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Organotin Sulfides

Protolysis of Amino Acid-Functionalized Tin Sulfide Clusters

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Abstract: In order to gain information about the behavior of tin sulfide clusters with bio-organic ligand shells under acidic conditions, such as found in undesirable cells for instance, we systematically treated amino acid-functionalized tin sulfide clusters with different acids. For Boc-protected amino acid derivatives, we could show that this treatment causes either cleavage of the protecting group of the amino acid or protolysis of the tin sulfide core under release of H_2S and formation of the correspondingly functionalized organotin trichloride, depending on the nature of the acid. This points towards a potential future use of such species for targeted cytotoxic applications.

Introduction

Organometallic compounds in general show great opportunities for medical application. Besides showing a high structural diversity (linear up to octahedral), while they are mostly uncharged, they are able to bind to a target through coordinative bonds including the metal atom.[1–5] This may include ligand exchange, for instance upon release of a small biologically active molecule (like the messenger molecule CO) and subsequent bonding to the target through a newly attached ligand. The substituents are also capable of affecting the lipophilicity, size, charge and even solubility as well as the cytotoxic effect.[4–6]

Over the last years, transition metal compounds became popular in application against different types of cancer, HIV, and malaria.[7] The most common one is *cis*-platin {*cis*-[$Pt(NH_3)_2Cl_2$]}. Up to 70 % of the known cancer treatments are conducted with Pt complexes like *cis*-platin.[6–8] Upon replacement of chlorine ligands by aqua ligands, the complex is capable of attacking the tumor cell's DNA.[9] However, some tumors are platinum-resistant, and the commonly used Pt complexes still show side effects as they are nephrotoxic.[2] Due to this fact, and as many other transition metals do also show high biological activity, corresponding complexes were studied with regard to cancer therapy. Ti, Fe, Re, Ru and Ir compounds with cyclopentadienyl (Cp) or arene substituents are the most frequently used complexes in medical applications.[1,3,7,10–12] Bulky substituents, such as Cp ligands in metallocenes, protect the complexes from further reactions, like acid- or base-catalyzed substitution or bond cleavage steps.[1,7]

More recently, also main group metal compounds have attracted attention as potential biologically active molecules. In first studies organotin compounds showed promising results. Owing to their specific properties, organotin compounds have been used since many years in the manufacturing process of PVC as stabilizer,[13] catalyst,[14,15] or owing to their biological acidity, they were applied for wood protection against microorganisms, and as fungicides.[16] In fact, Sn(IV) compounds do show high in vitro tumor-inhibiting activity, and they are able to induce apoptosis in different cancer cells.[17,18] It was shown that trialkyltin compounds are more biologically active than di- and monoalkyltin compounds, which correlates with their higher toxicity. Phenyl substituents led to the highest activity, whereas compounds with small-chain organic substituents showed no effect in cells. Although diorganotin complexes can be used against bacterial strains and different fungi,[19,20] the commonly tested organotin compounds possess the coordination number four, but species with higher coordination numbers (five or six), leading to trigonal bipyramidal or octahedral coordination of the tin atom and a rich structural chemistry, have also been investigated.[21–25] As an example, tin compounds with octahedrally coordinated carboxylate moieties were proven to be biological active against certain fungi.[26–28] First tests showed, that the cytostatic activity against tumor cells is higher than that of *cis*-platin, and that the effect is also due to the interaction with the DNA.[21,29] In this case, the organotin moiety shows cytotoxic effects while the role of the organic ligands is the transport of the molecule to the target.[11] Based on the wide structural diversity of tin compounds, selectivity towards cells was achieved in first studies.[30]

Beyond the background of the use of tin compounds in medical applications, and based on the cytotoxicity of H_2S,[31,32] we recently developed the vision of creating organotin sulfide clusters. The latter may be designed to be target-specific through the nature of their ligands, and at the same time cytotoxic owing to in-situ degradation in the somewhat more acidic

