Preparation and NMR studies of 3-selenaheptadecanoic and 4-selenaoctadecanoic acid, $RSe(CH_2)_nC(O)OH$ (R = $C_{14}H_{29}$, n = 1 and 2), and their methyl esters

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The synthesis of the title compounds and their precursor, ditetradecyl diselenide, R_2Se_2, in high yield and of high purity is described. A 600 MHz ^1H NMR study at 298 K in $CDCl_3$ and CCl_4 has revealed that 4-selenaoctadecanoic acid displays a singlet for the 2- and 3-H_2 protons integrating for four protons, while the corresponding sulfur compound shows the expected doublet of triplets. Only in C_6D_6, and partly in $(CD_3)_2SO$, are the signals due to these protons sufficiently separated to give two triplets. No obvious relationship between the form of the spectra and any of the usual solvent parameters could be found. The particular form of the ^1H NMR spectrum in $CDCl_3$ and CCl_4 was found to be independent of the concentration, *i.e.* the monomer : dimer ratio. A temperature study has revealed that while the signal due to the 3-H_2 protons is essentially independent of the temperature, the 2-H_2 proton signal is shifted downfield with decreasing temperature, causing the close-lying signals to be indistinguishable in the 290–310 K range. NMR spectra of the carboxylic OH group and IR spectra of the carbonyl group of dilute solutions of 3-selena- and 3-thiaheptadecanoic acids in CCl_4 suggest that the monomers of these acids exist predominantly as 4-membered cyclic species with Se(S) · · · O=C or Se(S) · · · O(H) intramolecular interactions.

Introduction

It has been shown that administration of 3-thia fatty acids, $RSCH_2C(O)OH$, to rats and hamsters reduces their serum concentrations of triacylglycerol.[1] This class of compounds seems to exert 'anti-oxidant' properties[2,3] and various results suggest that these fatty acid analogues inhibit restenosis processes. The best results have been obtained with R being tetradecyl, $C_{14}H_{29}$, presumably due to an optimal balance between the hydrophobic and hydrophilic nature of the alkyl group and the carboxylic group.

The 4-thia fatty acids, $RSCH_2CH_2C(O)OH$, do not exert the same effects, due to their lack of ability to undergo β-oxidation.[4] The corresponding 3-oxa fatty acids, $ROCH_2C(O)OH$, resembling the 3-thia acids with regard to decrease of serum cholesterol and serum triacylglycerol, strongly inhibit mitochondrial fatty acid oxidation but may lead to development of fatty liver.[5] Since 3-thia fatty acids stimulate the latter type of oxidation it is apparent that the heteroatom in the 3-position plays an important role. This suggests that it would be of interest to examine the effect of the corresponding Se-substituted fatty acids, since selenium compounds in general are more easily oxidized than sulfur compounds, the difference in redox potential being ≈0.2 V.[6]

The main purpose of the present work was therefore to develop methods for the high-yield synthesis of pure samples of 3-selenaheptadecanoic acid, $RSeCH_2C(O)OH$, **1** and 4-selenaoctadecanoic acid, $RSeCH_2CH_2C(O)OH$, **2**, R being $C_{14}H_{29}$, and to investigate these compounds spectroscopically. Since gas chromatographic studies of the methyl esters of the two acids might be of interest to test the purity of the acids,[7] these esters, **3** and **4** respectively, were also prepared.

The synthesis of **1** and **2** was in principle, as outlined by Sadek and Basmadjian,[8] based upon the simple reduction of elemental selenium to the very nucleophilic anions, Se^{2-} and Se_2^{2-} in aqueous or non-aqueous media,[9,10] depending upon the molar ratio between the reducing agent, sodium borohydride, and elemental selenium. Dialkyl selenides and dialkyl diselenides can then rapidly be formed according to equations (1) and (2).

$$Se^{2-} + 2RX \longrightarrow RSeR \quad (1)$$

$$Se_2^{2-} + 2RX \longrightarrow RSeSeR \quad (2)$$

Dialkyl diselenides, equation (2), are readily reduced by two equivalents of sodium to two moles of sodium alkylselenolates, RSe^-,[11] equation (3)

$$RSeSeR + 2Na \longrightarrow 2RSeNa \quad (3)$$

Unsymmetrical dialkyl selenides, like $RSe(CH_2)_nC(O)OH$, n = 1 and 2, compounds **1** and **2**, can then be prepared by a method similar to the Williamson ether synthesis, taking advantage of the high nucleophilicity of alkylselenolate anions, RSe^-, equation (4).

$$RSe^- + Br(CH_2)_nC(O)OH \longrightarrow RSe(CH_2)_nC(O)OH \quad (4)$$

The methyl esters of the acids were prepared according to standard esterification procedures.[12] The synthesized compounds were characterized by mass spectra, IR and particularly by NMR. Palmitic acid was used as a reference compound in the spectroscopic study.

Experimental

The IR spectra were recorded with an OMNIC 410 FT-IR system. The Nujol mulls were analysed between NaCl windows. 1D ^1H and 2D ^1H–^{13}C HMBC NMR spectra were recorded at a ^1H frequency of 600 MHz on a Bruker DRX-600 spectrometer. (Internal TMS was used as a chemical-shift reference.) 1D ^{13}C

