PhD Theses

SYNTHESIS, PROPERTIES AND SELECTED APPLICATIONS OF SOME SULFUR CONTAINING ORGANIC COMPOUNDS

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1. Introduction and goals

Chemistry of sulfur and organosulfur has been an important and extensively explored area for chemists for a long time. Thanks to their special properties as well as sulfur's capacity of forming a divert range of compounds, they still draw a lot of attention. Organosulfur compounds can be defined as any molecule carrying one or more sulfur-carbon bonds in the structure. It should have been expected that behavior of organosulfur compounds is similar to that of oxygen analogue. In reality, the observed stunning differences earned them interesting features compared to oxygen analogues. Along with many applications of organosulfur compounds found in various fields such as biology, medicine, industry, agriculture and organic synthesis, chemistry of organosulfur compounds is still an exciting research area for chemists.

The ultimate goal of our work was to gain a deeper insight into the chemistry of some selected organosulfur compounds with subjects including thio-cyanoximes, imidazole-2-thiones and cysteine, a sulfur-bearing essential amino acid, respectively. Firstly, we focused on synthesis of a thio-cyanoxime named 2-cyano-2-(hydroxyimino)-dithioacetic acid, with the aim of employing it as complexing ligand with metal ions like Ni^{2+}, Co^{2+} and Cu^{2+}. In this first work, an efficient and facile route for the synthesis of the thio-cyanoxime was established. Structure of the ligand was elucidated by NMR, MS, IR or Raman spectroscopic methods. Next, a study on imidazole-2-thione derivatives involved their hydrogen bonding interaction as well as their aggregation behavior in solution, the solid state and over polycrystalline gold surface was examined. During this work, we explored the mechanism of formation and types of their hydrogen bonding interaction that is responsible for short-range and long-range ordering in solution, in the solid state and over polycrystalline gold surface as well as mechanism of formation of their self-assembly monolayers by using the IR, Raman spectroscopies, tmolecular modelling method and SEM-EDX, AFM techniques. Finally, an attempt to address a synthetic challenge, selective synthesis of important cystein derivatives via the selective oxidation route, motivated our third research. Accordingly, we fixed the anionic form of cysteine among the layers of CaAl-LDH and investigated various oxidizing reagents in different solvents. The results indicated significant contribution of the layered structure to the enhanced selectivity of oxidation of cysteinate anions.

2. Experimental part

2.1. Synthesis of 2-cyano-2-(hydroxyimino)dithioacetic acid and its complexation with metal ions

Ligand, 2-cyano-2-(hydroxyimino)dithioacetic acid, was prepared from starting material cyanoacetic acid methylester via a three-step route. The intermediate, 2-cyano-2-(hydroxyimino)acetic acid methylester, was firstly produced by the Mayer reaction of cyanoacetic acid methylester using sodium nitrite in acidic solution (HCl) in only one hour. After a purification by recrystallization, this intermediate was subjected to a basic hydrolysis with the optimal conditions which was proved as following: solvent methanol, catalyst solid potassium hydroxide, temperature at 40^0C and time one hour to yield 2-cyano-2-(hydroxyimino)acetic acid. Lastly, this acetic acid derivative underwent a thionation reaction using reagent P_4S_{10} in toluene at reflux condition in two hours to give the desired product. All reaction conditions were optimized and structures of the intermediates as well as product were confirmed by spectral data.

2.2. Preparation of the self-assembled layers of imidazole-2-thione derivatives

The first work was preparation of the polycrystalline gold surfaces using the gold-coating facility of a SEM-EDX (energy dispersive X-ray analyzer coupled to the scanning electron microscope) instrument. The gold surfaces were studied by scanning electron microscopy (SEM). Films of imidazole-2-thione derivatives were deposited onto the polycrystalline gold surface by the dip-coating technique. For thickening the film formed, the procedure was repeated several times. The success of immobilization was checked by infrared micro spectroscopy (IRM). The topology of the adsorbed molecular layers on gold surfaces was studied by atomic force microscopy (AFM). Unfortunately, only one of three studied imidazole-2-thiones could form stabile overlayer over the gold surface, the other two compounds dissolved the deposited gold, and possibly gold coordination compounds were formed with yet unknown structure.

