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Boron coordination compounds derived from organic molecules of biological interest

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Contents

Abstract . . . 86
1. Introduction . . . 86
2. Reaction of boron compounds with difunctional ligands . . . 87
   2.1 Reactions with ethanolamines . . . 87
   2.2 Reactions with phenolamines . . . 88
   2.3 Reactions with *o*-substituted anilines . . . 89
   2.4 Reactions with pyridine derivatives . . . 90
   2.5 Reactions with ephedrines . . . 90
   2.6 Reactions with aminoacids . . . 92
   2.7 Reactions with hydroxyacids . . . 93
   2.8 Diphenylborinic esters derived from ephedrines and *pseudo*ephedrines . . . 94
   2.9 Diphenylborinic esters derived from pyridylalcohols . . . 95
3. Polycyclic compounds . . . 96
   3.1 Reactions with diethanolamines . . . 96
   3.2 Reactions with diethylenetriamines . . . 97
   3.3 Reactions with 2,2′-diphenolamine . . . 98
   3.4 Reactions with iminodiacetic acids . . . 98
   3.5 Reactions with ethanolphenolamines . . . 99
   3.6 Boron spiranic compounds . . . 101
   3.7 Synthesis of *pseudo*atranes . . . 102
4. Boron coordination to nitrogen heterocycles . . . 103
   4.1 Borane coordination to optically active oxazolidines . . . 103
   4.2 *N*-borane opening reactions in five membered rings . . . 105
   4.3 Borane imine adducts . . . 108

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4.4 Boron imidazole derivatives 108
4.5 Determination of the relative acidity of boron Lewis acids in pyridine complexes 114
4.6 Borane aniline complexes 114
4.7 Six-membered ring N–BH_3 complexes 115
5. Phosphorus–borane coordination complexes 120
Acknowledgements 122
References 122

Abstract

Herein we describe our findings in the study of new boron coordination complexes derived from organic molecules of biological interest. The reported compounds have a coordinative bond between an acidic tricoordinated boron and a nitrogen, oxygen, sulfur or phosphorus atom. It is a summary of 17 years of investigation on this subject in our department. We are interested in the study of the boron coordination effects on organic molecules, in their stereochemistry, electronic density, atomic hybridization and spectroscopic behavior.

Keywords: Nitrogen–boron compounds; Phosphorus–boron compounds; Boron heterocycles; Boron hydrides

1. Introduction

By combination with its neighboring elements in the periodic table boron results in an important number of molecules. The acidic tricoordinated sp^2 boron atom coordinates to organic compounds bearing lone pairs. Boron forms coordinative bonds with nitrogen, oxygen, sulfur or phosphorus atoms with small charge separations. Boron coordination transforms the structure of organic molecules, as for example neutralizing the basic centers or forming heterocycles. It also changes the physicochemical properties of the ligand as in solubility or reactivity. For a given reaction, many different compounds can be formed by changing only the reaction conditions or the reagents ratio.

The stereoselective synthesis of optically active boron compounds bearing B–H bonds is important in the development of reducing agents. We have contributed some new examples of optically active boron hydrides used as chiral reducing agents [1–4].

Coordination fixes the configuration at the boron atom and at the coordinating heteroatom. These configurations and even those of the neighboring atoms can be assigned by NMR, thus boron functions as a stereochemical probe. We have reported some examples where boron and nitrogen atoms are tetracoordinated stereogenic centers of stable configuration [3,5–18].

In some of the coordination systems the boron atom acts as a pseudometallic cation BX_2^+ (X = electroattracting group) that forms complexes with bidentate ligands. These compounds provide good diamagnetic models for the study of metal coordination using NMR spectroscopy [19,20].

In the study of dynamic systems such as inversion of atomic configuration, helixes interconversion, conformational and tautomeric equilibria, hydrogen bonding, etc. boron coordination plays an important role in freezing these processes, trapping conformers or tautomers or fixing the inversion of the configuration in labile atoms [7,8,15–17,21–33].

Organic boron compounds can be studied by multinuclear NMR techniques. Particularly, ^{11}B-NMR provides valuable structural information because of its sensitivity to electronic and steric effects as well as to the boron coordination number [34,35]. The structures of several new compounds have been determined by X-ray diffraction analyses [3,14,18–20,26,31,36–40].

In heterocycles borane coordination promotes ring opening and alkylation of amines [13,28,41]. It also provides information on the basic sites and electron density distribution in organic molecules [6,8–11,25,27,36,41–48].

2. Reaction of boron compounds with difunctional ligands

2.1. Reactions with ethanolamines

One of the aims of our investigation was to develop methods to obtain BH_2 heterocycles as the one shown in Fig. 1. In search of these compounds we discovered that the reactions of ethanolamines with boron compounds afford with high regioselectivity different derivatives depending on the reaction conditions and the nature of the reagents. In our hands, all attempts to obtain the BH_2 heterocycles derived from ethanolamines (Fig. 1) were unsuccessful, because the $ROBH_2$ group is unstable and disproportionates to the corresponding borate and borane compounds [6].

The reaction of three equivalents of aminoalcohol and four of BH_3–THF at -20°C gives borate *N*-boranes. The ^{11}B-NMR spectra show two signals, one for the borate group near $+18$ ppm and another for the N–BH_3 group. The chemical shift of the latter depends on the N-substitution and can be found in the range of -8 to -19 ppm, whereby the lower frequency signals belong to primary amines. Alkaline hydrolysis of the borate *N*-boranes afforded ethanolamine N–BH_3 which can also be prepared directly from reaction with BH_3–DMS (Fig. 2). Equimolar reactions of ethanolamines and BH_3–THF, provide di-N–BH_3 borates with a strong N-coordination, as is denoted by the shift of the coordinated borate group signal (between $+5$ and $+7$ ppm) [6] (Fig. 3).

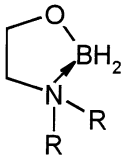


Fig. 1. Boron dihydride derived from ethanolamine, not yet prepared.

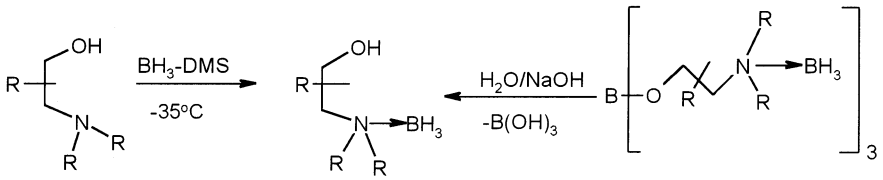


Fig. 2. Preparation of borate *N*-boranes and *N*-boranes derived from ethanolamines.

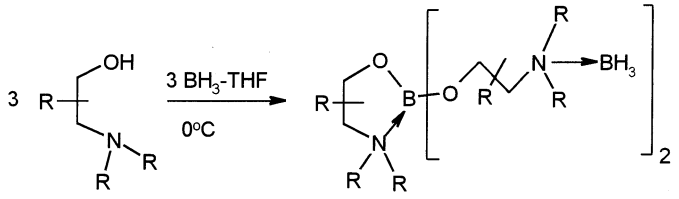


Fig. 3. Preparation of di *N*-borane borates derived from ethanolamines.

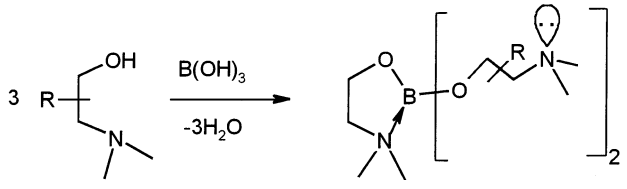


Fig. 4. Borates derived from ethanolamines present a fluxional intramolecular coordination of the three nitrogen atoms to the boron atom.

The reaction of ethanolamines and $B(OH)_3$ in refluxing benzene results in the corresponding borates and their ^{11}B-NMR spectra show an N-borate coordination. The ^{1}H-NMR spectra show no difference between coordinated and free ligands and this fact was attributed to a fast exchange between the three ligands. The intramolecular nature of the coordination was demonstrated by using model reactions where intramolecular coordination was not possible [6] (Fig. 4). A similar phenomenon was observed for the borate derived from 4-hydroxypiperidine [25] (Fig. 5).

2.2. Reactions with phenolamines

In our further search for ligands to stabilize the $ROBH_2$ group we have investigated the preparation of more acidic boron groups by binding the boron to a weak conjugate base as a phenoxy or carboxylic group in a rigid chelate bearing a strong basic atom. Thus, we have prepared dihydride borinic esters from phenol derivatives. The reaction products gave triplets in the ^{11}B-NMR spectra indicating BH_2 groups, whereby the strong coordinative bond was confirmed by the shift to lower frequencies in comparison to model compounds in which coordination is not possible [49] (Fig. 6).

2.3. Reactions with o-substituted anilines

In this context, we were also interested in the reaction of BH_3–THF with *o*-substituted anilines. We have found that phenolamines, thiophenolamines and phenylenediamines afforded a benzoborole with one B–H group. The reaction pathway passes through N–BH_3 and N–BH_2 intermediates, the latter being observed as a stable compound only for X = S [50,51] (Fig. 7). In boroxazolines, the sp^2 boron and its neighboring atoms are in a plane, so that the heteroatoms share electron density with the boron through π bonds decreasing its Lewis acidity. In the phenolamine boroline the N–B retrocoordinative bond can be broken by addition of a phenol molecule to give tetracoordinated B and N atoms [50] (Fig. 8).

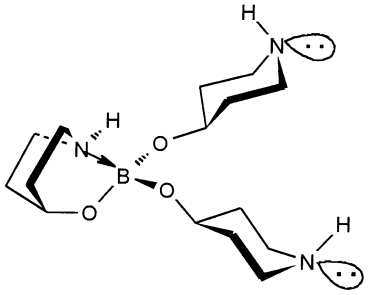


Fig. 5. Fluxional intramolecular coordination of the three nitrogen atoms to the borate derived from 4-hydroxypiperidine.

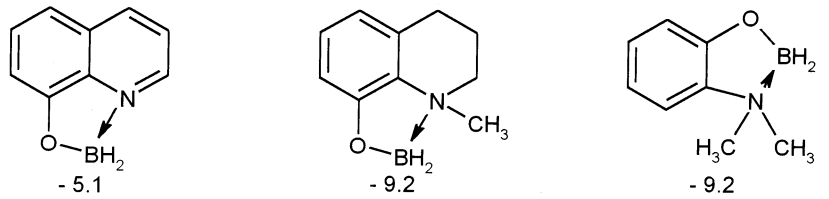


Fig. 6. ^{11}B-NMR data (ppm) and structures of dihydride phenolborinic esters with an N–B coordinative bond.

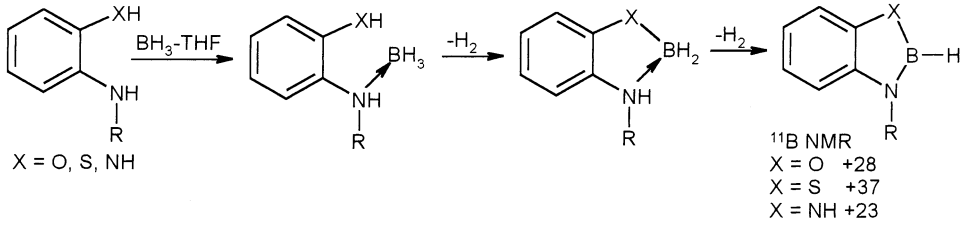


Fig. 7. Pathway of the reaction of borane with *o*-substituted anilines.

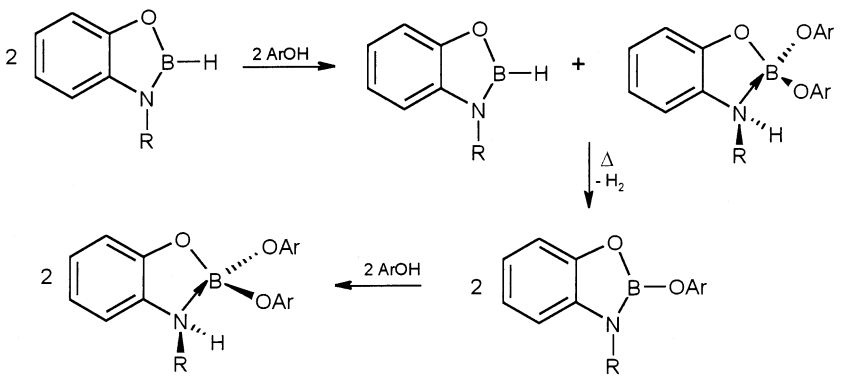


Fig. 8. Phenol addition reactions to boroxazoline derived from phenolamine.

