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Bifunctional Ligands in Discerning and Developing the Fundamental and Medicinal Chemistry of Bismuth(III)

by

Glen G. Briand

Submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

at

Dalhousie University

Halifax, Nova Scotia

July 1999

DALHOUSIE UNIVERSITY

FACULTY OF GRADUATE STUDIES

The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled "Bifunctional Ligands in Discerning and Developing the Fundamental and Medicinal Chemistry of Bismuth (III)"

by Glen Briand

in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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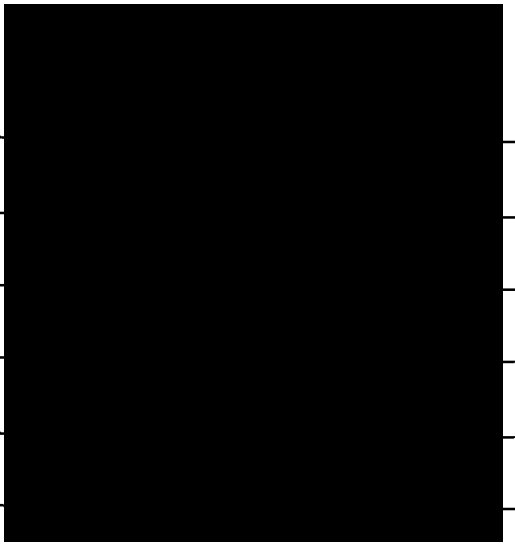

DALHOUSIE UNIVERSITY

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For Janice

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Abstract

The serendipitous discovery and pharmaceutical use of bismuth compounds, along with fundamental interests, has prompted a century of chemical and clinical studies of bismuth complexes and preparations. The characteristic hydrolytic instability and polymeric nature of these materials has deterred comprehensive chemical studies. As a result, the chemistry of bismuth, as for many elements of the periodic table, remains in its infancy. This work establishes the utility of bifunctional ligands as a method to overcoming these obstacles, and represents significant developments in the thiolate and carboxylate chemistry of bismuth, the latter of which encompasses pharmaceutical implications. The synthetic guidelines outlined are likely to be generally applicable to other metals and various bifunctional ligand combinations.

List of Abbreviations

18-crown-6	1,4,6,10,13,16-hexaoxacyclooctadecane	Cys	cysteine
		d	decomposition point
APCI	atmospheric pressure chemical ionization	dipy	dipyridine
		dmf	*N*,*N*-dimethylformamide
avg.	average	dmpu	*N*,*N*'-dimethylpropylene-urea
bio.	biological		
bipy	bipyridine	dmso	dimethylsulfoxide
br	broad	$(dpm)^-$	dipivaloylmethanate
BSC	bismuth subcarbonate	DTA	differential thermal analysis
BSN	bismuth subnitrate		
BSS	bismuth subsalicylate	dtc	dithiocarbamate
calc	calculated	dtx	dithioxanthate
CBS	colloidal bismuth subcitrate	pol	polarography
		EA	elemental analysis
Ch	chalcogen	EI	electron impact ionization
CI	chemical ionization	ESI	electrospray ionization
ccord	coordination	FT	Fourier transform
conc.	concentrated	gSH	glutathione
con	conductivity	Glu	glutaric acid
crys	crystals	Gly	glycine
CV	cyclic voltammetry	$H_2$2mpa	2-mercaptopropionic acid

$H_2$3mpa	3-mercaptopropionic acid
Habt	aminobenzenethiol
Hacac	acetylacetone
H_3bal	British anti-Lewisite
Hbdmap	1,3-bis(dimethylamino)-2-propanol
Hbzt	4,5-benzotropolone
H_4cit	citric acid
H_2cys	cysteine
H_4cydta	*trans*-cyclohexane-1,2-diaminetetraacetic acid
H_4cydtpa	*N*- (2-aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*-*N'*-*N''*-pentaacetic acid
H_2dapts	2,6-diacetylpyridine bis(thiosemicarbazone
Hdbt	dimethoxybenzenethiol
H_5dtpa	diethylenetriaminepenta-acetic acid
H_2dz	3-mercapto-1,5-diphenylformazan, dithizone
Heacd	2-aminocyclopent-1-ene-1-dithiocarboxylic acid
H_4edta	ethylenediamintetraacetic acid
$(mal)^-$	ethylmaltolate
H_4gal	gallic acid
H_2lac	lactic acid
H_3nta	nitrilotriacetic acid
H_3mal	malic acid
Hmmq	2-methyl-8-mercaptoquinolinol
H_2mnt	maleonitriledithiol, dicyanoethylene-1,2-dithiolate
Hmt	methionine
hmpa	hexamethylphosphor-amide
H_4oedta	*N*-hydroxyethyl-ethylenediaminetetra-acetic acid
H_3onda	*N*-hydroxyethyl-nitrilodiacetic acid
H_2ox	oxalic acid

H_2pdc	pyridine-2,6-dicarboxylic acid
H_2pen	D-(-)-penicillamine
H_2phthal	phthalic acid
Hpmq	2-phenyl-8-mercaptoquinolinol
Hqui	quinaldic acid
H_2sal	salicylic acid
Htsc	thiosemicarbazone
H_6ttha	triethylenetriaminehexa-acetic acid
hTF	human serum transferrin
H_4tar	tartaric acdi
H_2tga	thioglycolic acid
H_2tsal	thiosalicylic acid
^{i}Pr	isopropyl
IR	infrared
m	medium
M^+	molecular ion
Me	methyl
med.	medicinal
mp	melting point
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MT	metallothionein
MTP	metallothionein-like proteins
MW	molecular weight
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance
param.	parameters
Ph	phenyl
phen	1,10-phenanthroline
pot	potentiometry
ppm	parts per million
prep	preparation
py	pyridine
Ram	Raman spectroscopy
pwdr	powder
RBC	ranitidine bismuth citrate
ref	reference
rel.	relative
RMBP	renal metal binding proteins

s	singlet (strong w.r.t. IR and Raman)	tms	tetramethylsilane
		tsc	thiosemicarbazide
sh	shoulder	tu	thiourea
sol	solubility	UV	ultraviolet-visible
sp	sublimation point		spectroscopy
t	triplet	V	volts
^{t}Bu	tertiary butyl	vs	very strong
TGA	thermogravimetric analysis	w	weak
		XR	X-ray diffraction studies
thf	tetrahydrofuran		

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Chapter 1. Introduction

1.1 Bifunctional Ligands as a Means to Defining the Coordination Chemistry of Bismuth

In light of the potential bioactivity of bismuth compounds, the prelude to this project[1-3] involved the synthesis of series of bismuth thiolate compounds as simple models for complex commercial pharmaceutical bismuth materials. A variation in antimicrobial bioactivity among series members suggests a structure/activity relationship for the bismuth environment,[4] highlighting the need for universally applicable synthetic procedures to control the coordination chemistry of bismuth. Further, the comprehensive structural and spectroscopic characterization of systematic series of compounds represents the most reliable fundamental foundation for rational chemical development.

This work represents significant advances in the thiolate chemistry of bismuth, a movement toward development of general procedures for preparing and studying the chemistry of bismuth carboxylates, and illustration of the role of secondary functional groups in bridging the gap between these areas. These goals have been achieved through the preparative, spectroscopic and structural study of compounds containing bismuth complexed with hydrocarbon ligands bearing two (bifunctional) or more (polyfunctional) donor sites, as shown in Figure 1.1.

Bifunctional ligands are excellent tools for probing the fundamental and biological chemistry of bismuth for various reasons. Firstly, they provide simpler models of organic polyfunctional ligands, which are components of medicinal compounds such

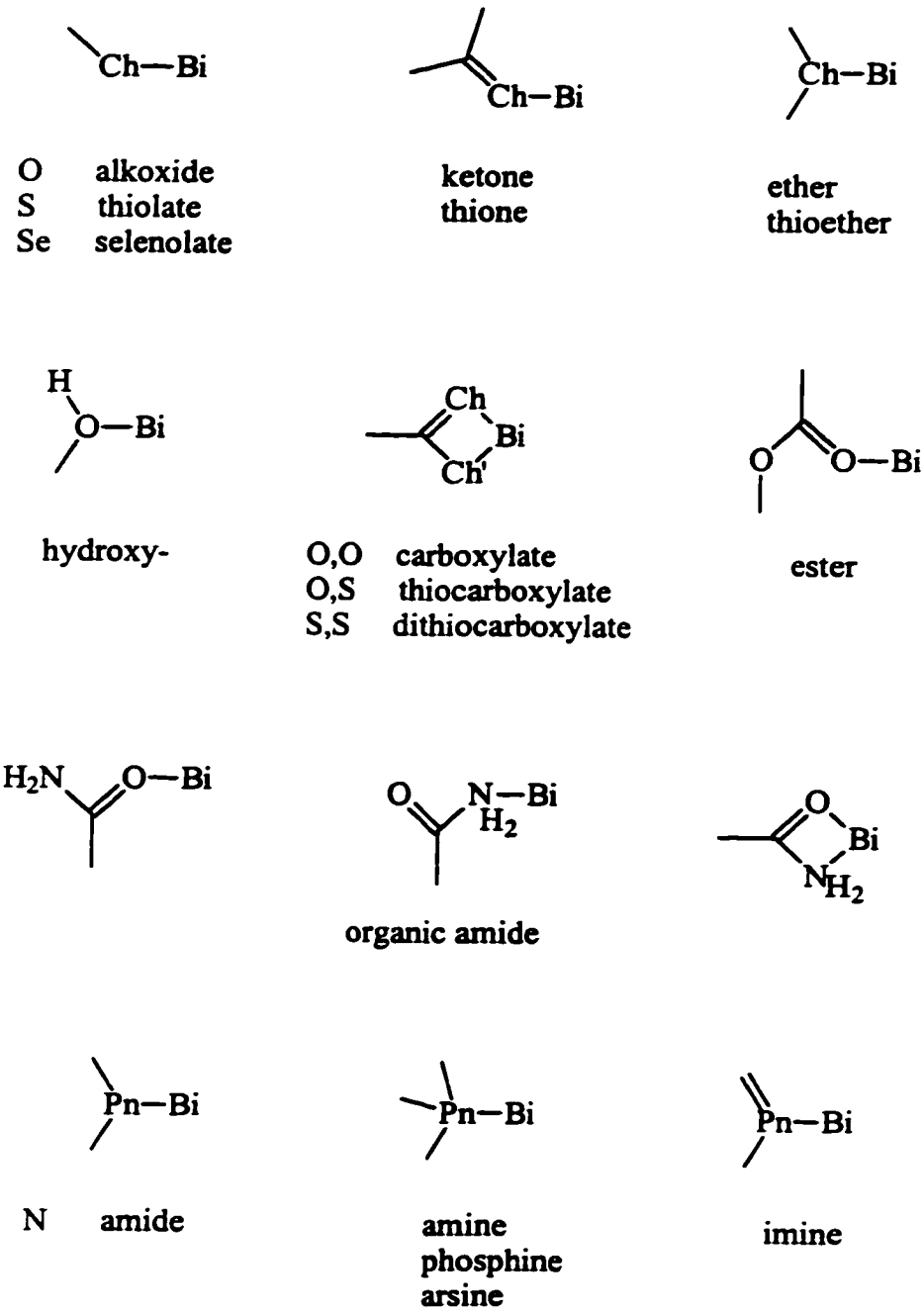


Figure 1.1 Bismuth bonding arrangements with organic functional groups and their heavier group 15 and 16 analogues.

as 'colloidal bismuth subcitrate' (citrate) and 'bismuth subsalicylate' (salicylate). Secondly, introduction of the thiolate moiety stabilizes components with respect to hydrolysis and the precipitation of basic bismuth salts in aqueous media under various pH conditions. Subsequently, this allows for the study of the interaction of the bismuth center with other biological and organic functional groups, and gives a greater understanding of the role of bismuth in biological systems. Discussions in this thesis, therefore, focus primarily on the chemistry of bismuth compounds containing the ligand or ligand fragments shown in Figure 1.2. These ligands facilitate the formation of five-membered rings which have proven to be the most favourable structural arrangement for chelate complexes of bismuth.[2] Systematic alteration of one functionality imposes subtle changes on the chemistry of bismuth. Ten of these bifunctional combinations have been studied to some degree in the literature or as part of this project and are discussed in this thesis (designated by *).

By employing these bifunctional ligands, this thesis outlines some general and important observations concerning the significance of chelate ability and pH in the isolation of bismuth dicarboxylates (Chapter 3) and aminocarboxylates (Chapters 4) in aqueous media. Similarly, control of the Lewis acidity and thiolation of bismuth are explored (Chapter 6), and simple models for CBS and other bismuth complexes in biological systems are developed (Chapter 7). Also provided as an introduction to these topics is the preparation, structure and aqueous chemistry of commercial bismuth products and bismuth chemistry relevant to biological and medicinal activity (Chapter 2), as well as the preparation and structure of established bismuth thiolate compounds

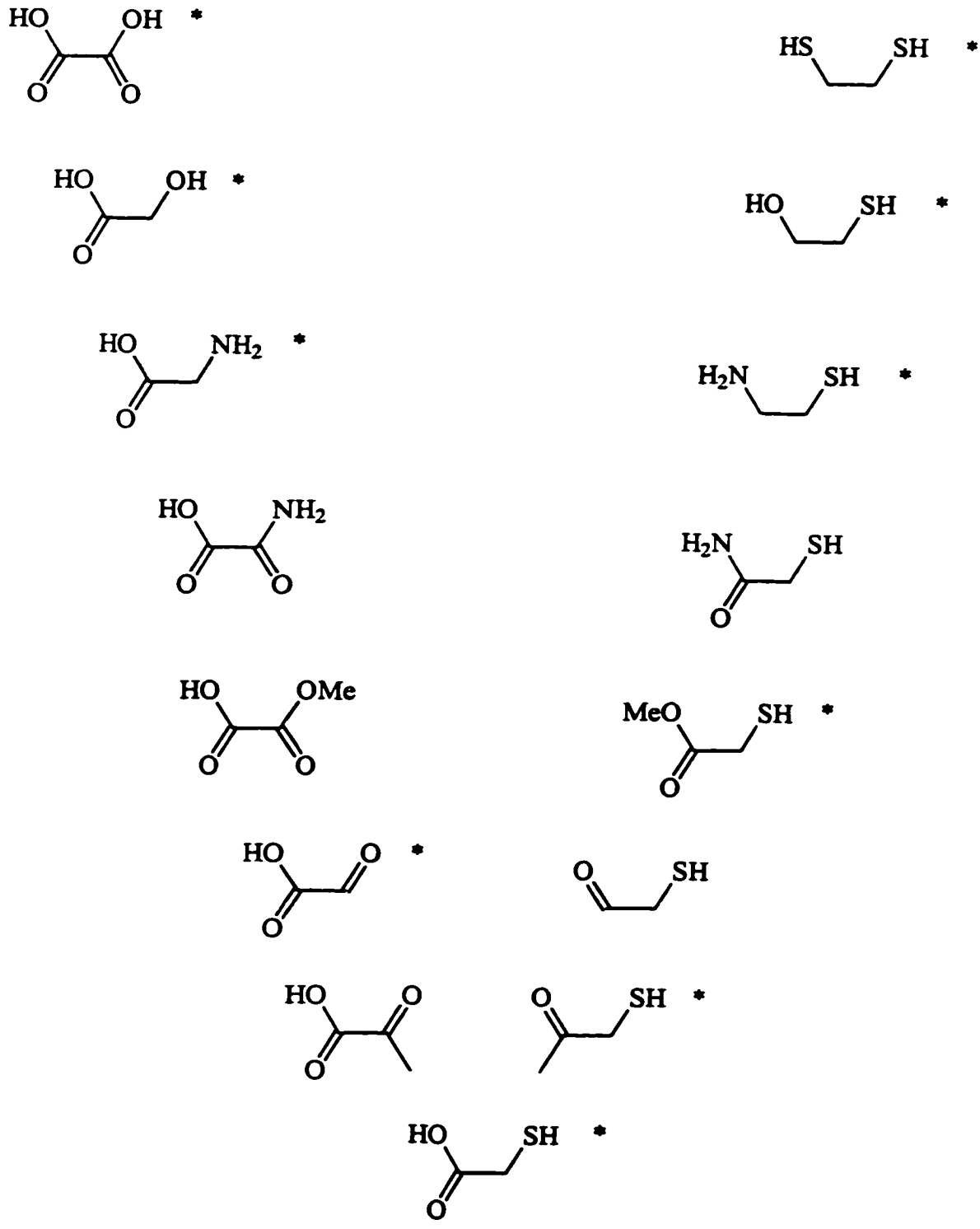


Figure 1.2 Bifunctional combinations for developing the chemistry of bismuth. Designated compounds (*) have been used as reagents with bismuth, as discussed in this thesis.

(Chapter 5). Structural studies demonstrate a variety of bonding situations which are the basis for the majority of discussions in this thesis.

1.2 Structural Diversity in Bismuth Chemistry

As a main group heavy metal, compounds of bismuth exhibit immense structural diversity with characteristics of all areas of the periodic table. The atom adopts covalent-type bonding common to main group elements, and can accommodate Lewis bases to form labile adduct complexes typical of transition metals, which may include intramolecular interactions (e.g. amino-/esterthiolates). Bismuth is the heaviest non-radioactive element, and its large atomic radius (1.52Å) allows for higher coordination numbers (typically three to ten) and more variable geometries than those achieved by transition metals. As a consequence, bismuth is capable of coordinating larger polydentate ligands (e.g. polyaminocarboxylates, larger crown ethers) and extensive intermolecular bonding. Secondary interactions are mediated through introduction of sterically bulky ligands (e.g. 2,4,6-*tert*-butylphenylthiolate), manipulation of the Lewis acidity of the bismuth center (e.g. electron withdrawing pentafluorothiophenolates), and utilization of bifunctional ligands (e.g. aminothiolates), suggesting potential utility in supramolecular chemistry and development of novel materials. Further, structural diversity results from relativistic effects which induce an unpredictably variable stereochemical activity or inactivity of the Bi(III) lone pair.

In addition to their fundamental interest, structural studies play a key role in establishing and confirming accurate formulae assignments. As part of the extensive

characterization of compounds prepared in this thesis, several other techniques have also been utilized.

1.3 Characterization Techniques

A majority of the compounds in this thesis have been comprehensively characterized in both the solid state (EA, mp, FT-infrared and FT-Raman spectroscopies, X-ray crystallography) and in solution (^{1}H and ^{13}C NMR spectroscopy, and APCI or ESI mass spectrometry). In addition to X-ray crystallography, mass spectrometry and particularly FT-Raman spectroscopy have proven to be useful techniques for product identification.

Bismuth compounds are typically thermally unstable, that is they decompose before melting, and are of low volatility. Therefore, mass spectrometry sampling techniques which involve heating the sample into the gas phase under high vacuum, such as electron impact ionization (EI) and chemical ionization (CI), are generally not ideal. Atmospheric pressure chemical ionization (APCI) (see Figure 1.3) and electrospray ionization (ESI) provide the advantage of introducing the sample in solution and involve minimal (APCI) or no (ESI) thermal heating. Moreover, due to the high sensitivity of the mass spectrometer, minimal sample concentrations are required.

Bismuth compounds, particularly bismuth thiolates, are strong Raman scatterers below ~350cm^{-1}, a spectral region that is not typically probed by infrared spectroscopy. This provides an intense and distinctive fingerprint for identifying recovered reactants and new products. In addition, the speed and minimal sample preparation required in

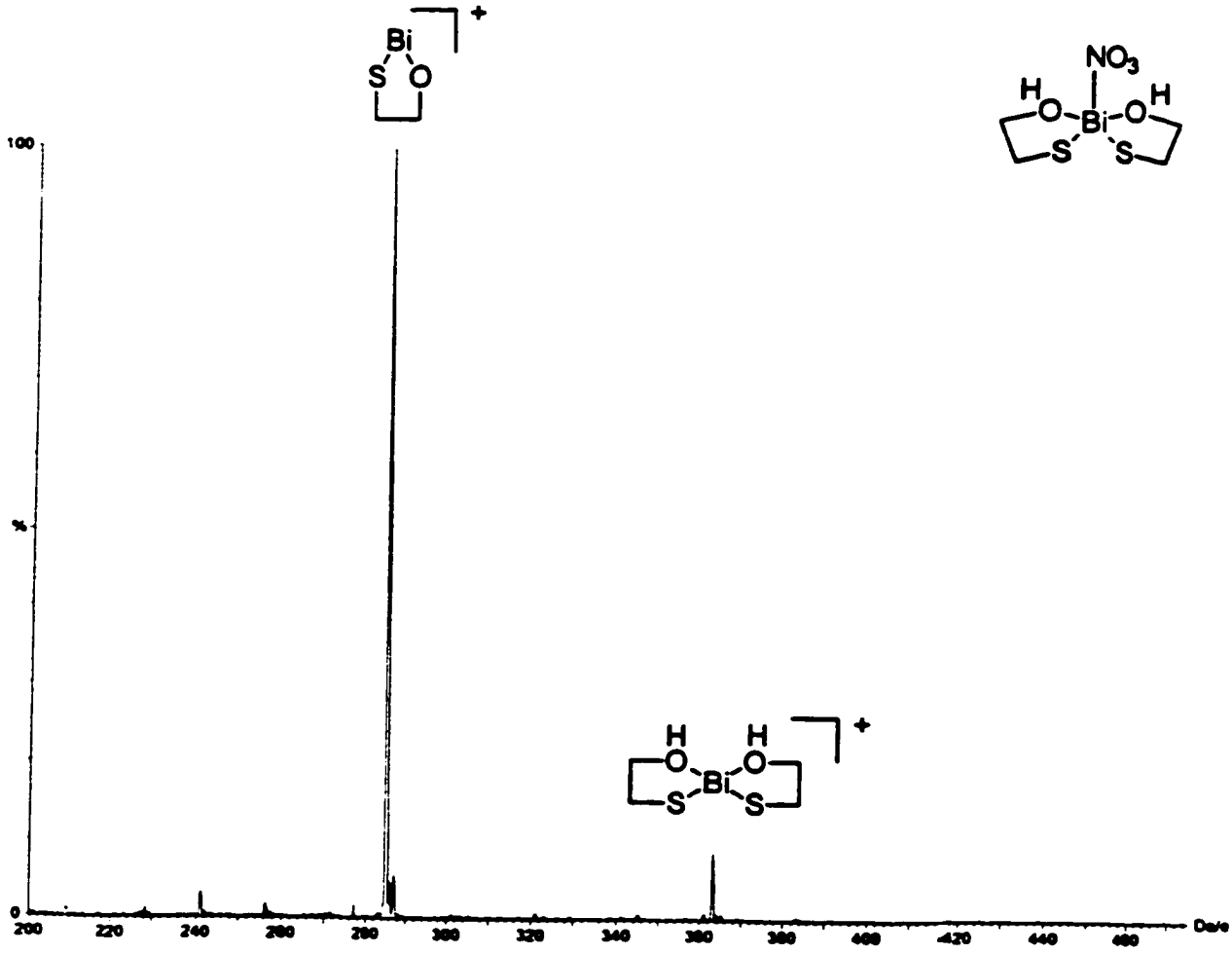


Figure 1.3 APCI-mass spectrum of bis(hydroxyethanethiolato)bismuth(III) nitrate **550** in acetonitrile.

collecting spectra establishes FT-Raman as a valuable technique for studying these compounds.

Complexes prepared and discussed herein have been chosen based on specific criteria. To enhance readability of this manuscript, some brief comments regarding this topic as well as some general remarks concerning formatting of this manuscript are provided.

1.4 Scope of Thesis and General Comments

Since, the majority of medicinal chemistry of bismuth involves Bi(III), this work concentrates on the trivalent chemistry. Although there have been examples of Bi(V) complexes of tropolone derivatives prepared as potential antimicrobial agents,[5,6] these are not discussed in this manuscript.

In keeping with a biomimetic theme, all manipulations have been performed without exclusion of water. Because of their hydrolysis to bismuth oxides in aqueous media and their minimal role in medicinal chemistry, organo-bismuth compounds (compounds containing bismuth-carbon bonds) are generally not discussed, except to provide a comprehensive account of a specific subsection. Also excluded from discussion are complexes which involve bismuth as a Lewis base (e.g. bismuth-transition metal complexes).

Generally, drawings are intended to illustrate connectivity and the coordination geometry of bismuth only [dashed lines (-----) represent long or intermolecular contacts]. Drawings of these compounds aimed at describing bonding features, such as Lewis structures, are not meaningful or are misleading for bismuth complexes, while they are

employed for the description of some ligands. Crystallographic figures are drawn with 50% probability thermal ellipsoids.

Tables of characterization data are presented in discussions of established compounds to demonstrate the favorability of product formation (i.e. yield) and the reliability of structural and formulae assignments. The following series of reaction equations, which are referred to within each table, incorporate synthetic reactants described by the original authors and are intended to illustrate the breadth of synthetic approaches employed. Reaction balancing schemes and by-products are not meaningful.

Previously prepared compounds and substructures are numbered according to the chapter in which they are discussed, followed by a two or three digit number signifying the order in which they appear in the chapter (e.g. **309** signifies Chapter 3, compound nine). New compounds prepared as a focus of this thesis are numbered by chapter followed by a sequential capital letter (e.g. **7B** signifies Chapter 7, second compound). General structures and bonding situations are numbered sequentially throughout the thesis and are labeled with upper case roman numerals (e.g. **II**).