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NMR spectra were recorded on a Bruker AC-200 spectrometer. 2D ^{1}H–^{13}C HMBC spectra (not shown) were used to assign the various proton resonances. This was particularly necessary for the assignment of the 2-H_2 and 3-H_2 protons in **2**. The NMR solvent employed, deuteriochloroform, Fluka 99.8%, stored over silver wool, had to be distilled prior to use to obtain satisfactory reproducibility for some of the compounds. This solvent was the most commonly used but $(CD_3)_2SO$, C_6D_6 and CD_3OD were also used when the spectral resolution in $CDCl_3$ was not satisfactory. These solvents were used as received. 1-Bromotetradecane, $C_{14}H_{29}Br$, Fluka purum, 97%, was distilled in a vacuum and stored in darkness at ≈273 K. Bromoacetic acid and 3-bromopropanoic acid, both Fluka puriss, were used as received. Selenium, Merck, was of 99.5% purity. Tetrahydrofuran, THF, Fluka puriss, and triethylamine, Merck 99% purity, were distilled, prior to use, in an argon atmosphere. All other solvents were of highest purity available and were, if necessary, distilled, prior to use, under argon. Tetrachloromethane, Fluka puriss, was distilled from CaH_2 in a stream of argon, stored only for short periods at ≈253 K in darkness and was carefully shielded from atmospheric moisture. Palmitic acid, hexadecanoic acid, $C_{15}H_{31}C(O)OH$, Fluka puriss, was crystallized from diethyl ether. All operations, including crystallizations, were performed strictly under argon. 3-Thiaheptadecanoic acid, $RSCH_2C(O)OH$, **5**, mp 67 °C, and 4-thiaoctadecanoic acid, $RSCH_2CH_2C(O)OH$, **6**, mp 74 °C, were prepared as previously described[13] and were crystallized from hexane and finally from diethyl ether; ν_{max} C=O (Nujol) 1712 and 1681 cm^{-1} for **5**, 1689 cm^{-1} for **6**.

Ditetradecyl diselenide, RSeSeR

To a suspension of 3.54 g (0.045 mol) of selenium in 150 ml of 1:1 THF–water was slowly added a solution of 3.93 g (0.10 mol) of sodium borohydride at room temperature. **CAUTION:** The reaction proceeds most readily and is exothermic. After the initially formed reddish brown colour of the solution had disappeared an equal amount of Se (3.54 g) was added, forming once more a reddish brown solution. After 15 min at room temperature and finally 15 min with gentle heating all the selenium had dissolved. To the reaction mixture was then slowly added a solution of 24.9 g (0.090 mol) of RBr in 100 ml of THF. After 3 h of stirring at room temperature the solution attained a yellow colour indicating the reaction to be complete. The reaction mixture was repeatedly extracted with chloroform and the combined extracts were filtered, and dried with anhydrous magnesium sulfate. After removal of the solvent a yellow oil remained which solidified upon cooling. One crystallization from diethyl ether gave 21.5 g of pure product (87%), as yellow needles, mp 43 °C (lit.,[8] 43 °C); ν_{max}(Nujol) C–Se 632 cm^{-1}; ^{1}H NMR ($CDCl_3$) $(CH_2Se)_2$ δ 2.91, t, 4H; *m*/*z* for ^{80}Se: 554 (M^+, 50%), 474 (M − Se, 4), 358 (M − R + H, 8) and 275 (M − R − 2H, 9).

Ditetradecyl selenide, R_2Se

This compound was made in 58% yield in a similar way but without the extra portion of selenium. Mp 47–48 °C; ν_{max}(Nujol) C–Se 653 cm^{-1}; ^{1}H NMR ($CDCl_3$) $(CH_2)_2Se$ δ 2.55, t, 4H; *m*/*z* for ^{80}Se: 474 (M^+, 62%), 277 (M − R, 27).

3-Selenaheptadecanoic acid $RSeCH_2C(O)OH$ 1

To a mixture of 10 g of ditetradecyl diselenide RSeSeR (0.018 mol) in 125 ml of THF was added dropwise, with stirring, a solution of 3.44 g (0.091 mol) of $NaBH_4$ in 100 ml of 1:1 THF–water. After the colour had disappeared a solution of 9.0 g (0.065 mol) of bromoacetic acid together with 7.5 g (0.074 mol) of triethylamine in 125 ml of water was added dropwise. The solution was stirred overnight. A sufficient amount of water was then added to the reaction mixture to make a homogeneous solution whereupon unchanged organic materials were removed with repeated washings with diethyl ether. After acidification to pH ≈ 2 the product was extracted with diethyl ether. The combined extracts were dried and filtered and, after removal of the solvent, a white solid remained, which was crystallized from hexane and finally from diethyl ether. The product (11.0 g, 91%) appeared as colourless crystals with mp 62–63 °C (lit.,[8] 62–63 °C); ν_{max}(Nujol) C=O 1712 and 1682, C–Se (br) 648 cm^{-1}; ^{1}H NMR ($CDCl_3$) CH_2CH_2Se δ 2.79, t, 2H, $SeCH_2C(O)$ δ 3.16, s, 2H; *m*/*z* for ^{80}Se: 336 (M^+, 39%) 277 [M − CH_2-C(O)OH, 41].

4-Selenaoctadecanoic acid $RSeCH_2CH_2C(O)OH$ 2

This acid was prepared in a similar way from 1.0 g of RSeSeR and 0.27 g of $NaBH_4$ in 10 ml of 1:1 THF–water and 0.90 g of 3-bromopropionic acid and 0.70 g of Et_3N in 25 ml of 1:1 THF–water. Yield 0.60 g (48%), mp 70 °C (lit.,[8] 70–71 °C); ν_{max}(Nujol) C=O 1697, C–Se 637 cm^{-1}; ^{1}H NMR ($CDCl_3$) CH_2CH_2Se δ 2.60, t, 2H, $SeCH_2CH_2C(O)$ δ 2.77, s, 4H; *m*/*z* for ^{80}Se: 350 (M^+, 34%), 277 [M − $CH_2CH_2C(O)OH$, 19].

