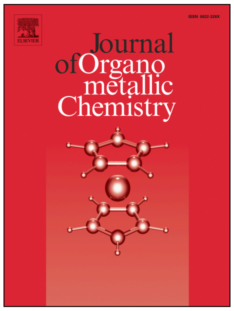

A^{77}Se NMR study of elemental selenium reduction using $NaBH_4$

Alfredo Ricardo Marques de Oliveira, Leandro Piovan, Fabio Simonelli, Anderson Barison, Maria de Fatima C. Santos, Murilo Belini Marcondes de Mello

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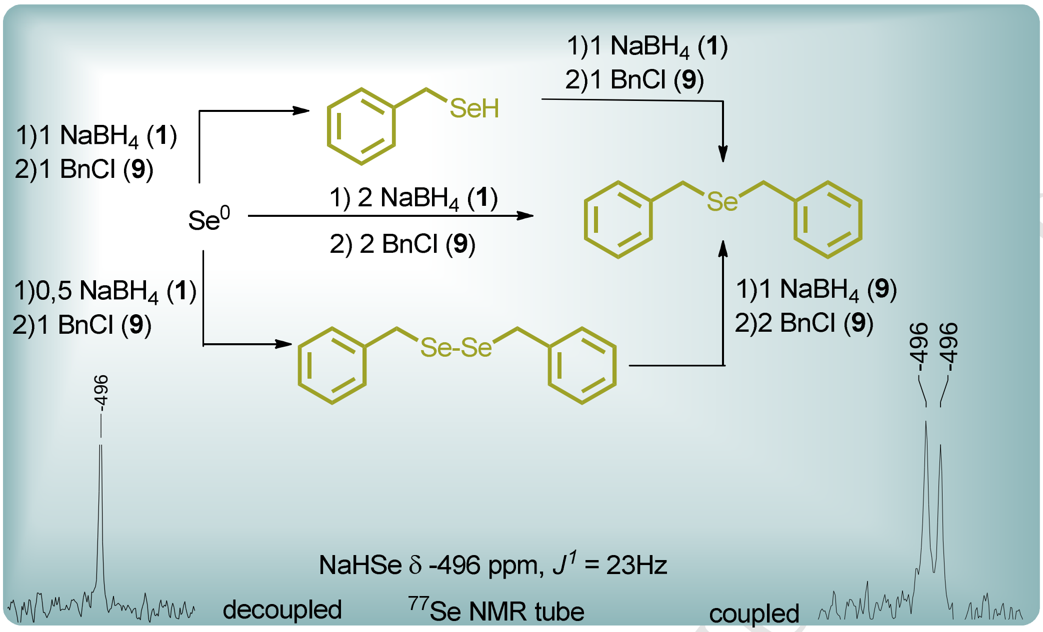

1)1 NaBH$_4$ (**1**)
2)1 BnCl (**9**)
SeH
1)1 NaBH$_4$ (**1**)
2)1 BnCl (**9**)
Se^0
1) 2 NaBH$_4$ (**1**)
2) 2 BnCl (**9**)
Se
1)0,5 NaBH$_4$ (**1**)
2)1 BnCl (**9**)
Se-Se
1)1 NaBH$_4$ (**9**)
2)2 BnCl (**9**)
-496
-496
-496
NaHSe δ -496 ppm, J^1 = 23Hz
decoupled
^{77}Se NMR tube
coupled

A^{77}Se NMR study of elemental selenium reduction using $NaBH_4$

Murilo B. M. de Mello, Maria de Fátima C. Santos, Fabio Simonelli, Leandro Piovan,
Andersson Barison, Alfredo R. M. Oliveira*