1.5 Conclusions - Industry and the Scientific Method

Industrial influence on the sciences is evident in this work through the study of models of commercial pharmaceuticals and deserves a brief comment. On the one hand, the need for "practical" science generates new ideas and directions that would probably not be considered otherwise. However, there is often a societal requirement for immediate applications, and problems potentially arise when premature conclusions are

drawn. A compromise involves assessment of fundamental attributes with practical application in the foreseeable, but not necessarily immediate, future.

Bismuth containing preparations and compounds have been used for over 200 years to treat a variety of medical disorders. As a primary industrial interest for bismuth chemistry, the pharmaceutical utilization of bismuth compounds would lead one to believe that the mechanism of action of these compounds is well understood and their pharmaceutical usage validated. In fact, the serendipitous discovery and use of these compounds has led to centuries of medical empirical support with minimal underlying chemical basis for these observations, yet they are still widely used today.

This is not to insinuate that studies in this area have not been numerous. Despite difficulties associated in working with bismuth compounds several observations have been made, but with few comprehensive chemical studies or general conclusions. Further, vague and false statements plague the literature and have been utilized as a basis for conclusions and hypotheses for further studies. This "snowball effect" results in the misconception of acquired knowledge, and, therefore, the importance of valid conclusions based on accurate empirical observations without over-interpretation must be stressed.

The logical approach to understanding more complex situations, such as biological systems, is rational and involves simpler, more easily understood models. The fundamental knowledge gained in the process does not only provide insight into the immediate problem, but also any other complex system that we hope to understand now or in the future. This thesis embraces this approach.

In the author's opinion, the attractiveness of the following work is in the simplicity of the approach employed. Therefore, there is the potential for an increased appeal to a wider scientific audience and a decline in the number of assumptions required. Despite its simplicity, some very general conclusions can be made regarding not only the specific topics addressed in this thesis, but about the systematic approach employed.

Chapter 2. The Chemistry of Medicinal Bismuth Compounds: Hydroxy-/ Alkoxycarboxylates and Inorganic Salts

2.1 Introduction

The bio-utility of bismuth and its compounds has a 250 year history, which is described in a number of key review articles,[7-13] but the appearance of bismuth compounds in the British Pharmaceutical Codex,[14-18] the French Pharmacopeia,[19] the German Pharmacopeia[20] and the new Czechoslovakian Pharmacopeia,[21] is more recent. Some compounds have been approved for human use under the Federal Food, Drug and Cosmetic Act[22] for more than 30 years. After extensive use in the treatments of syphilis, as well as other bacterial infections, the heavy metal label effected a decline in usage with the advent of antibiotics, and incidents of reversible bismuth encephalopathy in France and Australia in the 1960's and early 1970's. Nevertheless, bismuth compounds remain important components of stomach remedies, such as Pepto-Bismol® (bismuth subsalicylate, BSS) and De-Nol® (colloidal bismuth subcitrate, CBS), and derivatives of CBS, such as ranitidine bismuth citrate (RBC), are currently under development.

This chapter provides an overview of the data available for prominent bismuth compounds which have been discovered, developed or designed to have biological (with the exception of botanical) activity or medicinal utility, while a more complete review of the topic has been written.[23] A number of compounds have been sufficiently well characterized to assign formulae accurately, however, a wide variety of materials, mixtures or preparations containing bismuth have been examined and documented, many of which have ill-defined formulae or vague name designations. The chemical aspects of

compounds for which definitive formulae or characterization data are available are discussed and compared. Tables 2.1 and 2.2 are lists of compounds with literature references to each item of characterization data.

2.2 Inorganic Compounds

The earliest bismuth compounds to be used for medical purpose were inorganic bismuth salts, typically the basic bismuth salts, such as bismuth subnitrate (BSN), which was known as early as the 17th century as "magisterium bismuti",[24] and bismuth subcarbonate (BSC). A listing including assigned formulae and references to characterization data are given in Table 2.1. Some named compounds have a variety of formulae (e.g. subcarbonate and subnitrate) arising from the variable preparations, procedures and subsequential characterisation. Their designation as 'sub' salts has likely been justified on the basis of high oxygen content and the assignment of Bi-O moieties. Most formula designations are based on elemental analyses and maybe overinterpreted, for example, bismuth hydroxides are sometimes written as BiO(OH), but could be bismuth oxide (Bi_2O_3) with variable water content.

Bismuth is mined as bismuth oxide (Bi_2O_3, "bismite") as well as the sulfide (Bi_2S_3, "bismuthinite"), the former of which may be prepared from other inorganic bismuth salts (nitrate subnitrate, subchloride, sulfate) by reaction with a carbonate or alkali hydroxide[25-32] or by thermal decomposition,[33-35] or by other methods including heating bismuth metal with sodium nitrate and hydrolysis of bismuth alkoxides.[36] Bismuth oxide exists as a number of polymorphs. α-, β-, γ- and δ-bismuth sesquioxide form at various temperatures and have been studied extensively by DTA[92] and X-ray[37]

Table 2.1 Compound designations and assigned formulae for medicinal inorganic bismuth compounds.

compound designation	formula	references
oxide (bismite)	Bi_2O_3	37
hydroxide		38-42
	$Bi(OH)_3$	43-45
	$BiO(OH)$	45
carbonate		40,46,47
basic carbonate		48,49
subcarbonate		50
subcarbonate (bismutite)	$(BiO)_2CO_3$	32,51-54
	$(BiO)_4(OH)_2CO_3$	52
	$Bi_2(OH)_4CO_3$	43
	$BiOHCO_3$	55
	$5Bi_2O_3 \bullet Bi_2(CO_3)_3$	53
	$BiO(HCO_2)$	54
nitrate/ trisnitrate		56-60
	$Bi(NO_3)_3$	55,61,62
	$Bi(NO_3)_3 \bullet 5H_2O$ **202**	63-70
basic bismuth nitrate		71-74
subnitrate		75
	$BiONO_3 \bullet H_2O$	76
	$BiONO_3 \bullet 0.5H_2O$	77
	$Bi_6O_4(OH)_4(NO_3)_6 \bullet H_2O$	78
	$[Bi_6(H_2O)(NO_3)O_4(OH)_4](NO_3)_5$	79
	$[Bi_6O_5(OH)_3](NO_3)_5 \bullet 3H_2O$	80,81
	$[Bi_6O_4(OH)_4](NO_3)_6 \bullet 4H_2O$	24

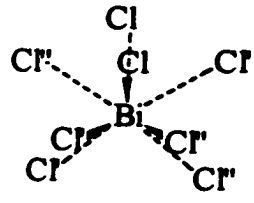
Table 2.1 Compound designations and assigned formulae for medicinal inorganic bismuth compounds (continued).

compound designation	formula	references
chloride/ trichloride	$BiCl_3$ **201**	82
oxychloride/ subchloride	BiOCl **203**	83
subiodide		84
oxyiodide	BiOI	85
aluminate		86,87
	$Bi_2(Al_2O_4)_3 \bullet 10H_2O$	88,89
	$Bi_2O_3 \bullet 10Al_2O_3 \bullet 20H_2O$	90
	$Bi_2O_3 \bullet 3Al_2O_3 \bullet CO_2 \bullet 5H_2O$	91

and neutron powder diffraction.[51] The crystal structure of the α-oxide[37] shows parallel layers of oxygen atoms with bismuth atoms located between them. The oxygen atoms form a pattern of three and five sided polygons, with the corners being bridged by bismuth atoms in a three dimensional lattice. There are two unique bismuth atoms, one five- and one six-coordinate, in distorted octahedral environments, the latter of which has a corner of removed. Each bismuth atom has three short Bi-O bonds [2.08-2.29Å] and two or three longer Bi-O contacts [2.48-2.80Å].

The chloride ($BiCl_3$ **201**)[82] and nitrate [$Bi(NO_3)_3 \bullet 5H_2O$ **202**][63] salts of bismuth are typically prepared from the reaction of bismuth oxide with the corresponding strong mineral acids, and have both been structurally characterized. $BiCl_3$ **201**[93] is molecular in the solid state, with one unique eight coordinate bismuth center. Each bismuth atom has three closely bound chlorine atoms [Bi-Cl 2.468-2.518Å] in a near pyramidal

arrangement and five long chlorine contacts [Bi---Cl 3.216-3.450Å]. The nitrate pentahydrate **202**,[64] on the other hand, is ionic in the solid state, consisting of Bi^{3+} cations,



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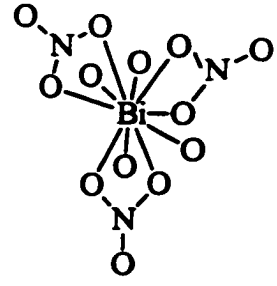


202

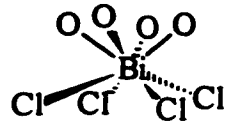
NO_3^- anions and lattice water molecules. Here, bismuth is bound to one asymmetrically [Bi-O 2.60(1) and 2.99(2)Å] and two symmetrically [Bi-O 2.43(2)-2.66(1)Å] chelated nitrate ions, and four water molecule oxygen atoms [Bi-O 2.32(1)-2.67(1)Å], giving a ten coordinate geometry.

In weakly acidic to basic conditions the inorganic salts are "hydrolysed" to the corresponding oxide products, commonly referred to as "basic," "oxy-" or "sub-" salts, which have a tendency toward the formation of the favorable BiO^+ bismuthyl subunit. Such is demonstrated by the hydrolysis of bismuth chloride in water to form bismuth oxychloride:

2.1) $BiCl_3(s) + H_2O \rightleftharpoons BiOCl + 2\,HCl$

It has been argued that the solubility of BiOCl in acid species is not simply due to the liberation of Bi^{3+} from BiO^+ by the hydronium ion,[94] but to the formation of the anionic species $BiCl_4^-$.[95] Supporting data include the greater solubility of BiOCl in hydrochloric

acid than in nitric acid, and the increase in solubility of $BiCl_3$ and $BiONO_3$ in nitric acid with the addition of NaCl. Solution studies of the complexation of bismuth(III) with the chloride ion encompass not only aqueous media[96] but also organic solvents.[97-99] Investigations into aqueous reactions of bismuth chloride[100-102] involve the effect of temperature on hydrolysis[103] with formation of BiOCl **203**, $BiOCl \bullet 2H_2O$, and $BiCl_3 \bullet H_2O$ solid phases,[104] while the hydrolysis of bismuth subiodide has similarly been studied.[105] The crystal structure of BiOCl **203**,[106] the only structurally characterized hydrolysis product of $BiCl_3$, shows one unique eight coordinate bismuth center surrounded by four oxygen atoms and four chlorine atoms [Bi-O 2.3165(12) Å] and [Bi-Cl 3.059(8) Å]. The atoms create asymmetric decahedrons around the bismuth centers, which are linked in a three dimensional array.

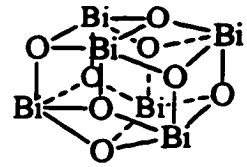


203

Unlike the hydrolysis of bismuth chloride, the lability of the nitrate ion allows for a much greater range of hydrolysis products of bismuth nitrate,[55,75,107-116] with product formation (degree of hydrolysis) being sensitive to specific precipitation conditions.[116-121] The majority of these products have been identified by physical techniques, such as chemical analysis, while species in solution have been determined by electrical conductivity.[115]

This sensitivity to reaction conditions is demonstrated by the formation of: $[Bi_6O_5(OH)_3](NO_3)_5 \bullet 3H_2O$ **204a**[80,81] (modified formula $BiONO_3 \bullet 0.1Bi_2O_3 \bullet 0.9H_2O$),

obtained in the 1.2 to 2.4 pH range; slightly less basic $[Bi_6O_4(OH)_4](NO_3)_6 \bullet H_2O$ **204b**[78,79] (modified formula $BiONO_3 \bullet 0.5H_2O$), isolated by crystallizing $Bi(NO_3)_3 \bullet 5H_2O$ from boiling 0.05M HNO_3 or by heating crystals of $[Bi_6O_4(OH)_4](NO_3)_6 \bullet 4H_2O$; and $[Bi_6O_4(OH)_4](NO_3)_6 \bullet 4H_2O$ **204c**[24] (modified formula $BiONO_3 \bullet H_2O$), recovered as the first solid hydrolysis product below pH 1.2. The structures of all three compounds are very similar and are composed of $[Bi_6O_n(OH)_{8-n}]^{(10+n)+}$ hexanuclear polycation clusters **204**



204

with loosely coordinated bidentate nitrate anions and water molecules. The hexanuclear units **204** show six bismuth atoms sitting at the corners of a slightly distorted octahedron with the eight oxygen atoms capping the octahedron faces. The structure of $[Bi_6O_5(OH)_3](NO_3)_5 \bullet 3H_2O$ **204a**[80,81] is composed of $[Bi_6O_5(OH)_3]^{5+}$ cages, which dimerize through a Bi-O edge. The Bi-O bond distances fall into three ranges, corresponding to the $Bi\text{-}O_{oxide}$ [2.10(4)-2.23(3)Å], $Bi\text{-}O_{hydroxide}$ [2.22(4)-2.52(3)Å], and $Bi\text{-}O_{bridging}$ [2.55(4)Å] bonding situations. The structure of $[Bi_6O_4(OH)_4](NO_3)_6 \bullet H_2O$ **204b**[77-79] contains a monomeric hexacationic $[Bi_6O_4(OH)_4]^{6+}$ cluster with four oxide oxygen atoms and four hydroxide oxygen atoms. A short $Bi\text{-}O_{nitrate}$ [2.62(3)Å] and a short $Bi\text{-}O_{water}$ [2.64(3)Å] contact gives two five-coordinate bismuth atoms. The structure of $[Bi_6O_4(OH)_4](NO_3)_6 \bullet 4H_2O$ **204c**[24] shows a similar arrangement.

Further evidence for the preferred formation of the bismuth-oxygen polycation is its presence in the hydrolysis products of bismuth perchlorate in solution[122,123] and in the solid state in the hydrolysis product $[Bi_6O_4(OH)_4](ClO_4)_6 \bullet 7H_2O$ **204d**.[124]

Bismuth oxide itself may be hydrolyzed or hydrated [e.g. $Bi(OH)_3$ bismuth hydroxide, BiO(OH)], and aqueous mixtures have been studied at various pH values.[42,125,126]

Bismuth carbonate may be formed from the reaction of Bi_2O_3 with excess CO_2, or the reaction of $Bi(NO_3)_3 \bullet 5H_2O$ with excess Na_2CO_3 or K_2CO_3.[43,51,52,55] As with bismuth subnitrate, the composition of bismuth subcarbonate is sensitive to reaction conditions. This accounts for references to "light" and "heavy" bismuth subcarbonate and subnitrate in the pharmaceutical and medical literature,[127] which exhibit variable therapeutic action depending on basicity and degree of subdivision.[128]

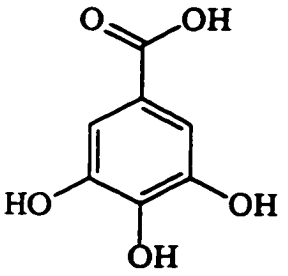
"Bismuth aluminate" is a variable composition of Bi_2O_3, Al_2O_3 and H_2O and possibly CO_2. It is employed mainly as an antacid, combining the antacid properties of the basic bismuth and aluminum oxides.

Of the inorganic salts employed in medicine, only bismuth chloride, oxychloride, and nitrate pentahydrate have definite compositions. The variability in the subnitrate, subcarbonate, hydroxide and aluminate results from the sensitivity of product formation to reaction conditions. This variability in composition may account for variability in the medicinal/ biological activity of these compounds.

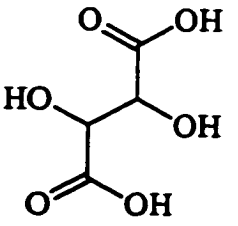
2.3 Carboxylates and Derivatives

2.3.1 Hydroxycarboxylic Acid Complexes

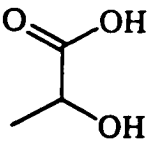
Bismuth complexes of hydroxycarboxylic (aliphatic hydroxy acid) acids, including gallic (H_4gal), tartaric (H_4tar), lactic (H_2lac), malic (H_3mal), and citric (H_4cit) acids, have been used in a wide range of medicinal capacities since the turn of the century. An overview of the characterization data that have been obtained for isolated bismuth polyhydroxycarboxylates is presented in Table 2.2.



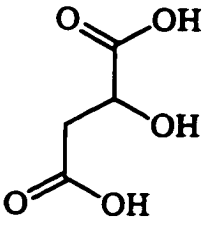
H_4gal



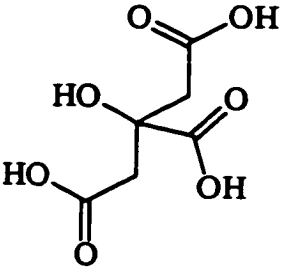
H_4tar



H_2lac



H_3mal



H_4cit

As with bismuth subnitrate, the lability of the bismuth-carboxylate interaction allows for variable compositions of these compounds, which are very sensitive to reaction conditions.[153,170-172] Moreover, the formulae are sometimes speculatively assigned on the basis of preliminary identification.[156] There have been two crystallographically

Table 2.2 Characterization data for isolated bismuth hydroxy-/alkoxycarboxylates.

Compound designation	Formula	Characterization Data
subgallate		prep,[49,129] DTA[130]
"Dermatol"	$C_6H_2(OH)_3COOBi(OH)_2 \bullet H_2O$	prep,[131] EA[132]
basic bismuth gallate		EA[133]
gallate		EA[134]
Na Bi Gallate		prep, EA[135]
Na Bi Digallate		prep, EA[135]
Na Bi Me Gallate		prep, EA[135]
oxyiodogallate "Airol"	$C_6H(OH)_3(CH_3)COOBi(OH)I$	prep,[136] mp[137,138]
iodogallate		DTA[130]
tartrate		prep,[139] EA,[140-142] IR[143]
bismuthotartaric acid		prep[144]
bismuthotartrates		IR[145]
sodium tribismuth tartrate	COO(Na)CHO(BiO)CHO(BiO)COO-(BiO)	prep[146]
sodium bismuth tartrate		prep,[147] EA,[148] DTA[130]
	d- and *meso*- $BiO(H_3\underline{tar}) \bullet nH_2O$, *d*-$Bi(H_4\underline{tar})(H\underline{tar}) \bullet 3H_2O$, *dl*-$MBiO(H_2\underline{tar})$ and $MBi(\underline{tar})$	prep, IR[149]
	$Bi(H_3\underline{tar})(H_2\underline{tar}) \bullet 3H_2O$	prep, EA, XR[150]
	$MBi(H\underline{tar})$ (M = K, Na, Li, NH_3, Hpy)	prep, IR[151]
	$KBiO(H_2\underline{tar})$, $KBi(\underline{tar})$	prep, IR[152]
	$Bi_2H_2(\underline{tar})_2$, $NaBi_2O_2H(\underline{tar})$	prep, EA[153]

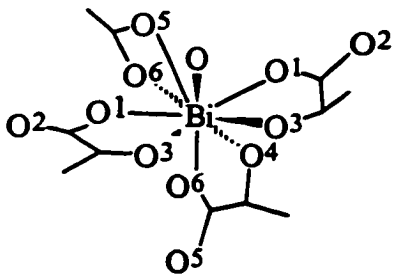
Table 2.2 Characterization data for isolated bismuth hydroxy-/alkoxycarboxylates (continued).

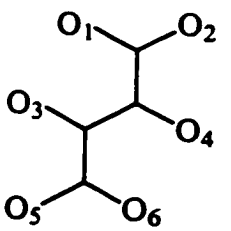
Compound designation	Formula	Characterization Data
	$NaBiO(H_2\underline{tar})$, $Na(BiO)_3(\underline{tar})$	prep[154]
	$Bi_2(H_2\underline{tar})_3 \bullet 2(H_4\underline{tar})$	prep[155]
Bi Na acid tartrate		prep[16]
sodium potassium bismuth tartrate		EA[156]
ammonium aquabis [(+)-tartrato(2-)] bismuthate(III) hydrate	$NH_4[Bi(H_2\underline{tar})_2(H_2O)] \bullet H_2O$	prep, XR[157]
dilactobismutho-tartaric acid	$BiH_5(\underline{lac})_2(\underline{tar})$	prep[158]
lactate	$BiH(\underline{lac})_2 \bullet 7H_2O$	prep,[159] DTA[160]
	$BiH(\underline{lac})_2$	prep,[158,160] IR[160]
	$Bi(H\underline{lac})_3$	prep, EA, XR, NMR[161]
		prep, EA[162,163]
bismutholactic acid		prep[144]
malate	$Bi(\underline{mal}) \bullet H_2O$	prep, EA, XR[150]
citrate		prep, EA,[141] DTA[130]
	$Bi(H\underline{cit})$	prep[164]
	$Bi(H\underline{cit}) \bullet H_2O$	prep, IR, DTA[165]
	$Bi_3(Hcit)_2(OH)_3$	prep, EA[163]
"pentabismol"	$16NH_4OH \bullet 11Bi(H\underline{cit}) \bullet Bi(OH)_3 \bullet 6H_2O$	prep[166,167]
bismuthocitric acid		prep[144]
sodium bismuth citrate		prep[168]

Table 2.2 Characterization data for isolated bismuth hydroxy-/alkoxycarboxylates (continued).

Compound designation	Formula	Characterization Data
dibismuthyl monosodium citrate		sol[169]

characterized bismuth tartrate compounds, which are isostructural and involve two five-membered bidentate chelate ligands. In the ammonium salt, $NH_4[Bi(H_2\underline{tar})_2(H_2O)]\bullet H_2O$ **205**,[157] four bidentate doubly deprotonated tartaric acid ligands surround each bismuth center. The two crystallographically unique ligands are bound to the bismuth center via a carboxylate (O^1) and an α-alkoxide (O^3) oxygen atom [$Bi\text{-}O_{carboxylate}$ 2.372(7) and 2.438(6); $Bi\text{-}O_{alkoxide}$ 2.462(6) and 2.460(6)Å] forming five-membered rings. One of these ligands bridges a second bismuth center in a similar manner via its remaining carboxylate (O^6) and the α-hydroxy (O^4)groups [$Bi\text{-}O_{hydroxy}$ 2.608(6), $Bi\text{-}O_{carboxylic\ acid}$ 2.622(6)Å]. This carboxylate group asymmetrically chelates a third bismuth center in an *O,O'* (O^5, O^6) manner [$Bi\text{-}O_{O,O'\text{-}carboxylic\ acid}$ 2.476(6) and 2.738(6)Å] forming a four-membered -BiOCO- ring. The oxygen atom of a water molecule completes the coordination sphere [$Bi\text{-}O_{water}$





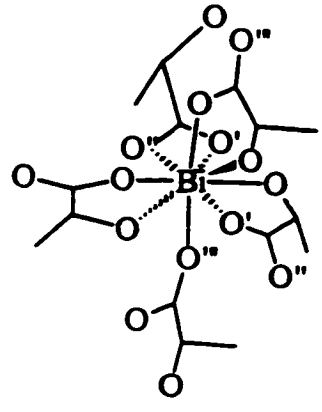
205-6

2.400(6)Å], for a total coordination number of nine around bismuth and a trigonal prismatic geometry. The resulting structure is a complex one-dimensional coordination polymer with extensive hydrogen bonding. The complex $Bi(H_3\underline{tar})(H_2\underline{tar})\bullet 3H_2O$ **206**[150] contains a singly deprotonated $(H_3\underline{tar})^-$ tartrate ligand, but retains an analogous structure to the ammonium salt [Bi-$O_{carboxylate}$ 2.381(10)-2.615(11); Bi-$O_{hydroxy}$ 2.467(9)-2.588(10); Bi-$O_{O,O'\text{-carboxylate}}$ 2.482(10) and 2.754(11); Bi-O_{water} 2.409(9)Å].

There have been several solution studies of bismuth tartrate compounds and systems[148,173-175] employing several spectroscopic and physical techniques including visual,[176] spectrographic[177] and solubility methods,[178] optical rotation (D-tartrate),[174] ^1H NMR,[175] polarimetry,[174,177,179] potentiometry,[180-183] polarography,[180,184-186] electrometry[179,187] and oscillography.[186] These approaches have been employed to determine the compositions[178,180] and stability constants[180,183,188] of complexes at a variety of pH values[180,181,186-188] and at various tartrate concentrations.[176,180] Other investigations involve extraction of bismuth tartrate complexes from solution using diisoamyl amine[189] and hydrolysis studies with the isolation of $NaBiO(H_2\underline{tar})$ and $Na(BiO)_3(\underline{tar})$ sodium bismuth "sub"tartrate complexes.[154,190]

Few bismuth compounds of lactic acid ($H_2\underline{lac}$) have been reported.[144,158,159,162,163,191,192] $Bi(Hlac)_3$ **207**,[161] the only structurally characterized example, shows three chelating lactate ligands, all of which are singly deprotonated at the carboxylate functionality and form five-membered -BiOCCO-rings. Two of the ligands are tightly bound [Bi-$O_{carboxylate}$ 2.205(7) and 2.364(8); Bi-$O_{hydroxy}$ 2.474(8) and 2.457(9)Å], while one is weakly bound [Bi-$O_{carboxylate}$ 2.628(9)Å, Bi-$O_{hydroxy}$ 2.800(1)Å]. The carboxylate group of the weakly bound ligand coordinates a second bismuth center

asymmetrically in an *O,O'* manner [Bi-O 2.328(9) and 3.104(9)Å], forming a four-membered -BiOCO- ring. The exocyclic carboxylate oxygen of a tightly bound ligand coordinates a third bismuth center [Bi---O 2.580(1)Å], giving each bismuth atom a total



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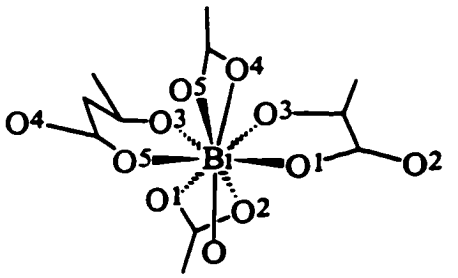
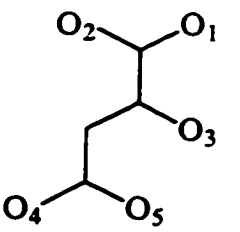
coordination number of nine and an overall complex three-dimensional network structure. A mixed lactate-tartrate complex dilactatobismuthotartaric acid $C_{10}H_{15}O_{12}Bi$ has also been prepared from the reaction of lactic acid with Bi nitrato tartrate,[158] while no solution studies of bismuth-lactate systems have been reported.