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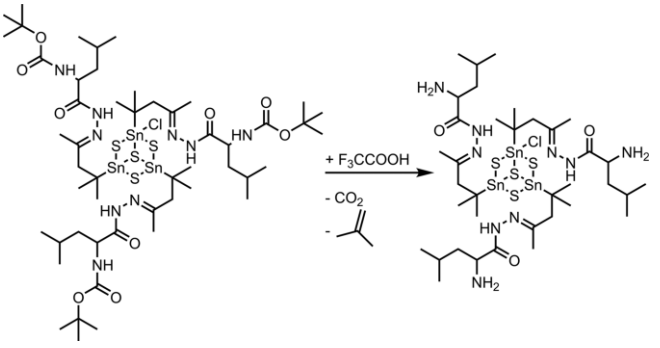
environment of undesirable cells (pH ≈ 5.8 to 7.6) as compared to that of healthy cells (pH ≈ 7.00 to 8.06),[33] under release of H_2S and organotin derivatives with potential biological activity. This work describes our first experiments into this direction, in which we explored the behavior of amino-acid terminated organotin sulfide clusters upon treatment with different acids. Note that organic solvents were used in this preliminary study, which naturally affects the acidity of the respective acids. The compatibility and solubility of the clusters in water requires the corresponding expansion of the ligand shell, which is the second step of the research plan. While the final goal is to form H_2S and organotin trihalides with octahedrally surrounded tin atoms, the acid is also needed in the first step to de-protect the amino acid substituents for specific ligand design, yet without untimely protolysis of the cluster core. For this purpose, we tested the effect of different types and amounts of acids added to the solutions containing the clusters.

The studies presented herein may be understood as very first steps towards the above-mentioned vision, which needs to be followed by sophisticated expansion of the substituents, and eventually application to physiologic environments in the future.

Results and Discussion

On the long run, we aim at a targeted expansion of the organic groups attached to the tin atom via post-synthetic growth of oligopeptides. For this, we used amino-acid terminated organotin compounds, which we recently introduced into this field.[34,35] In order to prevent an intramolecular condensation reaction of between the amino acid's amino group and a keto group bound to the organotin sulfide cluster during cluster formation,[35,36] the terminal amino functions of the amino acid molecules were protected by a *tert*-butyloxycarbonyl (Boc) group.[36] Growth of an oligopeptide at the surface of the organotin sulfide cluster for molecular recognition would be allowed upon cleaving off the protection group with acids (Scheme 1). As it is not intended to degrade the cluster core during this step, it was necessary to test its behavior under acidic conditions. For this, the cluster $[(\mathbf{R^1}Sn)_3S_4Cl]$ (**A**; $\mathbf{R^1}$ = $CMe_2CH_2C\{N(L\text{-Leu-Boc})\}Me$) was chosen as a test candidate and synthesized as reported.[35] To examine the de-protection of **A**, it was dissolved in dichloromethane (DCM), and different equivalents of trifluoroacetic acid (F_3CCOOH, TFA) were added, whereupon the mixture was allowed to stir for two hours. Sub-



Scheme 1. De-protection of the amine group at a Boc-protected leucine-substituted tin sulfide cluster $[(\mathbf{R^1}Sn)_3S_4Cl]$ **A** with trifluoroacetic acid.