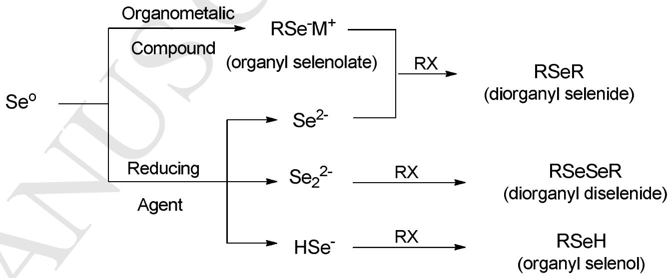
Abstract: Alkylation or arylation of selenide or diselenide anions is a well-established method to obtain organoselenium compounds. Nevertheless, detecting inorganic selenium anions using ^{77}Se NMR is still a challenge. In a previous work, alkylation of Na_2Se was found sometimes to yield a mixture of organyl selenides/diselenides in variable amounts. In the literature, this mixture is sometimes attributed to the oxidation of an intermediate alkyl selenol during the extraction. To understand this process, a series of experiments using ^{77}Se NMR were performed. It was clear from the ^{77}Se NMR experiments that $NaHSe^-$ and Se_2^{2-} formation was very dependent on the $NaBH_4$ stoichiometry used. After alkylation, alkyl selenol and dialkyl diselenide were identified, proving they were not formed during the extraction step. As a result, alkyl selenols, dialkyl selenides or dialkyl diselenides with a high purity degree were obtained. To achieve high purity and selectivity of the organoselenium compound, the stoichiometric ratio between $Se^0/NaBH_4$ has to be carefully measured.

Keywords: NaHSe ^{77}SeNMR detection, selenium reduction, selenide trapping.

1. **Introduction**

Over the last 50 years or so, the status of organoselenium compounds has changed from being considered highly toxic to a point where some of its members can be bought as food supplements, at local markets or pharmacies. Selenium is an essential trace element and lower levels of it in humans has been associated to several diseases including cancer and heart diseases.[1,4a] One illustrative disease related to selenium deficiency was the Keshan disease, which was identified some 50 years ago in northeast part of continental China and recently reviewed.[2] Selenium ingestion is almost exclusively *via* food and it´s bioavailability contents in it depends of the selenium level in soil.[3] Selenium plays an important role as participant of several antioxidant enzymes such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD).[4a-c] Selenocistein, recognized as the 21th amino acid essential for life, is found in several proteins. In mamals at least 30 selenoproteins were identified,[5,6] and there is an estimative that humans have about 25 selenoproteins.[7]

Organoselenium compounds can be obtained mainly through two synthetic strategies starting from elemental selenium: a) reaction with a convenient organometallic compound (RLi, RMgBr, etc.) to generate an organyl selenolate anion (RSe^-M^+); or b) reduction of Se^0 to selenide or diselenide anion (Se^{2-} or Se_2^{2-}), followed by alkylation (Scheme 1). To accomplish reduction, several agents, such as alkaline metals in liquid ammonia[8], $Li(Et)_3BH$,[9] SmI_2[10], NaH in DMF,[11] or Rongalite[12], can be used.



Scheme 1. Methods to selectively synthesize selenium compounds.