2.4. Reactions with pyridine derivatives

Searching for conditions that allow the preparation of borinic dihydrides, molecules derived from pyridines bearing an alcohol or a carboxylic acid group were prepared in order to study the role of the conjugated base and the ring size in the stabilization of the O–BH_2 group. Therefore, reactions of pyridylmethanols with BH_3–DMS or BH_3–THF under soft conditions were investigated by ^{11}B-NMR. The first derivatives observed were the N–BH_3 adducts, followed by the triplets corresponding to OBH_2 esters ($\approx +3$ ppm), that continued to react to borates. The reactions with BH_3–DMS gave borate bis-*N*-boranes with an intramolecular coordination. In the reactions with BH_3–THF only the borate *tris*-*N*-boranes were obtained indicating that pyridine–borate has a stronger coordinative bond than BH_3–DMS [46] (Fig. 9). Investigation of pyridylmethanol and pyridyl-2-ethanol boron derivatives by VT-NMR showed that the B–N coordinative bond is more stable in five than in six membered rings ($\Delta\Delta G^{\neq} = 28$ kJ mol^{-1}). Pyridine-2-carboxylic acids gave exclusively the OBH_2 anhydrides, which were isolated as very stable species, indicating the importance of an acidic boron atom and the appropriate geometry of the N–B coordinative bond for the stabilization of the OBH_2 group [46] (Fig. 10).

2.5. Reactions with ephedrines

Amine boranes derived from optically active ethanolamines as ephedrines are stereochemically interesting compounds. If the nitrogen has two identical substituents they become diastereotopic by coordination, as has been observed in the ^{1}H- and ^{13}C-NMR spectra. If the three N-substituents are different, two diastereomers appear after BH_3 coordination, which are stable compounds that can be separated without hydrolysis or N-epimerization [6,7,16] (Fig. 11).

Two *N*-epimers N–BH_3 adducts of ephedrine or *pseudo*ephedrine have been obtained and separated. However, we were unable to crystallize them in order to

determine the N-configuration by an X-ray diffraction study [7]. Therefore, we decided to deduce it from the NMR data. We first determined by molecular mechanic calculations the more stable conformer of each N-epimer and then estimated the electronic and steric effects of the BH_3 coordination on the chemical shifts of ^{1}H, ^{11}B and ^{13}C spectra for that conformer. The effects were systematic, as was also found for oxazolidines $N-BH_3$ [9,10] and the N-configuration of each epimer could be established [16] (Fig. 12).

We have observed that D_2O addition to the ephedrine or to the *pseudo*ephedrine $N-BH_3$ adducts results in an immediate exchange of the OH hydrogen by deu-

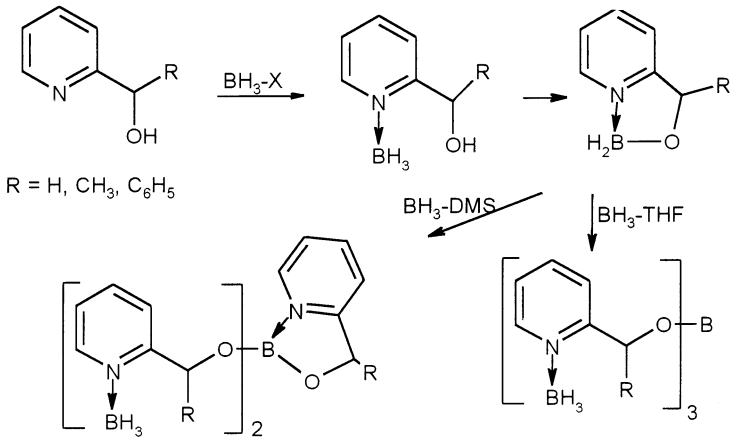


Fig. 9. Reaction products of pyridylmethanols and borane.

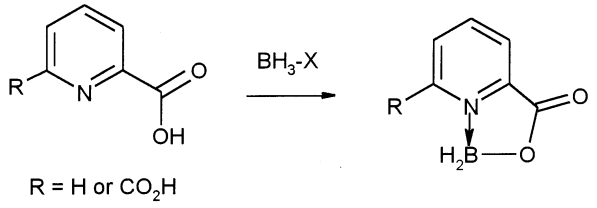


Fig. 10. Preparation of dihydride pyridine-2-carboxylic borinic esters.

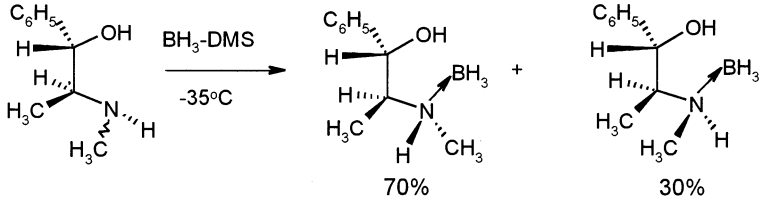


Fig. 11. *N*-epimers of *N*-borane adducts derived from *pseudo*ephedrine.

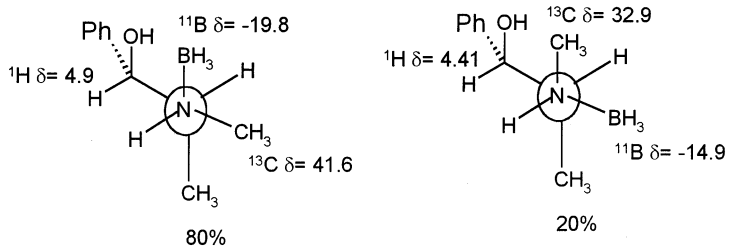


Fig. 12. The N-configurations of N–BH_3 adducts derived from ephedrine were deduced from ^{1}H-, ^{13}C- and ^{11}B-NMR data.

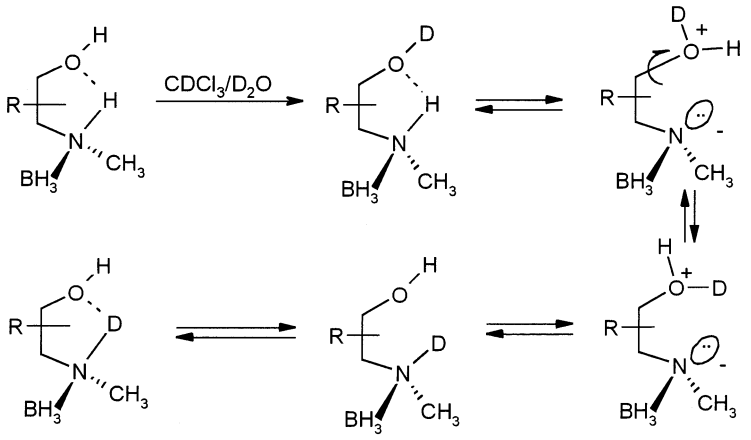


Fig. 13. Deuteration mechanism proposed for ephedrine N–BH_3 adducts.

terium, whereas the NH hydrogen is only slowly substituted. Examination of other resonances shows that deuteration does not involve N-epimerization. However, deuteration and N-epimerization occur very fast in the presence of NaOD. The experiments showed that the energy of inversion of the B–N anion is low compared to the deprotonation–protonation process and that the OH group assists the N-deuteration. In the presence of base, deuteration is fast because the O-anion removes the hydrogen from N–H, and therefore, deuteration becomes a slower process than N-epimerization [7,16] (Fig. 13).

2.6. Reactions with aminoacids

Preparation and structures of diphenylborinic anhydrides derived from α-aminoacids were reported. These cyclic compounds have strong N → B coordinative bonds (Fig. 14). In compounds **a** of Fig. 14, R is an alkyl or aryl group bearing different functional groups such as an amine, carboxylic, hydroxylic or thiomethyl ether group [52]. The boron derivatives prepared from L-ornithine, L-methionine, kainic acid and 2,6-pyridinedicarboxylic acid have been studied by X-ray diffraction

[53] (Fig. 15). A comparison of the structural data of boroxazolidones with the corresponding boroxazolidines, bicyclic boronates and tricyclic borates has shown that in the first ones the B–O bond is longer in comparison to similar complexes with a boroxazolidine ring. At the same time the N→B bond length is shorter indicating that the hydrolytic stability of the complexes with boroxazolidone rings is enhanced.

2.7. Reactions with hydroxyacids

Formation of dioxaborolanes by reaction of optically active α-hydroxyacids and BH_3–DMS afforded very acidic boron atoms which gave strong complexes with Lewis bases. Reduction of the carbonyl group is avoided by adding only one equivalent of BH_3–DMS at low temperature. With an excess of BH_3 the corresponding 1-phenyldioxaborolane derivative is obtained by cyclization and carbonyl reduction [54] (Fig. 16). The quinic acid gives different BF_2 anhydrides [54,55] (Fig. 17). Reaction products depend on the experimental conditions. The phenyl boronic anhydrides bound to hydroxyacids are very acidic and the solvent (X = THF or DMSO) coordinates to them (Fig. 18).

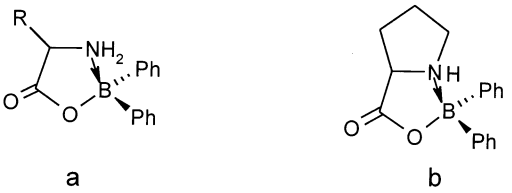


Fig. 14. Structural types of diphenylborinic anhydrides derived from aminoacids.

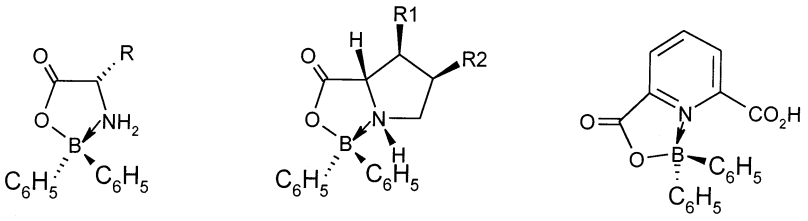


Fig. 15. Structure of diphenylborinic anhydrides derived from aminoacids.

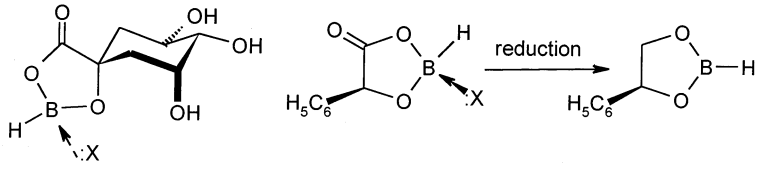


Fig. 16. Examples of two boron hydrides derived from hydroxyacids and the reduction product of one. X is THF or DMSO.

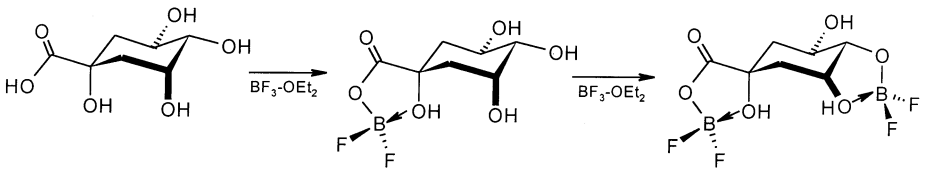


Fig. 17. Difluoroborinic anhydrides derived from quinic acid.

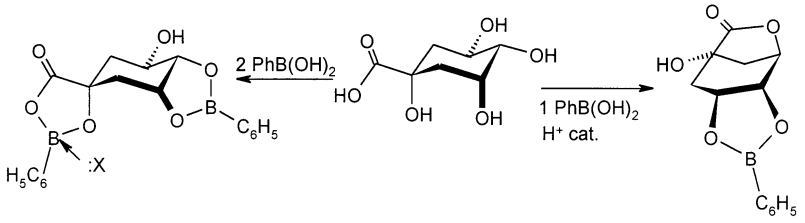
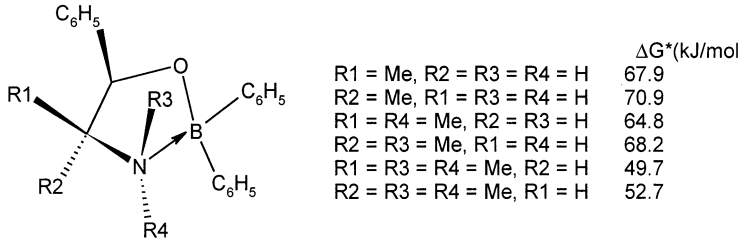


Fig. 18. Phenylboronic heterocycles derived from quinic acid.



	ΔG*(kJ/mol
R1 = Me, R2 = R3 = R4 = H	67.9
R2 = Me, R1 = R3 = R4 = H	70.9
R1 = R4 = Me, R2 = R3 = H	64.8
R2 = R3 = Me, R1 = R4 = H	68.2
R1 = R3 = R4 = Me, R2 = H	49.7
R2 = R3 = R4 = Me, R1 = H	52.7

Fig. 19. Stereoisomers of diphenylborinic esters derived from ephedrines and the free activation enthalpy of the B–N bond obtained by VT-NMR.

