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Synthesis and antibacterial activity of pyridylselenium compounds: Self-assembly of bis(3-bromo-2-pyridyl)diselenide via intermolecular secondary and π⋯π stacking interactions

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ABSTRACT

Various pyridylseleniums and their hydrochloride salts have been synthesized and evaluated for their antibacterial activities. SEM, TEM and enzyme profiling techniques have been used to investigate the mode of action of these compounds as antibiotics. Single crystal X-ray study of bis(3-bromo-2-pyridyl) diselenide (**6b**) has also been reported. The molecule **6b** displays π⋯π stacking and π⋯Br secondary interactions leading to a supramolecular self-assembly. A search on Cambridge Structural Database was undertaken to identify the π⋯π stacking interactions in various other bis(2-pyridyl)diselenides.

Introduction

The potential of pyridylseleniums as biological active materials has inspired intense studies related to this field [1–4]. The binuclear platinum complexes of bis(4-pyridyl)selenide and bis(3-methyl-4-pyridyl)selenide have comparable or higher antitumour activity than cisplatin [1]. Bis(2-pyridyl)diselenide has displayed superior *in vivo* antioxidant activity than diaryl diselenides [2,3]. The presence of pyridine ring has been found to be responsible for the increased antioxidant effect of bis(2-pyridyl)diselenide [2]. Recently, we have shown that the methyl substituted bis(2-pyridyl) diselenides exhibit far better DPPH and NO scavenging activity than ebselen [4]. The later study has also demonstrated that the pyridylseleniums enhance the magnitude and the rate of antioxidant activity of poly(acrylamide) hydrogels [4]. In continuation of our study on the pyridylselenium compounds [4–6], we report herein the synthesis and antibacterial evaluation of the pyridylseleniums and their hydrochloride salts. The SEM and TEM characterisation have been used to investigate the effect of these compounds on the bacterial cell morphology. The enzyme profiling with respect to β-galactosidase induction in *Bacillus pumilus* has been used to establish the mode of action of these compounds as antibiotics.

The π⋯π stacking interaction in the aromatic molecules plays a crucial role in the biological systems and molecular recognition [7–9]. X-ray structure of various bis(2-pyridyl)diselenides with diverse structural features has been reported in the literature [5,6,10–20]. However, there is no report on the π⋯π stacking interactions in these molecules. We present herein the first ever report on the intermolecular π⋯π stacking interactions in a substituted bis(2-pyridyl)diselenide that leads to a self-assembled supramolecular architecture. A search on Cambridge Structural Database (CSD) was undertaken to identify the π⋯π stacking interactions in various other bis(2-pyridyl)diselenides.

Results and discussion

Synthesis of 3-chloro- and 3-bromopyridylselenium compounds

A modified procedure of our recently developed methodology to lithiate 3-chloro- and 3-bromopyridine (**1a** and **1b**,

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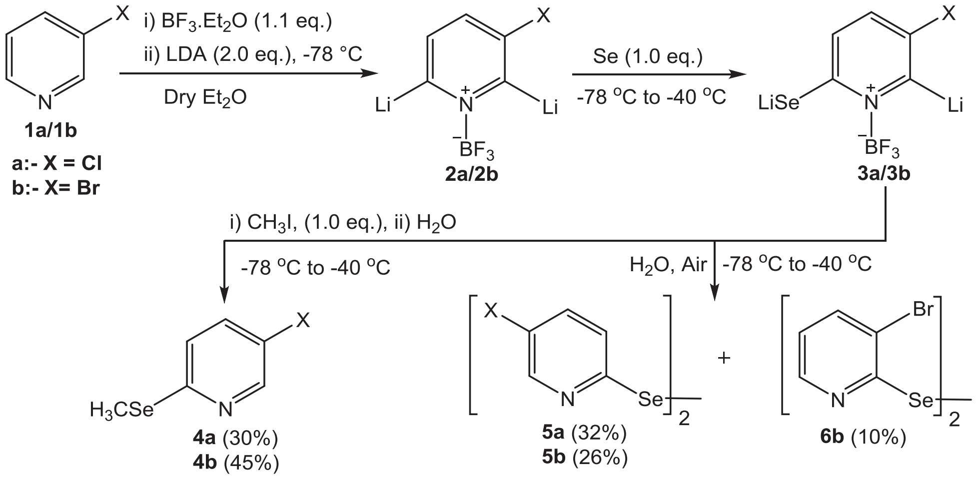


Scheme 1. Synthesis of monosubstituted selenium derivatives of 3-chloro- and 3-bromopyridine.