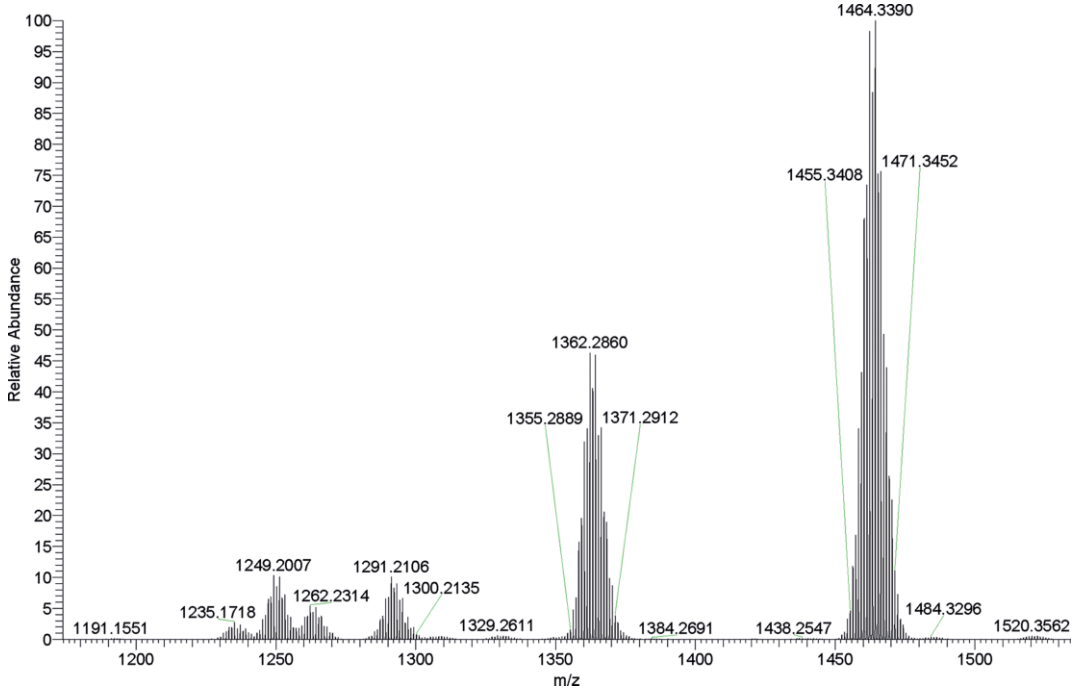


Figure 1. Zoom (m/z = 1150 to 1550) of the ESI(+) mass spectrum of a fresh solution of compound **A** in DCM after addition of 4 equiv. of TFA. The signal at 1464.3390 m/z was assigned to a species with the sum formula $[C_{51}H_{96}N_9O_9S_4Sn_3]^+$, correlating to a fully Boc-protected amino acid-functionalized cluster. The signal at m/z = 1362.2860 indicates mono-de-protection of the starting material to form $[C_{46}H_{88}N_9O_7S_4Sn_3]^+$, and the signal at m/z = 1262.2314 belongs to a cluster with only one remaining Boc group, $[C_{41}H_{80}N_9O_5S_4Sn_3]^+$.

sequently, DCM and excess TFA were removed in vacuo, and the remaining solid was investigated by means of ESI(+) mass spectrometry.

As the use of an excess of TFA is reported for de-protection in the literature,[37,38] the clusters were treated with 4 to 6 equivalents of TFA, which lead according to the mass spectrometric results to partial de-protection of the amino group (Figure 1). Addition of a larger excess of TFA (12 equiv.) causes complete degradation of the organotin sulfide cluster. The best results regarding de-protection were obtained with 4 equivalents of TFA. The mass spectrum shows the triply protected amino acid-functionalized cluster at m/z = 1464.3390, the mono-de-protected cluster at m/z = 1362.2860, the doubly de-protected and the completely de-protected cluster at m/z = 1262.2314 and m/z = 1162.1743, respectively (see Figure 1 and Figure 2). Reactions of $[(\mathbf{R^2}Sn)_3S_4Cl]$ (**B**; $\mathbf{R^2}$ = $CMe_2CH_2C\{N(L\text{-Phe-Boc})\}Me$) with TFA show similar results. According to ESI(+) mass spectroscopy, we were able to de-protect this sterically more demanding organotin sulfide cluster once by addition of 4 to 6 equivalents of TFA. Mass spectra of a fresh solution of the obtained colorless solid indicate no further degradation of the inorganic cluster, which would inevitably afford brown decomposition products. Again, addition of 12 equiv. of TFA leads to complete degradation of the cluster within minutes. The studies indicate that de-protection with TFA is feasible, at least to a certain extent, without degradation of the cluster core. ^{1}H-NMR spectroscopy was not carried out because the product mixture gives rise to a lot of signals.

