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Efficient Chiral Discrimination by ^{77}Se NMR

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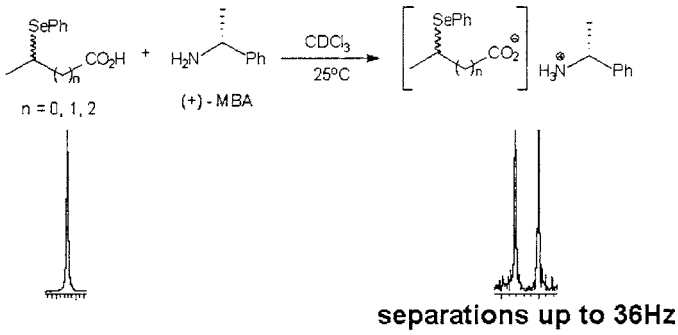
ABSTRACT



Several ^{77}Se NMR experiments were performed by titrating a sample of selenides with the chiral shift reagent methylbenzylamine (MBA), followed by acquisition of ^{77}Se NMR spectra. Eventually, we observed the appearance of two anisochronous resonances, with a relatively large separation, from 37 to 56 Hz, corresponding to the formation of the diastereomeric complexes. This methodology avoids derivatization processes, and the studied compound can be easily recovered from the NMR tube.

Recent advances in stereoselective synthesis and asymmetric catalysis have created an increasing demand for more accurate and convenient methods of measuring enantiomeric purity.[1]

In the mid-1960s, the chiroptical methods were the most used techniques for the determination of enantiomeric purity.[2] They involved measurement of the optical rotation of the sample, under rigorously controlled conditions, with a properly calibrated polarimeter. This method, however, is not entirely accurate, since optical and enantiomeric purities are not necessarily equivalent.[3]

Nowadays, most nonchiroptical methods for the determination of enantiomeric purity are indirect. Indeed, recent progress in GC-,[4] HPLC-,[5] and NMR-based methods[6] has made them widely used.

Chiral derivatizing agents[7] (CDAs) for NMR spectroscopy are commonly used for the determination of enantiomeric purity, the standard reagents for the determination of enantiomeric excesses of alcohols and amines being α-methoxy-α-(trifluoromethyl) phenylacetic acids (MTPA, Mosher's esters).[8]

Techniques have already been described for the determination of enantiomeric excesses via ^{77}Se NMR spectroscopy,

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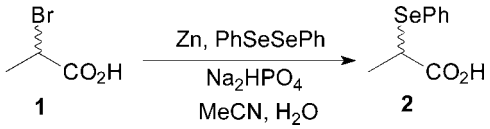
more specifically for the assignment of absolute configurations of acids and acid chlorides,[9] amino acids,[10] and alcohols.[11] Indeed, there are definite advantages in using ^{77}Se as opposed to using ^{13}C. By comparison, while the sensitivity of the ^{77}Se nucleus is three times higher than that of ^{13}C, its natural abundance is 7.5% (the natural abundance of ^{13}C is 1.10%). Additionally, selenium is very sensitive to its electronic environment and possesses a large chemical shift range (approximately 3400 ppm). These characteristics make selenium an excellent nucleus for NMR research.[12]

Recently, we described an efficient methodology for the preparation of selenides **2** from the corresponding halides **1**, promoted by zinc in aqueous media (Scheme 1).[13]

Scheme 1

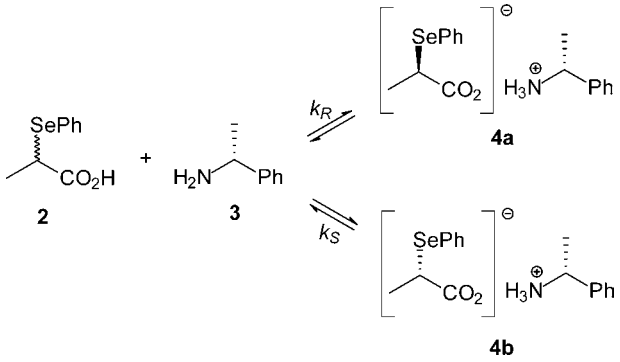


1 **2**

However, the reaction mechanism is yet to be determined.

To accurately determine if the reaction proceeded via an enantioselective pathway, we turned our attention to analyzing the enantiomeric composition of the obtained selenides. Our strategy was based on the formation of diastereomeric complexes as shown in Scheme 2, each yielding a different

Scheme 2



NMR signal, the signal separation being dependent on the sizes of the diastereomeric complexation constants, K_R and K_S.

