Dalton Transactions

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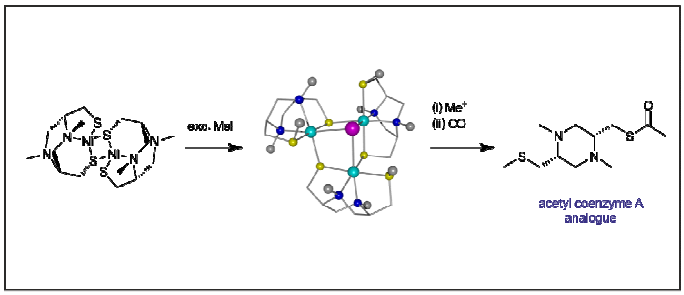
A nickel(II) complex of a cysteine-based ligand reacts with methylating reagents followed by results CO treatment via acetylation of the thiolate function, which corresponds to the ACS reactivity.



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ARTICLE

Reaction of a polydentate Cysteine-based ligand and its nickel(II) complex with electrophilic and nucleophilic methyl-transfer reagents - From S-methylation to acetyl coenzyme A synthase reactivity

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The L-cysteine derived N_2S_2 ligand precursor H_2L and its nickel(II) complex L_2Ni_2 were investigated with respect to their behaviour in contact with electrophilic and nucleophilic methylation reagents (H_2L = (*N*,*N*´-Dimethyl-(2*R*,5*R*)-*bis*-(sulfanylmethyl)-piperazine). Treatment of deprotonated L^- with MeI led to the selective methylation of the thiolate groups thus generating a novel potential ligand, Me_2L, which is neutral and contains two thioether donors. The coordinating properties of Me_2L were demonstrated by the synthesis of a first nickel(II) complex: Reaction with $NiBr_2$ led to a mononuclear complex **2** where all donor atoms coordinate to the nickel ion, which completes its octahedral coordination sphere by the two bromide ligands. If, however, the complex $[LNi]_2$ (**1**) is treated with MeI only one thiolate function per ligand moiety is methylated, while the other one remains a thiolate. This leads to $[MeLNi]^+$ complex metal fragments, which trimerize including a μ_3-bridging iodide ion to give the compound **3** that was tested with regards to ACS reactivity. While it behaved inert towards CO, attempts to replace the bridging iodide ligand by methyl units in reactions with nucleophilic methylation reagents led to a product, which could not be identified but reacted with CO. Work-up showed that this protocol had converted the thiolate function of MeL^- into a thioester function, which corresponds to an ACS-like reactivity.

Introduction

The active sites of metalloproteins like acetyl coenzyme A synthase (ACS)[1] or [NiFe] hydrogenase[2] contain nickel ions that are coordinated exclusively by donors derived from cysteine. For the preparation of structural or functional model compounds for such centers, various polydentate thiolates have been employed in the past to mimic the cysteinate ligand environments.[3,4] However, these were often electronically and structurally quite different from cysteinate donors. In this context, we have recently reported a novel polydentate, chiral ligand precursor H_2L that has been constructed starting from natural L-cysteine and whose thiolate donor functions thus closely resemble cysteinate electronically.[3i] Investigating their coordination chemistry in combination with nickel(II) ions the new chiral nickel complexes obtained were found to represent interesting structural models. For instance, $[LNi]_2$, **1**, resembles the active dinickel core (A cluster) of the acetyl coenzyme A synthase (ACS) (Fig. 1).

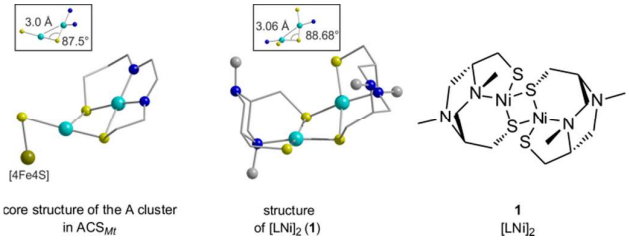

Fig. 1 Structure of $[LNi]_2$ (**1**) in comparison with the core structure of the A cluster in ACS_{Mt} (PDB File: 1OAO).

The ACS mediates the generation of an acetylthioester CH_3-C(O)-SR (R = CoA, a central metabolite) setting out from CO, a thiol (HSCoA) and a methyl moiety, which is provided by a corrinoid iron sulfur protein (ultimately a methyl cobal(III)amine).[1,3h,5-8] The mechanism is still discussed controversially, with a main point of debate being the binding sequence of the three substrates.[1,5,9-13] Today, there is wide agreement that CoASH is the last substrate to bind,[9] and that the distal Ni center mainly serves to stabilize the structure. It is clear, too, that the resting state contains both Ni centers in the

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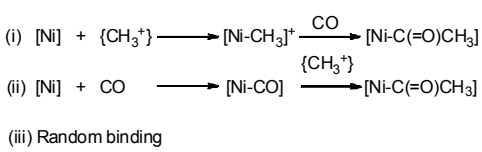
† Electronic Supplementary Information (ESI) available: ^{1}H NMR, ^{13}C NMR, ATR-FTIR and mass spectra of the synthesized compounds as well as a UV/vis absorption spectrum of $[(MeLNi)_3I]I_2$ (**3**). See DOI: 10.1039/x0xx00000x

oxidation state +II, and reduction of the proximal Ni center, either to the oxidation state +I or even to 0, then produces the active state, that binds the substrates CO and methyl to create the acetyl moiety.[14] This conversion could proceed via two alternative mechanistic routes: (i) a CH_3-Ni^{II} unit is generated and then reacts with CO, or (ii) CO is bound first at the reduced Ni_p initially, and subsequently CH_3^+ is transferred (Scheme 1).[1,14] There has even been the suggestion that a "random binding" of either methyl or CO, takes place.[9,13,15]



Scheme 1 Mechanistic alternatives for the formation of the acetyl group at the proximal nickel atom of the ACS active site.