Methyl 3-selenaheptadecanoate $RSeCH_2C(O)OCH_3$ 3

To a solution of 2.0 g of $RSeCH_2C(O)OH$ in 25 ml of methanol was added 1 ml of conc. sulfuric acid, poured slowly down the wall of the reaction flask. The mixture was refluxed overnight. After cooling of the mixture, 50 ml of saturated aq. sodium chloride were added. The reaction mixture was extracted with diethyl ether and the extracts were washed several times with 5% aq. sodium carbonate, dried with magnesium sulfate, and filtered prior to removal of the solvent. A colourless viscous oil was left which did not solidify upon cooling. No formation of elemental selenium was observed at any step during the reaction. The ester was not subjected to further purification. ν_{max}(Nujol) C=O 1735, no OH stretch, C–Se 670 and 633 cm^{-1}; ^{1}H NMR ($CDCl_3$) CH_2CH_2Se δ 2.70, t, 2H, $SeCH_2C(O)$ δ 3.17, s, 2H, $C(O)OCH_3$ δ 3.73, s, 3H; *m*/*z* 350 (M^+, 8%), 277 (16), 154 (14).

Methyl 4-selenaoctadecanoate $RSeCH_2CH_2C(O)OCH_3$ 4

This compound was made in a similar way from 2.0 g of $RSeCH_2CH_2C(O)OH$; ν_{max}(Nujol) C=O 1743, no OH stretch, C–Se 624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ CH_2CH_2Se δ 2.58, t, 2H, $SeCH_2CH_2C(O)$ δ 2.77, t, 2H, $SeCH_2CH_2C(O)$ δ 2.70, t, 2H, $C(O)OCH_3$ δ 3.70, s, 3H; *m*/*z* 364 (M^+, 7%), 277 (17), 154 (14).

Results and discussion

As shown in the Experimental section all the desired compounds, the two alkylseleno-substituted acids, $RSeCH_2C(O)OH$ **1** and $RSeCH_2CH_2C(O)OH$ **2**, and their methyl esters, **3** and **4**, could be isolated in good to excellent yield. Apparently, properly used, sodium borohydride can compete in efficiency with $Li(C_2H_5)_3BH$ to cleave grey selenium.[14] The reactions, however, have to be performed with carefully purified chemicals at room temperature or with only gentle heating and with complete exclusion of oxygen at all steps to avoid difficulties during purification. The yield of the precursor, RSeSeR, was particularly dependent upon the purity of the reactants and the amount of the reducing agent, $NaBH_4$; the optimal yield was obtained with 1.1 mol per mol of selenium. As viewed by IR, MS, ^{1}H NMR (600 MHz) and ^{13}C NMR (50.3 MHz) all compounds were also of high purity, even the two esters, although no attempts were made to purify the latter compounds. It is notable that no elemental selenium was formed during the synthesis of the esters. All purified selenium compounds appeared stable as viewed by their NMR spectra and their lack of coloration after storage for several months in darkness at ≈273 K under argon.

Table 1 600 MHz ^{1}H NMR chemical shifts in $CDCl_3$, 0.01 M solutions, at 298 K with TMS as internal standard (R′ = $C_{13}H_{27}$)

Compound	4-H_2, 5-H_2	3-H_2	2-H_2	OCH_3
$(R'CH_2)_2Se$	2.55 (4H, t)			
$(R'CH_2Se)_2$	2.91 (4H, t)			
1 $R'CH_2SeCH_2C(O)OH$	2.79 (2H, t)		3.16 (2H, s)	
2 $R'CH_2SeCH_2CH_2C(O)OH$	2.60 (2H, t)	2.77 (4H, s)		
3 $R'CH_2SeCH_2C(O)OCH_3$	2.70 (2H, t)		3.17 (2H, s)	3.73 (3H, s)
4 $R'CH_2SeCH_2CH_2C(O)OCH_3$	2.58 (2H, t)	2.77 (2H, t)	2.70 (2H, t)	3.70 (3H, s)
5 $R'CH_2SCH_2C(O)OH$	2.66 (2H, t)		3.25 (2H, s)	
6 $R'CH_2SCH_2CH_2C(O)OH$	2.53 (2H, t)	2.78 (2H, t)	2.66 (2H, t)	

^{1}H NMR spectra at 298 K

The ^{1}H NMR spectral details of the synthesized compounds for 0.01 M solutions in $CDCl_3$ at 298 K are summarized in Table 1. The numbering of the carbon atoms, and thus the methylene groups and the hydrogen atoms, is as follows:

$$\underset{1\ \ 2\ \ \ 3\ 4}{HO(O)C–CH_2–X–CH_2–C_{13}H_{27}} \qquad X = Se, \mathbf{1}; X = S, \mathbf{5}$$

$$\underset{1\ 2\ \ \ 3\ \ \ 4\ \ 5}{HO(O)C–CH_2–CH_2–X–CH_2–C_{13}H_{27}} \qquad X = Se, \mathbf{2}; X = S, \mathbf{6}$$

For 0.01 M solutions in $CDCl_3$ the acid protons, 1-H, could not be detected due to rapid exchange. Lazaar and Bauer[15] have been able to detect signals due to the acid proton of formic acid in $CDCl_3$, but only for concentrations approaching ≈0.5 M (2%). The 1-H resonances in dilute solutions, ≈0.01 M, were therefore determined in CCl_4; see below.