Since the clusters decompose upon addition of a large excess of TFA, we decided to extend the studies of the behavior of organotin sulfide clusters with acid-resistant substituents against a variety of strong and weak acids to get more insight in the general stability of the organotin cluster core under such conditions. Employment of other acids, such as hydrochloric acid (HCl_{aq}) or hydrobromic acid (HBr_{aq}), induces the degradation of the cluster with formation of the corresponding organotin trihalide and H_2S. Our studies regarding the protolysis of pre-formed clusters started out with the keto-functionalized tin sulfide cluster $[(\mathbf{R^3}Sn)_3S_4Cl]$ {**C**; $\mathbf{R^3}$ = $CMe_2CH_2C(O)Me$}, which was treated with different equivalents of HCl_{aq} (37 %). The untreated solution, and the reaction mixtures upon addition of 3 equivalents of HCl_{aq} and of excess HCl_{aq}, respectively, were monitored by means of ^{1}H-NMR spectroscopy (Figure 3).

The spectrum shown in Figure 3, top, reveals the presence of the keto-functionalized cluster along with the starting material $\mathbf{R^3}SnCl_3$ and the intermediate $[(\mathbf{R^3}SnCl_2)_2S]$, which occurs during the synthesis of the cluster. The spectrum that was recorded upon adding three equivalents of 37 % hydrochloric acid indicates that original compound **C** disappears completely, while the amount of the intermediate $[(\mathbf{R^3}SnCl_2)_2S]$ is decreased and that of the organotin trichloride $\mathbf{R^3}SnCl_3$ increases. Addition of an excess of HCl_{aq} (15 equivalents and more) causes the signals of the intermediate to disappear completely, while the remaining signals represent the organotin trichloride $\mathbf{R^3}SnCl_3$ to be the only remaining tin species in solution. Throughout the experiment, no solid precipitated, which indicates complete degradation of **C** to the keto-functionalized organotin trichloride and H_2S (see Scheme 2 top) in accordance with previous reports.[39] To verify the release of H_2S, the gas was introduced into a solution of $AgNO_3$, leading to an immediate precipitation