To this sort of discussion bioinorganic model compounds can make important contributions, as they provide insights, whether a reaction pathway proposed for an enzyme is plausible from the point of view of molecular chemistry or not based on the existence or elusiveness of precedent cases from that area. Indeed the ACS has been the subject of various model studies, including mono- and dinuclear nickel compounds.[3a,b,h,4a,f,7,8,12,16-21] These mainly brought about evidence that option (i) is principally feasible, while we recently reported the first nickel-based reactivity that supported option (ii), and thus also random binding.[22]

Given this background and the structural similarities between **1** and the A cluster, we have investigated both CO and methyl binding at LNi moieties and tested for biomimetic reactivity. For comparison and to access a novel ligand that may be suitable for mimicking methionine ligation we have also investigated the methylation of the ligand H_2L.

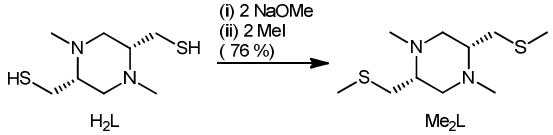
Results and discussion

First of all the reactivity of **1** towards CO was tested. It is known that binding of CO to nickel(II) is only weak, although some nickel(II)-CO complexes are existing,[3h,4a,23-29] and hence we were not surprised to find that complex **1** does not react with CO.

CO binds more favorably to nickel after reduction to nickel(I)[3b,4b,8,17,30-36] or even to nickel(0)[3a,b,30,31,39,40] and this is what has been suggested also as part of the ACS turnover.[1,6,7,9,11,12,14,15,19] Hence, attempts were made to reduce **1** with KC_8, cobaltocene or sodium amalgam, respectively, which, however only led to the decomposition of $[LNi]_2$ (**1**). Also attempts to generate nickel carbonyl moieties by reduction of **1** in the presence of CO failed.

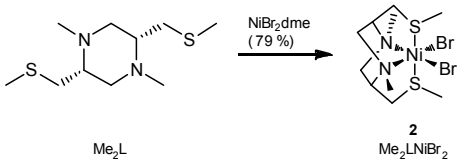
We continued with methylation studies, and first of all examined the behavior of the uncomplexed ligand precursor H_2L towards the electrophilic reagent MeI. Deprotonation of H_2L with NaOMe followed by treatment with MeI led to the isolation of Me_2L, which was isolated in diastereomerically pure form with yields above 76 % and fully characterized (Scheme 2).

In the ^{1}H NMR spectrum of a $CDCl_3$ solution of Me_2L, the absence of a broad singlet signal at δ = 1.61 ppm confirmed complete conversion of the original thiol functions in H_2L (see Fig. S15). Instead the spectrum contained a new singlet signal at a chemical shift of δ = 2.09 ppm, which could be assigned to the new methyl thioether groups; the corresponding signal in the ^{13}C NMR spectrum appears at a chemical shift of δ = 16.4 ppm (see Fig. S16).



Scheme 2 Synthesis of Me_2L.

After replacement of the thiolate functions by thioether units, Me_2L may be regarded as an interesting potential ligand for the simulation of methionine ligand spheres of metal ions in enzymes. To test the coordinating properties of Me_2L a first nickel complex was synthesized. The reaction of Me_2L with $NiBr_2$dme in thf led to a green suspension, from which Me_2LNiBr_2 (**2**) could be isolated after work-up in good yields (Scheme 3).



Scheme 3 Synthesis of Me_2LNiBr_2 (**2**).

Complex **2** is soluble in methanol and acetonitrile, while solubility in thf, dichloromethane, diethyl ether, *n*-hexane and toluene is only moderate. It was characterized by single-crystal X-ray diffraction, ^{1}H NMR and IR spectroscopy, mass spectrometry as well as elemental analysis. Single crystals were obtained through slow diffusion of diethyl ether into a methanol solution of **2**. Me_2LNiBr_2 (**2**) crystallizes in the chiral space group *P*1 and Figure 2 shows the molecular structure of **2**. All stereocenters within **2** are *R* configured and the compound is stereoisomerically pure.

2 represents a mononuclear compound, and the nickel(II) ion of **2** has a distorted octahedral coordination sphere. In contrast to the dimeric nickel complex **1** (see Fig. 1) the nickel ion in Me_2LNi (**2**) experiences a N_2S_2 coordination: The ligand folds around the metal ion so that all four donor atoms of Me_2L, the two sulfur and two nitrogen atoms, can coordinate to the nickel(II) atom. The piperazine ring thus adopts a boat configuration and the two thioether groups are positioned *trans* each other. The coordination sphere of the Ni atom is completed by the two bromide ligands. The

Ni^{II}-thioether bonds in **2** amount to 2.41 Å and are thus longer than other Ni^{II}-thioether bonds in known nickel complexes (2.1-2.2 Å).[4a,41] The Ni^{II}-N bond of **2** is also longer than the Ni^{II}-N bonds of known nickel complexes (1.8-1.9).[3i,42-45] This is likely due to the restrictions imposed by the framework of the ligand Me_2L.

