Chemical Science International Journal

Volume 33, Issue 4, Page 45-53, 2024; Article no.CSIJ.119733
ISSN: 2456-706X
(Past name: American Chemical Science Journal, Past ISSN: 2249-0205)

Synthesis, Characterization and Evaluation of Antibacterial activity of Amine-Boranes

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/CSJI/2024/v33i4905

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/119733

Original Research Article

Received: 07/05/2024
Accepted: 09/07/2024
Published: 16/07/2024

ABSTRACT

Amine-Boranes (AB) are an elite class of reagent and belongs to the Borane-Lewis family, has found extensive use in chemical synthesis. Interesting aspect of AB reagents are to display chemo selectivity among the functional groups. The present investigation highlights on the innovative, green synthesis and characterization of the three of unique AB complexes, including triethylamine-borane (aliphatic), aniline-borane (aromatic), and (aromatic substituted) N,N-dimethylaniline-borane (DMAB) under an open air condition. The ^{11}B NMR technique was used to characterize the synthesized AB reagents. The chemical shift values obtained were in accordance with the results of previous research studies, and it's interesting to note that there is a difference in ^{11}B-NMR chemical shift values between the borane complexes of aromatic and aliphatic amines. The antibacterial efficacy of three AB reagents has been stated for the first instance by using disc diffusion method against four bacterial strains: *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. When compared to other AB complexes, the DMAB reagent demonstrated significant antibacterial properties against the four different bacterial species.

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Cite as: *Jayakumar, S. Venkatesan. 2024. "Synthesis, Characterization and Evaluation of Antibacterial Activity of Amine-Boranes". Chemical Science International Journal 33 (4):45-53. https://doi.org/10.9734/CSJI/2024/v33i4905.*

Keywords: Amine-Borane; ^{11}B-NMR; P. aeruginosa; S. typhimurium; S. aureus; E. coli.

1. INTRODUCTION

Despite the fact that AB reagents have been known for an extended period and have been thoroughly investigated, they are less useful for the synthetic processes due to their stability and inertness. Rather than AB complexes prefer to react with nucleophilic sites and other reagents [1-6]. Without a doubt, they might serve as substitutes for frequently used borane reagents, and in comparison, to other electrophilic boron reagents, the majority of the complexes demonstrate stability, inertness, and slow reactivity has been documented by various researchers [7-9] and the multitude applications of AB complexes are displayed (Fig. 1 Multitude applications of AB complexes).

When it comes to organic synthesis, AB reagents have the following benefits over other electrophilic boron reagents: 1. They are easy to work with and favourable to handle; 2. They exhibit chemo- and regio-selectivity; 3. They are stable and interdependent [10-12]. Dimethylamine-Borane and Morpholine-Borane complexes are frequently employed as reducing agents in the electronics sector for the fabrication of circuit boards and electroplating applications due to their solubility and mild reducing capabilities [13]. In accordance with the recent study reports, transition metal catalysts are currently applied in an attempt to enhance their reactivity in hydrogenation reactions [14-17].

In the study by PV Ramachandran *et al* (2020), the AB reagents have a dual function in direct amidation, whereby they may activate both aromatic and aliphatic carboxylic acids and then deliver amines to produce corresponding functionalized amides with a yield of 99%. The utilization of these AB complexes was reported in hydrogen storage fuel cells, due to its stability and high gravimetric content of hydrogen [18-19].

The reducing ability of AB reagents can be affected by the steric effects and electronic characteristics of the groups bonded to the nitrogen atom. The incorporation of acetic acid, mineral acid, Lewis acid, and high reaction temperature is necessary to activate the stable AB complexes such as Trimethylamine-borane, Pyridine-borane [20-21].

The nature of bond present in AB's is coordinate bond which is semi-dative polar bond as shown in the Fig. 2. The reactivity of AB complexes depends on the nature and bond strength of N-B bond. If AB is less stable then it is less reactive, inert and easy to prepare. The reverse is true if the AB adduct is unstable and difficult to prepare.