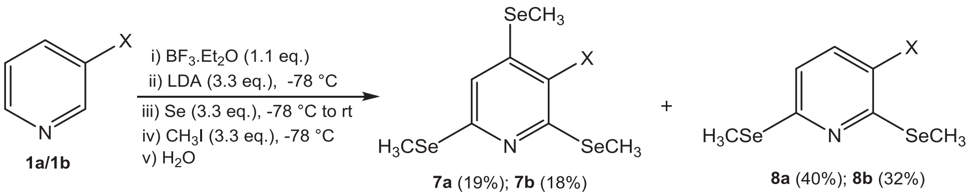
respectively) [21] was used to synthesize the halogen substituted pyridylselenium derivatives. BF_3 complexed **1a**/**1b** [21] was treated with LDA (2.0 equiv) followed by elemental selenium (1.0 equiv) at −78 °C. The resulting mixture was first warmed to −40 °C and then cooled again to −78 °C. The addition of iodomethane (1.0 equiv) followed by hydrolysis at −40 °C afforded **4a**/**4b** in a moderate yield (Scheme 1). The formation of **4a**/**4b** indicates the preferential insertion of selenium atom into the C(6)–Li bond to afford **3a**/**3b** (Scheme 1). The subsequent selenium insertion into C(2)–Li bond only takes place at a temperature higher than −40 °C. This is evident from the fact that when the reaction is performed above −40 °C it invariably gives a diselenated product [21]. We further extended this methodology and obtained bis(5-chloro-2-pyridyl)diselenide (**5a**) by subjecting the selenolate anion, **3a**, to hydrolysis and aerial oxidation at −40 °C. In a similar reaction involving **1b**, we obtained bis(5-bromo-2-pyridyl)diselenide (**5b**) and bis(3-bromo-2-pyridyl)diselenide (**6b**) in a 26% and 10% yield, respectively. We have also synthesized the triselenated and biselenated derivatives of **1a**/**1b** by the treating BF_3-complexed **1a**/**1b** with 3.3 equiv of LDA, selenium and iodomethane (Scheme 2). The present methodology affords halogen-substituted pyridylselenium compounds in moderate to low yields, by employing cheaper starting materials. The other possible routes to these compounds employ highly expensive di- and trihalogenated pyridines [22].

Synthesis of hydrochloride salt of bis(2-pyridyl)diselenides

Bis(2-pyridyl)diselenide (**5c**) and the methyl substituted bis(2-pyridyl)diselenides (**5d**–**5i**) were synthesized by the literature methods [5,6,11]. All the prepared diselenides are insoluble in water and soluble in conventional organic solvents, like THF, ethanol etc. To evaluate biological activities of these compounds in aqueous media, hydrochloride salts of bis(2-pyridyl)diselenides were prepared by addition of an aqueous HCl solution to an ice cooled immiscible mixture of the respective diselenide in water (Scheme 3). The hydrochloride salts of the diselenides are dark yellow in colour and are readily soluble in water. The acid-base (NaOH) titration [23] and elemental analysis indicate that there are two molecules of HCl attached per bis(2-pyridyl)diselenide molecule.

Spectroscopic studies

The ^1H NMR spectrum of **4a** showed three signals in the aromatic region. The spectrum of **4a** contains a doublet at δ 8.39–8.39 ppm with a small coupling constant value of 2.18 Hz. This indicates that the selenium atom is attached to the C-6 carbon of the pyridine ring. There are two other aromatic signals, at δ 7.47–7.49 (dd, $J = 2.40$ and 8.16 Hz) and δ 6.97–6.99 (d, $J = 8.60$ Hz, 1H) ppm. The $-SeC\underline{H}_3$ signal appears as singlet at δ 2.44 ppm. All the corresponding signals in **4b** appear slightly upfield. The ^1H NMR spectrum of **7a** contains only one singlet in the aromatic region at δ 6.77 ppm. The spectrum also contains three singlets in the aliphatic region at δ 2.41, 2.38 and 2.22 ppm due to $-SeC\underline{H}_3$ at C-2, C-6 and C-4 position, respectively. It is interesting to note that the ^1H NMR signals of **5c·HCl**, **5g·HCl** and **5h·HCl** show substantial downfield shift when compared with the parent diselenide. The protonation of bis(2-pyridyl)diselenides changes the electronegativity of the nitrogen atom and induces a deshielding effect on the molecule. The molecule **7a** has three, and **8a** has two non-equivalent selenium atoms which is evident from their ^{77}Se NMR spectra. In the spectrum of **7a**, the selenium signals appear at δ 222.4, 269.5 and 275.1 ppm. The signal at δ 222.4 ppm corresponds to the selenium atom at the C-4 position. The ^{77}Se signals in **8a** appear at δ 268.4 and 273.5 ppm. It is clearly evident that the addition of selenium induces a deshielding effect on the other selenium atom in the molecule.



Scheme 2. Synthesis of triselenium derivatives of 3-chloro- and 3-bromopyridine.