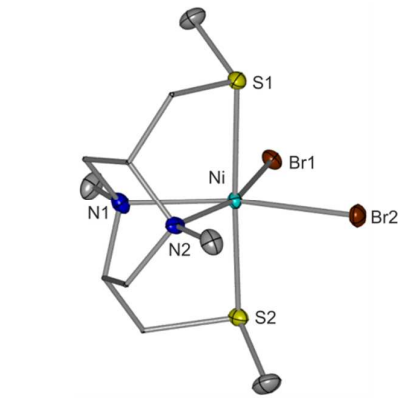


Fig. 2 Molecular structure of **2**. Ellipsoids are drawn at the 60 % probability level. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni-S(1) 2.4079(16); Ni-S(2) 2.4264(16); Ni-Br(1) 2.5405(8); Ni-Br(2) 2.5333(8); Ni-N(1) 2.1810(5); Ni-N(2) 2.1940(5); N(1)-Ni-S(1) 86.78(15); N(1)-Ni-N(2) 68.85(17); N(1)-Ni-S(2) 92.87(15); N(1)-Ni-Br(1) 93.56(13); N(1)-Ni-Br(2) 166.92(15); N(2)-Ni-S(1) 87.40(13); N(2)-Ni-S(2) 84.90(13); N(2)-Ni-Br(2) 100.77(12); N(2)-Ni-Br(1) 161.42(13); S(1)-Ni-S(2) 171.86(5); S(1)-Ni-Br(1) 97.87(4); S(1)-Ni-Br(2) 84.75(4); S(2)-Ni-Br(1) 90.27(4); S(2)-Ni-Br(2) 94.10(5); Br(1)-Ni-Br(2) 97.46(3).

In the next step the methylation of L^{2-} coordinated to nickel was investigated. While employment of MeOTf as a methylating agent only provided product mixtures, MeI reacted more selectively. Treatment of $[LNi]_2$ (**1**) with an excess of methyl iodide in thf / dichloromethane led to a light green suspension, and after work-up $[(MeLNi)_3I]I_2$ (**3**) was isolated in diastereomerically pure form with very good yields (see Scheme 4). The ligand MeL^- in $[(MeLNi)_3I]I_2$ (**3**) contains one thiolate, one thioether and two tertiary amine functions. Hence, the reaction of **1** with MeI led to the methylation of one thiolate function per ligand, so that formally $MeLNi^+$ units were generated aggregating via the thiolate functions to give a trinuclear nickel core, that is further stabilized by a μ_3-bridging iodide ligand.

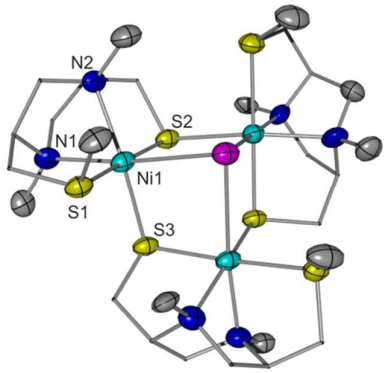
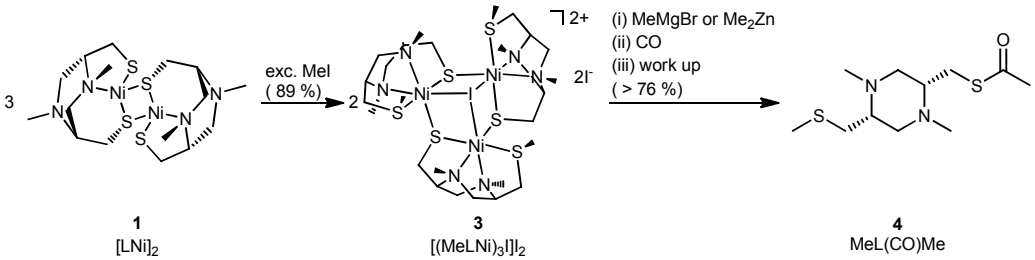


Fig. 3 Molecular structure of **3**. Ellipsoids are drawn at the 60 % probability level. All hydrogen atoms and the two non-coordinated iodide ions are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni(1)-I(1) 2.9413(15), Ni(1)-N(1) 2.1440(9); Ni(1)-N(2) 2.1950(8); Ni(1)-S(1) 2.3800(3); Ni(1)-S(2) 2.3970(3); Ni(1)-S(3) 2.4110(3); S(1)-Ni(1)-S(2) 175.65(11); S(1)-Ni(1)-N(2) 94.70(2); S(1)-Ni(1)-N(1) 84.50(2); S(1)-Ni(1)-S(3) 94.74(10); S(1)-Ni(1)-I(1) 89.32(8); N(1)-Ni(1)-N(2) 69.40(3); N(1)-Ni(1)-S(2) 99.90(2); N(1)-Ni(1)-S(3) 100.50(2); N(1)-Ni(1)-I(1) 169.50(2); N(2)-Ni(1)-S(2) 86.30(2); N(2)-Ni(1)-I(1) 102.90(2); N(2)-Ni(1)-S(3) 165.40(2); S(2)-Ni(1)-I(1) 86.33(7); S(2)-Ni(1)-S(3) 85.09(9); S(3)-Ni-I(1) 88.39(8).

Single crystals could be grown by slow evaporation of the volatiles from an acetonitrile solution of $[(MeLNi)_3I]I_2$ (**3**).

