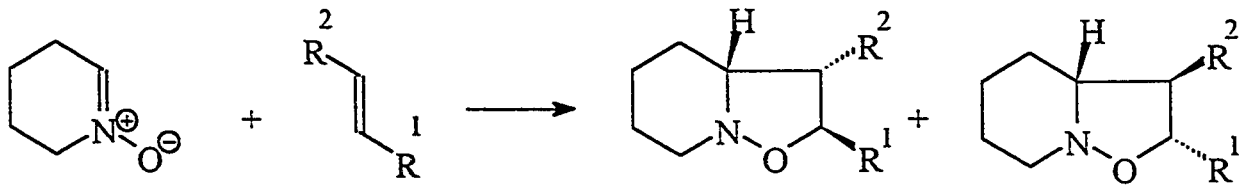
c, $R^1 = NHCOCH_3$; $R^2 = CO_2Et$

d, $R^1 =$; $R^2 = Ph$

2.2.3_ Nitrone Cycloaddition with 1,2-Disubstituted Alkenes

There is an array of highly regioselective addition reactions of nitrones with the *trans*-1,2-disubstituted alkenes. It has been demonstrated that the addition reaction of nitrones with *trans*-1,2-disubstituted alkenes occurs with complete regioselectivity and high stereoselectivity. Thus, the cyclic nitrone (**41**) undergoes a

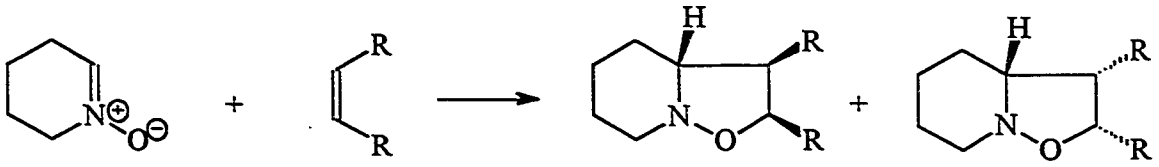
regio-and stereo-selective addition reaction with both crotonaldehyde (**54b**) and cinnamaldehyde (**54a**) to give a single adduct (**55b**) and (**55a**) respectively. The addition of *trans*-methyl cinnamate (**54c**) and dimethyl fumarate (**54d**) gives a mixture of adducts (**55c**), (**56c**) and (**55d**), (**56d**) respectively.[28] Formation of the major adducts with endo orientation of the aldehyde and carbomethoxy groups certifies their superiority the over phenyl ring in manifestation of secondary orbital interactions.[36]



(41) (54) (55) (56)

a, R^1 = Ph , R^2 = CHO	100	0
b, R^1 = CH_3 , R^2 = CHO	100	0
c, R^1 = Ph, R^2 = CO_2Me	87	13
d, R^1 = R^2 = CO_2Me	60	40

On the other hand, the stereochemical analysis of the cycloadditions of nitrone (**41**) with both *cis*-dimethyl maleate (**57a**) and maleic anhydride (**57b**), to give a mixture of adducts (**58a**), (**59a**) and (**58b**), (**59b**) respectively, reveals the exo orientation of the substituents, in which, the steric factors overwhelm the favorable secondary orbital interaction in deciding the stereochemical outcome of the addition reaction.[28]



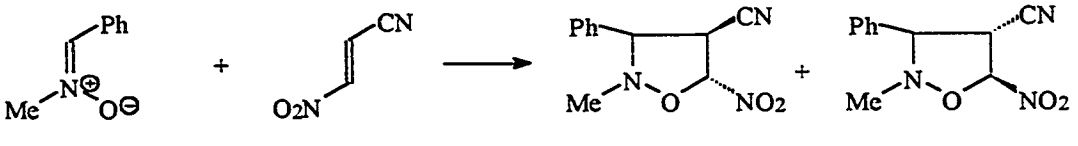
(41) (57) (58) (59)

a, R = CO_2Me	84	16
b, R = $(CO)_2O$	81	19

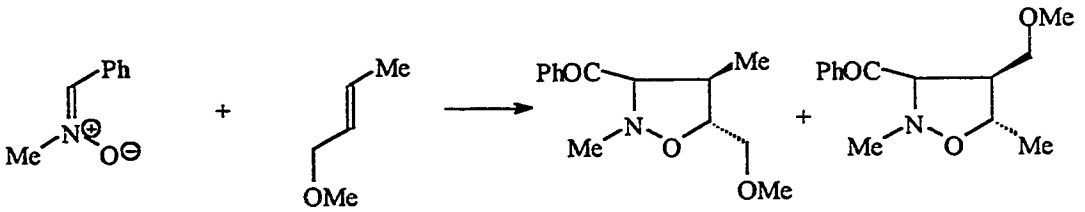
Recently, the regiochemical effect of the allyl silicon or oxygen atom has been reported in nitrone cycloaddition. It has been found that the addition of the nitrone (**60**) with aryl vinyl silane (**61**) gives a single adduct (**62**) regio-and stereo-specifically.[41]

(60) (61) (62)

The cycloaddition behavior of the nitrone with alkenes bearing electron-deficient substituents (**63**)[34] and normal substituents (**67**)[42] at both ends have been reported and a mixture of regioisomers is observed in each case.

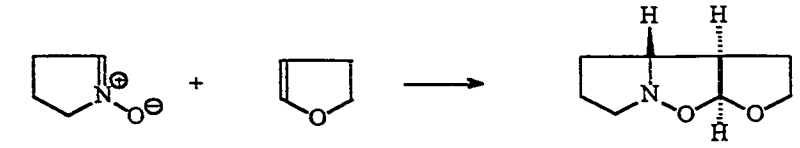


(53) (63) (64) (65)

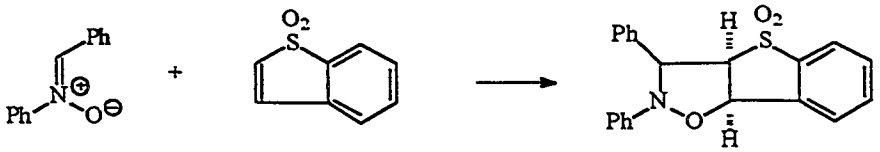


(66) (67) (68) (69)

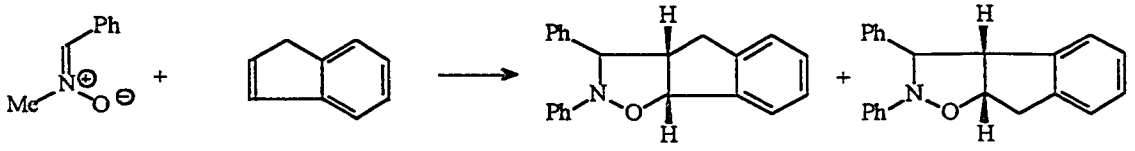
While, the oxygen terminal of the nitrone functionality favors attachment to the end of the electron-rich cycloalkene bearing a heteroatom,[43] the carbon terminal attaches to the end of the electron poor alkene bearing the heteroatom..[44] On the other hand, if the dipolarophile does not possess a strongly activating or deactivating substituent a loss of regiochemical control is anticipated.[45] Representative examples are given below.



(70) (71) (72)



(51) (73) (74)

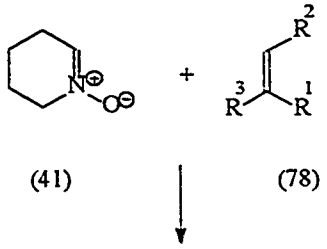


(35) (75) (76) (77)

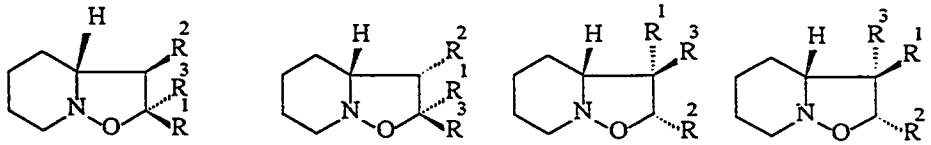
2.2.4 Nitrone Cycloaddition with Trisubstituted Alkenes

The regio- and stereo-chemical features of nitrone cycloaddition reaction with trisubstituted alkenes has been examined only to a limited extent.[28,46] Addition of nitrone (**41**) to dimethyl mesconate (**78a**) gives the sole regiomer (**79a**), and to 3,3-

dimethylacrylate (**78b**) a mixture of adducts (**79b**) and (**80b**) is obtained regiospecifically in a ratio of (57:43) respectively. Herein, the major adduct (**79b**) had carbonyl substituents in the exo orientation, however, the major adduct in the case of addition dimethyl citraconate (**78c**) has the carbonyl substituents in the endo orientation. For electron deficient dipolarophiles the nitrone carbon becomes bonded to the less substituted end of the alkene, however, regioselection is reversed with electron rich dipolarophiles. Thus, the addition of diethyl ethoxylmethylene malonate (**78d**)[47] and trimethyl ethylene tricarboxylate (**78e**) on to cyclic nitrone (**41**) give a mixture of isomers (**81d**), (**82d**) and (**81e**), (**82e**) respectively.[48]



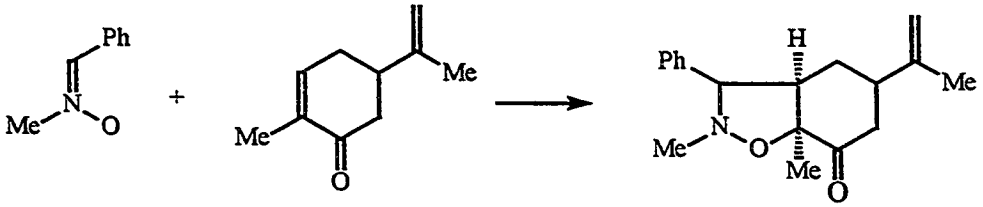
(41) (78)



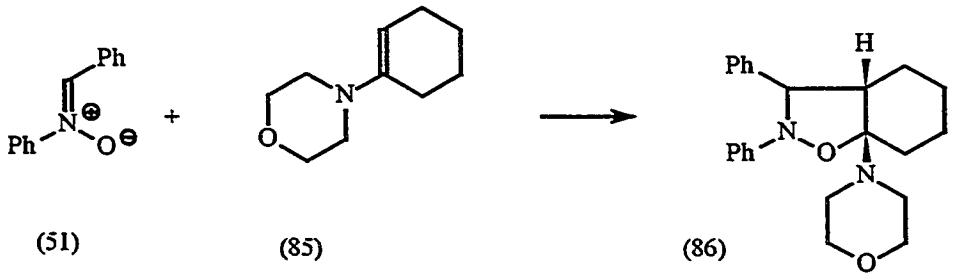
(79) (80) (81) (82)

a, R^1= Me , R^2= R^3= CO_2Me	100	0	0	0
b, R^1=Me, R^2=CO_2Me, R^3=Me	57	43	0	0
c, R^1= R^2= CO_2Me R^3= Me	25	75	0	0
d, R^1= R^2= CO_2Et , R^3= OEt	0	0	30	70
e, R= R= R= CO_2Et	0	0	34	64

The acyclic nitrones (**35**) and (**51**) undergo regio-and stereo-specific reaction with trisubstituted alkene of the type (**83**)[49] and (**85**) [50] respectively to give the adduct (**84**) and (**86**).



(35) (83) (84)



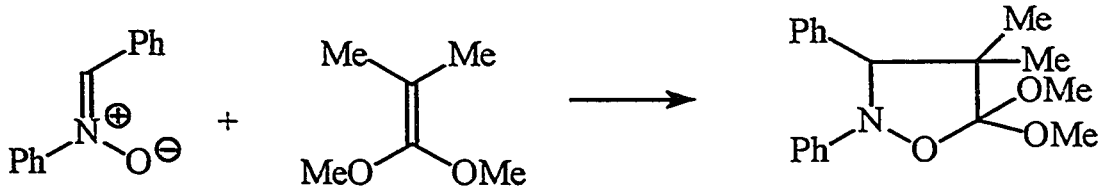
(51) (85) (86)

2.2.5 Nitrone Cycloaddition with Tetrasubstituted Alkenes

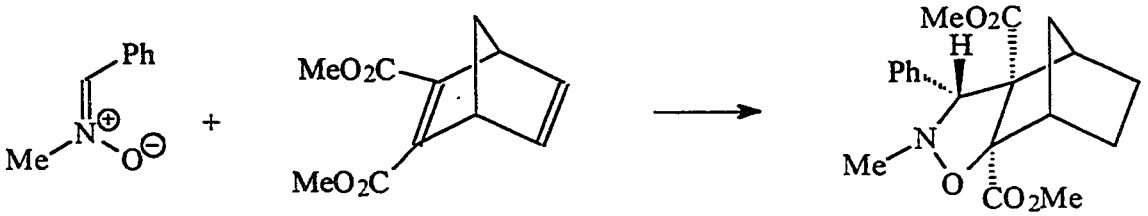
The azetidone (**107**) has been obtained by the reaction of nitrone (**51**) with copper acetylide via rearrangement of the initial adduct (**106**).[58]

Very few examples of cycloaddition reactions involving tetra substituted alkenes have been studied. The regiochemical outcome observed for the addition of

C, N-diphenyl nitrone (**51**) with dimethyl ketone dimethyl acetal (**87**) affords product (**88**), in which, the oxygen end of the nitrone, as expected, is bonded to the carbon of the alkene bearing the electron releasing substituents.[49] Moreover, the reaction of C-phenyl-N-methyl nitrone (**35**) to the norbornadiene (**89**) affords a single adduct (**90**) stereospecifically.[51]



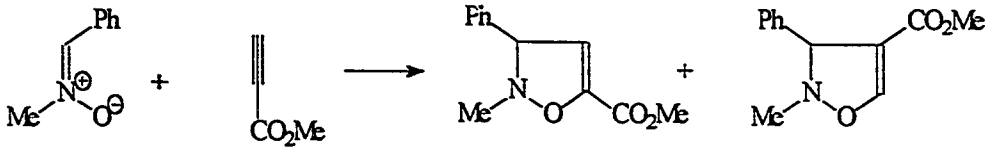
(51) (87) (88)



(35) (89) (90)

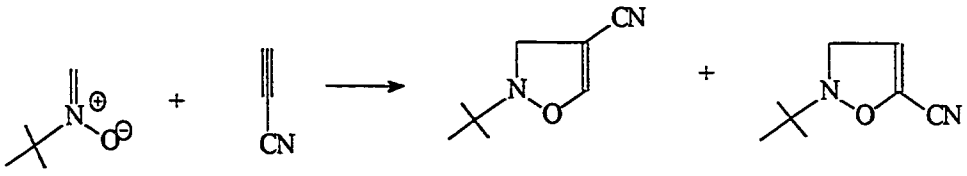
2.2.6 Nitrone Cycloaddition with Acetylenes

Nitrones react with substituted alkenes and yield different regioisomeric distributions than are found for the corresponding alkenes. Thus, the regiochemical outcome observed for the addition of nitrone (**35**) with methyl propiolate (**91**) and cyanoacetylene (**95**) with nitrone (**94**) are found to be non-regioselective[52] affording a mixture of adducts (**92**), (**93**) and (**96**), (**97**) respectively.



(35) (91) (92) (93)

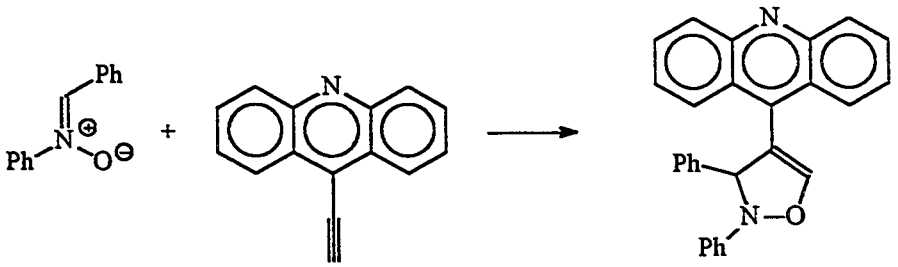
42 : 58



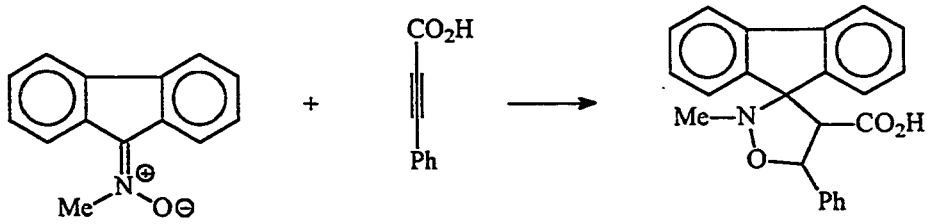
(94) (95) (96) (97)

50 : 50

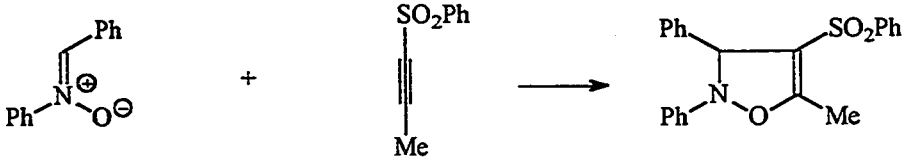
The reaction of nitrones with electron-deficient alkynes have a tendency to show a higher regioselectivity than the corresponding alkenes. For example, the addition of nitrone (**51**)[53] to ethylacridine (**98**), nitrone (**100**) to phenylacetylenecarboxylic acid (**106**),[54] nitrone (**51**) to phenylsulfonyl alkene (**103**),[35] and nitrone (**105**) to methyl propiolate (**106**)[56] react in a regiospecific manner.



(51) (98) (99)



(100) (101) (102)

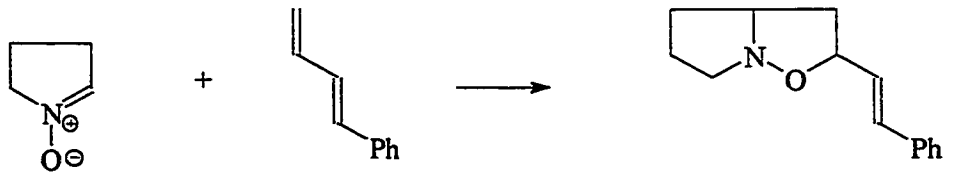


(51) (103) (104)

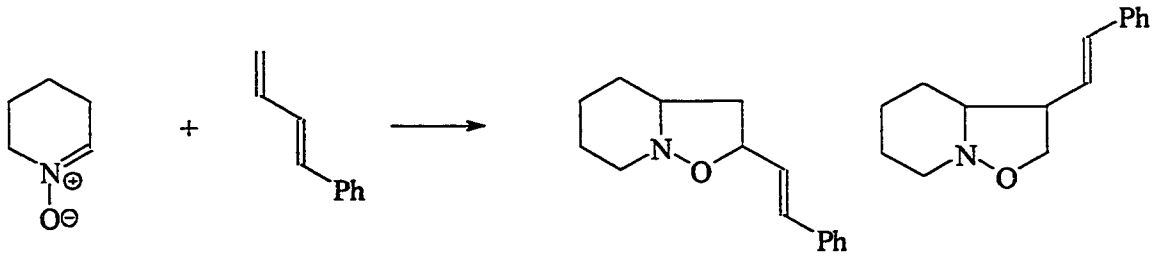
2.2.7 Nitrone Cycloaddition with Conjugated Dienes and Cumulative Multiple Bonded Systems

The azetidone (**107**) has been obtained by the reaction of nitrone (**51**) with copper acetylide via rearrangement of the initial adduct (**106**).[58]

The nitrone cycloaddition to unsymmetrical conjugated dienes has received little attention. In fact, the cycloadditions could proceed at either olefinic center and suggest the possible formation of eight isomeric monoadducts. The cyclization of nitrone (**70**) with *trans*-1-phenyl-1,3-butadiene (**108**) was found to be regiospecific to give the adduct (**109**), while, low regioselectivity is observed in the reaction of nitrone (**41**) with the same diene (**108**).[59]

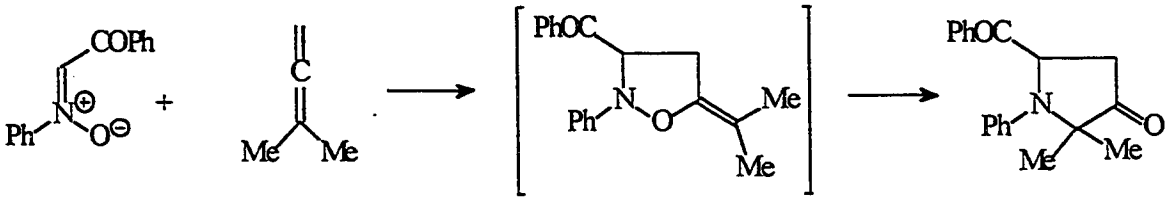


(70) (108) (109)

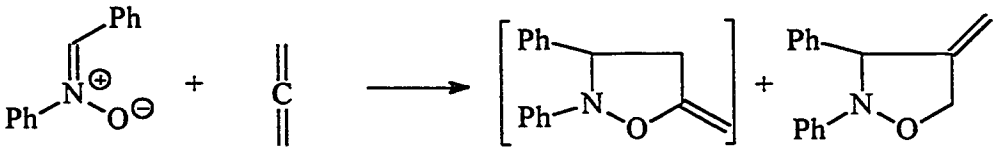


(41) (108) (110) (111)

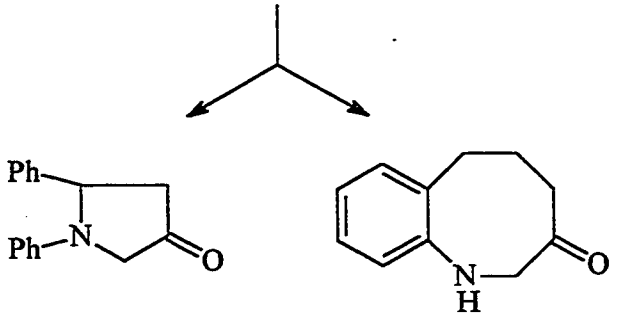
Nitrone cycloaddition to cumulative system involves the reaction of carbodiimides, ketenes, carbon disulfide, and isothiocyanates were studied.[60] The cycloaddition reaction of nitrone (**112**) with allene (**113**) was reported to provide a sole product (**115**)[61] via the initial adduct (**114**), whereas, the reaction of C, N-diphenyl nitrone (**51**) with excess allene (**116**) is found to be non-regioselective to give a mixture of regiomers (**117**) and (**118**). Furthermore, the unstable adduct (**114**) is rearranged by means of ring opening and closure leading to a mixture of compounds (**119**) and (**120**).[62]



(112) (113) (114) (115)

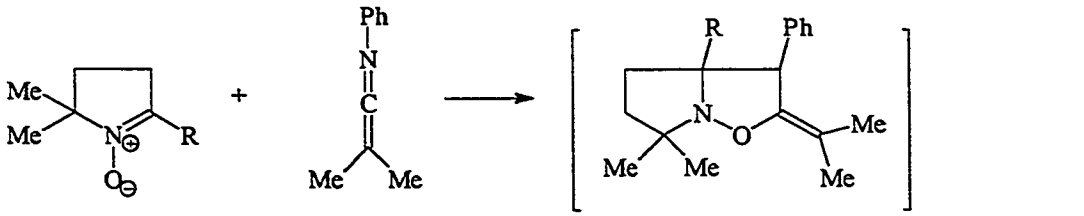


(51) (116) (117) (118)

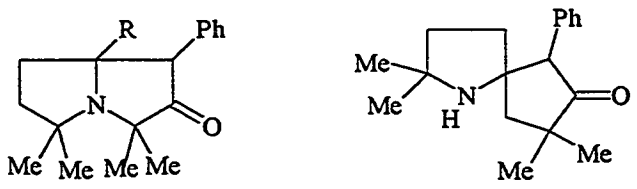


(119) (120)

It has been reported that ketenimine (**121**) readily reacts with 5,5-dimethyl-1-pyrroline 1-oxide (**122a**) to give a single adduct (**124a**) via the unstable adduct (**123a**). However, the reaction of 2,5,5-trimethyl-1-pyrroline-1-oxide (**122b**) with the ketenimine (**121**) gives a mixture of compounds (**124b**) and (**125b**) in 32 and 34% yield respectively.[63]



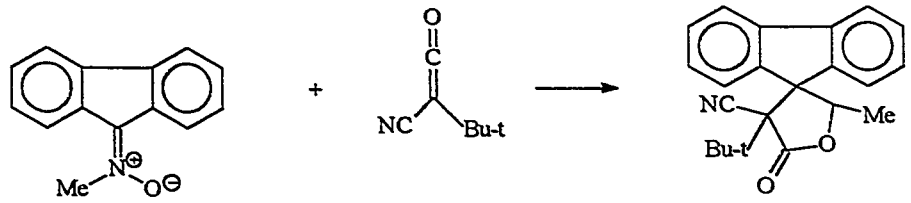
(122) (121) (123)



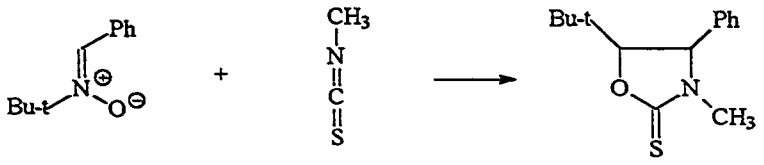
(124) (125)

(a , R = H : b , = Me)

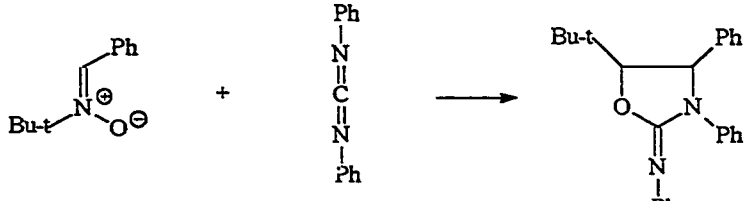
The cycloaddition of nitrone (**126**) with *t*-butylcyanoketone (**127**) to give the adduct (**128**), is found to be a regiospecific and concerted reaction.[64] Furthermore, the addition reaction of nitrone (**129**) with isothiocyanates (**130**)[65] and with carbodiimide (**132**)[66] proceed in analogous manner, to give oxadiazolidine thiones (**131**) and oxadiazolidine imine (**133**) respectively.



(126) (127) (128)



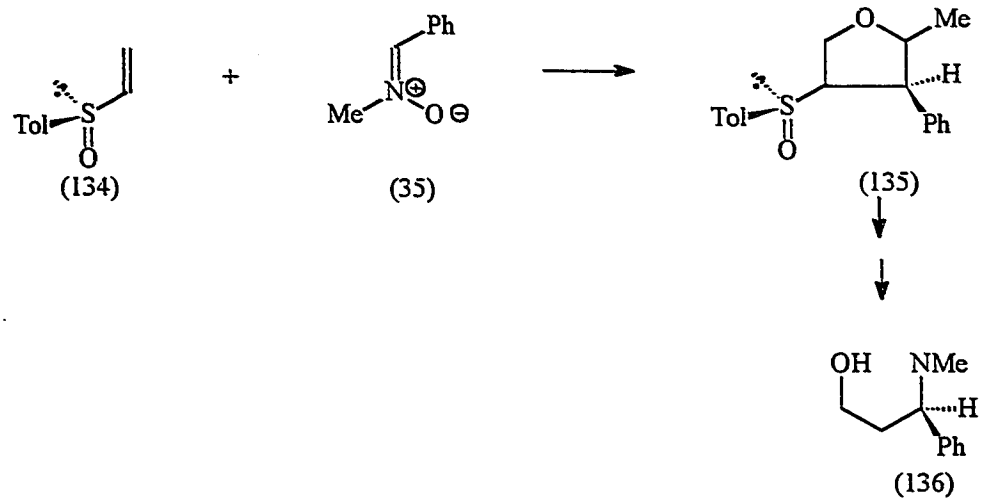
(129) (130) (131)



(129) (130) (133)

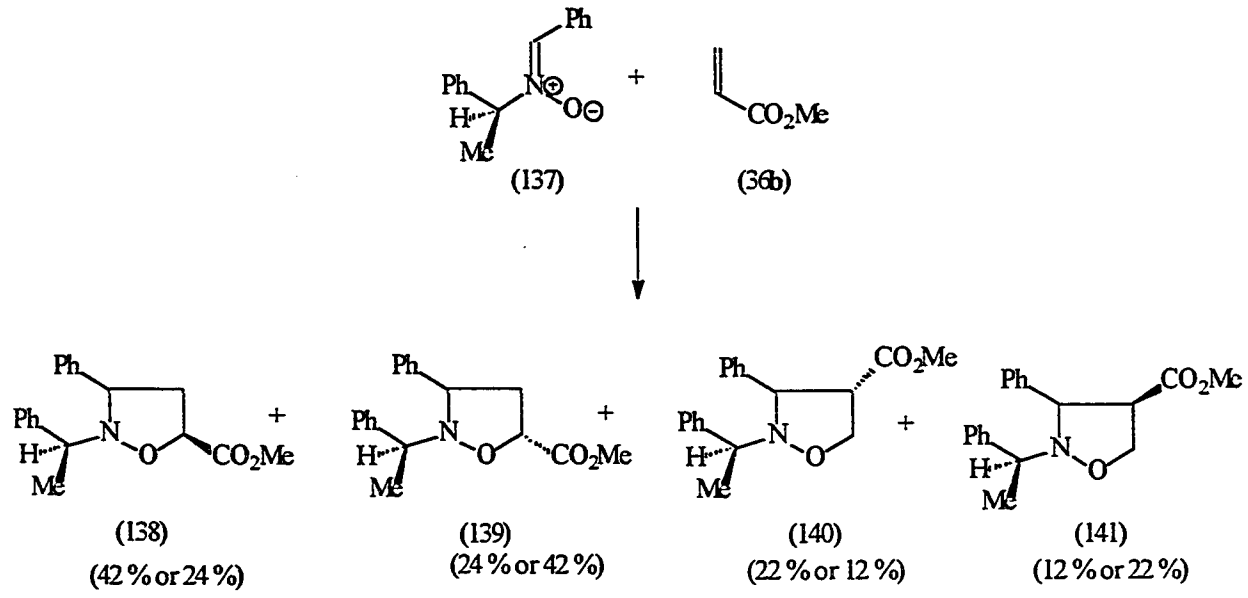
2.2.8 Asymmetric Induction in Nitrone Cycloaddition

Asymmetric induction in the cycloaddition have been reported by Uskokovic[67] and Belzacki.[68] A chiral vinyl sulfoxide (**134**) undergoes a high chiral induction with nitrone (**35**) to give almost solely product (**135**), in 54 % yield, that is converted to (-)3-(dimethyl amino)-3-phenyl-1-propanol (**136**) with no less than 80% optical purity. [69]



(134) (35) (135) (136)

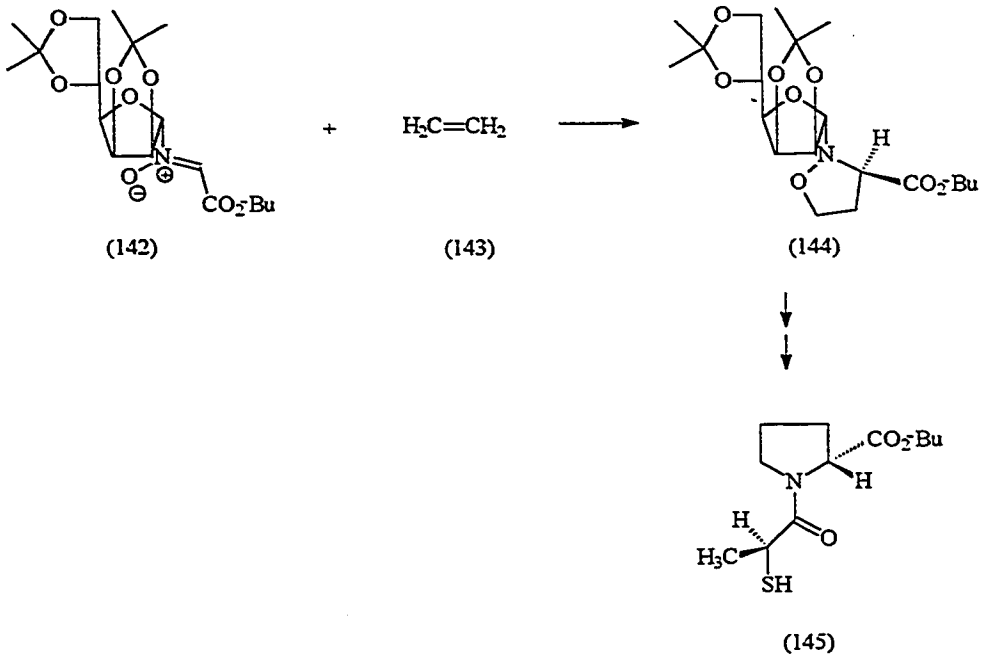
On the other hand, the cycloaddition reaction of (S)-nitrone (**137**) with methyl acrylate (**36b**) is observed to give a mixture of four optically active products as pairs of diastereoisomers (**138**), (**139**) and (**140**), (**141**).[70]



(137) (36b)

(138) (42 % or 24 %) (139) (24 % or 42 %) (140) (22 % or 12 %) (141) (12 % or 22 %)

The (R)-C-t-butyloxy carbonyl-N-mannosyl-nitrone (**142**) undergoes 1,3-dipolar cycloaddition with ethylene (**143**) to give a single adduct (**144**) that is converted into captopril analog (**145**).[71]



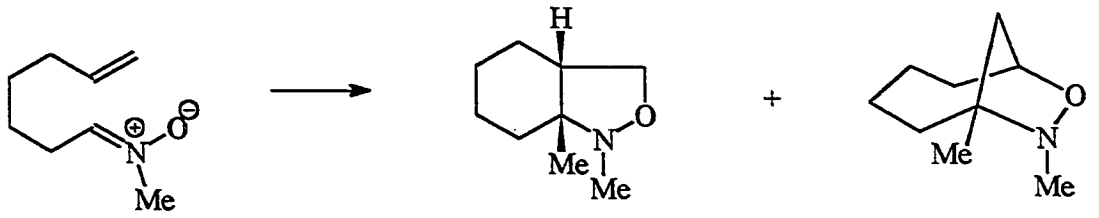
(142) (143) (144)

(145)

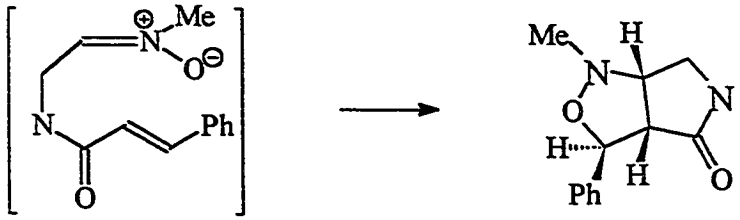
2.2.9 Intramolecular Nitrone Cycloaddition

Much attention has recently been focused on the intramolecular 1,3-dipolar nitrone cycloadditions.[72] The regiochemical aspects of it is observed to be markedly influenced by the number of carbon atoms between the nitrone functionality and the double bond.[6] Thus, a mixture of adducts (**147**) and (**148**) is obtained in a ratio of (2:1) respectively from the intramolcular nitrone (**146**) cycloaddition,[73] whereas,

nitrone (**149**) undergoes spontaneous intramolecular cycloaddition to give the adduct (**150**) regioselectively.[74]

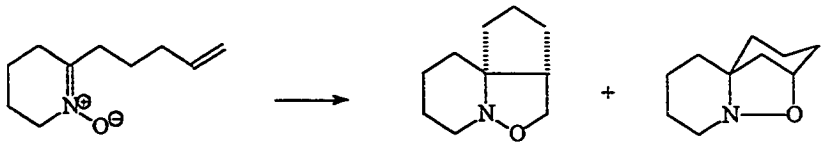


(146) (147) (148)

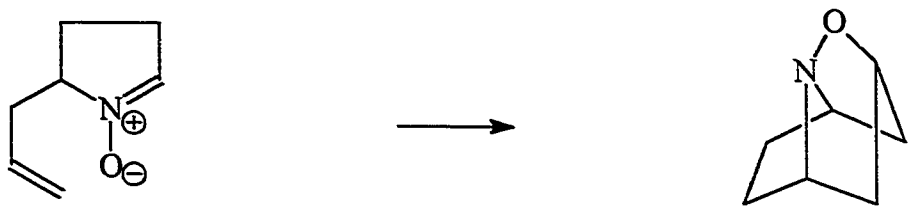


(149) (150)

While the intramolecular cycloaddition of nitrone (151) affords a mixture of regiomers (152) and (153),[75] the cyclic nitrone (154) is observed to give a single adduct (155).[76]



(151) (152) (153)



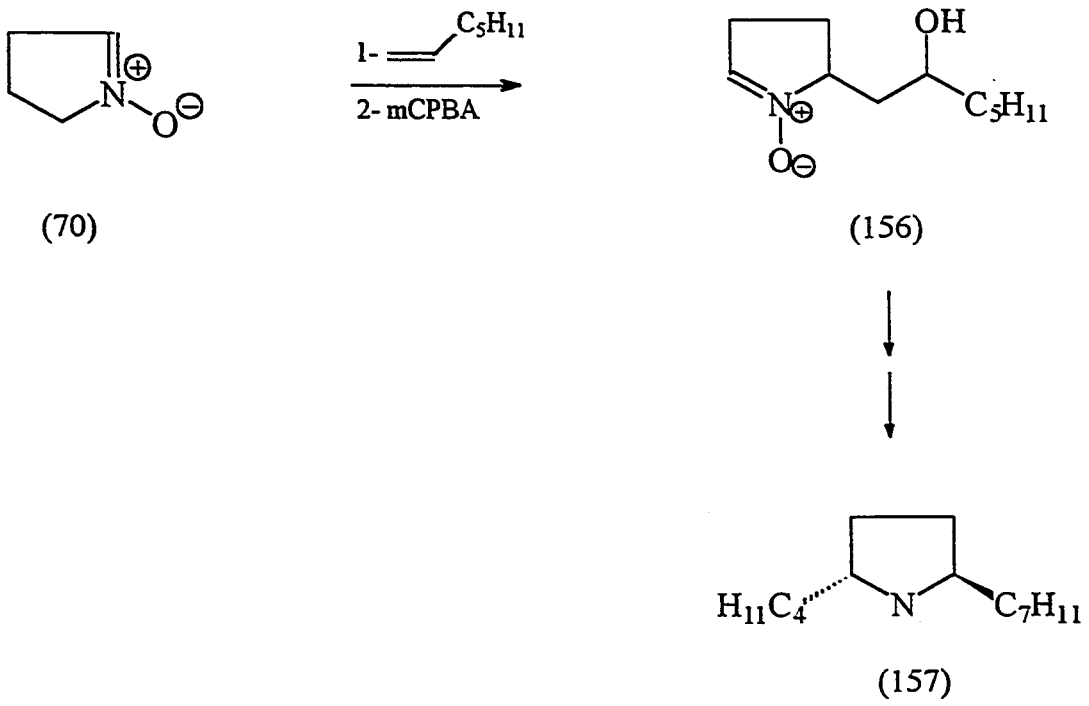
(154) (155)

2.2.10 Natural Products Synthesis Based on Nitrone-Olefin Cycloaddition Reactions

Nitrone-olefin [4+2] cycloaddition reaction enjoys a number of advantages for the synthesis of natural products. It may be considered as one of the most powerful methods for the synthesis of five-membered heterocyclic ring systems having one or more heteroatoms. Also, the reaction leads to the formation of both carbon-carbon and carbon-oxygen bonds in a single step. Furthermore, ring cleavage of the formed isoxazolidines has been a useful in preparing intermediates suitable for conversion to natural product target molecules.

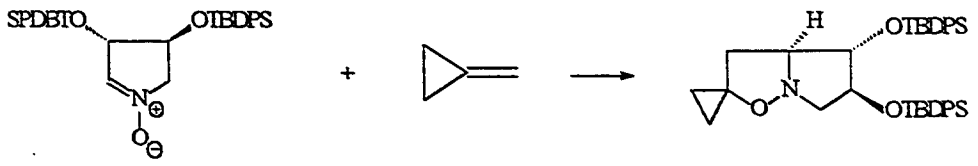
A number of pyrrolidine, pyrrolizidine, and piperidine alkaloid have been synthesized through the use of nitrone-based strategy. For example the solenopsis alkaloid (**157**) which has been identified as characteristic poison gland products of

the south African ant solenopsis punctaticeps,[77] synthesized from pyrroline-1-oxide (**70**) via a double nitrone cycloadditon sequence[78].