It is well known that the reaction of inorganic selenium anion (Se^{2-} or Se_2^{2-}) with an organic electrophile (RX) allows the synthesis of organyl selenols (RSeH), diorganyl selenides (RSeR) or diorganyl diselenides (RSeSeR). Moreover, selectivity depends on the stoichiometry ratio used at the reduction step.[13] Since the use of liquid ammonia imposes a series of experimental restrictions, the reduction reaction of selenium with $NaBH_4$ (**1**) in ethanol is a convenient method to prepare selenide anion. In addition, to simplify the experimental procedure, Yang reported that the presence of NaOH in this reaction eliminates hydrogen generation, when synthesizing sodium diselenide (Na_2Se_2).[14] Recently we had reported that during the synthesis of bis-2-methylene-2-oxazolinyl selenide (which involved the use of Na_2Se from the reduction of Se^0 (**2**) using $NaBH_4$ (**1**) in ethanol), a mixture of dioxazolinyl selenides and dioxazolinyl diselenides has sometimes been observed, even when oxygen and water was carefully avoided.[15] The available literature about this reduction reports conflicting results, where different stoichiometric ratios of reducing agent to Se^0 have been used to generate the same species or even worse, mixed species in different ratios (Se^{2-} + Se_2^{2-}).[16] This apparent contradiction prompted us to make a deeper ^{77}Se NMR study to investigate which selenium species were generated under selected conditions.^{77}Se has a ½ spin nucleus, no quadrupolar moment and isotopic abundance around 8%. These properties allows to acquire high resolution NMR spectra with sharp and high intensity signals over a wide chemical shift range.^{77}Se NMR spectroscopy can be used as a tool to follow reaction progress in an easy and direct way than those by ^{1}H and ^{13}C, where spectra are far more complex. ^{77}Se NMR spectroscopy was previously used by McFarlane[17] to investigate the Se_x^{2-} (x>2) anion. Eggert[18] and Björgvinsson[19] used the same tool to investigate the formation and

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[a]

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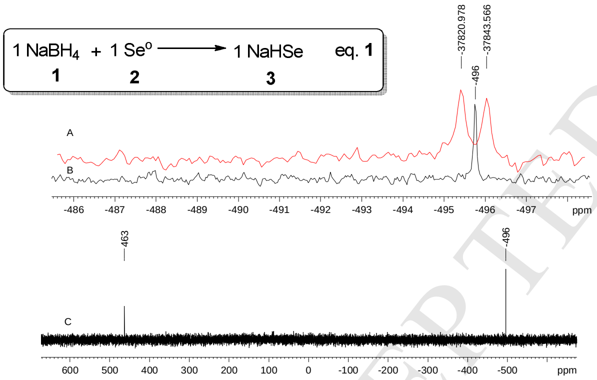
stability of polyselenides. However, the results were disappointing, since none of the authors could identify Se_2^{2-} species.[20] Similarly, in 1991 Cusik and Dance[21] reported the characterization of $[HSe]^-$ and $[Se_x]^{2-}$ ions using ^{77}Se NMR but were unable to identify the $[Se_2]^{2-}$ ion. Low temperature studies from the same group, shows that δ_{Se} for $[HSe]^-$ in DMF is large, around 1 ppm per degree. Having this in mind, we decided to trap any selenium species formed in the reduction reaction using an alkylating agent and following the results with ^{77}Se NMR analysis.

2. Results

2.1 Synthesis and ^{77}Se NMR study of NaHSe (3) species.

We began our work[22] by using ^{77}Se NMR to investigate the nature of the selenium species generated from the reaction of Se^0 with different stoichiometric ratios of $NaBH_4$ (**1**) in ethanol, into NMR tubes. For all NMR assays, diphenyl diselenide (**14**) (463 ppm) was employed as external reference. Thus, one equiv. of Se^0 (**2**) (19.7 mg, 0.25 mmol) and one equiv. of $NaBH_4$ (**1**) (9.4 mg. 0.25 mmol) (eq. 1) were placed into a 5 mm NMR tube followed by careful addition of 1 mL of anhydrous ethanol. The tube was capped with a small rubber septum with an outlet needle and degassed using purified nitrogen gas. This solution was limpid and light reddish-brown colored. The ^{77}Se hydrogen decoupled NMR spectrum for this solution showed only one signal at -496 ppm. When a coupled spectrum was acquired, this signal split into a doublet with a coupling constant of 23 Hz (Figure 1) that was assigned to NaHSe (**3**). Cusik[14] reported a similar result in water, with a chemical shift of -519 ppm and a coupling constant of 26 Hz.



$$\underset{\mathbf{1}}{1\,NaBH_4} + \underset{\mathbf{2}}{1\,Se^o} \longrightarrow \underset{\mathbf{3}}{1\,NaHSe} \qquad \text{eq. } \mathbf{1}$$

Figure 1. (**A**) NaHSe ^{77}Se NMR spectrum. Expanded ^{77}Se $\{^1H\}$ NMR (**B**). (**C**) ^{77}Se $\{^1H\}$ NMR full spectrum of NaHSe (**3**) in ethanol solution.