The trinuclear complex **3** crystallizes in the chiral space group $P2_1$, and Figure 3 shows the molecular structure of **3**. All stereocenters within **3** are *R* configured and the ^1H NMR spectrum of the complex **3** contained paramagnetically shifted signals. The UV-vis spectrum of a 0.025 mM solution of **3** in MeCN showed two intensive absorption bands at 247 nm (ε = 74.32 $mmol^{-1}$ cm^{-1}) and 338 nm (ε = 10.93 $mmol^{-1}$ cm^{-1}), originating presumably from and S→Ni charge transfer transitions (see Fig. S24).[46, 47]

The ligands MeL^- folds around the nickel centers so that all four donor atoms of MeL^- coordinate the nickel ions. Again, the piperazine ring adopts a boat configuration and the two sulfur donors are located *trans* with respect to each other. The three nickel ions, the three thiolate groups of the $MeLNi^+$ units and the μ_3-bridging iodide ion are arranged in form of a cube with a missing corner.

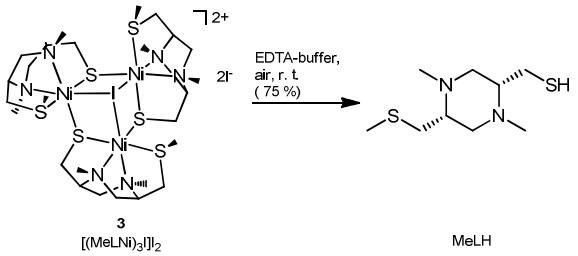


Scheme 4 Synthesis of $[(MeLNi)_3I]I_2$ (**3**) and reaction of $[(MeLNi)_3I]I_2$ (**3**) with MeMgBr or Me_2Zn followed by treatment with CO.

All nickel(II) ions of **3** have a distorted octahedral coordination sphere with angles close to 90°. Again, the Ni^{II}-S and the Ni^{II}-N bonds in **3** are longer than typical Ni^{II}-S (2.1-2.2 Å)[4a,41] and Ni^{II}-N bonds known for nickel complexes (1.8-1.9 Å).[3i,42–45]

Attempts to remove iodide in **3** by treating it with different silver salts of weakly coordinating anions such as AgOTf, $AgBF_4$ or $AgPF_6$ proceeded successfully, as judged by MS and IR studies but the resulting product eluded crystallisation.

Notably, the treatment of the complex $[(MeLNi)_3I]I_2$ (**3**), with EDTA-buffer under aerobic conditions led to demetallation, and the pure ligand precursor MeLH (Scheme 5) could be obtained, as confirmed by NMR and ATR spectroscopy as well as mass spectrometry. Hence, the complete series H_2L, MeLH and Me_2L is now available for future biomimetic work on metal ions in sulfur-rich coordination spheres. The reaction of MeLH with NiI_2 yielded back the complex $[(MeLNi)_3I]I_2$ (**3**), as suggested by a mass spectroscopic analysis of the reaction mixture.



Scheme 5 Synthesis of MeLH by demetallation of $[(MeLNi)_3I]I_2$ (**3**) with EDTA-buffer.

3 can be viewed formally as a source of MeLNi-I, and hence it was used as a precursor compound in reactions with nucleophilic methylation reagents like MeMgBr and Me_2Zn, aiming at the creation of a MeLNi-Me complex that can be subjected to reactivity studies according to route (i). These reactions were carried out at low temperatures and led to yellow solutions, which proved very sensitive to air and water and upon annealing to room temperature converted to black suspensions. In consequence, it has not yet been possible to characterize the product.

Accordingly, the product resulting from the methylation reaction was treated directly with CO without prior isolation. The yellow solution turned into a white suspension, and after work-up a colorless oil was obtained. The oil was characterized trough mass spectrometry, NMR and IR spectroscopy and could thus be identified as the compound S-(((2*R*,5*R*)-1,4-dimethyl-5-((methylthio) methyl)piperazine-2-yl) methyl) ethanethioate MeL(CO)Me (**4**) (Scheme 4). The NMR investigation of a CD_3CN solution indicated the presence of an acetyl unit as part of **4**: The ^1H NMR spectrum showed a singlet at δ (C(O)C*H*$_3$)=2.35 ppm (see Fig. S20) and the APT NMR spectrum of **4** contained a low-field *C*(O)CH_3 resonance at 196.2 ppm (Fig. 4), which is characteristic for acetyl functions. Further investigation of the product via mass spectrometry revealed a signal at *m/z* = 263.1291 on positive ground. This signal could be assigned to **4** + H^+ and the isotope patterns of the calculated and experimental spectra are identical.

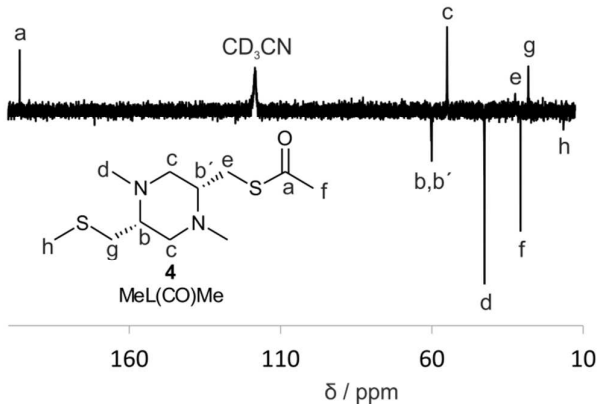


Fig. 4 APT NMR spectrum of MeL(CO)Me (**4**) in CD_3CN.

