Simple enantiomeric excess determination of amines using chiral selones:† unusual N–H···Se bonding detected by HMQC $^{1}H/^{77}Se$ NMR spectroscopy

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One-pot coupling of a chiral selone derivatizing agent to a series of chiral and racemic amines mediated with triphosgene gives adducts in yields ranging from 80–99%; ^{77}Se NMR spectroscopy evaluation of the diastereoisomeric adduct conveniently allows the determination of the enantiomeric excesses of the parent chiral amines.

The development of new NMR spectroscopic methods and reagents for the convenient determination of ees and absolute configuration of chiral compounds is important to both the pharmaceutical and chemical industries.[1] We[2a–e,i] and others[2f] have been exploiting the extreme chemical shift sensitivity of the ^{77}Se nucleus for the detection and quantitation of chirality at remotely disposed chiral centres in alcohols, carboxylic acids and acid chlorides using a single multifunctional chiral selone derivatizing agent (CDA) **A** (Fig. 1). In some cases **A** has proven to be useful for the assignment of the absolute configuration in several derivatized amino acids.[3] Others are applying the use of the extreme δ_{Se} sensitivity to the development of new selenium based CDA's.[1c,2g,h] Here we disclose that amine–selone adducts can be constructed in a one-pot process, while maintaining the ability of the observing selenium nucleus to discern remotely disposed chiral centres. Moreover, by employing ^{1}H-^{77}Se HMQC NMR experiments we have uncovered a unique selenium–hydrogen bonding interaction in these complexes. These studies indicate that this class of selenium-based CDA's is the first which has been designed to have broad applicability for a range of functional groups with enhanced chemical shift sensitivity.

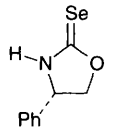


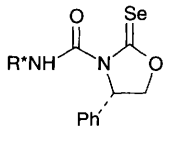
Fig. 1

In an effort to increase the utility of these selone CDA's we developed a one-pot triphosgene-mediated coupling of both chiral and racemic amines to the chiral selone **A** (Fig. 1).‡ Evaluation of the resulting adducts by ^{77}Se NMR spectroscopy demonstrated that the outstanding chemical shift sensitivity of the selenium nucleus in these systems has been preserved (Table 1). Coupling the amine of choice to **A** is accomplished using a triphosgene derived carbonyl bridge. We examined the use of both pyridine (method A) and potassium *tert*-butoxide (method B) as the base used to promote the coupling reaction. For amines with an α-chiral centre, method A was generally observed to provide the adduct **3** without kinetic resolution. However, method B gave erratic results when using enantiomeric mixtures of the same parent amine. When the amine chiral centre was further removed from the coupling site method B gave results comparable to method A, with the absence of kinetic resolution. The use of 1° amines in the coupling reaction gives good to excellent yields. Of the compounds tested, this coupling process tolerates other functional groups such as ethers, esters, alkyl and aromatic groups.

The $\Delta\delta_{Se}$ of our amine adducts indicates that the chemical shift sensitivity of the selenium nucleus found in our studies of carboxylic acids, alcohols and acid chlorides has now been extended to these systems. Remarkably, for entry 1 (Table 1) the chiral centre is 7 bonds removed from the observing selenium nucleus and the $\Delta\delta_{Se}$ = 54 ppm. In general, these adducts gave a greater $\Delta\delta_{Se}$ for the same bond distances when compared to the $\Delta\delta_{Se}$ in carboxylic acid or alcohol adducts.[2]

During the course of this work we measured both the proton coupled and decoupled ^{77}Se spectra of a number of selone amine adducts and have determined that there exists one distinct $J_{Se\text{-}H}$ for each diastereoisomeric adduct. These coupling constants were of the order of 13 Hz (Fig. 2 and Table 1). This proton coupling is too large for a $^{5}J_{Se\text{-}H}$, and in an effort to

Table 1 Coupling and ^{77}Se NMR data of (+, −) amine adducts



Compound	R	Δδ/ppm ($CDCl_3$)[a]	Ratio of adducts[b]	$^{1}J_{SeH}$ /Hz	Number of bonds[c]	Yield (%)[d]
1	$Me(Ph)CHCH_2CH_2$	0.54	49.9:50.1	12.1	7	80
2	$Me(Ph)CHCH_2$	0.98	49.9:50.1	12.3	6	86
3	Me(Ph)CH	0.87	49.8:50.2	12.3	5	91
4	$Et(Me)CHCH_2$	0.22	49.6:50.4	12.2	6	95
5	Et(Me)CH	0.43	49.9:50.1	12.4	5	82
6	$MeOCH_2(Me)CH$	0.11	50.0:50.0	13.1	5	99
7	$p\text{-}ClC_6H_4CH_2(CO_2Me)CH$	2.45	49.8:50.2	12.7	6	82

[a] Selenium chemical shifts have been shown to be solvent, concentration and temperature dependent.[2e] [b] Integration of the ^{77}Se NMR resonances. [c] Number of bonds from the observing selenium nucleus to the chiral centre. [d] Using method A.