Except for **2**, the 3-alkylseleno-substituted propanoic acid, the shifts of the various methylene hydrogens and the form of the spectra are, in principle, as expected. It is notable that the 4-H_2 hydrogens in **1** and the 5-H_2 hydrogens in **2**, at 2.79 and at 2.60 ppm, are slightly but distinctly more downfield than in the corresponding sulfur compounds, **5** and **6**, at 2.66 and at 2.53 ppm. This downfield shift of α-H_2 groups in R_2Se as compared with R_2S species has been observed repeatedly but is apparently not general; see Table 1. The presence of very weak $Cl_3CH(D)\cdots X$ hydrogen bonds[16,17] or intra- or intermolecular interactions may be the origin of the erratic shift differences observed in corresponding sulfur and selenium compounds. The pronounced downfield shift of the α-methylene hydrogens in $(RSe)_2$ from R_2Se (*cf.* the first two entries in Table 1), has been discussed by Landon.[18]

The ^{1}H NMR spectrum of **2**, 4-selenaoctadecanoic acid, in $CDCl_3$ reveals some interesting features. This compound, in principle a 1,2-disubstituted ethane, ACH_2CH_2B, with two distinctly different substituents, RSe and C(O)OH, exhibits a singlet at 2.77 ppm at 298 K, integrating for 4 protons. While the ^{1}H chemical-shift difference between 2-H_2 and 3-H_2 vanishes almost completely for this compound this is not the case for the corresponding sulfur compound, **6**, for which two well separated triplets are detected, centred at 2.66 and at 2.78 ppm for 2-H_2 and 3-H_2. In the methyl ester of **2**, compound **4**, the separation is less distinct but two triplets can still be observed, centred at 2.70 (2-H_2) and at 2.77 ppm (3-H_2). The ^{1}H-shift of the 2-H_2 protons decreases in the following order: 3-X [3.16 (Se), 3.25 (S)] > 4-X [2.77 (Se), 2.66 (S)] > palmitic acid (2.35). This sequence accords with the known acidifying effect of sulfur and selenium substituents in carboxylic acids, particularly when being in the 3-position.[19–21]

The question arises, however, as to which kind of species are present in 0.01 M solutions of this class of compounds in $CDCl_3$. Numerous studies have shown that carboxylic acids are extensively dimerized in chloroform with dimerization constants, K_d, in the range 100–400 l mol^{-1} at 298 K,[22] the most extensively studied fatty acid being probably lauric acid, dodecanoic acid,[23,24] for which K_d is 231 l mol^{-1} at 300 K. With

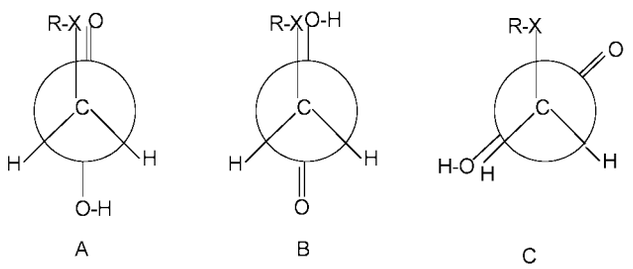

Fig. 1 Newman projections along the C-1–C-2 bond of 3-heteracarboxylic acids $RXCH_2CO_2H$.

dimerization constants in this range a 0.01 M solution in $CDCl_3$ will contain approximately equal amounts of monomers and dimers, the concentration of larger aggregates being probably negligible. In the case of the monomers, and possibly also the dimers, the configurational problem also arises; *i.e.* whether the carboxylic OH group is '*cis*' or '*trans*' to the group in the 3-position.[25] In this respect carboxylic acids with a sulfur or a selenium atom in this particular position may differ significantly from the usual fatty acids due to intramolecular $X\cdots O{=}C$ and $X\cdots O(H)–C{=}O$ interactions; *cf.* Fig. 1 for Newman diagrams with the C=O group being periplanar (**A**), antiperiplanar (**B**) and synclinal (**C**) to the heteroatom, X. Based upon standard bond lengths and bond angles in the $XCH_2C(O)OH$ fragment one may calculate the $X\cdots O$ distance in **A** and **B** to be ≈2.75 Å, significantly less than the van der Waals distances, 3.25 Å (X = S) and 3.40 Å (X = Se).[26] Furthermore, solute–solvent interactions are known to be important and several IR studies of dilute solutions of carboxylic acids have shown the carbonyl group of the monomer to be hydrogen-bonded to the chloroform proton; the OH group may further interact with a chloroform Cl atom.[27] Although suggested,[27] dimers appear to be less susceptible to interaction with solvent molecules; *cf*. the small effect on ν(C=O) of dimers in various solvents.[25]

No detailed spectroscopic studies on fatty acids with a heteroatom in the 3- and 4-position in chloroform or in other solvents seem to have been reported. The possible presence of intramolecular $X\cdots O$ interactions, particularly in the case of **1** and **5** for which four-membered cyclic species are possible, may, as outlined above, cause an additional complication. The crystal structure of $S[CH_2C(O)OH]_2$[28] has clearly shown the presence of $S\cdots O(C)$ interactions in the solid state, the $S\cdots O(C)$ distance being 2.91 Å, well within the van der Waals distance of 3.25 Å.[26] The crystal structure of $S[CH_2CH_2C(O)OH]_2$, however, has revealed a '*trans*' configuration of the sulfur atom and the carboxylic groups with no short $S\cdots O$ contacts.[29] As shown in the Experimental section the Nujol IR spectra of the substituted acetic acids, **1** and **5**, show a well separated doublet for the C=O group while the substituted propanoic acids, **2** and **6**, show only a singlet. This may suggest that intramolecular five-membered cyclic species are less conceivable in the case of the 4-X-substituted propanoic acids. Cyclic monomers will undoubtedly make the C=O group less available for hydrogen bonding and thus decrease K_d. However, the

Table 2 600 MHz ^{1}H NMR chemical shifts in CCl_4, 0.01 M solutions, at 298 K with TMS as internal standard (R′ = $C_{13}H_{27}$)