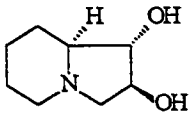


(70) (156) (157)

A mixture of adducts is obtained with a high degree of stereoselectivity in which the desired diastereoisomer (**158**) is predominantly obtained in the cycloaddition. The isoxazolidine (**158**) undergoes clean thermal rearrangement to give a ketone which is converted into the alkaloid lentiginosine (**160**),[79] isolated from Astragalus lentiginosus,[80] and known as the least hydroxylated glycosidase inhibitor.[81]

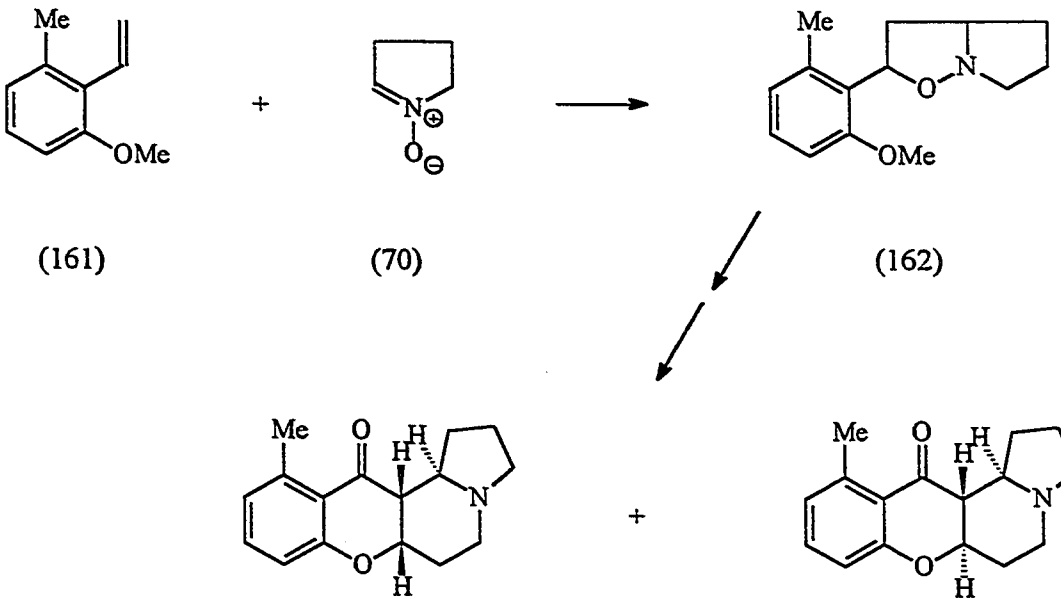


(158) (159)



(160)

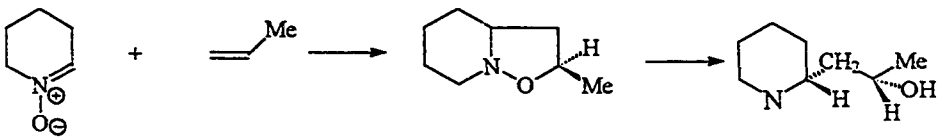
Nitrone-based strategy provides routes to the indolizidine class of alkaloids. For example, dl-eleaocarpine (**163**) and isoelaeocarpine (**164**) are derived from Elaeocarpus polydactylus, found in the forests of New Guinea and in India. An efficient total synthesis of dl-eleaocarpine (**163**) and dl-isoelaeocarpine (**164**) are carried out by cycloaddition of nitrone (**70**) with ortho-disubstitued styrene to produce the isoxazlidine (**162**). Through a standard sequence of steps the isoxazolidine (**162**) is converted to the alkaloids of the products.[82]



(161) (70) (162)

(164) (163)

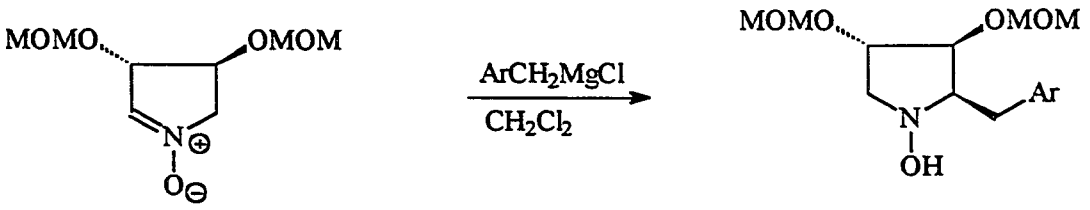
The reaction of nitrone (**41**) with propylene (**42a**) is carried out regio- and stereospecifically to give a single adduct (**165**) that has been utilized in the synthesis of dl-sedridine (**166**) via the isoxazlidine (**165**) which is reduced to give the naturally occurring alkaloid dl-sedridine.[82]



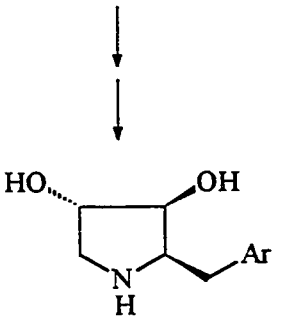
(41) (42a) (171) (172)

Synthesis of (-)-anisomycin (**169**) has been achieved through the use nitrone-based strategy [83] in which electrophilic attack of (4-methoxybenzyl) magnesium

chloride occurs with nitrone (**167**) to give a mixture of regioisomers. Catalytic hydrogenation in the presence of Raney Ni gives a pyrrolidine that has been utilized in the synthesis of the (-)-anisomycin. The later is a fermentation product of various species of streptomyces[84] and has an interesting biological activity such as strong and selective activity against pathogenic protozoa and fungi.[85]



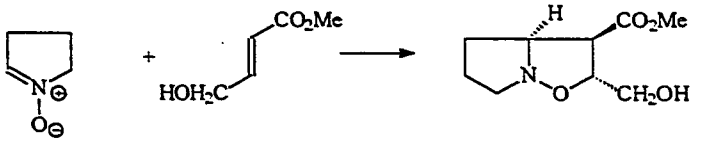
(167) (168)



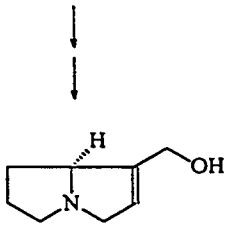
(169)

Synthesis of dl-supine (**171**) which occurs widely in nature in various species and has hepatotoxic properties, has been successfully achieved using nitrone methodology.[86] The key step in the synthesis is the 1,3-dipolar addition of 1-pyrroline-1-oxide (**70**) with methyl 3-hydroxycrotonate. The adduct (**170**) is formed

with apparent regiospecificity and stereospecificity. Hydrogenolysis of the nitrone-oxygen bond in (**170**), liberating 1,3-amino alcohols, accompanied by the cyclization of the resulting amino alcohol to give a hydroxypyrroline which is converted to dl-supinidine (**171**).[87]

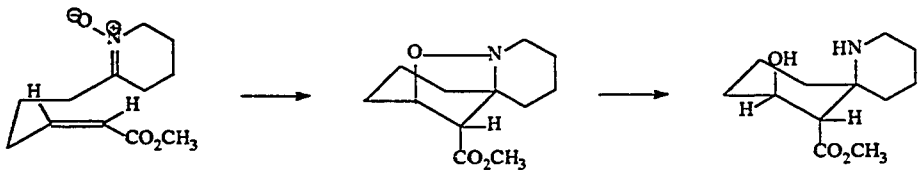


(70) (170)



(171)

The natural alkaloid toxin (**174**) with anticholinergic activity, found in skins of certain frogs, has been regio- and stereo-selectively synthesized through the intramolecular nitrone cyclization (**172**), followed by hydrogenolysis of the nitrone-oxygen bond of the isoxazolidine (**173**).[88]



(172) (173) (174)

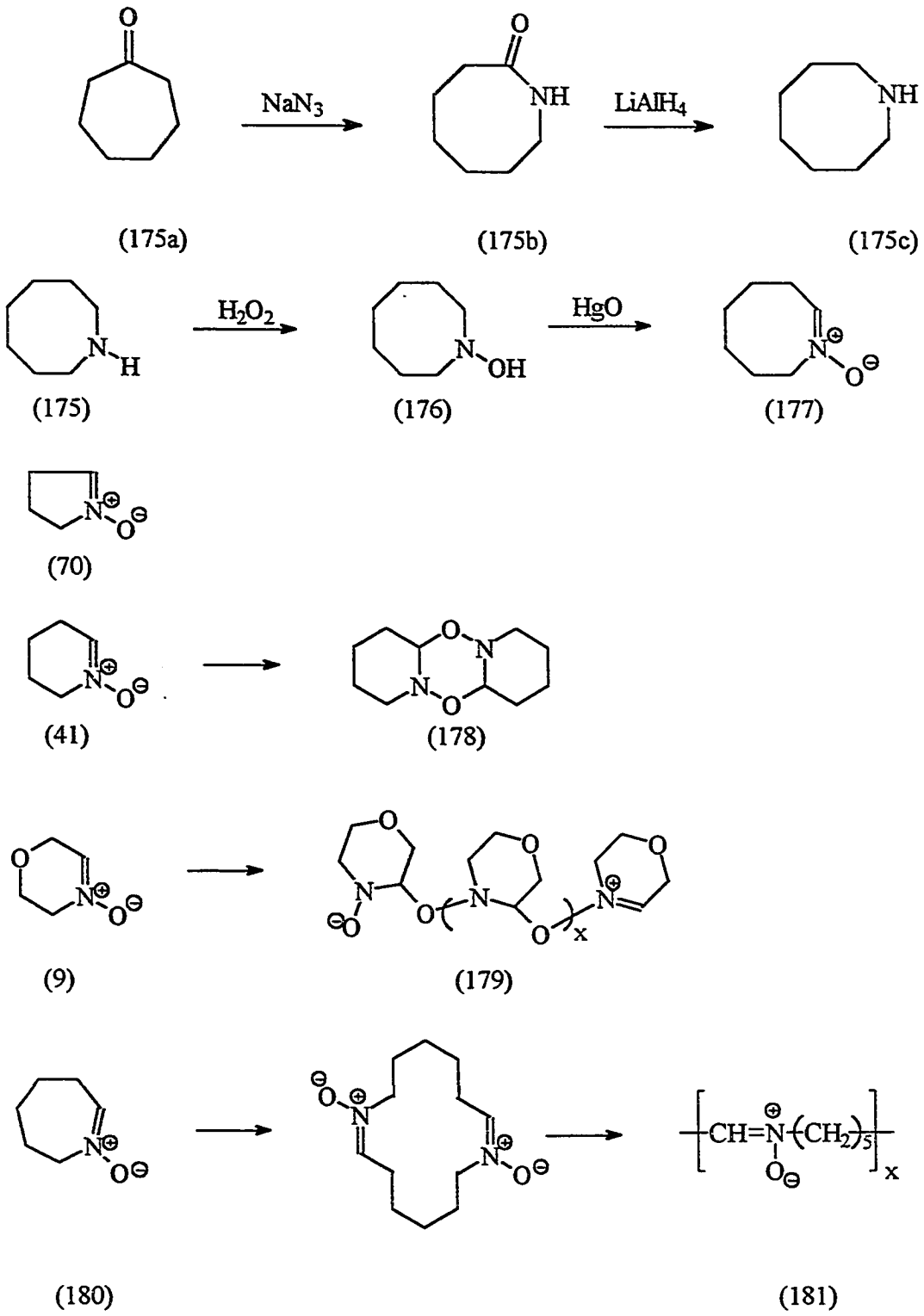
CHAPTER 3

REGIO- AND STEREOCHEMISTRY OF CYCLOADDITION REACTION OF THE NITRONE (177)

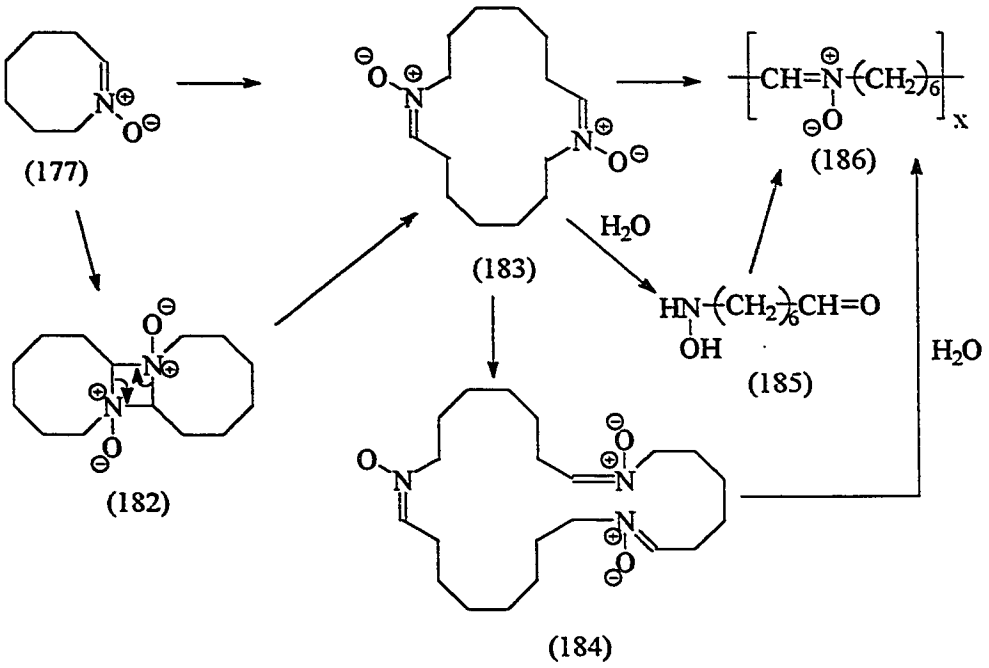
3.1 Results

3.3.1 Polymerization of the Nitrone (177)

Synthesis of 8-membered nitrone (**177**) was achieved through the use of cycloheptanone (**175a**) (Scheme 1). The behavior of the concentrated solution of nitrone (**177**) was examined, before proceeding with the cycloaddition reactions. While, the nitrone (**70**) is stable, the nitrone (**41**) dimerizes to the tricyclic dimer (**178**), nitrone (**9**) polymerizes to the cyclic polymer (**179**)[107] and nitrone (**180**) dimerizes to the mono-cyclic nitrone which polymerizes to the linear polymeric nitrone (**181**). The nitrone (**177**) has been found to undergo dimerization to the mono-cyclic nitrone (**183**) followed by polymerization to the linear nitrone (**186**) (Scheme 2). Reasons for these puzzling differences are not well understood.


O
NaN3
O
NH
LiAlH4
NH
(175a)
(175b)
(175c)
N
H
H2O2
N
OH
HgO
N
O
(175)
(176)
(177)
N
O
(70)
N
O
O
N
N
O
(41)
(178)
O
N
O
O
N
O
O
N
O
x
(9)
(179)
O
N
O
N
O
(180)
CH=N
(CH2)5
O
x
(181)

(Scheme 1)

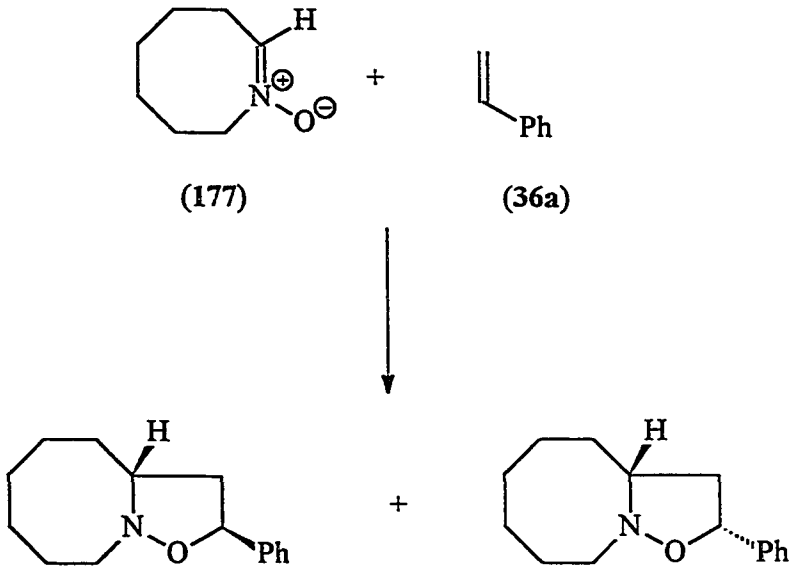


(Scheme 2)

A solution of nitrone (**177**) (0.20 M) in dichloromethane remained stable without any noticeable formation of the dimer (**183**) or the polymer (**186**). However, the nitrone (**177**), after stripping of the solvent, deuterated chloroform, immediately polymerizes. The formation of the dimeric nitrone (**183**) was found to be irreversible. The ^{1}H NMR spectrum of 0.32 M solution was taken, after 3 hours and 20 hours at 26°C, in which it revealed the formation of 46% and 65%, respectively of the dimeric nitrone (**183**). As a result of the problem associated with the dimerization, the concentration of the nitrone (**177**) was kept low and the alkenes were used in excess in the subsequent addition reactions. We did not notice any unwanted dimerization under the specified reaction conditions (see Experimental).

3.1.2 Addition of Styrene (36a) to nitrone (177)

The cycloaddition reaction of nitrone (**177**) with styrene (**36a**) in refluxing dichloromethane, was carried out for 24 h which afforded a mixture of two separable isomers (**187a**) and (**188a**) regiospecifically in a ratio of 91:9, respectively with a yield of 86.3% yield. The major isomer, separated by silica gel chromatography, was assigned the stereochemistry as depicted in (**187a**) with *exo* orientation of the phenyl substituent (Scheme 3).

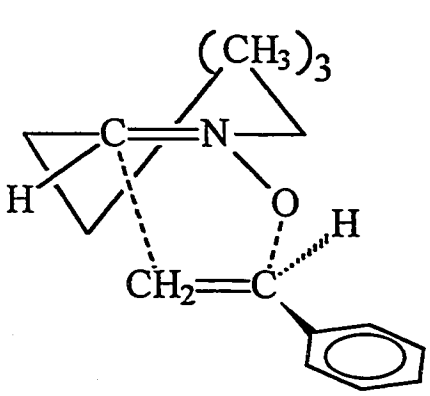


(**177**) (**36a**)

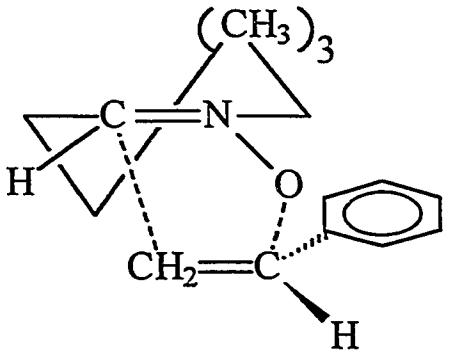
(**187a**) (**188a**)

(Scheme 3)

Formation of the major adduct (187a) is in accordance with the precedent literature and thus certifies the dominance of the steric encumbrance in the stereoselection over the stabilization of the *endo transition* state by favorable secondary orbital interactions by the phenyl ring (Figure 1).



Exo Transition State



Endo Transition State

(HOMO)

(LUMO)

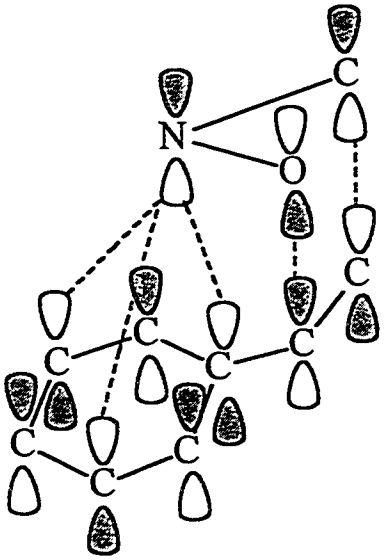
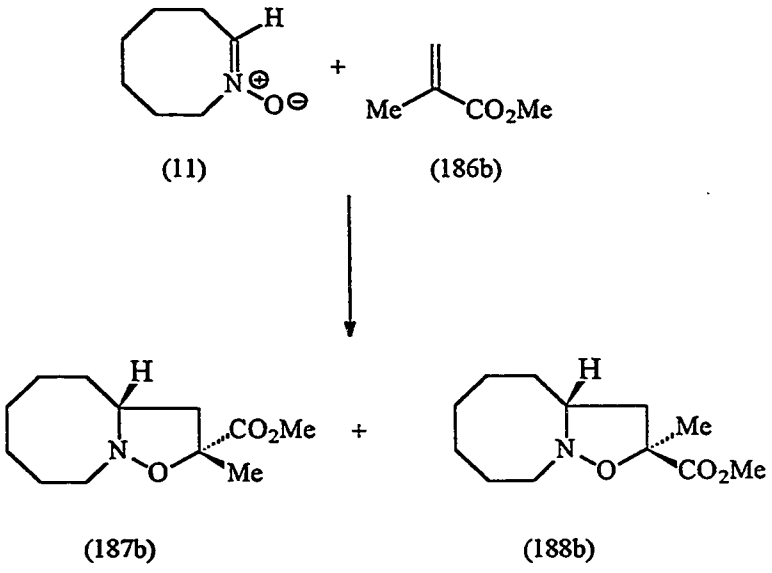


Figure 1

3.1.3 Addition of Methyl Methacrylate (47a) to Nitrone (177)

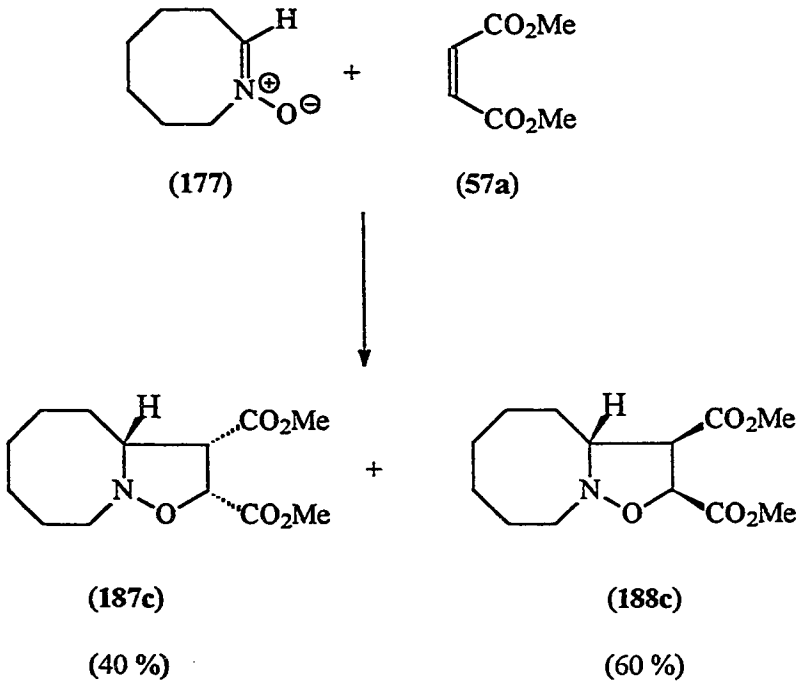
Methyl methacrylate (**47a**) underwent cycloaddition reaction with the nitrone (**177**) at 20°C to give a separable mixture of two isomers (**187b**) and (**188b**) regiospecifically in 72% yield (Scheme 4). The absorption band at 1757 cm^{-1} in the IR spectrum is a confirmation of the presence of an ester functional group. The ratio of (**187b**) and (**188b**) was determined to be 90:10, respectively by integration of the methoxy singlets (see Experimental). The stereoselective formation of the isomer (**187b**), with an *endo* oriented CO_2Me clearly demonstrates the ability of the carbomethoxy group to manifest favorable secondary orbital interaction which stabilizes the transition state leading to the adduct (**187b**).



(Scheme 4)

3.1.4 Addition of Dimethyl Maleate (57a) to Nitrone (177)

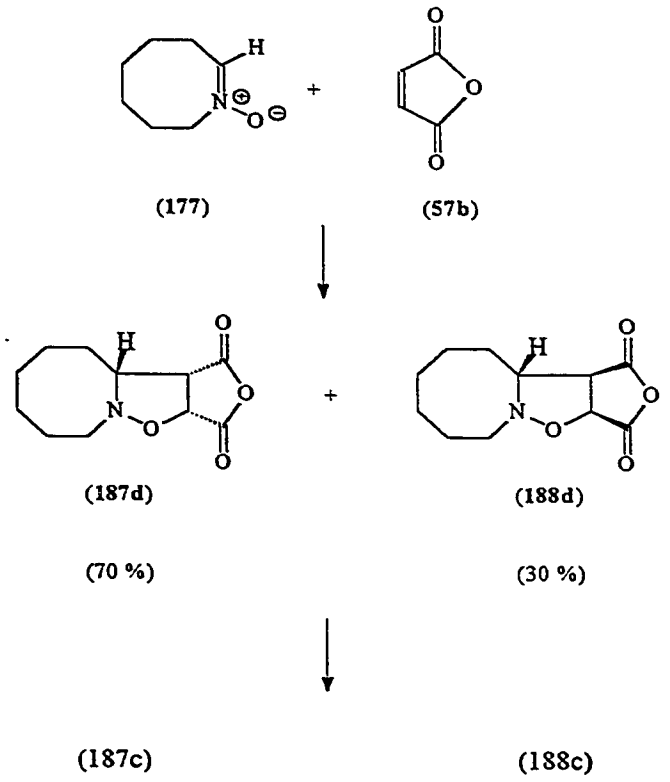
A solution of the nitrone (**177**) and dimethyl maleate (**57a**) in dichloromethane was heated at 57°C in a closed vessel for 6 h. Chromatographic purification of the adducts, using 4:1 hexane-ether mixture as an eluant, afforded the isoxazolidines (**187c**) and (**188c**) (Scheme 5) in a 69 % isolated yield. The IR spectrum showed absorption bands at 1768 and 1736 cm^{-1} which are attributed to the double ester functional groups. Assignment of the stereochemistry of the major adduct (**188c**), as depicted in (Scheme 5), was based on the assumption that the *exo* transition state, leading to (**188c**) would be sterically favored.[28,41] The ratio of the isomers (**187c**) and (**188c**) was estimated by the integration of C-2 proton signals and was found to be 40:60, respectively.



(Scheme 5)

3.1.5 Addition of Maleic Anhydride (57b) to Nitrone (177)

Nitrone (177) cycloaddition onto maleic anhydride (**57b**) at room temperature afforded an adduct which slowly converted to unknown insoluble material. When the reaction was done in $CDCl_3$ in NMR tube, the spectrum revealed the presence of a triplet at δ 3.68 (J 8.0 Hz) and a doublet at δ 4.98 (J 8.0 Hz) assigned respectively to the C(3) and C(2) protons of the major adduct (**187d**) (Scheme 6). Due to the overlapping of the minor signals, we were unable to determine the ratio of the adducts. When crude the reaction mixture was treated with methanol HCl (3:2, w/w), a mixture of the adducts (**187c**) and (**188c**) in a respective ratio of 70:30 was obtained. The major adduct (**187d**) would result from *endo* mode of attack, in which, the favorable secondary orbital interaction in *endo* transition state will overcome the steric hindrance. The assignment of the *exo* structure to the major (**187d**) or (**187c**) is based on the reasonable assumption that switching the alkene from dimethyl maleate to sterically less demanding maleic anhydride brings about on expected increase in the *endo* / *exo* ratio.

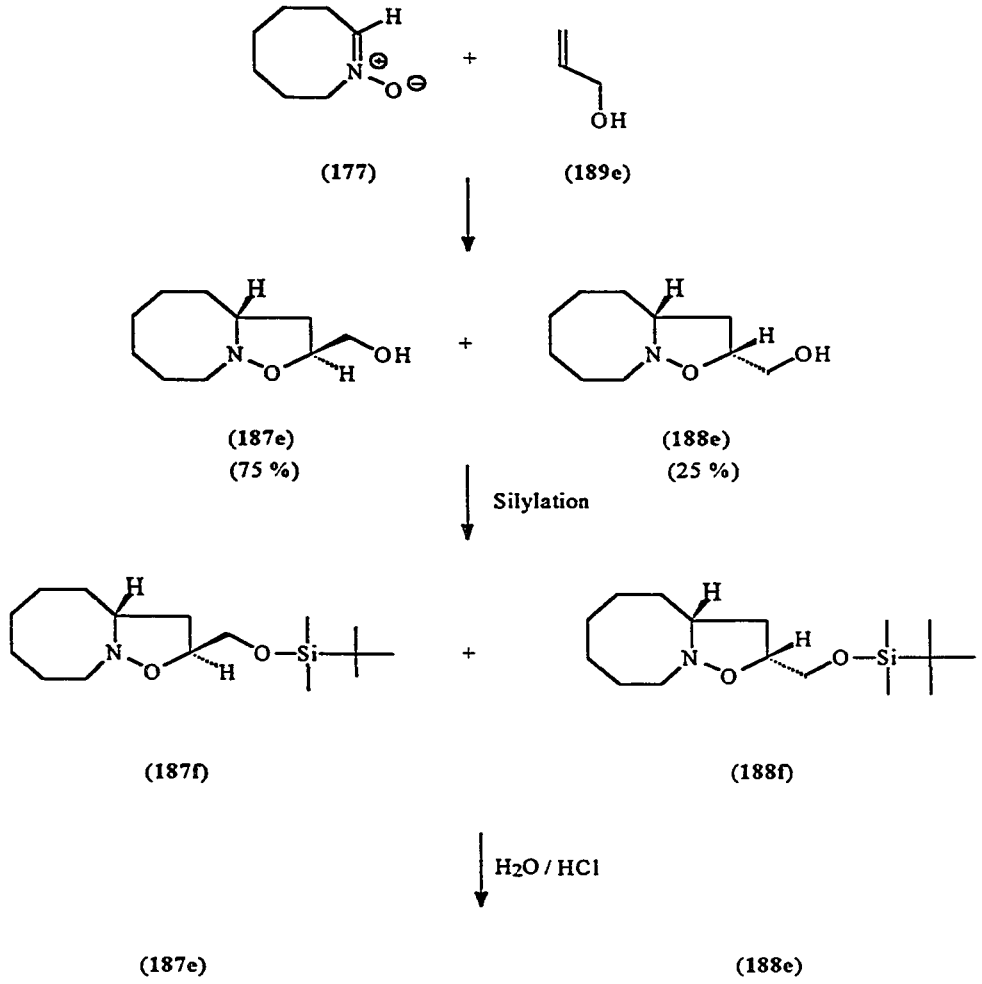


(Scheme 6)

3.1.6 Addition of Allyl Alcohol (189e) to Nitrone (177)

Allyl alcohol (**189e**) underwent cycloaddition reaction with the nitrone (**177**) at 70C° as shown in Scheme 7. The overall yield of the reaction was 59.8%. Chromatographic purification of the crude reaction mixture provide a non separable mixture of the two adducts (**187e**) and (**188e**) regiospecifically in a ratio of 75:25. The strong absorption band at 3308 cm^{-1} in the IR spectrum revealed the presence of hydroxyl group in the two isoxazolidines (**187e**) and (**188e**) . The regiochemical outcome of this addition was determined by silylation of the adducts with dimethyl-(*t*)-butylsilyl chloride in DMF solvent in presence of imidazole. Silylation afforded a

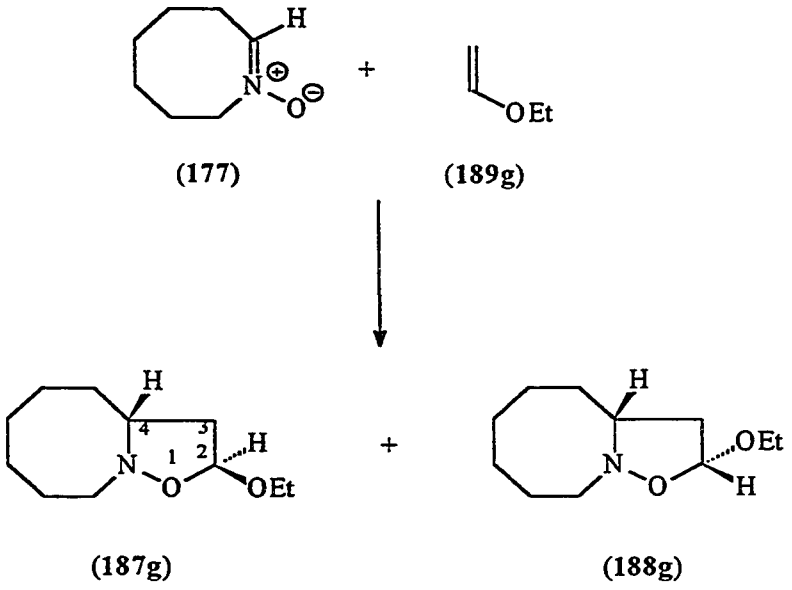
separable mixture of the two regioisomers (**187f**) and (**188f**). The stereochemical outcome of this cycloaddition reaction reflects the preference for the *exo* transition state which is sterically favorable and hence gives (**187e**) as the major stereoisomer. A considerable amount of isomer (**188e**) was also obtained through sterically dis-favored *endo* transition state. The formation of the *endo* isomer is attributed to the stabilizing interaction between the oxygen lone pair of the alkene (HOMO) with the nitrogen atomic orbital of the nitrone (LUMO).



(Scheme 7)

3.1.7 Addition of Ethyl Vinyl Ether (189g) to Nitrone (177)

Chromatographic purification (eluant 95:5 hexane-ether) of the crude reaction mixture resulting from the addition of ethyl vinyl ether (**189g**) to the nitrone (**177**), at 57C° in a closed vessel for 18h, afforded a mixture of isomers (**189g**) and (**188g**) followed by the pure isomer (**187g**) in 70.4% yield. Integration of the C-2 proton signals gave a ratio of 88:12 of the adducts (**187g**) and (**188g**) respectively. The major adduct was assigned the stereochemistry as depicted in (**187g**) with an *exo* ethoxyl substituent due to steric effects. We believe that the transition state with an *endo* orientation of the ethoxy is stabilized due to the favorable interaction between the orbital of the nitrogen LUMO of the nitrone with the oxygen lone pair of the alkene (HOMO).



(Scheme 8)

3.2 Discussion

The regio- and stereochemical details of the nitrone (**177**) alkene cycloaddition along with the reaction temperature, solvent, isolation yield and information about the reaction condition are reported in Table 1. Nitrone cycloaddition is a type (II) process where both HOMO-LUMO interactions can contribute effectively to the stabilization of the transition state. The regiochemistry observed in these additions can be interpreted by the HOMO-LUMO considerations of the interacting species. In the case of electron rich alkenes both HOMO-LUMO combinations prefer the formation of the 2-substituted isoxazolidine by uniting larger terminal coefficients of the interacting atomic orbital in the transition state. Bulkiness of the substituent may also have some effect. For instance, the cycloaddition reaction of the nitrone (**177**) onto styrene, methyl methacrylate, dimethyl maleate, allyl alcohol, and vinyl ethyl ether addition reaction afforded a mixture of regioisomers in which the interactions in these additions dictate the formation of a C-2 substituted adducts.

The configuration of the major 2-substituted stereoisomer in styrene, allyl alcohol, and vinyl ethyl ether adducts is assumed to have the *exo* orientation of the C-2 substituent obtained via the favorable *exo* mode of attack. This observation

Table 1: Regio-and Stereo-Chemistry of Cycloaddition of the Nitrone (177) with Alkenes.

Alkene	Temperature (°C)	Solvent	Reaction Time (h)	% Composition of Adducts (187)	(188)	Isolated Yield
(a), Styrene	reflux	CH_2Cl_2	24	91	9	86.3
(b), Methyl methacrylate	20	CH_2Cl_2	6	90	10	73.0
(c), Dimethyl maleate	57	CH_2Cl_2	6	40	60	69
(d), Maleic anhydride	20	$CDCl_3$	0.8	70	30	77.0[a]
(e), Allyl alcohol	70	neat	10	75	25	59.8[b]
(f),Vinyl ethyl ether	57	CH_2Cl_2	18	88	12	70.4

[a]Isolated yield of the corresponding dimethyl maleate adduct.
[b]Isolated yield of the corresponding silly derivative adduct.

demonstrates that in these cycloadditions the *endo* transition state benefited from favorable secondary orbital interaction. This is not sufficient to override the steric compression associated with the interaction of the substituent in the incoming dipolarophile and the appropriate ring hydrogens of the nitrone. The influence of steric factors appears to dominate in the cases of styrene, allyl alcohol and vinyl ethyl ether adducts in which we assume to have the *exo* mode of attack.

The substituents methyl and methoxycarbonyl have similar effects on the size of the HOMO coefficients of the alkene, the LUMO orbital are affected in the opposing direction. Thus, the LUMO coefficients on both carbon atoms in methyl methacrylate are nearly the same (Figure 2). The stereochemistry, as depicted in (**187b**) for the major adduct in the methyl methacrylate (**47a**) addition is based on analogy.[90,91] It can be confidently assumed that the methoxycarbonyl (CO_2Me) group would manifest favorable secondary orbital interaction and would be *endo*-oriented in the major isomer (**187b**).

Recently, the role of secondary orbital interaction as major *endo* orienting factors are repeatedly being questioned.[92] In one such report[93] it has even been concluded that secondary orbital overlap involving the orbitals of the nitrogen atom of a nitrone and maleonitrile gives rise to a destabilization of the *endo* transition state with respect to the *exo* form.

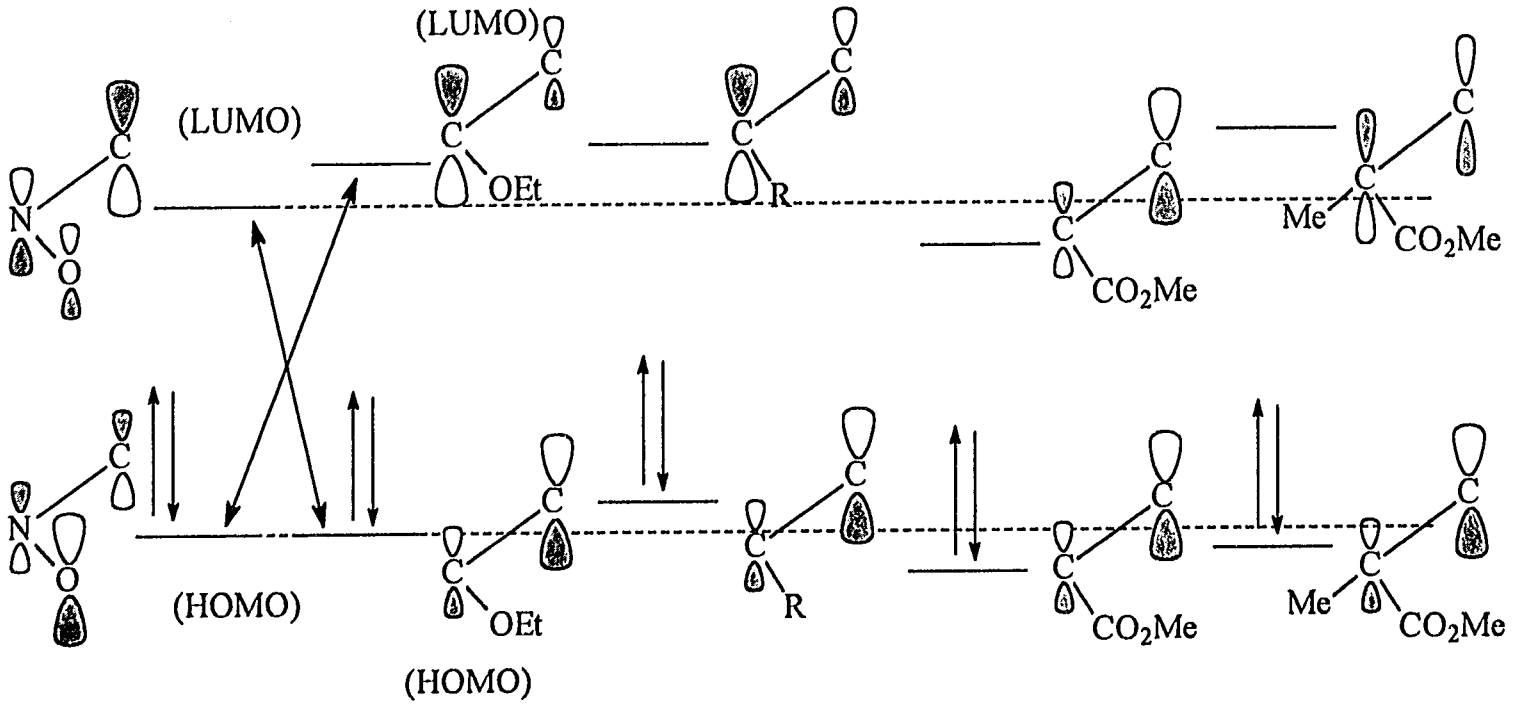


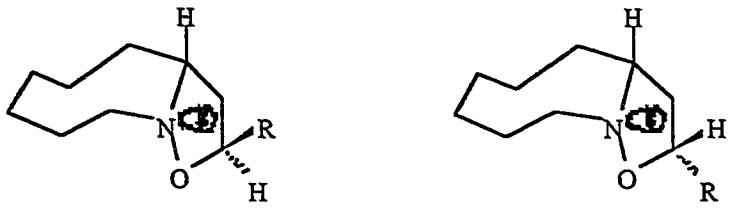
Figure 2 : A qualitative representation of the energies and orbital coefficients of the nitrone and alkenes.

For nitrone cycloaddition reaction, nitrone (HOMO)-maleic anhydride (LUMO) energy gap is much smaller that of the other HOMO-LUMO combinations. In fact, nitrone (LUMO)-maleic anhydride (HOMO) interaction could be considered negligible. Unexpected formation of major adduct (**188c**) in the cycloaddition of dimethyl maleate, resulted via the *exo* mode of attack, is an ample demonstration of steric factor dominating over secondary orbital interaction in the transition state. Whereas, maleic anhydride affords compound (**187d**), as the major adduct with *endo* orientation of the substituents (Scheme 6). This is in line with the favored *endo* mode of attack observed in the case of maleic anhydride, where favorable secondary orbital interaction is large enough to override the relatively smaller steric factor in comparison to the addition of dimethyl maleate present in the *exo* transition state.