When one equivalent of benzyl chloride (BnCl) (**9**) was added to quench the reactive intermediates, the signal at -496 ppm rapidly was replaced by three new signals: one at 85 ppm, assigned to benzyl selenol (**6**), one at 330 ppm referring to dibenzyl selenide (**7**) and one at 401 ppm, assigned to dibenzyl diselenide (**8**) (Figure 2).[23] These assignments were supported by the multiplicities of the signals observed on the corresponding coupled ^{77}Se NMR spectra (See supplementary information). Formation of dibenzyl diselenide (**8**) was not expected to occur in a reductive medium. In order to verify if any oxidation process was taking place, oxygen was bubbled in the NMR tube for 30 minutes and a new spectrum was acquired. The changes in signal intensities for benzyl selenol (**6**) and for dibenzyl diselenide (**8**) were not evident, showing that the oxidation process is relatively slow. Benzyl selenol (**6**) was still the major compound in the mixture. Compounds **7** and **8** were present in small varying amounts and their presence was related with the reaction color, where a darker solution indicated greater amounts of **7** and/or **8** in solution, as confirmed by ^{77}Se NMR analysis.

It is known that $NaBH_4$ (**1**) slowly decomposes in the presence of ethanol.[24]Thus, to study its influence on the reduction of Se^0 (**2**), one equiv. of $NaBH_4$ (**1**) was carefully weighed and dissolved in 1 mL of anhydrous ethanol. It was immediately possible to detect a small amount of gas being slowly released. Upon addition of this solution to a flask containing solid Se^0 (**2**), a copious amount of hydrogen was released. This indicates that most $NaBH_4$ (**1**) was active, but the final solution had a reddish-brown color. Titrating the resulting solution with a small volume of diluted $NaBH_4$ (**1**) ethanol solution yielded a colorless limpid solution. As expected, further addition of BnCl (**9**) yielded only benzyl selenol (**6**). This result indicates that generation of pure NaHSe (**3**) is very sensitive to the amount/quality of $NaBH_4$ (**1**) used and any deviation can result in formation of varying amounts of alkyl selenol (from NaHSe (**3**)), dialkyl selenide (from double alkylation of NaHSe (**3**)) and dialkyl diselenides (from Na_2Se_2(**5**)) (Figure 2).

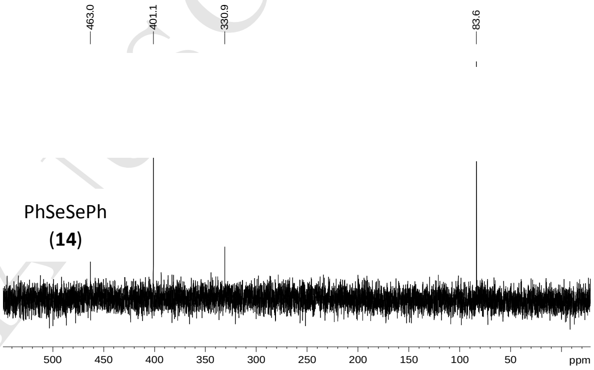


Figure 2. ^{77}Se $\{^1H\}$ NMR spectrum showing the signals for benzyl selenol (**6**) (83.6 ppm), dibenzyl selenide (**7**) (330.9 ppm), dibenzyl diselenide **8** (401.1 ppm) and diphenyl diselenide(**14**) (463 ppm).