As with lactic acid, few bismuth complexes of malic acid have been prepared.[162,191] The single structurally characterized example Bi(mal)•H_2O **208**[150] shows bismuth chelated by four triply deprotonated malate ligands in various modes [Bi-O^3 2.244(6) and Bi-O^1 2.407(8)Å; Bi-O^3 2.255(6) and Bi-O^5 2.571(9)Å; Bi-O^1 2.959(9) and Bi-O^2 2.553(8)Å; Bi-O^4 2.351(9) and Bi-O^5 3.233(9)Å] forming a five-membered, a six-membered, and two four-membered rings. The oxygen atom of the lattice water molecule [Bi-O_{water} 2.80(1)Å] completes the coordination sphere for a total coordination number of seven. The bonding of each ligand to four bismuth atoms again results in a highly coordinated polymeric network.



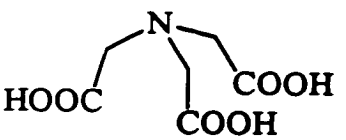


208

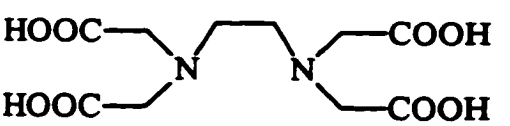
Few solution studies of bismuth-malic acid systems have been performed and all involve physical methods, including electrometry,[179] polarimetry,[179] polarography,[186] oscillography[186] and a bismuth ion-selective electrode.[193] Stability constants[188] have been determined at various pH values[186,188,193] and malic acid concentrations.[193]

2.3.2 Polyaminocarboxylates and Thiolatocarboxylates

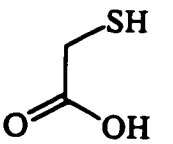
In addition to hydroxycarboxylic acid complexes, bismuth complexes of the polyaminocarboxylic acids nitrilotriacetic acid (H_3nta), also commonly referred to as triglycollamate, and ethylenediaminetetraacetic acid (H_4edta) have also been employed in medicine[194] and pharmacy and studied pharmacologically.[195] Similarly, a number of bismuth complexes of the thiol-carboxylic acid ligand H_2tga have been assessed for pharmacological[196] and antimicrobial activity. Synthetic and structural data for isolated bismuth Bi-nta and Bi-edta complexes is presented in Chapter 4.2.



H_3nta



H_4edta



H_2tga

There have been several studies of Bi-nta complexes in solution,[197] at various pH conditions,[198,199] and employing both spectroscopic[198,200] and physical[183,197,199,201-206] techniques. A number of physical constants have been determined for these systems including formation,[201] stability,[183,199,200,203-205] protonation,[205] hydrolysis,[205] and rate constants,[198] as well as dissociation potentials[206] thermodynamic functions[203] and mechanism of complex formation.[203] The interaction of nta and edta with $BiCl_6^{3-}$ has also been studied.[199,201] For the bismuth-edta system, both spectroscopic[207-214] and physical[183,185,201,204-207,209,215-221] techniques have been employed to determine complex compositions,[207] dissociation potentials,[206] molar absorbances,[209] and formation,[201,209] stability,[183,204,205,207,211,214,222-224] protonation constants,[205] as well as hydrolysis constants[205] and kinetics.[221,223]

Isolated bismuth complexes of thioglycolic acid include bismuth dithioglycolic acid,[225] $Bi_2(tga)_6Ca_3$,[226] Bi(tga)(Htga),[227] Na Bi thioglycolate,[196] ethylbismuthothioglycolate,[196] and Bi thioglycolate-triamide,[196] while Bi-tga solution systems have been studied by spectroscopic techniques only.[228]

2.4 'Colloidal Bismuth Subcitrate' (CBS), 'Bismuth Subsalicylate' (BSS) and 'Ranitidine Bismuth Citrate' (RBC)

Citrate salts of bismuth represent the most extensively studied series of bismuth compounds by virtue of the widespread medicinal use. Bismuth citrate is essentially insoluble in water, but a dramatic increase in solubility with increasing pH has been exploited as a bio-ready source of soluble bismuth, a material referred to as colloidal bismuth subcitrate (CBS). Formulation of these solutions is complicated by the

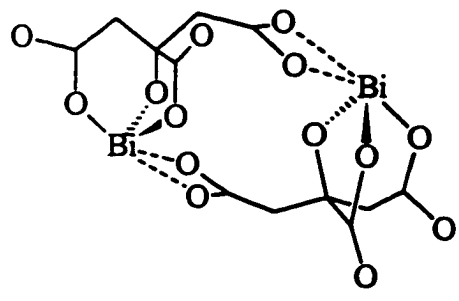
variability of the bismuth:anion stoichiometry, the presence of potassium and/or ammonium cations, the susceptibility of bismuth to oxygenation to Bi=O and the incorporation of water in isolated solids. Consequently, a variety of formulae are classified in the literature as CBS. [141,144,162-164,166,167,173,229,230] Solutions have been examined by a variety of approaches, including visual studies[176] and physical[183-185,190,193,231,232] techniques, to determine compositions[190,232] and stability constants[183] of bismuth citrate solution complexes, at various pH[184,193] and citrate concentrations.[176,193] ^{1}H and ^{13}C NMR spectroscopy [233-236] indicate rapid exchange of citrate moieties at low concentration and the existence of oligomeric or polymeric units at higher concentrations.

Solids isolated from various, often ill-defined combinations of bismuth citrate, citric acid, potassium hydroxide or ammonium hydroxide have been assigned formulae on the basis of elemental analysis data or by determination of water and ammonia content.[233,237] Additional speculation is made for their presentation as modified formulae ($\underline{cit} = C_6H_4O_7^{4-}$; $H\underline{cit} = [CO_2CH_2C(OH)(CO_2)CH_2CO_2]^{3-}$), however, assignments for such complex systems are of low significance in the absence of complementary data other than thermal analysis,[237] infrared spectroscopy[237] or NMR spectroscopy.[238] In this context, the Merck index lists the chemical formula of CBS as $K_3(NH_4)_2Bi_6O_3(OH)_5(C_6H_5O_7)_4$ in the 11th edition,[239] but in the most recent edition provides a less precise name "*tripotassium dicitrato bismuthate*"[240].

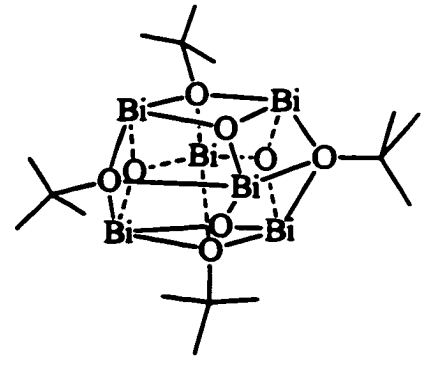
More definitive formulae have been determined by X-ray crystallography and are listed for structural comparison in Table 2.3. The conditions for isolation of these crystalline materials from solutions similar to those defined above are provided in some cases, but are sometimes incomplete and often involve time periods of months. Isolation

of the sodium salt **213** was somewhat unusual in that it was unexpectedly obtained from reaction mixture of ranitidine bismuth citrate, glutathione, D_2O and NaOD.[238]

The structures in Table 2.3 are all closely related and are generally composed of a citrate anion (cit) intimately bound to a bismuth center, an appropriate number of potassium or ammonium cations (to balance the charge) and solvated or coordinated water molecules. Three of the structures **214-16** contain an additional citrate trianion (Hcit = $C_6H_5O_7^{3-}$) and one structure **216** is constructed around a hexanuclear bismuth oxygen cluster (Bi_6O_4), similar to that found in bismuth subnitrate (**204**). The stoichiometries of the components are variable, including the bismuth citrate relationship, but most involve a well defined chelate interaction with the tridentate citrate bismuth complex. The potassium and ammonium cations are essentially interchangeable, and the ammonium salt **211** is isostructural with compound **212**. The variety of reported structures is somewhat misleading when one recognizes that of the eight structures listed in Table 2.3 (nine structural types have been previously incorrectly proposed[12]), only compounds **214-16** can be considered unique. Structures **209-13** are constructed from the simple monoanionic complex, composed of Bi^{3+} with a tridentate citrate tetra-anionic ligand. This unit is also evident in **214-16**, but these structures involve additional



209-15



216

Table 2.3 X-ray crystallographic data for solids described as colloidal bismuth subcitrate.

Formula	Bi:cit ratio	Coord # at Bi	Space Group	Cell param., a, b, c, β
$K(Bicit)(H_2O)_3$ **209**[241]	1:1	9	$P2_1/n$	10.924, 15.280, 14.967, 105.48
$K_{0.5}(NH_4)_{0.5}(Bicit)(H_2O)_3$ **210**[234]	1:1	9	$P2_1/n$	10.923, 15.424, 15.037, 105.67
$(NH_4)(Bicit)(H_2O)_2$ **211**[242]	1:1	8	C2/c	16.805, 12.544, 10.401, 91.27
$K_{0.5}(NH_4)_{0.5}(Bicit)(H_2O)_2$ **212**[234]	1:1	8	C2/c	16.860, 12.395, 10.328, 91.79
$Na_2(Bicit)_2(H_2O)_7$ **213**[238]	1:1	8	C2/c	15.723, 13.899, 10.423, 94.39
$K_{4.75}(NH_4)_{0.25}(Bicit)_2(Hcit)(H_2O)_{13}$ **214**[233]	2:3	9	P-1	11.801, 12.973, 15.856, 98.15, 108.39, 100.91
$(NH_4)_4(Bicit)(Hcit)(H_2O)_3$ **215**[233]	1:2	8	$P2_1/c$	8.998, 9.492, 27.021, 99.42
$(NH_4)_6(Bi_6O_4)cit_4(H_2O)_5$ **216**[235,243] [initially assigned $(NH_4)_6(Bi_6O_4OH)cit_3(H_2O)_5Hcit$]	3:2		R-3	17.807, 17.807, 31.596

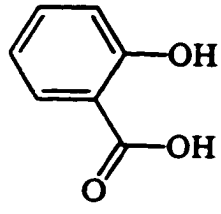
chemically different units. This unit together with one or two cations and three or six water molecules, defines the asymmetric unit of compounds **209-13**, but adopts a well defined dimeric arrangement imposed by chelate coordination of the pendant carboxylate moiety to a neighbouring bismuth center. Differences in the macrostructures of compounds **209** and **210** ($P2_1/n$) and **211-13** (C2/c) result from distinctions in the interactions between these dimers, which is likely only a function of the degree of hydration, i.e. the number of water molecules coordinated to bismuth. Compounds **214-**

16 also involve the tridentate coordinated citrate tetraanion (cit). However, the presence of an additional citrate trianion (Hcit = $[CO_2CH_2C(OH)CO_2CH_2CO_2]^{3-}$), and an additional citrate tetraanion for compound **214**, complicates and opens the structures, enabling the incorporation of additional water. Nevertheless, the familiar pendant carboxylate bound dimer is evident in **214** and **215**. Although compound **216** does not display the distinct dimer unit, the tridentate chelation of one of the two unique bismuth centers is clear.

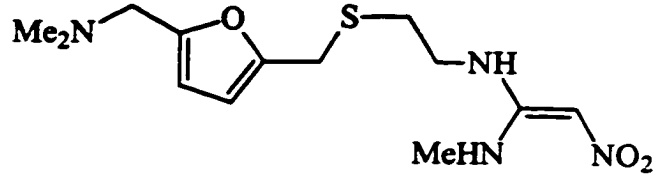
The ubiquitous tridentate citrate chelation of bismuth, which has also been observed for aluminum citrate complexes,[244] implies a special stability for the biscarboxylate/alkoxide interaction enforcing a pendant carboxylate. The coincident coordination of this third carboxylate is precluded by the required tetrahedral geometry of the central carbon center of the citrate anion. The consequential five- and six-membered chelate heterocycles are favoured over two seven-membered heterocycles imposed by coordination of three carboxylate oxygen atoms. More importantly, the alkoxide has a substantially higher basicity than the carboxylate. In the carboxylate chemistry of bismuth, the citrate salts are uniquely water soluble at high pH with avoidance of hydrolysis, which typically gives BiO for other salts. The tridentate chelate involving the alkoxide dominates this behaviour relative to other polycarboxylates and relative to bismuth citrate [Bi(Hcit)] at neutral or low pH, which is deprotonated at high pH.

The very low solubility of bismuth subsalicylate (BSS) has hindered characterisation,[49,130] while the more recently developed ranitidine bismuth citrate (RBC) **217**, a new therapy for peptic ulcer disease, is highly water-soluble. RBC is obtained from the reaction of ranitidine hydrochloride [*N,N*-dimethyl-5-(3-nitromethylene-7-thia-2,4-diazaoctyl)furan-2-methanamine] and bismuth citrate. Characterization has included

elemental analysis, ^{1}H and ^{13}C NMR and IR spectroscopy, polarography and X-ray powder diffraction, however, definitive structural assignment has been complicated by extensive hydrogen bonding. The proposed structure is speculated to involve the formation of a five membered ring by chelation of the bismuth center by NMe_2 and O_{furan}.[245-247]



salicylic acid (H_2sal)

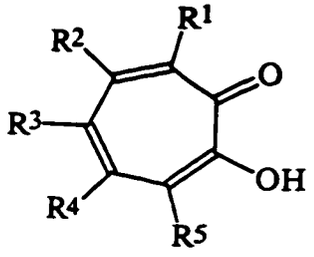


ranitidine

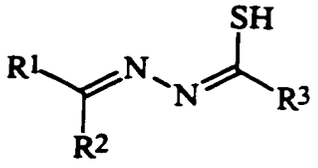
2.5 Models and Alternatives for Bioactive Bismuth Compounds

The apparent chemical complexity of the commercial bismuth containing pharmaceutical agents, which is imposed by the lability of the ligands has prompted the development of simpler model compounds and the search for alternatives to the established systems. Therapeutic or anti-bacterial activity has been speculated upon or suggested for many bismuth compounds, and some have been assessed *in vivo* and/or *in vitro*. Table 2.4 lists examples of compounds for which a medicinal effect has been suggested or evaluated, together with the preparative method. Most compounds of this type are superficially characterized and the molecular structures or even the formulae have not been defined, with some cases illustrating varying composition depending on specific reaction condition.[248,249]

Systematic and comprehensive synthetic studies have recently been coupled with bioactivity studies to confirm the bio-significance of bismuth and reveal important trends in activity. Extensive series of bismuth (III) and bismuth (V) tropolones and bismuth (III) thiosemicarbazones and dithiocarbazonic acid methylester derivatives have been assessed for their anti-*Helicobacter pylori* activity illustrating a substantially lower minimum inhibitory concentration for the former.[6]



tropolone



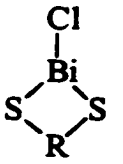
thiosemicarbazone

As a heavy metallic element, bismuth has a prominent thiophilicity responsible for the facile formation of sulfido and thiolato complexes, and a consequential thermodynamic and kinetic stability, which has enabled synthesis and isolation of the most extensive array of derivatives. Numerous examples have been assessed for their bioactivity, but more importantly systematic series of compounds have been prepared and evaluated. Antimicrobial bioactivity assessment of three systematic series of comprehensively characterised thiobismuth compounds, **217**, **218**[2] and **219**[3] (syntheses and characterization of these compounds are discussed further in Chapter 5.3), against *Clostridium difficile*, *Helicobacter pylori*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis* reveals significant differences in activity across each series, suggesting a structure/activity relationship for the bismuth environment.[4] In addition, a rat model of gastric ulceration has revealed distinct differences in the ulcer healing efficacy of the

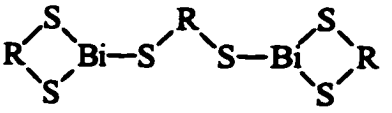
Table 2.4 Examples of other bioactive bismuth compounds.

Compound designation	formula	Chemical (Bio./ Med.) Data	Suggested or evaluated medicinal effect (Mode of Admin.)	Ref
phenylbismuthbis (2-pyridinethiol 1- oxide)	$PhBi(C_5H_4NOS)_2$	prep (*in vitro* - gram positive, gram negative)	detergents, soaps, shampoos	250, 251
organobis(thio-phenylato) bismuth(III)	$C_6H_5Bi(SC_6H_4Cl\text{-}p)_2$, $CH_3Bi(SC_6H_4NH_2\text{-}p)_2$, $[CH_3Bi(SC_6H_4NH_2CH_3\text{-}p)_2]I_2$, $[CH_3Bi(SC_6H_4NH_2CH_3\text{-}p)_2][NO_3]_2$	prep, spectroscopy (bacterial)	bactericide	252
3-phenylthio- and phenylsulfonyl-acrylic acid bismuth salt	Bi salts of $RC_6H_4S(O)_nCH{=}CHCO_2H$ (R = H; halo, C_{1-4} alkyl or alkoxy, NO_2; n = 0, 2)	prep (cytoprotective and gastric acid secretion-inhibitory)	ulcers	253
p-chlorophenoxy-isobutyric acid bismuth salt	mono- and bis-*p*-$Cl(C_6H_4)OC(Me)_2CO_2H$ salts	prep	depressant for blood cholesterol	254
bismuth *o*-mercapto-benzamide	$Bi(SC_6H_4CONH_2)_3$	prep, sol (fungicidal, bactericidal activity)	(ointments, talc)	255
dipropylacetic acid bismuth salt	$Bi[(C_3H_7)_2CHCO_2]_3$	prep, mp, sol	throat infections (rectal suppository with cocoa butter)	256
p-amino- and *p*-benzamidosalicylic acid bismuth salts	$[Bi(C_7H_5NO_3)_2]I$, $[Bi(C_{14}H_{10}NO_4)]I_2$	prep	tuberculostatic	257
bismuth subcompounds	*o*-$AcOC_6H_4CO_2BiO$	prep (stable in stomach - no data)	intestinal (oral, rectal)	258
bismuth allantoinate	$C_4H_5N_4O_3{\bullet}Bi(OH)_2$	prep	external and internal ulcers, wounds, etc.	259
basic bismuth guaiacol-carboxylate	$C_6H_3(OH)(OCH_3)COOBiO$	prep, sol	syphilis (ointment, subcutaneous)	260
bismuth hydroxy-quinolinate	$Bi(OH)_2OC_9H_6N$	prep, sol	(antiseptic on wounds)	261
double iodide of emetine and bismuth	emetine$\bullet$2HI$\bullet$1.5BiI_3	prep, EA	(gelatin capsules)	262

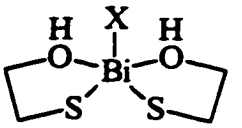
ethylene [R = $(CH_2)_2$] derivatives of compounds **217** and **218**.[263]



217



218



219

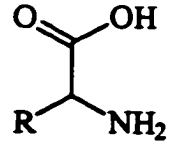
2.6 Interactions with Biomolecules and Pharmaceutical Agents

One proposed mode of action of anti-ulcer bismuth compounds is the ability of bismuth to bind to proteins of exposed tissue and provide a protective coating over the ulcer.[264] It is crucial, therefore, to have an understanding of the bismuth bonding ability of amino acids, proteins, and other biomolecules, which may also provide a basis for conclusions of pharmacological and pharmacokinetic studies. Further, bismuth complexes of amino acid derivatives, such as D-penicillamine[265] and other dialkylcysteines,[266] have been suggested for medicinal use, while polypeptide complexes, such as those of glutathione, have been suggested for treatment of syphilis and other diseases.[267] Investigations of systems and isolated compounds incorporating bismuth and amino acids or other biomolecules are described below.

2.6.1 Amino Acids

The bismuth methionine (Hmt) complex $Bi(mt)_3$[268] was prepared in non-aqueous media and characterized mainly by infrared spectroscopy. The reaction of a slight excess of cysteine (H_2cys), which contains a thiol functionality, with bismuth subcarbonate in

aqueous media gave Bi(cysH)$_3$•H_2O, in which the ligand retains one labile proton.[269] This compound was also characterized mainly by infrared spectroscopy. A bismuth



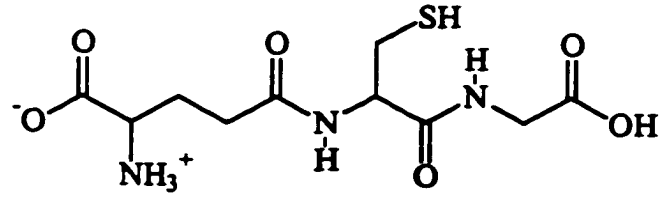
R = H, glycine
= $(CH_2)_4NH_2$, lysine
= CH_2OH, serine
= CH_2SH, cysteine
= $CH_2(CH_3)_2SH$, penicillamine
= $CH_2CH_2SCH_3$, methionine

complex of D-(-)-penicillamine (pen) [Bi(pen)Cl], a cysteine dimethyl derivative, has been structurally characterized and is discussed further in Chapter 5.3.[270]

Solution studies of bismuth amino acid complexes include amperometry of bismuth-glycine complexes,[271] spectrometry of cysteine complexes,[272] pH-metric investigations of L-lysine complexes,[273] and polarography of serine complexes[274].

2.6.2 Peptides and Proteins

The complexation between RBC and the tripeptide glutathione (gSH) (γ-L-Glu-L-Cys-Gly) has been studied in both aqueous media and in red blood cells via ^{1}H NMR spectroscopy,[275,276] and sulfur has been found to be the strongest binding site for bismuth. Stability constants have been determined for the Bi(gS)$_3$ species, and binding was found to be competitive between gSH and edta and is pH dependent.



glutathione (gSH)

The binding of the Bi^{3+} cation to human serum transferrin (hTF), an iron transport glycoprotein, has been examined by UV-vis and NMR spectroscopies,[277,278] while the effect of the concentration of bismuth on plasma protein and red blood cell binding, as well as bismuth binding to human serum albumin, bovine serum albumin and human serum, have also been studied.[279] The interaction of CBS with erythrocytes and erythrocyte lysate has been investigated using ^1H spin echo NMR.[280]

The binding of tripotassium dicitrato bismuthate to the bile acids has been investigated *in vitro* using ^3H labeled acids and measuring radioactivity at high and low pH.[281] Bismuth was found to bind each acid to varying degrees and only at low pH (2.0), suggesting a mode of action in ulcer healing. Pepto-Bismol, as well as its individual components bismuth subsalicylate and montmorillonite, have been found to sequester bile acids from aqueous solutions *in vitro*.[282] Other studies examine the effect of pH on the formation of bismuth protein complexes[283] and bismuth-gelatin compounds,[284] the interaction of bismuth compounds with alkaline protein solutions under the biuretic reaction conditions,[285] and the behavior of elemental bismuth with various proteins under anaerobic conditions.[286,287] Bismuth compounds have also been found to retard the action of enzymes.[288]

Bismuth salts are widely used in the catalysis of organic reactions, such as the hydrolysis of ribonucleic acids to dinucleoside phosphates[289-292] and the production of prostaglandins.[293]

Bismuth(III) has been found to form a saturated 7:1 complex with rat liver metallothionein (MT), with similar results for other metal ions, suggesting little binding specificity for bismuth.[294] There has been a debate over whether the proteins binding

bismuth are related to MT, so alternative terms such as "metallothionein-like proteins (MTP)" and " renal metal binding proteins (RMBP)" have been used.[295] Isolation, separation and amino acid analysis of these proteins showed that they were different from cadmium induced rat MT.[295] These bismuth induced RMBPs in rats have been divided into two major components which have been studied spectroscopically.[296] The hepatic protein spectra show predominantly zinc thiolate transitions, while the renal protein transitions can be accounted for by both bismuth and copper thiolate binding sites.

2.6.3 Interaction of Bismuth Compounds with Other Drugs and Food Components

Many studies have been dedicated to determining the effect of medicinal bismuth compounds on the activity of other medicinal components, or vice versa, *in vitro*, and *in vivo* to evaluate drug bioavailabilities. Many drugs have been found to adsorb on inorganic bismuth salts employed as antacids,[297-303] while adsorption does not occur between all bismuth salt-drug combinations.[304] Other *in vitro* studies involve the adsorption of diazepam,[305] anticoagulants[306] and preservatives[307] on both inorganic and organic bismuth salts.