Table 2: Chemical shifts in ppm for C(2) protons of various adducts[a] in $CDCl_3$ at 20°C.

C(2)-*Endo*-proton	**C(2)-*Exo*-proton**
5.12 (188a)	5.03 (187a)
4.78 (187c)	4.68 (188c)
4.98 (188d)	4.93 (187d)
4.15 (188e)	4.10 (187e)
4.08 (188f)	4.02 (187f)
5.02 (188g)	4.98 (187g)

3.3 Chemical Shifts of the C(2) Protons of Several Cycloadducts



C-2 endo-proton C-2 exo-proton

Figure 3

The chemical shifts for the absorption of C(2) *endo* and *exo* protons of several pairs of cycloadducts are summarized in Table 2. A generality is observed in the proton chemical shifts. The C(2) *endo* protons, invariably, appear downfield among all the listed pair of adducts. A plausible explanation for the upfield shift for the C(2) *exo* proton might be due to the *cis*-orientation of the nitrogen lone pair and C(2) hydrogen.

CHAPTER 4

KINETICS OF CYCLOADDITION REACTIONS

RESULTS AND DISCUSSION

The nitrone-olefin cycloaddition is a second order reaction, first order with respect to each component of the reaction system. Second order rate constants k_2 for dimerization the nitrone (**177**), its cycloaddition onto the methyl methacrylate (**47b**) at 26°C and on to methyl acrylate (**189g**) at 16°C, 26°C, and 36°C in deuterated chloroform was determined by ^{1}H NMR spectroscopy. All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors. The nitrone, alkenes, and the cycloadducts were all stable under the mild reaction conditions.

Nitrone cycloadditions were monitored by proton NMR by following the change in the intensity of the ^{1}H NMR signals of 2-H of nitrone and α-H of alkene. The ^{1}H NMR ($CDCl_3$) signals of the 2-H and 8-H signals of the nitrone (**177**) appeared at δ 7.06 and 3.97, respectively. The signals of the olefinic protons of the alkenes were centered around δ 5.62, and 6.16 for methyl methacrylate and at δ 5.81, 6.10, and 6.39 for methyl acrylate. These signals and in most cases C-2 H

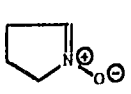
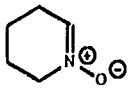
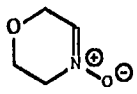
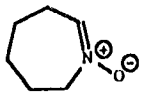
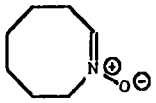
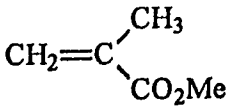
of the cycloadducts were free of overlapping signals. Therefore, the ratio of the concentration of the nitrone and alkene were frequently determined during the kinetic runs by integrating the ^{1}H NMR signals of the olefinic protons of the nitrone and the alkene. The second order rate constants were then obtained by linear regression analysis of the data. The additions were followed up to 30-90% of chemical conversion.

Kinetic results obtained for the cycloaddition of the nitrone (**177**) with different alkenes in $CDCl_3$ are represented in Table 3 and Table 4. Kinetic measurement of k_2 for other nitrones (**70**), (**41**), (**9**) and (**180**) with the same alkenes are also tabulated for the purpose of comparison (Table 4). In order to avoid any possible polymerization, the concentration of nitrone (**177**) was kept low and the alkene was used in excess. We did not notice any unwanted polymerization under the specified reaction conditions. The most reactive nitrone was the nitrone (**9**) (see Table 4). For example, the rate ratio for the addition reaction of the nitrones (**9**), (**70**), (**41**), (**180**) and (**177**) with methyl acrylate in deutereochloroform at 36°C was found to be 39:1:5.5:7.3:4.7, respectively.[94]

Table 3 : Rate Constants and Activation Parameters for the Cycloaddition Reaction of the Nitrone (**177**) with Alkenes in Deuterated Chloroform.

Alkene	Temp/°C	$10^5 k_2$/l mol^{-1} s^{-1}	E_a/kJ mol^{-1}	$\Delta H^{\#}$/kJ mol^{-1}	$\Delta G^{\#}$/kJ mol^{-1}	$\Delta S^{\#}$/J mol^{-1} k^{-1}
$CH_2{=}CHCO_2Me$						
	16	70.5				
	26	155	52.7	50.2	89.3	-131
	36	290				
$CH_2{=}C(CH_3)CO_2Me$						
	16	52.1				
	26	93.9	48.5	46.0	90.6	-148
	36	193				

Table 4 : Rate Constants (k_2) for the Cycloaddition Reactions at 36°C in deutereochloroform.

	 (70)	 (41)	 (9)	 (180)	 (177)	
Alkenes	$k_2 \times 10^5$ l mol^{-1} s^{-1}					k_2 (70) : k_2 (41) : k_2 (9) : k_2 (180) : k_2 (177)
CH_2=$CHCO_2Me$	62.0	340	2400	453	290	1 : 5.5 : 39 : 7.3 : 4.7
	23.4	105	453	407	193	1 : 4.5 : 19.4 : 17.4 : 8.3

The methyl acrylate cycloaddition reaction onto nitrone (**177**) was found to be 1.5 times as reactive as methyl methacrylate (Table 3). This observation can be related to the steric retardation caused by the introduction of the methyl group.

According to Sustmann`s classification[89] (Figure 4), the cycloaddition reaction of nitrone on to alkene is a type II process. In this type, the HOMO and LUMO energies in dipole and dipolarophile are similar, and hence, both HOMO (nitrone)-LUMO (alkene) and LUMO (nitrone)-HOMO (alkene) interactions contribute effectively to the stabilization of the transition state, and therefore may be important in determining the reactivity and regiochemistry. The interaction that dominates in a particular case will depend on the nature of both the dipole and the dipolarophile. Both electron-deficient and electron-rich alkenes, because of smaller energy gap, would undergo additions faster than normal alkenes. For instance, the LUMO (dipole)-HOMO (dipolarophile) interaction dominates in the case of electron-rich alkenes, and the alternative HOMO (dipole)-LUMO (dipolarophile) interaction is dominant for very electron-poor dipolarophiles.

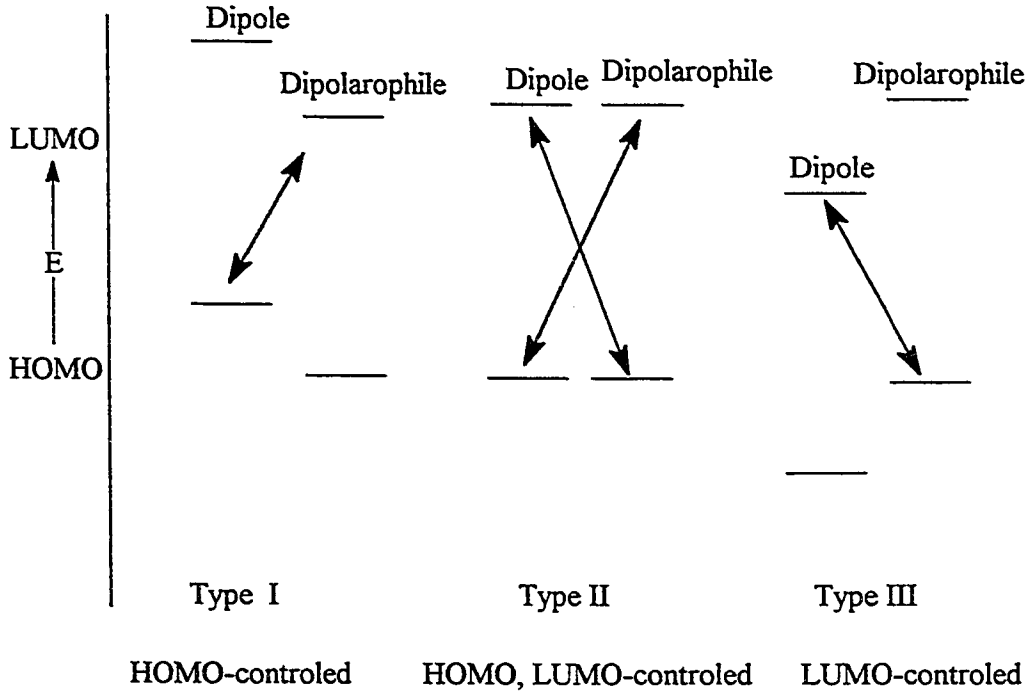


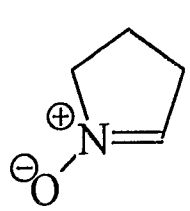
Figure 4 : Frontier molecular orbital classification[89] of cycloaddition

The cyclic nitrones (41), (9), (180) and (177) are found to be more reactive than their five-membered counterpart (70). Some constraint or its relief must be introduced to give a better picture of the transition state. The angular strain present in nitrone (70) is more than offset by the greater eclipsing strain (peculiar to the cyclopentene system) introduced in the transition state due to a change in the hybridization from sp^2 to sp^3. The absence of similar destabilizing strains in the transition state makes nitrones (41), (9), (180), and (177) more reactive than nitrone (70). Steric factors (non-bonded repulsions) are expected to be unfavorable in the

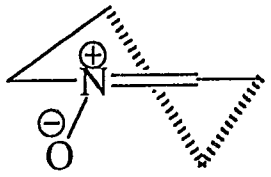
transition state leading to 5-5 ring system in comparison to 6-5, 7-5 and 8-5 systems.

Differences in the rates of cycloaddition of the cyclic nitrones might be due to a combination of various factors (including non-bonded repulsions) in the transition state.[95] Like cycloalkenes,[96] the cyclic nitrone (**41**), (**9**), (**180**), and (**177**) are expected to adopt the most stable flattened chair (or half-chair) conformations, as depicted in scheme 9. A minor portion of the boat form is expected to be in equilibrium with the chair form. The difference in energy between the half-chair and the half-boat conformations of cyclohexene has been approximated to be 2.7 Kcal/mol[99]. The cyclic nitrone (**41**), like cyclohexene, should have similar energy difference between the two conformers. It is anticipated that the presence of the heteroatom oxygen[100] in the ring skeleton of the nitrone (**9**) would make the energy difference between its chair and boat form smaller than the corresponding energy difference for its carbocyclic counterpart (**41**). Thus, in comparison to the nitrone (**41**), the proportion of the boat form for the nitrone (**9**) should be considerably higher.

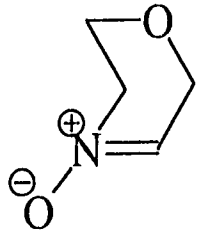
A study[97] involving diimidic reductions of double bonds at 80°C, cyclopentene and cycloheptene were found to be much more reactive than cyclohexene. Further studies, including the rates of diisoamylborane addition[98] to cyclopentene and cycloheptene relative to the cyclohexene at 0°C were found to be 108 and 500,



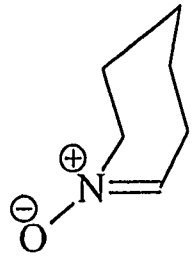
(70)



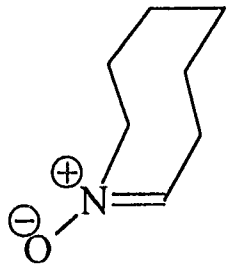
(41)



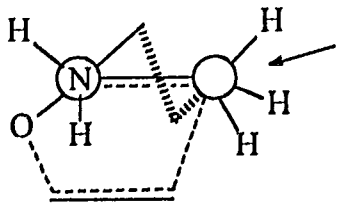
(9)



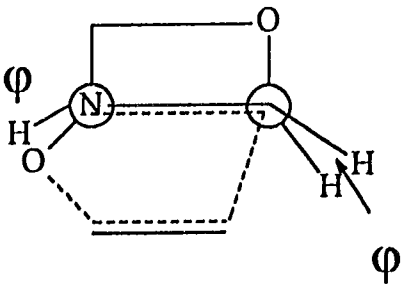
(180)



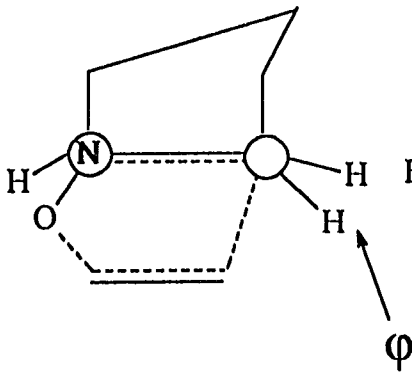
(177)



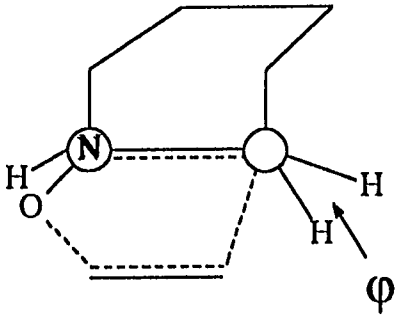
T.S **(41)**



T.S **(9)**



T.S **(180)**



T.S **(177)**

Scheme 9

respectively. The greater reactivates of cyclopentene and cycloheptene were explained as originating from a combination of angle bending and torsional strains in these alkenes that are relieved as the reactions proceed to the transition states. In our study, the nitrone (**70**) was found to be the least reactive and nitrone (**9**) was the most reactive.

An experiment for the greater reactivity of the seven-membered nitrone (**180**) than five, six, and eight-membered nitrone using explanations similar to that used for the cycloheptene case. In the stable chair (or half-chair) conformation the torsional angle φ in the nitrone (**180**), like cycloheptene, is about 15° (almost eclipsed), whereas, the corresponding angle in nitrone (**70**), (**41**), and (**177**) is about 40°. While, the torsional strain in the nitrone (**9**) is expected to decrease as the angle φ widens in the transition state (Scheme 9), the transition state for the addition of nitrone (**41**) acquires an increased torsional strain as the angle φ decreases. But, this does not explain the greater reactivity of nitrone (**41**) in a comparison to the nitrone (**70**), and (**177**). Other effects need to be considered, steric factors (non-bonded repulsions) are expected to be unfavorable in the transition state leading to the 5-5 ring system in comparison to 6-5, 7-5 and 8-5 systems. Also, the nitrone (**41**) may not react via the chair form. The corresponding boat form which has slightly more strain energy is expected to be more reactive as it is associated with a

high torsional strain (φ 15°) which will be relieved as the reaction proceeds to the transition state.

It might be argued that the nitrone (**9**) and (**41**) may not react via chair form alone, active participation by the corresponding boat form, especially in the addition of the nitrone (**9**), is expected. The torsional strain in the chair form is expected to increase as the angle φ decreases in the transition state, the transition state for the addition of the boat form acquires a decreased torsional strain as the angle φ widens. Presumably, the nitrone (**9**) undergoes cycloaddition mainly via its boat form as it is associated with a high torsional strain which will be relieved as the reaction proceeds to the transition state. This may account, in part, for the greater reactivity of the cyclic nitrone (**9**).

Our activation parameters, shown in Table 3, are derived from rate constants determined at different temperatures by ^{1}H NMR spectroscopy. The results are consistent with those reported for cycloaddition reactions involving acyclic nitrones.[56] These low activation energies and large negative entropies of activation are a necessary condition for multicentered concerted cycloaddition reactions.[27a]

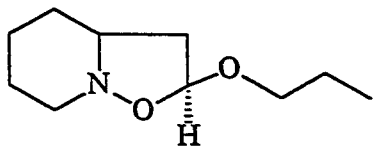
CHAPTER 5

NITROGEN INVERSION

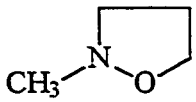
5.1 Introduction

The potential barrier of pyramidal nitrogen (sp^3) inversion process has been evaluated from IR spectra as a small value [25-29 kJ mol^{-1} for NH_3, 29-34 kJ mol^{-1} for $N(CH_3)_3$].[101] It is mainly through tunnelling, causing very high inversion frequencies (for example, 10^{11} s^{-1} at room temperature for NH_3). The presence of heteroatom oxygen slows down the electron pair inversion in nitrogen to such an extent that at ambient or lower temperature the presence of two interconvertible diastereoisomeric isoxazolidines could be identified by NMR spectroscopy. The causes for the increase in nitrogen inversion barrier have been explained by both valence bond[102] and molecular orbital approaches,[103] which attribute the destabilization of the planar transition state due to the presence of heteroatoms attached to the nitrogen. While, the electronegative substituents (O, N, halogen) on nitrogen increase the inversion barrier by their σ inductive electron withdrawing ability and π repulsive character due to electron pair, the relative contribution of these two effects still remains a challenging question.[104] Recent studies[105-107] of nitrogen inversion in bicyclic isoxazolidines have lead to a better understanding of these isoxazolidines.

Nitrogen inversion barrier in the isoxazolidine (**199**), a nitrone cycloaddition product, is large enough to be observable by dynamic nuclear magnetic resonance spectroscopy. The cycloadduct (**199**) interchanges between the invertomer at a rate of ca. 10 s^{-1} at 30 °C.[108]

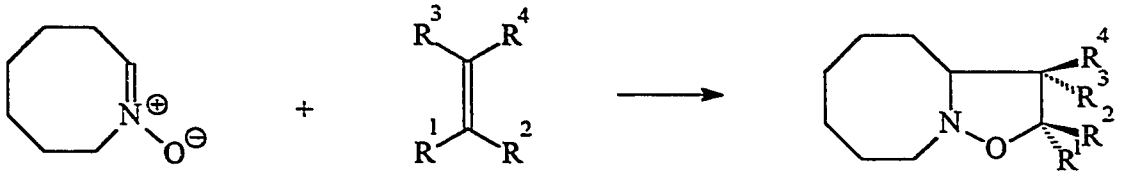


(199)

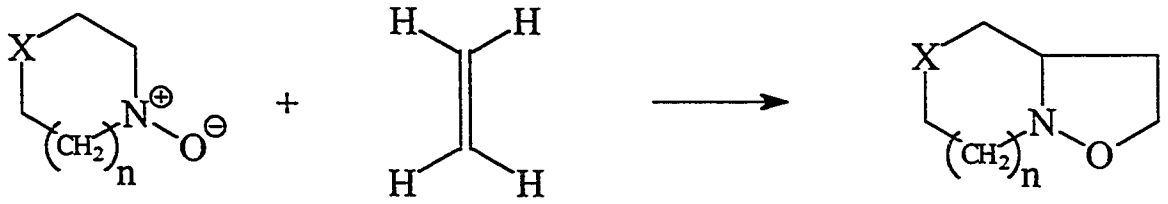


(200)

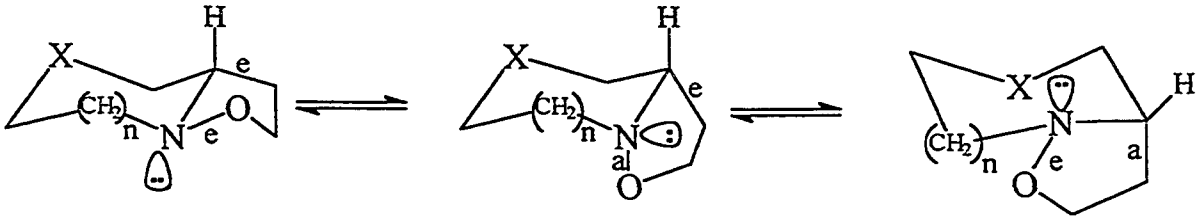
The cycloadducts (**202**) can, in principle, exist in three different conformations the *trans* conformer (**202a**) and the *cis*-pair (**202b**) and (**202c**). Whereas, the *cis*-pair is in rapid equilibrium by chair inversion (C_i), one of the *cis* conformers (**202b**) is converted into *trans* conformer by a relatively slow nitrogen inversion process (Scheme 10). Conformation analysis of the cycloadducts (**202**) is thus of both theoretical and practical importance. Hence, we undertook a systematic study to determine the major<=>minor equilibrium constant (K) and nitrogen inversion barrier for several cycloadducts by NMR spectroscopy. The compound's studies are shown in Table 5.



(177) (201) (202)



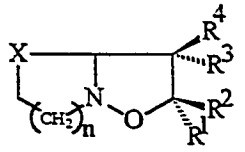
(203) (194) (204)



(204-A) (204-B) (204-C)

Scheme 10

Table 5: List of Compounds Studied

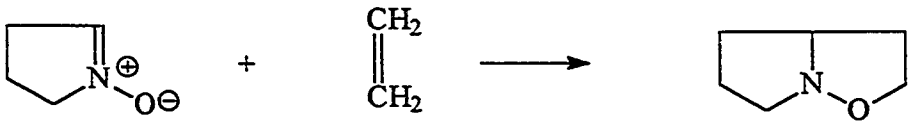


Isoxazolidine	R^1	R^2	R^3	R^4
X= CH_2, n =4 (187a)	H	Ph	H	H
X= CH_2, n=4 (187b)	CH_3	H	H	H
X= CH_2, n=4 (187c)	CO_2CH_3	H	CO_2CH_3	H
X= CH_2, n=4 (188c)	H	CO_2CH_3	H	CO_2CH_3
X= CH_2, n=4 (187e)	H	CH_2OH	H	H
X= CH_2, n=4 (188e)	CH_2OH	H	H	H
X= CH_2, n=4 (187f)	H	$OSi(CH_3)_2C(CH_3)_3$	H	H
X= CH_2, n=4 (188f)	$OSi(CH_3)_2C(CH_3)_3$	H	H	H
X= CH_2, n=4 (187g)	H	OCH_3	H	H
X= CH_2, n=1 (195a)	H	H	H	H
X= CH_2, n=2 (195b)	H	H	H	H
X= O, n= 2 (195c)	H	H	H	H
X= CH_2, n=3 (195d)	H	H	H	H
X= CH_2, n=4 (195e)	H	H	H	H

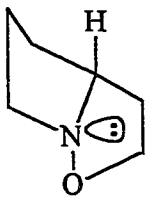
5.2 NITRONE ETHYLENE CYCLOADDITION REACTIONS

5.2.1 Addition of Nitrone (70) to Ethylene (194).

Vacuum distillation of the crude reaction mixture resulting from the addition of the nitrone (**70**) to the ethylene (**194**) at 125 °C and a pressure of 3.0 atm for 7 hours, afforded the cycloadduct (**195a**) (Scheme 11). A yield of 74% was recovered from this cycloaddition reaction. The cycloadduct (195a) existed solely as one isomer throughout the temperature range -50 to +50 °C as it was shown by carbon-13 NMR spectra.



(70) (194) (195a)

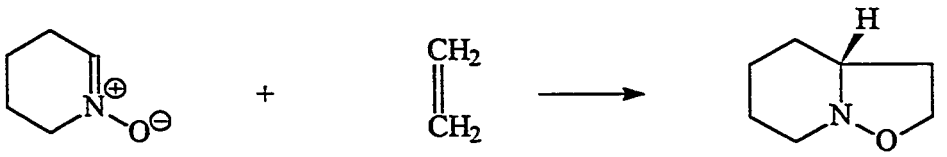


(196a)

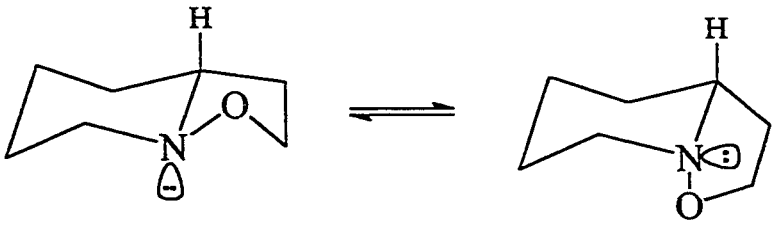
Scheme 11

5.2.2 Addition of Nitrone (41) to Ethylene (194)

Nitrone (**41**) underwent cycloaddition reaction with the ethylene (**194**) in a pressure bottle at a pressure of 3.0 atm and temperature of 120°C for 10 hours. Vacuum distillation of the crude reaction mixture afforded the isoxazolidine adduct (**195b**) in 85% yield (Scheme 12). The ratio of the isomer (**196b**) and (**197b**) was estimated by the integration of the C-2 proton signals and was found to be 80:20, respectively at -50 °C.



(41) (194) (195b)

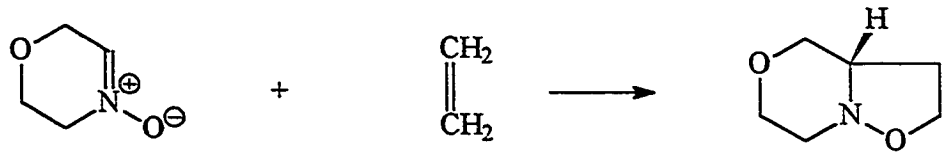


(196b) (197b)

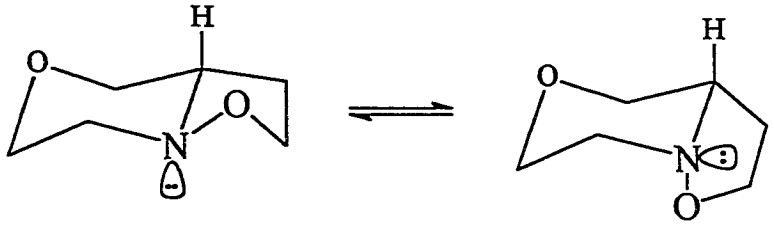
Scheme 12

5.2.3 Addition of Nitrone (192) to Ethylene (194)

Nitrone (**192**) cycloaddition onto ethylene (**194**) was carried out at 100 °C. Vacuum distillation of the product afforded the cycloadduct (**195c**) and the isolated yield was 45%. The ratio of the isomer (**196c**) and (**197c**) was estimated by integration of the relevant ^{13}C NMR peaks and found to be 14:86, respectively at 25°C (Scheme 13).



(192) (194) (195c)

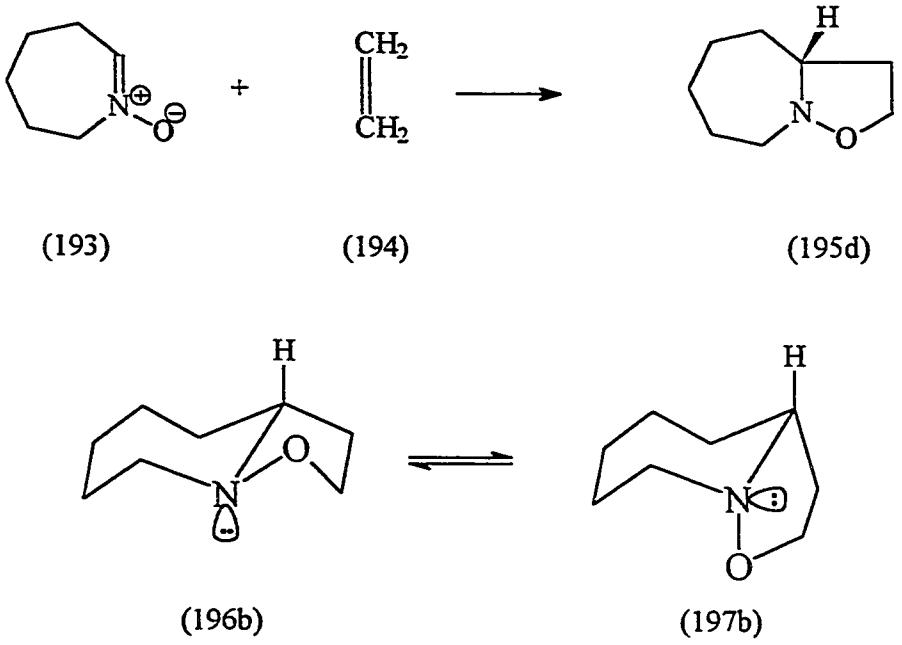


(196c) (197c)

Scheme 13

5.2.4 Addition of Nitrone (193) to Ethylene

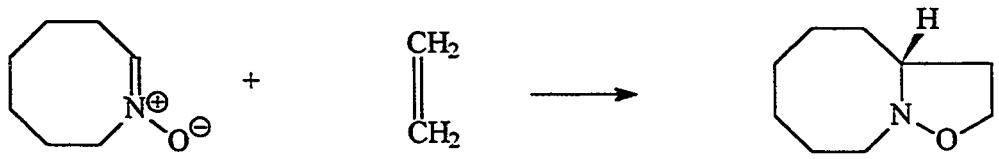
From the cycloaddition reaction of ethylene onto the nitrone (**193**), at a pressure of 3.0 atm and a temperature of 120 °C for 14 hours, the isoxazolidine (**195d**) was obtained in 41% yield (Scheme 14). The ratio of (**196d**) and (**197d**) was estimated by the integration of the relevant ^{13}C NMR signals, and was found to be 85:15, respectively.



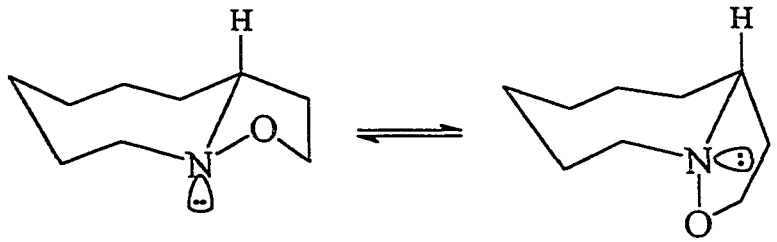
Scheme 14

5.2.5 Addition of Nitrone (177) to Ethylene (194)

The product afforded by the addition reaction of the nitrone (**177**) onto ethylene (**194**) at 130 °C and a pressure of 4.0 atm for 12 hours. Chromatographic purification of the crude reaction product using 97:3 dichloromethane-ether mixture as eluant gave the cycloadduct (**195e**) in a total yield of 52%. The major and minor conformers are assigned as depicted in (**196e**) and (**197e**), respectively. The ratio of (**196e**) and (**197e**) was determined to be 86:14, respectively by the integration of ^{13}C NMR signals.



(11) (194) (195e)



(196e) (197e)

Scheme 15

5.3 Results and Discussion

Slow nitrogen inversion in these isoxazolidines has been observed to give broadened peaks in ^{1}H and ^{13}C NMR spectra recorded at the ambient temperature. On lowering the temperature the spectral lines become sharper and show two distinct forms of the isomers. The ^{13}C NMR chemical shifts of compounds (102) were assigned on the basis of the published data[109,110] on isoxazolidines, general chemical shift arguments, consideration of substituent effects, and DEPT ^{13}C NMR spectrum. They are given in Table 6 as well as in Table 7.

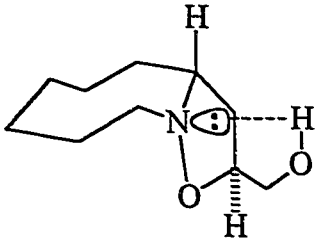
In any one compound in the case of nitrone (**177**), the C-3, C-5, and C-10 resonances of the major conformer are more deshielded than the corresponding carbons of the minor conformer, whereas, the C-2 and C-4 resonances of the major conformer are more shielded than the corresponding carbons of the minor conformer (Table 6). In the 6-5 system[110] and 7-5 system[111], the carbons of the minor isomer are more shielded than the corresponding carbons of the major isomer, excepting the C-2 which is less shielded in the minor isomer. As far as the five-membered ring carbons and C-10 of the 8-5 system are concerned, the trends in the chemical shifts between the major and the minor isomer are similar to that of the 6-5, and 7-5 systems. The trends in the chemical shifts of eight-membered ring carbons between the two isomers are expected to be different from that of six and seven-membered

Table 6 : ^{13}C NMR Chemical Shifts[a] of Adducts (202)

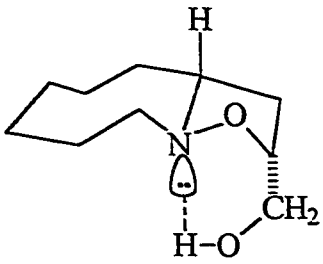
Compound		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Other[b]
(187a)	cis	77.6	43.5	65.3	30.7	25.6	24.1	24.1	26.9	52.9	i-141.5; o-128.1; m-127.4; p-126.3
	trans	77.2	45.4	64.4	35.9	25.4	21.9	23.6	26.3	58.5	i-138.3; o-128.3; m-128.0; p-126.8
(187b)	cis	76.1	55.5	76.9	30.4	24.0	23.8	23.6	24.3	69.3	OCH_3-53.9; Me-21.9; CO-159.5
	trans	77.4	58.1	75.2	33.6	24.5	23.8	24.9	26.7	67.2	OCH_3-52.8; Me-21.9; CO-171.0
(188c)	cis	82.7	44.0	65.3	30.9	26.7	25.4	25.6	26.9	53.6	OCH_3-52.9; CO-175.8
	trans	79.8	47.1	63.7	32.6	24.9	23.6	24.0	26.9	57.5	OCH_3-53.6; CO-175.9
(187e)	cis	75.9	36.0	64.4	30.2	25.8	22.6	24.0	26.7	53.0	CH_2-64.5
	trans	76.7	40.0	62.9	34.4	25.8	24.0	24.0	26.7	58.4	CH_2-65.2
(188e)	cis	79.4	43.4	57.6	37.6	23.9	15.2	21.9	24.0	54.1	CH_2-60.7
	trans	76.0	40.4	62.5	33.8	26.0	23.0	22.9	26.0	58.6	CH_2-65.2
(187f)	cis	76.4	36.4	64.3	30.5	26.9	25.3	26.9	25.2	52.9	CH_3-(-5.5, -5.4), 25.3; C-18.3; CH_2-63.8
	trans	75.6	40.3	64.3	34.4	25.7	23.9	24.0	25.7	58.2	CH_3-(-5.5, -5.4), 25.7; C-18.3; CH_2-63.8
(188f)	cis	79.9	38.2	66.1	31.7	25.1	25.1	25.1	28.3	55.9	CH_3-(-4.5, -4.4), 27.0; C-19.3; CH_2-66.1
	trans	76.5	43.3	65.3	35.6	26.7	24.0	24.0	26.7	59.3	CH_3-(-4.5, -4.4), 26.7; C-19.3; CH_2-65.3
(195e)	cis	64.4	34.5	64.8	30.6	26.1	24.2	24.2	27.2	52.4	
	trans	64.4	39.4	63.8	35.7	25.8	23.1	23.4	26.0	58.5	

a,in ppm relative to internal TMS at -50°C.
b,i,o,p,m,refers to ipso,ortho,para,meta carbons of the phenyl group.

ring carbons, as the conformations of the two ring systems are entirely different. So, we may assume the conformation of the ring junction is similar for the major isomers of 6-5, 7-5 and 8-5 and also, that of the minor isomer of 6-5, 7-5 and 8-5 isoxazolidine systems. So it follows that the major isomer of the 8-5 system should have a *trans* junction, as shown for the 6-5 system by X-ray diffraction study[112]. This assignment is further supported by the isomer ratios of the hydroxy methyl compounds. Importance of the intramolecular H-bonding is further demonstrated in the methyl allyl alcohol adducts (**187e**) and (**188e**), where the major isomer is found to be the *trans* isomer from the chemical shift data. The intramolecular H-bonding in (**187e**) is possible only in the *cis* conformation, whereas, in (**188e**) is possible only the *trans* conformation and hence this conformer predominates. Changing the methyl allyl alcohol adduct (**187e**) to its silyl derivative (**187f**), results in the *trans/cis* ratio changing from 53:47 to 67:33. On the other hand, the N:---H-O bonding which is possible only in the *trans* form of (**188e**) allows this adduct to be the predominant conformer that might be proved when we change the methyl allyl alcohol adduct (**188e**) to it's silyl derivative (**188f**), results in the *trans/cis* ratio change from 96:4 to 90:10.



(187e)



(188e)

Furthermore, we undertook a systematic study of the conformation of the isoxazolidines in 5-5, 6-5, 7-5 and 8-5 parent systems, which had not previously been synthesized and studied, by ^{13}C NMR spectroscopy, as the proton NMR spectra of these systems are insufficiently resolved to allow a detailed study. Geometric constraints thus prevent the *trans-cis* interconversion by nitrogen inversion in isoxazolidine (**195a**), the ^{13}C NMR spectra of compound (**195a**) show sharp signals over the temperature range -50 to +50°C, confirming that the *cis* isomer is the sole isomer as it observed from the ^{13}C NMR chemical shifts compare with the other parent systems. The chemical shifts are reported in Table 7.

The ^{13}C NMR spectra of cycloadducts (**195b**), (**195c**), (**195d**) and (**195e**) at low temperatures (ca. -20°C), show peaks due to distinct isomers, a major and a minor isomer. Our study indicates that the major conformer is the *trans* isomer, which is favorable over the *cis* isomer in all parent compounds that were studied,

Table 7 : ^{13}C NMR Chemical Shifts[a] of Adducts (204).

Compound		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
(195b)	cis	65.4	30.5	59.5	25.4	23.5	19.2	49.4	-	-
	trans	64.5	34.3	66.3	29.3	24.8	23.9	55.1	-	-
(195c)	cis	65.6	28.9	59.1	64.9	-	65.3	49.1	-	-
	trans	70.3	30.4	64.4	64.5	-	65.0	55.7	-	-
(195d)	cis	63.6	35.5	65.8	29.9	25.0	24.9	29.8	52.0	-
	trans	64.9	37.7	66.2	30.3	24.0	25.0	25.4	57.4	-
(195e)	cis	64.4	34.5	64.8	30.6	26.1	24.2	24.2	27.2	52.4
	trans	64.4	39.4	63.8	35.7	25.8	23.1	23.4	26.0	58.5

a,in PPM relative to internal TMS at -25°C.

with exception of cycloadduct (**195c**) in which the opposite is true. The ^{13}C chemical shifts of C-2, C-3, C-4 and C-8 of isomers of cycloadduct (**195b**) are similar to those of the isomer of cycloadduct (**195c**). However, the major isomer in the case of cycloadduct (**195b**) showed similar chemical shifts to those of the minor isomer of isomer in the case of cycloadduct (**195c**), and the minor isomer of cycloadduct (**195b**) showed similar chemical shifts to those of the major isomer of cycloadduct (**195c**). The major isomer of the nitrone (**41**) adduct was shown to be the *trans* isomer from X-ray diffraction[105] and chemical shift data. It follows that the major isomer of cycloadduct (**195c**) should have the *cis* conformation, whereas, the minor isomer should have the *trans* conformation. All this evidence support that the facts that the *trans* conformation of all nitrone (**177**) adducts are more stable than the *cis* conformation.

5.2.1 Nitrogen Inversion

The low temperature ^{1}H and ^{13}C NMR spectra of compounds studied except cycloadducts (**187c**), (**187g**) and (**195a**) show the presence of separated signals for the two isomers, the *trans* conformer and the *cis* pair down to -50 °C, due to slow nitrogen inversion. The complete band shape analysis yielded the rate constants and the free energy of activation ($\Delta G^{\#}$) for the nitrogen inversion calculated using transition state theory.

$$k = (k_b T/h)\exp(-\Delta G^{\#}/RT)$$

The activation parameters $\Delta H^{\#}$ and $\Delta S^{\#}$ were calculated from the plot of ln(k/T) vs. 1/T. Integration of the relevant peaks gives the population trends in these systems. The calculated equilibrium constant (K) along with the corresponding ΔG° for major <=> minor equilibrium is given in Table 7 as well as in Table 8. The ^{13}C NMR integrations were found to be satisfactory when compared with ^{1}H integration in the case where proton spectra gave non overlapping signals for the two isomers.

To measure the barrier to nitrogen inversion, the coalescence method could not be used as the populations for the exchanging sites are not equal. Hence a complete band shape analysis, corresponding to a coupled and non-coupled two-site

exchange with unequal populations was employed. Obtaining accurate exchange rate constants by fitting NMR band shapes is well known to be fraught with difficulties and considerable errors result in the thermodynamic parameters $\Delta H^{\#}$ and $\Delta S^{\#}$ if Eyring plots are used. In fact, many of the errors are systematic in nature, and those resulting for $\Delta H^{\#}$ and $\Delta S^{\#}$ are often mutually compensatory so that $\Delta G^{\#}$ is better defined. Although $\Delta H^{\#}$ and $\Delta S^{\#}$ values were obtained we attach little significance to them for reasons above, and they are not reported here. The C-(2)H proton afforded convenient signals to study the band shapes changes with variation in temperature, as these signals are away from any overlapping signals and show only first-order coupling, otherwise, the band shapes of the ring carbon resonances were utilized in which three ring carbon signals were used at each temperature and the rate constants obtained are an average of three calculated values. The methyl methacrylate adduct (**187b**) does not have C-2 protons, while, the methoxyl protons at C-2 were singlets and the band shape of these were used in analysis. The $\Delta G^{\#}$ values calculated for the nitrone (**177**) cycloadducts at -20°C (near the coalescence temperature) are reported in Table 8 and for the parent ethylene cycloaddition adducts are reported in Table 9 at +25 °C (near the coalescence temperature). In making use of the Eyring plots, it was assumed that the transmission coefficient was unity.