2.8. Diphenylborinic esters derived from ephedrines and pseudoephedrines

Information on N–B intramolecular coordination in five membered rings has been obtained from diphenylborinic esters with an acidic boron atom that provides a strong N–B bond. The complexes are diamagnetic models for metal coordination. Several examples of diphenyl ephedrine borinic esters with a different degree of methyl substitution on the nitrogen atom have been studied [18]. In order to obtain information on substituent effects around the N–B bond coordination, their geometries, electrostatic charge, bond order obtained from the Mulliken population analysis and hybridization of the different atoms were calculated. Molecular ab-initio calculations were performed on these compounds [56]. In addition six X-ray diffraction structures were obtained. The ^{15}N-NMR is not sensitive to the N-substitution, free amines appear between -347 and -352 ppm, however the B-coordination shifts the signals ≈ 20 ppm to higher frequencies [18] (Fig. 19). The ^{11}B-NMR data were very similar for all N–B coordinated compounds ($\delta = +5$ to

+9.6 ppm) and are not affected by N-substitution. The derivatives showed diastereotopic signals for the B-phenyl groups. Compounds with two $N-CH_3$ groups presented a single signal for both groups at r.t. in ^{13}C-NMR, but at low temperature they became non-equivalent. The $N-CH_3$ *cis* to the $C-CH_3$ appears at lower frequencies due to a steric effect.

The reaction of ephedrine and diphenylborinic acid afforded two *N*-epimers, whereas the reaction of the *pseudo*ephedrine gives stereoselectively only one, with the two methyl groups in *trans* position. The B–N free activation enthalpy can be measured by VT-NMR experiments (Fig. 19). It is higher for NH_2 and lower for $N-CH_3$ ligands. The *pseudo* compounds form a more stable coordination because of their *trans* relationship of the C-substituents [18].

The 2-phenyl-1,3,2-oxazaborolines derived from (+) *nor*ephedrine, (+) ephedrine and (+) *pseudo*ephedrine and phenylboronic were prepared. Addition reactions of CH_3OH and H_2O to the B–N bond were investigated and the reactions afforded the corresponding boronic acid or esters. The reaction of the *nor*ephedrine derivative with water provides a mixture of the two possible isomers in equilibrium, whereas methanol gave only one isomer (Fig. 20). The ephedrine B-heterocycle gave two isomers with H_2O, whereas with CH_3OH only one of four isomers was obtained (Fig. 21). In contrast, same reactions with the *pseudo*ephedrine derivatives are completely stereoselective [5] (Fig. 22).

2.9. Diphenylborinic esters derived from pyridylalcohols

In order to get more information on the ring size effect on the chelate stability, the diphenylborinic esters derived from 2-methanolpyridine and 2-ethanolpyridine

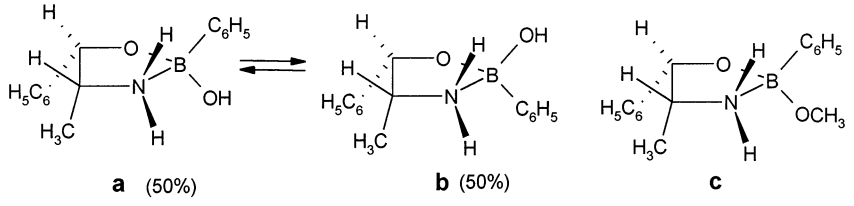


Fig. 20. a and b, stereoisomers of *nor*ephedrine phenylboronic esters. c, only one isomer was obtained of *nor*ephedrine methanol boronic ester.

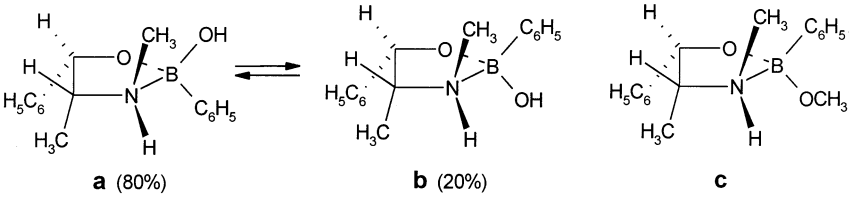


Fig. 21. (a,b) Stereoisomers of ephedrine phenylboronic esters. (c) Only one isomer was obtained for ephedrine methanol boronic ester.

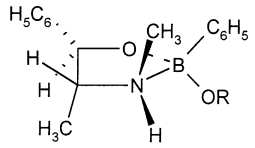


Fig. 22. Phenylboronic esters derived from *pseudo*ephedrine present only one stereoisomer.

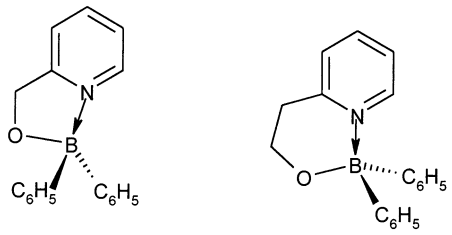


Fig. 23. Diphenylborinic esters of pyridyl alcohols, five membered rings formed by N–B coordination bonds are more stable than six membered ones.

were prepared and the B–N bond energy compared. The ^{11}B-NMR data were in accordance with tetracoordinated boron atoms ($\delta + 13.5$ and $+ 6.2$ ppm), (Fig. 23). The X-ray diffraction structures show that the N–B length for the five membered ring is 1.642 Å whereas for the six membered ring it is 1.685 Å. The differences in bond length and bond energy between five and six membered rings are explained by the TBI (through-bond interactions) theory. The latter considers that if an odd number of bonds are involved between the N and B atoms, the antisymmetrical combination of the atomic orbitals of N and B gives the lower molecular orbital energy and forms the HOMO before ring closure. In order to form the coordinative bond both electrons of the antisymmetrical HOMO have to be promoted to the LUMO and therefore the bond energy is smaller, as it was found in the experiments [26].

Macrocyclic oligoboronates can easily be formed, when aminodialcoholic ligands of appropriate geometry are present. A key point is the formation of a dative N → B bond providing rigidity to the structure [57] (Figs. 24 and 25).

3. Polycyclic compounds

3.1. Reactions with diethanolamines

Reactions between thexylborane and diethanolamines in THF gave bicyclic compounds stabilized by N–B coordination. The strength of this bond depends strongly on steric effects, bulky substituents on boron or nitrogen atoms weaken this bond. Observation of the dynamic behavior by VT-NMR shows inversion of

the heterocycle that proceeds first by opening the N–B bond followed by ring inversion and closure of the N–B coordination. The free activation enthalpy values of these N–B bond have been calculated [22] (Fig. 26).

3.2. Reactions with diethylenetriamines

The first examples of 1,4,7,8-triazaborabicyclooctanes have been reported. The ring size induces a tetrahedral geometry of the boron, and N–B retrocoordination is inhibited giving a very electrodeficient boron atom. Normally, stabilization of similar phosphorus heterocycles is attended by dimerization. In the present compounds dimerization is avoided by bulky substituents, therefore the heterocycles

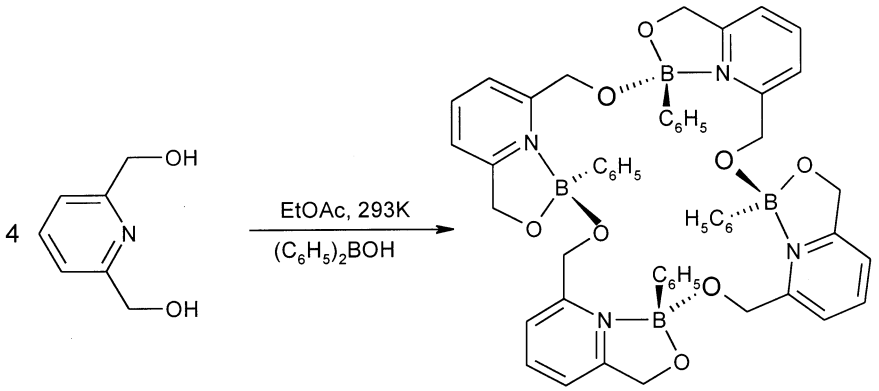


Fig. 24. Macrocyclic oligoboronates.

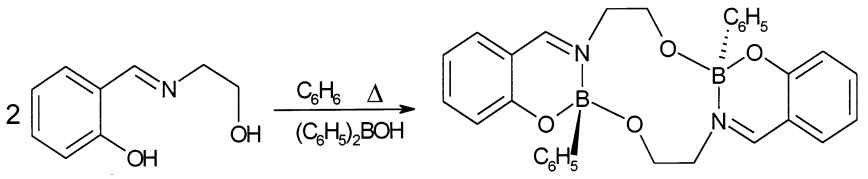


Fig. 25. Macrocyclic diboronates.

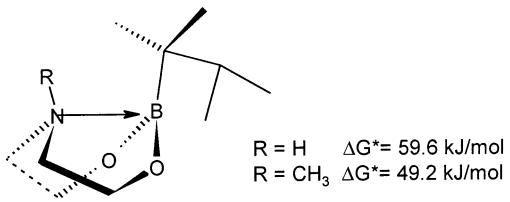


Fig. 26. Boron bicyclic compounds formed from diethanolamines. The free activation enthalpy of the N–B bond determined by VT-NMR is shown.

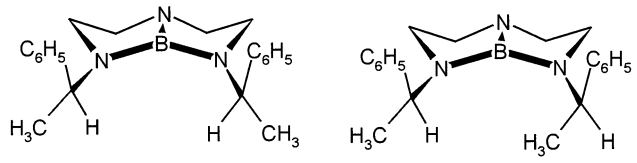


Fig. 27. First examples of 1,4,7,8-triazaborabicyclooctanes reported.

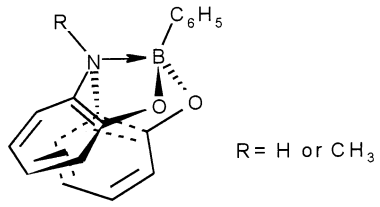


Fig. 28. Structure of 2,2′-diphenolamine phenylboronic esters.

could be isolated and studied. Their structures and conformations were established by ^{1}H-, ^{13}C- and ^{11}B-NMR. Examples of *meso* and optically active derivatives are shown [58] (Fig. 27).

3.3. Reactions with 2,2′-diphenolamine

We were interested in the question if N–B coordination is possible between a weak base such as a diaromatic amine and an acidic boron atom. The new bicyclic compounds derived from phenylboronic acid were very stable to hydrolysis and could be handled in air. Comparison of diphenolamine derivatives to those of diethanolamine indicates that the N-basicity is not the only relevant factor in the stability of nitrogen–boron coordinated heterocycles, rigid structures and the conjugated base of the ligand play an important role too. Structures were confirmed by X-ray diffraction analyses [39] (Fig. 28).

3.4. Reactions with iminodiacetic acids

Boron compounds react with iminodiacetic acids to give very stable and rigid bicyclic compounds as observed by the AB methylenic coupling pattern of the ring in ^{1}H-NMR. The compounds are stable even with bulky B-substituents. From the ^{1}H-NMR spectrum (200 MHz) at 130°C no ring opening and closing could be observed, indicating a very high energy for the N–B bond. In the N–H compounds coordination makes this proton less labile and coupling of it with the neighboring CH_2 is observed. By adding D_2O a H/D exchange occurs without ring opening or hydrolysis [24] (Fig. 29).

We decided to prepare ligands by the combination of an aminoacid moiety, which could guarantee high stability of the resulting boron complex and an optically active ligand such as an ephedrine in order to produce configurationally

stable chiral centers at the N and B atoms. Thus, the reaction of phenylboronic acid with ephedrine *N*-acetate afforded two isomers for each ephedrine and by fractional crystallization one isomer was isolated. The stereochemistry was determined from ^{1}H- and ^{13}C-NMR data and NOE experiments. The isomer obtained in higher yield corresponds to the one with the ring substituents on the *exo* face [12] (Fig. 30). The X-ray diffraction structure of the compound derived from *pseudo*ephedrine corresponds to that assigned from the NMR studies in solution [14].

3.5. Reactions with ethanolphenolamines

Addition of two ephedrine or *pseudo*ephedrine molecules to 1,4-catechol gave ligands that reacted with boronic acid to give pentacyclic compounds. The synthesis is stereoselective, it gives only one isomer, so that the nitrogen and boron atoms become stereogenic centers of fixed stereochemistry. Their configurations were established by ^{1}H- and ^{13}C-NMR. The compounds belong to the C_2 symmetry group and each one possesses eight stereogenic centers [11] (Fig. 31). A different arrangement of a phenyl group and two bicyclic optically active fragments has been prepared from hydroxyethylglycine ligands and 1,4-phenylenediboronic acid [14] (Fig. 32).

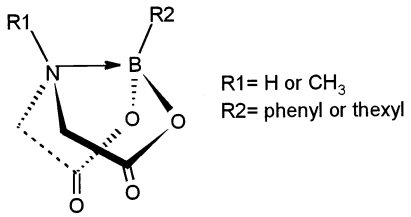


Fig. 29. Boronic anhydride derived from iminodiacetic acids.

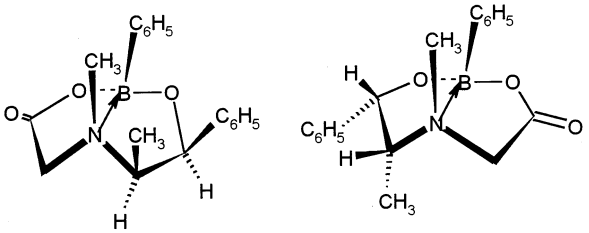


Fig. 30. Optically active boronic anhydrides derived from ephedrine *N*-acetate ephedrine.