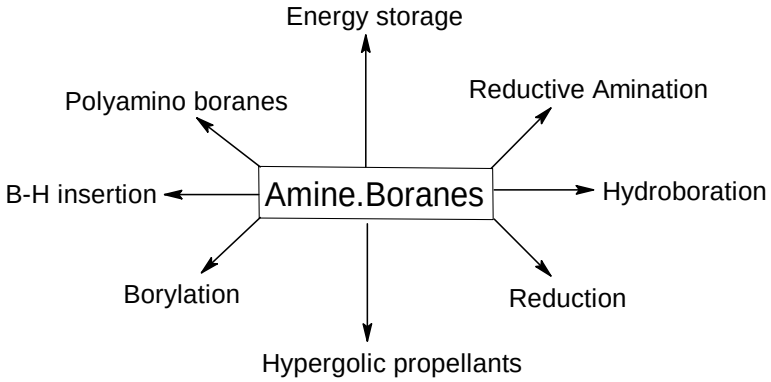


Fig. 1. Multitude applications of Amine.Borane complexes (Kulkarni & Ramachandran, 2017)

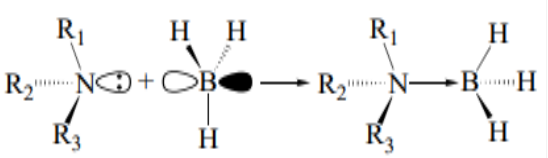


Fig. 2. Dative bond formation in an Amine-Borane complex (Kulkarni & Ramachandran, 2017)

In the previous research studies, we select a moderately reactive DMAB reagent, microwave irradiation and ultrasound sonication techniques were chosen for activating the AB complex *in situ*. The ease of recovery of the amine after the reaction and the possibility of recycling it make the AB as environmentally friendly reagents of choice. We first reported the preparation, properties and synthetic utility of DMAB (N,N-dimethyl aniline.borane) under microwave and ultrasound conditions [22-26]. It is evident by just examining the different synthetic approaches, how AB complexes have remained relevant and significant ever since they were discovered. A thorough review of the literature revealed that interest in these important compounds is expanding at an exponential rate [27, 28]. Despite being aware that there have been several well-documented methods used to synthesize AB complexes, the author devised an ecofriendly and viable synthetic procedure employing sodium borohydride and a chloroform-water system in conjunction with phase transfer catalyst. The approach used in this methodology generates borane gas *in situ* by reacting sodium borohydride with water, and the resultant AB complex is subsequently dissolved in chloroform.

2. MATERIALS AND METHODS

2.1 Experimental Work

The chemicals used for the experiment are purchased from Fluka and Aldrich and the technical bulletin procedure of Sigma-Aldrich is followed to handle the air-sensitive reagents [29]. Liquid substrates and solvents were distilled prior to use. NMR spectra for product were recorded on Bruker AVANCE spectrometer, 400 MHz for ^{11}B NMR. The Perkin-Elmer equipment is used to record the infrared spectra of AB complex. Solvents used to dissolve the products are $CDCl_3$, CD_3OD and DMSO and the chemical shift values were referenced to TMS and coupling constants were calculated in hertz (Hz).

2.2 Test Microorganisms

The strains of bacteria that were employed were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhimurium*. Gentamicin was used as a positive control in the antimicrobial analysis utilising the antibiotics disc. The pathogenic strains were collected from the Department of Microbiology, Devi Ahilya Vishwavidyalaya (DAVV), Indore, MP. The bacteria were kept on nutrient agar slants at 4°C and cultivated in nutrient agar medium.

2.3 Processes Involved in Synthesising AB Reagents

The novel method is used for preparing the DMAB reagent is as follows, taking 3.80 ml of N,N-dimethyl aniline (0.03 moles) and adding it to a 100 ml two-necked RB flask in addition to 15 ml of chloroform, 10 ml of water, and 5 mg of phase transfer catalyst while stirring. After 15 minutes of cooling the reaction mixture in an ice bath, 2.3g of sodium borohydride (0.06 moles) was added portion-wise, and the temperature was kept below 10^{o}C. After that, the reaction ingredients continue to remain to stir for furthermore two hours. The complexation propensity of an amine can be monitored using ^{11}B-NMR spectroscopy, and the reaction mixture is filtered under vacuum once complexation is accomplished. The filtrate is blended with 10 millilitres of 2N HCl, and the DMAB complex can be extracted with chloroform. After that, the collected extractions using chloroform get dried over anhydrous sodium sulphate, and the solvent is removed under vacuum to yield the DMAB reagent.

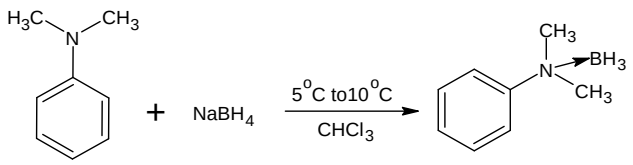
The DMAB stock solution is kept in an amber colour bottle and further confirmed by ^{11}B NMR spectra, which show chemical shift values of -4 ppm (decoupled) and -4 to -9 ppm (coupled).

The other two AB reagents (triethylamine and aniline) are prepared using the same methodology as described above and the ^{11}B NMR spectra of the synthesized AB reagents are presented as (Figs. 3-6).