Nitrogen inversion barrier is expected to be high when an oxygen atom is directly bonded to the nitrogen as in the isoxazolidines,[113] a barrier of 65.3 kJ mol^{-1} has been reported[113] for isoxazolidine (**200**) in deuterochloroform. For the adducts of nitrone (**41**),[110] nitrone (**192**)[107] and the nitrone (**193**) [111] the nitrogen inversion barriers are in the range of 65 to 69, 66 to 73 and 53 to 56 kJ mol^{-1} , respectively. In this study, the nitrogen inversion barriers of the adducts of the nitrone (**177**) which are similar to those of nitrone (**193**), are in the range of 53.5 to 57.4 kJ mol^{-1} (Table 8). It is well known[114] that the barriers to nitrogen inversion are very dependent on the ring size. Hence, in our study of the parent systems of various nitrones, the inversion barrier found in eight-membered ring (**195e**) is the lowest, whereas, it is the highest in the six-membered ring (**195c**). The data indicate a slight increase in the barrier in going from the six-membered ring adduct (**195b**) to the six-membered ring adduct (**195c**) (Table 9). The structural change of introducing an oxygen atom in the six-membered ring may lead to an increase in the barrier. The similarity in the range of values further confirms that we indeed measuring the nitrogen inversion barrier rather than the chair inversion barrier[115] and also, the small effect on the barrier from the groups at C-2 and C-3, that are at the β-position to nitrogen, is in accordance with two methods reported[114,116] for predicting electronic and steric increments to the nitrogen inversion barriers in heterocycles.

Table 8 : Free Energy of Activation ($\Delta G^{\#}$) for Nitrogen Inversion, Equilibrium Constant (K), and Standard Free Energy Change (ΔG^{o}) for *Trans* <=> *Cis* Isomerization of the Studied Cycloadducts of (202) in $CDCl_3$.

Compound	$\Delta G^{\#}$ (kJ/mol)[a]	*Cis*	*trans*	K	ΔG^{o} (kJ/mol)[b]
(187a)	55.4	75	25	0.33	+2.0
(187b)	54.8	78	22	0.28	+2.4
(187c)	-	100	0	0	-
(188c)	53.5	79	21	0.28	+2.4
(187e)	53.6	53	47	0.89	+0.22
(188e)	ND[c]	96	4	0.042	+5.9
(187f)	57.4	67	33	0.49	+1.3
(188f)	55.1	90	10	0.11	+4.1
(195e)	56.2	86	14	0.16	+3.8

a, At -20°C; b, At -50 °C; c, not determined.

Table 9 : Free Energy of Activation ($\Delta G^{\#}$) for Nitrogen Inversion, Equilibrium Constant (K), and Standard Free Energy Change (ΔG^{o}) for Major <=> Minor Isomerization of the Studied Cycloadducts of (204) in $CDCl_3$.

Compound	$\Delta G^{\#}$ (kJ/mol)[a]	*trans*	*cis*	K	ΔG^{o} (kJ/mol)[b]
(195b)	70.4	76	24	0.32	+2.8
(195c)	72.2	14	86	0.16	+4.5
(195d)	54.9	85	15	0.18	+3.2
(195e)	54.7	86	14	0.16	+4.5

a, At -25°C; b, At -50 °C

CHAPTER 6

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Nicholet 5 DBX FT IR and are reported in wave numbers (cm^{-1}). The ^{1}H NMR spectra were recorded on a Brucker AC 80 NMR spectrometer operating at a proton frequency of 80.0 MHz using deutereochloroform as solvent and TMS as internal standard. A Varian XL-200 and Jeol GX 270 NMR spectrometers operating at a proton frequency of 200.0 and 270.0 MHz, respectively were used to record ^{1}H and ^{13}C NMR Spectra. Mass spectra at 70 ev E.I. were recorded on a Ribermag GC-MS system, R-10-10 with quadrupole mass filter and Riber 400 acquisition system.

Thin layer chromatography silica gel plates with florescent indicator (Eastman, No. 6060) were used to monitor the reaction progress, and to determine appropriate solvent system for elution of the silica gel chromatographic separations which were performed with flash chromatography silica. All the liquid alkenes and N-hydroxyl amines were distilled before use in order to avoid any polymerization. The nitrone was assumed to be quantitative in the percentage yield calculation for the subsequent cycloadditions. Cycloadditions reactions were carried out under a positive pressure of nitrogen.

6.1 Cycloaddition Reactions of Nitrone (177) with Alkenes.

6.1.1 2-Ketoheptamethyleneimine (175b)

In a one liter three-neck flask fitted with reflux condenser, cycloheptanone (22.4 g, 200 mmol) was dissolved in a concentrated hydrochloric acid (300 ml). The mixture was stirred and cooled in an ice bath. Then sodium azide was slowly added as rapidly as evolution of N_2(g) would permit. The reaction flask was stirred for 4 hours in an ice bath and allowed to come to room temperature (25°C) for 2 hours. The mixture was made slightly alkaline with sodium carbonate, water was added to dissolve the inorganic salts and the product (**175b**) was extracted with chloroform (4 x 100 ml). Anhydrous sodium sulfate was used to dry the extract and the chloroform was removed by steam bath and then vacuum to obtain the adduct (175b) (65.6 g, 78.7%). It became a crystalline solid that melted at near room temperature (25°C) δ_H ($CDCl_3$, 25°C) 1.40-1.90 (8H, m), 2.30-2.50 (2H, m), 3.11-3.52 (2H, m), 5.80 (1H, br); δ_C (C_6D_6, 25°C) 24.9, 26.1, 28.3, 32.2, 32.6, 41.8, 179.0 [middle C_6D_6 δ_C 127.9].

6.1.2 Heptamethyleneimine (175c)

Lithium aluminum hydride (20.0 g) suspended in ether (150 ml) was placed in a one liter three-neck flask equipped with reflux condenser, then the 2-

ketoheptamethylene imine (**175b**) (62.3 g, 491 mmol) was added dropwise. A U-shaped trap filled with oil was used to prevent any air entering the reaction flask. The reaction mixture was stirred and refluxed for 52 hours and completion of the reaction was ensured by TLC. The solvent ether was removed under reduced pressure and the product was freed from the byproduct by vacuum distillation, $b.p._{25\ mm}$ 72°C, to give the adduct (**175c**) (21.6g, 38.9%) as a colorless liquid δ_H ($CDCl_3$, 20°C) 1.30-1.60 (10H, m), 1.76 (1H, s), 2.60-2.90 (4H, m); δ_C ($CDCl_3$, 20°C) 25.1 (2C), 28.1, 29.2 (2C), 48.5 (2C), [middle $CDCl_3$ δ_C 77.0].

6.1.3 N-hydroxylheptamethyleneimine (175)

To a stirring sample of heptamethyleneimine (20.0 g, 177 mmol) cooled in an ice bath 25 ml of 30% hydrogen peroxide was added. The addition was carried out over a period of 25 minutes maintaining the temperature of the mixture below 10°C. After complete addition of hydrogen peroxide (about 35 min), when the temperature exceeded 70°C, the flask was immediately immersed in the ice bath. The mixture temperature continued to rise to 110°C and the reaction mixture was slowly brought to room temperature. A sufficient amount of anhydrous potassium carbonate was added to the mixture. In a separatory funnel, the organic layer was collected, and the remaining aqueous layer was extracted with ether (4 x 50 ml). The extracts were collected and dried over anhydrous sodium sulfate. The organic layer and

extracts were distilled to obtain the adduct (**175**), b.p.$_{10mm\ Hg}$ 100-110°C, (4.27g, 19.4%) as a colorless liquid.

6.1.4 N-hydroxypyrrolidine (11a)

Preparation of the n-hydroxypyrrolidine (**11a**) by the oxidation of tetramethyleneimine (**10a**) was prepared using the same procedure as described for N-hydroxylheptamethyleneimine (**175**).

6.1.5 N-hydroxypipridine (11b)

N-hydroxypiperidine (**11b**) was prepared by the oxidation of the pentamethyleneimine (**10b**) using the same procedure described for N-hydroxylheptamethyleneimine (**175**).

6.1.6 4-Hydroxymorpholine (7)

Preparation of the 4-hydroxymorpholine (**7**) was completed by the oxidation of morpholine (**5**) using the same procedure as described for N-hydroxylheptamethyleneimine (**175**).

6.1.7 N-hydroxyazepine (11c)

N-hydroxyazepine (**11c**) was prepared from hexamethyleneimine (**10c**) using the same procedure as described for N-hydroxylheptamethyleneimine (**175**).

6.1.8 3,4,5,6,7-Pentahydro-2H-undecane-1-oxide (177)

Preparation of the nitrone (**177**) was accomplished by the oxidation of the corresponding hydroxyl amine (**175**). To N-hydroxyheptamethyleneimine (4.27 g, 33.1 mmol) in CH_2Cl_2 (200 ml) at 0 °C was added yellow mercuric oxide (15.0g, 69.3 mmol) in three portion over a period of 15 min. Within minutes after HgO addition, the reaction mixture become grayish, presumably due to liberation of Hg and formation of mercuric salts. Stirring was continued for an additional 0.5 hour at 0 °C. The progress of the reaction was monitored by TLC. After the completion of reaction, it was filtered through a bed of $MgSO_4$. Cold (0 °C) CH_2Cl_2 was used to wash the bed and the filtrate was collected in an ice-cooled flask. The nitrone (**177**) solution in dichloromethane was kept in the freezer in order to avoid any polymerization. The formation of the nitrone (**177**) was assumed to be quantitative in the percent yield calculation for the subsequent cycloadditions. When the reaction was run in solvents other than CH_2Cl_2 the required amount of the nitrone solution was evaporated and the appropriate solvent was added.

6.1.9 1-Pyrroline-1-oxide (70)

The nitrone (**70**) was prepared from N-hydroxypyrrolidine using identical procedure as described above for 3,4,5,6,7-pentahydro-2H-undecane-1-oxide (**177**).

6.1.10 2,3,4,5-Tetrahydropyridine1-oxide (41)

The nitrone (**41**) was prepared from N-hydroxypiperidine using an identical procedure as described above for 3,4,5,6,7-pentahydro-2H-undecane-1-oxide (**177**).

6.1.11 3, 4, 5, 6-Tetrahydro-2H-azepine-1-oxide (180)

The nitrone (**180**) was prepared from N-hydroxyazepine using an identical procedure as described above for 3,4,5,6,7-pentahydro-2H-undecane-1-oxide (**177**).

6.1.12 5,6-Dihydro-1,4-oxazine-4-oxide (9)

Preparation of the nitrone (**9**) was accomplished by the oxidation of 4-hydroxymorpholine using the same procedure as described above for 3,4,5,6,7-pentahydro-2H-undecane-1-oxide (**177**).

6.1.13 Isomers of 2-Phenyl-1-oxa-177-azabicyclo (6,3,0) undecane (187a)-(188a)

Styrene (2.0 cm^3) was added to a solution of the nitrone(**177**) (3.0 mmol) in 25 cm^3 of dichloromethane and was refluxed for 24 hours. Completion of the reaction was ensured by TLC. The crude reaction mixture was freed from the solvent and excess styrene by passing a stream of nitrogen through the mixture. The

crude residue was purified by silica gel column chromatography using hexane-ether (9:1) mixture as the eluant to give a mixture of the adducts (**187a**) and (**188a**) (598 mg, 86.3%). The ratio of the two isomers (**187a**) and (**188a**) was found to be 91:9, respectively as determined by integration of various ^{1}H and ^{13}C NMR signals. ν_{max} (KBr) 3030, 2926, 2849, 1595, 1452, 1384, 1353, 1330, 1281,1160, 1156, 1129, 1114, 1088, 1060, 1031, 1004, 988, 941, 906, 899, 758, and 697 cm, δ_H, ($CDCl_3$, +20 °C, major isomer) 1.20-2.00 (9H, m), 2.35(3H, m), 2.90 (1H, m), 3.24 (1H, m), 5.00 (1H, t, J 7.4 Hz), and 7.36 (5H, m); ^{1}H NMR at -50 °C displayed the C(2) H signals at δ 4.91 (0.75 x 1H, dd, J 6.1, 9.1 Hz) and δ 5.07 (0.25 x 1H, dd, J 4.7, 9.8 Hz) and the C(2) minor isomer (**188a**) at -50 °C appeared at δ_H 5.08 as overlapping dd(J 4.2, 9.0 Hz); δ_C (CDCl3, +50, major isomer) 24.7, 26.2, 26.5, 23.1, 33.7, 46.3, 57.8, 65.8, 77.5, 126.8 (2C), 127.9, 128.6 (2C), 140.9 [middle $CDCl_3$ δ_C 77.3]; δ_C ($CDCl_3$, -50 °C, major isomer, major conformer) 22.3, 23.9, 25.7, 26.6, 36.2, 45.7, 58.8, 64,7, 77,5, 127.1 (2C), 128.3, 128.6 (2C), 138.6 [middle $CDCl_3$ δ_C 77.3]. δ_C ($CDCl_3$, -50 °C, major isomer, minor conformer) 24.4 (2C), 25.9, 27.2 31.0, 43.8, 53.2, 65.6, 77.9, 126.6 (2C), 127.7, 128.5, (2C), 141.8 (middle $CDCl_3$ δ_C 77.3); ^{13}C spectrum of the minor isomer (**188a**) was deduced from the spectrum of a mixture containing major (**187a**) and minor isomer (**188a**); δ_C ($CDCl_3$, +50°C, minor isomer) 24.9, 25.1, 26.8, 30.0, 34.7, 48.7, 59.2, 66.7, 77.5, the aromatic five carbons are

buried under the signals of the major isomer (**187a**), and 140.5 [middle $CDCl_3$ δ_C 77.3].

6.1.14 Isomers of Methyl-2-methyl-1-oxa-11-azabicyclo [6,3,0] undecane-2-carboxylate (187b)-(188b)

To a stirred solution of nitrone (**177**) (3.0 mmol) in 25 cm^3 of dichloromethane, was added 2.0 cm^3 of methyl methacrylate (186b) at 20°C. After stirring for 6 hours under a N_2(g) atmosphere, the solvent and excess alkene were evaporated by a stream of nitrogen. Chromatographic purification of the product residue with 4:1 mixture as eluant on silica gel yielded the adduct (**187b**) followed by a non-separable mixture of the adducts (**187b**) and (**188b**) (497mg, 73%). ν_{max} (KBr) 2955, 2931, 2859, 1757, 1735, 1455, 1371, 1298, 1264, 1255, 1203, 1166, 1139, 1096, 1062, 989, 950, 735 cm-1; δ_H ($CDCl_3$, +25°C, major isomer) 1.20-1.95 (9H, m), 1.48 (3H, S), 2.23 (2H, m), 2.58 (1H, m), 2.83 (1H, m) 3.06 (1H, m), 3.55 (1H, m), 3.77 (3H, s). At a temperature below -25°C, the methoxyl singlet of the major isomer started to split in two singlets; at -50°C the ^{1}H NMR spectrum of the major isomer showed the two invertomers of the major and minor conformer that appeared δ_H 3.77 and δ_H 3.75 as two singlets in a ratio of 78:22 respectively; δ_C ($CDCl_3$, +50°C, major isomer) 24.1, 24.8 , 26.1, 26.5, 27.4, 31.5, 47.7 52.5, 57.3,

65.9, 80.7, 175.7 [middle $CDCl_3$, 77.4]; δ_C ($CDCl_3$, -50°C, major isomer, major conformer).

6.1.15 Isomers of *cis*-Dimethyl-1-oxa-11-azabicylo [6.3.0] undecane-2,3-dicarboxylate (187c)-(188c)

Dimethyl maleate (2.0 cm^3) was added to a solution of nitrone (**177**) (2.25 mmol) in 20 cm^3 of dichloromethane. The reaction mixture was stirred and heated at 57°C in a close vessel for 6 hours. A steam of nitrogen, removed the solvent and excess alkene from the reaction mixture. Chromatographic purification of the product residue with 4:1 mixture hexane-ether as eluant gave the major isomer (**187c**) as a white solid (225 mg, 41.7%). Continued elution afforded the minor isomer as a white solid (167 mg, 27.3%). The ratio of the major and minor isomer was found to be 60:40 which was supported by the NMR integration of the C(2) signals. δ_H ($CDCl_3$, +25°C, major isomer) 1.20-2.08 (10H, m), 3.00 (1H, m) 3.38 (2H, m), 3.72 (3H, s), 3.75 (1H, m, underneath the methyl singlets 4.68 (1H, d, J 7.8 Hz); on lowering the temperature the C(2) H at δ_H 4.68 started to broaden at -35°C, the NMR spectrum displayed two separate doublet at -58°C, the C(2) H of the major and minor conformer of the major isomer appeared at δ_H 4.76 (d, J 6.7 Hz) and δ_H 4.78 (d, J 10.1 Hz) in a ratio of 80:20 respectively; δ_C ($CDCl_3$, +50°C, major isomer) 24.2, 25.8 (2C), 26.8, 32.0 52.2, 57.8, 58.6, 68.0, 75.8, 75.9, 169.6, 170.9,

169.6, 170.3 [middle $CDCl_3$ δ_C 77.1]; δ_C ($CDCl_3$, -50°C, major conformer of major isomer] 23.6, 24.9, 26.9, 32.6, 47.1, 52.9 (2C), 57.5, 63.7, 79.8, 175.9 (2C); δ_C ($CDCl_3$, -50°C, minor conformer of major isomer) 25.4, 25.6, 25.7, 26.7, 26.9, 30.9, 44.0 (2C), 53.6, 65.3, 82.7, 175.8 (2C) [middle $CDCl_3$ δ_C 77.2]; δ_H ($CDCl_3$, +25°C, minor isomer) 1.28-1.90 (10H, m), 2.00 (1H, m), 3.44 (2H, m),3.72 (3H, s), 3.78 (3H, s), 3.80 (1H, m), 4.98 (1H, d, J 7.6 Hz); The ^1H NMR spectrum at -50°C did not have a split C(2H) signal or any other split signals except for the broadening of some signals, presumably due to ring inversion; δ_C ($CDCl_3$, +50°C, minor isomer) 24.8, 24.9, 26.0, 26.1, 18.9, 51.8, 52.2, 57.1, 67.2, 75.8, 75.8, 169.9 [middle $CDCl_3$ δ_C 77.0]; δ_C ($CDCl_3$, -50°C, minor isomer) 21.2, 21.7, 23.9, 24.9, 28.2, 51.3, 55.6, 56.2, 73.7, 76.2, 168.7, 169.4 [middle $CDCl_3$ δ_C 77.0]. The ^{13}C NMR spectrum showed broaden peaks but did not show the invertomer of the major and minor conformer as in the case with the major isomer; ν_{max} (neat) 3002, 2917, 2875, 1768, 1736, 1478, 1452, 1362, 1280, 1234, 1208, 1183, 1056, 935, 867.

6.1.16 Reaction of the Nitrone (177) with Maleic Anhydride (57b)

Reaction of the nitrone with maleic anhydride in $CDCl_3$ initially gave an adduct which quickly decomposed to unknown insoluble material.

In another trial maleic anhydride (0.6 mmol) was added to a solution of nitrone (5.0 mmol) in NMR tube at 20°C for 10 min. The NMR spectrum revealed the presence of the two adducts (**187d**) and (**188d**) in ration of 70:30 respectively as determined by the integration of C(2H) single at δ_H 4.93 (d, J 8.0 Hz) for the minor isomer and δ_H 4.98 (d, J 8.0 Hz) for the major isomer. To the above reaction mixture after removal of the solvent, 2.0 ml of a mixture of methanolic-HCl (3:2 W/W) at 20°C was added to the residue and allowed to stand for 48 hours. After removal of the excess methanol the residue was taken up in saturated K_2CO_3 solution and extracted with ether (3 x 20 ml). The organic layer was dried ($MgSO_4$) and was purified by silica gel chromatography (As describe before in the case of dimethyl maleate adducts) to give the adducts (**187c**) and (**188c**) (isolated yield 104 mg, 77%). δ_H ($CDCl_3$, 20°C) 1.10-2.26 (10H, m), 2.70-3.20 (2H, m), 2.40-2.90 (2H, m, including a major triplet at δ_H 3.68 (0.70 x 1 H, J 8.0 Hz) and a minor dd at δ_H 3.58 (0.30 x 1H , J 3.0, 8.0 Hz), 4.93 (0.30 x 1H, d, J 8.0 Hz) and δ_H 4.98 (0.70 x 1H, d, J 8.0 Hz). The ratio of (**187d**) and (**188d**) was also determined by their conversions into (**187c**) and (**188c**) and was found to be 30:70, respectively.

6.1.17 **Isomers of 2-Butyl dimethyl siloxy methyl-1-oxa-11-azabicyclo [6,3,0] undecane (187f)-(188f)**

A solution of the nitrone(**177**) (6.3 mmol) in allyl alcohol (10 ml) was heated at 70°C for 10 h in a close vessel. After removal of the excess alkene by a gentle stream of N_2(g), the residue was taken up in DMF (10 ml) and to this solution was added imidazole (33.8 mmol) and dimethyl-t-butylsilyl chloride (23.1 mmol) at 0°C. The reaction mixture was stirred for 2 hours at 0°C and for an additional 1 hour at 20°C. Methanol was added to it and it was taken up in ether (100 ml). The organic layer was washed with $NaHCO_3$ (5%, 100 ml) and water (4 x 100 ml), dried (Na_2SO_4), and concentrated. The residue liquid was purified by chromatography over silica gel using hexane ether (90:10) as eluant, the first component isolated as a colorless liquid was assigned as a minor isomer (**188f**) (233 mg, 12.4%), followed by a mixture of both minor and major isomer (210 mg, 11.1%), further elution afforded the major isomer (**187f**) (684 mg, 36.3%). The isolated yield was found (1127 mg, 59.8%). δ_H ($CDCl_3$, 20°C, major isomer) 0.06 (6H, s), 0.88 (9H, s), 1.25-1.90 (10H, m), 1.96 (1H, m), 2.18 (1H, m) 2.75(1H, m), 2.96 (1H, m), 2.28(1H, m), 3.60 (2H, ABX, J 5.0, 10.5, 15.0 Hz), 4.02 (1H, m); the proton NMR spectrum of the major isomer at -50°C, showed the presence of the two invertomer of the major and minor conformer, the C(2H) of the major and minor conformer appeared at δ_H

4.03 (0.67 x 1H, m) and δ_H 4.19 (0.33 x 1H, m); δ_C ($CDCl_3$, +50°C, major isomer) -5.2 (2C), 18.4, 24.8, 26.0 (3C), 26.3, 26.4, 26.9, 32.4, 40.5, 57.3, 64.5, 64.9, 76.2 [middle $CDCl_3$ δ_C 77.1]; δ_C ($CDCl_3$, -50°C, major conformer of the major isomer) -5.5, -5.4 , 18.3, 25.2, 25.3, 25.5 (3C), 26.9 (2C), 34.4, 40.3, 58.2, 63.8, 64.3,74.6 [middle $CDCl_3$ δ_C 77.0]; at -50°C ^{13}C NMR spectrum showed the presence of the two invertomer of the major and minor conformer with a ratio of 66:34 respectively; δ_H ($CDCl_3$, 20°C, minor isomer) 0.06 (6H, S), 0.88 (9H, s), 3.55 (1 H, dd, J 5.0, 10.5 Hz), 3.76 (1H, dd, J 5.75, 10.5 Hz) , 4.08 (1H, m); the ^1H NMR spectrum of the minor isomer at -50°C remained virtually unchanged. Signals of the C(2) H of the major and minor conformer, if any, remained overlapped; δ_C ($CDCl_3$, +50°C, minor isomer) -4.7, -4.6, 18.8, 25.2, 26.0, 26.6 (3C), 27.5 (2C), 33.9, 42.7, 58.6, 65.7, 66.1, 76.1, 76.9 [middle $CDCl_3$ δ_C 77.7]; δ_C ($CDCl_3$, -50°C, major conformer of the minor isomer) -4.5, -4.4, 19.3, 24.0 (2C), 26.7 (5C), 35.6, 43.3, 59.3, 65.3, 76.5 [middle $CDCl_3$ δ_C 78.1]; δ_C ($CDCl_3$, -50°C, minor conformer of the minor isomer) -4.5, -4.4, 19.3, 25.1 (2C), 27.0 (3C), 28.3 (2C), 31.7, 38.2 55.9, 66.1, 79.9 [middle $CDCl_3$ δ_C 78.1]; The ^{13}C NMR spectrum showed the presence of the two invertomers of the major and minor with a ratio of 90:10 respectively.

6.1.18 Isomers of 2-Hydroxymethyl-1-oxa-11-azabicyclo[6,3,0] undecane (187e)-(188e)

Major isomer (**187f**) (684mg) was mixed with HCl solution (100 mg, 10%) for 15 min. at room temperature. The mixture was washed with hexane (3 x 20 ml) and then basified (K_2CO_3) and extracted with ether (4 x 15 ml). The ether layer dried (Na_2SO_4) and concentrated to give the isomer (**187e**) (405mg, 96%) as a colorless liquid, δ_H ($CDCl_3$, +50°C) 1.28-1.88 (10H, m), 1.96(1H, m) 2.23 (1H, m), 2.78 (1H, m), 3.01 (2H, m), 3.30(1H, m), 3.54 (1H, dd, J 6.08, 13.5 Hz), 3.69 (1H, dd, J 3.38, 12.5 Hz), 4.10 (1H, m); The ^1H NMR spectrum at -50°C was broaden and failed to indicate the presence of the two singlets for the C(2H) of the major and minor invertomer (187e); δ_C ($CDCl_3$ +50°C) 24.7, 25.4, 26.3 (2C), 31.5, 39.3, 56.4, 63.4, 65.2, 75.9 [middle $CDCl_3$ δ_C 76.9]; δ_C ($CDCl_3$, -50°C, major conformer) 24.0 (2C), 25.8, 26.7, 34.4, 40.0, 58.4, 62.9, 65.2, 76.7 [middle $CDCl_3$ δ_C 77.3]; δ_C ($CDCl_3$, -50°C, minor conformer) 22.6. 24.0, 25.8, 26.7, 30.2 36.0, 53.0, 64.4, 64.5, 75.9 [middle $CDCl_3$ δ_C 77.3]. The ^{13}C NMR spectrum at -50°C showed the presence of the two invertomers of the major and minor conformer with a ratio of 53: 47 respectively. Minor isomer (**188f**) (233 mg) was treated the same as the major isomer to give adduct (**188e**) (135 mg, 94%) as a colorless liquid; δ_H ($CDCl_3$, +50°C) 1.20-2.08 (11H, m), 2.44 (1H, m) 2.81 (1H, m), 3.33 (1H, m), 3.65 (1H,

hidden underneath) 3.60 (1H, dd, J 6.08 Hz), 3.72 (1H, dd, J 3.38, 13.5 Hz), 4.15 (1H, m); δ_C ($CDCl_3$, +50°C) 24.7, 25.2, 26.1, 27.3, 32.8, 40.9, 64.6, 66.1, 76.2 [middle $CDCl_3$ δ_C 77.8]; δ_C ($CDCl_3$, -50°C, major conformer) 22.9, 23.0, 26.0 (2C), 33.8, 4.4, 58.6, 62.5, 65.5, 65.2, 76.0 [middle $CDCl_3$ δ_C 77.3]; δ_C ($CDCl_3$, -50°C, minor conformer) 15.2, 21.9, 23.9, 24.0, 37.6, 43.4, 54.1, 57.6, 60.0, 79.4 [middle $CDCl_3$ δ_C 77.3]; at -50°C the ^{13}C NMR spectrum showed the two invertomer of the major and minor conformer with a ratio of 95:05 respectively.

6.1.19 Isomers of 2-Ethoxy-1-oxa-11-azabicyclo[6,3,0]undecane (187g)-(188g)

A solution of nitrone (2.25 mmol, 286 mg) and vinyl ether, (186g) (2 cm^3) in a dichloromethane (20 cm^3) was heated at 57°C for 18 h in a closed vessel. After removal of the solvent, the residue mixture was chromatographed on silica gel using (95:5) mixture of hexane/ether as an eluant to give a mixture of adducts (**187g**) and (**188g**) (215 mg, 48.1%) followed by the pure compound (**187g**) (100 mg, 22.3%) as a colorless liquid. The ratio of the isomer (**187g**) and (**188g**) was estimated by the integration of the C(2H) signals and was found to be 88:12 respectively. ν_{max} (neat) 2982, 2920, 2852, 1456, 1444, 1402, 1370, 1357, 1339, 1239, 1195, 1171, 1157, 1139, 1113, 1083, 1045, 1031, 992, 973, 957, 940, 861; δ_H ($CDCl_3$, +50°C, major isomer) 1.14, (3H, t, J 4.4 Hz), 1.37 (3H, m) , 1.52-1.88 (7H, m) 1.95 (1H, dt , J

5.02 12.5 Hz), 2.40 (1H, dd, J 7.53, 12.5 Hz), 3.26 (1H, m) 3.41 (2H, m), 3.74 (1H, dq, J 2.51, 10.0 Hz), 2.92 (1H, m) 3.26 (1H, m) 3.41 (2H, m) 3.74 (1H, dq, J 2.51, 10.0 Hz), 4.94 (1H, d, J 4.84 Hz). At -50°C the H NMR spectrum remained virtually unchanged for the major isomer and did not have a split C(2H) signal or any other split signals, also, the C(2H) of the minor isomer (**188g**) appeared at δ_H 5.02 as dd (J, 3.02, 5.96 Hz); δ_C ($CDCl_3$, +50°C, major isomer) 15.0, 24.7, 25.2, 26.2, 26.4, 35.4, 46.5, 62.3 (2C), 63.1, 101.3 [middle $CDCl_3$, δ_C 77.0]. At -50°C, the ^{13}C NMR spectrum showed broadening some signals of the major isomer and failed to show the two invertomer of the major and minor conformer.

6.1.20 Hexahydropyrrolo [1,2-b] isoxazole (195a)

The nitrone (**70**) (prepared from (44.7 mmol, 3.80 g) of corresponding hydroxylamine by HgO oxidation) in xylene (200 ml) was put into a pressure bottle and was reacted with ethylene at a pressure of 3.0 atm at 125°C for 7 hours with shaking. The reaction mixture then cooled and extracted with aqueous HCl solution (2 x 20 ml, 10%) , the acid layer was washed with ether (2 x 25 ml) and then basified and saturated with K_2CO_3. The aqueous layer was extracted with ether (2 x 10 ml) and the resulting organic layer was dried (Na_2SO_4), concentrated, and distilled under vacuum using a vigreux column to obtain the cycloadduct (**195a**) as a colorless liquid, b.p.$_{30\ mm\ Hg}$ 74°C, (3.74g, 74%) δ_H ($CDCl_3$, +50°C) 1.58 (1H,

m),1.70 (1H, m), 1.83-2.46 (1H, m), 3.06 (1H, dt, J 6.75, 14.2 Hz), 3.78 (1H, m), 3.89 (1H, m); δ_C ($CDCl_3$, +20°C) 65.6, 64.6, 56.7, 37.3, 31.9 , 34.1 [middle $CDCl_3$ δ_C 77.2]. At -50°C both the ^1H and ^{13}C NMR spectrum remained virtually identical.

6.1.21 Hexahydro-2H-isoxazolo [2,3-a] pyridine (195b)

The nitrone (41) (prepared from (32.3 mmol, 3.20 g) of corresponding hydroxylamine by HgO oxidation) in ethanol (200 ml) was put into a pressure bottle and was reacted with ethylene at a pressure of 3.0 atm at 125°C for 10 hours with shaking. The reaction mixture was then cooled and concentrated HCl (10 ml) was added, the solvent ethanol was removed by blowing with N_2(g). The remaining material was basified and saturated with K_2CO_3, the aqueous layer was then extracted with ether (3 x 10 ml). The organic layer was dried (Na_2SO_4), concentrated, and distilled under vacuum using a vigreux column to obtain the cycloadduct (**195b**) as a colorless liquid, b.p. $_{27\ mm\ Hg}$ 75°C, (3.53 g, 86%). δ_H (CDCl3, -50°C), 1.11-1.23 (8H, m), 2.33 (0.80 x 1H, dt, J 6.75, 13.5 Hz), 2.50 (0.80 x 1H, br t), 2.65 (0.20 x 1H, m), 3.04 (0.20 x 1H, m), 3.48 (0.80 x 1H, m), 3.60 (0.20 x 1H overlapping), 3.96 (0.80 x 2H, m and 0.20 x 1H, m), 4.22 (0.20 x 1H, m). The ^1H NMR spectrum showed the presence of the two invertomers at +50°C and all the signals are broadened. δ_C (CDCl3, +20°C, major conformer) 23.9, 24.8, 29.3, 34.3, 55.1, 64.5, 66.3 [middle $CDCl_3$ δ_C 77.2]; δ_C ($CDCl_3$, +20°C,

minor conformer) 19.2, 23.5, 25.4, 30.5, 49.4, 59.5, 65.4 [middle $CDCl_3$ δ_C 77.2]. The ^{13}C NMR spectrum showed the invertomer of the major and minor conformer in a ratio of 76:24 respectively at +20°C.

6.1.22 Perhydro-1-2oxazolo[3,2-c] oxazine (195c)

The nitrone (9) (prepared from (2.50 g, 24.8 mmol) of the corresponding hydroxylamine by HgO oxidation) in ethanol (150 ml) was reacted with ethylene at a pressure of 3.0 atm and 100°C for 10 hours. The reaction mixture then cooled and extracted with aqueous HCl solution (2 x 15 ml, 10%), the acid layer was washed with ether (2 x 25 ml), basified and saturated with K_2CO_3. Then, it was extracted with ether (3 x 10 ml), dried (Na_2SO_4) and the residue was concentrated and distilled under vacuum using vigreux column to obtain the cycloadduct (**195c**) as a colorless liquid, b.p. $_{14\ mm\ Hg}$ 77°C, (1.44 g, 45%). δ_H ($CDCl_3$, -50°C) 1.88 (0.11 x 1H, m), 2.21 (1H, m), 2.21 (1H, m), 2.35 (1H, m), 2.90 (2H, m), 3.30 (1H, m), 3.53 (1H, m), 3.73-4.06 (4H, m), 4.16 (1H, m). The major and minor conformer proton signals of the adduct (**195c**) are overlapping at -50°C expect for a minor multiplet at δ1.88 (1H) for the minor conformer. At +50°C the ^1H NMR spectrum is very similar and had started to broaden, δ_C ($CDCl_3$, +50°C) 29.4, 49.7, 59.8, 65.3, 66.0 (2C) [middle $CDCl_3$ δ_C 77.8]. All signals of ^{13}C NMR spectrum at +50°C are broadened. δC ($CDCl_3$, +25°C, major conformer) 28.9, 49.1, 59.2, 64.9, 65.3, 65.6

[middle $CDCl_3$ δ_C 77.3]; δ_C ($CDCl_3$, +25°C, minor conformer) 30.4, 55.7, 64.4, 65.0, 70.3 [middle $CDCl_3$ δ_C 77.3]. The ratio of the major and minor conformer was estimated at +25°C by integration of the ^{13}C NMR signals and was found to be 86:14, respectively.

6.1.23 (2, 3a) 1,2-Oxazolodino perhydro azepine (195d)

The nitrone (**180**) which was prepared from (2.70 g, 23.9 mmol) of corresponding hydroxylamine by HgO oxidation was taken in ethanol (150 ml) in a pressure bottle and was reacted with ethylene at a pressure of 3.0 atm at 120°C for 14 hours. To the reaction mixture concentrated HCl (7.0 ml) was added, the solvent ethanol was removed by blowing with N_2(g). The residue was basified and saturated with K_2CO_3 and the aqueous layer was then extracted with ether (3 x 10 ml). The organic layer was dried (Na_2SO_4), concentrated, and the residue was distilled under vacuum using a vigreux column to get the cycloadduct (**195d**) as a colorless liquid, b.p.$_{7\ mm\ Hg}$ 74°C, (1.38 g, 41%). δ_H ($CDCl_3$, +50°C) 1.43-2.05 (9H, m), 2.41 (1H, m), 2.68 (1H, m), 2.83 (1H, m), 3.45 (1H, m), 3.85 (2H, t, J 7.43 Hz). There were changes in ^1H NMR spectrum at -50°C especially the signal for the C(2)H at δ(3.80-4.11) became very complex. δ_C ($CDCl_3$, +55°C) 26.1, 26.3 (2C), 31.3, 38.6, 57.2, 65.6, 66.8 [middle $CDCl_3$ δ_C 77.5]; δ_C ($CDCl_3$, -40°C, major conformer) 24.0, 24.7, 25.4, 30.3, 37.7, 57.4, 64.9, 66.2 [middle $CDCl_3$ δ_C 77.1]; δ_C

($CDCl_3$, -40°C, minor conformer) 24.9, 25.0, 29.8, 29.9, 35.5, 52.0, 63.6, 65.8 [middle $CDCl_3$ 77.1]. Integration of the ^{13}C NMR signals gave a ratio of 85:15 of the major conformer (**196d**) and the minor conformer (**197d**), respectively.

6.1.24 1-Oxa-11-azabicyclo [6, 3, 0] undecane (195e)

In a pressure bottle, the nitrone (**177**) (550 mg, 4.87 mmol) was dissolved in ethanol (50 ml) and reacted with ethylene at a pressure of 4.0 atm at 130°C for 12 hours. To the reaction mixture concentrated HCl (7 ml) was added, the solvent ethanol was removed by blowing N_2(g). The residue was basified and saturated with K_2CO_3. The aqueous layer was then extracted with ether (3 x 10 ml) and the organic layer was dried (Na_2SO_4). The residue was concentrated and chromatographed using (97:03) dichloromethane/ether mixture as an eluant to give the cycloadduct (**195e**) as a colorless liquid (390 mg, 51.7%) δ_H ($CDCl_3$, +50°C) 1.33-1.98 (11H, m), 2.38 (1H, dt, J 6.75, 12.3 Hz), 2.76 (1H, m), 2.95 (1H, m), 3.29 (1H, m), 3.80 (1H, m) and was reacted with ethylene at a pressure of 3.0 atm. At -50°C the ^1H NMR spectrum was virtually identical and failed to separate the major and minor conformer signals. δ_C ($CDCl_3$, -50°C, major conformer) 23.1, 23.4, 25.8, 26.0, 35.7, 39.4, 58.5, 63.8, 64.4 [middle $CDCl_3$ δ_C 77.1]; δ_C ($CDCl_3$, -50°C, minor conformer) 24.2 (2C), 26.1, 27.2, 30.6, 34.5, 52.4, 64.4, 64.8 [middle

$CDCl_3$ δ_C 77.1]. The ratio of the major and minor conformer was found to be 86:14, respectively as it was estimated by the integration of the ^{13}C NMR signals.

6.2 Kinetics of Cycloaddition Reaction

The kinetic study of the cycloaddition of the nitrone (**177**) onto several alkenes, was monitored by the ^1H NMR technique. The NMR spectra for the kinetic runs were recorded on a Varian XL-200 spectrometer operating at a proton frequency of 200.0 MHz and in the Pulse Fourier Transformer Mode.

A known mass of the investigated alkene was placed in an NMR tube and purged with $N_2(g)$. A suitable volume of the nitrone in $CDCl_3$ was then transferred to the NMR tube and sealed immediately. The mixture was thoroughly mixed and quickly scanned by the NMR spectroscopy. The NMR tube was kept at $\pm$0.2°C of the run temperature throughout the kinetic measurements. The initial concentration of the nitrone was determined by NMR integration and using the known concentration of the alkene. Concentration of the nitrone (**177**) was kept low to avoid any polymerization. The ratio of the concentrations of nitrone, alkene, and cycloadducts was determined at various time intervals by integration of the signals due to 2-H of the nitrone and the olefinic protons of the alkene. Measurements were continued up to 30-90% chemical conversion of the alkene. The second-order rate

constants, k_2, were determined by means of the least-mean squares of the data, and was reproducible within 5-10%.

6.2.1 Addition of the Nitrone (177) to Methyl Methacrylate (47a) at 16.0°C

The initial concentration of methyl methacrylate = (a) = 0.854 M, and that of the nitrone = (b) = 0.312 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 1.01; 10.0 min; 1.21; 15.6 min; 1.29; 35.0 min 1.62; 60.0 min, 2.06. The linear regression analysis of this data gives the following: Correlation Coefficient = 1.00; Slope = 2.82×10^{-4} s^{-1}; Intercept = 1.02; k_2 = 52.1×10^{-5} l mol^{-1} s^{-1}.

6.2.2 Addition of the Nitrone (177) to Methyl Methacrylate (47a) at 26.0°C

The initial concentration of methyl methacrylate = (a) = 0.511 M, and that of the nitrone = (b) = 0.256 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 0.696; 5.33 min, 0.794; 15.4 min, 0.941; 30.8 min, 1.201; 64.4 min, 1.627. The linear regression analysis of this data gives the following: Correlation Coefficient = 0.998; Slope = 2.40×10^{-4} s^{-1}; Intercept = 0.717; k_2 = 93.9×10^{-5} l mol^{-1} s^{-1}.

6.2.3 Addition of the Nitrone (177) to Methyl Methacrylate (47a) at 36.0°C

The initial concentration of methyl methacrylate = (a) = 0.392 M, and that of the nitrone = (b) = 0.287 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 0.312; 8.00 min, 0.405; 14.0 min, 0.474; 35.0 min, 0.738; 64.2 min, 1.092. The linear regression analysis of this data gives the following: Correlation Coefficient = 1.00; Slope = 2.04×10^{-4} s^{-1}; Intercept = 0.308; k_2 = 193×10^{-5} l mol^{-1} s^{-1}.