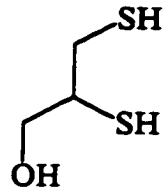
Antacid bismuth salts may also have an effect on the absorption[308-312] and excretion[313] of other drugs in the body when taken concurrently. Bismuth subcarbonate has been found to have a variable effect on the antimicrobial activity of various antibiotics *in vitro*.[314,315] Conversely, biologically active molecules may have an effect on the therapeutic action of bismuth salts.[316] The bioactivity of bismuth compounds (thioloprives) is inactivated by molecules containing thiol groups, such as cysteine,

sodium thioglycolate, and sodium thiosulfate, while it is unaffected by sulfide and thioether containing molecules, such as cystine and methionine.[317] While it has been reported that penicillin is decomposed by bismuth ions in the presence of water,[318] there were synergistic effects observed between bismuth compounds and penicillin, which has no activity alone, against *Trypanosoma equiperdum* infected rats.[319]

The formation of soluble chelates of bismuth has also been studied in various drugs and foods.[320] Atomic absorption studies show an enhanced solubility of insoluble bismuth salts in the presence of certain drugs and food components including polyalcohols, hydroxycarboxylic acids, ascorbic acid, aspirin, tetracyclines, vinegars, fruit and citrus juices.[321] The effect of the complexation of a variety of antibiotics on the migration of Bi^{3+} has been determined by paper chromatography and electrochromatography.[322] Other bismuth-biomolecule solution studies involve chlorophyll, pheophytin,[323] D-mannitol[324] and ascorbic acid,[325,326] while complexes of uracil and thiouracil,[327] mucate, saccharate and other polyhydroxcarboxylates[328] have been isolated.

2.6.4 Antidotes

Many ligands have also been used as antedotes for bismuth poisoning. Chelating ligands such as British anti-Lewisite (H_2bal) (2,3-dimercaptopropanol), ethylenediaminetetraacetic acid (H_4edta), *p*-aminobenzoic acid[329] and cystine[330] offer some degree of protection against common medicinal bismuth compounds. Mucin solutions have been suggested as a possible antidote after ingestion of toxic metal compounds as mucin solutions precipitate the metals from suspensions of $BiOHCO_3$ or



British anti-Lewisite (H_3bal)

other metals at low pH.[331] A series of dithiol ethers have been synthesized as chelators for heavy metals, forming complexes of lower toxicity.[332] British anti-lewisite has been found to chelate bismuth strongly enough to react with bismuth sulfide,[333] while studies of bismuth-bal compounds involve stability measurements in comparison to other dithiol ligands[334] and employ polarography.[335] Further, Bi-edta[336] and Bi-bal complexes[337] have also been assessed for antimicrobial activity *in vitro* and *in vivo*.[338-340]

2.7 Conclusions

The vast array of medicinal or anti-microbial uses for bismuth compounds indicates a diverse biorelevance for the element, which is likely valid, but has not yet been unequivocally demonstrated. A wide selection of compounds and complexes of bismuth have been investigated for potential bioactivity without justification other than bismuth content. Some therapeutic utility is best described as 'suggested', and most experimental studies are impeded by the chemical complexity of the bismuth compound or the superficial chemical knowledge base that is currently available for bismuth. Most importantly, few definitive identifications of bio-bismuth interactions have been reported. Nevertheless, the unquestionable antimicrobial activity of some bismuth compounds at low concentrations, the relatively low elemental human cell cytotoxicity, and the ill defined gastric cytoprotective properties of certain bismuth salts highlights the chemistry

of bismuth as an important focus for the development or discovery of new pharmaceutical agents. The efficiency of such developments will depend on the systematic assessment of bismuth chemistry as a foundation for understanding biochemical interactions.

Chapter 3. Toward the General Synthesis of Bismuth Dicarboxylates and the Structural Characterization of Bismuth Oxalate

3.1 Introduction

As discussed in Chapter 2, emphasis in medicinal bismuth chemistry has been placed on bismuth salts of carboxylic acids and hydroxycarboxylic acids, of which colloidal bismuth subcitrate (CBS) and bismuth subsalicylate (BSS) are the most obvious examples. However, the characterization of bismuth carboxylates is hindered by their hydrolytic instability,[341] the lability of the ligands in solution and the consequential sensitivity of the conditions for isolation of solids. Also, the ability of the carboxylate functional group to achieve extensive intermolecular contacts is responsible for complex structures in the solid state and likely in solution. The medicinal importance of bismuth carboxylates has prompted extensive studies of complexes involving simpler ligands including lactate[161], tartrate[150,157] and malate[150], all of which have been characterized by X-ray crystallography. Although the solid state structures of the simplest bismuth monocarboxylates (i.e. formate, acetate) have been determined, bismuth oxalate (the simplest dicarboxylate) has only been superficially characterized as a guanidinium salt.[342]

This chapter outlines approaches to minimizing hydrolysis and enabling isolation of bismuth complexes of simple carboxylate ligands. These developments have led to the isolation of the parent oxalate salt, which has been structurally characterized as bismuth oxalate octahydrate **3A**. Section 3.2 provides an overview of the data available for mono- and dicarboxylate complexes of bismuth.

3.2 Synthesis and Structure of Bismuth Carboxylates

Characterization data for both carboxylate and dicarboxylate compounds of bismuth are contained in Table 3.1, followed by reaction equations for synthetic procedures. Yields are typically not reported and formulae assignments are based on single crystal X-ray diffraction studies. Most compounds sublime rather than melt, therefore measurement of sublimation point (sp) is indicated. There are examples of formally molecular and anionic species and Lewis base adducts (e.g. **301, 313** and **317**, respectively), as well as an example of a mixed alkoxide/carboxylate complex (**318**). Structural details are illustrated below.

Bismuth carboxylates are typically prepared by reaction of a basic inorganic bismuth compound with concentrated carboxylic acid under reflux conditions, while the anhydride is often introduced to remove by-product water. These compounds may also be prepared by similar reactions with $BiPh_3$, while partial metatheses give organo bismuth carboxylates. Ligand exchange reactions with bismuth acetate (reaction 3.2), in particular, have been extensively utilized to prepare a series of bismuth tris(monocarboxylate) species **301** and **303-310**.[341,343,344] The synthesis of $[NaBi(CF_3COO)_4]$ **312**[345] (reaction 3.6) is unique in that it involves the reduction of pentavalent bismuth. The two thiourea adducts of bismuth acetate $[Bi_2(CH_3COO)_6(\underline{tu})_3(H_2O)]$ **316** and $[Bi(CH_3COO)_3(\underline{tu})_3]$ **317** are prepared from similar reactants under different isolation conditions. The favorable hydrolysis of bismuth carboxylates allows for the preparation of the acetate oxide or "sub"acetate $[BiO(CH_3COO)]$ **319** by dilution of a solution of Bi_2O_3 in acetic acid and distillation of the excess acid.[346] Other "sub" carboxylates, including [BiO(RCOO)] (R =

Table 3.1 Analytical data for carboxylate and dicarboxylate compounds.

Compound	yield (rxn 3.*n*)*	XR	sp	EA	sol	IR	NMR	MS	DTA
$[Bi(O_2CH)_3]$ **301**[341,343,347]	100 (1,2)	x	x	x	x	x	-	-	x
$[Bi(CH_3CO_2)_3]$ **302**[341,348-350]	90-95 (1,3-5)	x	x	x	x	x	-	-	x
$[Bi(CD_3CO_2)_3]$ **302-d_9**[348]	- (1)	-	-	-	-	x	-	-	-
$[Bi(O_2CCH_2CH_3)_3]$ **303**[341]	100 (2)	-	x	x	x	x	-	-	x
$[Bi(O_2CCH_2CH_2CH_3)_3]$ **304**[341]	100 (2)	-	x	x	x	x	x	-	x
$[Bi\{O_2CCHMe_2\}_3]$ **305**[341]	100 (2)	-	x	x	x	x	x	-	x
$[Bi\{O_2C(CH_2)_3CH_3\}_3]$ **306**[341]	100 (2)	-	x	x	x	x	-	-	x
$[Bi(O_2CCH_2CHMe_2)_3]$ **307**[341]	100 (2)	-	x	x	x	x	-	-	x
$[Bi(O_2CCMe_3)_3]_4$ **308**[341,351]	100 (2)	x	x	x	x	x	x	-	x
$[Bi\{O_2C(CH_2)_4CH_3\}_3]$ **309**[341]	100 (2)	-	x	x	x	x	-	-	x
$[Bi(C_6H_5CO_2)_3]$ **310**[344]	- (2)	x	-	x	-	-	-	-	-
$[Bi(CF_3CO_2)_3]$ **311**[345,352]	- (4,6)	-	x	x	-	x	x	x	-
$[NaBi(CF_3CO_2)_4]$ **312**[345]	- (7)	-	-	x	-	x	-	-	-
$[H_2\underline{teed}][Bi(O_2CCF_3)_5]$ **313**[353]	- (8)	x	x	x	-	x	-	-	-
$K_2[Bi(O_2CH)_5]$ **314**[354]**		x							
$[Bi(O_2CF_3)_3(HO_2CF_3)]$ **315**[355]	94 (3)	x	-	-	-	-	-	-	-
$[Bi_2(CH_3CO_2)_6(\underline{tu})_3(H_2O)]$ **316**[356]	- (9)	x	-	-	-	-	-	-	-
$[Bi(CH_3CO_2)_3(\underline{tu})_3]$ **317**[356]	- (9)	x	-	-	-	-	-	-	-
$[Bi(O_2CCH_3)_2(\underline{bdmap})]_2[H_2O]$ **318**[357]	52 (10)	x	-	x	x	-	x	-	-
$[BiO(CH_3CO_2)]$ **319**[346]	- (1)	x	-	x	-	-	-	-	-
$[C(NH_2)_3][Bi_2(\underline{ox})Cl_3]$ **320**[342]**		x							
$[Bi(\underline{phthal})(OH)]$ **321**[358]	97 (11)	-	-	x	-	x	-	-	-

** The original report could not be obtained. Crystallographic information was extracted from *Chemical Abstracts* and the Cambridge Crystallographic Database.

*Syntheses:

3.1) $Bi_2O_3 + 6\,RCOOH \rightarrow 2\,Bi(RCOO)_3 + 3\,H_2O$

3.2) $Bi(CH_3COO)_3 + 3\,RCOOH \rightarrow Bi(RCOO)_3 + 3\,CH_3COOH$

3.3) $Bi_2O_3 + 4\,RCOOH + RC(O)OC(O)R \rightarrow 2\,Bi(RCOO)_3 + 2\,H_2O$

3.4) $Bi_2O_3 + 3\,RC(O)OC(O)R \rightarrow 2\,Bi(RCOO)_3$

3.5) $Bi(NO_3)_3 \bullet 5H_2O + 5\,RC(O)OC(O)R \rightarrow Bi(RCOO)_3 + 7\,RCOOH + 3\,HNO_3$

3.6) $BiCl_3 + 3\,Ag(RCOO) \rightarrow Bi(RCOO)_3 + 3\,AgCl$

3.7) $NaBiO_3 + 2\,RC(O)OC(O)R \rightarrow Na[Bi(RCOO)_4] + \frac{1}{2}\,O_2$

3.8) $BiPh_3 + 5\,RCOOH + 2\,L \rightarrow [H_2L][Bi(RCOO)_5] + 3\,PhH$

3.9) $Bi(RCOO)_3 + n\,L + RCOOH \rightarrow Bi(RCOO)_3L_n + RCOOH$

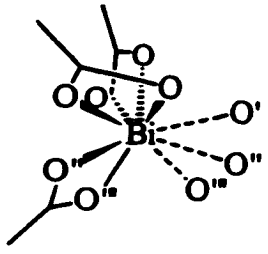
3.10) $Bi(RCOO)_3 + HL \rightarrow [Bi(RCOO)_2(L)] + RCOOH$

3.11) $Bi_2O_3 + 2\,R(COOH)_2 \rightarrow 2\,Bi\{R(COO)_2\}OH + H_2O$

H, C_2H_5, C_3H_7, C_4H_9), were reportedly prepared by similar methods, but are poorly characterized. Preliminary X-ray structural data was obtained for **319**. An attempt to prepare an *O,O'*-dibenzoic acid analogue of [Bi(phthal)(OH)] **321**[358] by a similar method was unsuccessful (i.e. no reaction occurred).

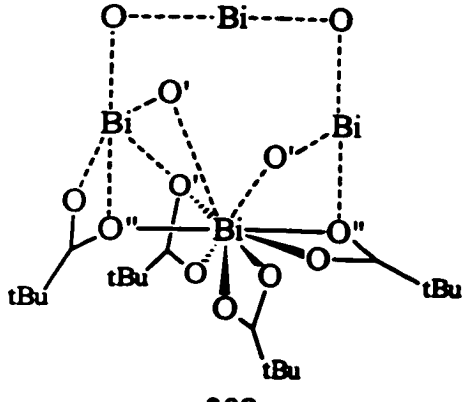
3.2.1 Carboxylates

Bismuth formate [$Bi(OOCH)_3$] **301**[341,343,347] shows monodentate formate groups at three different Bi-O distance ranges [avg. 2.38, 2.52, and 2.77Å], all of which bridge to neighbouring bismuth centers. The central bismuth atoms are nine-coordinate within tricapped trigonal prisms, which share basal triangular faces and form a three-dimensional network through bridging formate groups. Bismuth(III) acetate [$Bi(CH_3COO)_3$] **302**[341,348-350] shows the bismuth center asymmetrically chelated by three acetate groups [Bi-O 2.25(2)-



302

2.62(2)Å]. Three oxygen atoms of two neighbouring complexes (O' and O"; O'") bridge bismuth centers [Bi-O 2.81(2)-2.94(1)Å] forming a layered structure and a nine-coordinate environment for bismuth. Bismuth 2,2-dimethylpropionate $[Bi(O_2CCMe_3)_3]_4$ **308**[341,351] is tetrameric in the solid state, with bismuth in a distorted nine coordinate environment. The coordination sphere contains six ligands bound in various modes: monodentate and bridging [avg. Bi-O 2.87-3.27Å]; *O,O'*-chelating and non-bridging [avg. Bi-O 2.24 and 2.50Å]; and *O,O'*-chelating and bridging [avg. Bi-O 2.25-2.73Å]. The tetrameric structure shows less intermolecular contacts than the three-dimensional framework of the formate **301** or the layered framework of the acetate **302**, so that **308** is much more volatile at lower temperatures. In addition, the relatively greater thermal and hydrolytic stability of the compound is accredited to the protection of the reactive sites by the bulky ligand.



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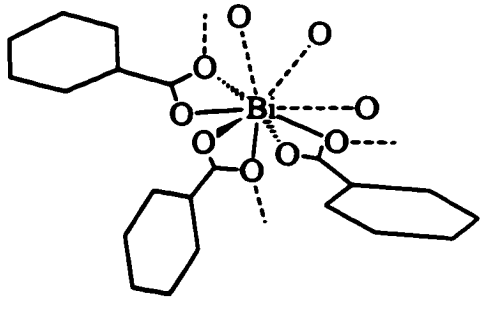
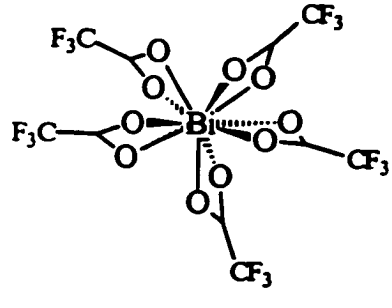


310

Bismuth benzoate $[Bi(C_6H_5COO)_3]$ **310**[344] shows a similar nine-coordinate environment, however intermolecular contacts create a one-dimensional polymer. The bismuth center is asymmetrically chelated by three benzoate ligands, forming four-membered -BiOCO- rings. One oxygen atom of each ligand bridges to another bismuth center [Bi-$O_{non\text{-}bridging}$ 2.198(14)-2.533(16); Bi-$O_{bridging}$ 2.243(14)-2.793(18)Å] and in turn each bismuth center receives a long contact from three ligand oxygen atoms [Bi-O 2.624(16)-3.380(16)Å].

Neutral $[Bi(CF_3COO)_3]$ **311**,[345,352] monoanionic $[NaBi(CF_3COO)_4]$ **312**[345] and the dianionic $[H_2\underline{teed}][Bi(O_2CCF_3)_5]$ **313**[353] trifluoroacetates have been prepared, as well as a dianionic pentakis(formate) complex $K_2[Bi(OOCH)_5]$ **314**.[354] $[Bi(CF_3COO)_3]$ **311** is very moisture sensitive, and a structure in which the three trifluoroacetate ligands are bound monodentate to the bismuth atom is suggested based on infrared data. However, high melting points and IR data suggest significant molecular associations via bridging trifluoroacetate groups. The monomeric anion of **313** shows bismuth in a symmetric ten coordinate bonding environment, occupied by five *O,O'*-bidentate trifluoroacetate groups [Bi-O 2.44(3)-2.62(2)Å]. The distorted pentagonal prismatic geometry can be simplified



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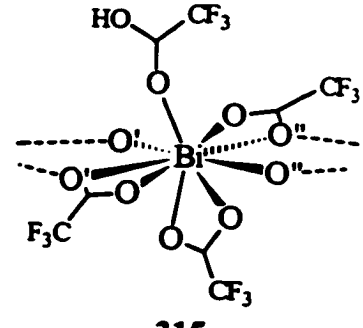
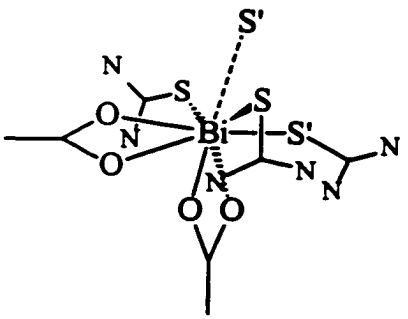


315

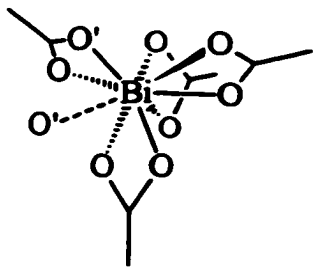
to distorted trigonal bipyramidal if each carboxylate group is considered to occupy a single coordination site. A similar ten coordinate structure is observed for **314**.

The trifluoroacetic acid adduct $[Bi(OOCF_3)_3(HOOCF_3)]$ **315**[355] shows bismuth bound to three asymmetrically chelated *O,O'*-trifluoroacetate groups [Bi-O_{short} 2.26(3)-2.27(3); Bi-O_{long} 2.64(3)-2.91(3)Å], with the three shorter Bi-O bond distances in a facial arrangement, and a monodentate *O*-trifluoroacetic acid ligand [Bi-O 2.71(3)Å]. A long Bi---O contact to and from each of two neighbouring molecules [Bi---O 2.79(3)-2.84(3)Å] creates a polymeric chain structure and gives an irregular nine coordinate geometry for bismuth.

The thiourea adduct $[Bi_2(CH_3COO)_6(\underline{tu})_3(H_2O)]$ **316**[356] is composed of dimeric $[Bi_2(CH_3COO)_8]^{2-}$ anions and dimeric $[Bi_2(CH_3COO)_4(\underline{tu})_6]^{2+}$ cations. The eight coordinate bismuth center of the cation is bound by two bidentate acetate ligands [Bi-O 2.31(1)-2.71(2)Å], three *S*-thiourea molecules [Bi-S 2.677(5) and 3.152(6)Å] and a long thiourea sulfur contact from a neighbouring group [Bi---S 2.909(5)Å]. In the anion, bismuth is nine-coordinate with four bidentate acetate oxygen groups [Bi-O 2.26(1)-2.78(1)Å] and a long acetate oxygen contact from neighbouring monomer [Bi---O

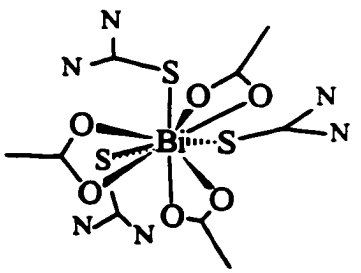


(cation)



(anion)

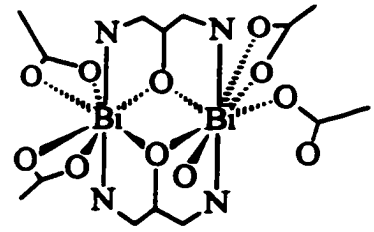
316



317

2.77(2)Å]. The adduct $[Bi(CH_3COO)_3(\underline{tu})_3]$ **317**[356] is composed of monomeric units, with three *O,O'*-bidentate acetate groups [avg. Bi-O 2.509(4)Å] and three *fac* thiourea sulfur atoms [avg. Bi-S 3.061(2)Å] in the bismuth coordination sphere. If each bidentate acetate group is considered to occupy one site, the nine-coordinate geometry may be reduced to near octahedral.

In the dinuclear mixed acetate-bdmap [1,3-bis(dimethylamino)-2-propanolato] complex $[Bi(OOCCH_3)_2(\underline{bdmap})]_2[H_2O]$ **318**[357] two bismuth atoms are bridged by the two aminoalkoxide ligands [Bi-O 2.18(2)-2.41(2); Bi-N 2.68(2)-2.76(3)Å]. In this instance, one bismuth center is asymmetrically chelated by two acetate ligands [Bi-O 2.32(2)-2.91(3)Å], while the introduction of the water molecule [Bi-O 2.75(2)Å] into the coordination sphere of the second, and the monodentate bonding of an acetate group [Bi-O_{mono} 2.48(2); Bi-O_{bi} 2.42(2) and 2.45(2)Å], allows for retention of the eight coordinate environment for both metal centers.



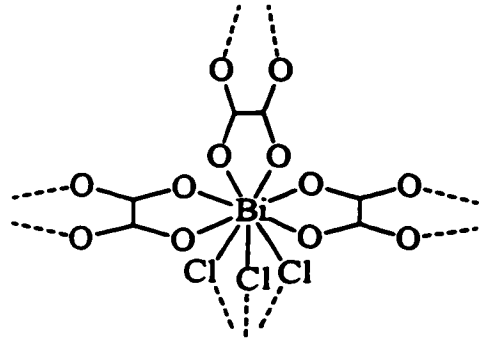
318

3.2.2 Dicarboxylates

A comprehensive search of bismuth oxalate (ox) compounds unveiled several reports:[130,359,360] nonhydrated and hydrated bismuth oxalate $[Bi_2(\underline{ox})_3]$[361] and $Bi_2(\underline{ox})_3 \bullet nH_2O$ (n = 5, 6, 7,[160,362]8)[363]]; ionic complexes $[LiBi(\underline{ox})_2 \bullet nH_2O$ (n = 2, 5[364]),[363] $NaBi(\underline{ox})_2 \bullet nH_2O$

(n = 2.5,[365] 3, 3.5, 4, 4.5, 5),[364] $KBi(\underline{ox})_2$,[366] $KBi(\underline{ox})\bullet 5H_2O$, $NH_4Bi(\underline{ox})_2$,[367] $NH_4Bi(\underline{ox})\bullet 5H_2O$, $NH_4Bi_2(\underline{ox})NO_3\bullet 3H_2O$, $(NH_4)_2Bi_2(\underline{ox})_3(NO_3)_2\bullet 3H_2O$, $(NH_4)_2Bi_2(\underline{ox})_2F\bullet 2H_2O$ and $(NH_4)_2Bi_3(\underline{ox})_5Cl\bullet 8H_2O$[363]]; complexes containing free acid [$m Bi_2(\underline{ox})_3\bullet n H_2\underline{ox}$[361]]; and a "sub"oxalate [$(BiO)_2(\underline{ox})$[368]]. There have been systematic studies of the effect of the [$\underline{ox}^{2-}$]/[Bi^{3+}] ratio, sequence of addition and stirring time on the composition of precipitated bismuth oxalate products from aqueous solutions of $Bi(NO_3)_3$ and $H_2\underline{ox}$[361], $K_2\underline{ox}$[366], $(NH_4)_2\underline{ox}$[367], $Na_2\underline{ox}$[369] or $Li_2\underline{ox}$.[370] Another solution study of oxalate complexes involves the determination of stability and solubility constants of the $Bi(ClO_4)_3$-$Na_2\underline{ox}$-H_2O system by UV spectroscopy.[371] Formulae assignments are typically based on chemical analysis or thermal decomposition data.

The only crystallographically characterized oxalate complex $[C(NH_2)_3][Bi_2(\underline{ox})Cl_3]$ **320**[342] shows bismuth in a nine-coordinate face centered trigonal prismatic environment. Bridging chlorine atoms form dimeric units. A series of organobismuth dicarboxylates has also been reported, which includes the oxalate complex [PhBi(ox)], and was characterized by EA and EI-MS.



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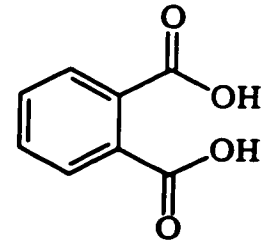


$H_2\underline{phthal}$

The IR spectrum of [Bi(phthal)(OH)] **321**[358] indicates an unsymmetrical bidentate coordination of both carboxylate groups.

3.3 Results and Discussion

Crystals of bismuth oxalate octahydrate $[Bi_2(C_2O_4)_3]\bullet 8H_2O$ **3A** were isolated in very low yield from the reactions of excess oxalic acid with either bismuth chloride or bismuth oxychloride in water under reflux conditions. As with the syntheses of other bismuth mono-and dicarboxylates, excess ligand is employed to minimize pH and decrease the formation of insoluble hydrolysis products.

As is typical of bismuth carboxylates, the structure of **3A** is highly coordinated, with each oxalate ligand bonding in a tetradentate manner and bridging two neighboring bismuth atoms, as shown in Figure 3.1. Each of the two unique bismuth atoms is chelated by three oxalate ligands [Bi-$O_{oxalate}$ 2.33(1)-2.60(1)Å] in a bidentate -OCCO- fashion (favorable five-membered rings). This is an unusual arrangement in that the carboxylate functionality typically chelates in an -OCO- manner, but is similar to that of **320**. Two water molecule oxygen atoms complete the coordination sphere [Bi-O_{water} 2.49(1)-2.57(2)Å], giving a total coordination number of eight. The lone pair on bismuth appears to be stereochemically active. The overall result is a complex three-dimensional polymeric network, as observed for bismuth formate **301** and the hydroxy/alkoxycarboxylates **205-08** discussed in Chapter 2. There are four non-bonded lattice water molecules.