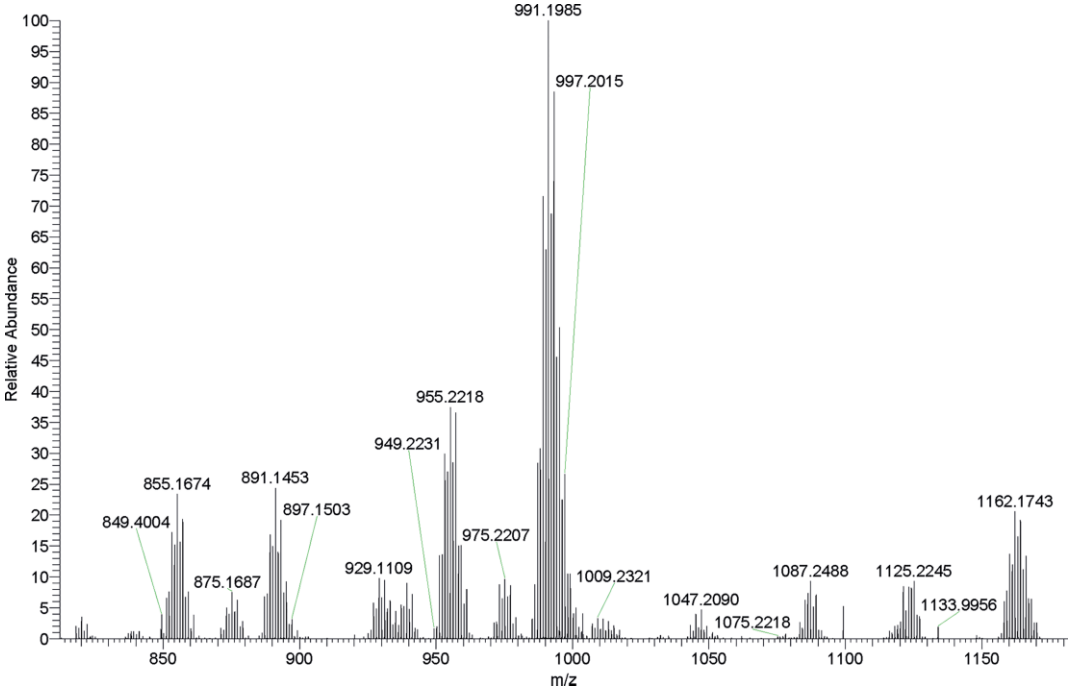


Figure 2. Zoom (m/z = 800 to 1200) of the ESI(+) mass spectrum of a fresh solution of compound **A** in DCM after addition of 4 equiv. of TFA. Note that the scaling factor of the y-axis is 0.01 with regard to the y axis in Figure 1. The signal at 1162.1743 m/z belongs to a species with the sum formula $[C_{36}H_{72}N_9O_3S_4Sn_3]^+$, which correlates to the fully de-protected, amino acid-functionalized cluster. The isotopic pattern of signals with smaller m/z values do not correspond to the $[Sn_3S_4]$ cluster core, and are most likely minor degradation products, which indicate some fragmentation of the cluster to occur under ESI mass spectrometry conditions.

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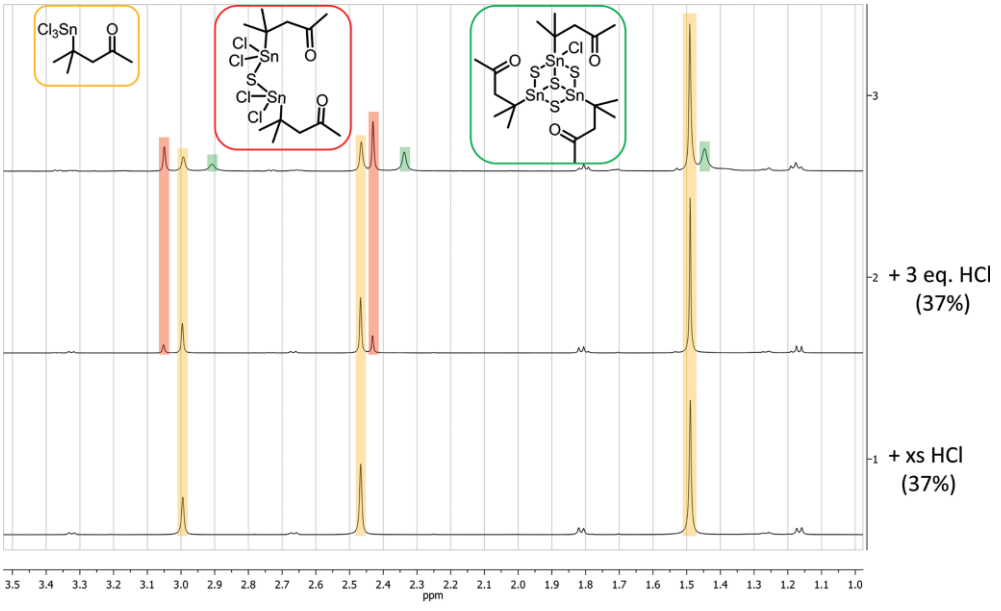
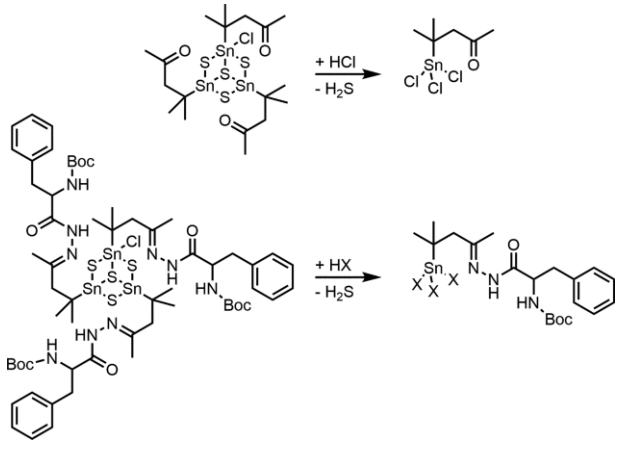