6.2.4 Addition of the Nitrone (177) to Methyl Acrylate (36c) at 16.0°C

The initial concentration of methyl acrylate = (a) = 0.434 M, and that of the nitrone = (b) = 0.259 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 0.515; 5.07 min, 0.566; 15.2 min, 0.643; 30.4 min, 0.767; 55.7 min, 0.916; 80.1 min, 1.12. The linear regression analysis of this data gives the following: Correlation Coefficient = 0.998; Slope = 1.23 x 10-4 s^{-1}; Intercept = 0.526; $k_2 = 70.2 \times 10^{-5}$ l mol^{-1} s^{-1}.

6.2.5 Addition of the Nitrone (177) to Methyl Acrylate (36c) at 26.0°C

The initial concentration of methyl acrylate = (a) = 0.362 M, and that of the nitrone = (b) = 0.321 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 0.118; 5.23 min, 0.138; 15.4 min, 0.173; 30.6 min, 0.229; 55.6 min, 0.329; 120 min, 0.329. The linear regression analysis of this data gives the following: Correlation Coefficient = 1.00; Slope = 2.36 x 10-5 s^{-1}; Intercept = 0.116; $k_2 = 155 \times 10^{-5}$ l mol^{-1} s^{-1}.

6.2.6 Addition of the Nitrone (177) to Methyl Acrylate (36c) at 36.0°C

The initial concentration of methyl acrylate = (a) = 0.182 M, and that of the nitrone = (b) = 0.121 M. The values of ln[(a-x)/(b-x)] at various times were as follows: 0 min, 0.406; 5.23 min, 0.458; 15.4 min, 0.545; 30.6 min, 0.701; 55.7 min, 1.02; 72.1 min, 1.16. The linear regression analysis of this data gives the following: Correlation Coefficient = 0.998; Slope = 1.76 x 10-4 s^{-1}; Intercept = 0.396; $k_2 = 290 \times 10^{-5}$ l mol^{-1} s^{-1}.

Addition of Nitrone (177) to Methyl Methacrylate (47a) at 16°C

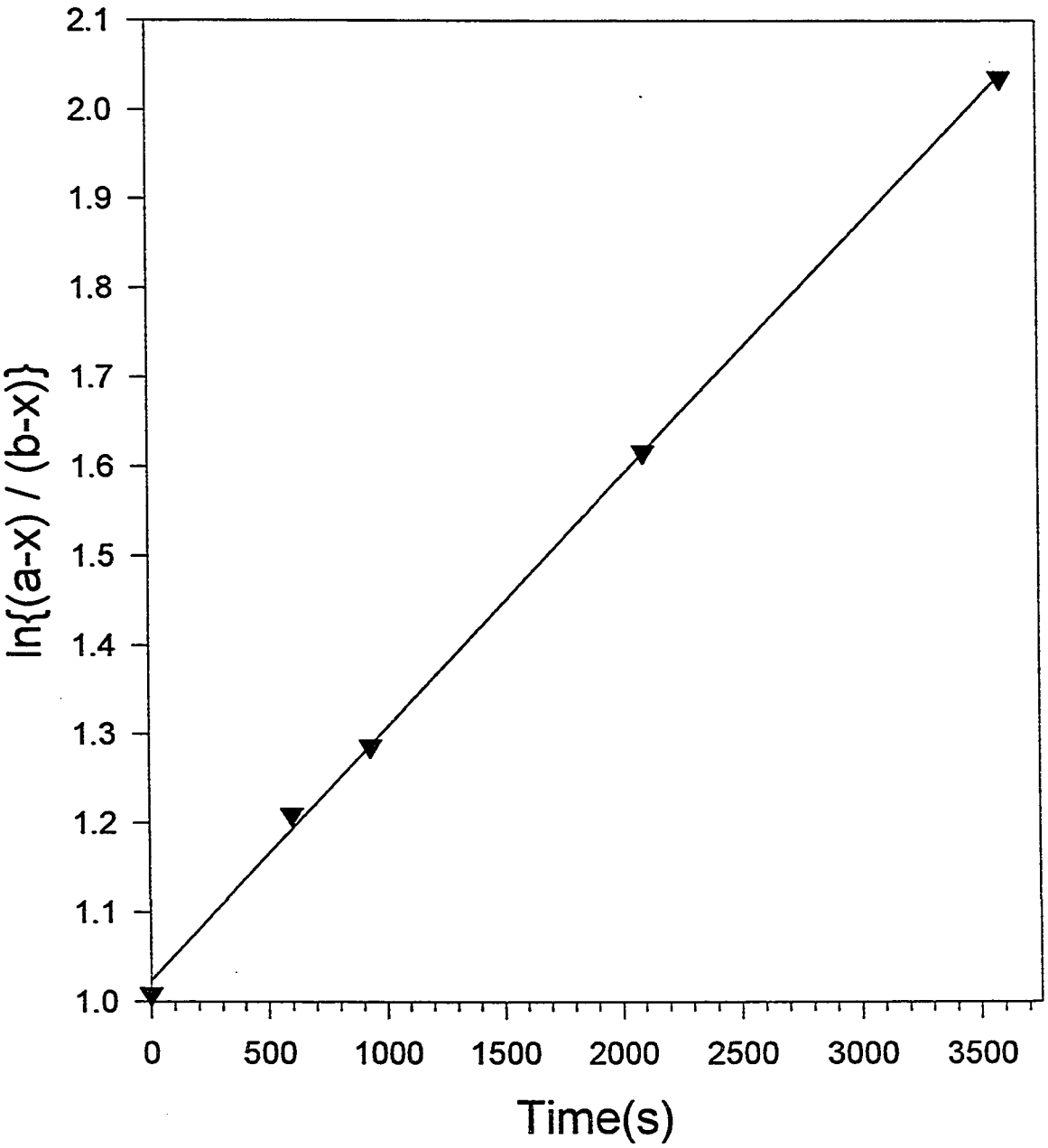


Figure 5

Addition of Nitrone (177) to Methyl Methacrylate (47a) at 26°C

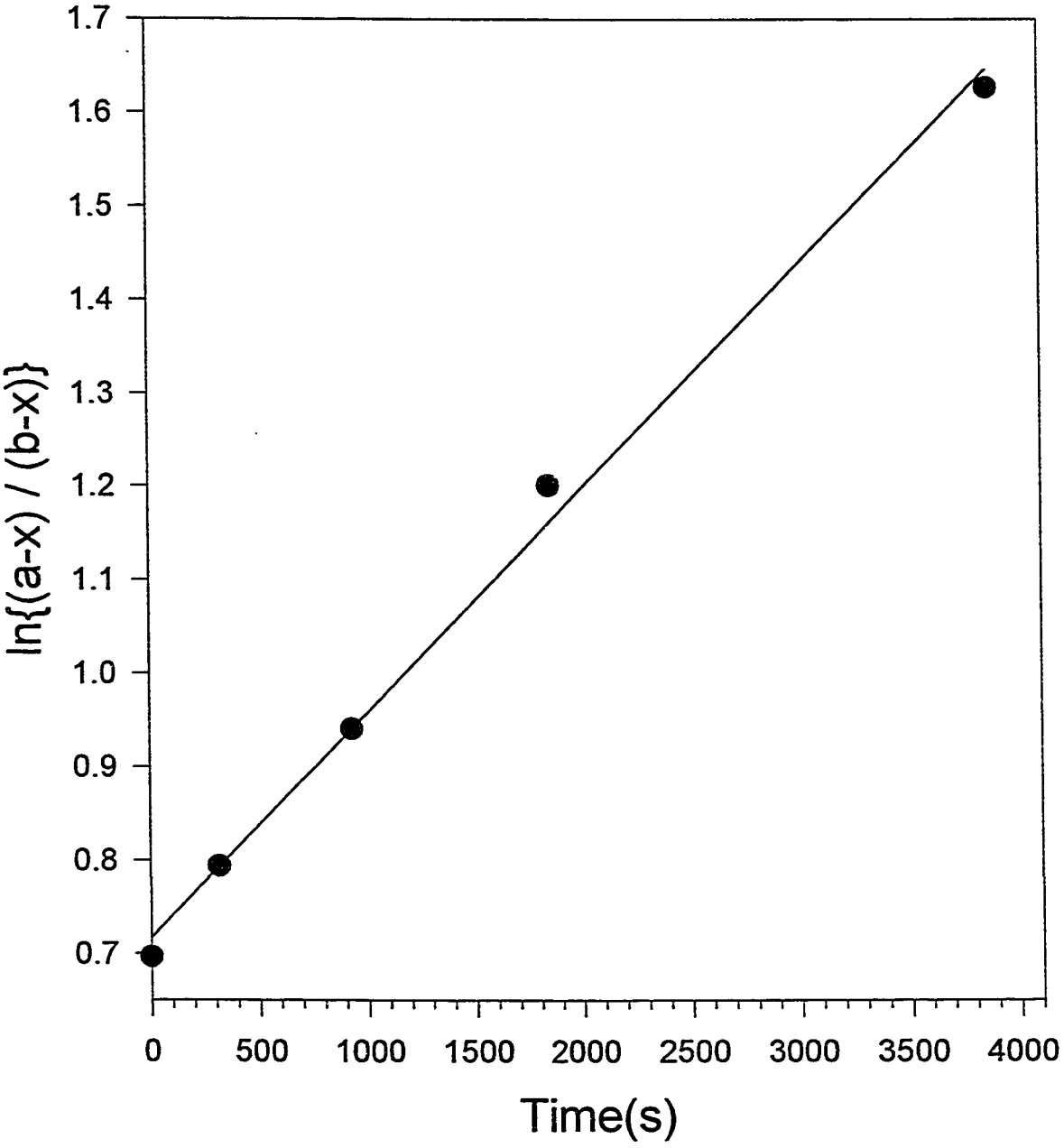


Figure 6

Addition of Nitrone (177) to Methyl Methacrylate (47a) at 36°C

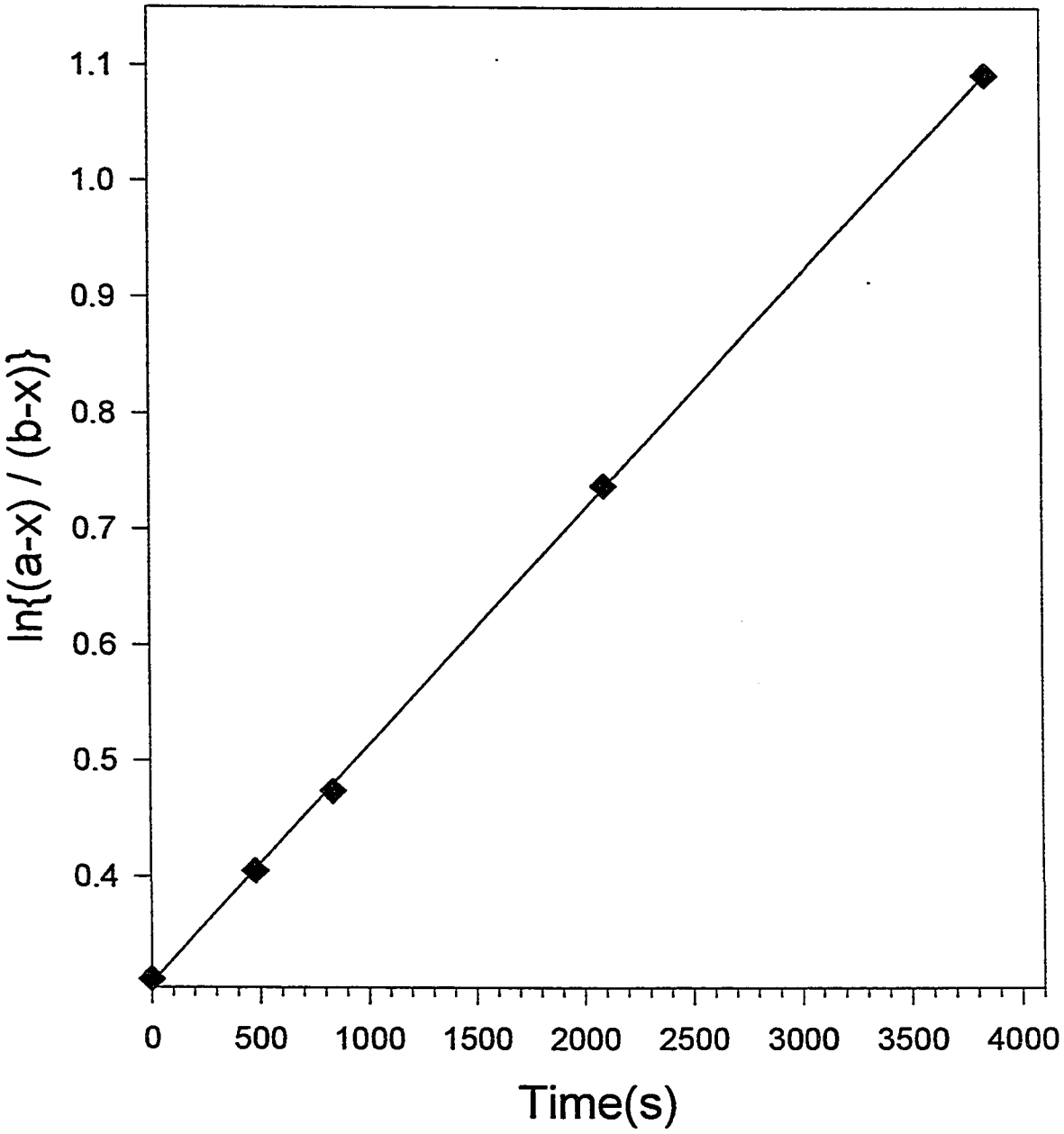


Figure 7

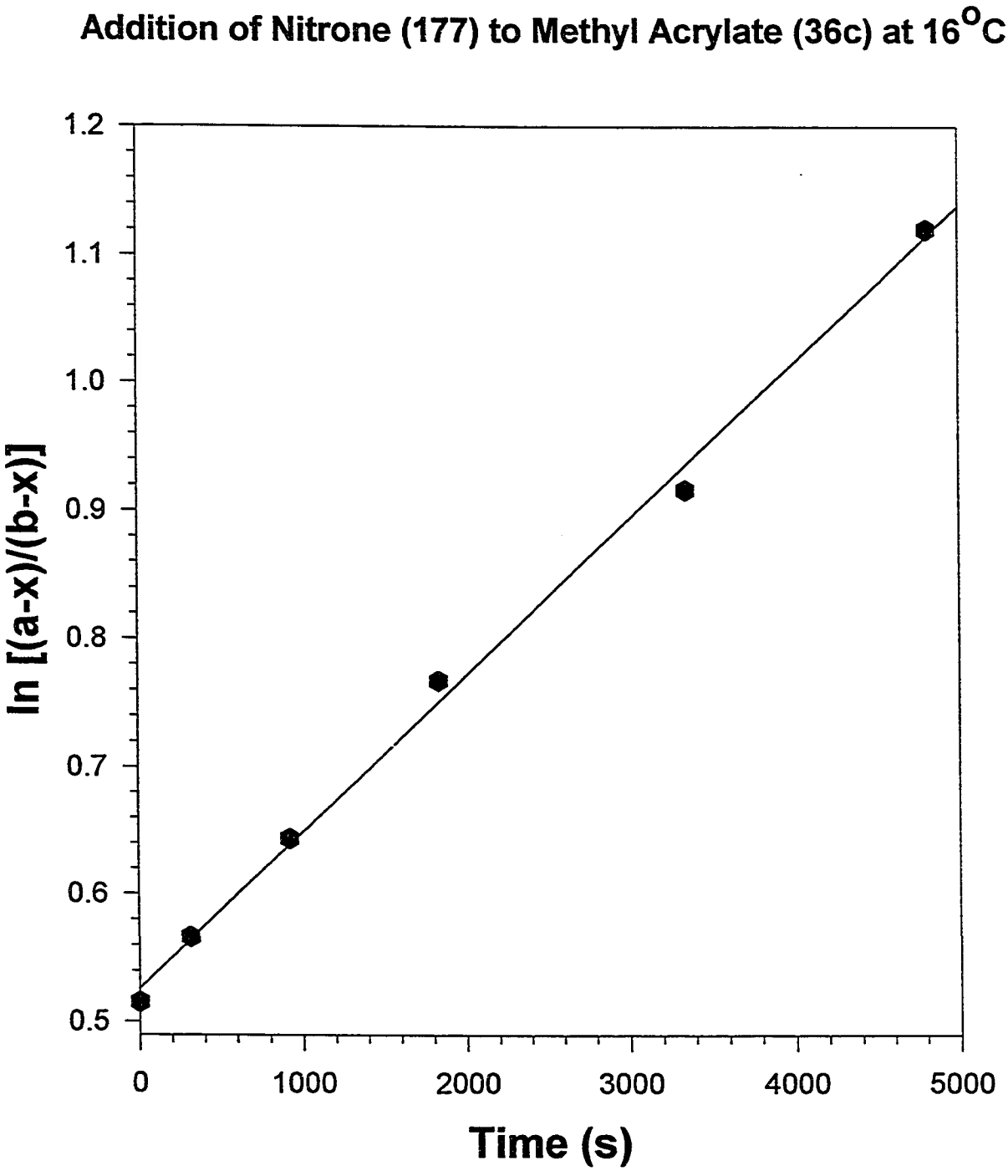

Addition of Nitrone (177) to Methyl Acrylate (36c) at 16°C
ln [(a-x)/(b-x)]
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0
1000
2000
3000
4000
5000
Time (s)

Figure 8

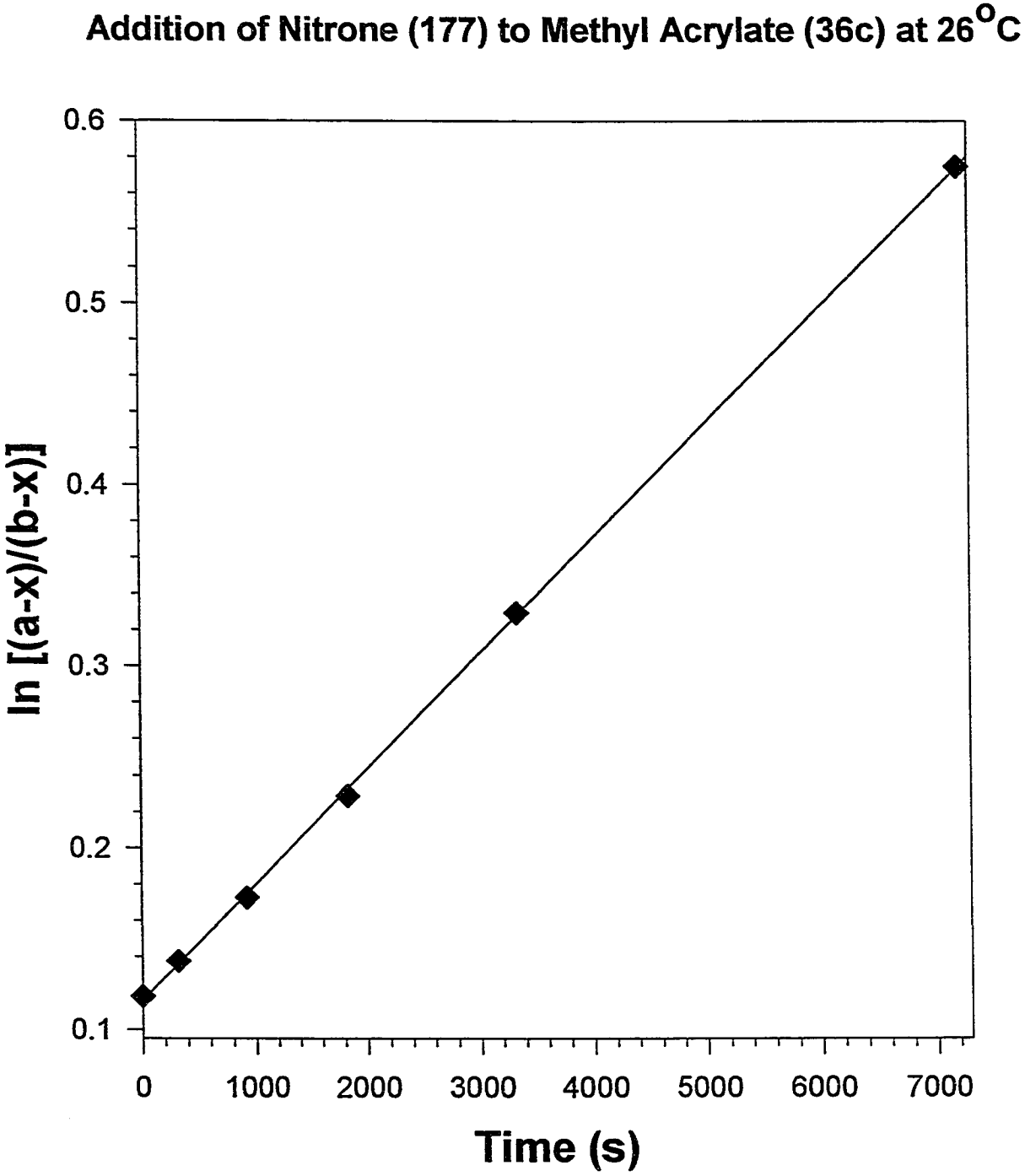

Addition of Nitrone (177) to Methyl Acrylate (36c) at 26°C
ln [(a-x)/(b-x)]
0.6
0.5
0.4
0.3
0.2
0.1
0
1000
2000
3000
4000
5000
6000
7000
Time (s)

Figure 9

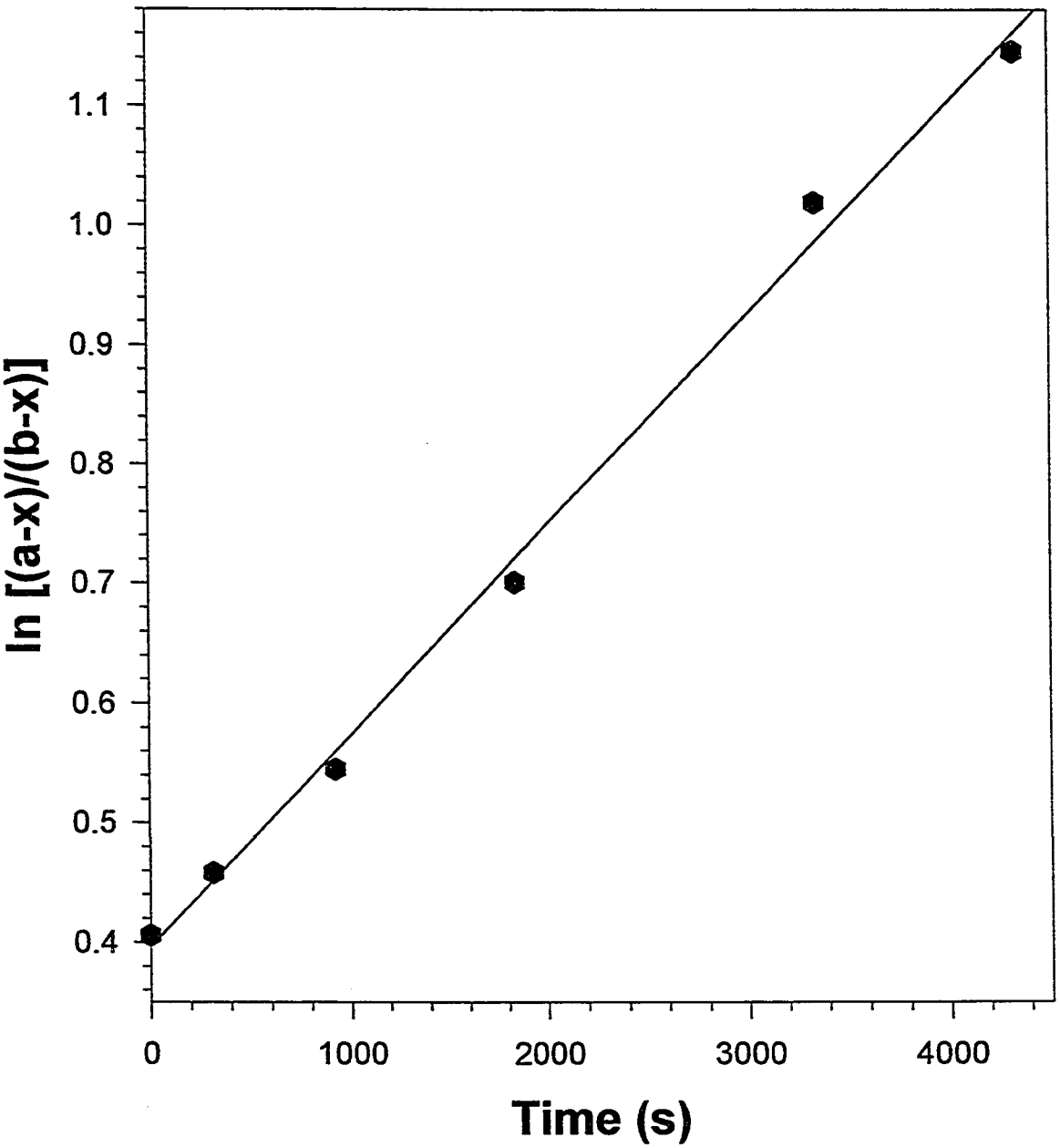

Addition of Nitrone (177) to Methyl Acrylate (36c) at 36°C
ln [(a-x)/(b-x)]
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
1000
2000
3000
4000
Time (s)

Figure 10

Addition of the Nitrone (177) to Methyl Methacrylate(47a)

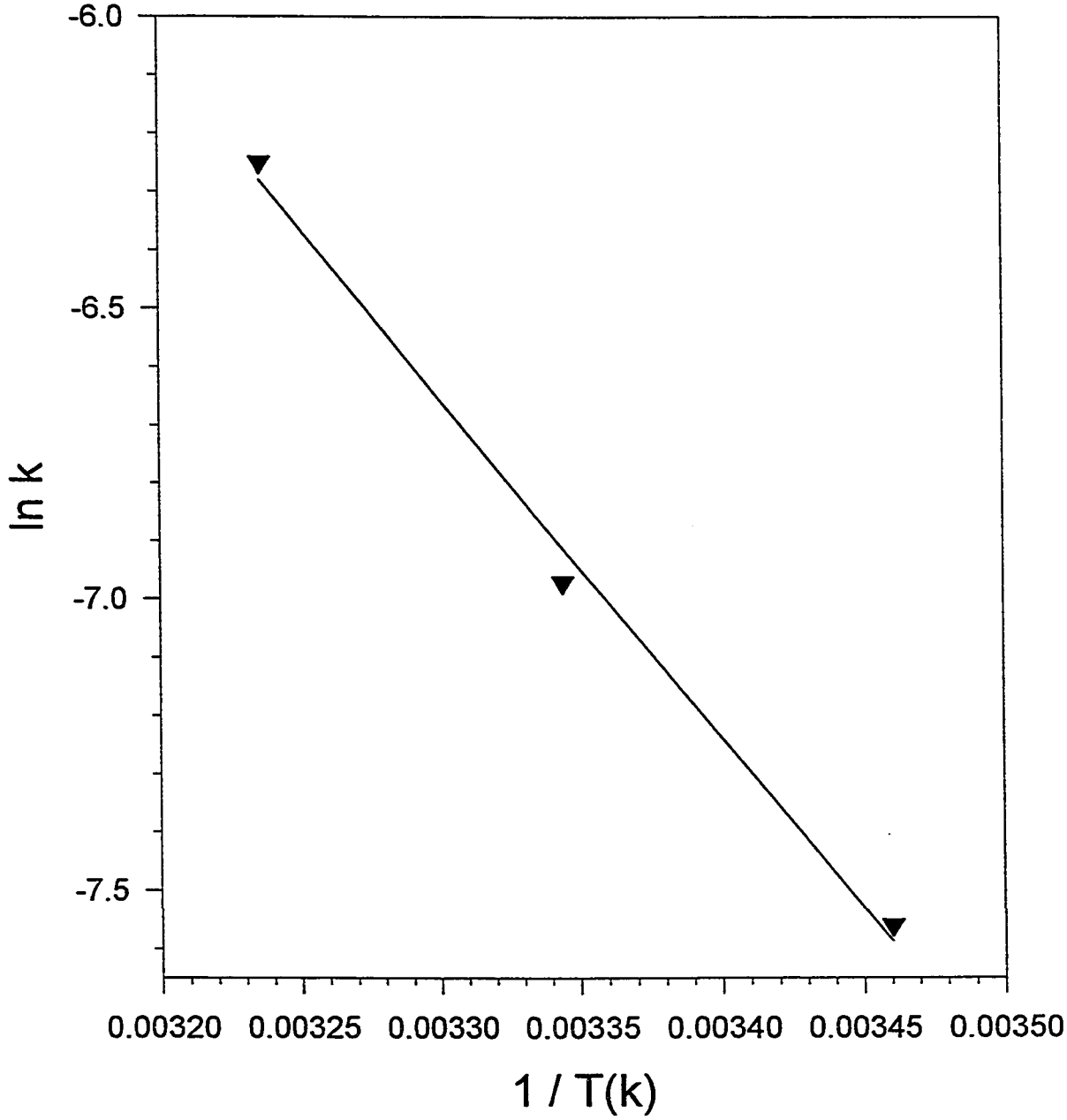


Figure 11

Addition of the Nitrone (177) to Methyl Acrylate(36c)

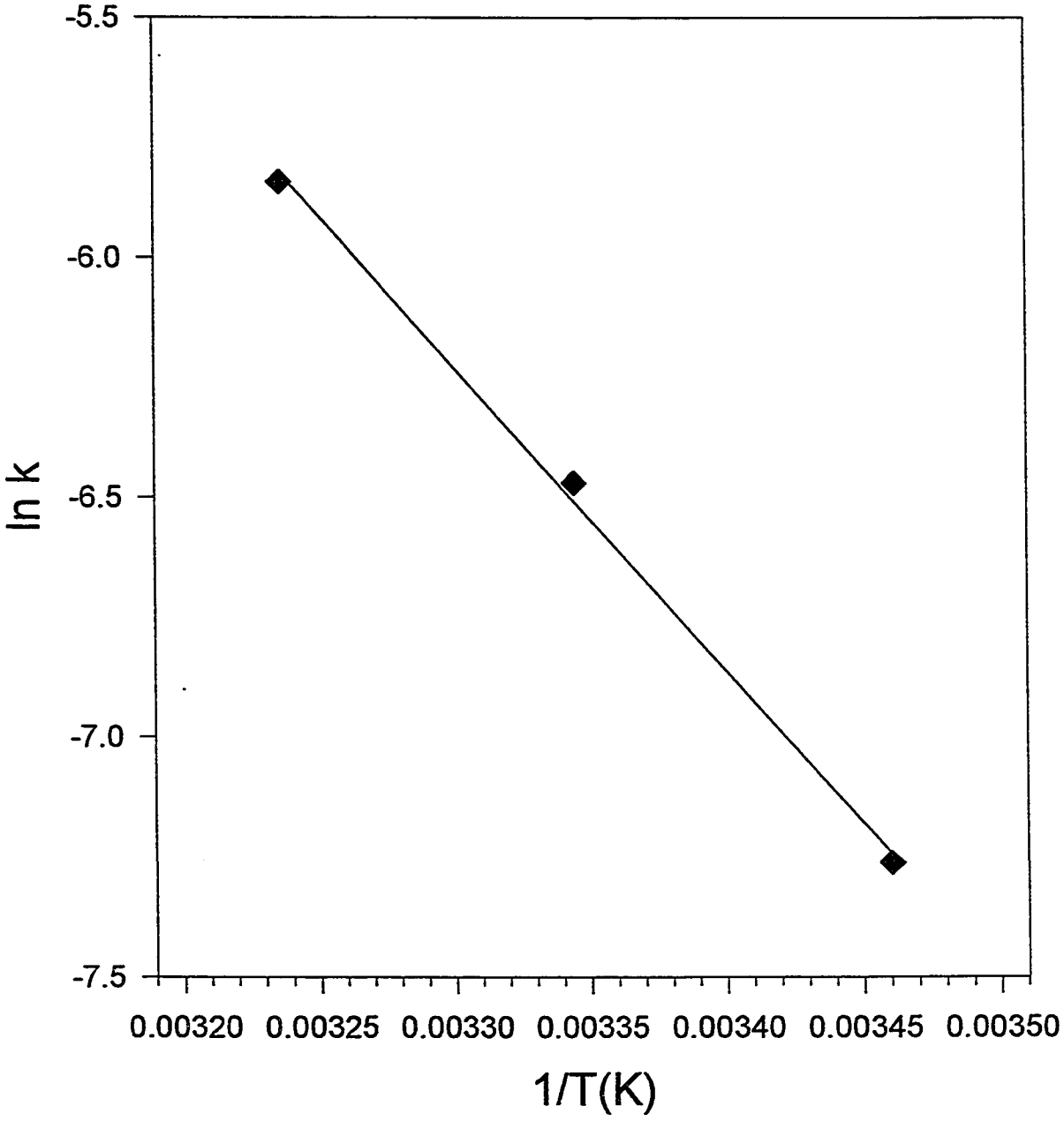


Figure 12

6.3 Dynamic Nuclear Magnetic Resonance Spectroscopy

The variable temperature of ^{1}H and ^{13}C-NMR spectra were recorded on a JEOL GX-270 spectrometer operating at 270 MHz for ^{1}H nuclei and at 54.0 MHz for ^{13}C nuclei. The ^{13}C-NMR spectra were also recorded on a Varian XL-200 NMR spectrometer, operating in the Fourier transform mode, with a digital resolution of 0.31 Hz at 50.3 MHz. The compounds were studied as 50 mg ml^{-1} solution in $CDCl_3$, with TMS as internal standard. The spectra were obtained in the usual way with wide Band Proton Decoupling, Single Proton Decoupling and DEPT. Temperature control was achieved using the GX-270 and the XL-200 temperature controller and calibrated using standard chemical shifts of methanol. The temperatures were accurate to $\pm$ 0.5 °C. ^{1}H-NMR spectra were recorded at 200.05 MHz on the XL-200 instrument.

Calculations for complete lineshape analysis were carried out using a computer program, based on Hahn, Maxwell[117] and McConnell[118] (HMM) equation, corresponding to a non-coupled two site exchanges, with unequal populations. At least three carbon resonances were utilized at each temperature and matching of simulated and experimental spectra was carried out by eye (superposing calculated spectra over the experimental spectra. Thus the rate constant obtained at each

temperature was an average of three calculated values. Simulation of exchange affected ^{1}H-NMR spectra were carried out by modifying the two-site exchange program used above. The first order coupling of the protons is simply assumed as giving overlapping two-site exchange with the same population ratio and equal rates of exchange. The intensity at each point is calculated applying the HMM equation for two site exchanges, for each overlapping case which are displaced form one another by certain frequencies corresponding to the coupling constant, and then the intensities were summed to give the band shape at that point. For cases of coupling to two and three equivalent protons appropriate intensity ratios were also taken into account. Theoretical spectra were calculated to obtain a best fit with the observed spectra by varying the rate constants at the various temperatures. The activation parameters were obtained from the Eyring equation.[119] Experimental and calculated spectra which were done to determine the nitrogen inversion barrier of the studied adducts are shown in the following figures.