Compound	4-H_2, 5-H_2	3-H_2	2-H_2	OCH_3, 1-H
$(R'CH_2)_2Se$	2.45 (4H, t)			
1 $R'CH_2SeCH_2C(O)OH$	2.73 (2H, t)		3.02 (2H, s)	11.5 (br)
2 $R'CH_2SeCH_2CH_2C(O)OH$	2.51 (2H, t)	2.67 (4H, s)		11.5 (br)
3 $R'CH_2SeCH_2C(O)OCH_3$	2.68 (2H, t)		2.99 (2H, s)	3.64 (3H, s)
4 $R'CH_2SeCH_2CH_2C(O)OCH_3$	2.51 (2H, t)	2.68 (2H, t)	2.60 (2H, t)	3.62 (3H, s)
5 $R'CH_2SCH_2C(O)OH$	2.62 (2H, t)		3.10 (2H, s)	11.2 (br)
6 $R'CH_2SCH_2CH_2C(O)OH$	2.45 (2H, t)	2.68 (2H, t)	2.56 (2H, t)	11.4 (br)
Palmitic acid			2.28 (2H, t)	11.6 (br)

higher acidity of this class of acids[19–21] may cause the hydroxylic proton to be a better H-donor and thus increase K_d. Finally, the recently documented $X\cdots HCCl_3$ interactions,[16,17] albeit very weak, may influence K_d. One may therefore assume that K_d for 3-X- and 4-X-substituted fatty acids in chloroform will be of the same order of magnitude as for unsubstituted fatty acids[23] and that 0.01 M solutions in this solvent will contain both monomers and dimers.

In an attempt to improve our understanding of the parameters listed in Table 1 most ^{1}H NMR spectra were also recorded for 0.01 M solutions in CCl_4, Table 2. Due to the lower permittivity of this solvent,[30] and significantly weaker monomer–solvent interactions,[27] K_d values for carboxylic acids in this solvent are considerably larger and values in the range 1000–4000 l mol^{-1} have been reported at 298 K,[25] including 3140 l mol^{-1} for lauric acid at 300 K.[24] Thus, a larger part of the dissolved acids will necessarily be present as dimers in CCl_4; still, the form of the ^{1}H NMR spectra and the proton shifts in the two solvents, Tables 1 and 2, are quite similar. It is notable that compound **2**, the 3-alkylseleno-substituted propanoic acid, also in this solvent exhibits a sharp singlet for the four 2-H_2 and 3-H_2 protons. The proton signals in CCl_4 are slightly more upfield, $\Delta\delta$ 0.05–0.10 ppm, than in $CDCl_3$, somewhat more for the 2-H_2 protons in the substituted acetic acids, from 3.16 to 3.02 ppm in **1** and from 3.25 to 3.10 ppm in **5**. The upfield shift of the 2-H_2 protons in the substituted acetic acids can hardly be due to the significant difference in the monomer : dimer ratio since the methyl ester of **1** (compound **3**) responds similarly to the solvent change, from 3.17 ppm in $CDCl_3$ to 2.99 ppm in CCl_4. This effect on the shift of the 2-H_2 protons may rather be due to differences in solute–solvent interactions or the presence of intramolecular 4-membered cyclic species as outlined above. Apparently, parallel ^{1}H NMR shift studies in $CDCl_3$ and CCl_4 do not appear to shed light upon the particular form of the spectrum of **2** in the two solvents.

The concentration dependence of the ^{1}H NMR spectrum of **2** in CCl_4 was further studied; this solvent was preferred to $CDCl_3$ owing to the better quality of the spectra. Apart from some minor shift changes with concentration, except for the 1-H proton (see below), a singlet, integrating for 4 protons, was always found for the 2-H_2 and 3-H_2 protons in the range 0.005–0.1 M. Based upon a K_d of ≈3000 l mol^{-1}, as for lauric acid,[23] this concentration range will cover a monomer : dimer ratio from ≈1 : 2 to ≈1 : 10 when larger aggregates are neglected. Since all proton signals, up to 6-H_2, were found to be well separated for the corresponding sulfur compound, **6**, this compound was the subject of a more detailed study. In Fig. 2 are plotted the proton shifts *versus* the concentration using the shifts for the 0.005 M solution as reference. A slight downfield shift with increasing concentration was found for all signals, particularly for the 2-H_2 protons. The difference in the concentration dependence of the signals due to the 2-H_2 and 3-H_2 protons, however, is indeed quite small and indicates why the form of the spectrum of the corresponding selenium compound, **2**, was found to be independent of the concentration in the same concentration range.

In Fig. 3 are shown the 600 MHz ^{1}H spectra of **2** at 298 K in several solvents in the 2.3–2.8 ppm range covering the 2-, 3- and 5-H_2 protons. Only in C_6D_6, and barely in $(CD_3)_2SO$, are the signals due to the 2- and 3-H_2 protons sufficiently separated to yield two well defined triplets for the CH_2CH_2 fragment, fragments which will generally constitute AA′BB′ ^{1}H spin systems. The appearance of these spectra will approach that of AA′XX′ spin systems for the smaller $^3J/[\Delta\delta(AB)]$ ratios between the vicinal coupling constants (^3J) and the chemical-shift difference [$\Delta\delta$(AB)]. However, for compound **2** we observe a collapsing AA′BB′ ^{1}H spin system. We note that there are no obvious relationships between the position of the peaks due to the 2-H_2 and the 3-H_2 groups in **2**, the form of the spectra, *i.e.* the $^3J/[\Delta\delta(AB)]$ ratios and any of the usual solvent parameters like the permittivity, the acceptor/donor numbers, or the solvent being protic or aprotic. One may therefore conclude that the particular form of the ^{1}H NMR spectra of **2** in $CDCl_3$ and CCl_4 is due to a coincidence of solvation and association phenomena.

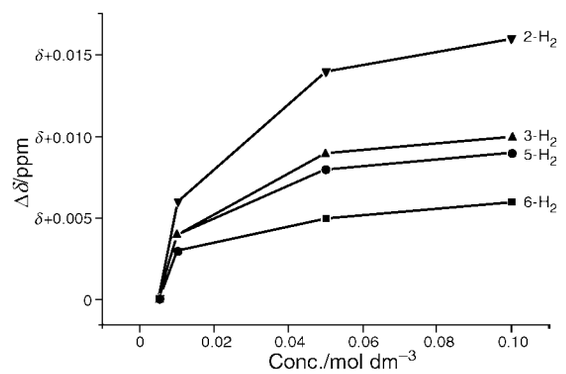

Fig. 2 A plot of proton shifts of 4-thiaoctadecanoic acid **6** *versus* the concentration using the shifts for the 0.005 M solution as reference.