Figure 3. Top: ^{1}H-NMR spectrum of the reaction mixture of as-prepared **C** in $CDCl_3$ (green), indicating the presence of the starting material $\mathbf{R^3}SnCl_3$ (yellow) and an intermediate structure [$(\mathbf{R^3}SnCl_2)_2S$] (red). Center: ^{1}H-NMR spectrum upon addition of 3 equiv. of HCl_{aq}, indicating full protolysis of the cluster, which ends up with increased amounts of $\mathbf{R^3}SnCl_3$ relative to the intermediate [$(\mathbf{R^3}SnCl_2)_2S$]. Bottom: ^{1}H-NMR spectrum upon addition of an excess of hydrochloric acid. The spectrum shows the signals of the organotin trichloride $\mathbf{R^3}SnCl_3$ only, which is formed under release of H_2S.

of black Ag_2S. To exclude a protolysis that had taken place due to traces of water, we repeated the studies with HCl gas dissolved in dioxane. The ^{1}H-NMR spectra obtained in these experiments were the same as shown above.



Scheme 2. Degradation of [$(\mathbf{R^3}Sn)_3S_4Cl$] (**C**) (top) and [$(\mathbf{R^2}Sn)_3S_4Cl$] (**B**) (bottom) with hydrogen halides (delivered as hydrohalogenic acids or solutions in dioxane) to form the corresponding organotin trihalide.

Subsequently, the study was extended by using HBr_{aq} and the amino acid-functionalized organotin sulfide cluster [$(\mathbf{R^2}Sn)_3S_4Cl$] (**B**; see Scheme 2 bottom). As we know that the organotin sulfide cluster decomposes completely even in the presence of only small amounts of acids, we monitored the reaction mixture via ESI(–) mass spectrometry to detect the organotin trihalides. Since the organic substituent is more complex than the substituent in compound **C**, and as we expected a product mixture to occur because of the use of HBr_{aq}, we refrained from carrying out ^{1}H-NMR spectroscopy. Addition of small amounts of HBr_{aq} (3 equiv.) causes the formation of a mixture of $[\mathbf{R^2}SnCl_3]^-$, $[\mathbf{R^2}SnBr_2Cl]^-$, and $[\mathbf{R^2}SnCl_2]^-$ according to ESI(–) experiments. As expected, the bromide anion replaces the sulfide ligands of the organotin compound, again under release of H_2S. Upon addition of excess HBr_{aq}, organotin bromide species become significantly more abundant. In this case, the spectrum shows $[\mathbf{R^2}SnBr_3]^-$, $[\mathbf{R^2}SnBr_2Cl]^-$, and $[\mathbf{R^2}SnBr_2]^-$ as dominant species.

To further investigate the degradation of the keto-functionalized tin sulfide cluster **C**, sulfuric acid (96 %) was used, which leads to the precipitation of polysulfides and SnO_2, both of which could not be analyzed by solution NMR spectroscopy nor mass spectrometry. None of the spectra showed any indications of remaining organotin chloride species or the cluster **C**, as expected in the light of the strong oxidation power of sulfuric acid.

To explore the effect of weaker acids, we used ammonium chloride and acetic acid. Ammonium chloride should additionally be able to form organotin trichloride species. However, in both cases, mass spectrometry indicated no reaction at all to take place. During reactions of **B** or **C** with ammonium chloride (15 equiv.), the solution remained clear and colorless for 12 hours. The same was observed for treatment with acetic acid.

Finally, we probed water itself as a source of protons. We were able to observe an enhancement in stability against degassed water if the cluster is protected by sterically more demanding substituents. The keto-functionalized organotin sulfide cluster degraded upon using more than six equivalents of degassed water, whereas the Boc-protected phenylalanine-substituted cluster remained intact according to ESI(+) mass spectroscopy even if treated with an excess of degassed water. This

was a welcome result, as it points towards application of such species (and their envisaged peptide derivatives) under physiologic conditions.

Conclusion

We presented studies on the de-protection of Boc-protected amino groups of amino acids attached to organotin sulfide clusters, as well as the controlled protolytic degradation of keto-functionalized and amino acid-functionalized organotin clusters.