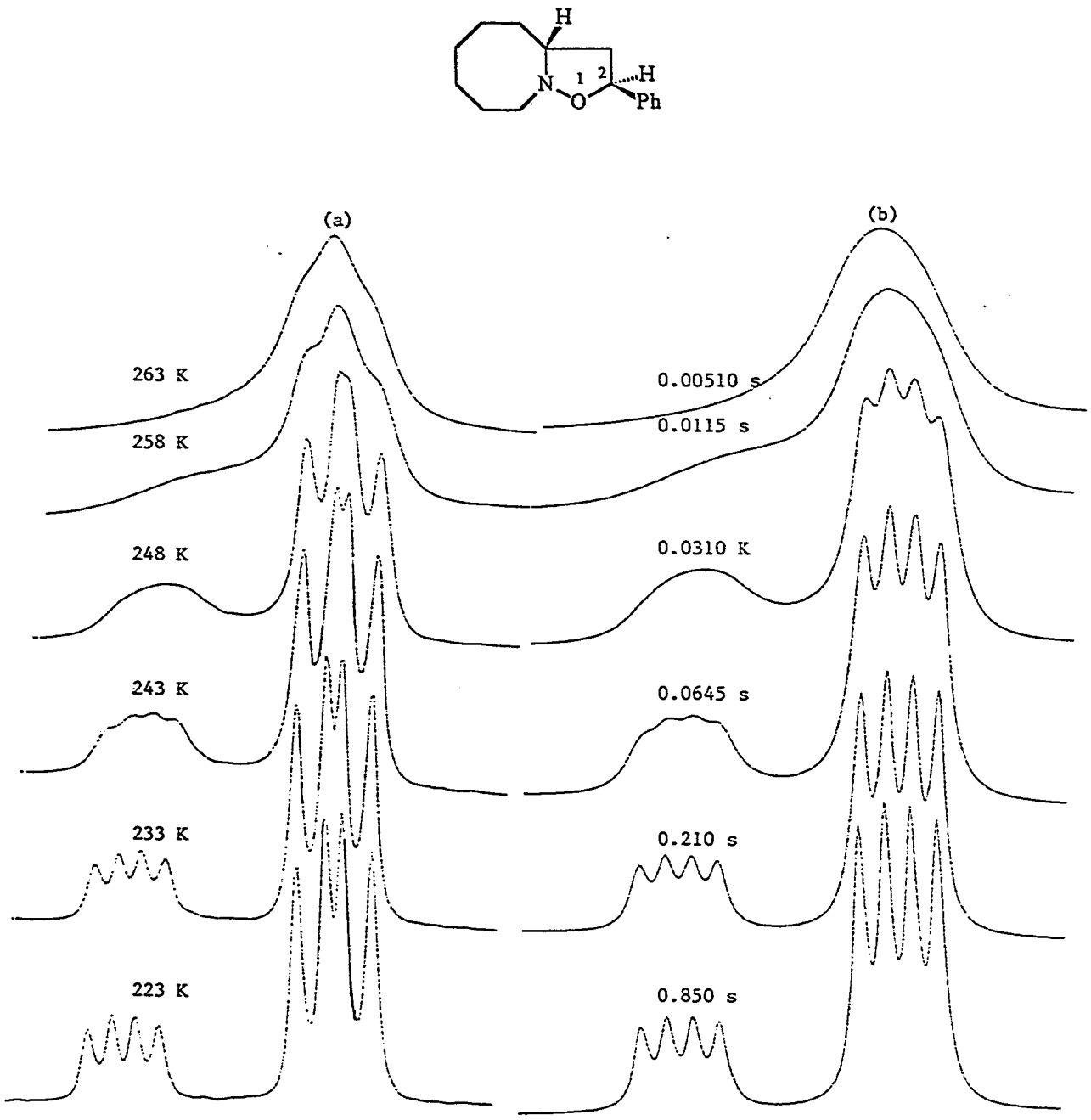


Figure 13. Experimental (a) and calculated band shapes (b) of the C-2H signals of styrene adduct (187a) at different temperatures. The temperatures and life times of the major specie are indicated respectively on the experimental and the calculated spectra. The chemical shifts difference $\Delta\nu$ at 223 K were 42.4, 43.7, 43.0 and 43.7 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (187a)

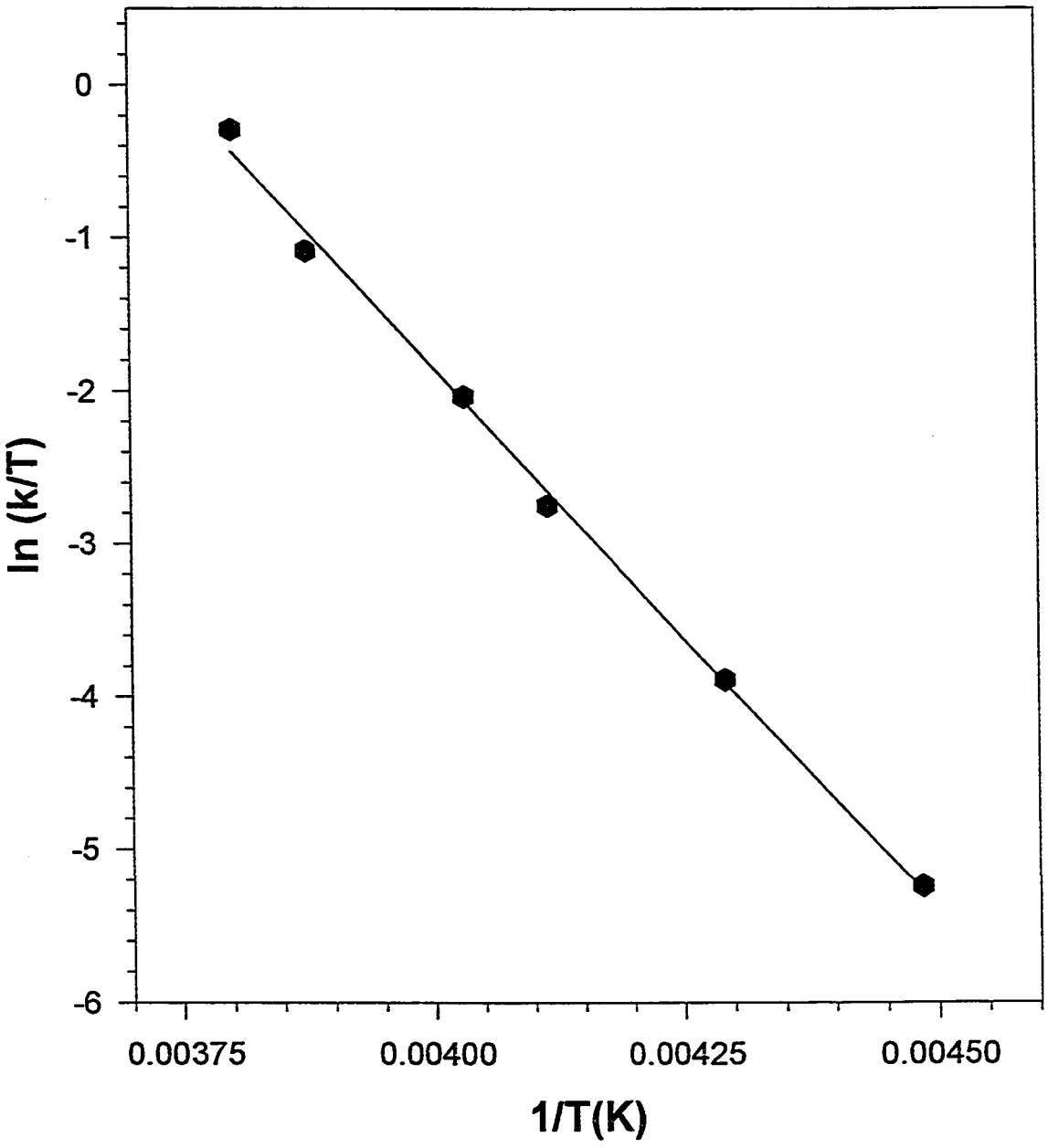
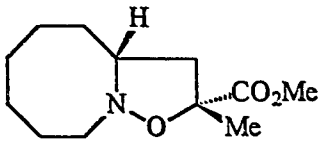


Figure 14



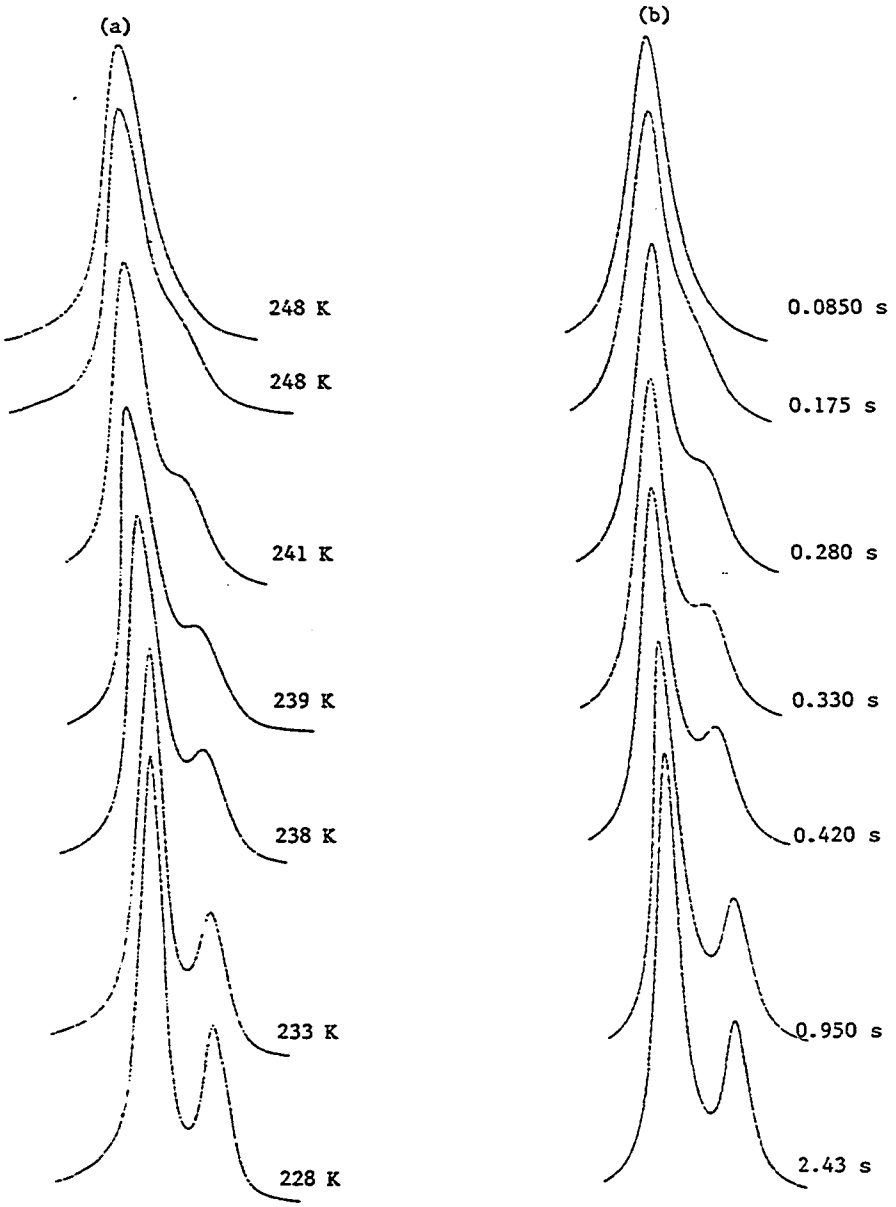


Figure 15. Experimental (a) and calculated band shapes (b) of the signals of methoxyl protons of methyl methacrylate adduct (187b) at different temperatures. The temperatures and life times of the major specie are indicated respectively on the experimental and the calculated spectra. The chemical shift difference $\Delta\nu$ at 228 K was 7.02 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (187b)

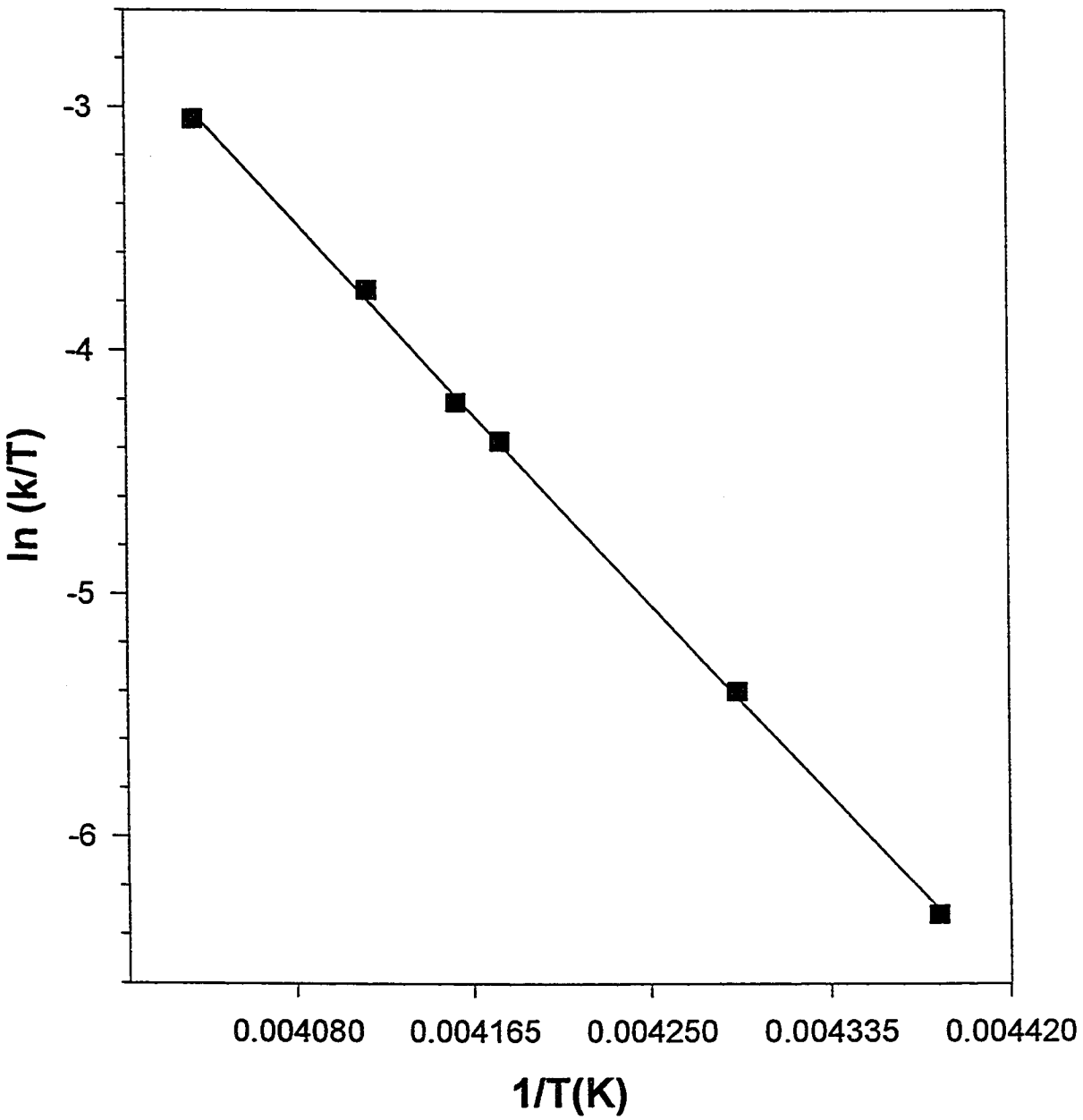


Figure 16

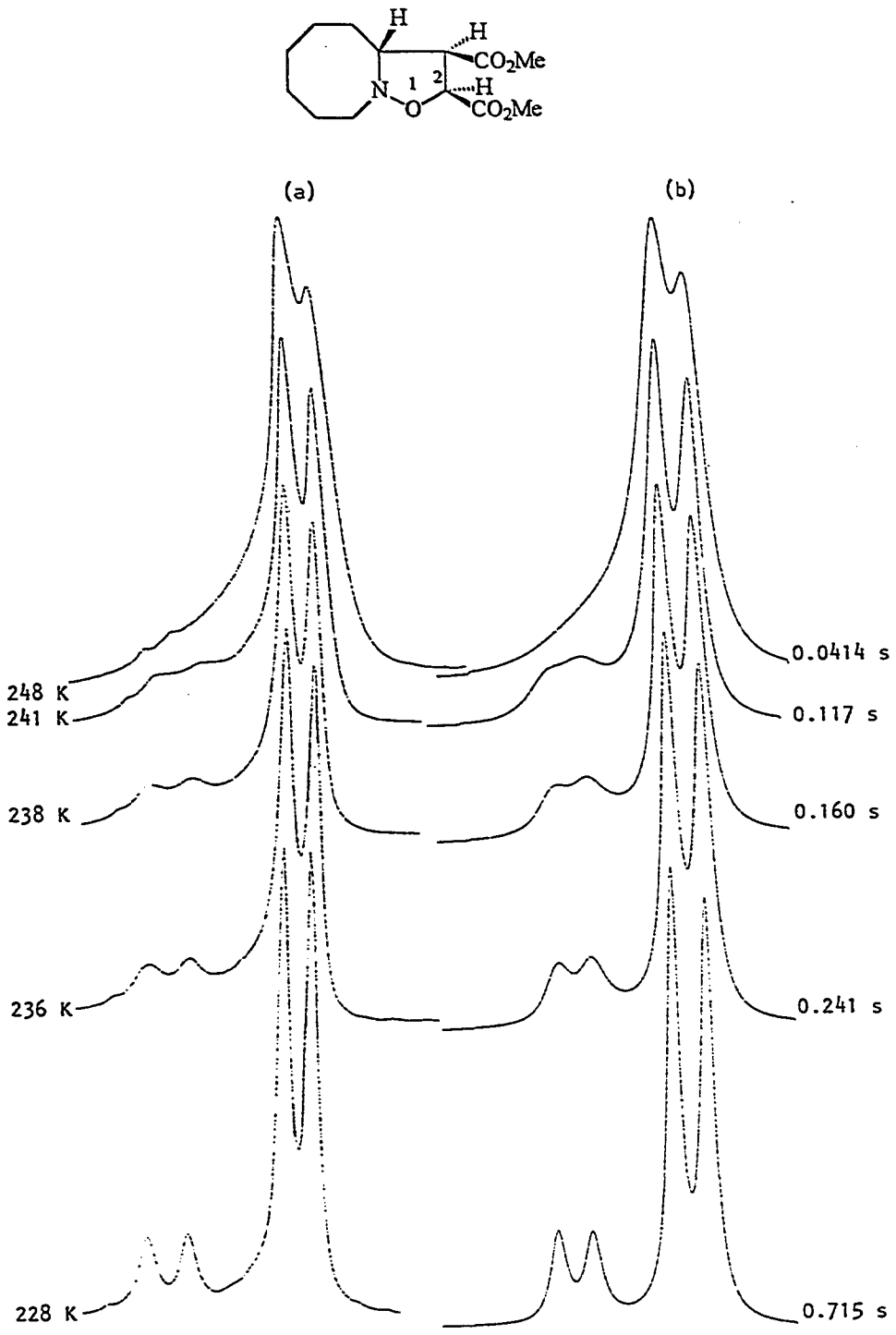


Figure 17. Experimental (a) and calculated band shapes (b) of the C-2H signals of dimethyl maleate adduct (188c) at different temperatures. The temperatures and life times of the major specie are indicated respectively on the experimental and the calculated spectra. The chemical shifts difference $\Delta\nu$ at 223 K were 31.6 and 29.7 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (188c)

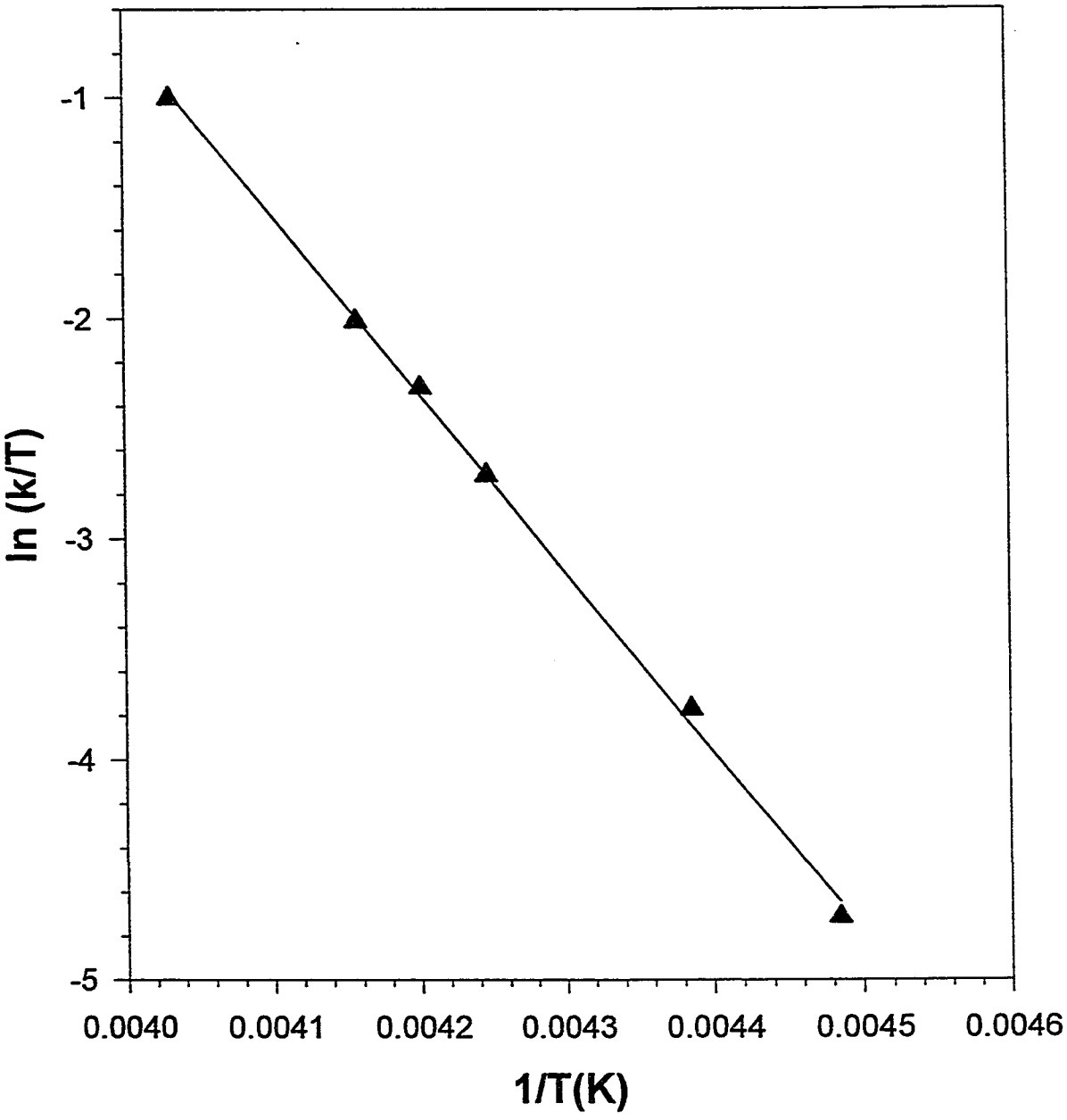


Figure 18

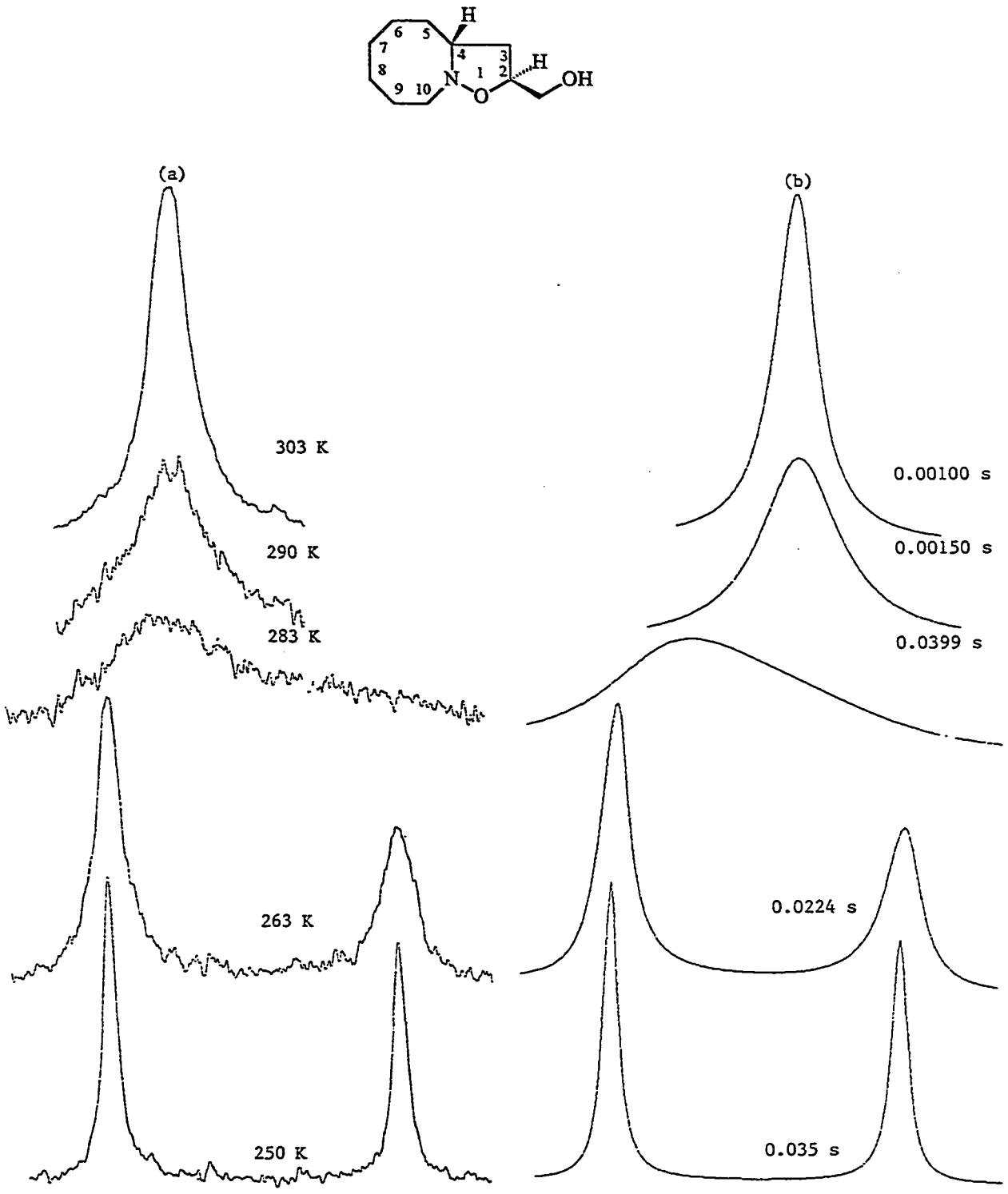


Figure 19. Temperature-dependent ^{13}C NMR spectra of C-10 in the (187e): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 253 K was 388 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (187e)

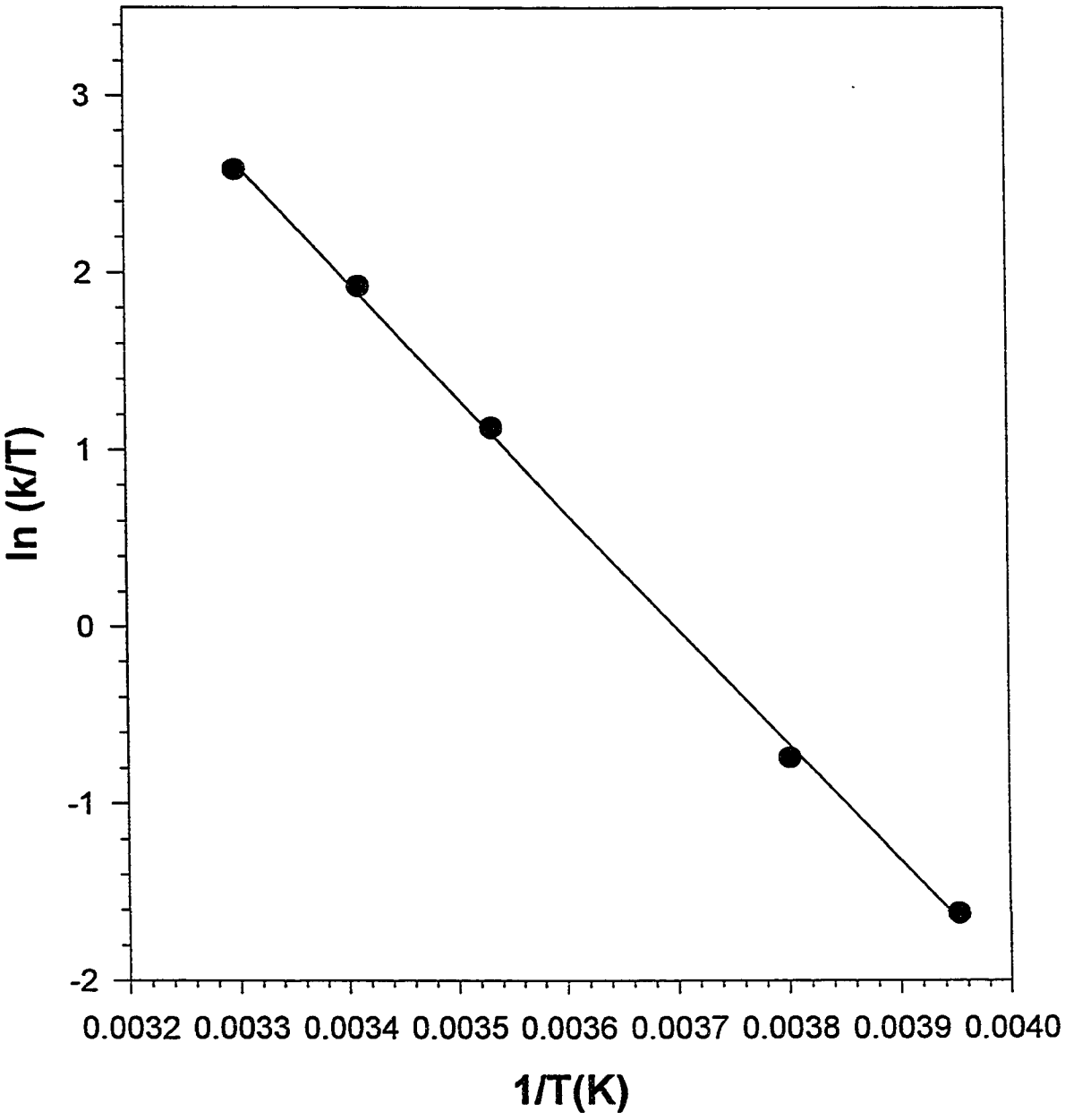


Figure 20

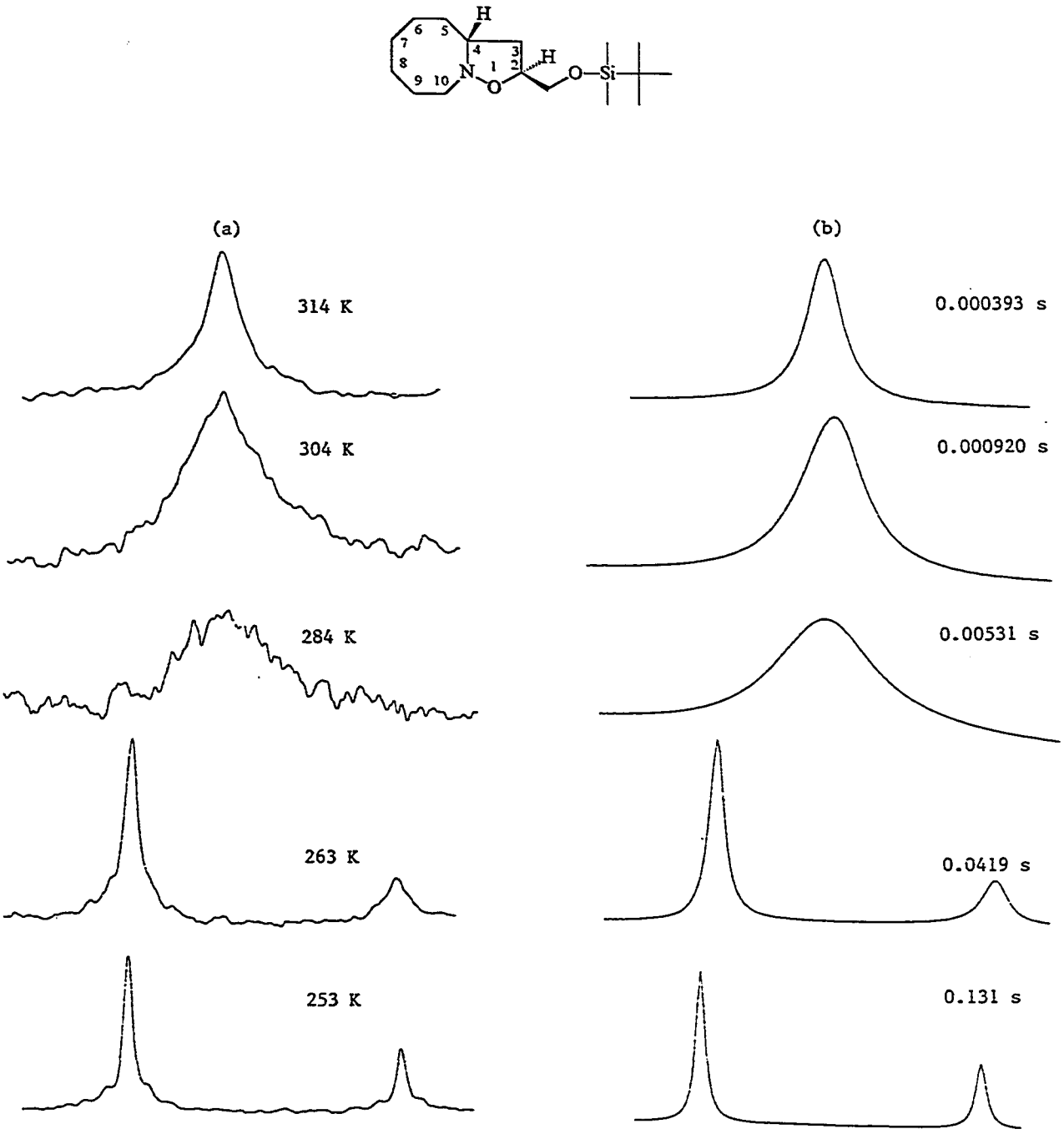


Figure 21. Temperature-dependent ^{13}C NMR spectra of C-10 in the (187f): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 253 K was 294 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (187f)

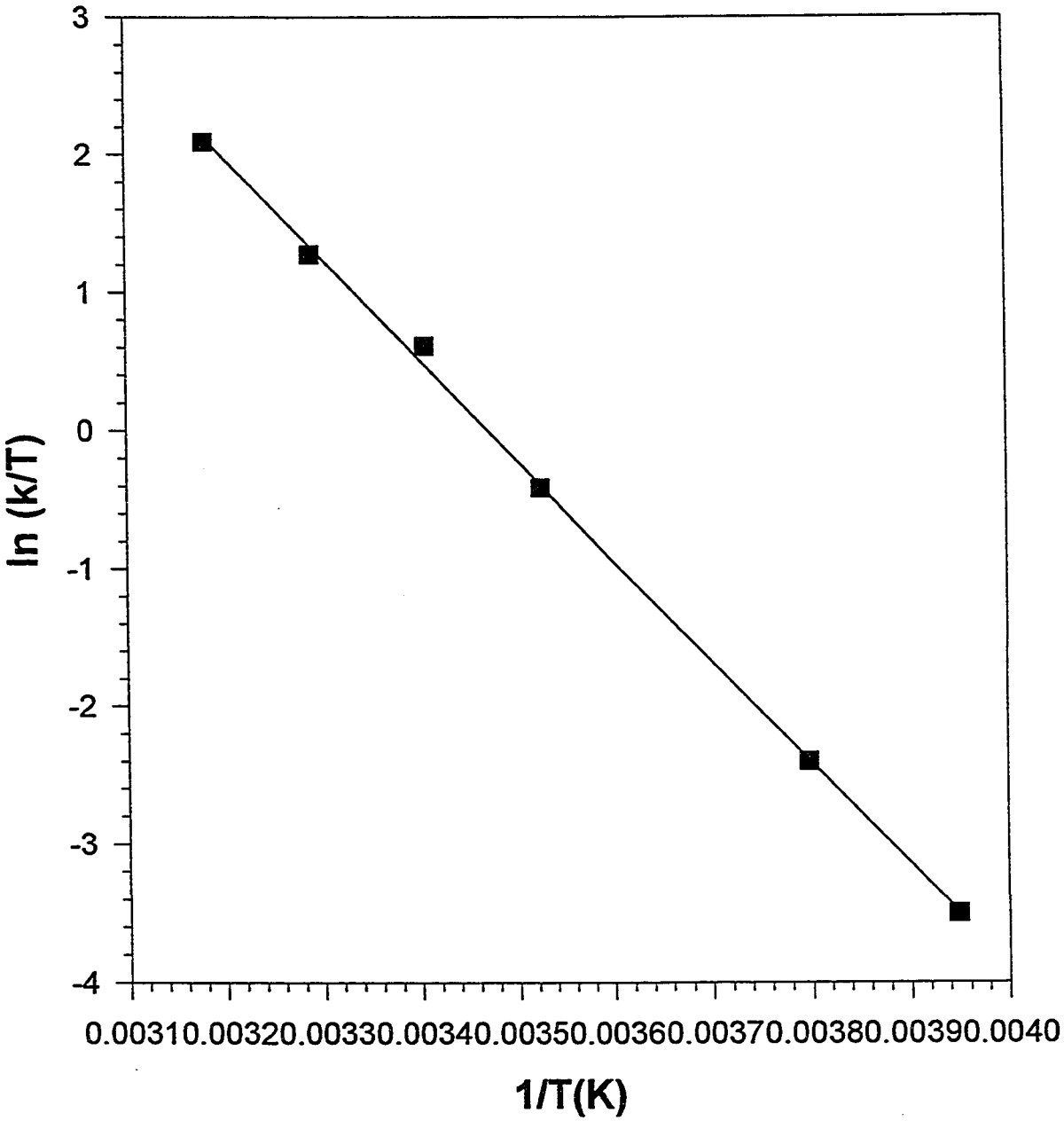


Figure 22

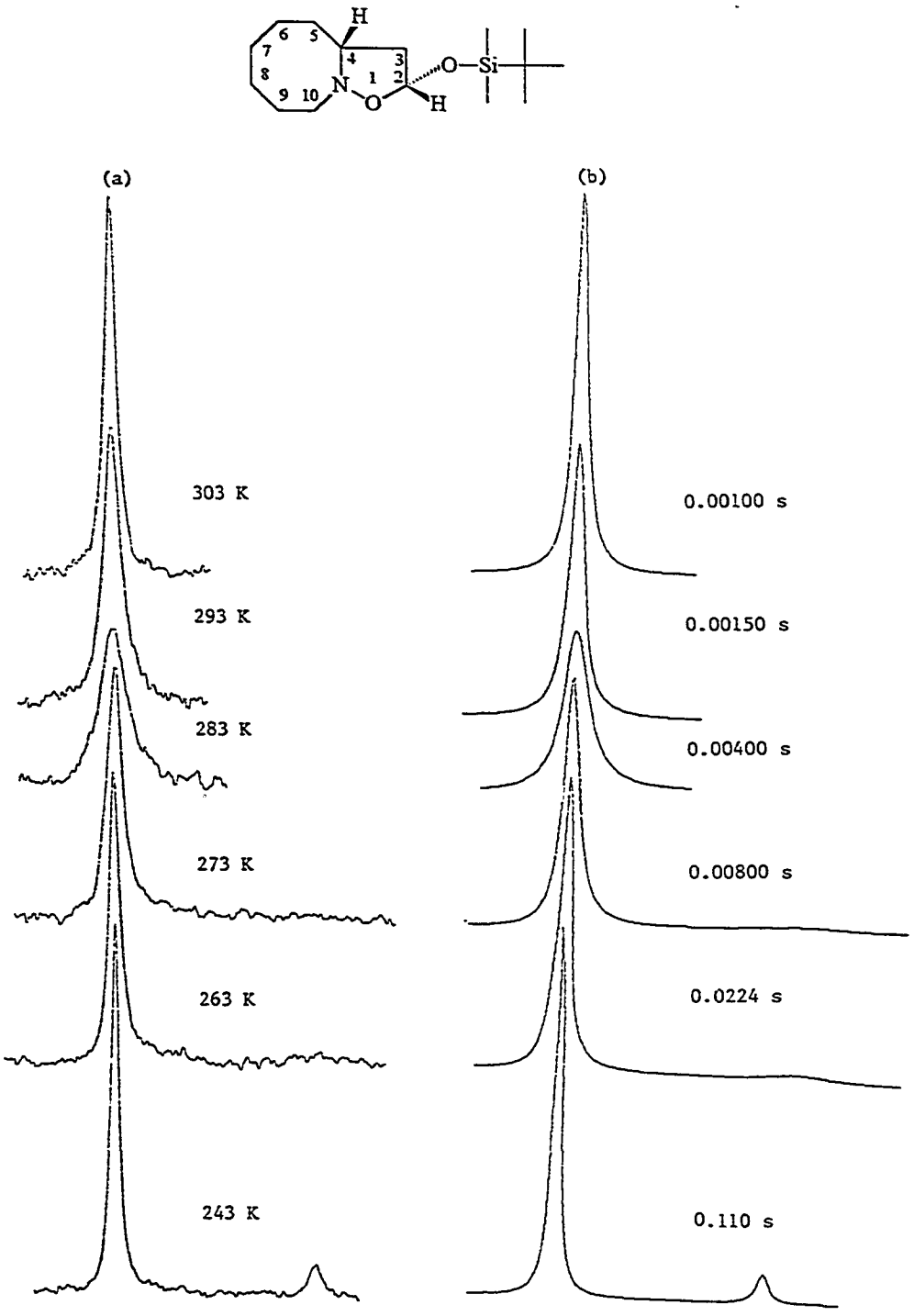


Figure 23. Temperature-dependent ^{13}C NMR spectra of C-10 in the (188f): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 243 K was 244 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (188f)

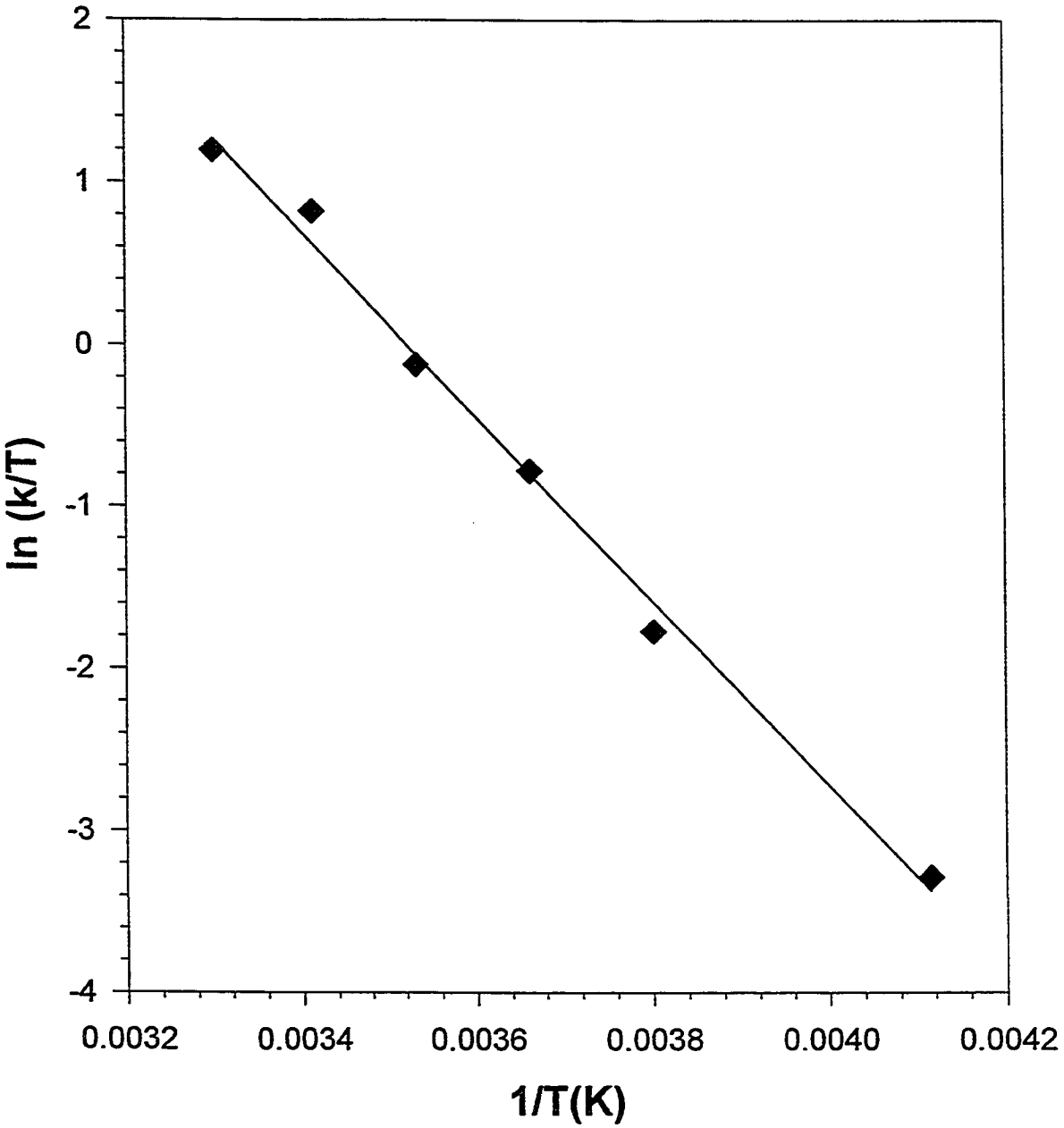


Figure 24

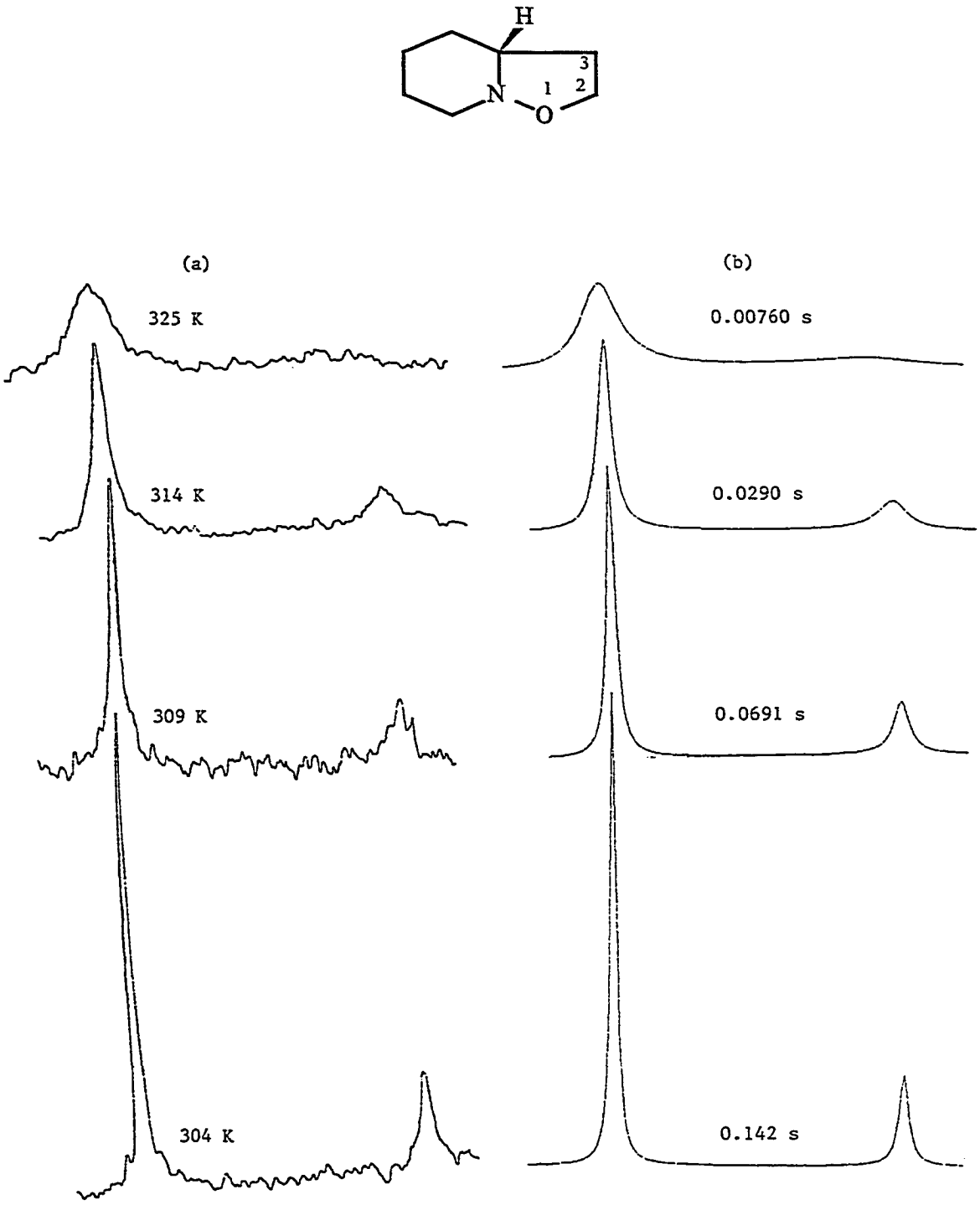


Figure 25. Temperature-dependent ^{13}C NMR spectra of C-3 in the (195b): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 304 K was 282 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (195b)