The conversion of **3** with MeMgBr or Me_2Zn followed by a reaction with CO in acetonitrile was also investigated by liquid ATR-FTIR spectroscopy: The ATR-FTIR spectrum of the reaction mixture featured three strong absorption bands at 1686, 1654 and 1568 cm^{-1} (black line in Fig. 5). After work-up, the ATR-FTIR spectrum contained only a very strong absorption band at 1686 cm^{-1} caused by the stretching vibration of the carbonyl group in MeL(CO)Me (**4**), which therefore had been part of the reaction mixture already (red line in Fig. 5).

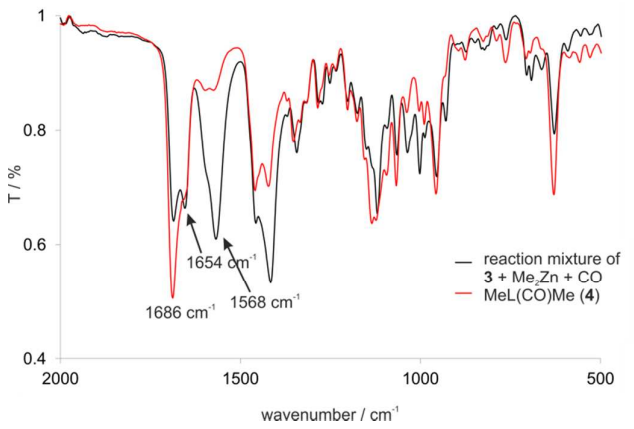
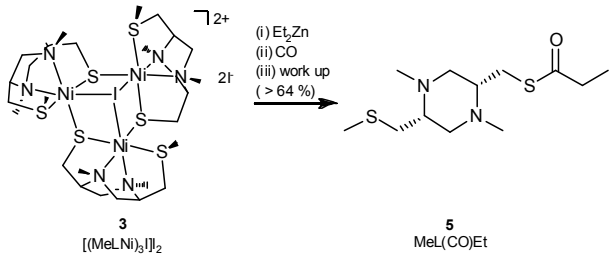


Fig. 5 Liquid ATR-FTIR spectra recorded for the product mixture after the successive reaction of $[(MeLNi)_3I]I_2$ (**3**) with Me_2Zn and CO (black line) and for MeL(CO)Me (**4**) (red line).

Hence, the substrates of the ACS or models thereof have been combined at a nickel center to produce an analogue of the ACS product, and the sequence of addition suggests that this proceeded via the mechanistic route (i). Notably, without prior treatment with an alkylating reagent dissolved **3** does not react with CO.

The transformation as in Scheme 4 is not restricted to methylation reagents. A similar reaction of $[(MeLNi)_3I]I_2$ (**3**) with the nucleophilic alkylation reagent Et_2Zn followed by direct treatment with CO analogously led to the isolation of S-(((2*R*,5*R*)-1,4-dimethyl-5-((methylthio) methyl)piperazine-2-yl)methyl) propanethioate MeL(CO)Et (**5**), i.e. to MeL acylated by a $[Et\text{-}C{=}O]^+$ group (Scheme 6). Compound **5** was characterized through NMR and IR spectroscopy as well as mass spectrometry (see Fig. S22, S23, S11, S12, S14).



Scheme 6 Reactivity of $[(MeLNi)_3I]I_2$ (**3**) with Et_2Zn followed by treatment with CO.

Conclusions

The reactions of L^{2-} and its nickel(II) complex $[LNi]_2$ with MeI led to the selective methylation of two thiolate functions or only one of them, respectively, so that now a series of N_2S_2 ligands – with two thiolate, one thiolate and one thioether or two thioether donors – is available for future studies. Through complex formation with nickel(II) it was demonstrated that in all cases the ligands wrap around the metal centers, so that both S donors are coordinating. The complex **3**, containing MeL, generated by reaction of $[LNi]_2$ with MeI, was found to react with Me_2Zn and MeMgBr to give a yet unidentified product that, however, inserts CO leading to the acetylation of the thiolate function of MeL^-. We propose an intermediately formed Ni-Me unit that inserts CO to give a Ni-acetyl entity, which is transferred then to the thiolate function, similarly to what has been proposed for the ACS reactivity.

Experimental

General

All manipulations were carried out in a glove box or by means of Schlenk-type techniques involving the use of a dry and oxygen-free argon atmosphere. Solvents were dried by using an MBraun Solvent Purification System SPS. NMR spectra were recorded on a Bruker AV 400 NMR spectrometer at 25°C (^{1}H 400.13 MHz, ^{13}C 100.6 MHz). The spectra were calibrated against the internal residual proton and natural abundance ^{13}C resonances of the deuterated solvent. The coupling constants are given in Hz. Microanalyses were performed with a HEKAtech Euro EA 3000 elemental analyzer. Infrared (IR) spectra were recorded in the region of 4000 – 400 cm^{-1} using solid samples prepared as KBr pellets with a Shimadzu FTIR 8400S. ATR-FTIR spectra were recorded with a Bruker Alpha in the region of 4000 – 400 cm^{-1} using dissolved samples. HRMS (ESI) were either recorded with an Agilent Technologies 6210 Time-of-Flight-LC-MS. Absorption spectroscopic measurements were performed for MeCN solutions of the respective compound using a Cary 100 UV/Vis NIR spectrometer from Varian employing the software Cary Win UV. SUPRASIL® Quartz cells from Hellma Analytics with a 10 mm path length were used.