Several ^{77}Se NMR experiments were attempted with (+)-methylbenzylamine [(+)-MBA] as a chiral solvating agent (CSA). These were performed by titrating a sample of racemic **2** with the chiral base followed by the acquisition of ^{77}Se NMR spectra. Figure 1 shows the ^{77}Se NMR spectra

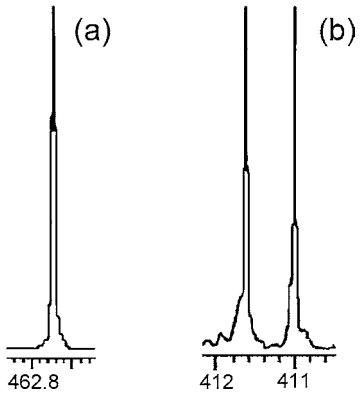


Figure 1. ^{77}Se NMR spectra (57.21 MHz, $CDCl_3$, parts) of compound **2** (a) neat in $CDCl_3$ and (b) after addition of 1.23 equiv of (+)-MBA.

of compound **2** in $CDCl_3$ at 25 °C in two different experimental conditions: before and after the addition of the CSA. Racemic **2** appeared as a single peak at 462.8 ppm (spectrum 1a) before the addition of (+)-MBA. After the addition of increasing amounts of (+)-MBA to a solution of **2**, two separate anisochronous resonances at 411.1 and 410.5 ppm, corresponding to a separation of 37 Hz, were obtained from the formation of the diastereomeric complexes. Results from experiments involving (+)-MBA and the racemic mixture of **2** are shown in Table 1. No separation was observed until 0.47 equiv of (+)-MBA was added to the NMR tube containing a solution of **2** in $CDCl_3$ (Table 1, entries 1−5). However, further additional amounts of (+)-MBA to the NMR tube did result in the signal separations of the corresponding diastereomeric salt complexes in solution.

This stoichiometry dependence suggests that the formation of a significant amount of 1:1 complex is required to maximize $\Delta\delta_{R,S}$. Beyond the 1:1 ratio, further additions of (+)-MBA do not substantially increase the signal resolution (Table 1, entries 10−12). A subsequent experiment using (−)-MBA instead of (+)-MBA yielded equivalent results, indicating that either CSA may be used.

This nonequivalent behavior was also observed in the ^{1}H NMR spectra. However, this time, the resonances corresponding to the methyl and methylene groups were not sufficiently resolved to allow an accurate integration.

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Table 1. Observed Nonequivalence of Selenides **2** in the Presence of (+)-Methylbenzylamine [(+)-MBA] in Different Solvents and Conditions

entry	molar fraction of (+)-MBA and **2** [conditions]	δ (ppm) ^{77}Se NMR	$\Delta\delta_{R,S}$ (Hz) ^{77}Se NMR
1	0.00 [$CDCl_3$, 25 °C]	462.9	0.0
2	0.11 [$CDCl_3$, 25 °C]	455.6	0.0
3	0.19 [$CDCl_3$, 25 °C]	448.8	0.0
4	0.26 [$CDCl_3$, 25 °C]	442.3	0.0
5	0.32 [$CDCl_3$, 25 °C]	436.2	0.0
6	0.37 [$CDCl_3$, 25 °C]	430.1 and 430.2	9.2
7	0.41 [$CDCl_3$, 25 °C]	424.4 and 424.6	14.9
8	0.45 [$CDCl_3$, 25 °C]	418.8 and 419.2	22.3
9	0.48 [$CDCl_3$, 25 °C]	413.3 and 413.8	33.2
10	0.50 [$CDCl_3$, 25 °C]	411.2 and 411.8	36.0
11	0.52 [$CDCl_3$, 25 °C]	410.7 and 411.3	36.6
12	0.56 [$CDCl_3$, 25 °C]	410.5 and 411.1	36.6
13	0.56 [$CDCl_3$, DMSO-d_6 (4 μL), 25 °C]	409.8 and 410.3	26.3
14	0.56 [$CDCl_3$, DMSO-d_6 (8 μL), 25 °C]	408.7 and 409.0	16.6
15	0.53 [C_6D_6, 25 °C]	411.5 and 412.5	56.6
16	0.44 [$CDCl_3$, −40 °C]	408.4 and 408.7	16.0
17	0.44 [$CDCl_3$, −25 °C]	410.2 and 410.7	27.5
18	0.44 [$CDCl_3$, −10 °C]	412.2 and 412.7	26.3
19	0.44 [$CDCl_3$, 5 °C]	414.3 and 414.7	22.8
20	0.44 [$CDCl_3$, 25 °C]	417.8 and 418.2	23.5
21	0.44 [$CDCl_3$, 40 °C]	420.7 and 421.0	16.6

We confirmed the observation that nonpolar solvents tend to increase the observed anisochrony, while polar solvents decrease the anisochrony by solvating the diastereomeric complexes to a point that $\Delta\delta_{R,S}$ tends toward zero.[14] As such, the addition of even a small amount of a polar solvent (e.g., 8.0 μL of dimethyl sulfoxide-d_6) to the NMR tube containing a solution of **2** and 1.23 equiv of (+)-MBA in $CDCl_3$ at 25 °C resulted in a severe reduction of the signal separation, from 37 to 16 Hz (Table 1, entries 12−14), that is, 21 Hz.