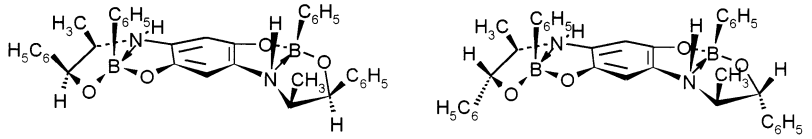


Fig. 31. Optically active pentacyclic boronic anhydrides derived from phenolephedrines.

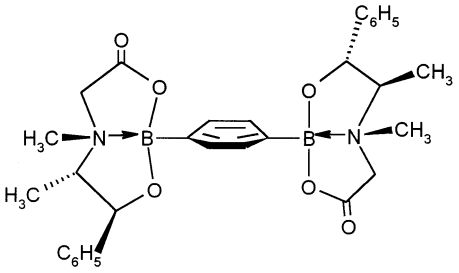


Fig. 32. Optically active benzo-bis-boronic esters derived from *N*-acetate ephedrine.

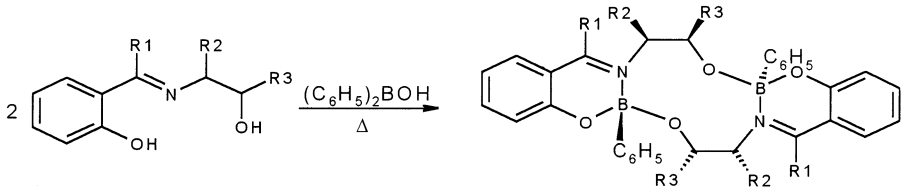


Fig. 33. Polycyclic phenylboronic esters derived from 2-salicylidene-aminoethanol.

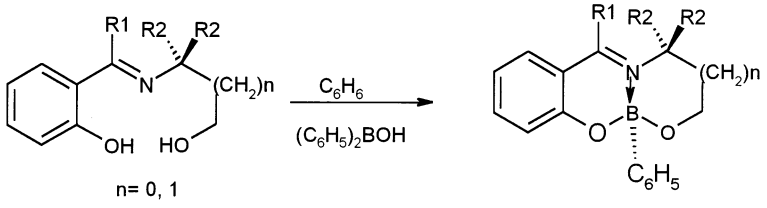


Fig. 34. Phenylboronic esters derived from 2-salicylidene-aminoethanol.

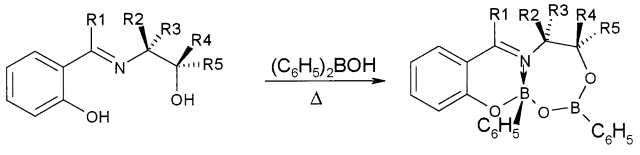


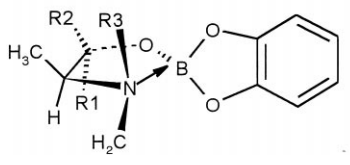
Fig. 35. Bis-phenylboronic esters derived from 2-salicylidene-aminoethanol.

A series of 2-salicylidene-aminoethanol derivatives of phenylboronic acid were prepared bearing substituents in different positions. Depending on the number and position of them in the ligand, three types of boronates have been obtained [57] (Figs. 33–35).

3.6. Boron spiranic compounds

Esters of boric and boronic acids react with alcohol amines in order to give spiranic compounds by internal coordination. Compounds derived from catecholborane and ephedrines were prepared. The rigid structure and an acidic boron atom fix the nitrogen configuration by a strong N–B coordination. The ephedrine derivative shows two isomers in $C_2D_2Cl_4$ at -30°C, whereby the isomer with two methyl groups in *trans* position is the predominating compound (75%). The *pseudo*ephedrine presents only one isomer with *trans* methyl groups even at -40°C (200 MHz). The *N*-methylephedrine and *N*-methyl-*pseudo*ephedrine show two diastereotopic N–CH_3 groups. Due to coordination, the ^{11}B-NMR signal is shifted about 10 ppm to lower frequencies indicating a strong coordination. The similar ^{11}B-NMR chemical shifts values for the NHMe and NMe_2 derivatives inform on the absence of steric interactions between the boron and nitrogen substituents as a consequence of the spiranic structure and the planar catechol. The steric effects between the methyl groups observed in the ^{13}C-NMR data allowed identify the stereoisomers. The B–N bond strength depends on the stereochemistry of the aminoalcohol, whereby the *pseudo*ephedrine with phenyl and methyl groups in *trans* position gives the stronger N–B bond [23] (Fig. 36). Similar VT-NMR experiments, on ethanol and propanolpyridine spiranic derivatives of catecholborane, show a very strong N–B bond. The data indicate that this bond is weaker in the compound with the six-membered ring in comparison to the five-membered one [26] (Fig. 37).

The reaction of catecholborane with *o*-substituted anilines gives other spiranic compounds, which were also prepared from catechol and the corresponding benzoborole [50] (Fig. 38). When two hydroxyacid molecules react with a borate, the corresponding spiroborates are formed [54] (Fig. 39). A series of new boron β-diketonates and tropolonates has been synthesized, crystallized and characterized



R1	R2	R3	ΔG* kJ/mol
H	Ph	H	61.4
H	Ph	Me	68.0
Ph	H	H	>80
Ph	H	Me	80.2

Fig. 36. Spiranic compounds derived from catecholborane and ephedrine, the free activation enthalpy of the B–N bonds obtained by VT-NMR measurements are shown.

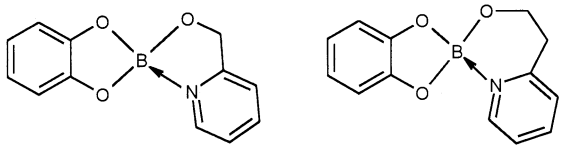


Fig. 37. Five and six membered spiranic compounds derived from catecholborane.

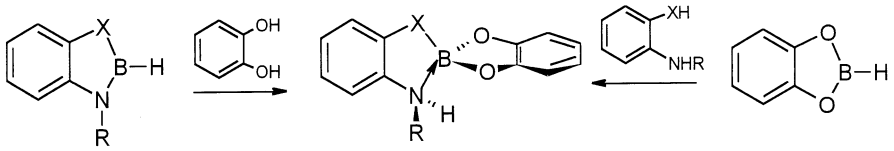


Fig. 38. Spiranic compounds derived from catecholborane and *o*-substituted aniline.

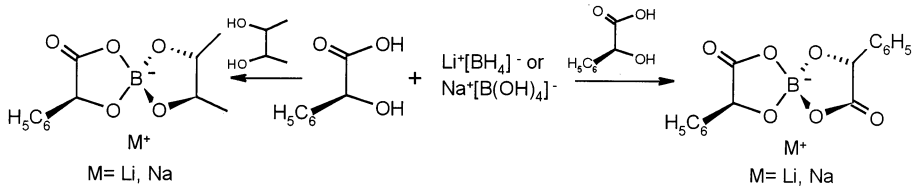


Fig. 39. Spiranic borate compounds derived from optically active hydroxyacids.

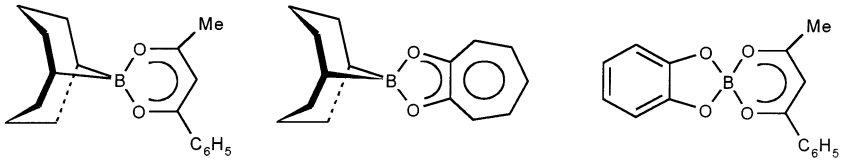


Fig. 40. Boron spiranic β-diketonate and tropolonate structures.

by X-ray diffraction analyses [59] (Fig. 40). In the boron tropolonates the positive charge is delocalized in the tropylium ring, while both oxygen atoms carry a negative charge. This is in contrast to corresponding metal chelates, where the delocalization includes also the oxygen atoms.

3.7. Synthesis of pseudoatranes

Triethanolamine reacts with BH_3–THF to give an ester that has an internal N→B bond (boratrane) [60]. The similar phosphorus heterocycle presents a N–P coordination when the phosphite group is P–BH_3 bonded (phosphatrane) [61a]. We have prepared analogues boron and phosphorus derivatives of triphenolamine but no internal coordinative bond was found in solution (r.t.). Thus, they are examples of *pseudo*atrane structures [47] (Fig. 41). Therefore Bürgi has reported that the same compound presents an N–B coordination in the ^{11}B-NMR spectra recorded below 210 K [61b]. X-ray diffraction structure of the crystals indicates an N–B bond, [61b].

In order to observe a conformational equilibrium between the chiral helixes of the boron *pseudo*atrane, benzylamine was added to the boron atom, with the idea to observe diastereotopic CH_2 protons, if the coordination was strong enough to freeze the exchange. Unfortunately, we could not see any effect besides the B–N

coordination. The basic sites were investigated adding borane, for the boron compound an $N \rightarrow BH_3$ complex was found while for the phosphorus compound the first molecule of borane afforded the $P-BH_3$ complex. In the latter any inductive effect of the $P-BH_3$ group on the formation of an internal $N \rightarrow P$ bond was found. Addition of a second borane group produced an insoluble compound that could not be characterized [47].

4. Boron coordination to nitrogen heterocycles

4.1. Borane coordination to optically active oxazolidines

Oxazolidines play an important role as optically active catalyzing agents or reagents for many asymmetric transformations. They have a basic nitrogen that coordinates to borane giving a stereogenic atom of stable configuration. The borane coordination helps to determine the configuration of the vicinal C2 and C4. Unambiguous structural determination of $N-BH_3$ oxazolidines has been performed by ^1H- and ^{13}C-NMR. Condensation of an aldehyde with ephedrine or *pseudo*ephedrine affords two isomers in equilibrium, in each pair one of them predominates (95%). The stereochemistry of C-2 was deduced by NOE experiments and was confirmed by the BH_3 adducts structure [8] (Fig. 42). By addition of BH_3–DMS at low temperature two *N*-epimers were obtained in each case. Thereby one epimer in each pair was always stable enough to be isolated. The second one was the kinetic product that underwent conversion to the thermodynamic one. The kinetic isomer was isolated only for the *pseudo*ephedrine oxazolidines. It appears that the kinetic isomer is formed, when the BH_3 approaches the N-lone pair in the most stable configuration of these oxazolidines with the methyl groups in *trans* orientation (Fig. 43). If the boron atom is located on a crowded face its chemical

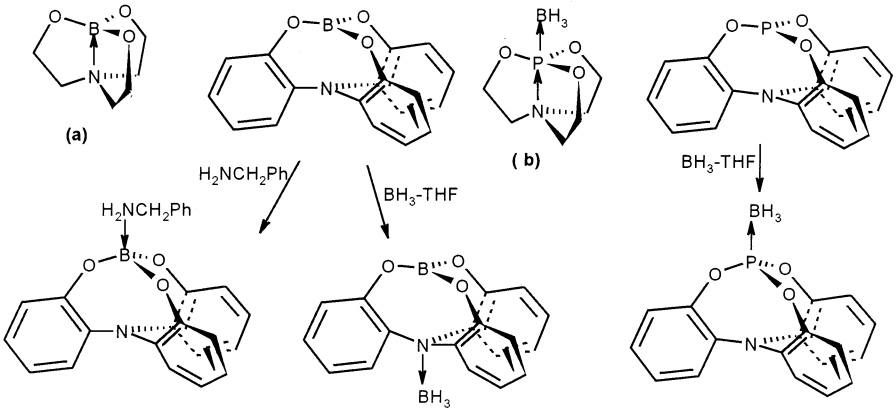


Fig. 41. Bora- and phospha*pseudo*atranes derived from triphenolamine. The structures are compared with those of (a) bora- [60] and (b) phosphatranes [61].

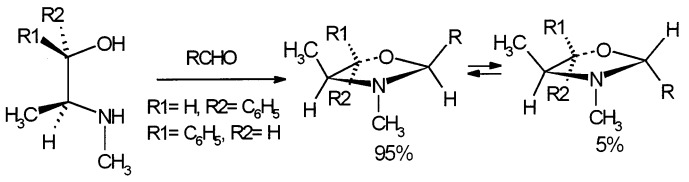


Fig. 42. Isomeric mixture in equilibrium of C-2 substituted oxazolidines derived from ephedrines.

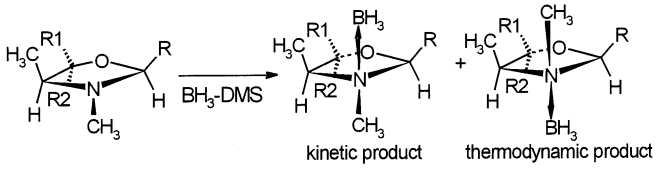


Fig. 43. *N*-epimers of N–BH_3 oxazolidines.