^{11}B-NMR spectra and gasometer analysis were used to periodically determine the stability of the three AB reagents.

2.4 Characterization of AB Complex

The characterization of the synthesized AB reagent is necessary, and this can be done mainly with the support of the ^{11}B-NMR spectral technique, and it is necessary for studying and comprehending the AB reagents the other techniques for characterization such as GC, MS, and UV is less helpful to analyse the AB complexes. The ^{11}B- chemical shift values can be used as criteria to measure the complexation strength of the N-B dative bond. Table 1 shows that there is a minimum fluctuation in ^{11}B-chemical shift values, despite the fact that aliphatic and aromatic amines differ significantly in their basicity.



Scheme 1. Preparation of DMAB

Table 1. Typical ^{11}B-NMR spectral values for various AB reagents [30, 31]

No.	Amine.Borane (AB) complex	^{11}B-NMR peak value (ppm)	Nature of the signal
1	Trimethylamine.Borane	-13 coupled -10 to -13 decoupled	Quatret
2	Triethylamine.Borane	-11 coupled -8 to -11 decoupled	Quatret
3	Pyridine.Borane	-12 coupled -9 to -12 decoupled	Quatret
4	N-ethyl-N-methyl aniline.Borane	-5 coupled -5 to -9 decoupled	Quatret
5	N,N-diethylaniline.Borane	-4 coupled -4 to -9 decoupled	Quatret

Further, Wang *et al* (2020) reported that the borane adducts of aniline and aminopyridines demonstrated unique ^{11}B-NMR chemical shift values, is due to paramagnetic anisotropic effects and along with hydrogen bonding [12]. The groups that are bound to the nitrogen atom of amine group in the AB reagent dictate the type and position of the ^{11}B-NMR signal in the spectra. Table 1. summarizes the type and position of the ^{11}B-NMR signal of AB reagents.

2.6 Antibacterial Activity

2.6.1 Procedure of antibacterial activity of AB complexes [32,33]

Microbes continue to be the most prevalent cause of death worldwide due to minimal or inadequate treatment. There is a pressing need at the moment for a novel class of antibacterial with an alternative method of action. The antibacterial capability of synthesized AB reagents was investigated using the following species of bacteria: *Salmonella typhimurium*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. AB samples were tested at a concentration level of 100 mg per millilitre, and the plates' medium was permitted to settle down for 10 to 20 minutes at room temperature for the compound to diffuse into the agar. In order to encourage the bacterial growth, the plates were eventually incubated for 24 hours at 35°C. The disc-diffusion method was used to test the antibacterial activity. Following incubation, a distinct zone of inhibition demonstrated the antibacterial activity, which was then measured using a ruler. The outcomes are shown in Table 2.