At the same time, dilute (~0.1 M) solutions containing three studied imidazole-2-thione derivatives were prepared first using chloroform as the solvent. Then, the IR as well as the Raman spectra of solid samples and the above solutions were recorded. For the measurements performed in solution, the spectrum of the solvent was subtracted from the solution spectra, and the resulting curves were compared to those obtained in the solid state. Shifts in the major bands were sought for to

determine short-range ordering in solution and long-range ordering in the solid state for studied imidazole-2-thione derivatives.

2.3. Synthesis of L-cysteinate-intercalated CaAl-LDH and investigation on interlayer oxidation of L-cysteinate

The preparation of CaAl-LDH and calcilation of L-cysteine among layers of CaAl-LDH were carried out using a modified co-precipitation method. Firstly, the organic compounds (most often 6.0×10^{-3} mol, but other quantities were also used, see later) were dissolved in 65 cm^3 of methanol, then 100 cm^3 aqueous solution containing $Ca(NO_3)_2\times4H_2O$ (0.3 M) and $Al(NO_3)_3\times9H_2O$ (0.15 M) was added, and the pH of 13.1 was set with NaOH solution (3 M). The mixture was stirred at 65°C for 3 days. Then the suspension was filtered, washed with water and methanol several times and dried at 85°C overnight. All operations were performed under nitrogen atmosphere to minimize carbonate intercalation from the airborne CO_2.

For examination of the oxidation process, the oxidizing agent (peracetic acid, bromine or hydrogen peroxide) was applied by dropwise addition of them into the suspensions containing the intercalated LDH suspended in studied solvents (100 cm^3). The suspensions were stirred for 60 min, then they were filtered and dried at 353 K. The amount of the intercalated LDH (0.1 g) and the temperature (298 K) were the same in all cases. The concentrations of used oxidizing reagents (from 0.4 M to 0.7 M) as well as solvents were optimized.

2.4. Experimental techniques

Infrared (IR) spectra were registered on a Bio-Rad FTS-40 FT-IR; BIO-RAD Digilab Division FTS-65A/896 FT-IR and a Bruker Vertex 70 spectrophotometer (equipped with a single reflection diamond ATR accessory), respectively. The 4000–600 cm^{-1} wavenumber range was recorded. 256 scans were collected for each spectrum and the resolution was 4 cm^{-1}. The spectra of the solid samples were taken in the diffuse reflectance mode using DTGS detector.

NMR measurements were performed in 0.5 mL DMSO-d6 or acetone-d6 (99.96 atom% D, from Sigma-Aldrich Chemical Co.) using Bruker Avance 500, 500-MHz NMR spectrometer with 5-mm glass NMR tubes from Wilmad.

Electrospray ionization mass spectrometric (ESI-MS) measurements were performed using a Micromass Q-TOF Premier (Waters MS Technologies) mass spectrometer equipped with electrospray ion source. The sample was introduced into the MS by applying direct injection method: the built-in syringe pump of the

instrument with a 25-mL Hamilton syringe was used. The electrospray needle was adjusted to 3 kV and N_2 was used as nebulizer gas. The computer program used to simulate the theoretical isotope distributions is included in the Masslynx software package.

The Raman spectra were recorded on: a Thermo Scientific TM DXRTM Raman microscope at an excitation wavelength of 635 nm applying 10 mW laser power and averaging 20 spectra with an exposition time of 6 seconds; and on a Raman Senterra II (Bruker) microscope at an excitation wavelength of 765 nm applying 12.5 mW laser power and averaging 20 spectra with an exposition time of 20 sec.