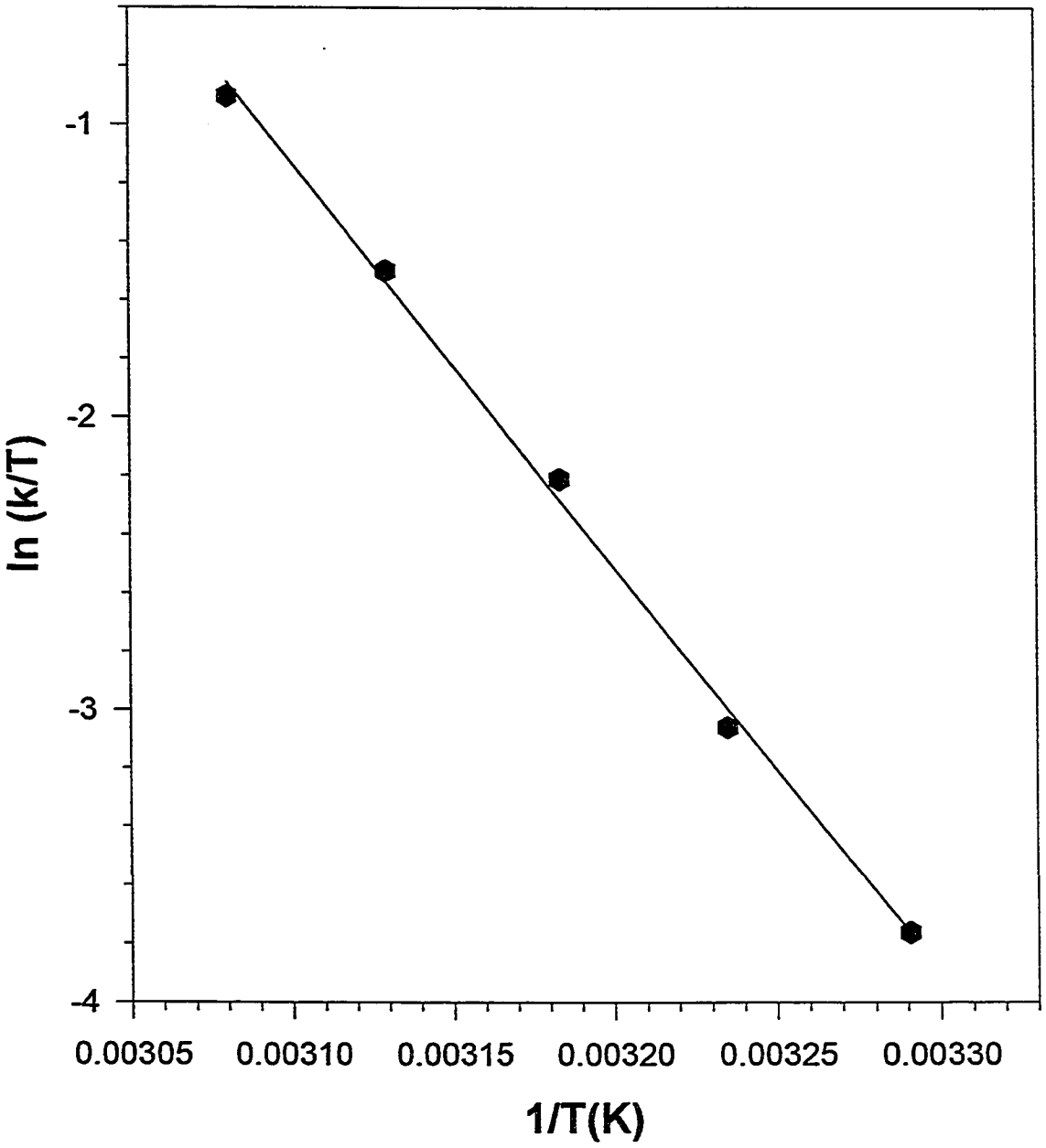


Figure 26

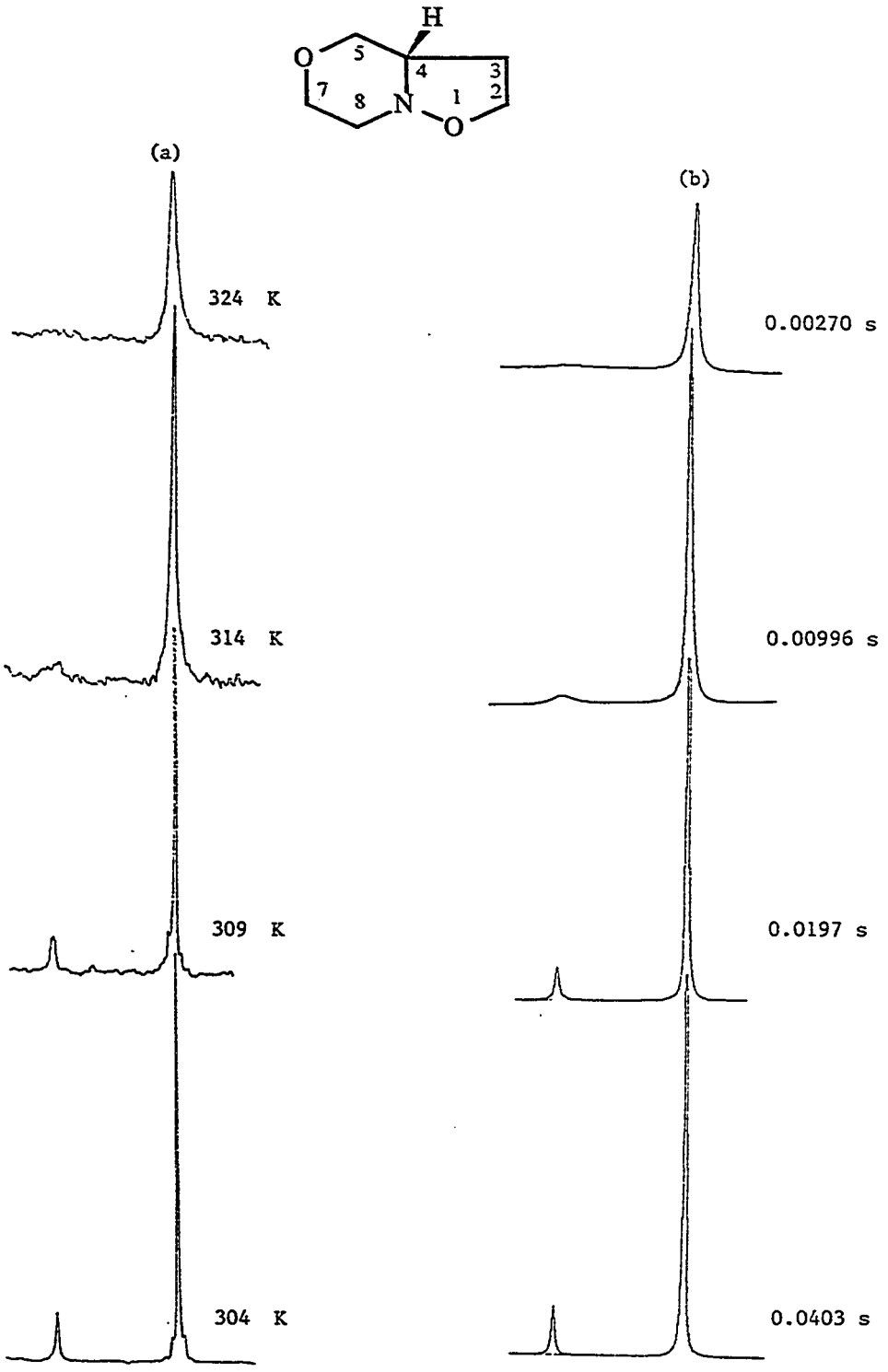


Figure 27. Temperature-dependent ^{13}C NMR spectra of C-8 in the (195C): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 299 K was 340 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (195c)

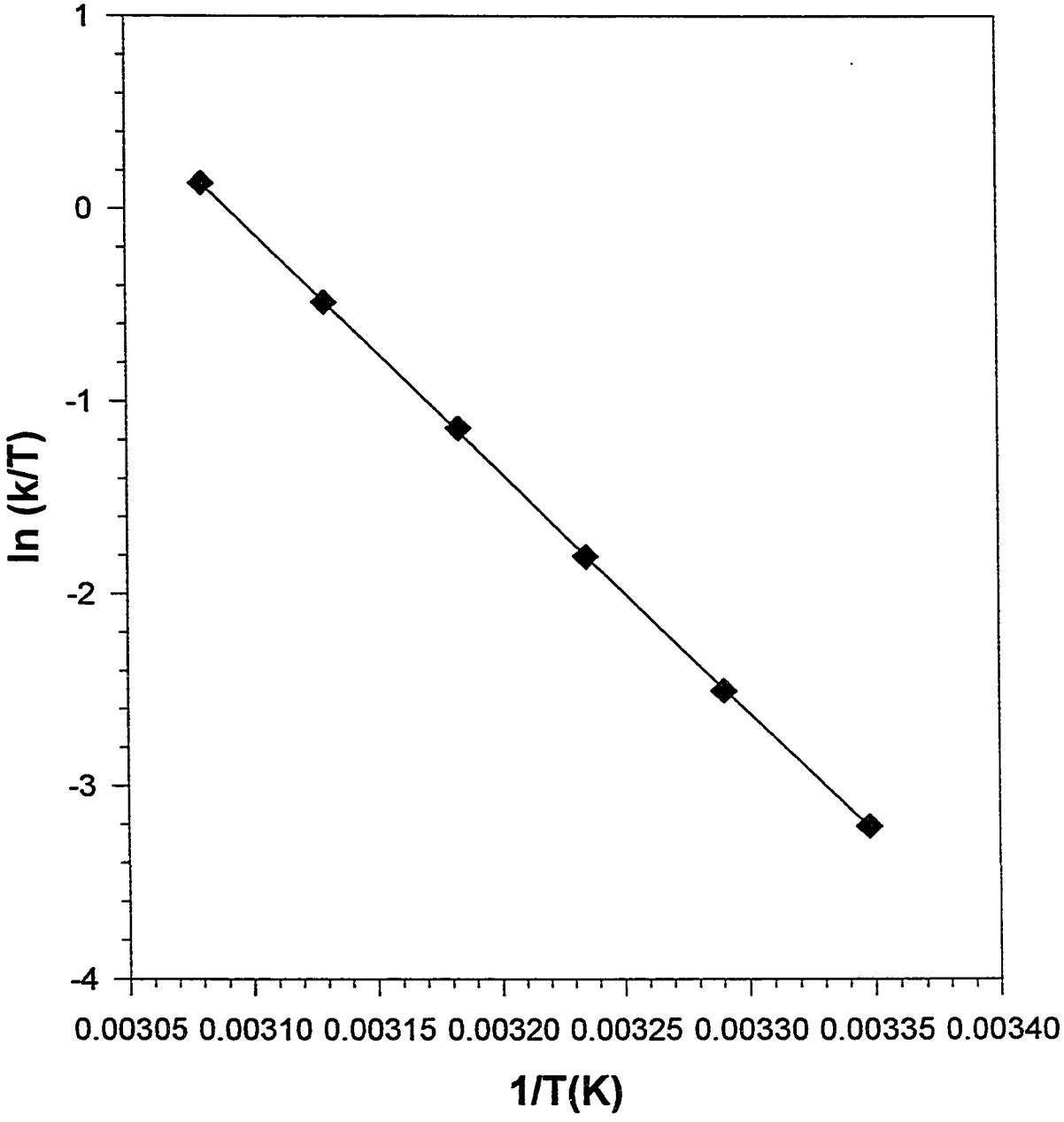


Figure 28

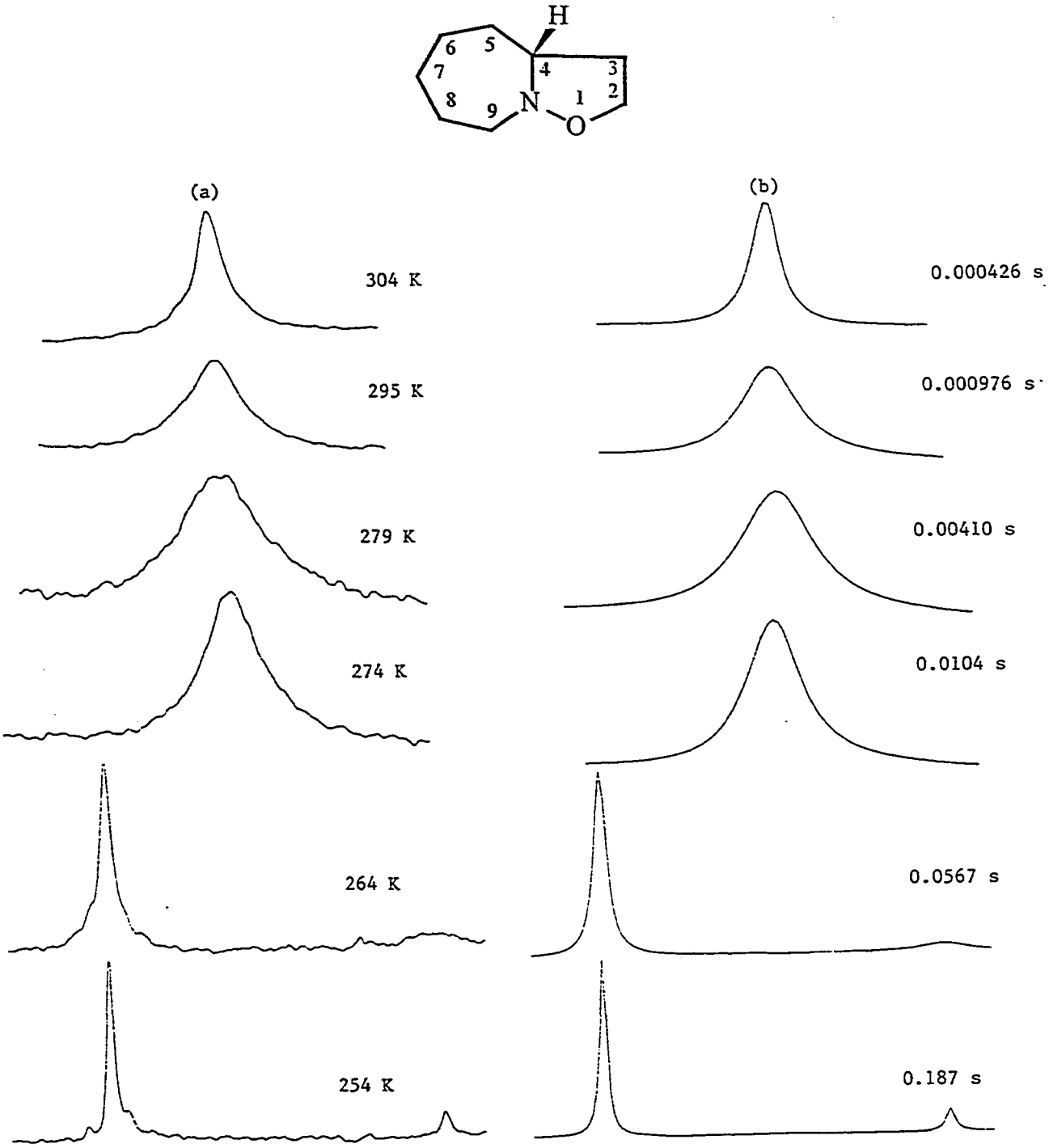


Figure 29. Temperature-dependent ^{13}C NMR spectra of C-9 in the (195d): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 254 K was 269 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (195d)

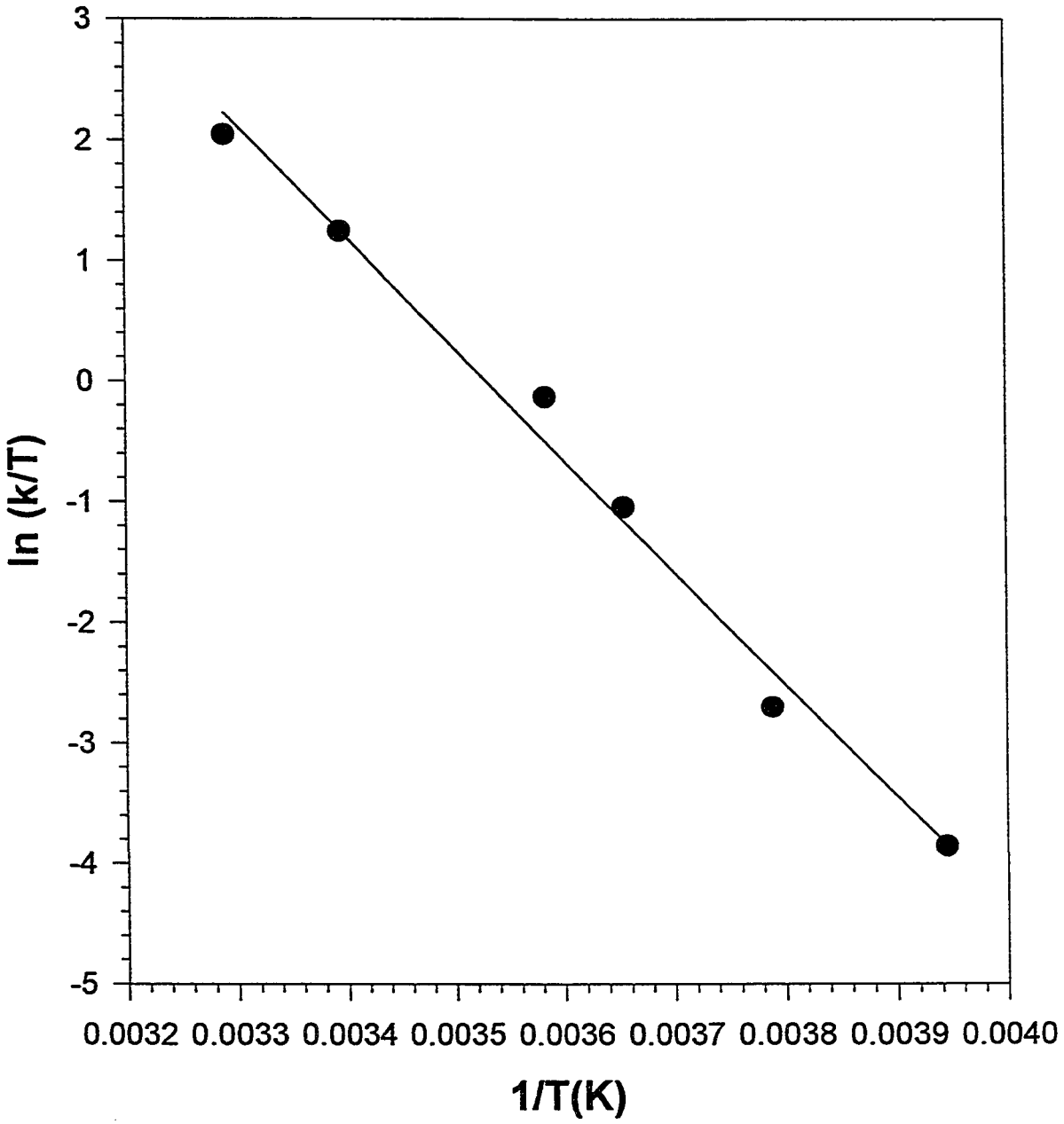


Figure 30

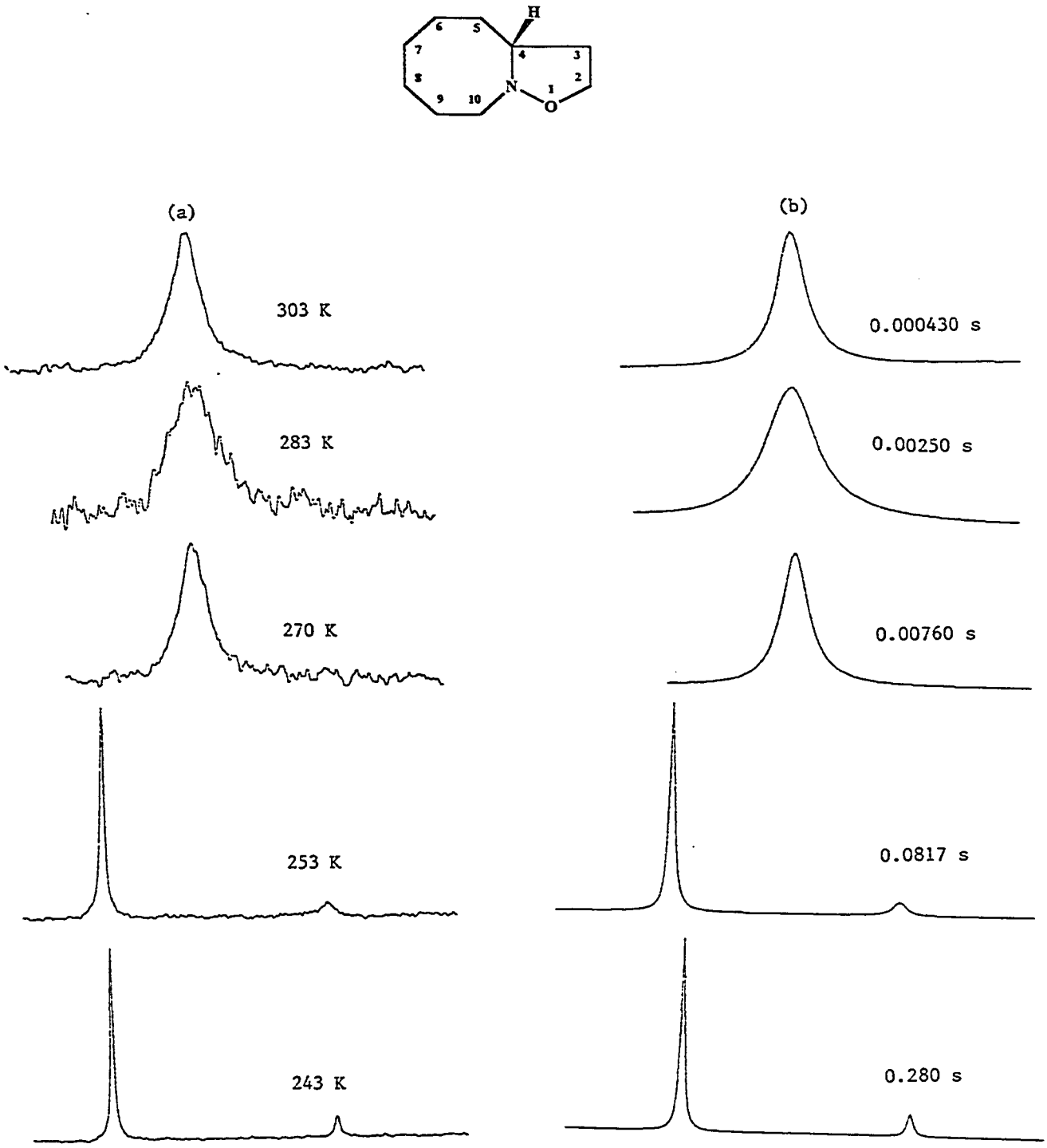


Figure 31. Temperature-dependent ^{13}C NMR spectra of C-10 in the (195e): (a) observed band shapes; (b) calculated band shapes. The chemical shift difference $\Delta\nu$ at 243 K was 412 Hz.

Eyring plot of ln(k/T) against 1/T for the nitrogen inversion of (195e)

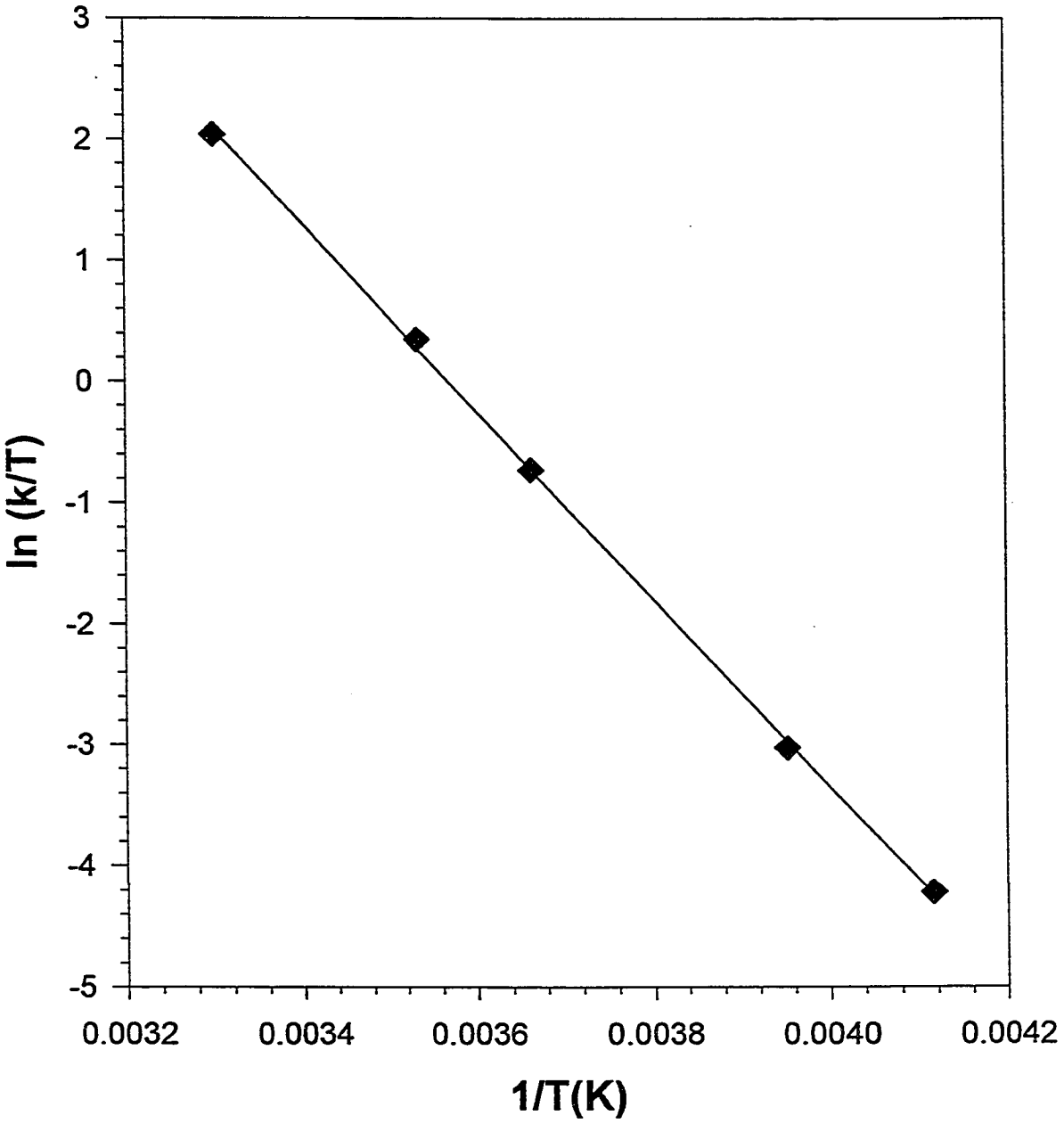


Figure 32

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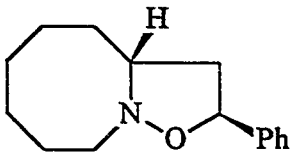
APPENDIX

MASS SPECTRA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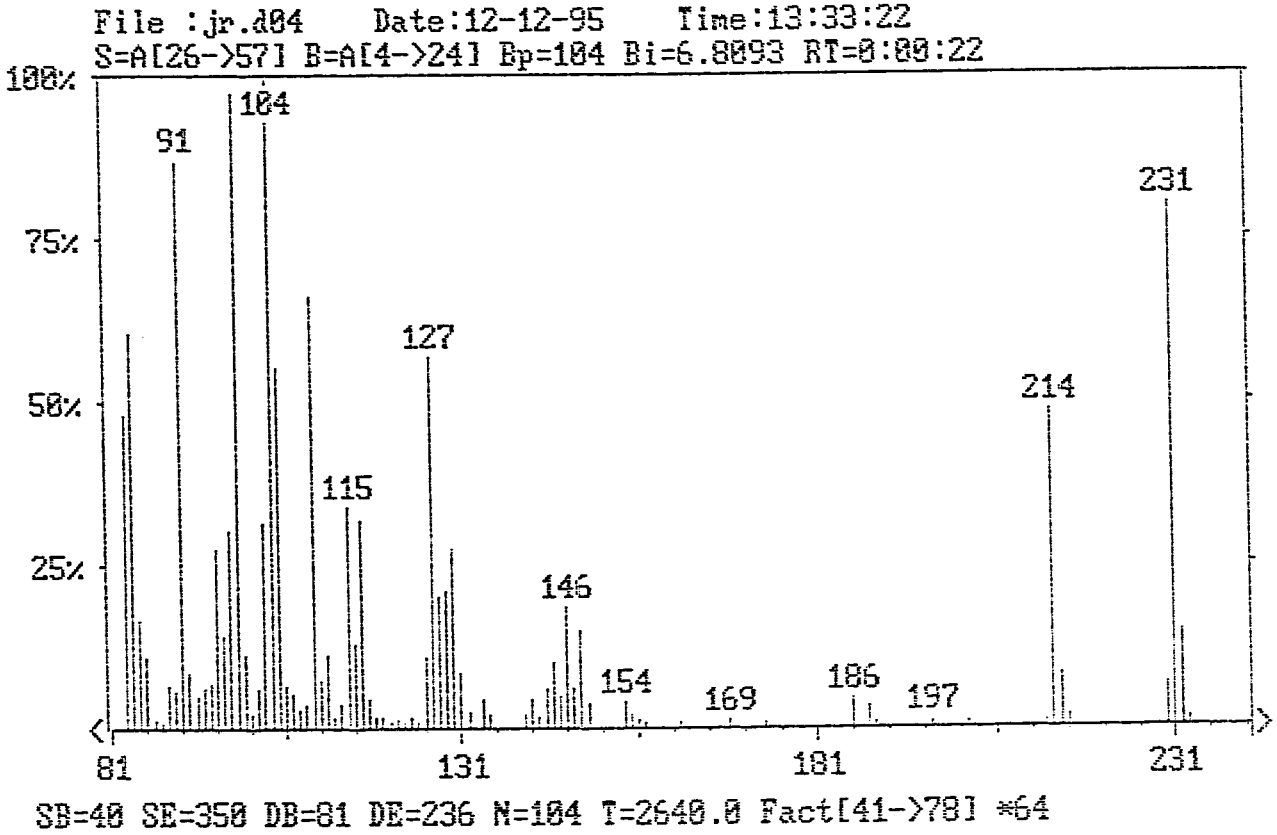
O
Ph

(187a)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75%
50%
25%
104
91
231
127
214
115
146
154
169
186
197
81
131
181
231
SB=40 SE=350 DB=81 DE=236 N=104 T=2640.0 Fact[41->78] *64

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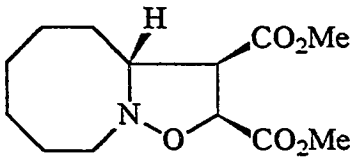
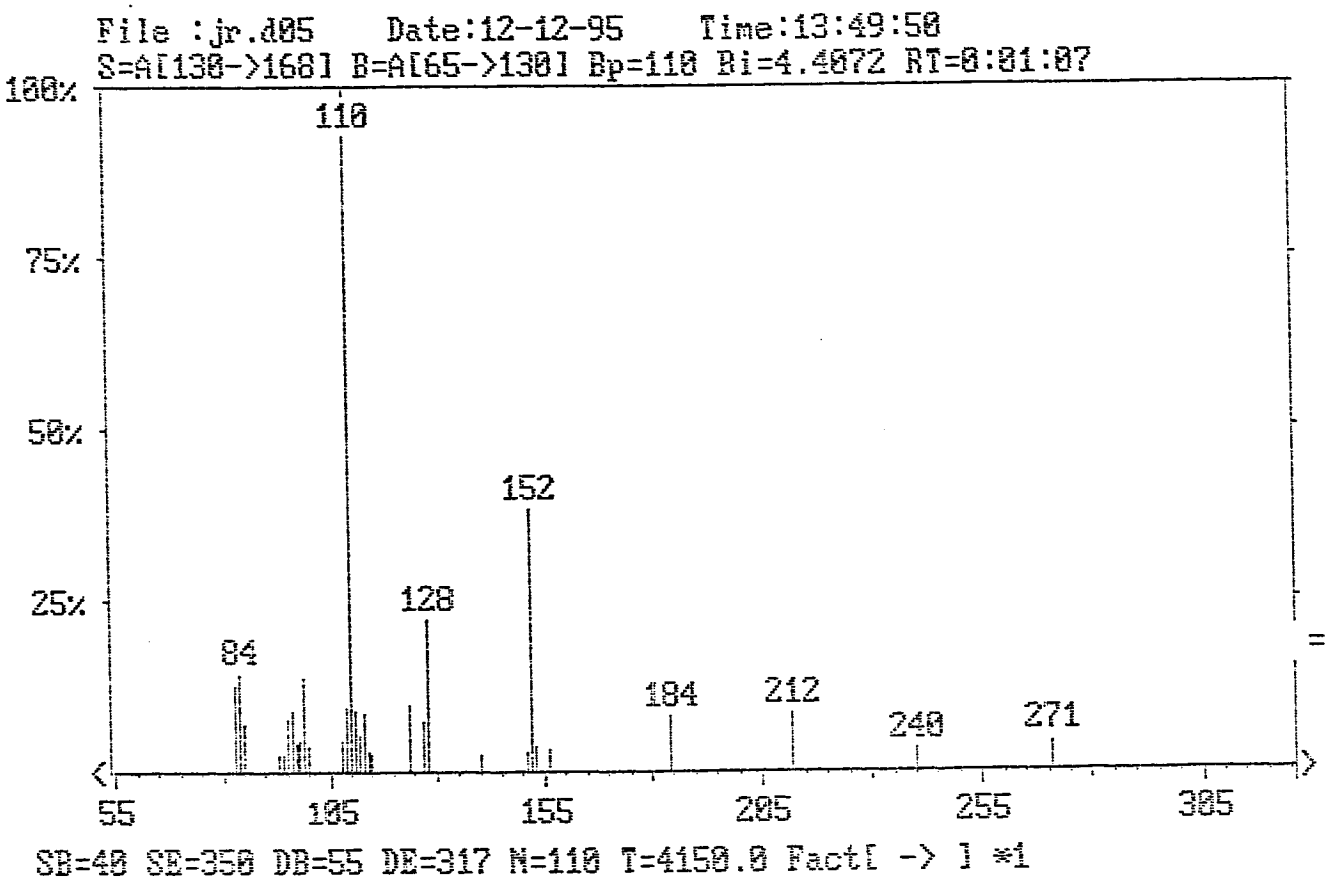
Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
83	48.09	84	60.80	85	16.69	86	11.10
87	1.31	88	1.01	89	6.58	90	5.97
91	87.00	92	8.53	93	4.91	94	6.07
95	6.93	96	27.71	97	14.14	98	30.25
99	97.52	100	11.30	101	1.99	102	6.17
103	31.57	104	100.00	105	55.55	106	6.58
107	5.45	108	2.91	109	3.69	110	66.33
111	7.44	112	11.43	113	1.97	114	3.91
115	33.86	116	13.24	117	32.16	118	4.64
119	1.72	120	1.84	121	1.16	122	1.51
123	1.00	124	1.94	125	1.15	126	10.97
127	56.93	128	20.20	129	20.94	130	27.42
131	8.47	132	2.44	134	4.71	135	2.10
140	2.29	141	4.53	142	1.74	143	6.31
144	10.29	145	4.92	146	18.80	147	6.30
148	15.10	149	3.99	154	4.30	155	2.37
156	1.43	157	0.96	162	0.95	169	1.20
174	1.10	186	4.44	188	3.50	189	1.12
197	1.15	202	1.14	213	1.17	214	48.48
215	8.19	216	1.88	230	6.78	231	79.94
232	14.70	233	1.40				


H
CO2Me
N
O
CO2Me

(188c)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75%
50%
25%
110
152
128
84
184
212
240
271
55
105
155
205
255
305
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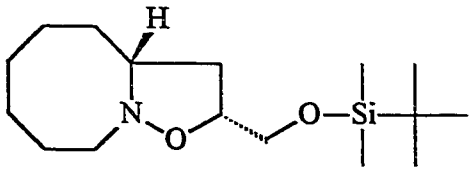
83	12.76	84	14.39	85	7.11	93	2.61
94	2.57	95	7.72	96	9.17	97	4.01
98	4.81	99	13.98	100	3.68	108	4.51
109	9.56	110	100.00	111	9.12	112	5.57
113	8.68	114	3.14	115	2.40	124	10.04
127	7.46	128	22.21	140	2.42	151	3.07
152	38.35	153	3.99	156	3.42	184	8.33
212	8.55	240	3.48	271	4.32		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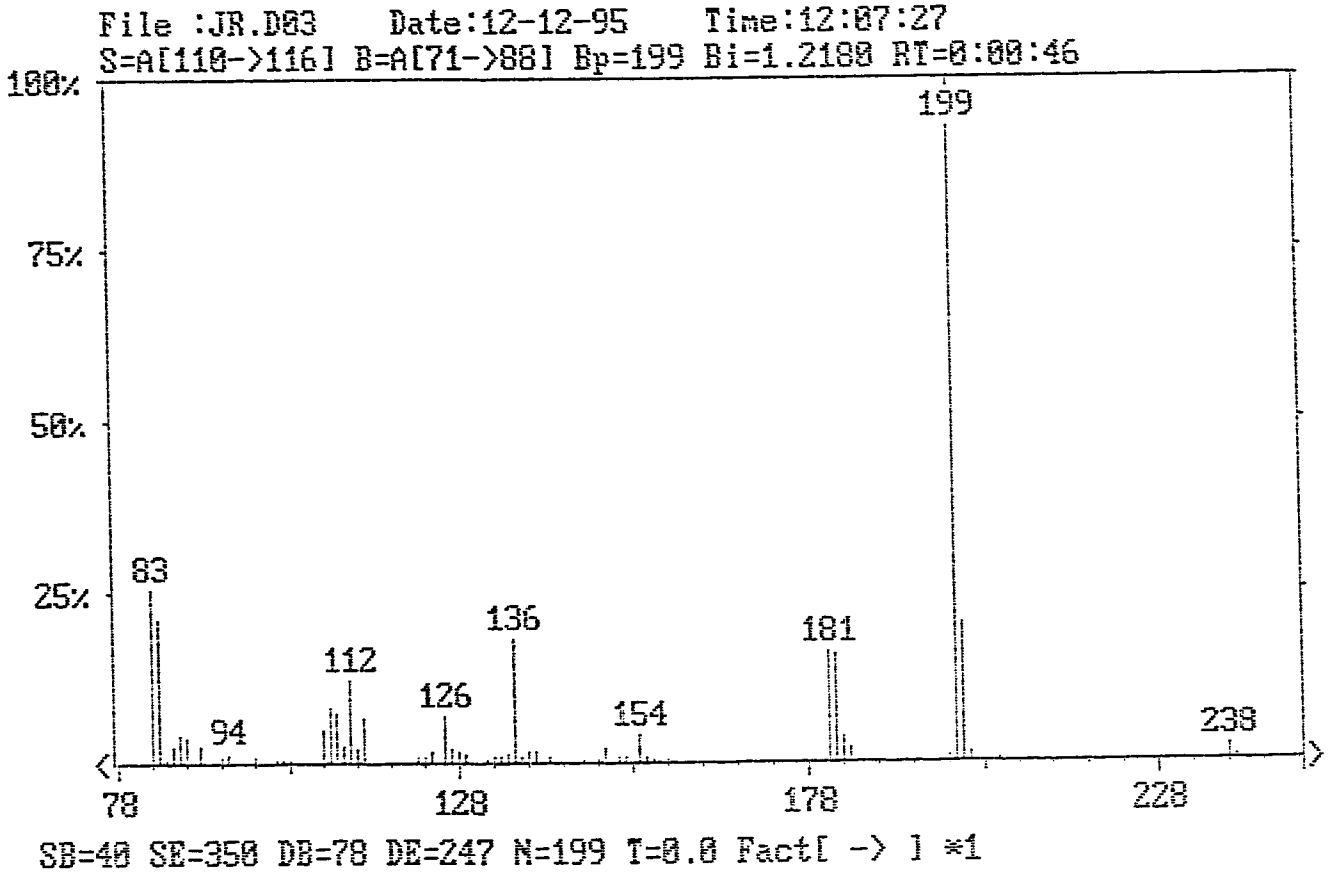
O
O
Si