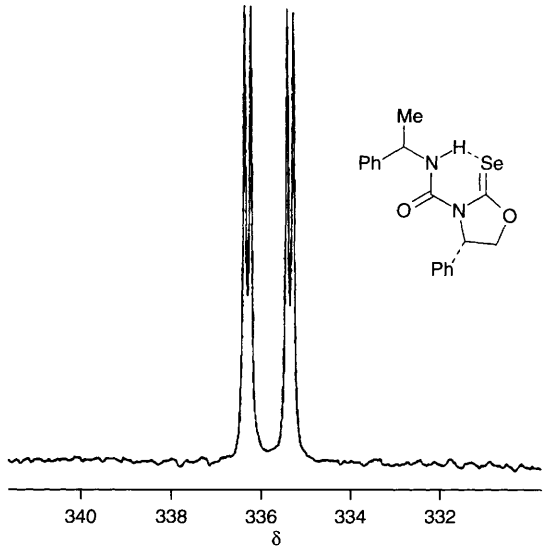


Fig. 2 ^{1}H coupled 1D ^{77}Se NMR spectrum of **3**

determine the origin of this coupling we performed HMQC ^{77}Se-^{1}H experiments.§ From the results of these experiments on **3**,¶ we concluded that the amine adduct assumes an *anti* carbonyl relationship and that the N–H must be hydrogen bonded to the selenium atom of the selenocarbonyl. Combined with the recent discovery of a C–H···Se through space 'hydrogen bond',[4] the results presented herein may signal the potential for significant hydrogen selenium bonding interactions within biomacromolecular systems which contain either selenomethionine or selenocystein.[5]

In summary, we have outlined a simple triphosgene mediated procedure for the formation of an adduct between 1° and 2° amines and **A**. From the ^{77}Se NMR analysis of the adducts we are confident that oxazolidin-2-selones represent a new class of CDA's with enhanced sensitivity which can be coupled to a wide variety of functional groups. These new CDA's are likely to enjoy widespread use for the detection and quantitation of chiral centres which are remotely disposed.

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Footnotes

† R & D Magazine 100 Award winner for 1993; US Pat Nos. 5 122 472 and 5 344 936.

‡ A representative procedure is as follows. Method A: To a solution of triphosgene (0.050 g, 0.166 mmol) in CH_2Cl_2 (5.0 ml) was added pyridine (0.040 ml, 0.500 mmol) dropwise at 0 °C. The mixture was then cooled to −78 °C and a solution of selone (0.113 g, 0.500 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise using a double tipped needle. The mixture was stirred at −78 °C for 1 h and (*R,S*)-2-methyl-1-butylamine (0.030 g, 0.333 mmol) followed by triethylamine (0.101 g, 1.0 mmol), were added dropwise. The mixture was allowed to warm to room temp. and stirred for 1 h. The resulting solution was filtered through silica gel and washed with CH_2Cl_2 (30.0 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, CH_2Cl_2) to provide 0.107 g (95%) of the adduct. Method B: To a solution of selone (0.0905 g, 0.400 mmol) in CH_2Cl_2 (10.0 ml) was added Bu^{t}OK (0.040 ml, 0.400 mmol, 1.0 mol l^{-1} in THF) dropwise at 0 °C. The mixture was allowed to warm to room temp and stirred for 1 h. To a solution of triphosgene (0.055 g, 0.180 mmol) in CH_2Cl_2 (5.0 ml) was added the above mixture dropwise, using a double tipped needle, at −78 °C. The resulting solution was stirred at −78 °C for 1 h. (*R,S*-2-Butylamine (0.015 g, 0.200 mmol) was added dropwise followed by dropwise addition of *N,N*-diisopropylethylamine (0.155 g, 1.200 mmol). The mixture was allowed to warm to room temp. and stirred for 1 h. The resulting solution was filtered through silica gel and washed with dichloromethane until the TLC showed the product was eluted. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, CH_2Cl_2) to provide 0.050 g (76%) of the adduct. All new compounds have been fully characterized (IR, ^{1}H, ^{13}C, ^{77}Se, HRMS and/or elemental analysis).

§ Natural abundance (^{1}H, ^{77}Se) HMQC spectra of **3** was recorded at 298 K in the phase sensitive mode[6] with 256 experiments, (56 scans per FID) and collected on a Bruker 500 MHz spectrometer. The carrier for ^{77}Se was centered at 95.4145 MHz with a sweep width of 19082.8 Hz and the proton carrier was centered at 500.1374 MHz with a sweep width of 6578.95 Hz. The ^{77}Se chemical shifts are referenced to diphenyldiselenide [460 ppm relative to a 60% solution (*v/v*) of dimethylselenide in $CDCl_3$ (0 ppm)] and ^{1}H chemical shifts are referenced to tetramethylsilane (0.0 ppm). Data was processed using a Silicon Graphics Indigo running Felix 2.3 (Biosym Technologies, Inc.) with zerofilling to 2 k and a sine square window function with a 90 phase shift applied in both dimensions prior to the Fourier transformation. To the best of our knowledge this represents the second example of a (^{1}H, ^{77}Se) HMQC NMR experiment.

¶ The HMQC experiment was performed on a sample which had unequal amounts of adduct diastereoisomers.

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