Scanning electron microscopy (SEM) was recorded on a Hitachi S-4700 instrument, accelerating voltage of 18 kV) in the pristine forms to check the homogeneity of the surface.

Atomic force microscopy (AFM) images were recorded on a NT-MDT Solver AFM microscope working in the "tapping" mode (the frequency of the cantilever was 278 kHz). The AFM needle 5 (manufactured by Nanosensors, Inc.) was an SSS-NCH-type 15 µm long silicon needle with 10° half cone angle and 2 nm radius of curvature.

Infrared microspectroscopy (IRM) measurements were carried out on a Bruker Vertex 70 IRM instrument collecting the spectra in total reflection mode from the focused area of the proper surface (1−0.1 mm^2). A liquid nitrogen cooled MCT detector was used to collect observable intensities. Each spectrum was created from 1024 accumulated scans with 2cm^{-1} resolution in the 4000−400 cm^{-1} region.

Molecular modelling calculations were performed at the B3LYP/6-31++G(d,p) level using the Gaussian 2009 Rev. E.01 package.

Powder X-ray patterns were recorded by a Rigaku XRD-6000 diffractometer using CuK_α radiation (λ = 0.15418 nm) at 40 kV and 30 mA with 2°/min scan speed.

3. Novel scientific results

T1. Systematically combining theoretical and numerous spectroscopic methods, we were able to scout the aggregation behaviour of the 2H-imidazole-2-thione and its derivatives as-prepared, involving the formation of an extended hydrogen bonding system.

By initializing IR- and Raman spectroscopic measurements, the existence of N–H⋯S type hydrogen bonding interaction of 2H-imidazole-2-thione

derivatives studied could be determined in both solution and solid phases, resulting in short-range ordering interactions. Moreover, exclusively in solid phase, S–H···N interactions could be also identified, being mainly responsible for the formation of long-range ordering interactions. These findings have been also strengthened by computational methods.

T2. On a polycrystalline gold surface, self-assembled multi layers of 2H-imidazole-2-thione and its derivatives studied have been identified, building around both coordinative and intermolecular bonding.

AFM, SEM and IR spectroscopic measurements indicated the perpendicular linkage of 2H-imidazole-2-thione derivatives into the polycrystalline gold surface. Additionally, it was found that the organic molecules studied were anchored on the gold surface by strong, coordinative S–Au interactions, which were responsible for the growth of the first organic layer on the polycrystalline surface. For long-range ordering, S–H···N hydrogen bonding system have been mainly identified experimentally as well as computationally.

T3. By using hydrocalumite (Ca_2Al-LDH; layered double hydroxides (LDH)) as molecular reactor, an effective and exclusively selective oxidation of cysteine into cystine under mild reaction conditions, especially in water, has been performed, upon using peracetic acid oxidant.

The successful intercalation of cyteinate anions among the layers of hydrocalumites (Ca_2Al–LDH) enabled to take place a selective oxidation of the intercalants into cystinate anions in water proven by spectroscopic methods. This was mainly due to the well-defined dimensions and hydrophilicity of the interlamellar region of hydrocalumites, allowing the components to react with each other exclusively in well-defined conformations. The main role of the host structure was also indirectly confirmed because significant decrease in the selectivity of the oxidation process was experienced in all cases if the layered formation of hydrocalumite was terminated as a result of the alteration of the reaction

conditions. Accordingly, it could be assumed that interlamellar region of hydrocalumite host behaved as a molecular reactor.

T4. Changing the hydration/dehydration state of the cysteinate-intercalated hydrocalumite molecular reactor by using non-aqueous reaction medium, significant shift in the selectivity of cysteinate oxidation was piossible to be reached. Systematically altering the reaction conditions, selective oxidation of cysteine into cysteine sulfenic acid was enabled among the layers of LDHs.