(188f)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50%
25%
199
83
136
181
112
126
154
94
238
78
128
178
228
SB=40 SE=350 DB=78 DE=247 N=199 T=0.0 Fact[->] *1

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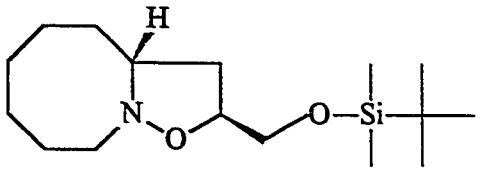
49	0.02	50	0.04	51	0.02	53	0.02
55	0.02	56	0.02	57	0.02	58	0.02
69	0.02	70	0.02	71	0.02	73	0.02
74	0.04	76	0.02	78	0.02	79	0.04
80	0.02	81	0.02	83	25.58	84	21.01
85	0.50	86	2.45	87	4.11	88	3.97
89	0.18	90	2.65	93	0.94	94	1.58
98	1.00	101	0.56	102	0.58	103	0.44
106	0.10	108	5.11	109	8.08	110	7.36
111	2.61	112	12.35	113	2.08	114	6.57
118	0.34	122	0.80	123	0.90	124	1.98
126	7.00	127	2.31	128	1.80	129	1.24
131	0.36	132	0.44	133	0.78	134	0.80
135	1.42	136	18.34	137	1.14	138	1.90
139	1.66	141	1.04	143	0.40	144	0.12
145	0.02	146	0.58	147	0.28	148	0.44
149	2.06	150	0.30	151	0.90	152	1.08
154	4.15	155	1.08	156	0.66	158	0.66
159	0.12	160	0.22	161	0.04	162	0.38
164	0.28	167	0.40	169	0.06	171	0.22
172	0.34	174	0.04	175	0.20	176	0.12
177	0.08	178	0.14	179	0.26	180	0.30
181	16.24	182	15.71	183	3.69	184	2.39
185	0.22	186	0.06	187	0.06	188	0.04
189	0.12	191	0.06	193	0.24	194	0.16
195	0.32	196	0.36	198	0.88	199	100.00
200	20.14	201	1.32	203	0.10	204	0.02
205	0.46	207	0.12	208	0.10	209	0.14
210	0.22	211	0.22	212	0.14	216	0.02
219	0.16	221	0.06	222	0.10	223	0.32
225	0.02	226	0.22	227	0.20	228	0.32
230	0.02	231	0.02	232	0.10	233	0.08
234	0.06	236	0.10	238	2.10	239	0.46
240	0.30	243	0.06	244	0.08	245	0.02
249	0.02	250	0.08	251	0.08	252	0.28
255	0.06	256	0.20	257	0.06	258	0.10
259	0.02	260	0.12	261	0.04	262	0.02
263	0.14	264	0.02	265	0.08	267	0.04
268	0.08	270	0.08	274	0.02	275	0.02
276	0.02	277	0.02	278	0.04	280	0.02
281	0.02	283	0.04	284	0.08	285	0.06
286	0.06	287	0.04	288	0.06	292	0.06
293	0.04	294	0.08	296	0.02	305	0.06
309	0.02	311	0.04	312	0.04	314	0.02
315	0.02	316	0.04	318	0.02	319	0.10
327	0.02	329	0.04	330	0.02	331	0.06
334	0.02	336	0.02	338	0.04	339	0.02
342	0.02						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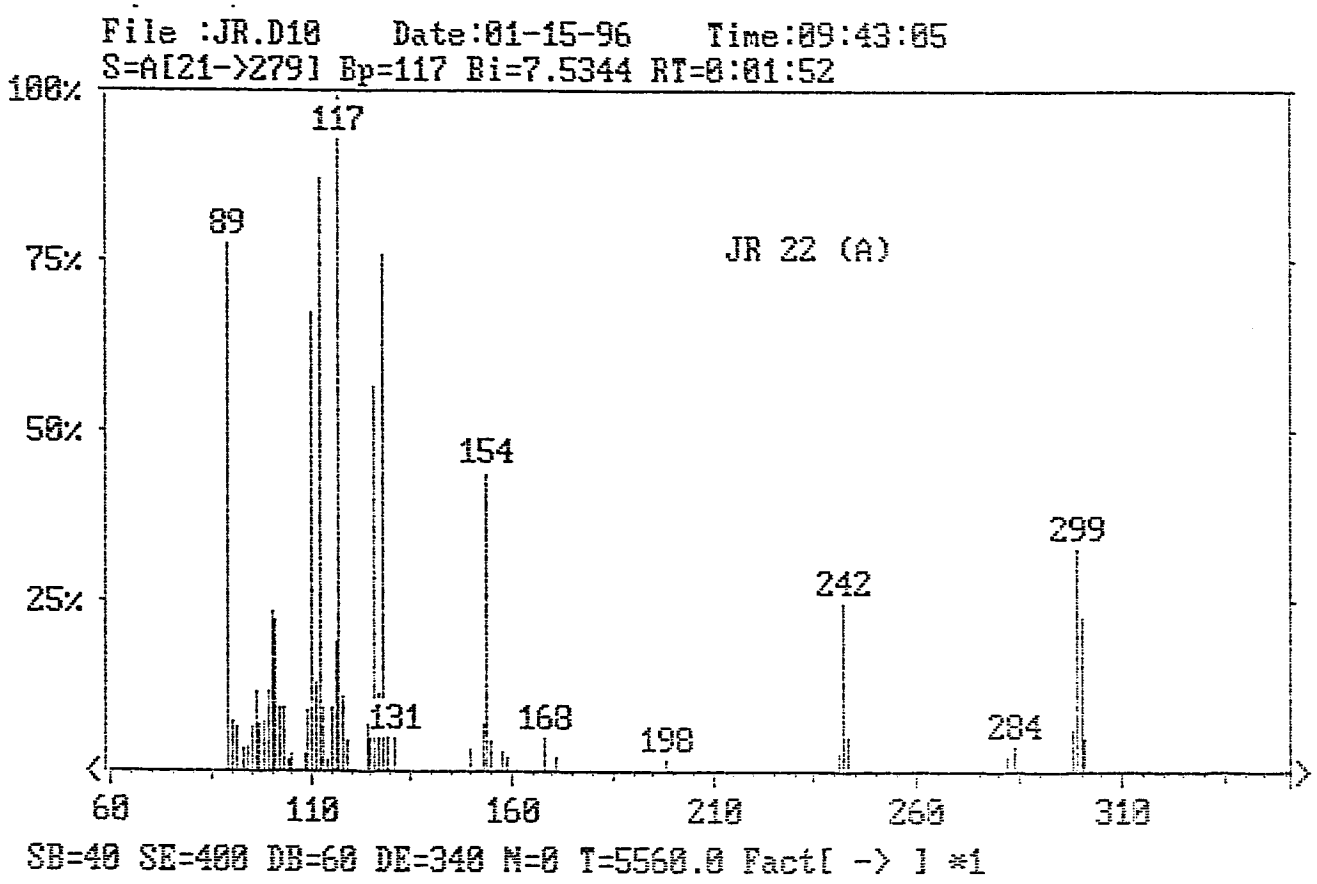
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25%
117
89
JR 22 (A)
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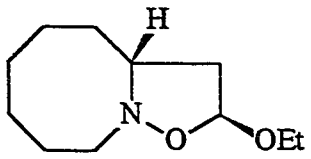
94	3.78	95	6.43	96	11.87	97	7.19
98	7.42	99	11.82	100	23.48	101	22.47
102	9.53	103	9.60	104	1.99	105	2.76
108	2.68	109	9.24	110	67.64	111	12.95
112	87.36	113	9.41	114	1.90	115	9.33
116	19.22	117	100.00	118	11.24	119	4.62
124	7.05	125	7.49	126	56.57	127	11.47
128	76.04	129	7.21	131	4.95	150	3.45
153	7.18	154	43.87	155	4.70	158	3.18
159	2.20	168	4.98	171	2.06	198	1.80
241	2.41	242	24.76	243	4.98	282	2.02
284	3.61	298	6.34	299	32.71	300	22.62
301	5.07						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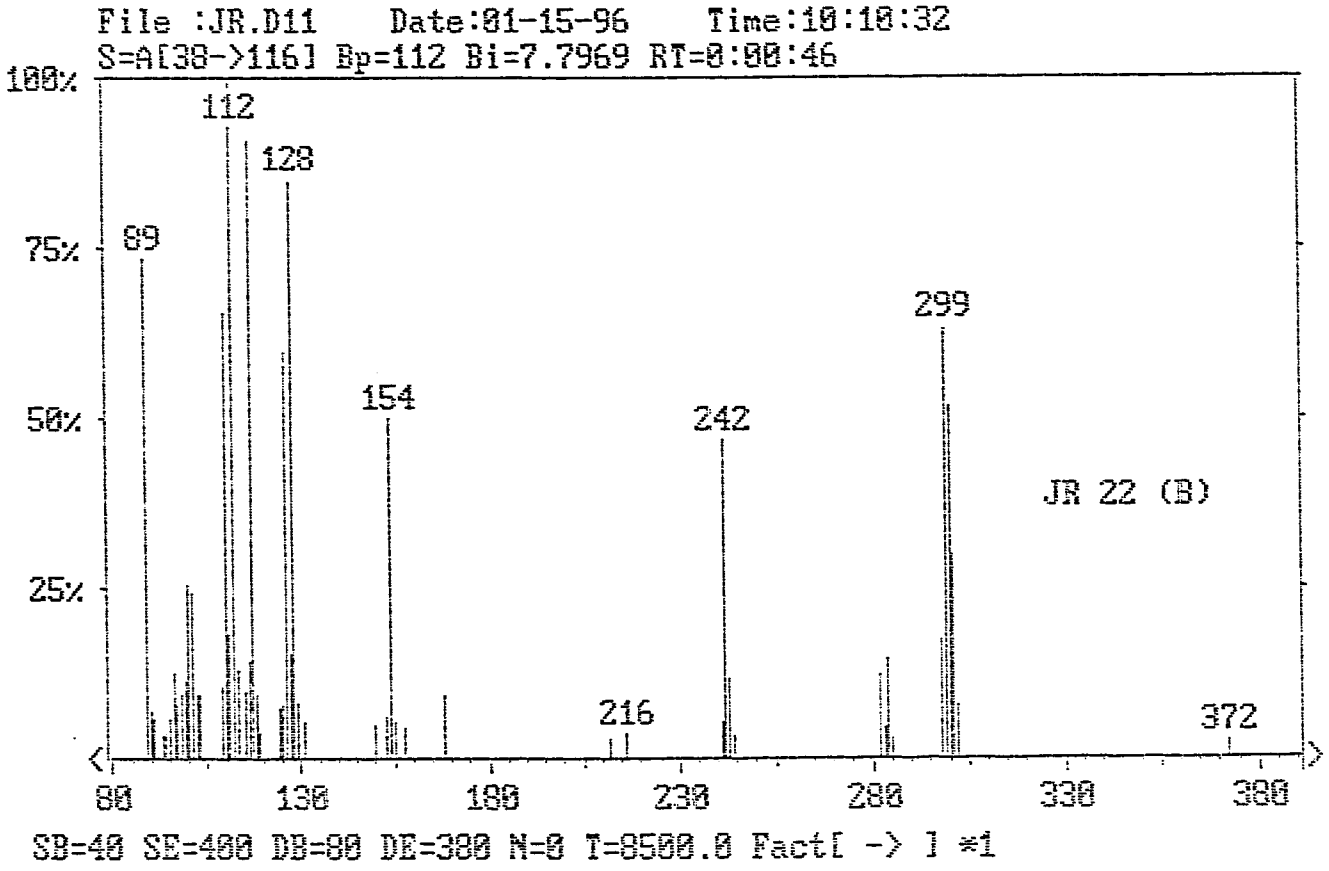
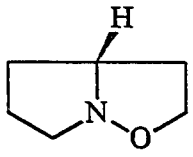

File :JR.D11 Date:01-15-96 Time:10:10:32
S=A[38->116] Bp=112 Bi=7.7969 RT=0:00:46
100%
75%
50%
25%
112
128
89
154
216
242
299
372
JR 22 (B)
80
130
180
230
280
330
380
SB=40 SE=400 DB=80 DE=380 N=0 T=8500.0 Fact[->] *1

File :JR.D11 Date:01-15-96 Time:10:10:32
S=A[38->116] Bp=112 Bi=7.7969 RT=0:00:46

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
89	73.53	90	7.13	91	5.89	93	3.21
94	3.72	95	5.87	96	12.86	97	7.93
98	9.48	99	11.65	100	25.74	101	24.37
102	9.53	103	9.47	109	10.82	110	65.46
111	18.28	112	100.00	113	12.92	115	9.91
116	14.38	117	90.81	118	9.36	119	3.99
124	7.57	125	7.90	126	59.85	127	15.69
128	84.99	129	8.08	131	5.28	150	5.14
153	6.27	154	49.95	155	5.32	158	4.57
168	9.42	212	3.04	216	3.87	241	5.47
242	46.90	243	11.83	244	3.46	282	12.21
283	4.58	284	14.73	285	3.15	298	17.45
299	63.16	300	51.83	301	30.11	302	7.63
372	2.66						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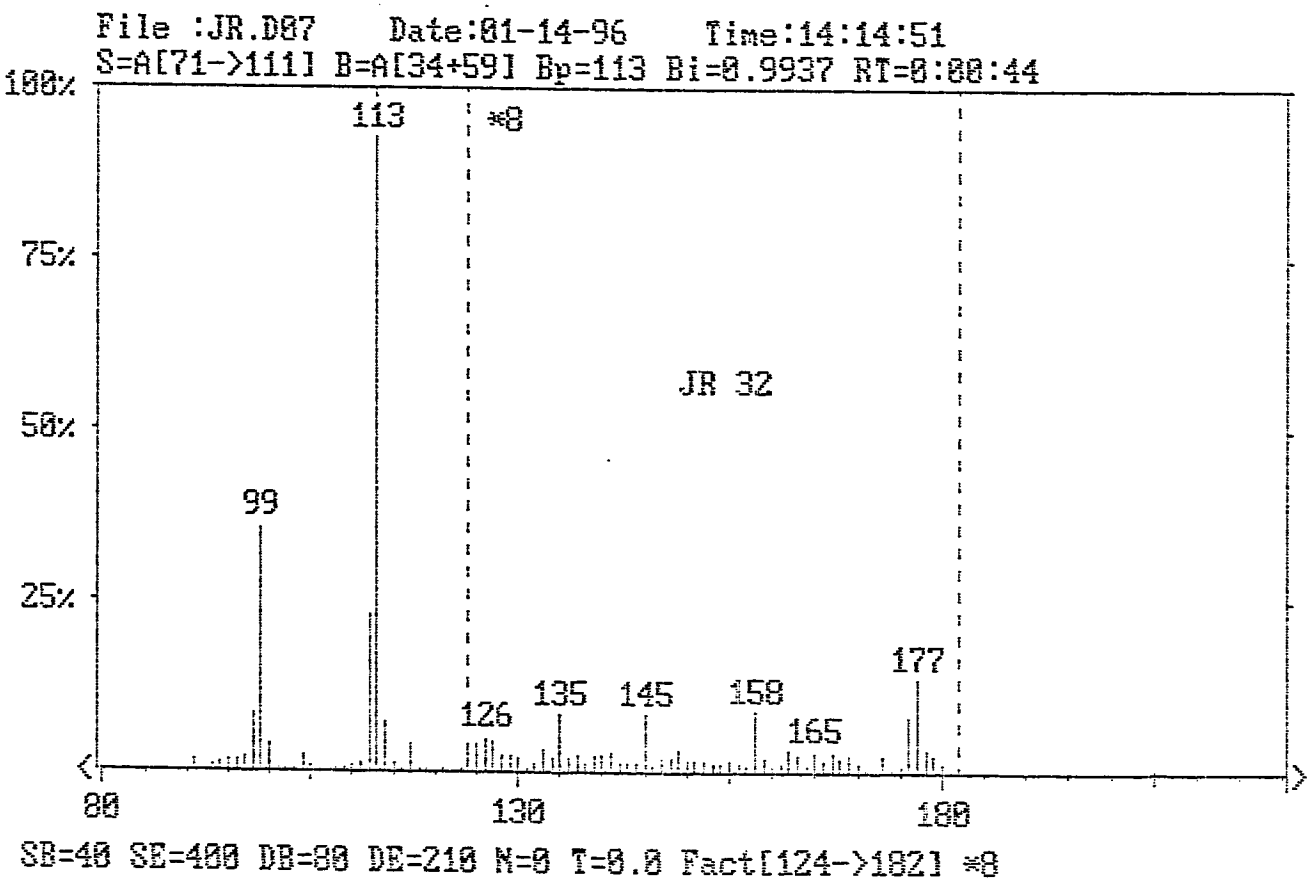
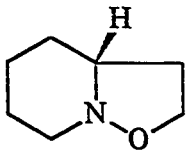

File :JR.D87 Date:01-14-96 Time:14:14:51
S=A[71->111] B=A[34+59] Bp=113 Bi=0.9937 RT=0:00:44
100%
75%
50%
25%
113
*8
JR 32
99
126
135
145
158
165
177
80
130
180
SB=40 SE=400 DB=80 DE=210 N=0 T=0.0 Fact[124->182] *8

File :JR.D07 Date:01-14-96 Time:14:14:51
S=A[71->111] B=A[34+59] Bp=113 Bi=0.9937 RT=0:00:44

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
89	0.20	90	0.22	91	1.70	92	0.39
93	0.88	94	1.25	95	1.60	96	1.87
97	2.04	98	8.55	99	35.80	100	4.00
101	0.59	102	0.44	103	0.57	104	2.75
105	1.13	106	0.37	107	0.42	108	0.66
109	0.61	110	0.96	111	1.25	112	23.17
113	100.00	114	7.47	115	1.35	116	0.69
117	4.05	118	0.64	119	0.49	120	0.29
121	0.47	122	0.22	123	0.61	124	0.34
125	0.54	126	0.64	127	0.59	128	0.32
129	0.32	130	0.27	131	0.07	132	0.17
133	0.44	134	0.29	135	1.08	136	0.27
137	0.32	138	0.20	139	0.32	140	0.34
141	0.37	142	0.17	143	0.17	144	0.17
145	1.08	146	0.12	147	0.27	148	0.27
149	0.42	150	0.25	151	0.22	152	0.25
153	0.20	154	0.20	155	0.22	156	0.20
157	0.12	158	1.11	159	0.29	160	0.10
161	0.17	162	0.57	163	0.34	164	0.12
165	0.39	166	0.22	167	0.37	168	0.27
169	0.34	170	0.20	171	0.07	172	0.05
173	0.34	174	0.07	175	0.15	176	1.01
177	1.72	178	0.42	179	0.32	180	0.20
181	0.05	182	0.15	183	0.17	185	0.10
186	0.22	187	0.07	188	0.02	189	0.12
190	0.12	191	0.32	192	0.20	193	0.12
194	0.17	195	0.20	196	0.15	197	0.15
198	0.02	199	0.07	200	0.10	201	0.05
202	0.07	203	0.07	204	0.10	205	0.47
206	0.15	207	0.29	208	0.12	209	0.15
210	0.12	211	0.10	212	0.07	213	0.02
214	0.07	215	0.02	216	0.02	217	0.05
218	0.02	219	0.07	220	0.05	221	0.10
222	0.05	223	0.10	224	0.12	225	0.12
226	0.07	227	0.12	228	0.05	230	0.02
231	0.05	232	0.07	233	0.05	234	0.05
235	0.05	236	0.05	237	0.05	238	0.07
239	0.05	240	0.07	241	0.02	242	0.02
244	0.05	245	0.02	246	0.05	247	0.02
248	0.05	249	0.05	250	0.02	251	0.02
252	0.05	253	0.05	255	0.02	257	0.02
258	0.02	261	0.02	262	0.07	263	0.07
264	0.05	265	0.02	267	0.05	268	0.05
273	0.02	274	0.02	276	0.05	277	0.05
278	0.05	280	0.02	281	0.15	282	0.05
284	0.05	288	0.02	290	0.02	292	0.02
294	0.05	296	0.02	297	0.02	298	0.02
302	0.02	307	0.02	310	0.02	319	0.02
322	0.02	323	0.02	324	0.02	327	0.02
336	0.02	339	0.02	344	0.02	354	0.02
361	0.02	364	0.02	390	0.02	392	0.02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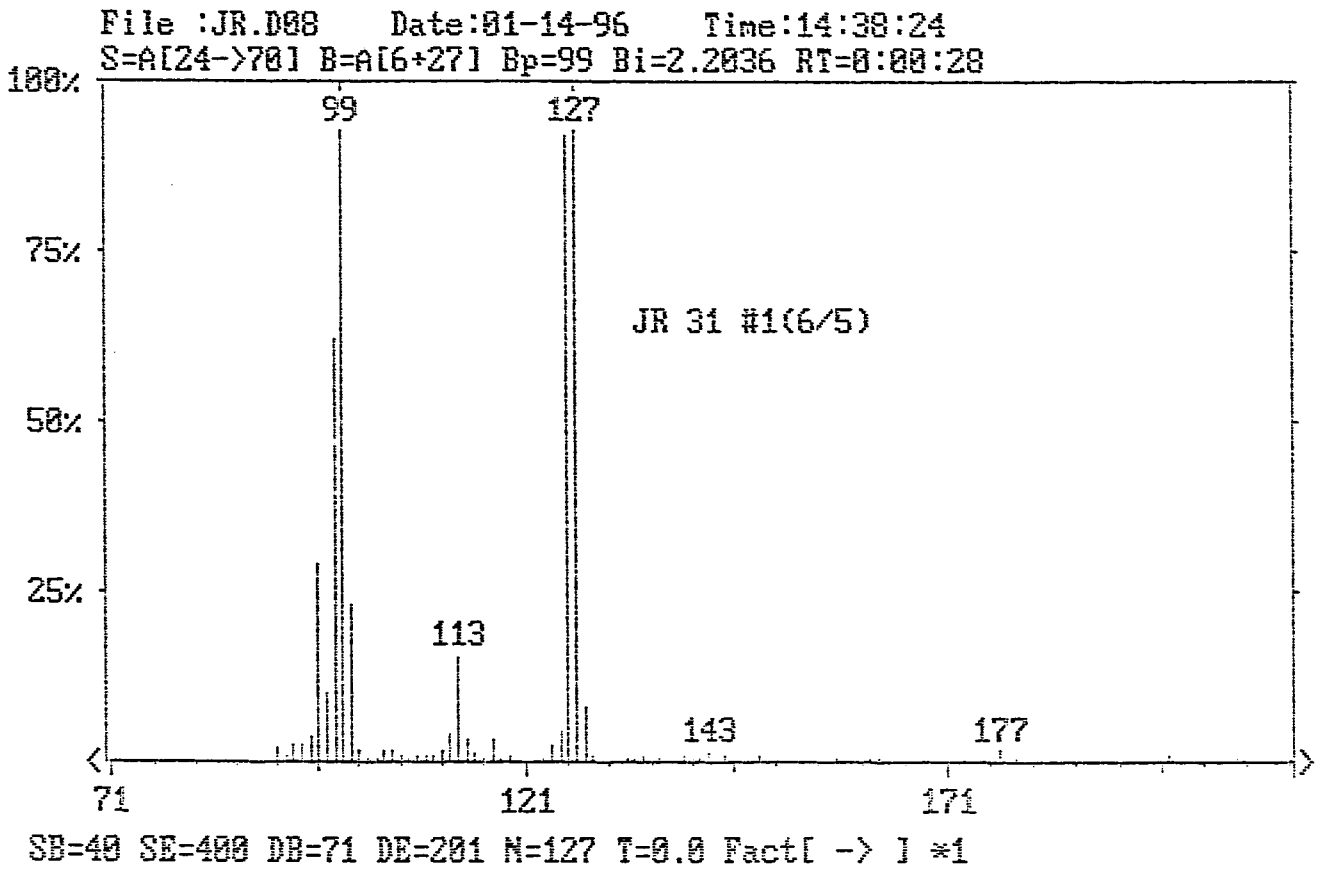
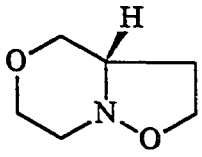

File :JR.D08 Date:01-14-96 Time:14:38:24
S=A[24->70] B=A[6+27] Bp=99 Bi=2.2036 RT=0:00:28
100%
75%
50%
25%
99
127
113
143
177
JR 31 #1(6/5)
71
121
171
SB=40 SE=400 DB=71 DE=201 N=127 T=0.0 Fact[->] *1

File :JR.D08 Date:01-14-96 Time:14:38:24
S=A[24->70] B=A[6+27] Bp=99 Bi=2.2036 RT=0:00:28

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
89	0.18	90	0.40	91	2.37	92	1.15
93	2.51	94	2.44	95	3.95	96	29.13
97	10.42	98	62.28	99	324.21	100	23.35
101	1.87	102	0.54	103	0.72	104	1.94
105	1.69	106	0.83	107	0.50	108	0.90
109	1.08	110	1.01	111	1.69	112	4.27
113	15.66	114	3.45	115	1.36	116	0.68
117	3.23	118	0.61	119	0.90	120	0.40
122	0.40	123	0.47	124	2.51	125	4.71
126	92.21	127	100.00	128	8.05	129	0.90
130	0.40	131	0.36	132	0.18	133	0.54
134	0.47	135	0.86	136	0.29	137	0.43
138	0.32	139	0.40	140	1.08	141	0.65
142	0.50	143	1.58	144	0.32	145	0.79
146	0.14	147	0.40	149	0.83	150	0.25
151	0.25	152	0.18	153	0.40	154	0.29
155	0.40	156	0.25	157	0.29	158	0.68
159	0.25	160	0.14	161	0.40	162	0.47
163	0.47	164	0.18	165	0.43	166	0.25
167	0.22	168	0.25	169	0.29	170	0.25
171	0.14	172	0.07	173	0.40	175	0.18
176	0.29	177	1.76	178	0.47	179	0.43
180	0.22	181	0.18	182	0.14	183	0.18
184	0.18	185	0.14	187	0.14	188	0.07
189	0.18	190	0.07	191	0.43	192	0.14
193	0.36	195	0.14	196	0.07	197	0.86
198	0.18	199	0.07	200	0.07	201	0.11
203	0.11	204	0.11	205	0.47	206	0.14
207	0.29	208	0.18	209	0.14	210	0.14
211	0.14	212	0.14	213	0.07	214	0.04
215	0.11	216	0.04	217	0.07	218	0.07
219	0.11	220	0.04	222	0.07	223	0.18
224	0.11	225	0.07	226	0.07	227	0.07
228	0.04	229	0.04	231	0.04	232	0.04
233	0.07	234	0.04	235	0.07	237	0.04
238	0.07	239	0.11	240	0.04	241	0.04
242	0.04	244	0.04	246	0.04	248	0.04
249	0.07	250	0.04	251	0.07	252	0.07
253	0.07	254	0.11	255	0.04	256	0.04
257	0.04	258	0.04	260	0.04	261	0.04
262	0.04	263	0.04	265	0.07	266	0.11
267	0.07	268	0.07	269	0.04	270	0.04
271	0.07	274	0.04	275	0.04	276	0.04
278	0.04	279	0.04	280	0.07	281	0.14
282	0.07	283	0.04	284	0.04	286	0.04
287	0.04	288	0.07	289	0.04	292	0.04
294	0.04	295	0.04	296	0.04	301	0.04
305	0.04	309	0.04	311	0.04	313	0.04
314	0.04	322	0.04	323	0.04	326	0.04
329	0.04	337	0.04	356	0.04	357	0.04
388	0.04						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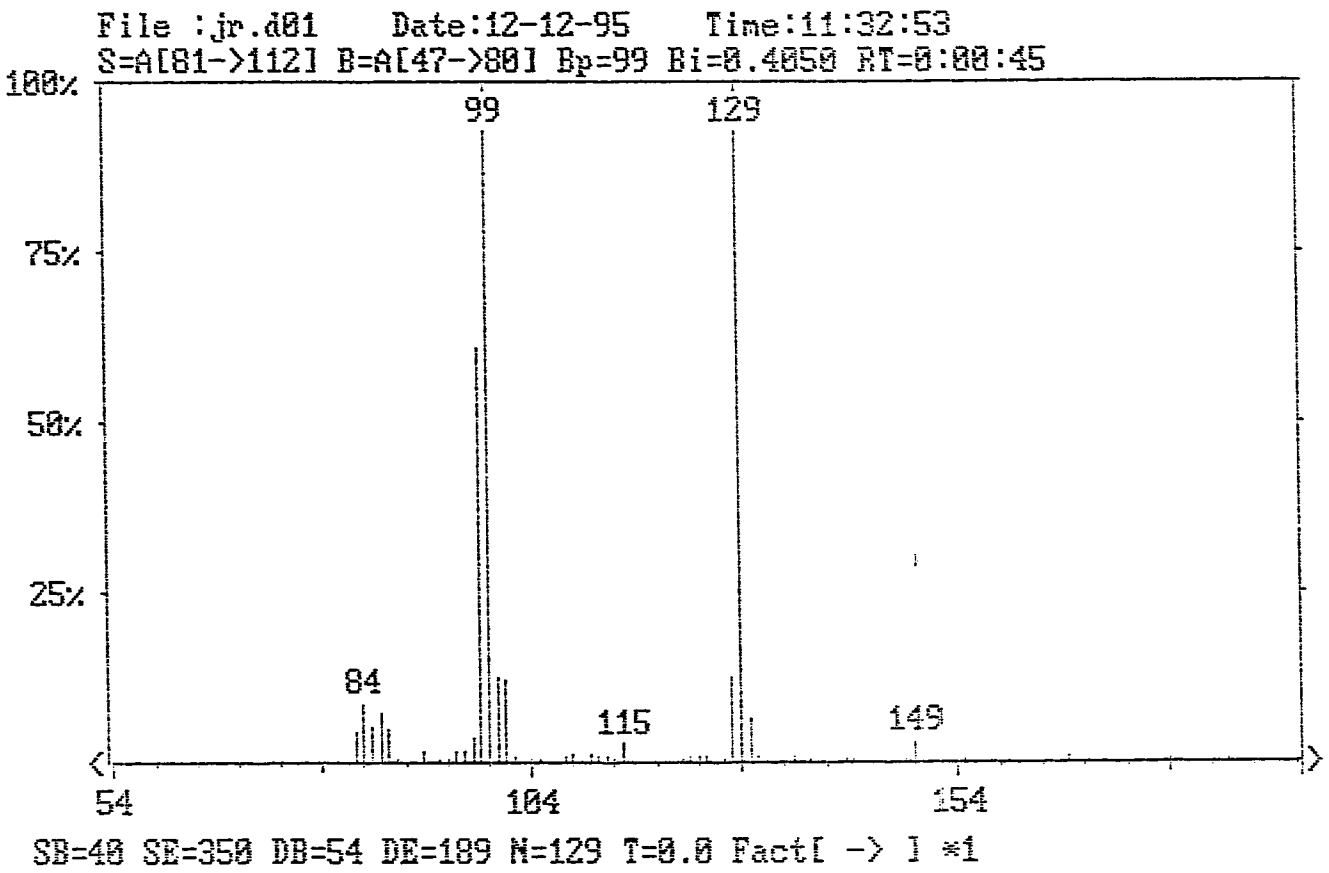
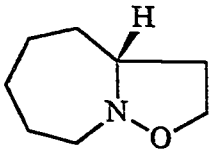

File :jr.d01 Date:12-12-95 Time:11:32:53
S=A[81->112] B=A[47->80] Bp=99 Bi=0.4050 RT=0:00:45
100%
75%
50%
25%
99
129
84
115
149
54
104
154
SB=40 SE=350 DB=54 DE=189 N=129 T=0.0 Fact[->] *1

ile :jr.d01 Date:12-12-95 Time:11:32:53
=A[81->112] B=A[47->80] Bp=99 Bi=0.4050 RT=0:00:45

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
82	0.34	83	4.50	84	8.74	85	5.43
86	7.55	87	5.17	88	0.76	89	0.25
90	0.25	91	1.61	92	0.34	93	0.59
94	0.76	95	1.95	96	1.95	97	3.90
98	61.15	99	140.71	100	12.64	101	12.30
102	1.10	103	0.25	104	0.51	105	0.51
106	0.25	107	0.42	108	0.85	109	1.27
110	0.34	111	1.27	112	1.10	113	1.02
114	0.59	115	2.97	116	0.34	117	0.08
118	0.17	119	0.42	120	0.25	121	0.25
122	0.51	123	1.02	124	0.93	125	0.93
126	0.34	127	0.76	128	12.47	129	100.00
130	6.70	131	1.10	132	0.34	133	0.42
134	0.17	135	0.85	136	0.34	137	0.59
138	0.42	139	0.34	140	0.25	141	0.51
142	0.76	143	0.42	144	0.17	145	0.17
146	0.25	147	0.25	148	0.59	149	3.14
150	0.25	151	0.34	152	0.25	153	0.25
154	0.34	155	0.68	156	0.17	157	0.17
158	0.08	159	0.17	160	0.08	161	0.08
162	0.17	163	0.34	164	0.08	165	0.25
166	0.34	167	0.93	168	0.42	169	0.34
170	0.17	171	0.17	172	0.08	173	0.08
174	0.08	175	0.08	176	0.08	177	0.25
178	0.08	179	0.51	180	0.25	182	0.08
183	0.08	184	0.17	185	0.08	186	0.51
187	0.08	189	0.08	190	0.08	191	0.08
192	0.08	193	0.17	194	0.17	195	0.25
196	0.17	197	0.34	198	0.17	199	0.08
203	0.08	205	0.17	206	0.08	207	0.25
208	0.08	209	0.08	210	0.08	211	0.08
214	0.08	217	0.08	219	0.08	220	0.08
221	0.08	222	0.08	223	0.08	224	0.08
225	0.08	230	0.08	231	0.08	232	0.08
233	0.08	238	0.08	239	0.08	241	0.08
246	0.08	247	0.08	248	0.17	249	0.08
250	0.08	253	0.08	255	0.08	256	0.08
259	0.08	261	0.08	262	0.08	265	0.08
272	0.08	276	0.08	277	0.08	280	0.08
281	0.08	288	0.08	291	0.08	298	0.08
300	0.08	302	0.08	323	0.08	348	0.08
350	0.08						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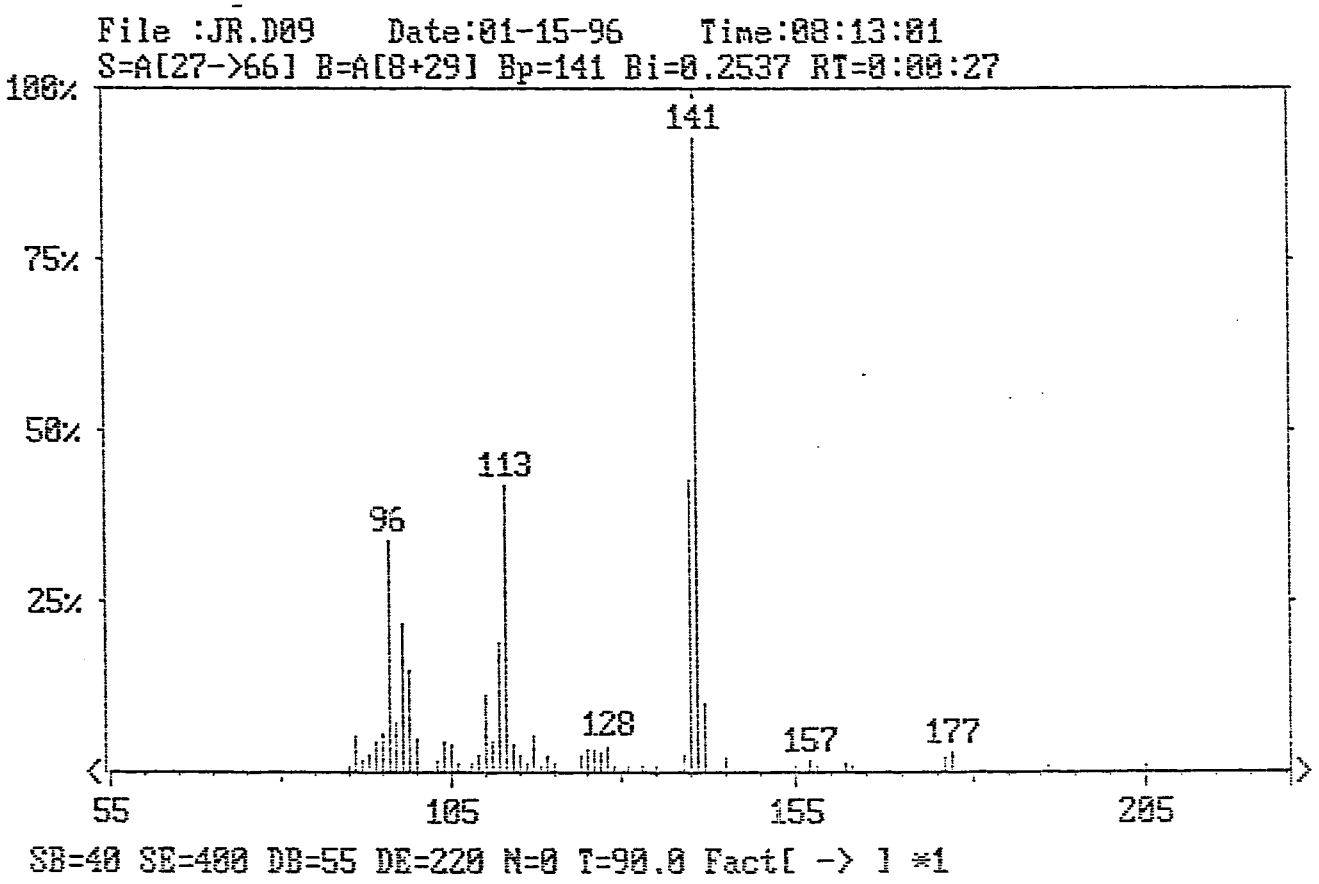
File :JR.D09 Date:01-15-96 Time:08:13:01
S=A[27->66] B=A[8+29] Bp=141 Bi=0.2537 RT=0:00:27
100%
75%
50%
25%
141
113
96
128
157
177
55
105
155
205
SB=40 SE=400 DB=55 DE=220 N=0 T=90.0 Fact[->] *1

File :JR.D09 Date:01-15-96 Time:08:13:01
S=A[27->66] B=A[8+29] Bp=141 Bi=0.2537 RT=0:00:27

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
90	0.96	91	5.49	92	1.64	93	2.50
94	4.52	95	5.97	96	34.07	97	7.51
98	21.85	99	15.11	100	4.81	103	1.83
104	4.62	105	4.14	106	1.54	108	1.25
109	2.41	110	11.26	111	4.43	112	19.25
113	42.06	114	4.14	115	2.41	116	1.25
117	5.29	118	1.06	119	2.60	120	1.35
124	2.60	125	3.27	126	3.46	127	2.89
128	3.95	129	1.15	131	0.87	133	1.15
135	0.87	139	2.79	140	42.93	141	100.00
142	10.39	145	2.21	155	0.96	157	1.73
158	0.96	162	1.54	163	0.87	176	2.02
177	2.89	191	0.87	205	0.87		