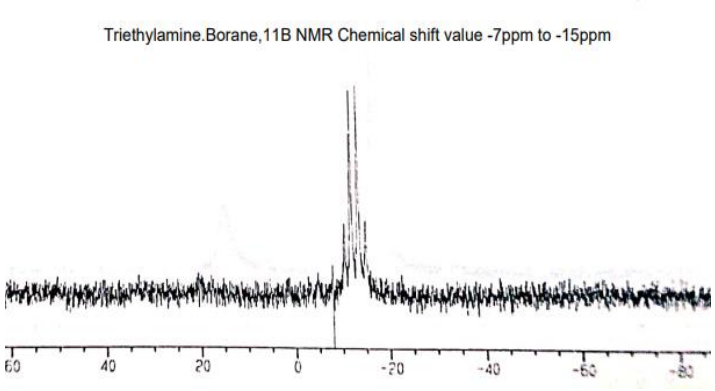


Fig. 3. ^{11}B-NMR spectra of Triethylamine. Borane

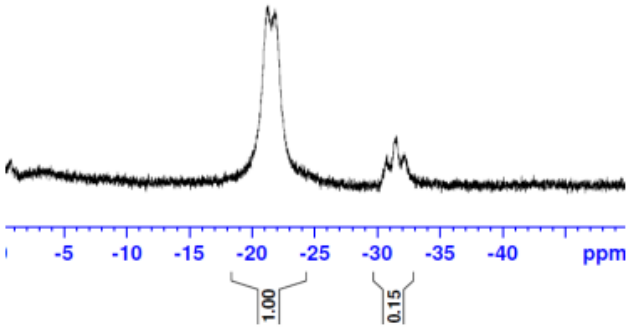


Fig. 4. ^{11}B-NMR spectra of Aniline. Borane

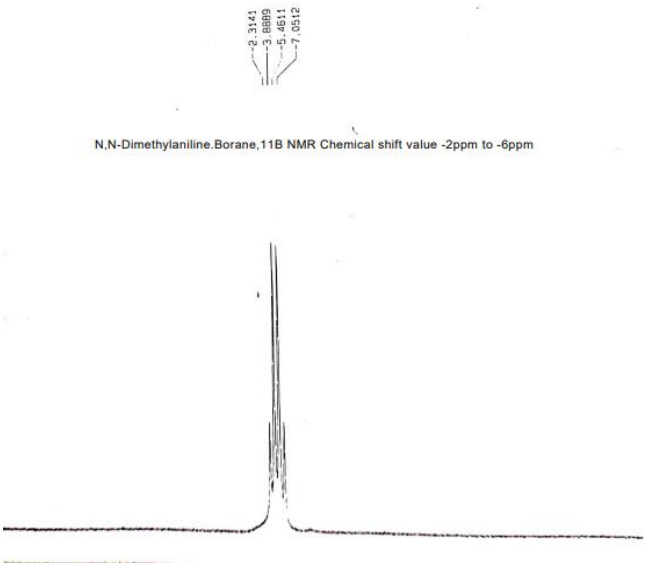


Fig. 5. ^{11}B-NMR spectra of DMAB Borane

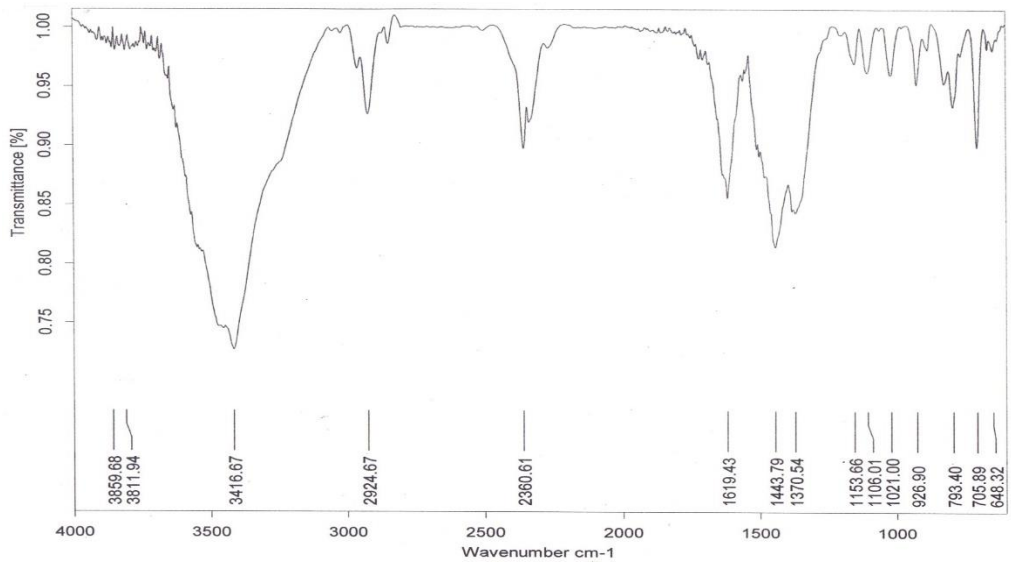


Fig. 6. IR Spectra of Aniline-Borane reagent

3. RESULTS AND DISCUSSION

3.1 Stability Studies of AB Reagents

While the much of AB complexes are widely recognised for their stability and inertness, reactive ABs are often less stable and more laborious to synthesize. ^{11}B-NMR spectrum investigations are used to examine the stability of the synthesized AB reagents.

3.1.1 Stability of DMAB Reagent

A sample of aliquot (about 1ml) is withdrawn from the stock solution, which is kept in an environment of nitrogen, and it is examined to see if any additional signals above -4 to -7 ppm are present. The DMAB reagent is stable for up to eight days, according to the results of ^{11}B-NMR spectral studies. After that, a new signal at +20 ppm is detected, which is associated with boric acid. DMAB reagent has a 7-day shelf life, after which it begins to gradually degrade into boric acid. The stock solution becomes progressively darker in blue colour over the course of seven days and the Fig. 7 demonstrates a variation in borane's molar concentration over the course of time.