Treatment with trifluoroacetic acid cause (partial) de-protection of the amino groups. Although the de-protection does not occur selectively nor complete, the results point towards the potential of synthesizing oligopeptides in subsequent steps.

Moreover, treatment of the clusters with different amounts of various acids indicated that hydrogen halides cause degradation of the clusters with formation of organotin trihalides and H_2S. This proceeds to different extents, depending on the nature and amount of the acid used.

In summary, treatment of organotin sulfide clusters with acids containing no halides, like TFA, in low concentration served to de-protect previously protected amine group, while higher concentration led to complete degradation of the clusters. The employment of hydrogen halides, in contrast, caused the formation of the corresponding organotin trihalides. We were also able to show that larger steric demand of the amino acid substituents enhance the stability against water.

Future studies regarding the first part will include an extension of the reaction time to achieve higher de-protection rates, de-protection over several steps, and the expansion of the organic substituent to oligopeptides and their corresponding study towards protolysis. We plan to eventually investigate the behavior of peptide-functionalized organotin sulfide clusters against acids in an aqueous milieu, and finally under physiologic conditions.

Experimental Section

General: All solvents were distilled prior to use. Dry and absolute solvents were prepared using standard laboratory procedures. The solvents were stored over 4 Å molecular sieves under argon atmosphere. All reactions were carried out under dry argon atmosphere using standard Schlenk technique.

Nuclear Magnetic Resonance Spectroscopy: ^{1}H-NMR (300 MHz) measurements were carried out using a Bruker Avance II spectrometer at 25 °C. Chemical shifts (δ) are given in ppm relative to the respective solvent residual peaks ($CDCl_3$: δ = 7.26 and 77.16 ppm).

Mass Spectrometry: ESI(+) and ESI(–) MS measurements were carried out using a LTQ-FT Ultra from Thermo Fischer Scientific with the syringe pump infusion method.

Cleaving Off the Boc-Protection Group of A with Trifluoroacetic Acid: 100 mg (0.067 mmol, 1.00 equiv.) of compound **A** were dissolved in 5 mL of dichloromethane. To this solution, different amounts of trifluoroacetic acid were added (see Table 1). The solution was stirred for two hours, and the solvent was then removed in vacuo to afford a colorless powder.

Table 1. Used amounts of trifluoroacetic acid.

Equivalents	*V*(TFA) /mL
4	0.02
5	0.025
6	0.03
9	0.045
12	0.06

Cleaving Off the boc-Protection Group of B with Trifluoroacetic Acid: 100 mg (0.063 mmol, 1.00 equiv.) of compound **B** were dissolved in 5 mL of dichloromethane. To this solution, different amounts of trifluoroacetic acid were added (see Table 2). The solution was stirred for two hours, and the solvent was then removed in vacuo to afford a colorless powder.

Table 2. Used amounts of trifluoroacetic acid.

Equivalents	*V*(TFA) /mL
4	0.019
5	0.024
6	0.029
9	0.044
12	0.058

Reactions of Phenylalanine-Substituted Cluster B with Hydrobromic Acid: 0.038 g (0.024 mmol, 1.00 equiv.) of compound **B** were dissolved in 5 mL of dichloromethane. Different amounts of hydrobromic acid (2 M) were added (see Table 3). After one day, the solvent was removed in vacuo to afford a white to light yellow solid.

Table 3. Used amounts of hydrobromic acid.

Equivalents	*V*(HBr) /mL
3	0.036
8	0.096
15	0.18

Reactions of Compound B with Ammonium Chloride: 0.038 g (0.024 mmol, 1.00 equiv.) of compound **B** were dissolved in 5 mL of dichloromethane. Different amounts of ammonium chloride were added (see Table 4). The colorless solution was stirred overnight, thereby turning cloudy. The solvent was removed in vacuo to afford a colorless solid.

Table 4. Used amounts of ammonium chloride.

Equivalents	*m*(NH_4Cl) /g
3	0.004
8	0.010
15	0.019

Reactions of Compound B with Acetic Acid: 0.038 g (0.024 mmol, 1.00 equiv.) of compound **B** were dissolved in 5 mL of dichloromethane. Different amounts of acetic acid (2 M) were added (see Table 5), and the colorless solution was stirred overnight. In all cases, a black solid precipitate appeared while the solutions stayed colorless.