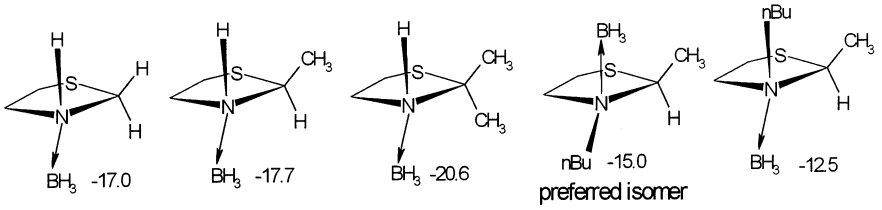


Fig. 44. ^{11}B-NMR shifts (ppm) and stereoisomers of N–BH_3 adducts of thiazolidines.

shift is displaced by 2.5–5 ppm to lower frequencies related to the shift of the compound bearing the borane group in the other face. The vicinal protons on the same side of the borane group are shifted by about 1 ppm to higher frequencies, due to the electronic effect produced by the proton–hydride interaction through the space [31]. ^{13}C-NMR is sensitive to steric effects and provides also information on the position of neighboring atoms. From the ^{13}C-NMR spectra it was found that BH_3 and CH_3 groups are very similar as far as their steric requirements are concerned. A parallel NMR behavior of the N–BH_3 oxazolidine adducts and the N–CH_3 oxazolidinium salts has been found, that indicates that steric interactions play the most important role in the NMR properties of these ring systems [8–10].

We have been studied how the interaction of N and S atoms bound together through a CH_2 group influences their basic behavior. Therefore we decided to extend our research to these heterocycles. We investigated the borane addition to thiazolidines. It was found that the borane prefers to coordinate the N atom stereoselectively in position *trans* to the C-methyl group [62] (Fig. 44). The reactions of borane with differently C-2 substituted diazolidines were performed with the aim to study the stereochemistry of the mono- and diborane adducts. With one equivalent of borane, the N–BH_3 group was stereoselectively added at the opposite face of the C-2 substituent [63] (Fig. 45).

When C-2 is a CH_2, or a CHR group, the monoborane is stable, but for CR_2, the adduct is weak and ring opening reactions occur [62]. For *N*,*N*-dimethyldiazolidine the two isomers of the BH_3 diadduct have been obtained and their structures determined by ^{1}H-, ^{13}C- and ^{11}B-NMR. The *trans* isomer of the diadduct is in conformational equilibrium whereas the *cis* isomer is anchored [63]. Dithiolanes give S–BH_3 adducts as it is denoted by the ^{11}B-NMR resonances (δ between -21 and -25 ppm), however when C-2 is disubstituted the corresponding complexes are not formed [62] (Fig. 46).

4.2. N-borane opening reactions in five membered rings

Diazolidines with two substituents at C-2 with an excess of BH_3–THF give N–BH_3 boradiazolidine compounds. They exhibit two ^{11}B signals, a triplet (δ between $+2.7$ and $+5.9$ ppm) for the BH_2 group and a quartet for the N–BH_3 group (δ between -9.9 and -18 ppm), and are isostructural with N–BH_3 coordinated diazolidines. The boron heterocycles are resistant to hydrolysis at r.t., however, they are converted to the corresponding aminoborane at 70°C [62] (Fig. 47). A similar reaction is observed for thiazolidines (Fig. 48). By heating, these compounds are transformed into the B–H heterocycles.

The reduction reactions of benzothiazolium and thiazolinium cations with $NaBH_3CN$ give a mixture of reduced compounds and BH heterocycles with stereogenic centers at nitrogen and boron. One interesting feature of these boron heterocycles is their stability to basic or acid hydrolyses [13] (Fig. 49).

The synthesis of boroxazolines derived from ephedrine amides with substituents of different size has been reported [1] (Fig. 50). We have found that the boroxazolines can add borane to the nitrogen atom in order to give the diborane (Fig. 51). Experiments with BD_3 showed that all the hydrides are in a fast exchange [2]. The reaction of 1,3-thiazolidine-2-thione with BH_3–THF afforded a stable thione–BH_3

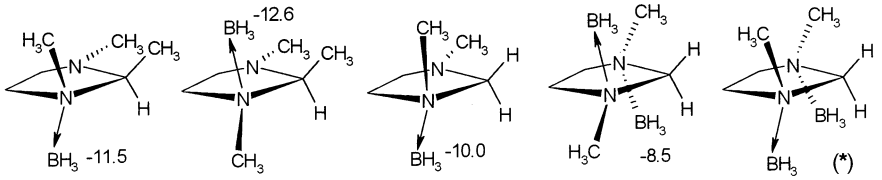


Fig. 45. ^{11}B-NMR shifts (ppm) and stereoisomers of N–BH_3 adducts of diazolidines, ^{11}B signal was not observed.

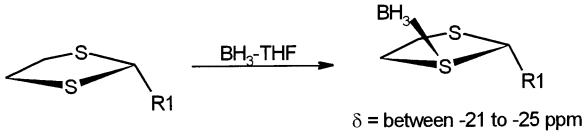


Fig. 46. ^{11}B-NMR shifts (ppm) and stereoisomers of S–BH_3 adducts of dithiolanes.

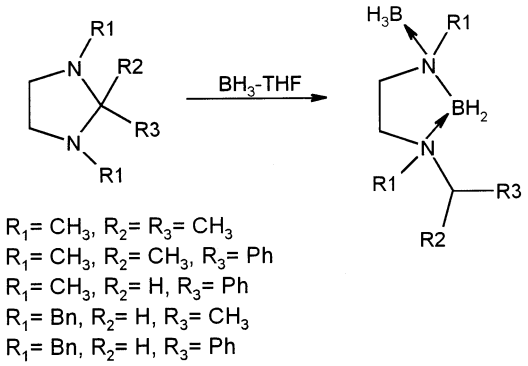


Fig. 47. Boron dihydride from the opening reducing reaction of diazolidines with BH_3–THF.

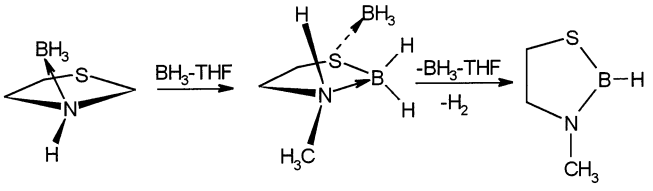


Fig. 48. Boron hydrides from the opening reactions of thiazolidine with BH_3–THF.

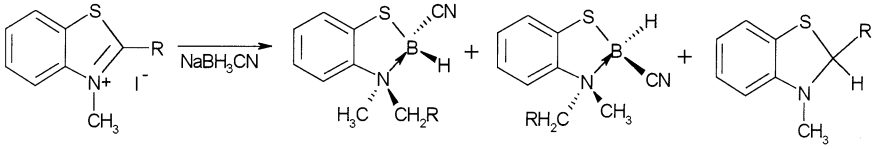


Fig. 49. Reducing reactions of benzothiazolinium cations with $NaBH_3CN$.

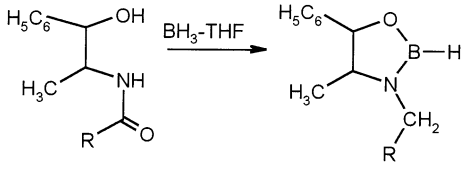


Fig. 50. Synthesis of B–H boroxazolidines from hydroxyamides.

complex that by heating is transformed into the BH_2 derivative with ring opening [3] (Fig. 52). Thio*pseudo*ephedrine reacts with BH_3–THF to give a series of optically active hydrides. The X-ray diffraction structure of the boron dihydride of *pseudo*ephedrine was obtained [3] (Fig. 53). Preparation of boroxazolines by

reduction of the corresponding cyclic imines has been reported [4] (Fig. 54). Similar reactions were performed for cyclic imines of thio- or seleno-heterocycles (Fig. 55). The selenoboroline crystallized on standing in solution as a dimer and its X-ray diffraction structure was determined [4] (Fig. 56).

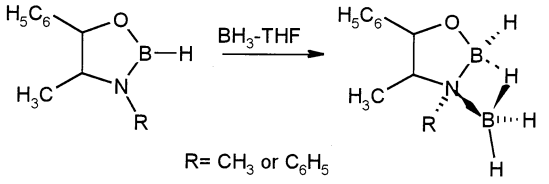


Fig. 51. Borane addition to boroxazoline.

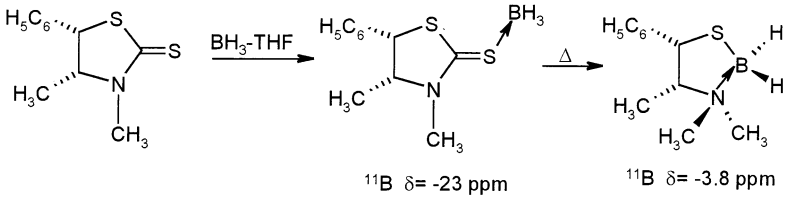


Fig. 52. Boron hydrides from the reaction of BH_3–THF and thiazolidine-2-thione.

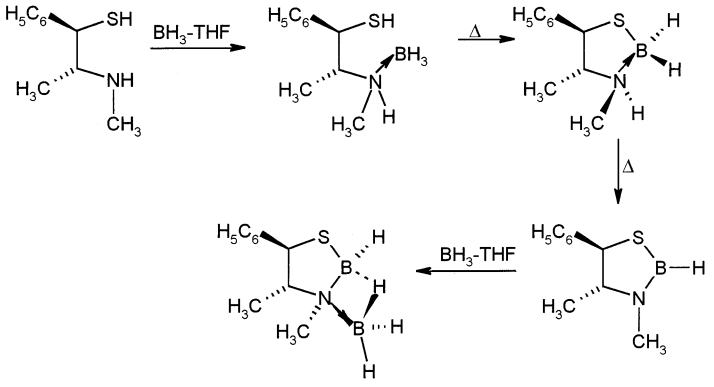


Fig. 53. Boron hydrides derived from thio*pseudo*ephedrine.

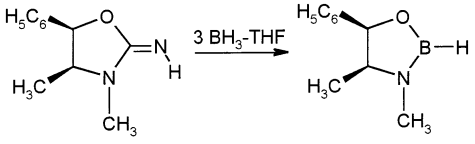


Fig. 54. Boroxazoline prepared from oxazolidine-2-imino ephedrine.

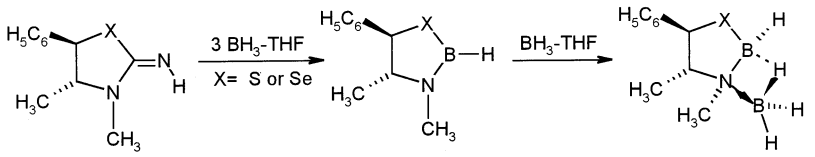


Fig. 55. Heteroborazolines prepared from heteroazolidine-2-imino *pseudo*ephedrine.

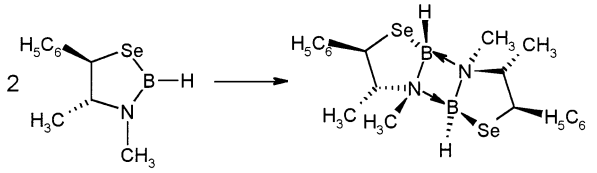


Fig. 56. Structure of the dimer of selenazoboroline derived from *pseudo*ephedrine.

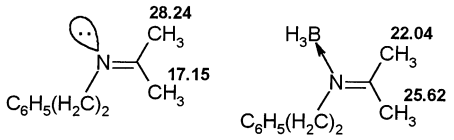


Fig. 57. Imine and its borane adduct, the ^{13}C-NMR signals of the methyl groups are shown.

4.3. Borane imine adducts

The chemical shift effects of N–BH_3 complexes have been used for the assignment of imine geometries. Imines are basic enough to form stable N–BH_3 adducts that can be isolated without hydroboration of the unsaturated bond. In non-symmetric imines borane addition gives two isomers. In order to study the effect of the borane group on the substituents of the imines accurately, we have performed some ^{1}H-, ^{13}C- and ^{11}B-NMR experiments to establish unambiguously the configuration of the free non-symmetric imines. Although iminium salts have lower isomerization barriers than free imines, borane addition does not change the isomer ratio indicating that borane adducts retain the imine configuration. We have observed two effects in the ^{1}H- and ^{13}C-NMR spectra of the adducts, a steric effect of the BH_3 on the *syn* substituents which are shifted to lower frequencies and a *trans* inductive effect of the borane that shift the *trans* substituent to higher frequencies [27] (Fig. 57).

4.4. Boron imidazole derivatives

The electronic effect of the N-lone pair and the steric effect of the N-substituents in N-heterocycles such as imidazole were studied by NMR. Imidazoles N–BH_3 and N–BF_3 can be used as models for cyclic aromatic imine complexes. Imidazole

presents a tautomeric equilibrium that averages the shift of CH-4 and CH-5 in the ^{1}H- and ^{13}C-NMR spectra at r.t. The $N \rightarrow BH_3$ adduct formation with imidazole stops this equilibrium, so that C-4 and C-5 can be differentiated. $^{13}C-H$ coupled spectra of *N*-borane adducts showed the coupling of the hydrides with the heterocyclic carbon atoms and allowed one to assign them unequivocally. The effects of the N-substituents (lone pair, H, CH_3 or BH_3) on the chemical shift of the ring carbons were measured [29] (Fig. 58).

If the $N-BH_3$ adduct of $N-CH_3$ imidazole is heated in the presence of Al or CH_3I, the dimers of the dehydrogenated derivative are obtained [19] (Fig. 59). The second compound isomerizes to the first, whose X-ray diffraction structure was reported. Stable monomeric units have been considered to participate in the isomerization, one is an organyl–BH_2 while the second is a carbene aminoborane $N-BH_2$ moiety (Fig. 60). Some other examples of imidazabole derivatives have been reported and the nature of the dimeric carbene–borane adducts was established [64] (Fig. 61).