The absence of chlorine in the isolated product is striking {c.f. $[C(NH_2)_3][Bi_2(ox)Cl_3]$ **320**[342]}. Chloride ion bonds favorably to bismuth in solution and in

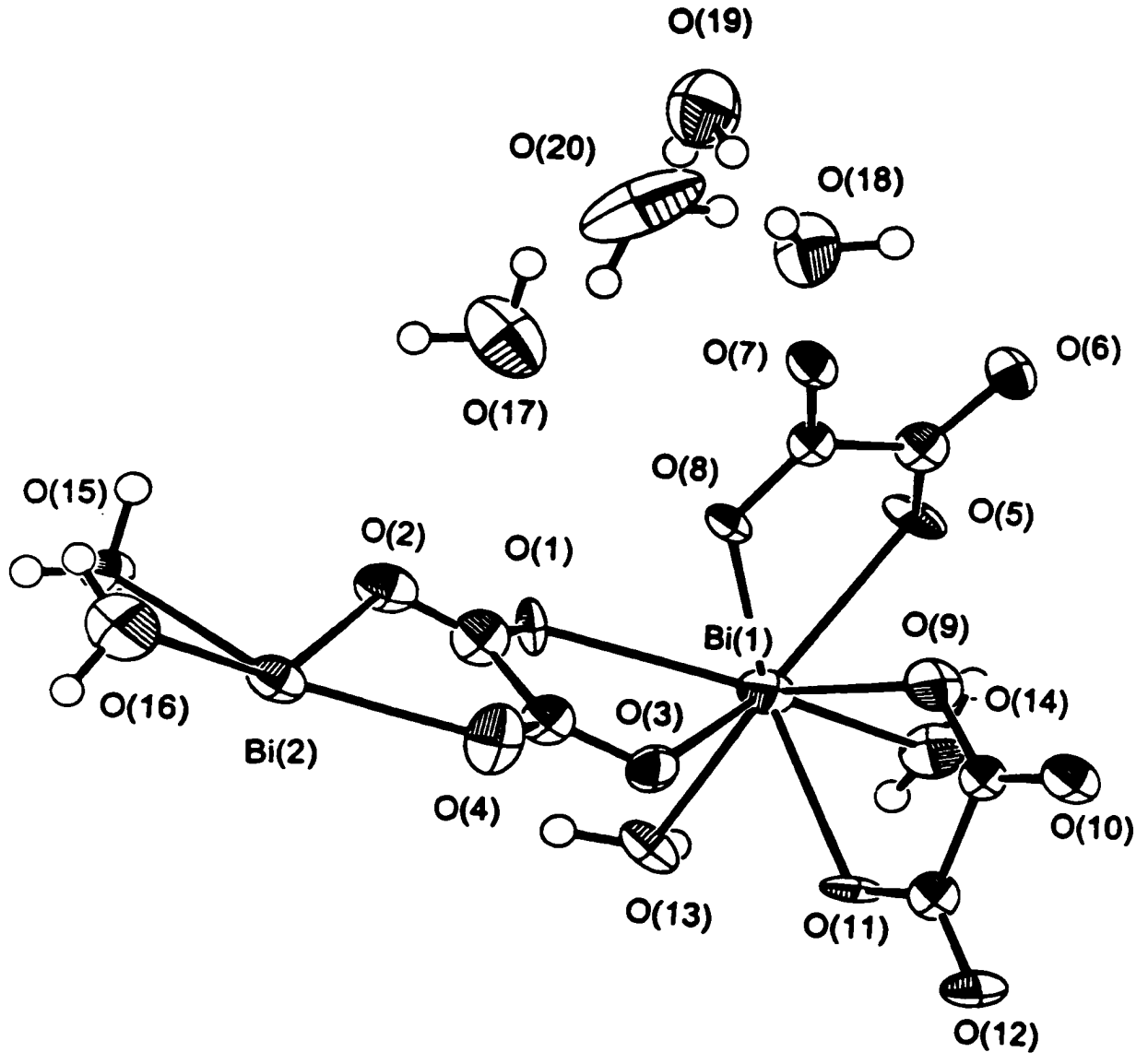


Figure 3.1 Crystallographic view of $[Bi_2(C_2O_4)_3]\cdot 8H_2O$ **3A**. Selected bond lengths [Å]: Bi(1)-O(1) 2.51(1); Bi(1)-O(3) 2.37(1); Bi(1)-O(5) 2.54(1); Bi(1)-O(8) 2.43(1); Bi(1)-O(9) 2.41(1); Bi(1)-O(11) 2.48(1); Bi(1)-O(13) 2.49(2); Bi(1)-O(14) 2.52(2); Bi(2)-O(2) 2.55(1); Bi(2)-O(4) 2.42(2); Bi(2)-O(6) 2.33(1); Bi(2)-O(7) 2.43(1); Bi(2)-O(10) 2.33(1); Bi(2)-O(12) 2.60(1); Bi(2)-O(15) 2.53(1); Bi(2) O(16) 2.57(1).

the solid state, and is in excess in the preparation of **3A**, as shown in the following proposed reaction equation sequence:

2.1) $2\ BiCl_3 + 2\ H_2O \rightarrow 2\ BiOCl + 4\ HCl$

3.12) $2\ BiOCl + 3\ H_2\underline{ox} \rightarrow Bi_2(\underline{ox})_3 + 2\ HCl + 2\ H_2O$

3.13) $2\ BiCl_3 + 3\ H_2\underline{ox} \rightarrow Bi_2(\underline{ox})_3 + 6\ HCl$

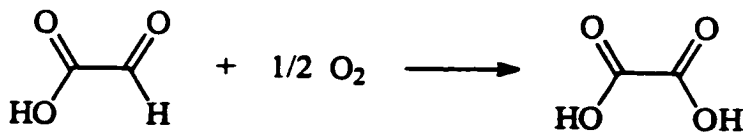
Attempts to isolate products from reactions involving bismuth nitrate or bismuth oxide were unsuccessful. In reactions involving bismuth chloride, generation of hydrochloric acid during the reaction may allow for an effective decrease of pH below ~1.3 (pK_{a1} of oxalic acid), the approximate pH at which bismuth subnitrate crystals have been isolated,[24,80,81] and a minimization of hydrolysis reactions. Also, the increased aqueous solubility of Bi^{3+} in the presence of chloride anion (Chapter 2) may facilitate crystal growth. The low yield of the isolated product precludes definitive conclusions regarding the bulk reaction. Nevertheless, the isolation of the parent oxalate is an important observation.

Interestingly, **3A** was also isolated in low yield from the reaction of $BiCl_3$ with excess glyoxylic acid after prolonged exposure to air. Aldehydes may be oxidized to carboxylic acids in the presence of mild oxidizing agents, such as Ag_2O in basic media (see equation 3.14).[372] In this case, the oxidizing agent is presumably O_2, which is a stronger oxidizing agent than BiO^+ under acidic conditions (see equations 3.15 and 3.16, respectively).[373]

3.14) $Ag_2O + H_2O + 2e^- \rightleftharpoons 2\,Ag + 2\,OH^-$ (E° +0.342V)

3.15) $O_2 + 4\,H^+ + 4\,e^- \rightleftharpoons 2\,H_2O$ (E° +1.229V)

3.16) $BiO^+ + 2H^+ + 3e^- \rightleftharpoons Bi + H_2O$ (E° +0.32V)



glyoxylic acid oxalic acid

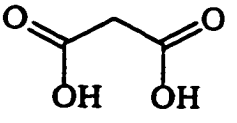
Monocarboxylates (e.g. formate **301**, acetate **302**) have been prepared by dissolving bismuth oxide in neat or concentrated acid (reaction 3.1).[347,348] The liquid state of these acids at room temperature allows for the essential absence of water and higher isolated yields. Solid acids, such as oxalic acid, require the presence of water as a reaction medium. This has been circumvented in the preparation of bismuth benzoate **310**, which involves ligand exchange of bismuth acetate with molten benzoic acid (mp 122.4°C) with distillation of the acetic acid by-product.[344] High yields are also obtained in the preparation of inorganic bismuth salts from concentrated strong inorganic acids due to the high acidities (low pH) achieved.

3.4 Conclusions and Future Directions

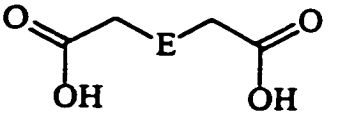
The preliminary isolation of the parent bismuth oxalate **3A** from acid solutions containing chloride anion illustrates a possible general synthetic route to the synthesis of bismuth carboxylates. The acidic reaction conditions prevent the formation of polymeric

and insoluble bismuth hydrolysis products, while the presence of the chloride anion may assist in preventing hydrolysis and solubilizing the Bi^{3+} cation.

Foremost to the continuation of this project is a comprehensive assessment into the effect of pH and chloride ion concentration on the formation of bismuth oxalate and other dicarboxylates (e.g. malonic acid, diglycolic acid and thiodiglycolic acid). This



malonic acid

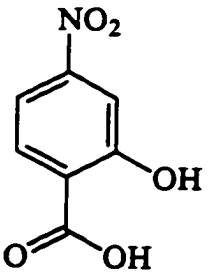


E = O, diglycolic acid
= S, thiodigylcolic acid

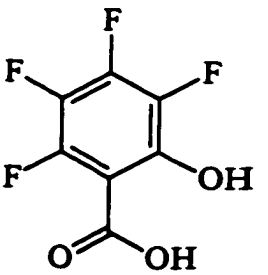
may be achieved through the addition of concentrated hydrochloric and nitric acid in various ratios. Lower pH conditions may facilitate the isolation of higher product yields, while the presence of excess chloride ion may promote the formation of various chemically interesting chloride/carboxylate products. Further, comparisons to reactions involving monocarboxylates would provide insight into the importance of the chelate ability of the ligand in product formation.

The polyprotic nature of lactic, malic and tartaric acids allows for the potential isolation of a variety complexes with bismuth. However, few examples (one or two for each ligand) have been structurally characterized (see Chapter 2) and there have been no systematic studies exploring sequential deprotonation. Again, the effect of reaction pH conditions, Bi^{3+} concentration and chloride ion concentration, as well as the chelate ability of these hydroxy-carboxylate ligands, on product formation must be determined. Further, systems involving other medicinally relevant ligands such as salicylic, citric and gallic acid must be examined.

In light of the prominence of the salicylate ligand in medical applications of bismuth, novel approaches to investigating these complexes are of immense interest. An alternative to the addition of excess mineral acid to increase solution acidity, salicylic acid may be derivatized to decrease its inherent pK_a value. This may be achieved through the substitution of electron withdrawing groups on the aromatic ring, such as a nitro-group in the *para* position to the carboxylic acid functionality (structure **I**) or fluorination of the aromatic ring (structure **II**).



I



II

Despite over 100 years of existence and medicinal utility, the structure of BSS has not yet been determined due to the insolubility of the compound. As of yet, only submicroscopic size crystals have been obtained, which have insufficient dimensions for X-ray diffraction studies. Three compounds closely related to BSS that have been structurally characterized are bismuth "sub"acetate **319**,[346] bismuth benzoate **310**[344] and bismuth thiosalicylate **548**,[374] however, only a preliminary structure was proposed for the subacetate. Since the subacetate and the "sub"formate, prepared in the same study, remain the only bismuth "sub"carboxylates that have been crystallized, a comprehensive reassessment of these preliminary results and a complete structural characterization may provide insight into the structures of this class of compounds and their relationship to the structures of subnitrates, which also contain a labile anion. Further, the techniques

employed to prepare bismuth subacetate could possibly be applied in preparing crystals of the "sub"salicylate, of sufficient size for crystallographic studies and structural characterization. A similar approach may yield isolates of the medicinally relevant and as of yet not structurally characterized "sub"gallate.

Chapter 4. Aminocarboxylates: New Investigations into the Bi-edta System Including Isolation of the First Cationic Complex

4.1 Introduction

H_4edta is a strong chelator of most metals including bismuth, and the Bi-edta system has been extensively studied in the solid state and superficially in solution. The Bi-edta complex is an analogous polycarboxylate system to the Bi-citrate system and is more soluble and rigid under various pH conditions, making it an excellent candidate model for the solution chemistry of CBS.

Polyaminocarboxylates, such as H_4edta, are derivatives of α-amino acids, the building blocks of proteins, and are themselves of biological interest. The cytoprotective nature of commercial bismuth products is believed to lie in the ability of bismuth to bond to protein molecules of exposed tissue,[264] and any chemical insight into bismuth-aminocarboxylate systems is therefore of value.

This chapter introduces the established syntheses and structures of bismuth polyaminocarboxylates, followed by the synthesis and structural characterization of the first cationic Bi-edta species $\{[Bi(Hedta)]_2H\}Cl \cdot 2H_2O$ **4A**. A preliminary ESI-MS study of the Bi-edta system, at low and high pH values, is also presented.

4.2 Synthesis and Structure of Bismuth-Aminocarboxylates

Several examples of bismuth polyaminocarboxylates have been prepared, the majority of which are edta complexes, and employ ligands which possess wide variations in chelate ability (i.e. number of functional groups). Derivatization of more common ligands

involves addition of a cyclohexyl ring to the hydrocarbon backbone (e.g. cydtpa) or substitution of acetate fragments for alkoxyethyl groups (e.g. oedta). The water solubility of bismuth polyaminocarboxylates increases with the number of carboxylate groups on the ligand, thereby facilitating crystal growth. However, yields are typically not reported and studies are commonly based on single crystal X-ray diffraction studies only. Characterization data for compounds discussed are contained in Table 4.1.

Bismuth polyaminocarboxylates are typically prepared by heating under reflux a suspension of a basic inorganic bismuth salt such as Bi_2O_3, $Bi(OH)_3$ or $(BiO)_2CO_3$ with the appropriate ligand in water. Addition of base, such as guanidinium carbonate or an alkali hydroxide, to the reaction mixture affords the anionic salt in most cases. The neutral dihydrated [Bi(Hedta)$(H_2O)_2$] **411**[375,376] and non-hydrated[377] complexes are reportedly synthesized by analogous reactions involving bismuth subcarbonate and bismuth hydroxide, respectively, while bismuth nitrilotriacetate dihydrate (H_3nta) [Bi(nta)$(H_2O)_2$] **406**[375,382] and the trihydrated product[396] are also isolated from similar reactions. The trihydrated product was characterized by elemental analysis and infrared spectroscopy only. The dihydrated

Table 4.1 Analytical data for aminocarboxylate compounds.

Compound	yield (rxn 4.*n*)*	XR	EA	IR	UV	NMR	MS	TGA	pot
[Bi(qui)$_3$$(H_2O)_2$] **401**[358]	80 (1)	-	x	x	-	-	-	-	-
[Bi(pdc)(Hpdc)(dmso)] **402**[378]	-(2)	x	-	x	-	-	-	-	-
[Bi(onda)$(H_2O)_2$] **403**[379]	-(-)	x	-	-	-	-	-	-	-
[NH_4][Bi(Honda)$_2$$(H_2O)_3$] **404**[380]	-(-)	x	-	-	-	-	-	-	-
[$C(NH_2)_3$]$_2$[Bi(onda)(Honda)$(H_2O)_3$] **405**[380]	-(-)	x	-	-	-	-	-	-	-

Table 4.1 Analytical data for aminocarboxylate compounds (continued).

Compound	yield (rxn 4.*n*)*	XR	EA	IR	UV	NMR	MS	TGA	pot
[Bi(nta)(H$_2$O)$_2$] **406**[375]	- (3,4)	x	x	-	-	-	-	-	-
[NH$_4$]$_3$[Bi(nta)$_2$] **407**[381,381]	- (5)	x	-	-	-	-	-	-	-
[NH$_4$]$_4$[Bi(nta)$_2$(NCS)]•2H$_2$O **408**[382]	- (6)	x	-	-	-	-	-	-	-
[Bi(Hoedta)(H$_2$O)] **409**[376,383]	- (1)	-	x	x	x	-	-	x	x
[NaBi(oedta)(H$_2$O)$_4$] **410**[383]	- (7)	-	x	-	x	-	-	x	x
[Bi(Hedta)(H$_2$O)$_2$] **411**[384,385]	- (3)	x	x	x	-	-	-	-	-
[Bi(Hedta)] **412**[386]	- (4)	x	-	-	-	-	-	-	-
[Bi(Hedta)(tu)$_2$] **413**[387]	-(8)	x	-	-	-	-	-	-	-
[C(NH$_2$)$_3$][Bi(edta)H$_2$O] **414** [388]	- (9)	x	x	-	-	-	-	-	-
[Ca(H$_2$O)$_7$][Bi(edta)]$_2$•2H$_2$O **415**[389]	-(10)	x	-	-	-	-	-	-	-
[Co(H$_2$O)$_6$][Bi(edta)]$_2$•3H$_2$O **416**[390]	- (7)	x	-	-	-	-	-	-	-
[Ni(H$_2$O)$_6$][Bi(edta)]$_2$•3H$_2$O **417**[390]	- (7)	x	-	-	-	-	-	-	-
[NaBi(edta)(H$_2$O)$_3$] **418**[391]	- (11)	x	x	-	-	-	-	x	-
[NH$_4$][Bi(edta)(H$_2$O)] **419**[386]	- (12)	x	-	-	-	-	-	-	-
[Bi(Hcydta)(H$_2$O)$_5$] **420**[392]	- (3)	x	x	x	-	-	-	-	-
[Bi(H$_2$dtpa)(H$_2$O)$_2$] **421**[376,393]	47 (13,14)	x	x	x	-	x	x	-	-
[Bi(Na$_2$dtpa)(H$_2$O)$_4$] **422**[376]	- (7)	-	x	x	-	-	-	-	-
[C(NH$_2$)$_3$]$_2$[Bi(dtpa)(H$_2$O)$_4$] **423**[375]	- (15)	x	x	-	-	-	-	-	-
[KBi(Hdtpa)(H$_2$O)$_5$] **424**[394]	- (-)	x	-	-	-	-	-	-	-
[C(NH$_2$)$_3$]$_2$[Bi(cydtpa)] **425**[393]	82 (15)	x	x	-	-	x	-	-	-
[Bi(H$_3$ttha)(H$_2$O)$_3$] **426**[392]	- (3)	x	x	x	-	-	-	-	-
[C(NH$_2$)$_3$]$_2$[Bi(Httha)(H$_2$O)$_4$] **427**[395]	- (15)	x	x	-	-	-	-	-	-

*Syntheses:

4.1) $Bi_2O_3 + 6\,HL \rightarrow 2\,BiL_3 + 3\,H_2O$

4.2) $Bi_2O_3 + 4\,H_2L + 2\,L' \rightarrow 2\,[Bi(HL)(L)(L')] + 3\,H_2O$

4.3) $(BiO)_2CO_3 + 2\,H_{3+n}L \rightarrow 2\,Bi(H_nL) + H_2CO_3 + 2\,H_2O$

4.4) $Bi(OH)_3 + H_{3+n}L \rightarrow [Bi(H_nL)] + 3\,H_2O$

4.5) $Bi(OH)_3 + 2\,H_3L + 3\,NH_4OH \rightarrow [NH_4]_3[Bi(L)_2] + 6\,H_2O$

4.6) $Bi(OH)_3 + 2\,H_3L + 4\,NH_4SCN \rightarrow [NH_4]_4[Bi(L)_2(NCS)] + 3\,HSCN + 3\,H_2O$

4.7) $m\,BiL + n\,M(OH)_m \rightarrow M_n[Bi(L\text{-}nH)]_m + mn\,H_2O$

4.8) $Bi(HL) + 2\,L' \rightarrow [Bi(HL)(L')_2]$

4.9) $2\,BiF_3 + 2\,H_4L + [C(NH_2)_3]_2CO_3 \rightarrow 2\,[C(NH_2)_3][Bi(L)] + 6\,HF + H_2CO_3$

4.10) $2\,Bi(HL) + MCO_3 + 7\,H_2O \rightarrow [M(H_2O)_7][Bi(L)]_2 + H_2CO_3$

4.11) $(BiO)_2CO_3 + 2\,H_4L + Na_2CO_3 \rightarrow 2\,[NaBi(L)] + 2\,H_2CO_3 + 2\,H_2O$

4.12) $Bi(OH)_3 + H_4L + NH_4OH \rightarrow [NH_4][Bi(L)] + 4\,H_2O$

4.13) $Bi(ClO_4)_3 + Na_3L \rightarrow Bi(L) + 3\,NaClO_4$

4.14) $Bi(NO_3)_3 + H_3L + 3\,NaOH \rightarrow BiL + 3\,NaNO_3 + 3\,H_2O$

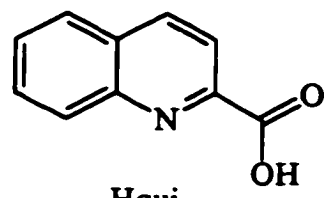
4.15) $(BiO)_2CO_3 + 2\,H_5L + 2\,[C(NH_2)_3]_2CO_3 \rightarrow 2\,[C(NH_2)_3]_2[Bi(L)] + 3\,H_2CO_3 + 2\,H_2O$

edta sodium salt $[NaBi(\underline{edta})(H_2O)_2]$[376] is reportedly prepared by adding an aqueous NaOH solution to a suspension of [Bi(H<u>edta</u>)], though the compound has not been comprehensively characterized. The sodium $[Bi(Na_2\underline{dtpa})(H_2O)_4]$ **422**[376] and guanidinium $[C(NH_2)_3]_2[Bi(\underline{dtpa})(H_2O)_4]$ **423**[375] salts are prepared from the neutral complex **421**, and the high water solubility in comparison to similar bismuth polycarboxylates is accredited to its anionic nature.

Complexes involving edta have been most extensively characterized[397,398] and include examples of both hydrated[209,384,399-401] and non-hydrated[402,399,400] [Bi(Hedta)], as well as the Na,[376,391,401] K,[399] NH_4,[386,399] Mg,[403] Ca,[389,403] Sr, Ba, Ni, Zn, Cd,[403] Co,[390,403] Cu[404] and Mo[390] salts of the $[Bi(edta)]^-$ anion, as well as the potassium fluoride complex $K_2[Bi(edta)F]\bullet 3H_2O$.[399] The extensive X-ray structural studies[209,384,389,390,400,404] include several examples of [Bi(Hedta)] (**411-13**) and $[Bi(edta)]^-$ (**414-19**) complexes.

Aminocarboxylate ligands typically exhibit maximum chelation with bismuth, forming five-membered -BiNCCN- and/or -BiNCCO- rings. The large covalent radius of bismuth (1.52Å) allows for chelation of ligands in the bidentate to decadentate range. Additional coordination sites are typically occupied by oxygen atoms of water molecules or exocyclic carboxylate oxygen atoms of neighbouring molecules, creating polymeric structures.

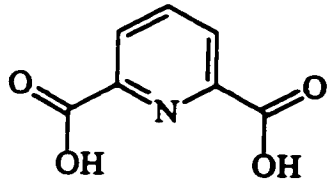
A structure containing three -BiNCCO- five-membered chelate rings has been proposed for the quinaldic acid (Hqui) complex $[Bi(qui)_3(H_2O)_2]$ **401**[358] from comparison of infrared spectra with previously characterized compounds.



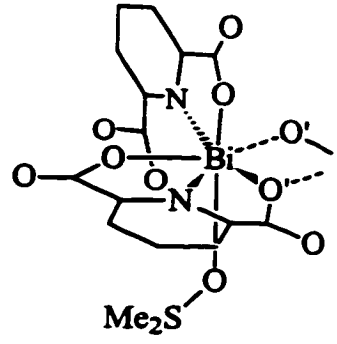
Hqui

The pyridine-2,6-dicarboxylic acid (H_2pdc) complex [Bi(pdc)(Hpdc)(dmso)] **402**[378] shows the bismuth center chelated by both an *N,O*-bidentate $(Hpdc)^-$ ligand and an *O,N,O'*-tridentate $(pdc)^{2-}$ ligand [Bi-O 2.209(8)-2.507(6); Bi-N 2.418(9) and 2.481(9)Å]. An *O*-dmso molecule in the remaining axial site [Bi-O 2.61(1)Å] and a long carboxylate oxygen

contact from a neighbouring molecule [Bi-O 2.578(4)Å] create a centrosymmetric dimeric structure and a seven coordinate distorted pentagonal bipyramidal geometry for bismuth. The protonated carboxylate group [Bi-O 2.738(6)Å] is not considered to be bonded to bismuth.