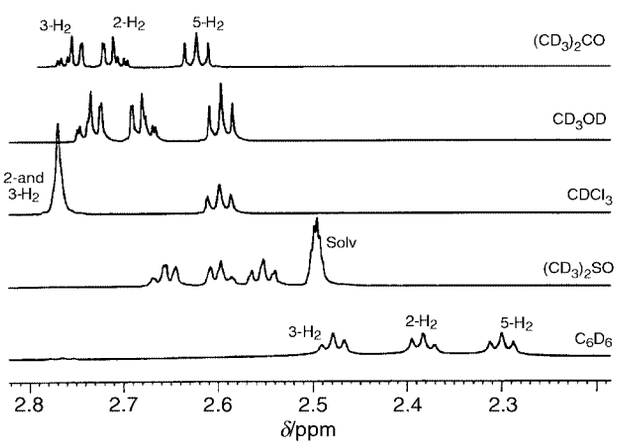

Fig. 3 600 MHz ^{1}H spectra of 4-selenaoctadecanoic acid **2** at 298 K in $(CD_3)_2CO$, CD_3OD, $CDCl_3$, $(CD_3)_2SO$ and C_6D_6 in the 2.3–2.8 ppm range covering the 2-, 3- and 5-H_2 protons.

Temperature dependence of ^{1}H NMR chemical shifts

In Fig. 4 are shown the shifts due to the 2-, 3- and 5-H_2 protons

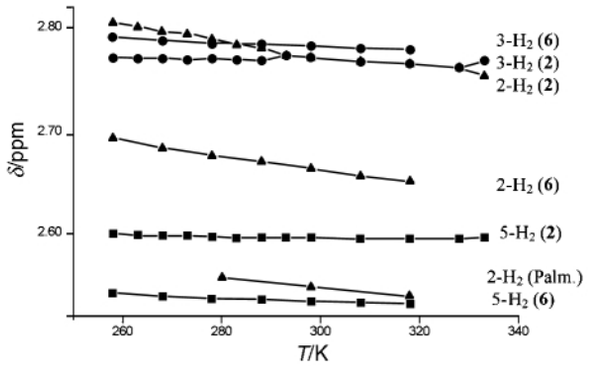

Fig. 4 600 MHz ^{1}H shifts due to the 2- (▲), 3- (●) and 5-H_2 protons (■) of 4-selena- and 4-thiaoctadecanoic acids, **2** and **6**, and the 2-H_2 protons in palmitic acid (+0.20 ppm) as a function of temperature; 0.01 M solutions in $CDCl_3$.

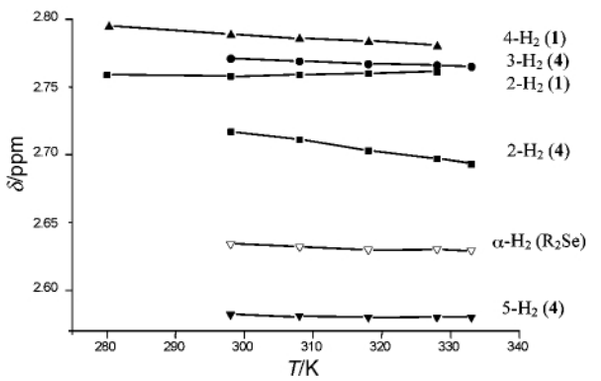

Fig. 5 600 MHz ^{1}H shifts due to the 2- (■), 3- (●), 4- (▲), 5- (▼) and α-CH_2 protons (▽) of 0.01 M solutions, in $CDCl_3$, of 3-selenaheptadecanoic acid **1**, the methyl ester of 4-selenaoctadecanoic acid compound **4** (−0.40 ppm), and α-H_2 protons in ditetradecyl selenide, R_2Se, (+0.10 ppm) as a function of temperature.

of 0.01 M solutions of 4-selena- and 4-thiaoctadecanoic acid, **2** and **6**, in $CDCl_3$ as a function of temperature. This solvent was chosen for a more detailed study since the negligible solubility of the acids in CCl_4 at temperatures below ≈280 K prevented measurements from being taken. The shift due to the 2-H_2 protons in palmitic acid is also included in Fig. 4; to the latter shifts has been added 0.20 ppm to allow for a better comparison. In Fig. 5 are shown the corresponding δ–T plots for 3-selenaheptadecanoic acid, **1**, the methyl ester of **2**, **4**, −0.40 ppm, and the α-H_2 protons in ditetradecyl selenide, R_2Se, +0.10 ppm.

While the 3- and 5-H_2 signals in **2** and **6** are shifted only slightly with increasing temperature the signal due to the 2-H_2 protons is far more dependent upon the temperature. As a result the δ–T plots for the 2-H_2 and 3-H_2 protons in **2** cross at ≈305 K causing these signals to be indistinguishable in the ≈290–310 K range giving rise to a singlet integrating for four protons; see Table 1 for shift values at 298 K. The plot for the methyl ester of **2**, compound **4**, shows a similar trend with regard to the temperature dependence of the 2-, 3- and 5-H_2 signals. However, as is also shown in Fig. 5, the 2-H_2 and 4-H_2 signals of the substituted acetic acid, **1**, and the α-H_2 signal of R_2Se, are fairly independent of the temperature. In CCl_4 this trend in the δ–T plots was in principle as observed in $CDCl_3$ but all slopes, as given by dδ/dT in Figs. 4 and 5, were found to be larger than in $CDCl_3$. Thus, the slopes for the 2-H_2 protons in the substituted propanoic acids and their methyl esters were less negative while all slopes, being ≈0 in $CDCl_3$, were slightly positive in CCl_4. In Fig. 6 is shown a plot of the shifts of the 2-, 3-, 5- and 6-H_2 protons in **6** *versus* the temperature using the values at 318 K as reference. The limited solubility of **2** in CCl_4 at low temperatures prevented the detection of a crossing of the δ–T