On the other hand, dissolving **2** in benzene-d_6, a nonpolar solvent, increased the separation between the two enantiomer signals by 19 Hz, in comparison to $CDCl_3$ (Table 1, entry 15).

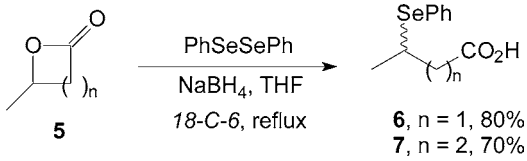
We also studied the effect of the variation of temperature, from −25 to 40 °C, on $\Delta\delta_{R,S}$. Raising the temperature decreases the signal separation, which we interpret as a displacement of the diastereomeric complexation equilibrium toward the reacting species, indicating an exothermic process[15] (Table 1, entries 16−21).

The existence of the complex dissociation equilibria should be taken into consideration when measuring enantiomeric purity by NMR spectroscopy. Clearly, dissociation can reduce the signals separation.

Moreover, since both diastereomeric dissociation constants need to be equal, the magnitude of the signal separation can change with variations in the enantiomeric purity. This phenomenon was observed in other diastereomeric salt systems.[16]

The efficiency of the present methodology for the detection of remote chiral centers was also evaluated. Compounds **6** and **7** were synthesized following a described procedure (Scheme 3).[17]

Scheme 3



To analyze its usefulness, the same methodology employed in the determination of the signal separation of **2** was used to determine the enantiomeric purity of selenium compounds when the carboxylic group, which reacts with (+)-MBA, is placed more and more distant from the chiral center.

Likewise, results from our experiments involving (+)-MBA and the racemic mixture of **6** are shown in Table 2. No separation was again observed until 0.47 equiv of (+)-MBA was added to the NMR tube containing a solution of **6** in $CDCl_3$ (Table 2). Further additions of (+)-MBA to the NMR tube led to larger separations of signals when compared to the results obtained for compound **2**. When the same experiment was repeated with compound **7**, no signal

Table 2. Observed Nonequivalence of Selenide **6** in the Presence of (+)-Methylbenzylamine [(+)-MBA] in Different Solvents and Conditions

entry	molar fraction of (+)-MBA and **6** [conditions]	δ (ppm) ^{77}Se NMR	$\Delta\delta_{R,S}$ (Hz) ^{77}Se NMR
1	0.0 [$CDCl_3$, 25 °C]	420.1	0.0
2	0.21 [$CDCl_3$, 25 °C]	417.5	0.0
3	0.30 [$CDCl_3$, 25 °C]	416.4 and 416.6	8.0
4	0.37 [$CDCl_3$, 25 °C]	415.6 and 415.9	17.2
5	0.40 [$CDCl_3$, 25 °C]	415.0 and 415.5	24.6
6	0.44 [$CDCl_3$, 25 °C]	414.6 and 415.2	32.0
7	0.47 [$CDCl_3$, 25 °C]	414.3 and 414.9	37.2
8	0.51 [$CDCl_3$, 25 °C]	414.1 and 414.8	41.2
9	0.54 [$CDCl_3$, 25 °C]	413.9 and 414.7	42.3

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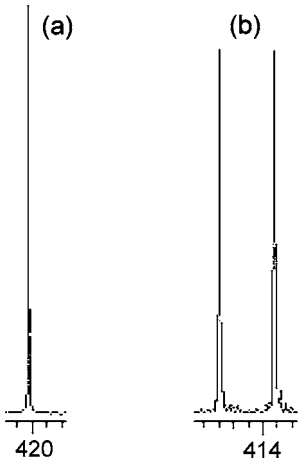

Figure 2. ^{77}Se NMR spectra (57.21 MHz, $CDCl_3$, parts) of compound **6** (a) neat in $CDCl_3$ and (b) after addition of 1.15 equiv of (+)-MBA.

separation was observed, but only a single peak appeared. This effect is similar to one previously described[9a] where, after six covalent bonds from the chiral center, the selenium NMR signal is unable to differentiate between the diastereoisomers. Our results show that such behavior is also true for salts, where bonds other than covalent bonds are present. Indeed, in compound **7**, the amine chiral center is seven bonds away from the selenium atom.

In summary, we have demonstrated on a racemic selenide a potential alternative method for the enantiomeric analysis of selenides. The methodology can be done in situ in an NMR tube and avoids derivatization processes and the compound under investigation can be easily recovered. Furthermore, either (+)-MBA or (−)-MBA can be used as a CSA. Moreover, the signal separations observed were relatively large, from 37 to 56 Hz, allowing for a clean diastereomeric signal resolution.

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Supporting Information Available: Typical ^{77}Se NMR spectra of the obtained compounds, before and after the addition of increasing amounts of (+)-MBA, and tables comparing the signal separation between ^{1}H and ^{77}Se NMR, showing that the ^{77}Se separation is much larger and resolvable than the corresponding ^{1}H ones. This material is available free of charge via the Internet at http://pubs.acs.org.

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