Materials

Unless otherwise stated the starting materials were obtained in the highest possible grade of purity from commercial sources and used as received. $[NiBr_2(dme)]$ was synthesized by stirring a suspension of $NiBr_2$ in dme under reflux for 3 days, filtration and drying of the salmon colored solid in vacuum.[48] H_2L and $[LNi]_2$ (**1**) were prepared as reported.[3i]

Ligand Synthesis

Me_2L: NaOMe (275.2 mg, 5.09 mmol, 2.1 equiv.) was added to a solution of *N,N'*-dimethyl-(2*R*,5*R*)-*bis*-(sulfanylmethyl)-piperazine H_2L (500.0 mg, 2.42 mmol) in thf (40 mL) and the resulting suspension was stirred for 24 h. Subsequently, methyl iodide (0.33 mL, 5.33 mmol, 2.2 equiv.) was added, and the resulting yellow solution was stirred for four hours. After evaporation of all volatiles in vacuum, the residue was extracted with dichloromethane (20 mL). After removing the solvent, the yellow oil was extracted with toluol and again the solvent was removed. Me_2L was obtained in form of an oily solid (436.7 mg, 1.86 mmol, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (m, 6H, SCH_2CH, CHCH_2N), 2.49 (m, 4H, CHCH$_2$N, CHCH_2N), 2.31 (s, 6H, NCH_3), 2.09 (s, 6H, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.1 (CHCH$_2$N), 55.2 (CHCH$_2$N), 42.4 (NCH$_3$), 32.0 (SCH$_2$CH), 16.4 (SCH$_3$); IR (KBr): $\tilde{\upsilon}$ = 2974 (s), 2912 (s), 2840 (s), 2787 (s), 2718 (w), 2642 (w), 1659 (w), 1456 (s), 1384 (w), 1367 (w), 1312 (m), 1333 (m), 1284 (s), 1253 (w), 1233 (w), 1200 (s), 1173 (s), 1157 (s), 1122 (m), 1092 (s), 1067 (s), 1036 (m), 987 (m), 958 (m), 872 (m), 829 (m), 790 (m), 765 (m), 704 (m), 653 (m), 471 (m); ESI-MS *m/z*: $[M+H]^+$ calcd for $C_{10}H_{23}N_2S_2$ 235.1297. Found: 235.1295. Anal. Calcd for $C_{10}H_{22}N_2S_2$: C, 51.23; H, 9.45; N, 11.94. Found: C, 51.06; H, 9.43; N, 11.96.

MeLH: $[(MeLNi)_3I]I_2$ (**3**) (75 mg, 0.06 mmol) was dissolved in 10 mL dichloromethane and stirred vigorously with 15 mL EDTA-buffer (10 mM H_4EDTA, 27 mM NaAc and 0.04 mM HAc) for 6 h. The organic layer was separated, washed with 5 % aqueous $NaHCO_3$, and dried over $MgSO_4$. After removing the solvent the brown oily residue was purified using silica column chromatography (acetone / ethyl acetate (1:1) → (1:0)). This method afforded MeLH as a yellow oil (28 mg, 0.13 mmol, 69 %). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.00 (m, 1H, SCH_2CH), 2.91 (m, 1H, SCH_2CH), 2.76 (m, 1H, CHCH_2N), 2.70 – 2.61 (m, 4H, SCH_2CH, CHCH_2N, CHCH$_2$N), 2.51 – 2.39 (m, 3H, CHCH_2N, CHCH$_2$N), 2.32 (s, 3H, NCH_3), 2.28 (s, 3H, NCH_3), 2.08 (s,

3H, SCH_3), 1.26 (s, 1H, S*H*); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 60.6 (*C*HCH$_2$N), 60.2 (*C*HCH$_2$N), 55.5 (CH*C*H$_2$N), 55.2 (CH*C*H$_2$N), 42.7 (N*C*H$_3$), 42.6 (N*C*H$_3$), 36.5 (S*C*H$_2$CH), 33.1 (S*C*H$_2$CH), 16.6 (S*C*H$_3$); ATR-FTIR: $\tilde{\upsilon}$ = 2913 (s), 2840 (vs), 2788 (s), 2719 (w), 2650 (w), 1455 (s), 1445 (s), 1367 (w), 1332 (m), 1312 (m), 1283 (m), 1253 (w), 1233 (w), 1198 (s), 1172 (s), 1157 (s), 1122 (m), 1090 (s), 1065 (vs), 1036 (w), 987 (s), 959 (m), 871 (w), 823 (w), 790 (w), 765 (w), 704 (w), 665 (w), 585 (w), 520 (w), 477 (m), 440 (w), 421 (w); ESI-MS *m/z*: $[M+H]^+$ calcd for $C_9H_{20}N_2S_2$ 221.1141. Found: 221.1206. Anal. Calcd for $C_{10}H_{22}N_2S_2$ + 1.5 equiv. of acetone: C, 52.7322; H, 9.51; N, 9.11. Found: C, 53.22; H, 9.66; N, 9.44.