There are few examples of $N-BH_2$ compounds derived from aromatic N-heterocycles because they disproportionate to BH_3 and $B(NR_2)_3$. However, some of them can be stabilized by coordination with a base. The NH proton substitution by

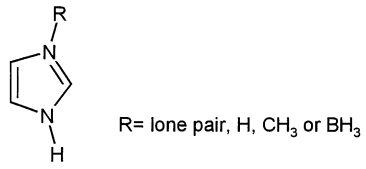


Fig. 58. ^{13}C- and ^{1}H-NMR signals of N-substituted imidazole were unambiguously assigned.

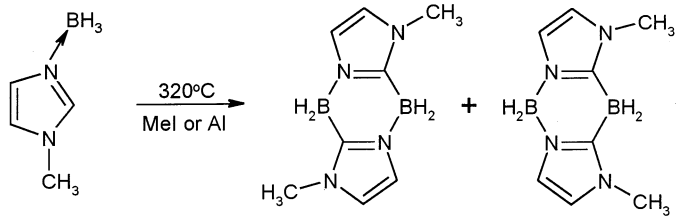


Fig. 59. Isomeric imidazaboles prepared from $N-BH_3$-*N'*-methylimidazole.

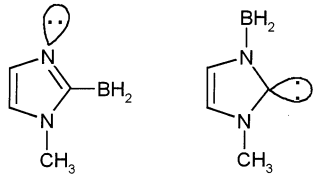
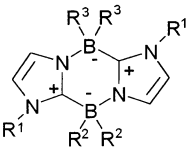


Fig. 60. Organyl–BH_2 and carbene $N-BH_2$ moieties as possible monomeric units in imidazabole.



1 $R^1 = CH_3$, $R^2 = R^3 = H$; **2** $R^1 = CH_2C_6H_5$, $R^2 = R^3 = H$
3 $R^1 = CH_3$, $R^2 = R^3 = F$; **4** $R^1 = CH_3$, $R^2 = F$, $R^3 = H$
5 $R^1 = CH_3$, $R^2 = R^3 = Cl$; **6** $R^1 = CH_3$, $R^2 = R^3 = CH_2CH_3$

Fig. 61. Reported imidazaboles, where the nature of a carbene $N–BR_2$ unit was established.

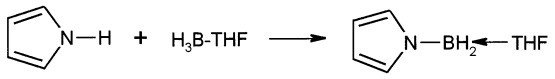


Fig. 62. Preparation of the reducing agent pyrrolylborane.

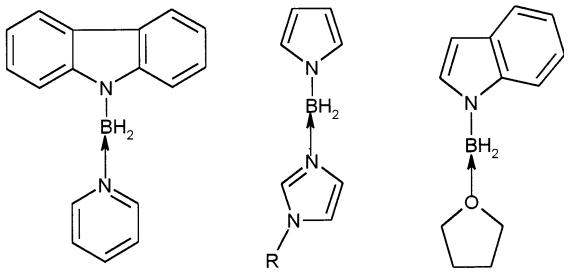


Fig. 63. Structure of aminoboranes prepared from acidic N-heterocycles.

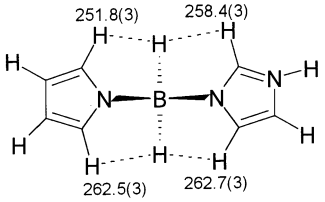


Fig. 64. Hydride-proton distances (pm) found by X-ray diffraction.

boron in acidic amines provides highly reactive aminoboranes useful as reducing agents. A first example is the pyrrolyl borane complex formed from the reaction of pyrrol and BH_3–THF. In this compound, boron is a very acidic site due to the lack of retrocoordination from the N-lone pair that is delocalized in the aromatic system [65] (Fig. 62). Pyrrolylborane–THF is an excellent reducing agent for alkenes, alkynes and ketones. It can selectively reduce the carbonyl function in α,β-unsaturated ketones affording the corresponding allylic alcohols. The aminoboranes of indole and carbazole were prepared and coordinated with THF, pyridine or imidazole (Fig. 63). We were interested in the factors that stabilize these complexes. The molecular structures of pyrrolylborane–pyridine, pyrrolylborane–imidazole, indolylborane-*N*-methylimidazole, carbazolyl–borane–pyridine, carbazolyl–bo-

rane, *N*-methylimidazole were determined by X-ray diffraction [31] (Fig. 64). In all structures, the B–N covalent bond was shorter than the N–B coordinative bond and the azolyl rings were delocalized. The solid state structures present the less stable conformations, but they allow the approximation of the B–H hydrides to the acidic C–H protons α to nitrogen. The interactions found were described as hydrogen bonding between hydrides and protons, whereby distances shorter than 2.65 Å were considered as contact distances. Fig. 64 shows the hydride–proton distances. ^{1}H-, ^{13}C-NMR and NOE experiments demonstrated that hydride–proton interactions are also present in solution.

A series of N–BH_3 adducts coordinated to the sp^2 nitrogen of benzazole compounds bearing different C-2 substituents (X = NR, S and O) have been prepared. Thereby, the borane coordination to these imines allowed the preparation of B–H heterocycles [51] (Fig. 65). This conversion implies the reductive transposition of boron and C-2. This is an example of a reaction in which the product is isolobal with the starting material and appears to be general for N–BH_3 coordination complexes. When the reactions are performed with 2-thiomethyl derivatives, borolane N–CH_3 products are obtained together with a methyl thioborane derivative (Fig. 66). In some cases, this reaction gives interesting results such as the synthesis of heterotetracyclic compounds (Fig. 67). Coordination and consecutive

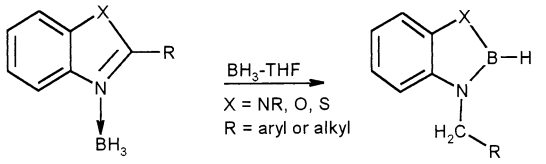


Fig. 65. Preparation of borolines by reductive transposition of boron and C-2.

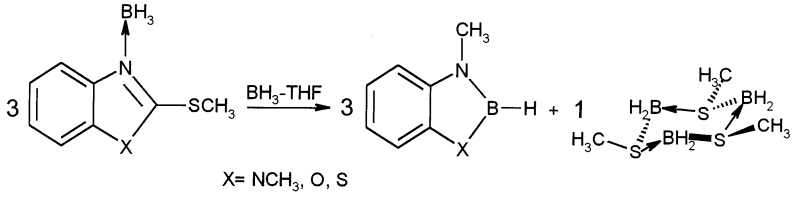


Fig. 66. Preparation of heteroborolines by reductive opening of 2-thiomethyl-heterocycles.

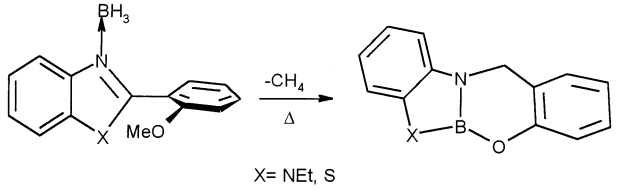


Fig. 67. Boron heterocycle formation by opening and closure of benzoheterocycles.

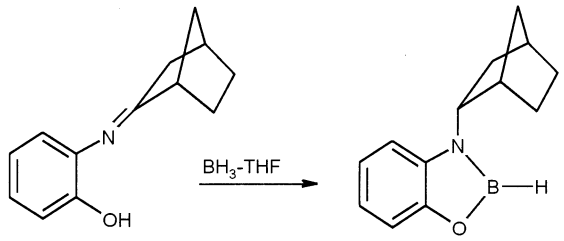


Fig. 68. Preparation of boroxazolines by reducing phenolimines with borane.

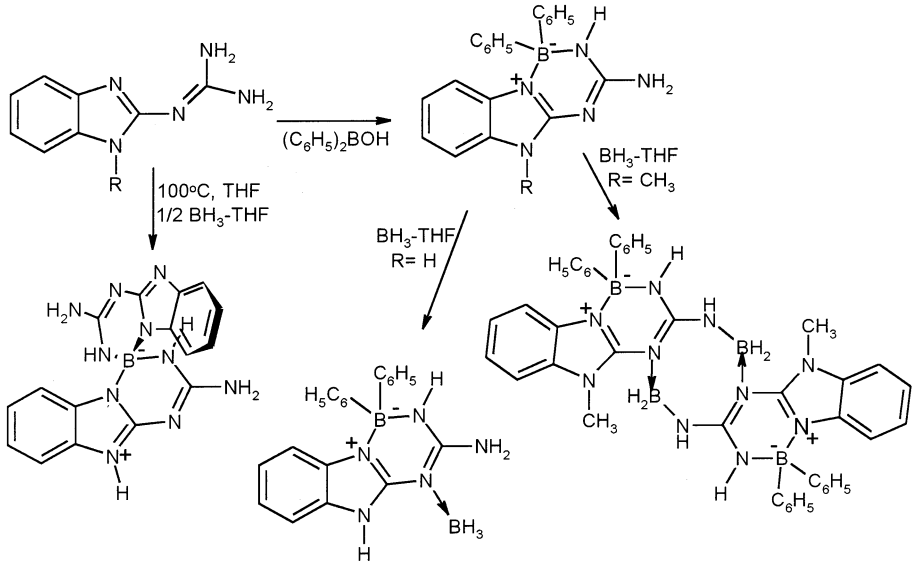


Fig. 69. Preparation of boron heterocycles from 2-guanidinobenzimidazole.

reduction of imines derived from *o*-phenolamines is an important method to obtain N-substituted benzoboroxazolines [51] (Fig. 68).

Borate complexes of 2-guanidinobenzimidazole which is a planar delocalized ligand with sp^2 nitrogen and carbon atoms have been reported [20]. The ligand acts as a bidentate with metal salts [66]. With boron reagents several compounds can be synthesized and their solid state structures have been obtained. They show that both B–N bond lengths are similar and have an averaged value between a coordinated and a covalent bond. The negative charge is located at the boron atom whereas the positive charge is delocalized in the heterocycle. A spiroborate was also prepared. The B-heterocycles act as Lewis bases and are protonated or give the $N \rightarrow BH_3$ complex with the pyridine type nitrogen (Fig. 69). They can also be deprotonated to give the corresponding anion [20] (Fig. 70).

Other N–BH_3 adducts derived from imines have been prepared stereoselectively by reaction with BH_3–THF (Fig. 71). In the selenium compound (Fig. 72) the addition was not stereoselective and two isomers were obtained, the N–CH_3 shift was used for the assignment of the stereochemistry. For the compound with a BH_3 group on the same side of the N–CH_3 group, there is a shift to higher frequencies in the ^{1}H-NMR spectra (Fig. 73). The adduct of the methylated imine was prepared under inversion of the imine configuration [4].

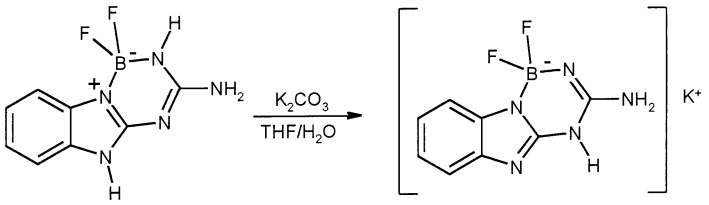


Fig. 70. Potassium amide derived from the BF_2 heterocycle of 2-guanidinobenzimidazole.

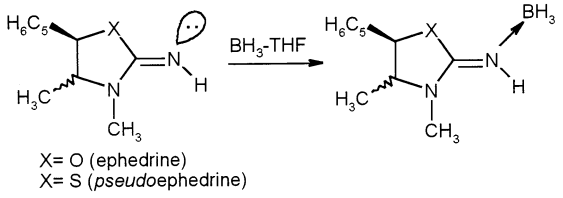


Fig. 71. Stereoselective formation of the imine–BH_3 adduct of ephedrine heterocycles.

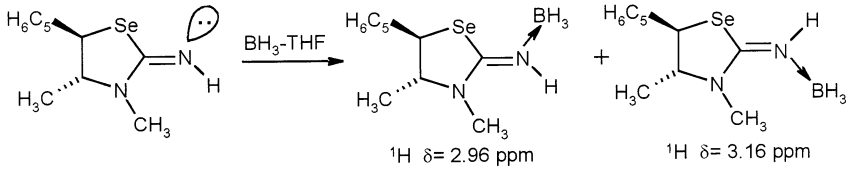


Fig. 72. Isomeric N–BH_3 adduct derived from selenium ephedrine heterocycles.

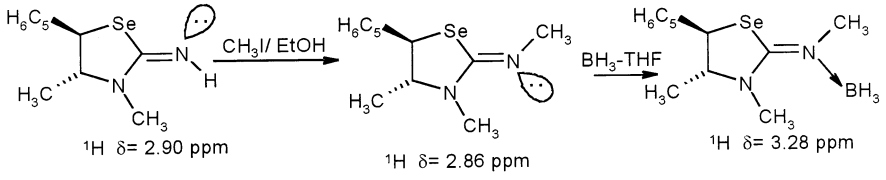


Fig. 73. Methylation and BH_3 adduct formation of selenium ephedrine heterocycles.