This reaction was repeated in an attempt to identify Na_2Se (**4**) and the NMR spectrum was swept for a wide spectral width, to look for the presence of any other selenium species. The only observed signal was the singlet at -496 ppm. Its coupled spectrum showed a doublet (*J*=23Hz) assigned to NaHSe. Upon treatment with a 5% NaOH aqueous solution, the coupled spectra changed to a deformed singlet at -491 ppm. This signal is not compatible with a Na_2Se (**4**) species since it has the same chemical shift of NaHSe (**3**).[25] The observed line broadening can be attributed to a fast exchange of Se^{2-} with HSe^-.[21] Once more, the NMR field was swept for a wide spectral width and no other signal was detected in this experiment (Figure 3).

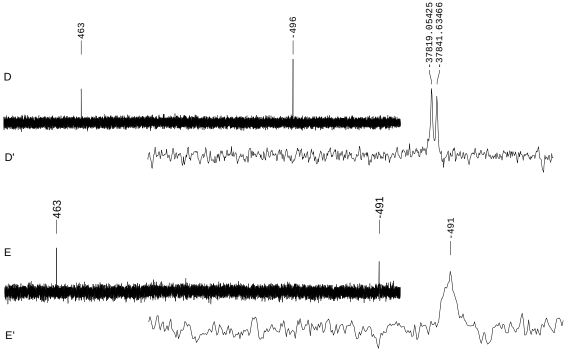


Figure 3: ^{77}Se $\{^1H\}$ NMR spectra (**D**) and ^{77}Se (**D'**) before addition of a 5% NaOH aq. sol. to the NaHSe (**3**) and (**E**) and (**E'**) after addition.

When a ratio of 2:1 equiv. of $NaBH_4$ (**1**):Se^0 (**2**) was used, the only observable signal[26] was at -496 ppm and its coupled spectra splits into a doublet, indicating Se-H coupling. This shows that the $NaBH_4$ (**1**) excess is not basic enough to promote the second deprotonation. However, when the reaction mixture was treated with two equivalents of BnCl (**9**), dibenzyl selenide (**7**) was exclusively formed. In order to get further information about this reaction, we also performed it in two steps. Thus, initial reduction of Se^0 (**2**) with one equiv. of $NaBH_4$ (**1**) followed by addition of one equiv. of BnCl (**9**) only furnished benzyl selenol (**6**). Then, addition of a second equivalent of $NaBH_4$ (**1**) (**CARE!** Rapid hydrogen evolution) followed by another equiv. of BnCl (**9**) yielded dibenzyl selenide (**7**) as the only product (Figure 4). Therefore, the above results indicate that $NaBH_4$ (**1**) is basic enough to promote the deprotonation of benzyl selenol (**6**) but not to deprotonate NaHSe (**3**).

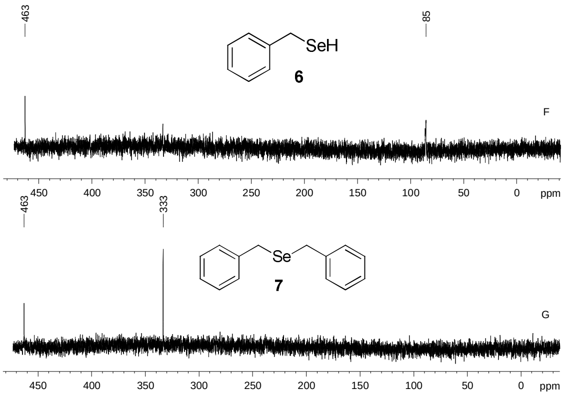


Figure 4: (**F**) ^{77}Se {^{1}H} NMR spectra of benzyl selenol (**6**) and (**G**) after alkylation yielding (**7**).