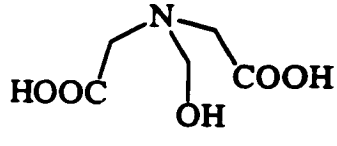


H_2pdc

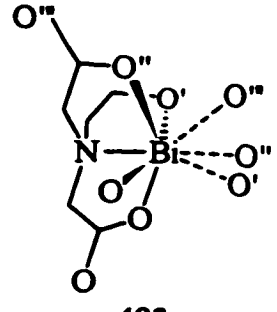


402

In the neutral *N*-hydroxyethylnitrilodiacetic acid (H_3onda) complex [Bi(onda)$(H_2O)_2$] **403**[379] the $(onda)^{3-}$ ligand chelates bismuth in a tetradentate manner [Bi-N 2.49(2); Bi-$O_{carboxylate}$ 2.33(1) and 2.34(1); Bi-$O_{alkoxide}$ 2.14(1)Å]. A long alkoxide oxygen (O') contact from a neighbouring molecule creates dimers [Bi---O 2.46(1)Å], which in turn are linked by long carboxylate oxygen contacts of other dimers [Bi-O 2.70(1) and 2.98(1)Å]



H_3onda

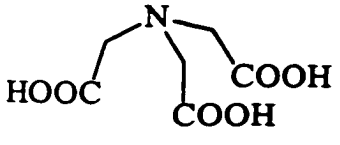


403

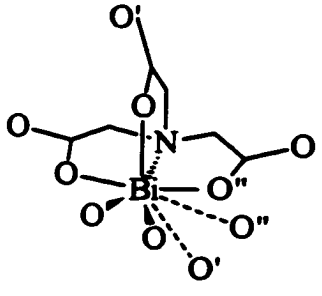
to form a layered structure. A water molecule [Bi-O 2.77(2)Å] completes the coordination sphere and gives an eight coordinate distorted bicapped trigonal prismatic geometry for bismuth. The ammonium and guanidinium salts $[NH_4][Bi(Honda)_2(H_2O)_3]$ **404**[380] and

$[C(NH_2)_3]_2[Bi(\underline{onda})(H\underline{onda})(H_2O)_3]$ **405**[380] also show the $(H\underline{onda})^{2-}$ ligand chelating in a tetradentate fashion, despite the lower basicity of the hydroxy- group in comparison with the alkoxide.

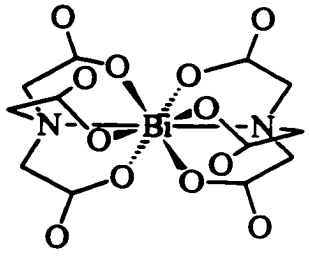
$[Bi(\underline{nta})(H_2O)_2]$ **406**[375] shows the bismuth center chelated in tetradentate fashion by one $(\underline{nta})^{3-}$ ligand [Bi-N 2.500(8); Bi-$O_{carboxylate}$ 2.258(6)-2.253(7)Å]. Two intermolecular contacts [Bi---O 2.665(6) and 2.435(6)Å] from a neighbouring molecule create a dimeric unit. The eight coordinate bicapped trigonal prismatic coordination sphere is completed by the oxygen atoms of two water molecules [Bi-O_{water} 2.403(6), 2.767(9)Å]. The monomeric anion of $[NH_4]_3[Bi(\underline{nta})_2]$ **407**[381,381] shows bismuth bound in



$H_3\underline{nta}$



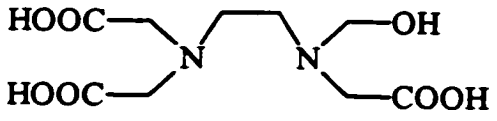
406



407

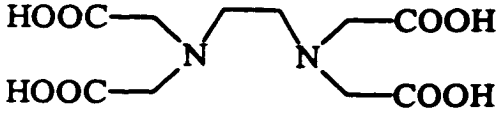
a tetradentate fashion by two $(\underline{nta})^{3-}$ ligands [Bi-N 2.58(1) and 2.60(2); Bi-O 2.44(1) and Bi-O 2.40(1)Å], giving a total coordination number of eight for bismuth and a doubly-capped trigonal prism geometry. The structure of the bis(nta) thiocyanate compound $[(NH_4)_4Bi(\underline{nta})_2(NCS)(H_2O)]$ **408**[382] is analogous [Bi-O 2.363(4)-2.551(5); Bi-N 2.605(4)Å], but also incorporates an *N*-isothiocyanate ligand [Bi-N 2.71(1)Å] into the bismuth coordination sphere, giving a nine-coordinate distorted tricapped trigonal prism geometry at bismuth.

The *N*-hydroxyethylethylenediaminetriacetic acid (H_4oedta) compound [Bi(Hoedta)(H_2O)] **409**[376,383] and the sodium salt [NaBi(oedta)(H_2O)$_4$] **410**[383] have not been structurally characterized.

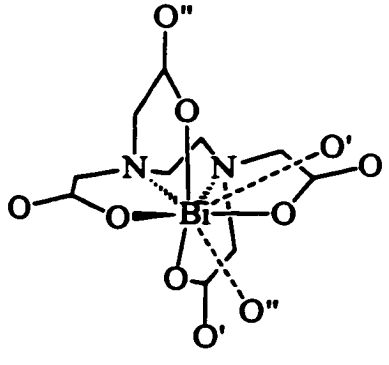


H_4oedta

Several bismuth complexes of ethylenediaminetetraacetic acid (H_4edta) have been studied by X-ray methods,[209,384,389,390,400,400,404] and all contain a hexadentate (Hedta)$^{3-}$or (edta)$^{4-}$ ligand. The structure of [Bi(Hedta)(H_2O)$_2$] **411**[384,385] shows the (Hedta)$^{3-}$ ligand [Bi-N 2.396(10) and 2.577(9); Bi-O 2.295(7)-2.700(10)Å]. The coordination sphere is again completed by two carboxylate oxygen atoms of a neighbouring molecule [Bi---O 2.678(7)- 2.697(8)Å], forming a dimer structure. The result is an eight coordinate bicapped trigonal prism geometry for bismuth.[388] The dehydrated analogue [Bi(Hedta)]



H_4edta

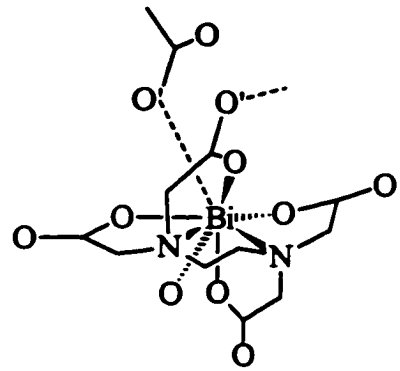


411

412[386] [Bi-N 2.465(5); Bi-O 2.399(3)-2.472(4)Å] also shows two long oxygen contacts, but from different neighbouring molecules [Bi---O 2.617(5)Å]. This creates a one-dimensional polymeric chain arrangement and a distorted square antiprism geometry at bismuth. The introduction of thiourea into the coordination sphere [Bi-S 3.035(4)Å] in

the adduct [Bi(Hedta)(tu)$_2$] **413**[387] [Bi-N 2.510(7); Bi-O 2.378(7) and 2.521(9)Å] prevents intermolecular coordinations and results in a monomeric structure, bound only through hydrogen bonding.

In the [C(NH$_2$)$_3$][Bi(edta)(H$_2$O)] **414**[388] anion, bismuth is similarly chelated in a hexadentate fashion but by (edta)$^{4-}$ [Bi-N 2.56(1) and 2.59(2); Bi-O 2.34(1)-2.46(1)Å]. A long Bi---O contact to and from two separate neighbouring molecules [Bi---O 2.70(1)Å] forms an infinite anionic chain. A bound water molecule [Bi-O 2.69(1)Å] gives a total coordination number of eight for bismuth and a distorted square antiprism

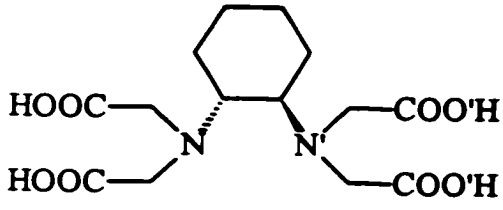


414

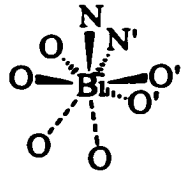
geometry. The calcium salt [Ca(H$_2$O)$_7$][Bi(edta)]$_2$•2H$_2$O **415**[389] [Bi-N 2.460(6) and 2.543(6); Bi-O 2.360(6)-2.463(7)Å] attains a similar polymeric chain structure, however, the absence of the water molecule in the bismuth coordination sphere allows for a second Bi---O long contact [Bi---O 2.778(6) and 3.038(7)Å] between monomers. Analogous structures are observed for the isostructural transition metal salts [Co(H$_2$O)$_6$][Bi(edta)]$_2$•3H$_2$O **416** and [Ni(H$_2$O)$_6$][Bi(edta)]$_2$•3H$_2$O **417**.[390] The sodium salt [NaBi(edta)(H$_2$O)$_3$] **418**[391] [Bi-N 2.495(5) and 2.508(5); Bi-O 2.315(4)-2.521(4); Bi---O 2.636(4) and 2.850(7)Å] and ammonium salt [NH$_4$][Bi(edta)(H$_2$O)] **419**[386] [Bi-N

2.479(9) and 2.490(10); Bi-O 2.290(9)-2.494(8); Bi---O 2.792(9) and 2.805(8)Å] also show two long Bi---O contacts from two neighbouring monomers, but in these cases a layered structure is created.

[Bi(Hcydta)$(H_2O)_5$] **420**[392] displays a similar bonding situation to the edta analogue **414** [Bi-N 2.491(11)-2.513(10); Bi-O 2.286(9)-2.497(11)Å]. Long Bi---O contacts from two neighbouring molecules [Bi---O 2.612(9)-2.916(10)Å] create a polymeric network.

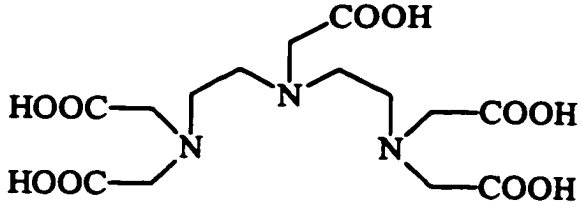


H_4cydta



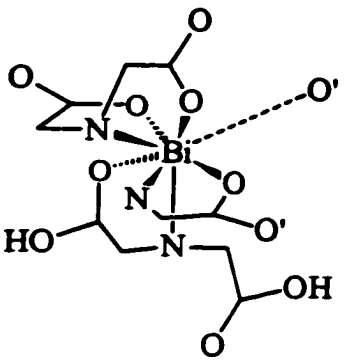
420
(Bi bonding environment)

[Bi(H_2dtpa)$(H_2O)_2$] **421**[376,393] shows the $(H_2dtpa)^{3-}$ ligand chelating in a heptadentate manner with one uncoordinated acetate group [Bi-N 2.449(4)-2.723(4)Å; Bi-O 2.290(3)-2.699(3)Å]. An eighth coordination site is occupied by a long Bi---O contact from a

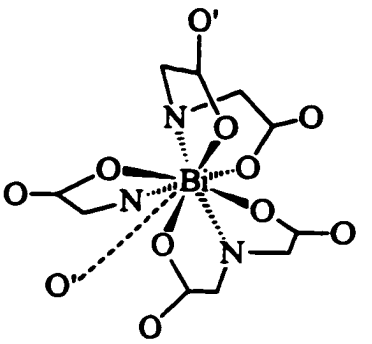


H_5dtpa

neighbouring molecule [Bi-O 2.620(3)Å], giving rise to an infinite polymeric chain and a bicapped trigonal prism environment for bismuth. The guanidinium salt $[C(NH_2)_3]_2$[Bi(dtpa)$(H_2O)_4$] **423**[375] shows that the $(dtpa)^{5-}$ ligand chelates in an octadentate manner [Bi-N 2.536(7)-2.639(6); Bi-O 2.368(5)-2.599(5)Å]. The coordination sphere is completed by an oxygen atom from an adjacent molecule [Bi---O 2.686(6)Å], creating a



421

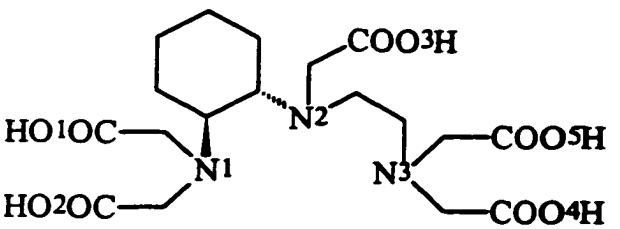


423

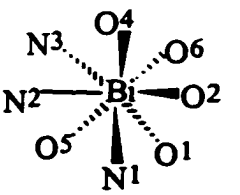
(CH_2CH_2 backbone omitted)

dimeric structure and a nine-coordinate monocapped square antiprism environment for bismuth. The potassium salt [KBi(Hdtpa)$(H_2O)_5$] **424**[394] shows a similar octadentate chelating situation, but with a water oxygen atom completing the coordination sphere and a monomeric structure.

In $[C(NH_2)_3]_2$[Bi(cydtpa)] **425**,[393] $(cydtpa)^{5-}$ chelates in an octadentate manner [Bi-N 2.458(5)-2.592(5); Bi-O 2.371(4)-2.610(4)Å] giving a monomeric structure. Here, bismuth is in an eight coordinate environment, which may be derived from a square antiprism.



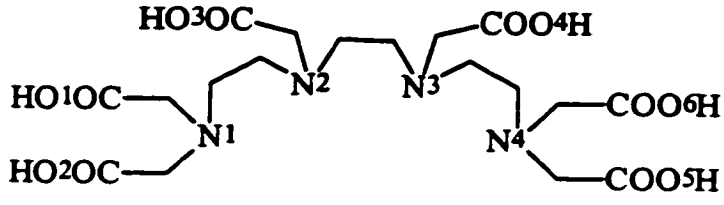
H_5cydtpa



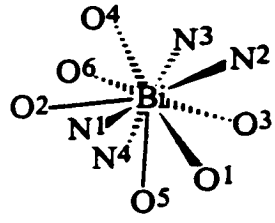
425

(Bi bonding environment)

[Bi(H_3ttha)$(H_2O)_3$] **426**[392] shows the $(H_3ttha)^{3-}$ ligand chelating in a decadentate manner [Bi-N 2.472(8)2.813(8); Bi-O 2.320(7)-3.055(8)Å]. The coordination geometry around bismuth may be described as distorted bicapped square antiprism, with the two external nitrogen atoms (N^1 and N^4) in capping positions. This is the first example of a



H_6ttha



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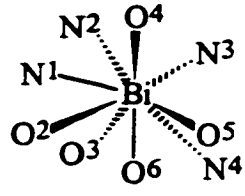


427

(Bi bonding environment)

polyaminocarboxylate complex with coordination number ten. The bis(guanidinium) salt $[C(NH_2)_3]_2[Bi(H$ttha$)(H_2O)_4]$ **427**[395] shows (Httha)$^{5-}$ chelating in only a nonadentate manner, with one noncoordinated carboxylic acid group (O^1) [Bi-N 2.619(7)-2.688(7); Bi-O 2.327(6)-2.560(6)Å].

4.3 Results and Discussion

4.3.1 Synthetic Studies

Hydrogen bis(bismuth hydrogen *N,N,N',N'*-ethylenediaminetetraacetate) chloride dihydrate $\{[Bi(H$edta$)]_2H\}Cl\bullet 2H_2O$ **4A** (Figure 4.1) is formed from the stoichiometric reaction of H_4edta and bismuth(III) chloride in water with addition of KOH. The isolation of the product from reaction mixtures containing 1-4 equivalents of KOH demonstrates the favorable crystallization of this structure and the resistance of the Bi-edta hexaadentate unit to small pH changes. However, reactions involving 0.5 and 5 equivalents of base gave non-crystalline materials, which were not definitively

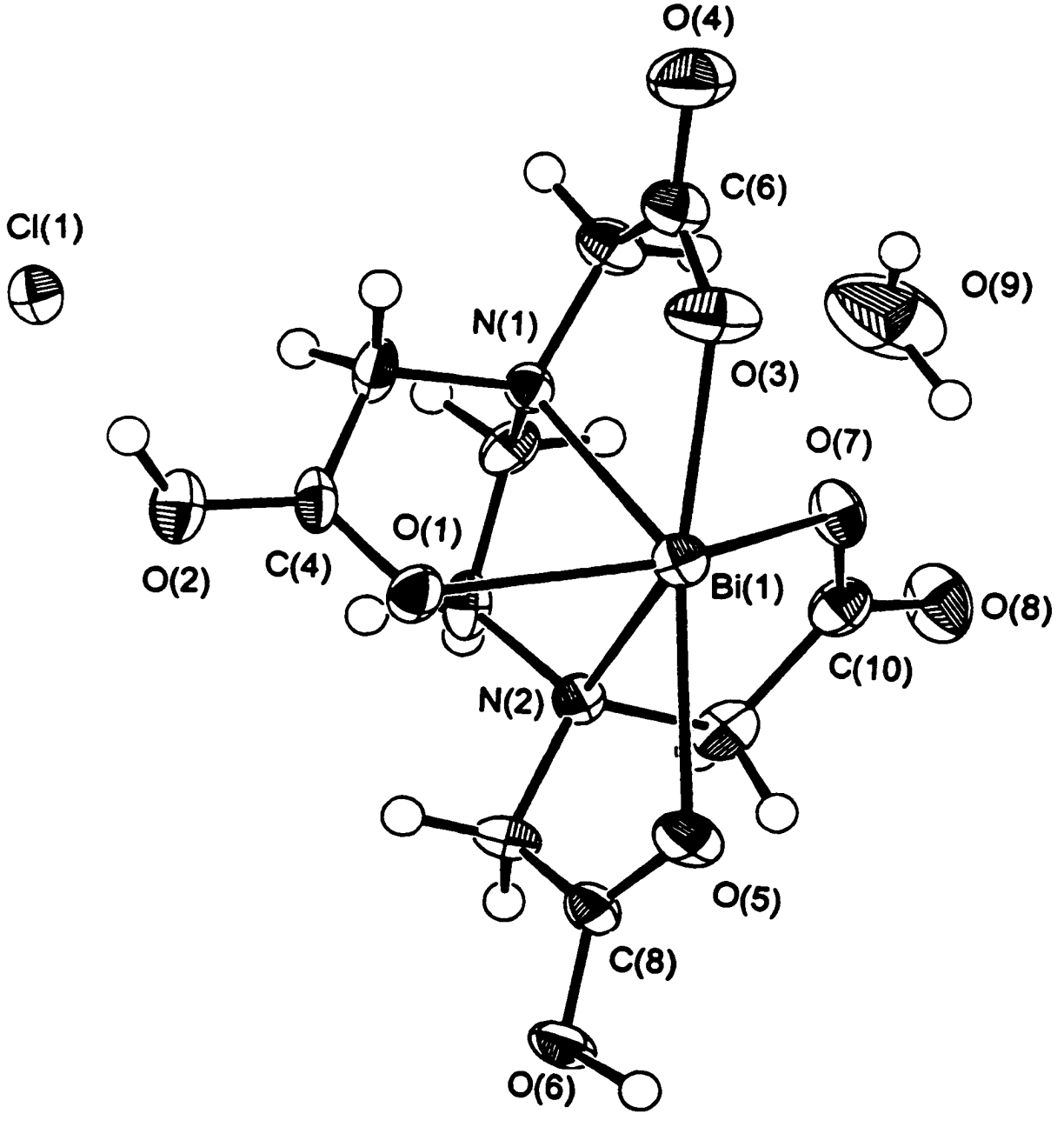
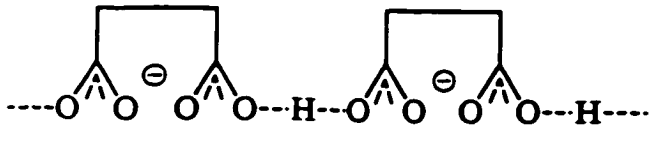


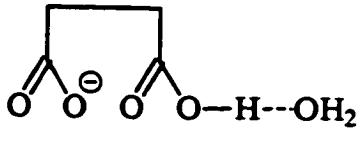
Figure 4.1 Crystallographic view of $\{[Bi(\underline{Hedta})]_2H\}Cl \cdot 2H_2O$ **4A**.

characterized but were determined by Raman spectroscopy not to be the said product. Reactions of bismuth subcarbonate typically yield the [Bi(Hedta)] hydrated species, while addition of a strong base such as guanidinim carbonate gives deprotonated anionic species. The favorable crystallization of the cationic complex **4A** is possibly a consequence of the presence of the chloride anion.

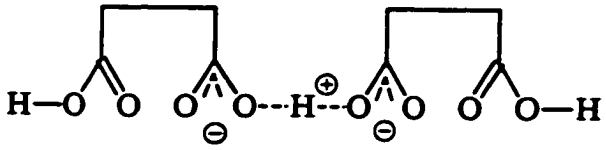
The solid state structure of **4A** (see Figure 4.1) shows edta bonding to bismuth in the familiar hexadentate manner. The absence of chlorine or water or long (Bi---O) intermolecular contacts results in unusually low coordination number of six for bismuth. Two neighboring [Bi(Hedta)] units are bound at O(6) to a common hydrogen atom (proton). This hydrogen bonding phenomenon is characteristic of metal-polyaminocarboxylate complexes and has been dubbed the "odd proton effect",[405] with two of the three examples of complexes involving $(Hedta)^{3-}$ exhibiting this feature. In the case of [Bi(Hedta)] **412** and the thiourea adduct **413**,[387] the "odd-proton" occupies an inversion center and each molecule contains two "half-protonated" carboxylate groups, resulting in the formation of hydrogen bound chains, schematically represented by **III**. The dihydrate **411** exhibits a specific location for the proton on a single carboxylate group, which is hydrogen bound to a water molecule and terminates the system (see diagram **IV**). For compound **4A**, the odd-proton is located on a C_2 axis between two Bi(Hedta) units without further perpetuation, and a fully protonated carboxylate group is expected for each moiety of the cationic dinuclear unit (see diagram **V**), such as that



III



IV



V

observed for **411**.

X-ray crystallographic data suggests that the proton exclusive to each mononuclear unit is bound at the exocyclic carboxylate oxygen O(2) and not the water molecule, though this could not be determined with certainty. The C-O bond lengths may be examined for clues to identify the remaining protonated groups (Table 4.2). For [Bi(H<u>edta</u>)(H_2O)$_2$] **411**,[384,385] the position of the hydrogen atom was inferred from the equivalence of the carbon-oxygen bond distances of the three deprotonated carboxylate groups, which is interpreted as conjugation of the double bond after deprotonation, and the nonequivalence of those in the fourth carboxylate group. No such conjugation is observed in <u>**4A**</u>, however, with the C-O bond distance discrepancy being ~0.04Å for three carboxylate groups and ~0.06Å for the fourth [C(6)]. Further, of the carboxylate groups in question, bond distances suggest greater double bond character (i.e. shorter bond distances) for all exocyclic oxygen atoms. In both <u>**4A**</u> and **411** the bismuth center sits asymmetrically in the O_4N_2 cavity and is more closely bound to three carboxyl oxygen atoms and one nitrogen atom. In the case of **411**, the carboxylic acid group is tightly bound to the bismuth center, and therefore is not an indicator as to which group is protonated. From a chemical standpoint, a hydrogen atom at O(2) would allow for hydrogen bonding of the chlorine atom to the <u>edta</u> ligand and is therefore a logical site for the proton.

Table 4.2 Selected bond lengths for [Bi(Hedta)] complexes.

4A					411	412
C(4)-O(1)	1.2633(3)	Bi(1)-O(1)	2.3376(4)	Bi-O	2.306(9)	2.399(3)
C(4)-O(2)	1.2267(2)					
C(6)-O(3)	1.2853(3)	Bi(1)-O(3)	2.3619(9)	Bi-O	2.400(9)	
C(6)-O(4)	1.2224(5)					
C(8)-O(5)	1.2446(2)	Bi(1)-O(5)	2.5594(9)	Bi-O	2.642(9)	2.472(4)
C(8)-O(6)	1.2838(4)					
C(10)-O(7)	1.2854(4)	Bi(1)-O(7)	2.3203(5)	Bi-O	2.295(7)	
C(10)-O(8)	1.2459(3)					
		Bi(1)-N(1)	2.4603(5)	Bi-N	2.461(8)	2.465(5)
		Bi(1)-N(2)	2.5345(5)		2.577(9)	

As discussed in Chapters 2 and 3, the hydrolysis of Bi^{3+} to BiO^{+} in all but strongly acidic conditions typically deters the formation of soluble bismuth tris(carboxylates) in aqueous media. The significance of pK_a in the preparation of aminocarboxylates has been alluded to as the pretense for the failed isolation of a bismuth picolinic or dipicolinic acid complex (i.e. pK_a of ~5 is too weak to react with bismuth subcarbonate), and in light of the successful preparation of nta, edta and dtpa complexes by similar methods.[384] However, the dipicolinic acid dmso adduct **402** was successfully prepared from the reaction of the acid and Bi_2O_3 in water, followed by further reaction and recrystallization of the resulting powder from hot dmso. This suggests that reaction in dmso is critical to isolation of the product, and the absence of excess water at this stage may allow for product formation. Further, the strong Lewis base character of dmso, which forms resilient complexes with bismuth, may aid in solvation of the Bi^{3+} cation. Although

ligand pK_a (pH of reaction mixtures) does play a role, the strong chelate ability of polyaminocarboxylates is most likely the dominant factor in the formation and stability of these compounds. The multidentate encapsulation of the bismuth center prevents formation of the BiO^+ bismuthyl ion in water. Therefore, bismuth complexes of bio-relevant α-amino acids, which possess high pK_a values relative to monocarboxylates (9.6 for glycine versus 4.7 for acetic acid) and the ability for bidentate chelation only, may not be prepared from aqueous media. Hydroxy-/alkoxycarboxylates, such as lactic, malic, tartaric and citric (CBS) acids are much weaker chelators for bismuth and complexation is expected to be much more sensitive to pH [e.g. citrate (CBS) requires an alkaline pH]. Only a small number of structures of this class of compound have been reported exclusively within the past decade.