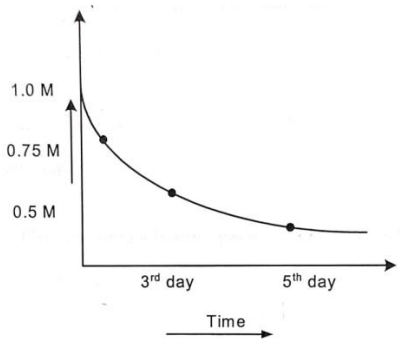


Fig. 7. Stability studies of DMAB Borane

With the assistance of the ^{11}B-NMR technique, stability inquiries of the synthesized AB reagents demonstrate that Triethylamine.Borane is inert and stable while Aniline.Borane is reactive.

3.2 Assessment of Antibacterial Effects Using the Agar Disc Diffusion Method

Whatman No. 3 filter paper discs (diameter 6 mm) that had been sterilized were placed on the surface of a petri dish for inoculation. The three different AB reagents had been added to the Petri dishes after being independently dissolved in DMSO. In brief, each disc contained 100µl of AB reagent as the test sample, 10µg of gentamycin of the positive control, and 100µl of DMSO as the negative control. A measuring tool can be used to measure the zone of inhibition, which represented the effectiveness of antibacterial agents. The zone of inhibition illustrated in Fig. 8 and the Table 2 reveal the findings. The diameters of the inhibitory zones induced by the AB complexes were interpreted as follows: resistant (12 mm or less), intermediate (13–15 mm), and susceptible (16 mm or above), following the standard.

3.3 Evaluation of Antimicrobial Properties of AB Complexes

The four known bacterial pathogens *S. typhimurium*, *P. aeruginosa*, *S. aureus*, and *E. coli* were employed to examine the three AB compounds antibacterial properties and percentage inhibition determined using the standard approach. The results are shown in Table 2, and it was discovered that DMAB complex demonstrated a significant inhibition zone against *E. coli* and *P. aeruginosa*. The type of substituent present on AB reagents has a consequence on the degree of activity. The highest zone of inhibition was observed against *S. aureus* and *P. aeruginosa* with Aniline.Borane reagent. Triethylamine- Borane complex exhibited the largest zone of inhibition against *S. typhimurium* and followed by *P. aeruginosa*.

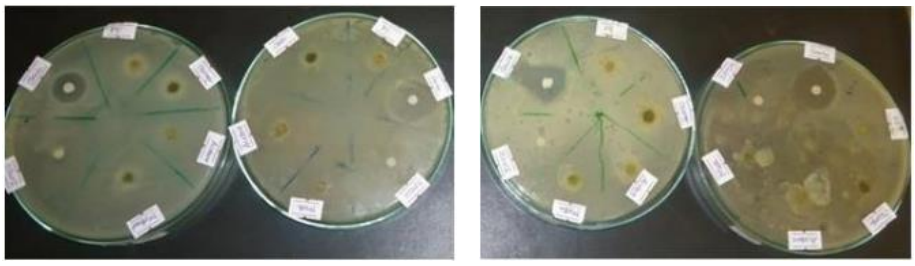


Fig. 8. Antibacterial activity of synthesized AB complexes A– *S. typhimurium* B– *P. aeruginosa* C– *S. aureus* D– *E. coli*

Table 2. Antibacterial properties of AB reagents

No.	AB reagent name	*E. coli*	*S. typhimurium*	*S. aureus*	*P. aeruginosa*
1	Triethylamine.Borane	12	16	14	15
2	Aniline.Borane	16	14	17	18
3	N,N-Dimethylaniline.Borane (DMAB complex)	21	18	17	22
4	Gentamicin*	26	24	25	27
5	DMSO solvent**	-	-	-	-

*The measurements are expressed in mm; *(+) ve control; **(-) ve control; No inhibition Zone; Solvent*

4. CONCLUSIONS

In the past few decades, lead bioactive compounds possessing nitrogen have become appealing synthetic targets owing to their structural diversity and biological significance. In consonance with current investigation outcomes, AB reagents will be the promising lead molecules for drug development in the future research. A great deal of work has gone into developing a new, easy-to-use method for synthesizing the AB complexes using sodium borohydride and chloroform-water system.

The *in vitro* evaluation of three AB reagents have demonstrated intriguing effectiveness against bacterial pathogens and DMAB complex exhibited excellent bacterial inhibition. The subsequent research project will be emphasized on the generation of substituted, pharmacologically active Aniline.Borane, reagent. The results of characterization, molecular docking, simulation, and *in vivo* research investigations will be presented in the near future.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ACKNOWLEDGMENT

The author expresses gratitude to Management and Research Council of SVVV University, Indore, Madhya Pradesh for providing the facilities. The author sincerely thanks the Hon'ble Vice-Chancellor, Dean of Research, and Director of SVIS at SVVV University in Indore for their unwavering support and for providing the solvents, and chemicals.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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