2.2 Synthesis and ^{77}SeNMR study of Na_2Se_2 (5) species.

To complete our investigation was necessary to obtain Se_2^{2-} in a reproducible way. There are two general methods described to generate Na_2Se_2 (**5**) from elemental selenium: a) using a 3:2 ratio of Se^0 (**2**):$NaBH_4$ (**1**) in ethanol as solvent, yielding a mixture of Na_2Se_2 (**5**) and H_2Se (**10**) (which was driven off by a stream of an inert gas), and b) formation of Na_2Se_2 (**4**), using $NaBH_4$ (**1**), followed by addition of one more equiv. of Se^0 (**2**). After generating Na_2Se_2 (**5**) using the first method no signal was observed in the ^{77}Se {^{1}H} NMR spectrum. However, addition of BnCl (**9**) rapidly generated a strong signal at 402 ppm, which was assigned to the dibenzyl diselenide (**8**). Reduction of **8** using one equivalent of $NaBH_4$ (**1**) followed by addition of one equivalent of BnCl (**9**) forms selectively dibenzyl diselenide (**7**) (Figure 5).

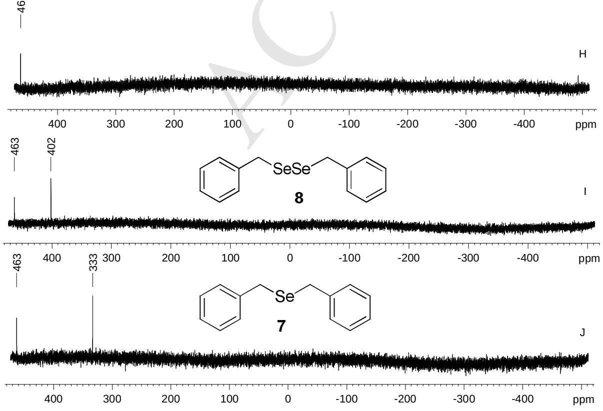


Figure 5. (**H**) ^{77}Se {^{1}H} NMR spectrum of Se^0 (**2**) reduction to Na_2Se_2 (**5**). (**I**) Compound **8** after alkylation. (**J**) Conversion to **7**.

The fact that Na_2Se_2 (**5**) has no detectable signal by ^{77}Se NMR spectroscopy is known and has been described elsewhere.[20, 21] Only HSe^- (**3a**) specie could be identified and no other selenium negative ions were observed. Therefore a freshly prepared Na_2Se_2 (**5**) solution was acidified with HCl and its ^{77}Se NMR spectrum was acquired. We were unable to detect any signal for H_2Se_2 (**12**) in this system even when exploring a very wide spectral window.

One last experiment was performed to try to detect the presence of the anion $BnSeSe^-$ (**14**). Dibenzyl diselenide (**8**) was synthesized in a 1 mmol scale and was isolated in 97% yield using Na_2Se_2 as a precursor. 0.1 mmol of compound **8** was reduced with 0.2 mmol of $NaBH_4$ (**1**) and the ^{77}Se NMR acquired to verify the presence of $BnSe^-$ (**13**). No signals were observed. To this solution was added another equivalent of Se^0 (**2**), forming a limpid and brownish solution (possibly $BnSeSe^-$) (**14**). Again, this solution gave no signal in the ^{77}Se {^{1}H} NMR spectrum. After 5 minutes, another equivalent of BnCl (**9**) was added to regenerate BnSeSeBn (**8**) was obtained as a major product and trace amounts of benzyl selenide (**7**) (Figure 6).

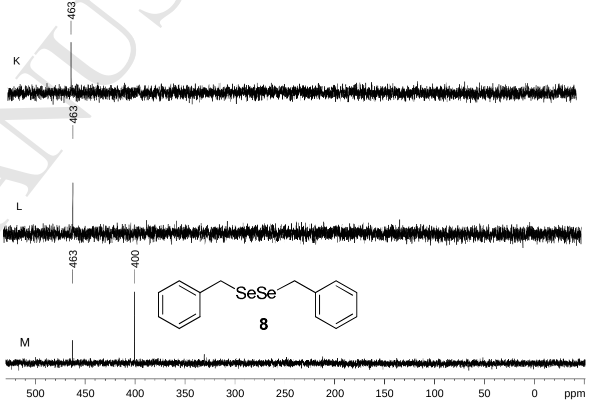
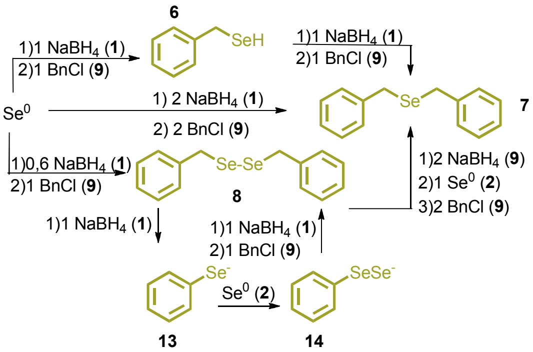