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Table 5. Used amounts of acetic acid.

Equivalents	$m(H_3CCOOH)$ /g
3	0.036
8	0.096
15	0.18

Reactions of Compound B with Degassed Water: 0.038 g (0.024 mmol, 1.00 equiv.) of compound **B** were dissolved in 5 mL of dichloromethane. Degassed water was added (see Table 6), and the solution was stirred overnight. Upon addition of an excess (20 equiv.) of degassed water, the solution turned brown after a few minutes, whereupon a black solid precipitated. The solvent was removed in vacuo, and the remaining solid was analyzed.

Table 6. Used amounts of degassed water.

Equivalents	$V(H_2O)$ /mL
6	0.003
20	0.009
100	0.044

Reactions of Keto-Functionalized Tin Sulfide Cluster C with Hydrochloric Acid: 0.01 g (0.012 mmol, 1.00 equiv.) of compound **C** was dissolved in 5 mL of dichloromethane. Different amounts of hydrochloric acid (37 %) were added (see Table 7), and the solution was stirred for one day. The solvent was then removed in vacuo to afford a colorless solid.

Table 7. Used amounts of hydrochloric acid.

Equivalents	V(HCl) /mL
3	0.003
15	0.015

Reaction with Hydrochloric Acid Dissolved in Dioxane: 0.02 g (0.034 mmol, 1.00 equiv.) of compound **C** was dissolved in 5 mL of dichloromethane, different amounts of a HCl solution in dioxane (4 M) were added (see Table 8), and the solution was stirred overnight. The solvent was then removed in vacuo to afford a colorless solid.

Table 8. Used amounts of hydrochloric acid dissolved in dioxane.

Equivalents	V(HCl) /mL
3	0.018
15	0.09

Reaction of Compound C with Sulfuric Acid (96 %): 0.01 g (0.012 mmol, 1.00 equiv.) of compound **C** were dissolved in 5 mL of dichloromethane. 0.002 mL (0.037 mmol, 2.00 equiv.) of sulfuric acid (96 %) were added, and the solution was stirred overnight. During this period, a yellow solid precipitated which was insoluble in common organic solvents and therefore not investigated further, while the solution turned brown-red.

Reactions of Compound C with Ammonium Chloride: 0.02 g (0.024 mmol, 1.00 equiv.) of compound **C** were dissolved in 5 mL of dichloromethane. Different amounts of ammonium chloride were added (see Table 9), and the colorless solution was stirred overnight. The solution remained clear and colorless, and no solid precipitated. The solvent was removed in vacuo to afford a colorless powdery solid.

Table 9. Used amounts of ammonium chloride.

Equivalents	$m(NH_4Cl)$ /g
3	0.004
8	0.010
15	0.019

Reactions of Compound C with Acetic Acid: 0.02 g (0.024 mmol, 1.00 equiv.) of compound **C** were dissolved in 5 mL of dichloromethane. Different amounts of acetic acid (2 M) were added (see Table 10), and the colorless solution was stirred overnight. The solvent was removed in vacuo to afford a colorless solid. At higher concentrations of the acid, small amounts of brown solid occurred.

Table 10. Used amounts of acetic acid.

Equivalents	$m(H_3CCOOH)$ /g
3	0.036
8	0.096
15	0.18

Reactions of Compound C with Degassed Water: 0.02 g (0.024 mmol, 1.00 equiv.) of compound **C** were dissolved in 5 mL of dichloromethane. Degassed water was added (see Table 11), and the solution was stirred for 24 hours. Upon addition of an excess (20 equiv.) of degassed water, the solution turned orange overnight. Higher concentration caused precipitation of a black solid precipitate and elemental tin, both indicating decomposition of the cluster.

Table 11. Used amounts of degassed water.

Equivalents	$V(H_2O)$ /mL
6	0.003
20	0.009

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Keywords: Organotin sulfides · Cluster compounds · Organotin trichlorides · H_2S release · Amino acids · Protolysis

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