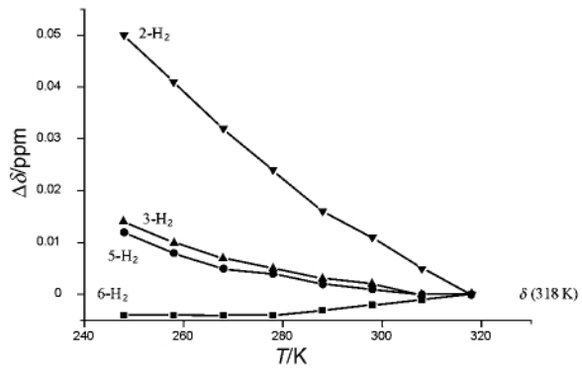

Fig. 6 A plot of the 2- (▼), 3- (▲), 5- (●) and 6-H_2 shift values (■) for 4-thiaoctadecanoic acid **6** in $CDCl_3$ solution *versus* the temperature relative to the values at 318 K.

plots for the 2- and 3-H_2 proton signals as observed in $CDCl_3$; *cf.* Fig. 4. However, a separation of the signals could be observed for temperatures from ≈305 K and upwards with an increasingly more downfield shift for the 3-H_2 protons as compared with that of the 2-H_2 protons.

The upfield shifts for the 2-H_2 protons in the substituted propanoic acids and palmitic acid with increasing temperature, particularly in $CDCl_3$, can readily be explained by an increase in the fraction of monomers[15] and by weaker solute–solvent interactions.[27] The negligible effect of the temperature on the shift due to the 2-H_2 protons in the substituted acetic acid, even in $CDCl_3$, Fig. 5, suggests that for this compound additional equilibria between an acyclic and various cyclic monomers have to be considered; *cf.* Fig. 1, equilibria which may not be important for the substituted propanoic acids.[29] Further evidence for this suggestion comes from an IR study of the acids in CCl_4 in the region 0.0025–0.1 M at 298 K.[31] The substituted propanoic acids and palmitic acid give rise to a strong peak at 1712 cm^{-1} due to the dimer and a far weaker peak at 1759 cm^{-1} (1740 cm^{-1} in $CHCl_3$) which increases in intensity with increasing dilution, the latter peak being assigned to an acyclic monomer.[24,25,27] The substituted acetic acids, however, do not display a peak at ≈1759 cm^{-1}, but rather a low-energy shoulder to the peak due to the dimer at 1680 cm^{-1}. Presumably this shoulder is due to a cyclic monomer of type **A**, see Fig. 1, with a weakened C=O bond. For extremely dilute solutions a new peak at 1765 cm^{-1} appears. This may be due to less polar species of type **B** with X···O(H) interaction and with a strengthened C=O bond. The complexity of the IR spectra and the considerable difference in the extinction coefficients of monomers and dimers[23–25] suggest that dimerization constants of 3-X-substituted acids can only be determined with difficulty by IR studies in the 1700 cm^{-1} region.

1-H Chemical shifts

The 1-H shifts, listed in the last column in Table 2, may at first sight indicate a relationship between shifts and assumed acidity constants of the acids. However, as shown in Fig. 7, where the 1-H NMR shifts for the present acids are plotted *versus* the concentration in the range 0.01–0.5 M in CCl_4, and also in numerous NMR studies of solutions of carboxylic acids in several solvents, these shifts are strongly dependent upon the concentration.[30]

The plot for palmitic acid is in principle as expected since a decrease in concentration will lead to an increase of the fraction of monomers with more shielded 1-H protons. The plots for the 3-X-substituted acids, however, and possibly for the 4-substituted ones (the experimental uncertainty is ≈0.1 ppm), pass through a minimum below ≈0.1 M, the concentration for which varies from one acid to another. Apparently, 1-H shifts, as listed in Table 2, are of no diagnostic value, particularly for 3-X-substituted acids, due to the equilibria between several

Table 3 50.3 MHz ^{13}C Chemical shifts of ≈0.05 M solutions in $CDCl_3$ (upper part) and of acids **2** and **6** in various solvents (lower part) relative to internal TMS, 298 K (R′ = $C_{13}H_{27}$)

$CDCl_3$	1-C	2-C	3-C	4-C	5-C	ω-C[a]
1 R′$CH_2SeCH_2C(O)OH$	177.7	21.7		26.0		14.1
2 R′$CH_2SeCH_2CH_2C(O)OH$	177.8	35.4	16.7		24.4	14.1
3 R′$CH_2SeCH_2C(O)OCH_3$	172.1	21.7		25.5		14.0
5 R′$CH_2SCH_2C(O)OH$	176.8	28.8		32.8		14.0
6 R′$CH_2SCH_2CH_2C(O)OH$	177.4	34.6	28.7		32.2	14.1
Palmitic acid	175.8	34.2	25.0	29.4		14.1
2 R′$CH_2SeCH_2CH_2C(O)OH$						
$CDCl_3$	177.8	35.4	16.7		24.4	14.1
C_6D_6	178.9	36.2	17.4		24.7	14.7
$(CD_3)_2C{=}O$	173.2	35.8	17.7		24.1	14.0
CD_3OD	176.0	37.0	18.5		24.0	14.7
6 R′$CH_2SCH_2CH_2C(O)OH$						
$CDCl_3$	177.4	34.6	28.7		32.2	14.1
$(CD_3)_2C{=}O$	173.1	35.1	30.3		31.5	14.2

[a] Terminal CH_3-carbon atom. The remaining ^{13}C chemical shifts are, for all compounds, in the 22.5–31.9 ppm range.