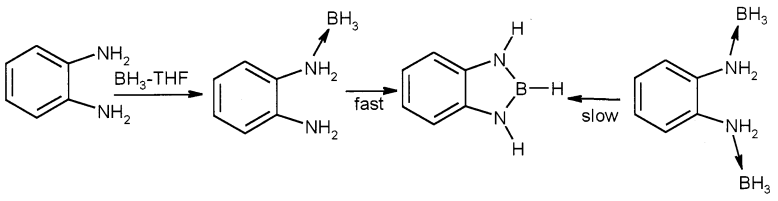


Fig. 74. Reaction products of phenylenediamine and BH_3–THF.

4.5. Determination of the relative acidity of boron Lewis acids in pyridine complexes

We have been interested in methods that permit the determination of the strength of the N–B coordinative bond. It has been reported that the pyridine coordination gives this information through the ^{13}C-NMR chemical shift of C-4. This atom is sensitive to inductive effects and is protected from steric effects. The coordination strength is related to the electronic donation from nitrogen to boron and therefore to the electronic density. Thus a series of N–B coordinated compounds with pyridine and ethylpyridine have been prepared in order to obtain a relative scale of acidity for boron acids based on the $\Delta\delta$ of C-4. The following approximate order of acid strength was proposed: $BF_3 > C_6H_4O_2BOC_6H_5 > C_6H_4O_2BOCH_3 > C_6H_4$-$O_2BC_6H_5 > (C_6H_5O)_3B > (C_5H_5)_3B > BH_3 > (C_2H_5)_3B$. The $B(OH)_3$, $B(OCH_3)_3$ and $C_6H_5B(OH)_2$ were not acidic enough to form complexes with pyridine. The data correlate well with enthalpy values of formation of the boron compounds that follow the same trend. On the other hand, we have found that the ^{11}B $\Delta\delta$ could not be used for the relative acidity determination [44].

4.6. Borane aniline complexes

Amine borane complexes are important reducing agents, and their reactivity is a function of the strength of the N–B bond. Aromatic amine boranes are less stable and more reactive adducts. We have investigated the reducing characteristics of diphenylamine borane, which is easily prepared from $NaBH_4$, BF_3–OEt_2 and diphenylamine in THF at 0°C. This stable solid can be used as a safe BH_3–THF source. It has been found that it is an exceptional reducing agent for ketones and alkenes and can be used in hexane or CH_2Cl_2 [67].

We decided to study the nature of the N–B bond in arylamine–BH_3, therefore, we have prepared a series of adducts and investigated the relative affinity with borane using a series of equilibrium reactions in order to establish a scale of relative basicity. The ^{11}B-NMR shifts do not give information on the N-basicity because ^{11}B chemical shifts depend more on the volume and the number of the nitrogen substituents. For aromatic amines, the decreasing order in borane affinity found was [68]:

$$\underset{130}{ArNHMe} > \underset{100}{ArNH_2} > \underset{90}{ArNHEt} > \underset{30}{ArNMe_2} > \underset{5.6}{(Ar)_2NH} \cong \underset{5}{ArNEt_2} > \underset{1}{ArNHBn}$$

Phenylene diamine monoboranes can be formed stereoselectively on addition of one equivalent of BH_3–THF. Diazaborolines B–H are formed by heating them. Reactions of BH_3–THF with *m*- and *p*-isomers of phenylenediamine with different substituents were also investigated [68] (Figs. 74 and 75). Analyses of the ^{13}C-NMR data of many aromatic amine–BH_3, aliphatic *N*-boranes and aliphatic N–$B(CH_3)_3$ adducts have been performed. Additivity of the substituent effects on the ^{13}C-NMR data of aromatic carbon atoms was found. A similar trend was observed for ammonium salts and hydrocarbons. Borane adducts present a strong shield at the *o*-carbon atom caused by electric field effects [45].

We have found an alkylation method for aliphatic, aromatic or difunctional primary amines with good yields and without secondary products by reaction of the amine with a ketone and BH_3–THF [41] (Fig. 76).

4.7. Six-membered ring N–BH_3 complexes

5-Methylperhydro-1,3,5-dithiazine reacted with BH_3–THF, BD_3–THF and BF_3–OEt_2 to yield the corresponding N-adducts [25,28]. The conformation and spectroscopic properties of the adducts were discussed. They have a fixed conformation with boron in the equatorial position. By heating the BH_3 or BD_3 adducts a 4-boratacyclohexane is formed by position exchange between a CH_2 and BH_2 or BD_2 groups. The amine borane adducts and borataheterocycles are isolobal isomers, the latter being in conformational equilibrium. By heating the borataheterocycles, $(CH_3)_3NBH_3$ or $(CH_2D)_2CH_3NBD_3$ are obtained [28]. Similar experiments

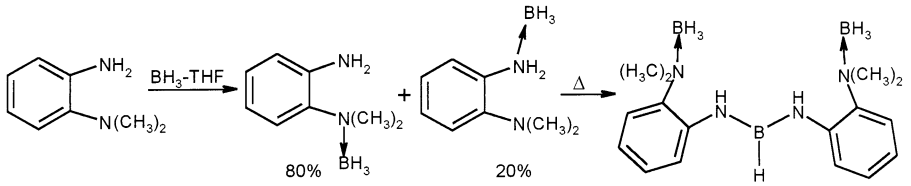


Fig. 75. Reaction products of *N*,*N*-dimethyl-phenylenediamine and BH_3–THF.

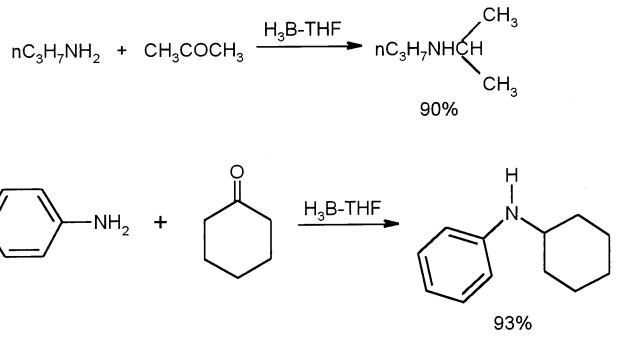


Fig. 76. *N*-Alkylation reactions with ketones promoted by borane.

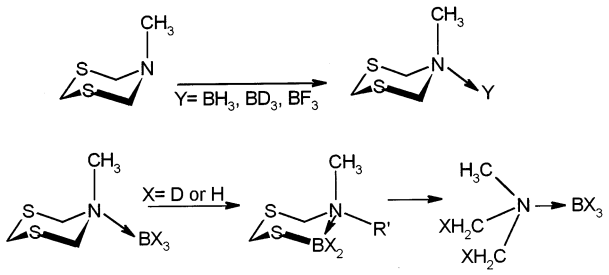


Fig. 77. Dithiazine N–boron adducts and ring reactions.

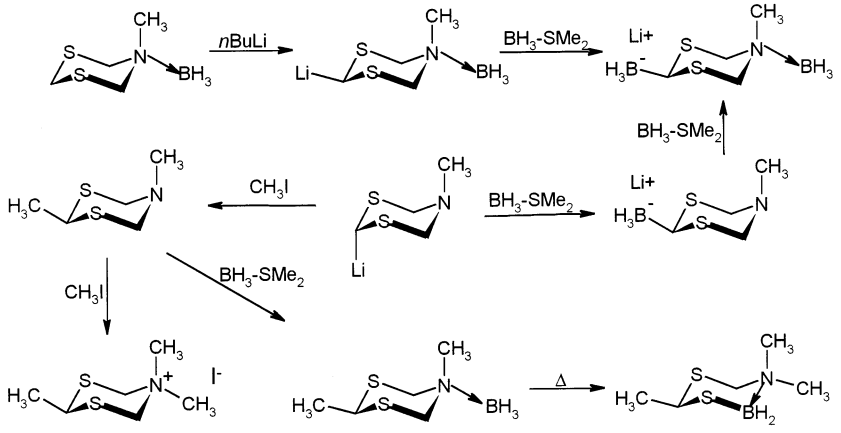


Fig. 78. Reactions at C-2 and at nitrogen atom of dithiazines with BH_3–DMS.

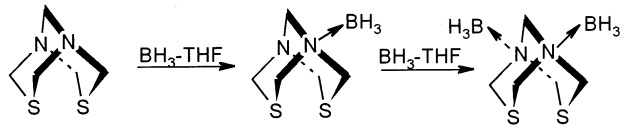


Fig. 79. BH_3 coordination to 1,5-dithia-3,7-diazabicyclo[3.3.1]nonane.

were performed for *N*-*t*-butyl- and *N*-methylbenzyldithiazine [15]. The BH_3 or BD_3 adducts of dithiazine may be used in organic synthesis for dimethylation of primary amines and preparation of $(CH_2D)_2NR$. Syntheses, NMR spectra and X-ray diffraction studies of several perhydrodithiazines were reported [15,69] (Fig. 77).

The dithiazine can be deprotonated with *n*-BuLi to give a stable C-2 carbanion. The same reaction can be performed with the dithiazine N–BH_3. Both organolithium compounds give mono- or diborane adducts. Similar reactions with CH_3I afforded the isolobal compounds of borane derivatives [70] (Fig. 78). We have prepared the 1,5-dithia-3,7-diazabicyclo[3.3.1]nonane and its structure was determined by NMR and X-ray diffraction. This heterocycle forms mono- or di-N–BH_3

adducts, S-adducts were not detected [71] (Fig. 79). The coordination behavior of a related molecule, the 3,7-dialkyl-3,7-diaza-1,5-dithiacyclooctane was studied. These molecules are opened readily to provide the $(CH_3)_2RN–BH_3$ adducts [15] (Fig. 80).

Trimethyltriazacyclohexane reacted with BH_3–THF in different ratios in order to get mono-, di- and tri-$N–BH_3$ adducts. With one equivalent of BH_3–THF only the mono-adduct was obtained. For the latter compound two different methyl groups and four different CH_2 hydrogen atoms observed by ^{1}H-NMR indicate a frozen conformer. ^{13}C- and ^{11}B-NMR showed that the BH_3 group is in equatorial position. The diadduct was prepared pure from the reaction with two equivalents of BH_3–THF, both $N–BH_3$ groups are in equatorial position. The stereochemistry informs us that the di-adduct is the thermodynamic product. Addition of a third molecule of BH_3 was not possible. The conformationally fixed molecules allowed study by ^{1}H- and ^{13}C-NMR of the electronic and steric effects of the borane group on the neighboring atoms [17] (Fig. 81). When the reactions were performed with N-bulky substituents only one molecule of BH_3 was added and it was placed in an axial position. With an excess of BH_3–THF some of the diadducts could be detected in the NMR spectra (Fig. 82).

Borane addition to piperidine gave the equatorial $N–BH_3$ adduct in a fixed chair conformation. Comparison with protonated, methylated and piperidinium derivatives allowed one to establish the steric and electronic effects of CH_3, H and BH_3

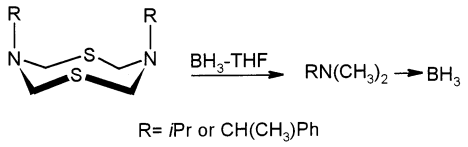


Fig. 80. Products of the reaction of borane with 3,7-diaza-1,5-dithiacyclooctane.

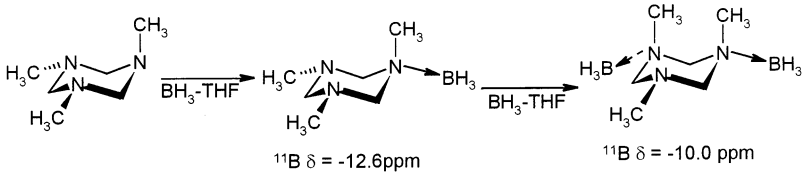


Fig. 81. ^{11}B-NMR shifts (ppm) and stereochemistry of borane addition to triazines.

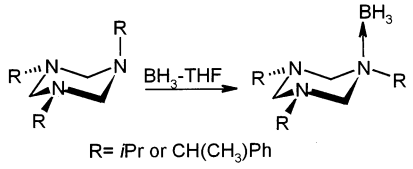


Fig. 82. Stereochemistry of borane addition to triazines.

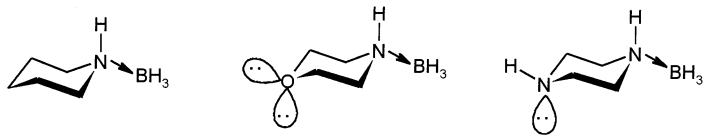


Fig. 83. Fixed conformations of N–BH_3 adducts derived from six-membered heterocycles allow one to establish the lone pair effects on neighboring atoms.