Complex Synthesis

*Me$_2$LNiBr$_2$ (**2**):* NiBr$_2$dme (203.1 mg, 0.65 mmol, 1 equiv.) was added to a suspension of Me$_2$L (154.0 mg, 0.65 mmol) in acetonitrile (10 mL) and the resulting green suspension was stirred for 12 h. After filtration, the green residue was washed twice with 5 mL hexane. Subsequent drying led to a green powder characterized as Me$_2$LNiBr$_2$ (**2**) (242.0 mg, 0.53 mmol, 79 %). Diffusion of diethyl ether into a solution of **2** in methanol provided green crystals within 1 d, which were suitable for an X-ray diffraction analysis. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.72 (m, 2H, C*H*CH$_2$N), 2.63 (m, 4H, SCH_2CH), 2.48 (m, 4H, CHCH_2N), 2.26 (s, 6H, NCH_3), 2.03 (s, 6H, SCH_3); IR (KBr): $\tilde{\upsilon}$ = 3010 (m), 3001 (m), 2978 (m), 2929 (m), 2914 (m), 2811 (m), 1483 (w), 1460 (m), 1419 (m), 1407 (w), 1384 (m), 1346 (m), 1336 (w), 1268 (w), 1251 (m), 1208 (w), 1184 (w) 1119 (m), 1070 (m), 1000 (m), 884 (w), 866 (w), 808 (m); ESI-MS (ESI) *m/z*: $[M-Br]^+$ calcd for $C_{10}H_{22}N_2S_2NiBr^+$ 372.9762. Found: 372.9720. Anal. Calcd for $Br_2C_{10}H_{22}N_2NiS_2$: C, 26.23; H, 4.90; N, 6.18. Found C 26.77, H 4.79, N 6.00.

*[(MeLNi)$_3$I]I$_2$ (**3**)* Methyl iodide (105 μL, 1.671 mmol, exc.) was added to a solution of [LNi]$_2$ (**1**) (97 mg, 0.18 mmol) in 7 mL thf and 3 mL dichloromethane. The resulting solution was stirred overnight, during which time a green solid precipitated. After filtration, [(MeLNi)$_3$I]I$_2$ (**3**) was obtained as a light green powder (133 mg, 0.109 mmol, 89 %). Single crystals for X-ray could be grown by evaporation of an acetonitrile solution of **3**. IR (KBr): $\tilde{\upsilon}$ = 3007 (w), 2983 (w), 2964 (vs), 2910 (vs), 2860 (vs), 2814 (w), 2803 (w), 1454 (vs), 1435 (m), 1416 (m), 1401 (w), 1385 (w), 1361 (w), 1341 (m), 1314 (w), 1268 (m), 1231 (w), 1208 (m), 1183 (w), 1170 (m), 1145 (m), 1117 (m), 1061 (m), 1041 (m), 1023 (m), 1000 (m), 971 (w), 952 (m), 931 (s), 809 (m), 724 (m), 705 (m), 694 (vs), 592 (w), 476 (w), 463 (w); UV (MeCN) λ_{max}, nm (ε, mmol^{-1} cm^{-1}): 247 (74.32), 338 (10.93); ESI-MS *m/z*: $[MeLNi]^+$ and $[(MeLNi)_2I]^+$ calcd for $[C_9H_{19}N_2S_2Ni]^+$ 277.0343 and for $[C_{18}H_{38}N_4S_4Ni_2I]^+$ 680.9731. Found 277.0334 and 680.9673. Anal. Calcd for $C_{27}H_{57}I_3N_6Ni_3S_6$: C, 26.69; H, 4.73; N, 6.92. Found: C, 26.82; H, 4.77; N, 6.46.

Reaction of [(MeLNi)$_3$I]I$_2$ (3) with MeMgBr or Me$_2$Zn followed by treatment with CO

*MeL(CO)Me (**4**)*: [(MeLNi)$_3$I]I$_2$ (**3**) (40 mg, 0.033 mmol) dissolved in acetonitrile was added to MeMgBr (33 μL, 0.099 mmol, 3 M, Et$_2$O, 3 equiv.) or Me$_2$Zn (17 μL, 0.099 mmol, 10 %, hexane, 3 equiv.) at -30°C. The green solution changed color to yellow, and it was exposed then to CO at -30°C for five minutes, resulting in a white suspension. The suspension was warmed to room temperature and after filtration and removal of the solvent, the residue was extracted with 3 mL dichloromethane. After removing the solvent, S-(((2*R*,5*R*)-1,4-dimethyl-5-((methylthio)methyl)piperazine-2-yl) methyl) ethanethioate MeL(CO)Me (**4**) was isolated as a colorless oil (20 mg, 0.075 mmol, 76 %). ^{1}H NMR (400 MHz, CD_3CN): δ = 3.19 (m, 1H, SCH_2CH), 3.02 (m, 1H, SCH_2CH), 2.77 (m, 3H, SCH_2CH, CHCH_2N), 2.59 (m, 2H, CHCH_2N, C*H*CH$_2$N), 2.50 (m, 3H, CHCH_2N, C*H*CH$_2$N), 2.35 (s, 3H, COCH_3), 2.32 (s, 3H, NCH_3), 2.30 (s, 3H, NCH_3), 2.13 (s, 3H, SCH_3); ^{13}C NMR (100 MHz, CD_3CN): δ = 196.2 (*C*O), 60.2 (*C*HCH$_2$N), 60.1 (*C*HCH$_2$N), 55.0 (CH*C*H$_2$N), 42.6 (N*C*H$_3$), 32.5 (S*C*H$_2$CH), 30.7 (*C*H$_3$CO), 28.1 (S*C*H$_2$CH), 16.5 (S*C*H$_3$); ATR-FTIR (MeCN): = 2915 (m), 2844 (m), 2793 (m), 1686 (vs), 1653 (s), 1597 (m), 1458 (s), 1420 (s), 1369 (m), 1351 (m), 1283 (w), 1252 (w), 1234 (m), 1201 (m), 1174 (s), 1133 (s), 1122 (s), 1092 (s), 1065 (m), 1036 (m), 1002 (m), 988 (m), 955 (s), 874 (w), 824 (w), 787 (w), 762 (w), 704 (w), 628 (s), 588 (w), 557 (w), 526 (w), 474 (w); ESI-MS *m/z*: $[M+H]^+$ calcd for $C_{11}H_{22}N_2S_2O$ 263.1246. Found: 263.1291. Anal. Calcd for $C_{11}H_{22}N_2OS_2$ + 2 equiv. of dichloromethane: C, 36.11; H, 6.06; N, 6.48. Found: C, 36.46; H, 6.16; N, 6.90.