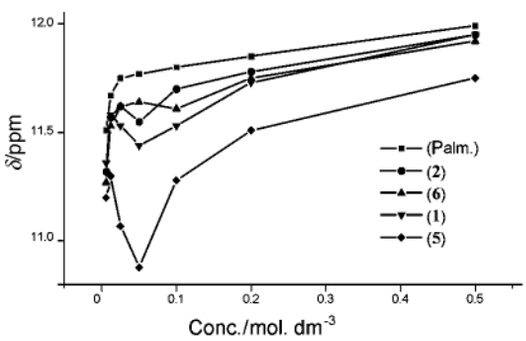

Fig. 7 The 1-H NMR shifts of palmitic acid (■), 4-selenaoctadecanoic acid **2** (●), 4-thiaoctadecanoic acid **6** (▲), 3-selenaheptadecanoic acid **1** (▼) and 3-thiaheptadecanoic acid **5** (◆) plotted *versus* the concentration in the range 0.01–0.5 M in CCl_4.

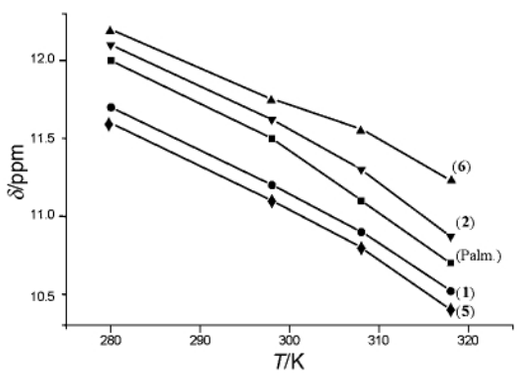

Fig. 8 1-H NMR shifts of 4-thiaoctadecanoic **6** (▲), 4-selenaoctadecanoic, **2** (▼), palmitic acid (■), 3-selenaheptadecanoic, **1** (●) and 3-thiaheptadecanoic acid **5** (◆) in 0.01 M CCl_4 solutions as a function of temperature.

possible monomeric species unless very detailed shift–concentration plots are available. This kind of study, which is in progress, has to be performed in carefully purified solvents since 1-H shifts of dilute solutions of carboxylic acids are known to be most sensitive to impurities, particularly traces of water.[32] The particular form of the plots in Fig. 7, the equilibria between various monomeric species (Fig. 1) combined with the experimental difficulties suggest that extrapolated shift values for pure monomers, δ_{mon}, for this class of acids can be determined only with difficulty. Thus, dimerization constants, K_d, of 3-X- and probably also 4-X-substituted acids, as considered in this study, may not be readily obtained from studies of 1-H shifts as a function of concentration.[15]

In Fig. 8 are shown the 1-H shifts of 0.01 M solutions in CCl_4 of the 3-X- and the 4-X-substituted acids together with palmitic acid as a function of temperature. When taking into account the greatly different appearance of the 1-H NMR spectra of dilute solutions of the various acids, see particularly Fig. 7, these plots are surprisingly similar. This apparent similarity, however, may have its origin in compensational effects due to differences in hydrogen bonding in the dimers, solvation effects and by variations in the electric field created by the solvent dipoles with temperature.[33] This latter effect may actually increase the acidity of a proton donor toward a proton acceptor as the temperature is lowered. It is notable that the effect of temperature on the 1-H shifts, Fig. 8, is fairly linear while the effect of the concentration, particularly for low concentrations, is dramatic (see Fig. 7).

^{13}C Chemical shifts

The ^{13}C NMR shifts of ≈0.05 M solutions of the synthesized compounds in $CDCl_3$ at 298 K are listed in Table 3. With an assumed K_d of 200 l mol^{-1} the monomer : dimer ratios for this concentration will be approximately 1 : 2. No other signals than the ones listed in Table 3 could be detected outside the 22–32 ppm region, the region for the remaining carbon atoms, confirming the purity of the synthesized compounds. All carbon atoms linked to selenium atoms were found to have signals shifted upfield, up to 12 ppm in the case of 3-C in **2**, as compared with the carbon atoms in the corresponding sulfur compounds. This is as expected when considering the difference in the strength of the C–Se and C–S bonds. The shifts for 2-C and 3-C in $RSCH_2CH_2C(O)OH$ are quite comparable with the corresponding shifts in palmitic acid.

Due to the particular ^1H NMR spectra of **2** and **6** the ^{13}C spectra of these two acids were also recorded in some other solvents (the lower entries in Table 3). These data indicate that only the shift due to 1-C is significantly dependent upon the solvent. The upfield shift of 1-C found in $(CD_3)_2CO$ suggests a $C(O)–OH\cdots O{=}C(CD_3)_2$ interaction. However, the larger permittivity of this solvent may change the monomer : dimer ratio significantly.

Conclusions

Satisfactory procedures for the synthesis of 3-selenaheptadecanoic acid and 4-selenaoctadecanoic acid, their methyl esters and the corresponding sulfur compounds in high yield and of high purity are described.

The ^1H NMR spectrum of 4-selenaoctadecanoic acid displays a singlet, *i.e.* a collapsing AA′BB′ spin system, for the 2- and 3-H_2 protons in $CDCl_3$ and CCl_4 at temperatures close to room temperature. This appears to be due to a coincidence of solvation, association and concentration phenomena.

NMR and IR data suggest that the monomers from the 3-X-substituted acetic acids, contrary to monomers from 4-X-substituted propanoic acids and fatty acids, exist as various types of cyclic species with X···O intramolecular interactions. As a result, dimerization constants of 3-X-substituted acetic acids may not be obtained from NMR (OH) or IR (C=O) studies.

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