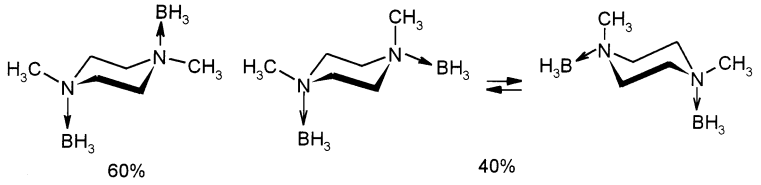


Fig. 84. Isomeric mixture of piperidine N–BH_3 adducts.

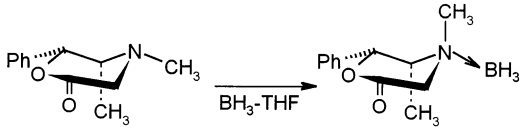


Fig. 85. Stereochemistry of the N–BH_3 adduct of a morpholone derived from ephedrine.

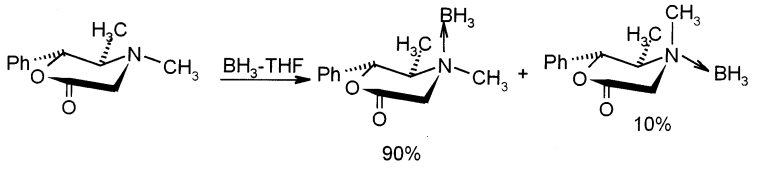


Fig. 86. Stereochemistry of the N–BH_3 adducts of a morpholone derived from *pseudo*ephedrine.

groups. The structure of the fixed conformers of N–BH_3 adducts of several C-methylated piperidines was determined by analysis of the ^{1}H- and ^{13}C-NMR data. The latter study was extended to piperazines and morpholine, whereby the fixed conformation of monoadducts informed one about the effects of lone pairs on their neighboring atoms [25] (Fig. 83). The diaddition of BH_3–THF to piperazines gave *cis* and *trans* isomers. The conformation of *trans* isomer (60%) is fixed with BH_3 groups in axial position, whereas the *cis* isomer is in conformational equilibrium [25] (Fig. 84). The stereochemistry of the BH_3 addition to optically active morpholones was studied. The morpholone derived from ephedrine (Fig. 85) showed an anchored conformation, that was indicated by comparison with the *N*-borane adduct, the borane and the phenyl group are in equatorial position. The morpholone derived from *pseudo*ephedrine (Fig. 86) gave two anchored isomers both with three substituents in equatorial position. The predominant isomer (90%)

has the BH_3 in axial position [25]. The free 3-hydroxypiperidine has the OH group in an axial position stabilized by hydrogen bond. Reaction of its hydrochloride with $LiBH_4$ gives two BH_3 *N*-epimeric adducts, one has the OH and BH_3 groups in equatorial orientation (70%), the other one is a preferred conformer with borane in equatorial and the OH group in axial position [25] (Fig. 87). Reaction of the same piperidine with diphenyl boronic acid gives a bicyclic compound with the diphenylboryl group and the oxygen atom in axial position [72] (Fig. 88). 2-Aminoethyl- and 3-aminopropyl-borinate heterocycles with a coordinative $N \rightarrow B$ bond have been prepared by reaction of piperidine and piperazine alcohols with diphenylborinic acid. The polycyclic derivatives were characterized by NMR and X-ray diffraction studies, with the exception of the ethanolpiperidine heterocycles [72] (Fig. 89). When the reactions were performed in diethylether at r.t., compounds were obtained in which the B-coordination was replaced by a hydrogen bond, as has been shown by their X-ray diffraction structures [72] (Fig. 90).

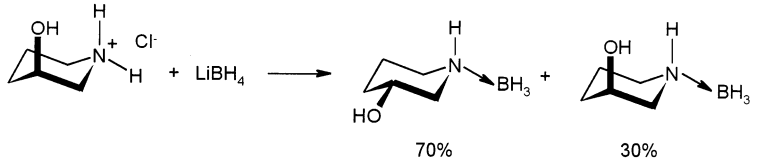


Fig. 87. Stereochemistry of the $N-BH_3$ adducts derived from 3-hydroxypiperidine.

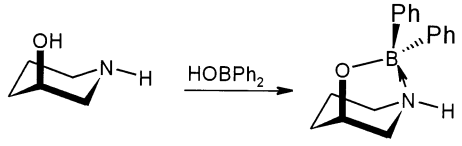


Fig. 88. Stereochemistry of the diphenylborinic ester of 3-hydroxypiperidine.

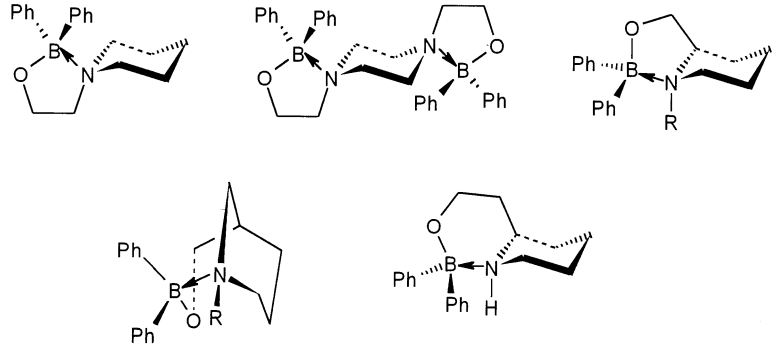


Fig. 89. Diphenylborinic esters derived from methanol or ethanol piperidines or piperazines.

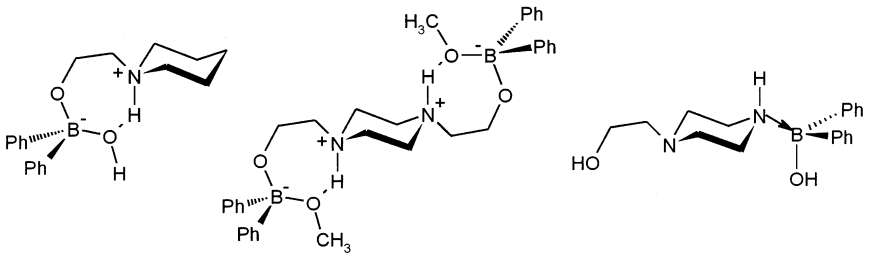


Fig. 90. Diphenylborinic esters derived from *N*-ethanol–piperidines or piperazines.

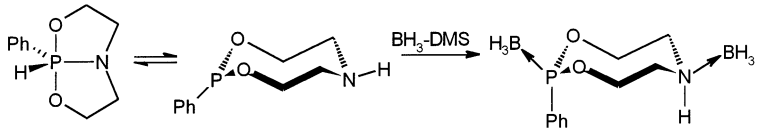


Fig. 91. Borane coordination was used to trap P(III)-tautomers.

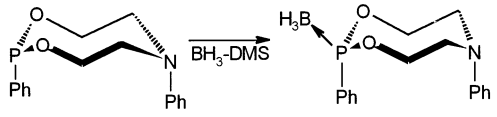


Fig. 92. Borane adduct formation was used as a basic sites probe.

5. Phosphorus–borane coordination complexes

Borane coordination is a useful tool in order to trap unstable tautomers of phosphorus compounds, for example in the equilibrium between diethanolamine phenylphosphorane and the corresponding phosphane. In this equilibrium, the phosphane is not detected by spectroscopical means, because its concentration is very low. However, it can be trapped by borane coordination [21] (Fig. 91). When the diethanolamine has an *N*-phenyl substituent the phosphorane can not be made. The phosphane reacts only with one molecule of borane to give the phosphane adduct. The ring conformation and the phenyl group inhibit the N-lone pair to be available for BH_3 coordination [36–38] (Fig. 92).

The reactivity of diphenolaminephosphorane with BH_3 has been also investigated, the phosphorane is a very stable molecule that reacts very slowly with BH_3–THF in CH_2Cl_2 to give partially the P-adduct. The diphenylamine was not basic enough to coordinate to the borane group or to the phosphorus [73] (Fig. 93). When the phosphorus of diphenolamine phosphorane bears an *O*-methyl ester and a proton, the phosphorane is in equilibrium with the corresponding phosphane and methanol. The equilibrium is shifted to the phosphorane therefore the phosphane is not detected by spectroscopy but can be detected by reaction with BH_3–DMS. The latter traps the CH_3OH and shifts the equilibrium to the phosphane that dimerizes

and is coordinated to the borane group [48] (Fig. 94). BH_3–THF was employed to explore the basic sites of heterocyclic P amides (Fig. 95). The reactions gave only the corresponding P-adducts, the BH_3 does not coordinate to the N of the amide and does not reduce the carbonyl or P atom [32].

We have prepared the phosphoranes derived from bis[2-hydroxyphenyl]ethylene amines. The compounds are in fast equilibrium between two helicoidal structures, and the borane group coordinates only to the basic apical N atom stopping the equilibrium and giving racemic mixture of adducts [33] (Fig. 96).

The phosphorane prepared stereoselectively from *N*,*N*′-bis[2-ephedrine]ethane gives two N–BH_3 adducts. The first one is formed by coordination of the boron

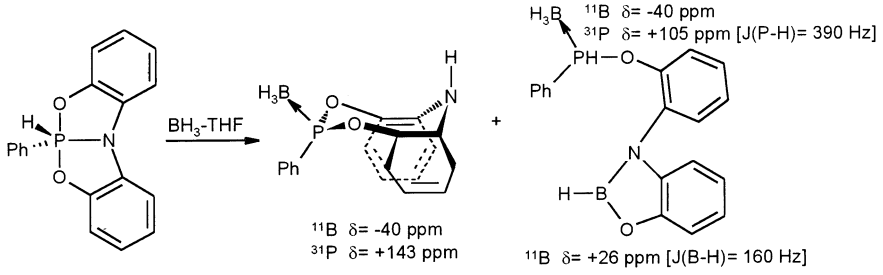


Fig. 93. Borane coordination was used to trap P(III)-tautomers.

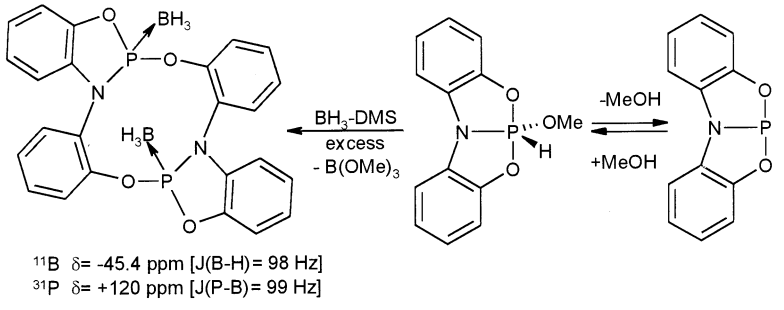


Fig. 94. Borane coordination was used to trap a P(III)-dimeric compound.

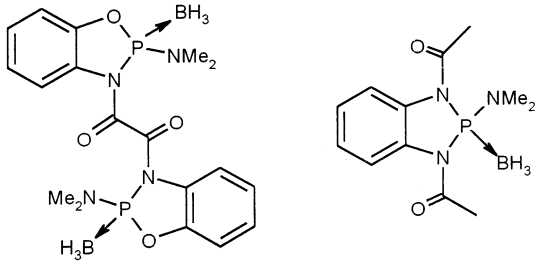


Fig. 95. P–BH_3 adducts of phospholanes derived from amides.

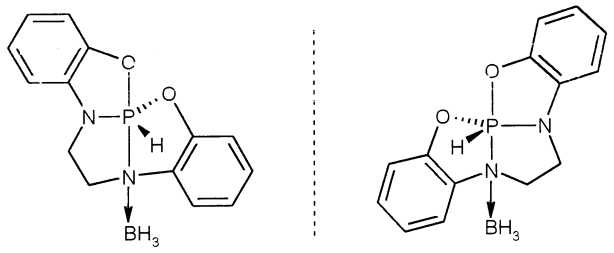


Fig. 96. Borane adduct formation was used as a basic sites probe.

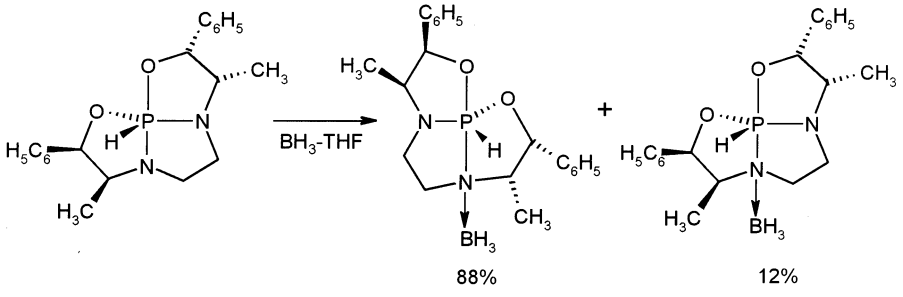


Fig. 97. N–BH_3 adducts derived from optically active phosphorus heterocycles.

group to the equatorial nitrogen atom which by inversion of the P-configuration by a *pseudo*rotation transforms to the more stable isomer, with the *N*-borane group in apical position and *trans* to the neighboring C-methyl group. The second isomer results from direct coordination of the boron atom to the nitrogen atom in apical position of the free phosphorane, in which the BH_3 and C–CH_3 groups are on the same side [33] (Fig. 97).

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