Reaction of [(MeLNi)$_3$I]I$_2$ (3) with Et$_2$Zn followed by treatment with CO

*MeL(CO)Et (**5**)*: [(MeLNi)$_3$I]I$_2$ (**3**) (40 mg, 0.033 mmol) dissolved in acetonitrile was added to Et$_2$Zn (50 μL, 0.099 mmol, 1 M, hexane, 3 equiv.) at -30°C. The green solution changed color to yellow, and it was exposed then to CO at -30°C for five minutes, resulting in a white suspension. The suspension was warmed to room temperature and after filtration and removal of the solvent, the residue was extracted with 3 mL dichloromethane. After removing the solvent, S-(((2*R*,5*R*)-1,4-dimethyl-5-((methylthio)methyl) piperazine-2-yl)methyl) propanethioate MeL(CO)Et (**5**) was isolated as a colorless oil (18 mg, 0.063 mmol, 64 %). ^{1}H NMR (400 MHz, CD_3CN): δ = 3.19 (m, 1H, SCH_2CH), 3.03 (m, 1H, SCH_2CH), 2.80 (m, 3H, SCH_2CH, CHCH_2N), 2.65 (m, 2H, C*H*CH$_2$N), 2.59 (q, $^3J_{H,H}$ = 7.5 Hz, 2H, COCH_2CH$_3$), 2.51 (m, 3H, CHCH_2N), 2.38 (s, 3H, NCH_3), 2.32 (s, 3H, NCH_3), 2.11 (s, 3H, SCH_3), 1.12 (t, $^3J_{H,H}$ = 7.5 Hz, 3H, COCH$_2$CH_3); ^{13}C NMR (100 MHz, CD_3CN): δ = 200.6 (*C*O), 60.4 (*C*HCH$_2$N), 60.2 (*C*HCH$_2$N), 55.0 (CH*C*H$_2$N), 42.6 (N*C*H$_3$), 38.0 (CH$_3$*C*H$_2$CO), 32.4 (S*C*H$_2$CH), 27.7 (S*C*H$_2$CH), 16.5 (S*C*H$_3$), 9.9 (*C*H$_3$CH$_2$CO); ATR-FTIR (MeCN): $\tilde{\upsilon}$ = 2974 (m), 2932 (m), 2927 (m), 2795 (m), 1686 (vs), 1561 (m), 1457 (vs), 1419 (s), 1371 (m), 1329 (m), 1325 (m), 1283 (m), 1281 (m), 1250 (w), 1234 (m), 1201 (m), 1173 (m), 1155 (m), 122 (m), 1087 (s), 1064 (s), 1015 (s), 988 (m), 934 (vs), 903 (m), 786 (w), 756 (w), 713 (m), 603 (w), 556 (w); ESI-MS *m/z*: $[M+H]^+$ calcd for $C_{12}H_{24}N_2S_2O$ 277.1408. Found: 277.1439. Anal. Calcd for $C_{11}H_{22}N_2OS_2$: C, 52.13; H, 8.75; N, 10.13. Found: C, 52.68; H, 8.92; N, 10.47.

Crystal Structure Determinations

Crystal data and parameters are listed in Table 1. All data collections were performed at 100 K with a STOE IPDS 2T diffractometer (Mo-*K*α radiation, λ = 0.71073 Å, graphite monochromator) area detector. The structures were solved by direct methods (SHELXS-97) and refined by full-matrix leastsquares procedures based on F^2 with all measured reflections (SHELXL-97).[49]

Multi-scan corrections were applied for complex **2** and for complex **3**. All non-hydrogen atoms were refined anisotropically. All hydrogen atom positions were introduced at their idealized positions and were refined using a riding model.

Crystallographic data (excluding structure factors) of **2** and 3 were deposited at the Cambridge Crystallographic Data Center, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository numbers CCDC-1414764 (**2**), and 1414763 (**3**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

Table 1 Crystal data and experimental parameters for the crystal structure analyses of **2** and **3**.

	2	**3**
Formula	$Br_2C_{10}H_{22}N_2NiS_2$	$C_{66}H_{131}I_6N_{18}Ni_6S_6$
Formula weight	452.91	2675.27
Crystal system	triclinic	monoclinic
Space group	*P*1	$P2_1$
a /Å	7.6096(4)	15.9082(3)
b /Å	8.1378(5)	11.5304(2)
c /Å	12.6006(7)	26.8321(5)
α /°	97.757(2)	90
β /°	91.847(2)	94.4470(10)
γ /°	101.157(2)	90
V /Å^3	757.18	4906.94(16)
Z	1	4
D(calc.) /g · cm^{-3}	1.987	1.811
μ(Mo-K$_\alpha$) /mm^{-1}	2.154	3.317
θ range /°	2.58 to 25.50	1.92 to 25.00
Rflns collected	155852	38311
Independent rflns	5511	16711
F(000)	452	2662
GOF on F^2	1.048	1.051
R_1 ($I_0 > 2\sigma(I)$)	0.0281	0.0494
wR_2 (all data)	0.0754	0.1384
Peak and hole /e·Å^{-3}	0.761/-0.842	3.320/-1.244

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