4.3.2 Preliminary Electrospray Mass Spectrometry Studies of the Bi-edta System

Bismuth complexes are typically very insoluble and are subject to hydrolytic reactions. Collection of solution data therefore often requires sensitive techniques which lend themselves to nonspecific experimental conditions. Although Bi-carboxylate solution complexes have been examined by a variety of physical and spectroscopic techniques, none of these provide definitive formulae or structural data. Electrospray mass spectrometry (ESI-MS) involves the introduction of pre-formed ions in solution into the mass spectrometer. The subsequent separation of ions according to their mass to charge ratio, as well as their controlled fragmentation, provides ample information as to the identity of solution species.

Bismuth complexes of citrate are complex in the solid state, while the multidentate encapsulation of bismuth by edta allows for the formation of simpler [Bi(Hedta)] and [Bi(edta)]$^-$ units. This, along with the similar polycarboxylate structure of the two ligands, highlights the Bi-edta system as a simple model for studying the solution chemistry of the Bi-citrate system and Bi-carboxylate systems in general.

Preliminary positive ion ESI-MS spectra[406] of the Bi-edta complex at low pH (1.4) show peaks at m/z 499 (100% rel. intensity) and m/z 293 (95% rel. intensity) assigned to the [Bi(H_2edta)]$^+$ and [H_5edta]$^+$ cationic species, respectively. At high pH (10.0), the negative ion spectrum shows a peak at m/z 497 (100% rel. intensity) assigned to the [Bi(edta)]$^-$ anion. These results contrast speculative conclusions based on spectrophotometric and pH metric data that suggests the decomposition of the complex to the bismuthyl ion (BiO^+) below pH 1.5 and the formation of [Bi(edta)(OH)]$^{2-}$ in the pH range 8-11.[209]

4.4 Conclusions and Future Directions

The strong chelate ability of polyaminocarboxylate ligands allows for the formation of hydrolytically stable complexes with bismuth, while bifunctional aminocarboxylate ligands (e.g. glycine) possess insufficient acidity or chelate ability to deter hydrolytic reactions. Investigation into sequential protonation of bismuth polycarboxylates may provide further insight into the significance of pH and chelate ability on product formation. Further, preliminary investigations demonstrate the inherent utility of ESI-MS to study Bi-carboxylate systems in solution, which may be developed to

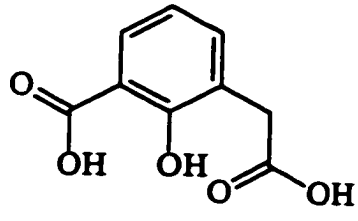
investigate the solution chemistry of CBS and other bismuth carboxylates and the resilience of dimeric and polymeric associations observed in the solid state.

Reaction of α-amino acids with bismuth salts under anhydrous conditions would eliminate the possibility for hydrolysis reactions associated with this system. This method has been employed successfully in the synthesis of an organobismuth complex of *N*-benzoylglycinate[407] and is a viable approach to preparing other stable amino acid complexes of bismuth.[408]

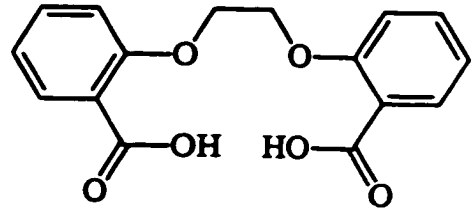
As with the study of bismuth complexes of α-amino acids, investigations involving di- and tripeptides would provide insight into bismuth-protein binding at ulcers and throughout the body. Further, the variety of functionalities associated with polypeptides creates the potential for interesting bonding situations. The only recent or significant study that has been undertaken involves the tripeptide glutathione and ranitidine bismuth citrate (RBC).[275] The thiolate (sulfhydryl) functionality was proposed as the only site of binding by ^{1}H NMR, but structural data could not be obtained. Reaction of glutathione with simpler bismuth starting materials (e.g bismuth halides) in a variety of pH conditions and solvents may allow for the isolation of chemically and structurally interesting products.

The insolubility of bismuth subsalicylate has prevented its structural characterization to date, and the favorable hydrolysis of bismuth salicylate compounds may be observed as a consequence of the weak chelate ability of the salicylate ion. Derivatization of the ligand to include additional carboxylate groups would increase the chelate ability of this ligand (cf. polyaminocarboxylates), possibly allowing for the formation of hydrolytically resistant and soluble products. Potential avenues of

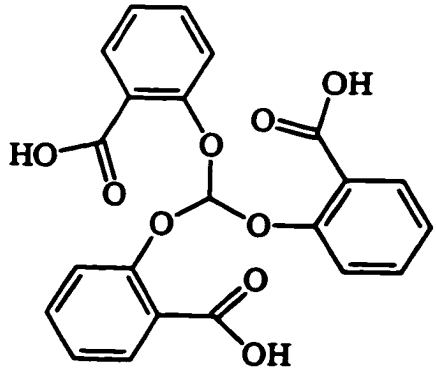
derivatization include addition of carboxylate groups to the salicylate phenyl ring (e.g. structure **VI**) or combination of two (e.g. structure **VII**) or more (e.g. structure **VIII**) carboxylate moieties:



VI



VII



VIII

As discussed in Chapter 2, the speciation of Bi^{3+} in acidic media is still a matter of debate.[94,95] ESI-MS, which now has a demonstrated utility for Bi-edta species in solution, may also prove advantageous over previously employed methods (e.g spectrophotometry,[209-213] and [209,215]potentiometic[207]) in the definitive identification of both positive ion and negative ion species preformed in solution.

Chapter 5. Introduction to Bismuth Thiolate Chemistry

5.1 Introduction

The prominent thiophilicity (the preference to form bonds to sulfur) of bismuth is responsible for the facile formation of sulfido and thiolato complexes, which are well established for most heavy metal elements.[409] Thiolatobismuth complexes represent the most extensive class of Bi(III) compounds for which a reliable set of data is available, and include examples of monothiolates, dithiolates and bifunctional ligands incorporating a thiolate group, as well as thio-substituted carboxylates. This chapter is provided as an introduction to the synthetic and structural chemistry of bismuth thiolates and as a background to the bifunctional thiolate chemistry discussed in Chapters 6 and 7 (for a more detailed and general overview of the structural features for bismuth complexes involving pnictogen and chalcogen donors see reference 410). A summary and conclusions regarding the extensive data presented is provided in section 5.5.

5.2 Monothiolates

Despite an extensive history, most examples of bismuth thiolates are poorly characterized, with the first structural studies of the more stable and soluble arythiolates occurring within the past decade.[411] Characterization data for bismuth-thiolate compounds are catalogued in Table 5.1.

Bismuth thiolates are typically prepared by reaction of the thiolate anion (generated *in situ*) with a bismuth salt, however, the thiol will also react with bismuth

Table 5.1 Analytical data for monothiolate compounds.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	IR	UV	NMR	MS	TGA
$Bi(SEt)_3$ **501**[412]	- (1)	-	x	-	-	-	-	-	-	-
$Bi(S^tBu)_3$ **502**[413,414]	100(2)	-	x	x	-	x	-	x	x	-
$Bi(SCH_2Ph)_3$ **503**[413,415]	61 (3), 72 (4)	-	x	-	-	x	x	x	-	x
$Bi(SPh)_3$ **504**[415,416]	79 (1)	x	x	x	x	x	-	-	-	x
$Bi(SC_6H_3Me_2\text{-}2,6)_3$ **505**[417]	78 (3)	-	-	x	-	-	-	x	-	-
$Bi(SC_6H_3Me_2\text{-}3,5)_3$ **506**[417]	49 (3)	-	-	x	-	-	-	x	-	-
$Bi(SC_6H_4Me\text{-}4)_3$ **507**[417]	62 (3)	-	-	x	-	-	-	x	-	-
$Bi(SC_6H_2Me_3\text{-}2,4,6)_3$ **508**[411]	86 (5)	-	x	x	-	-	-	x	-	x
$Bi(SC_6H_2{}^iPr_3\text{-}2,4,6)_3$ **509**[411]	85 (5)	-	x	x	-	-	-	x	-	-
$Bi(SC_6H_2{}^tBu_3\text{-}2,4,6)_3$ **510**[411,418]	77 (3), 86 (5)	x	x	x	-	-	-	x	-	x
$Bi(SC_6H_4F\text{-}p)_3$ **511**[419]	80 (3)	-	x	x	-	-	-	-	-	-
$Bi(SC_6F_5)_3$ **512**[416,417,420]	93 (1,3), 70 (6)	x	x	x	x	x	-	x	-	-
$[Na_2(\underline{thf})_4][Bi(SC_6F_5)_5]$ **513**[416]	- (3)	x	-	-	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(SPPh_3)]$ **514**[421]	~50 (7)	x	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(\underline{tu})]$ **515**[421]	~50 (7)	-	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(OPPh_3)_2]\bullet CH_2Cl_2$ **516**[421]	~50 (7)	x	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(\underline{hmpa})_2]$ **517**[421]	~50 (7)	x	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(\underline{dmpu})_2]$ **518**[421]	~50 (7)	x	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3(OSPh_2)_2]$ **519**[421]	~50 (7)	-	-	x	-	-	-	-	-	-
$[Bi(SC_6F_5)_3\{SC(NHMe)_2\}_3]$ **520**[421]	~50 (7)	x	-	x	-	-	-	-	-	-
[K(18-crown-6)] $[Bi(SC_6F_5)_3(NCS)]$ **521**[421]	~50 (8)	x	-	x	-	-	-	-	-	-

*Syntheses:

5.1) $Bi(NO_3)_3 + 3\,RSH \rightarrow Bi(SR)_3 + 3\,HNO_3$

5.2) $BiF_3 + 3\,Me_3SiSR \rightarrow Bi(SR)_3 + 3\,Me_3SiF$

5.3) $BiCl_3 + 3\,MSR \rightarrow Bi(SR)_3 + 3\,MCl$

5.4) $BiCl_3 + 3\,RSH + NEt_3 \rightarrow Bi(SR)_3 + 3\,NEt_4Cl$

5.5) $Bi[N(SiMe_3)_2]_3 + 3\,RSH \rightarrow Bi(SR)_3 + 3\,HN(SiMe_3)_2$

5.6) $BiPh_3 + 3\,RSH \rightarrow Bi(SR)_3 + 3\,PhH$

5.7) $Bi(SR)_3 + L \rightarrow Bi(SR)_3L$

5.8) $Bi(SR)_3 + [K(18\text{-crown-}6)]SCN \rightarrow [K(18\text{-crown-}6)][Bi(SR)_3NCS]$

nitrate or triphenylbismuth to give the thiolate product. Other metathesis reactions involve silylamine and silylsulfide reactants.

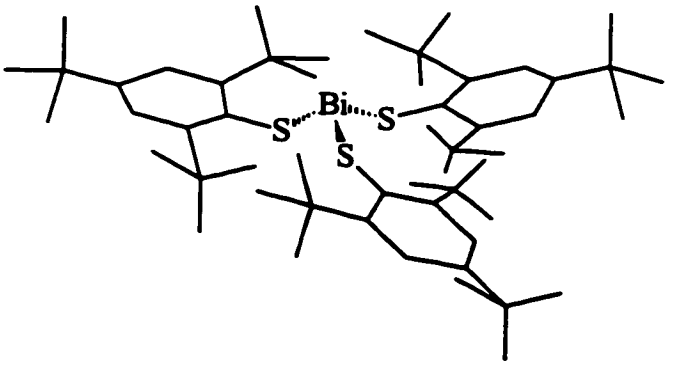
The pentafluorinated aryl derivative $Bi(SC_6F_5)_3$ **512**[416,417,420] is prepared from the reaction of the thiol with the bismuth cation in water or weakly acidic solution, or with $BiPh_3$ under reflux conditions, while the reaction of $BiCl_3$ with three equivalents of the thiolate results in the formation of the pentathiolate dianion $[Na_2(\underline{thf})_4][Bi(SC_6F_5)_5]$ **513**, instead of the tris(thiolate) **512**. The excessive thiolation of bismuth may be accredited to the increase in Lewis acidity of the bismuth center resulting from the electron withdrawing influence of the fluorinated ligands. Additionally, the greater nucleophilicity of the thiolate overcomes the kinetic barrier.

The earliest reported bismuth thiolates are those of simple alkyl thiolates, such as tris(ethylthiolato)bismuth **501**,[412] which are relatively reactive compared to other bismuth thiolates. $Bi(S^tBu)_3$ **502** is stable under vacuum, but decomposes in air and in dichloromethane solution while $Bi(SCH_2Ph)_3$ **503** is light sensitive.[413] Thermolysis of **503** and the unsubstituted phenylthiolate compound $Bi(SPh)_3$ **504**[415,416] compound results

in the formation of bismuth metal, Bi_2S_3 and/or disulfides.[415] The sterically encumbered arylthiolate compounds $Bi(SC_6H_2R'_3\text{-}2,4,6)_3$ **508-510**[411,418] are air stable, sublime under reduced pressures and are soluble in many organic solvents, while solutions oxidize to the aryl disulfides.

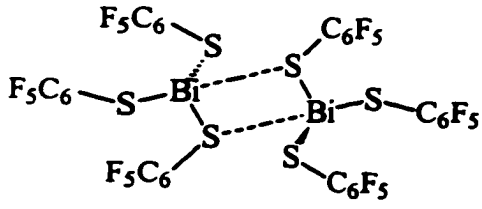
The tris(alkylthiolate) $Bi(S^tBu)_3$ **502** was determined to be monomeric in the gas phase from mass spectrometry data, while its monomeric nature in the solid state is inferred from comparison of infrared data with that of the arsenic and antimony analogues.[414]

The solubility of the unsubstituted tris(arylthiolate) compound $Bi(SPh)_3$ **504** [415,416] in weakly donating organic solvents suggests a monomeric or weakly polymeric structure, while preliminary X-ray analysis data suggest the compound has a similar structure to **510**.[416] The substituted arylthiolate $Bi(SC_6H_2{}^tBu_3\text{-}2,4,6)_3$ **510**[411,418] shows discrete monomers in the solid state, which is enforced by the steric bulk of the ligand. The bismuth center is in a three coordinate pyramidal environment [S-Bi-S 90.3(2)-104.5(2)°] with identical Bi-S bond distances [Bi-S 2.554(7)-2.569(8)Å].

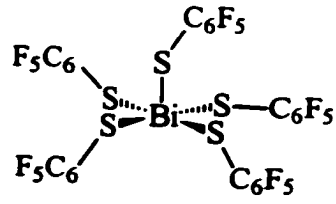


510

The pentafluorinated aryl derivative $Bi(SC_6F_5)_3$ **512**[416,417,420] [Bi-S 2.532(2)-2.584(2)Å] shows a loosely bound dimeric unit in the solid state via a longer bridging



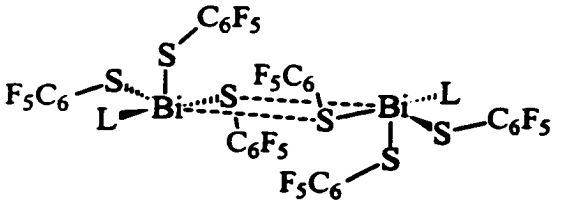
512



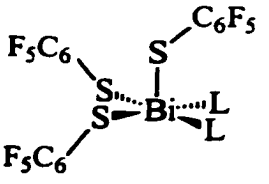
513

sulfur contact [Bi---$S_{terminal}$ 3.323(2)Å], with bismuth in a four coordinate disphenoidal bonding environment.[416] The dimerization of **512** as compared to **510** is presumably a result of the less sterically bulky ligand. The structure of the anion $[Bi(SC_6F_5)_5]^{2-}$ **513** shows bismuth bonded to five pentafluorothiolate ligands in a square pyramidal geometry [Bi-$S_{equatorial}$ 2.988(9), 2.703(9), 2.889(9) and 2.746(10); Bi-S_{axial} 2.609(10)Å]. The remaining apical site is occupied by a long intramolecular bismuth fluorine contact [Bi---F 2.94Å].

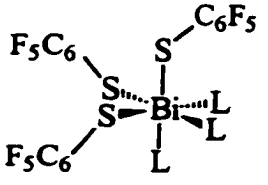
The increased Lewis acidity of the bismuth center of **512** allows for preparation of a number of Lewis base adducts $[Bi(SC_6F_5)_3(L)_n]$,[421] including examples of mono- (**514** and **515**), bis- (**516-519**) and tris- (**520**) adducts, and the anionic thiocyanate mono-adduct [K(18-crown-6)][$Bi(SC_6F_5)_3(NCS)$] (**521**). All structures are based on an octahedral geometry and contain a pyramidal BiS_3 unit. A *trans* influence is observed in all cases in that introduction of Lewis base donors effects significantly longer Bi-S bond distances in *trans* positions. The structure of mono- adduct **514** (L = $SPPh_3$) shows the compound as a centrosymmetric dimer in the solid state, with bismuth in a five coordinate square pyramidal geometry [Bi-$S_{thiolate}$ 2.57(1)-2.62(2); Bi-S_{SPPh_3} 3.01(1)Å] and involving a single long contact from a bridging sulfur of the neighboring molecule [Bi---S 3.15(1)Å]. A similar structure is observed for bismuth in the **521** anion $[Bi(SC_6F_5)_3(NCS)]^-$ [Bi-$S_{thiolate}$ 2.645(2), 2.2.614(2), 2.564(2)Å]. In this case, the isothiocyanate ligand bridges in an



514



516-18



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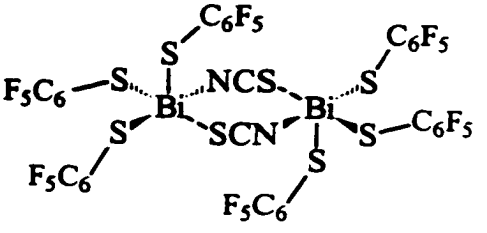


521

-NCS- manner, and is more tightly held to the monomer through the nitrogen atom [Bi-N 2.577(6); Bi---S 3.178(2)Å]. The bis- adducts **516-518** (L = $OPPh_3$, hmpa and dmpu, respectively) show similar structures but are now monomeric [Bi-S_{apical} 2.548(2)-2.588(2); Bi-$S_{equatorial}$ 2.574(2)-2.670(1); Bi-O 2.502(3)-2.728(5); Bi---F_{axial} 3.102(6)-3.254(7)Å]. The structure of the tris- adduct **520** [L = $SC(NHMe)_2$] is similar to the bis- adducts, but incorporates a third *S*-donor ligand into the remaining axial site, creating a six coordinate near octahedral environment for bismuth [Bi-$S_{thiolate}$ 2.721(2); Bi-S_{thione} 2.946(3)Å].

It is clear from these structural observations that there is a tendency toward a pyramidal facial arrangement for the BiS_3 unit of **512**. Secondary bonding characteristics are similar to that of the bismuth trihalides in the accommodation of one to three Lewis base ligands, while the steric bulk of the pentafluorothiophenolate ligand is sufficient to prevent the polymerization observed in mono- and bis- ligand complexes of bismuth trihalides and phenyl dihalides.[422-426] These observed octahedral-based geometries and

trans effects are consistent with a model involving Bi-S σ* acceptor orbitals, discussed further in Chapter 7.3.

5.3 Bifunctional Thiolates

Several examples of bismuth complexes of bifunctional ligands incorporating one or two thiolate groups have been prepared. With the exception of the dithiolate species, the increased solubility of these complexes (see Chapter 6) has allowed for more extensive structural studies, particularly in the case of hydroxyethanethiolates. Characterization data for these compounds is catalogued in Tables 5.2-5.5.

5.3.1 Dithiolates

Table 5.2 Analytical data for dithiolate compounds.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	con	IR	Ram	MS	pol
[Bi{S(CH$_2$)$_2$S}Cl] **522**[2,427]	82 (9)	-	x	x	-	x	x	x	-
522•2py[2,428]	85 (10)	x	x	x	-	-	-	-	-
[Bi{S(CH$_2$)$_3$S}Cl] **523**[2]	95 (9)	-	x	x	-	x	x	x	-
[Bi{S(CH$_2$)$_4$S}Cl] **524**[2]	97 (9)	-	x	x	-	x	x	x	-
[Bi{S(CH$_2$)$_2$S(CH$_2$)$_2$S}Cl] **525**[2,429]	87 (9)	x	x	x	-	x	x	x	-
[Bi{S(CH$_2$)$_2$O(CH$_2$)$_2$S}Cl] **526**[2,430]	60-92 (9)	x	x	x	-	x	x	x	-
[Bi$_2${S(CH$_2$)$_2$S}$_3$] **527**[2]	97 (11)	x	x	x	-	x	x	x	-
[Bi$_2${S(CH$_2$)$_3$S}$_3$] **528**[2]	92 (11)	-	x	x	-	x	x	x	-

Table 5.2 Analytical data for dithiolate compounds (continued).

Compound	yield (rxn 5.*n*)*	XR	mp	EA	con	IR	Ram	MS	pol
$[Bi_2\{S(CH_2)_4S\}_3]$ **529**[2]	98 (11)	-	x	x	-	x	x	-	-
$[Bi_2\{S(CH_2)_2S(CH_2)_2S\}_3]$ **530**[2]	67 (11)	x	x	x	-	x	x	x	-
$[Bi_2\{S(CH_2)_2O(CH_2)_2S\}_3]$ **531**[2]	99 (11)	-	x	x	-	x	x	x	-
$[Bi\{S(CH_2)_2S\}Br]$ **532**[427]	96 (9)	-	x	x	-	x	-	-	-
532•2py[428]	93 (10)	-	x	x	-	-	-	-	-
$[Bi(3,4\text{-}S_2C_6H_3Me)Cl]$ **533**[427]	86 (9)	-	x	x	-	-	-	-	-
533•2py[428]	- (10)	-	x	x	-	-	-	-	-
533•bipy[428]	98 (10)	-	x	x	-	-	-	-	-
533•phen[428]	100 (10)	-	-	x	-	-	-	-	-
$[Bi(3,4\text{-}S_2C_6H_3Me)Br]$ **534**[427]	87 (9)	-	x	x	-	-	-	-	-
534•bipy[428]	100 (10)	-	x	x	-	-	-	-	-
$[Bi_2(3,4\text{-}S_2C_6H_3Me)_3]$ **535**[430]	- (9)	-	-	x	x	-	-	-	x
$[Et_4N]_2[Bi_2(mnt)_2X_4]$ (X = Cl **536**, Br **537**, I **538**)[431]	- (12)	-	-	x	x	x	-	-	x
$[Et_4N]_2[Bi_2(mnt)_3X_2]$ (X = Cl **539**, Br **540**, I **541**)[431]	- (12)	-	-	x	x	x	-	-	x
$[Et_4N]_4[Bi_2(mnt)_5]$ **542**[431]	- (12)	-	-	x	x	x	-	-	x
$[Ph_4As][Bi(mnt)_2]$ **543**[427]	- (12)	x	-	-	-	-	-	-	-

*Syntheses:

5.9) $BiX_3 + HSRSH \rightarrow Bi(SRS) + 2\,HX$

5.10) $Bi(SRS)X + n\,L \rightarrow [Bi(SRS)X]L_n$

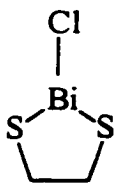
5.11) $2\,Bi(NO_3)_3 + 3HSRSH \rightarrow Bi_2(SRS)_3 + 6\,HNO_3$

5.12) $m\,BiX_3 + n\,NaSRSNa + s\,[PnR_4]Cl \rightarrow [PnR_4]_s[Bi_m(SRS)_nX_t] + s\,NaCl + (3m\text{-}t)\,NaX$

Bismuth dithiolates are prepared by similar metathesis reactions employed to prepare monothiolate complexes. Three series of anionic bismuth complexes $[Bi_2(\underline{mnt})_2X_4]^{2-}$ **536-38**, $[Bi_2(\underline{mnt})_3X_2]^{2-}$ **539-41**, and $[Bi_2(\underline{mnt})_5]^{4-}$ **542** of the dithiolate ligand dicyanoethylene-1,2-dithiolate (maleonitriledithiol = $H_2\underline{mnt}$) were isolated as the tetraethylammonium salts from single reactions by fractional crystallization.[431]

Dithiolate ligands have been employed to synthesize a number of monocyclic and "tethered" bicyclic thiabismuth heterocycles. These compounds are very insoluble and dissolve only in strong donor solvents with the formation of resilient Lewis base adduct complexes, such as **522**•2$\underline{py}$,[2,432] **532**•2$\underline{py}$[432] and **533**•2$\underline{py}$.[428]

The most comprehensive study of bismuth dithiolates undertaken involves the synthesis and spectroscopic characterization of series of dithiabismuth monocycles **522-26** and "tethered" trithiabismuth bicycles **527-31**.[2] The dithia- monocyclics are prepared generally from the reaction of $BiCl_3$ with the appropriate dithiol. A similar general reaction of $Bi(NO_3)_3$•$5H_2O$, which contains the more labile nitrate anion, with the same dithiol ligands results in a complete metathesis and affords the tethered bicyclic compounds. The kinetic stability of the dithiolate as compared to the trithiolate compound is demonstrated by the preparation of tethered bicycles **527** and **530** from monocycle chlorides **522** and **525**, respectively, by reaction with additional ligand in



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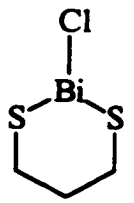

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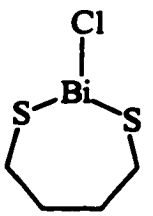

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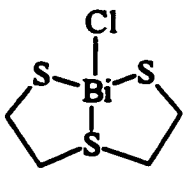

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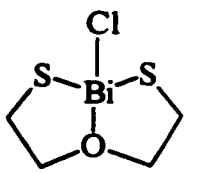

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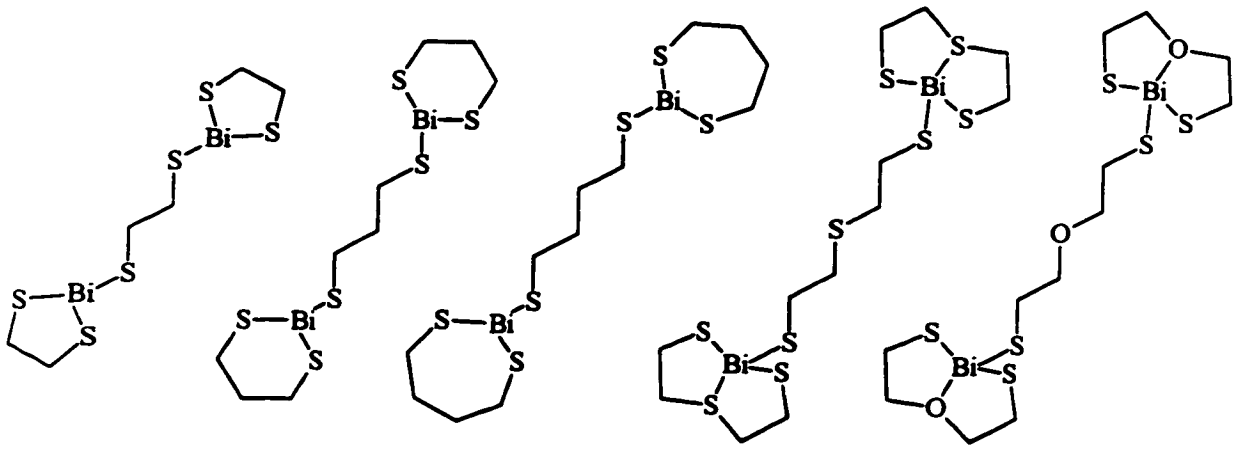
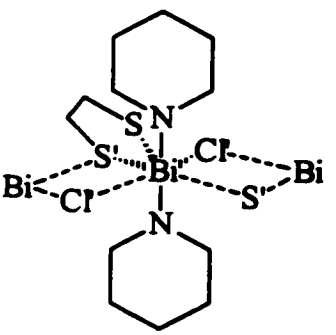


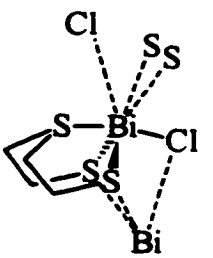
527 528 529 530 531

aqueous $NaNO_3$ solution. The sodium nitrate presumably promotes heterolytic Bi-Cl bond cleavage, while the tethering illustrates the thermodynamic preference for the Bi-S bond formation.