It was found that the selectivity of an oxidation reaction of the cysteinate among the layers of LDHs could be fine-tuned by varying the solvent applied as reaction medium. A clear relationship was established between the variations in the reaction selectivity and the polarity of the reaction medium applied. This phenomenon was possible to be associated with the alteration of the polarity/hydrophilicity of the interlamellar region of the host. In acetone (the most hydrophobic solvent used) the exclusive cystinate selectivity of the oxidation reaction, which was experienced in aqueous solvent, could be shifted toward the total cysteine sulfenic acid selective reaction pathway.

T5. A useful reaction pathway for the syntheses of a novel cyanoxime derivative, 2-Cyano-2-(hydroxyimino)dithioacetic acid was introduced based on using phosphorus pentasulfide thionation (P_4S_{10}) reagent and cyanoacetic acid methylester reagent.

2-Cyano-2-(hydroxyimino)dithioacetic acid was prepared starting from cyanoacetic acid methylester. Before thionation, the ester had to be hydrolyzed. It was found that the quality of the thionation reagent is a key determinant of the success of the mentioned thionation. phosphorus pentasulfide (P_4S_{10}) proved to be the most effective source for this role. The structure of the 2-Cyano-2-(hydroxyimino)dithioacetic was verified with a combination of IR, NMR and mass spectrometric measurements.

4. Application of the results

The results reported here are of fundamental research character; nevertheless, cyanoximes and their complexes with, e.g., Co(II), Ni(II), Cu(II) are expected to find a number of applications in catalysis, electrochemical and electrooptical sensors, waste water treatment, particularly in medicine. Therefore, the developed synthetic route in this work showed advantages including reasonable total yield, simple workup, cheap and available starting materials and mild condition reactions which are the key factors for the large-scale synthesis. Moreover, selective oxidation of L-cysteinate anions by fixing them in layers of CaAl-LDH might open a new, efficient and green approach in chemo-enzymatic syntheses.

5. Publications

5.1. Papers related to the Theses published in refereed journals

[1] **Truong N.H**., Ádám A. A., Varga G., Dudás Cs., Kele Z., Sipos P., Pálinkó I.:
Thionation of cyanoxime derivative to form the sulphur-containing derivative, a novel ligand for complexation with transitional metal ions,
Structural Chemistry **28**, 475–478 (2017)
Impact factor: 1.997_{2017}

[2] **Truong N. H.**, Varga G., Kónya Z., Kukovecz Á., Kozma G., Havasi V., Sipos P., Mloston G., Pálinkó I.:
The aggregation behaviour of imidazole-2-thione derivatives in solution, the solid state and over polycrystalline gold surface,
Journal of Molecular Structure, **1180**, 26-30 (2019)
Impact factor: 2.120_{2019}

[3] **Truong N. H.**, Varga G., Kónya Z., Kukovecz Á., Kozma G., Havasi V., Sipos P., Mloston G., Pálinkó I.:
Oxidation of Cysteinate Anions Immobilized in the Interlamellar Space of CaAl-Layered Double Hydroxide,
Materials, **14** (5), 1202 (2021)
Impact factor: 3.623_{2020}

5.2. Publications related to the Theses published as abstracts in conference proceedings

[1] **Truong N. H.**, Pálinkó I., Sipos P.:

A convenient route for preparation of a new cyanoximic thiocarboxylic acid,

14th International Congress of Young Chemists (Poland, 2016).

[2] **Truong N. H.**, Varga G., Pálinkó I., Sipos P.:

Complexation characteristics of a thionated cyanoxime ligand,

XXVI International Conference on Coordination and Bioorganic Chemistry (Slovakia, 2017).

[3] **Truong N. H.**, Varga G., Pálinkó I., Sipos P.:

The aggregation behaviour of 2H-imidazole-2-thione derivatives in the solid state,

*XXXIV European Congress on Molecular Spectroscopy (*Portugal 2018).

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Full journal papers

related to the topic of the Theses: 3 total: 3

Cumulative impact factor

related to the topic of the Theses total: 7.74