Figure 6. ^{77}Se {^{1}H} NMR spectra (**K**) showing the reduction of dibenzyl diselenide (**8**). (**L**) Reaction with elemental selenium. (**M**) Alkylation with BnCl (**9**). $BnSe^-$ (**13a**) and $BnSeSe^-$ (**13**) does not shows signals in ^{77}Se {^{1}H} NMR spectra.

Scheme 3 displays a summary of all reaction made to detect which selenium anion species were in solution after reduction of elemental selenium. It is worth of note that no polyselenides were trapped or detected using ^{77}Se NMR, coupled or decoupled, spectroscopy.



Scheme 3. Summary of all selenium anions species that could trapped and identified in this work.

No signal for polyselenides anions or dibenzylpolyselenides were detected. Eggert[18b] reported the ^{77}Se NMR shifts for $BnSe_xBn$ (x=2-4) and using the specified experimental conditions these higher selenides were not observed.

3. Conclusions.

The results shows that the generation of pure NaHSe (**3**) was very sensitive to the stoichiometric ratio between Se^0 (**2**) and $NaBH_4$ (**1**). If there is an excess of Se^0 (**2**), then selenides or diselenides (or a mixture) were obtained. If $NaBH_4$ (**1**) was in excess, dibenzyl selenide (**7**) was generated. Either way, the benzyl selenol (**6**) was always the main product when there was a small error in the measurement of $NaBH_4$ (**1**). We also demonstrated that Na_2Se_2 (**4**) formation is in equilibrium with NaHSe (**3**) and is not formed as part of an oxidation process on extraction. In addition, $NaBH_4$ (**1**) is not basic enough to deprotonate NaHSe (**3**) but can easily deprotonate benzyl selenol (**6**), yielding the corresponding selenolate. For the Na_2Se_2 (**4**) alkylation process, any deviation of the stoichiometry of $NaBH_4$ (**1**) used always leads to the formation of benzyl selenol (**6**) in small amounts and dibenzyl diselenide (**8**) as the major compound. In a last attempt to detect a negative selenium ion, (**8**) was reduced, using the established protocol and one equivalent of Se^0 (**2**) was added to the resulting colorless solution. No signal was observed for the presence of $BnSeSe^-$ (**13**), which after alkylation regenerates the dibenzyl diselenide (**8**). It is clear that Se^{2-} or Se_2^{2-} or any other selenium anion does not give any signal in the ^{77}Se {^{1}H} NMR spectrum although using an alkylating agent allowed the trapping of several selenium anions in solution. Moreover, several insights over the ^{77}Se NMR chemical shifts were presented that can help researches in their works in the synthesis of selenium compounds, been them organic or inorganic ones.

4. Acknowledgements

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[25] Selenium species are very sensitive with changes in electronegativity around the nucleus. Selenium negative species should have a low frequency while positive species should have a high frequency shift.

[26] The variations in the ^{77}Se NMR chemical shift can be attributed to its medium dependence properties, especially with temperature changes.

- An in-depth analysis of inorganic selenide anions ^{77}Se NMR is reported.
- Selenium anions species not detected by ^{77}Se NMR could be trapped by alkylation.
- Dialkyl selenides, dialkyl diselenides or alkylselenols were selectively obtained.
- ^{77}Se NMR spectra for organic and inorganic selenide anions is reported.