In addition to spectroscopic characterization, **522**•2py, **525-27** and **530** and have been crystallographically characterized and contain highly coordinated structures. Compound **522**•2py shows bismuth in a seven coordinate distorted pentagonal bipyramidal environment with the pyridine donors in the axial positions [Bi-N 2.534(8) and 2.592(9)Å]. The equatorial sites are occupied by two *cis* dithiolate sulfur atoms [Bi-S

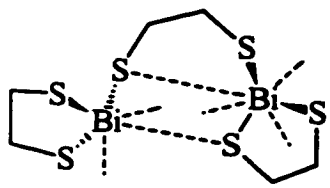


522•2py

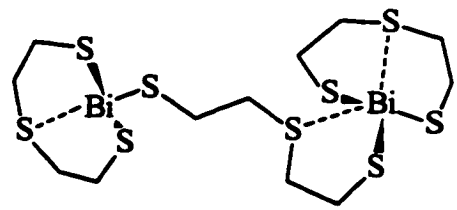


525

2.545(4) and 2.592(9)Å], an intermolecular sulfur contact [Bi---S 3.443(5)Å], and two nearly equivalently bound chlorine atoms [Bi-Cl 3.111(4) and 3.231(5)Å], which bridge to two separate bismuth centers and form an alternating Bi-Cl polymeric backbone. The seven coordinate environment of **525** (isostructural with **526**) is occupied by a chlorine atom [Bi-Cl 2.682(5)Å], the two thiolate sulfur atoms [Bi-S 2.541(6)Å], as well as a cross-ring intramolecular donation from the thioether sulfur (ether oxygen for **526**) [Bi-S 2.849(5)Å]. Two thiolate sulfur contacts [Bi---S 3.534(7)Å], and a long chlorine contact [Bi---Cl 3.285(6)Å], from a neighbouring molecule complete the coordination sphere. The tethered bicyclic compounds **527** and **530** show similar intramolecularly bound folded structures with bismuth in six or seven coordinate environments. Both compounds have similar endocyclic Bi-S bond distances [Bi-S 2.552(7)-2.599(4)Å], while **530** shows slightly longer cross-ring sulfur contacts [Bi-S 3.071(5) and 3.197(4)Å] than **525**.

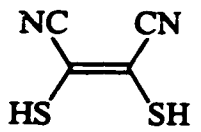


527

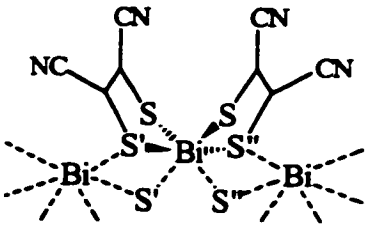


530

The anions $[Bi_2(\underline{mnt})_2X_4]^{2-}$ and $[Bi_2(\underline{mnt})_3X_2]^{2-}$ **536-41** are all speculated to be dinuclear species, though no supporting data were obtained. The structure of the tetraphenylarsonium salt $[Ph_4As][Bi(\underline{mnt})_2]$ **543**[427] shows a six coordinate bismuth center chelated by two dithiolate ligands [Bi-S 2.664(7)-2.836(8)Å]. Long sulfur contacts from



H_2mnt



543

two adjacent molecules [Bi---S 3.238(10) and 3.182(10)Å] create an infinite polymeric chain.

5.3.2 Thiolatocarboxylates

Table 5.3 Analytical data for thiolatocarboxylate compounds.

Compound	yield (rxn 5.*n*)*	X R	m p	E A	I R	N M R	M W
[Bi(tga)(Htga)] **544**[433]	80 (13,14)	-	x	x	x	x	x
[Bi(2mpa)(H2mpa)] **545**[433]	80 (13,14)	-	x	x	x	x	x
[Bi(3mpa)(H3mpa)] **546**[433]	65 (13,14)	-	x	x	x	x	x
[Bi(tsal)(Htsal)] **547**[433]	77 (13,14)	-	x	x	x	x	x
[{Bi_8(tsal)$_{12}$(dmf)$_6$}(dmf)$_6$] **548**[374]	28 (15)	x	-	-	-	-	-
[Bi(pen)Cl] **549**[434]	96 (16)	x	-	x	-	x	-

*Syntheses:

5.13) $BiPh_3 + 2\,H_2L \rightarrow Bi(L)(HL) + 3PhH$

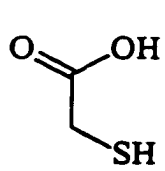
5.14) $Bi(OH)_3 + 2\,H_2L \rightarrow Bi(L)(HL) + 3\,H_2O$

5.15) $2\,Bi(NO_3)_3 + 3H_2L + 6NH_4OH \rightarrow Bi_2L_3 + 6\,NH_4NO_3 + 6\,H_2O$

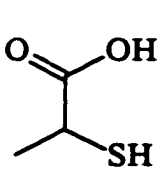
5.16) $BiOCl + H_2L \rightarrow Bi(L)Cl + H_2O$

The few isolated examples of bismuth thiolatocarboxylates have been prepared similarly to both thiolates and carboxylates. Syntheses typically involve reaction of the ligand with a basic bismuth salt or with the addition of base to ensure deprotonation of the carboxylic acid group.

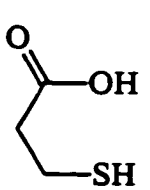
The infrared spectra of the thioglycolic acid (mercaptoacetic acid, H_2tga), 2-mercaptopropionic ($H_2$2mpa), 3-mercaptopropionic acid ($H_2$3mpa), and thiosalicylic acid (H_2tsal) complexes [Bi(L)(HL)] **544-47**[433] suggest a polymeric structure, with bridging mercaptocarboxylate ligands and four coordinate bismuth atoms.



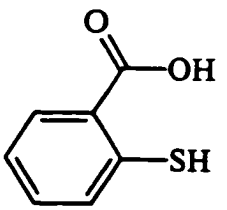
H_2tga



$H_2$2mpa

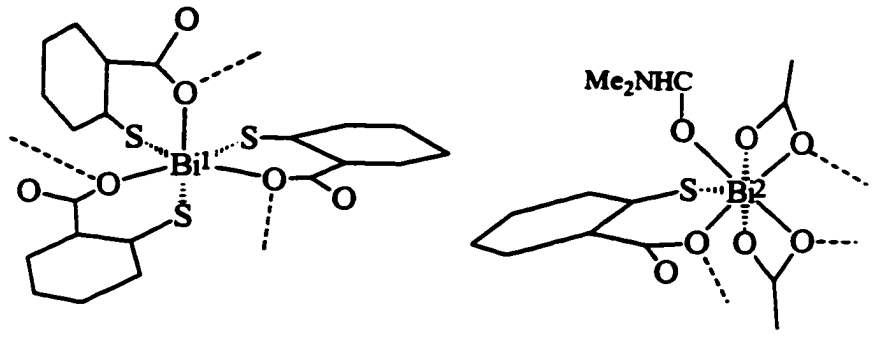


$H_2$3mpa



H_2tsal

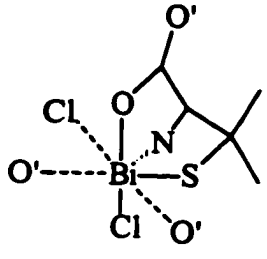
A very complex octanuclear arrangement is observed for the tris(thiosalicylate) compound [{Bi_8(tsal)$_{12}$(dmf)$_6$}(dmf)$_6$] **548**,[374] with a C_3 symmetry and two unique bonding situations for bismuth. One bismuth center (Bi^1) is chelated in an *S,O* (thiolate, carboxylate) manner by three tsal ligands forming six-membered -BiSCCCO- rings. The three sulfur atoms are in a *fac* arrangement [Bi-S 2.596(8)Å] and all three oxygen atoms bridge to other bismuth centers [Bi-O 2.74(2)Å]. The second unique bismuth center (Bi^2) is chelated by one ligand in an *S,O* manner [Bi-S 2.567(5)Å; Bi-O 2.46(2)Å] and two ligands in an asymmetrical *O,O'* manner [Bi-O 2.20(2)-2.79(1)Å] forming four-membered -BiOCO- rings. The oxygen atom of the *S,O* tsal ligand and the more weakly bound oxygen atoms of the *O,O'*-tsal ligands bridge to neighbouring bismuth atoms. The coordination sphere is



548

completed by a dmf oxygen atom [Bi-O 2.60(2)Å].

The unique trifunctional aminothiolatocarboxylate D-(-)-penicillaminato-*O,S,N* (pen) compound [Bi(pen)Cl] **549**[434] shows the ligand chelating bismuth in a *O,S,N* manner



549

[Bi-O 2.414(5)Å; Bi-S 2.527(2)Å; Bi-N 2.345(6); Bi-Cl 2.680(2)Å] forming both a -BiSCCN- and a -BiOCCN- ring. Long contacts from a chlorine atom [Bi---Cl 3.182Å] and two carbonyl oxygen atoms of neighbouring molecules [Bi---O 2.779(5) and 2.698(5)Å] create a polymeric structure and a seven coordinate environment.

5.3.3 Hydroxy-/Alkoxy- and Ketothiolates

Bifunctional thiolates incorporating a hydroxy- group have been extensively studied and show a rich reaction chemistry. The bis(hydroxyethanethiolate) compounds $[Bi(SCH_2CH_2OH)_2X]$ (X = NO_3,[435] Cl, Br) **550-52** are prepared from the reaction of two

equivalents of 2-mercaptoethanol with the appropriate bismuth salt,[3] while the perchlorate salt (R = ClO_4) **553**,[436] is prepared from a stoichiometric reaction in dilute perchloric acid. The impediment of maximum thiolation suggests some decrease in Lewis acidity of the bismuth center. The reaction of bismuth acetate with mercaptoethanol gives the alkoxy-hydroxy complex [$Bi(SCH_2CH_2O)(SCH_2CH_2OH)$] **554**.[3] In this case, alkoxide formation is enforced by the basic character of the acetate groups, and may also be achieved from

Table 5.4 Analytical data for hydroxy-/alkoxy- and ketothiolates.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	con	IR	Ram	UV	NMR	MS
[$Bi(SCH_2CH_2OH)_2(NO_3)(H_2O)_{0.5}$] **550**[3,435]	41-76 (17)	x	x	x	x	x	x	x	x	x	x
[$Bi(SCH_2CH_2OH)_2Cl$] **551**[3]	73-78 (17,18)	x	x	x	x	-	x	x	-	x	x
[$Bi(SCH_2CH_2OH)_2Br$] **552**[3]	19-22 (17,18)	-	x	x	x	-	x	x	-	x	x
[$Bi(SCH_2CH_2OH)_2(ClO_4)$] **553**[436]	- (17)	x	-	x	-	-	x	-	x	-	-
[$Bi(SCH_2CH_2O)(SCH_2CH_2OH)$] **554**[3,435]	29-47 (19,20)	x	x	x	x	x	x	x	-	x	-
[$Bi(SCH_2CH_2OH)_2(CH_3COO)$] **555**[3]	92 (21)	x	x	-	x	-	x	x	-	x	x
[$Bi(SCH_2CH_2OH)_3$] **556**[435,437]	33-70 (22,23)	-	x	x	x	x	-	-	x	x	-
[$Bi(\underline{dbt})_3$] **557**[438]	69-90 (24,25)	-	x	x	x	-	-	-	-	x	-
[$Bi(PhCH\{S\}CH_2C\{O\}Ph)_3]_2$ [CH_2Cl_2] **558**[439]	85-90 (26)	x	-	x	-	-	x	-	-	x	-
[$Bi(PhCH\{S\}CH_2C\{O\}C_6H_4X)_3$] (X = Me, **559**, Cl **560**)[439]	85-90 (26)	-	-	x	-	-	x	-	-	x	-

*Syntheses:

5.17) $BiX_3 + 2\,HSRH \rightarrow Bi(SRH)_2X + 2\,HX$

5.18) $Bi(SRH)_2X + NaX' \rightarrow Bi(SRH)_2X' + NaX$

5.19) $BiX_3 + 2\,HSRH \rightarrow Bi(SR)(SRH) + 3\,HX$

5.20) $Bi(SRH)_2X + NaOH \rightarrow Bi(SR)(SRH) + NaX + H2O$

5.21) $Bi(SR)(SRH) + HX \rightarrow Bi(SRH)_2X$

5.22) $Bi(SR)(SRH) + HSRH \rightarrow Bi(SRH)_3$

5.23) $Bi(OEt)_3 + 3\,HSRH \rightarrow Bi(SRH)_3 + 3\,EtOH$

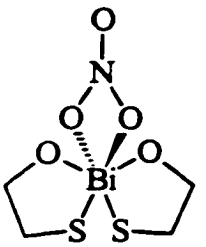
5.24) $Bi_2O_3 + 6\,HSR \rightarrow 2\,Bi(SR)_3 + 3\,H_2O$

5.25) $BiX_3 + 3\,HL + NEt_3 \rightarrow BiL_3 + 3\,(HNEt_3)X$

5.26) $BiX_3 + 3\,HSR + 3\,NaOAc \rightarrow Bi(SR)_3 + 3\,NaX + 3\,HOAc$

reaction of **550** in basic solution.[435] Recrystallization of **554** from acetic acid reprotonates the alkoxide and gives the acetate salt $[Bi(SCH_2CH_2OH)_2(CH_3COO)]$ **555**.[3] Further, the reaction of the hydroxythiolate-alkoxythiolate **554** with excess mercaptoethanol[435] also sees reprotonation of the alkoxide and the formation of the tris(thiolate) $[Bi(SCH_2CH_2OH)_3]$ **556**. Here, maximum thiolation is driven by the consequential formation of the nucleophilic thiolate group. The tris(thiolate) has also been prepared from metathesis reactions between mercaptoethanol and $Bi(OEt)_3$, and involves the favourable formation of ethanol.[437] The compound is stable under inert atmospheres but decomposes in air, contrasting the stability of the bis(thiolate) products. Compounds **551-52** may also be prepared by anion exchange reactions with weakly bound nitrate group of **550**.[3]

All bis(hydroxythiolate) structures show chelating hydroxy-/alkoxyethanethiolate ligands, forming a bicyclic arrangement of five-membered -BiSCCO- rings. The six coordinate bismuth center of **550** contains a near planar hydroxyethanethiolate ligand



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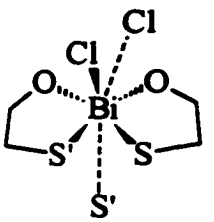

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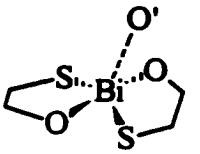

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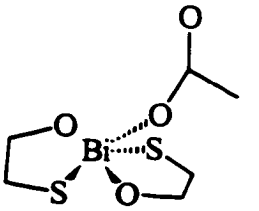
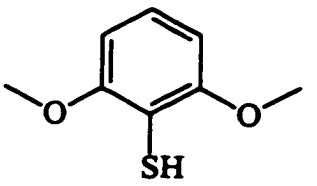


555

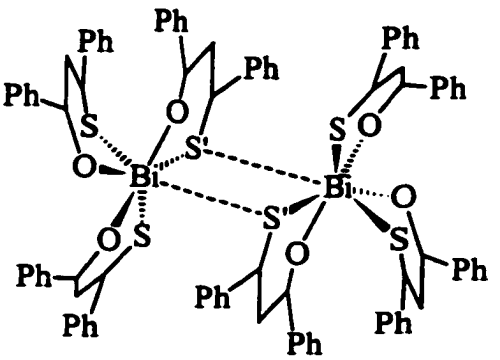
arrangement with *cis* sulfur atoms [Bi-S 2.639(5) and 2.655(5)Å; Bi-O 2.63(1)Å], and a bidentate nitrate group [Bi-O 3.01(2) and 3.17(2)Å] bound above and below the ligand plane and adjacent to both hydroxy- oxygen atoms. The structure of **551** is polymeric with bismuth in a seven coordinate environment [Bi-O 2.86(1) and 2.80(1); Bi-S 2.595(3) and 2.558(4)Å]. In this case, two μ_2-chlorine atoms, which bridge bismuth to a second bismuth center [Bi-Cl 2.589(3) and 3.488(4)Å], and a long sulfur contact from a third monomer [Bi---S 3.124(4)Å] complete the coordination sphere. Compound **555** shows a monodentate acetate oxygen atom [Bi-O 2.35(2)Å] and extensive hydrogen bonding [Bi-O 2.54(2) and 2.72(2); Bi-S 2.608(7) and 2.577(7)Å]. Preliminary structural data for **553** shows a similar bis-chelating structure with bridging thiolate sulfur atoms [Bi-S 2.61; Bi---S 2.97Å] to give a polymeric arrangement. Compound **554** is polymeric and shows a five coordinate bismuth atom, with the fifth contact provided by the alkoxide oxygen of a neighboring molecule [Bi-O 2.982(8)Å]. In this case, the bis-chelating arrangement [Bi-S 2.527(3) and 2.564(3)Å] has one shorter and one longer oxygen contact [Bi-O 2.195(9) vs. 2.577(9)Å] corresponding to the alkoxy- and hydroxy- Bi-O contacts, respectively.

The etherthiolate [Bi(dbt)$_3$] **557**[438] (Hdbt = 2,6-dimethoxybenzenethiol) has been characterized by elemental analysis and ^{1}H NMR only, although a crystalline material was reported.



Hdbt

The structure of the ketothiolate $[Bi(PhCH\{S\}CH_2C\{O\}Ph)_3]_2[CH_2Cl_2]$ **558**[439] shows two unique bismuth centers chelated by three ligands in an *S,O* manner, with a sulfur atom occupying the axial site [avg. Bi-S 2.581(4)Å] and the remaining atoms occupying the basal sites of the pentagonal pyramidal arrangement [Bi-S 2.627(5)-2.731(3); Bi-O



558

2.536(9)-2.650(9)Å]. Long Bi---S' contacts [Bi---S 3.494(5) and 3.551(5)Å] to the empty apical sites between neighbouring molecules creates a dimeric structure and a seven coordinate bismuth center.

5.3.4 Amino-, Imino- and Aza-Thiolates

As discussed in Chapter 2.5, bismuth(III) complexes of thiosemicarbazone derivatives have been prepared as antimicrobial agents. Synthetic procedures for these compounds are general (reactions 5.27 and 5.29) and, due to the large number of complexes isolated, only structurally characterized examples are discussed here.

Table 5.5 Analytical data for amino-, imino- and azathiolate compounds.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	con	IR	Ram	UV	NMR	MS	pot
Bi(abt)$_3$ **561**[443,444]	- (26,27)	-	x	x	x	x	x	-	-	-	x	x
Bi(Habt)$_3$Cl$_3$ **562**[444]	- (26)	-	-	x	x	x	x	-	x	-	-	-
[Bi(SCH$_2$CH$_2$NH$_2$)$_2$(NO$_3$)(H$_2$O)] **563**[445]	- (28)	x	x	-	x	-	x	x	-	x	-	-
[Bi(2-SC$_5$H$_3$N-3-SiMe$_3$)$_3$] **564**[446]	55 (27)	x	-	x	x	-	x	-	-	-	-	-
[Bi(pmq)$_2$Cl] **565**[447]	78 (28)	x	-	-	-	-	-	-	-	-	-	-
[Bi(mmq)$_3$] **566**[448]	- (-)	x	-	-	-	-	-	-	-	-	-	-
Bi(Hdz)$_3$ **567**[449]	- (27)	x	x	x	-	-	-	-	-	-	-	-
[Bi(tscR$_1$R$_2$)$_2$(NO$_3$)] **568**[450]	76 (27)	x	x	x	-	x	x	-	x	x	x	-
[Bi(tscR$_1$R$_2$)(HtscR$_1$R$_2$)Cl$_2$][450] **569** (R$_1$ = C$_4$H$_3$S, R$_2$ = C$_6$H$_{12}$)	55 (29)	x	x	x	-	x	x	-	x	x	x	-
[Bi(tscR$_1$R$_2$)$_2$(NO$_3$)] **570**[450]	71 (27)	x	x	x	-	x	x	-	x	x	x	-
[Bi(tscR$_1$R$_2$)Cl$_2$] **571**[450] (R$_1$ = C$_5$H$_4$N, R$_2$ = NC$_6$H$_{12}$)	91 (29)	x	x	x	-	x	x	-	x	x	x	-
[Bi(dapts)N$_3$] **572**[451]	- (30)	x	-	x	-	-	x	-	-	-	-	-

* Syntheses:

5.26) $Bi(NO_3)_3 + 3\,RSH + n\,HCl + (3+n)\,KOH \rightarrow Bi(SR)_3 + 3\,KNO_3 + 4\,H_2O + n\,KCl$

5.27) $Bi(NO_3)_3 + n\,RSH \rightarrow Bi(SR)_n(NO_3)_{3-n} + n\,HNO_3$

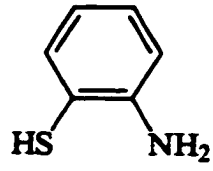
5.28) $BiCl_3 + 2\,NaSR \rightarrow Bi(SR)_2Cl + 2\,NaCl$

5.29) $BiCl_3 + RSH \rightarrow Bi(SR)Cl_2 + HCl$

5.30) $BiCl_3 + HSRSH + NaN_3 \rightarrow [Bi(SRS)N_3] + 2\,HCl + NaCl$

The earliest aminothiolate bismuth compounds prepared were of

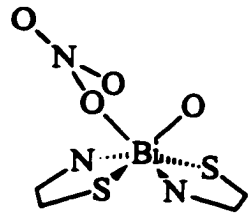
2-aminobenzenethiol (Habt).[440-442] The compound Bi(abt)$_3$ **561**[443] and the protonated ammonium analogue Bi(Habt)$_3$Cl$_3$ **562** are prepared similarly, with the resulting product determined by the final reaction pH.[444] **561** is poorly soluble in organic solvents and



Habt

appears to be air and moisture stable for a period of weeks. The tris(thiolate) compound [Bi(2-SC$_5$H$_3$N-3-SiMe$_3$)$_3$] **564** is unstable to weak electrophiles (e.g. RSCl), giving the bismuth halide and the sulfide.[446]

For Bi(abt)$_3$ **561**, participation of the amino- group in the binding of bismuth is not suggested by solid state IR, negating the presence of a chelating structure, while solution IR spectra also suggests the presence of an uncoordinated NH$_2$ group. The first structurally characterized amino-thiolate [Bi(SCH$_2$CH$_2$NH$_2$)$_2$(NO$_3$)(H$_2$O)] **563**[445] shows a similar bicyclic structure to the hydroxy-/alkoxythiolates **550-51** and **554-55**, but with five-membered -BiSCCN- rings [Bi-S 2.549(2) and 2.589(2)Å]. Coordination to the bismuth center by a monodentate nitrate group and a water molecule gives a formal coordination number of six, while intermolecular contacts from neighbouring sulfur atoms [Bi---S 3.517(2) and 3.550(2)Å] create an eight co-ordinate distorted octahedral environment for bismuth and a one-dimensional polymeric structure. The short bismuth-nitrogen [Bi-N 2.462(5) and 2.455(6)Å] and long bismuth-oxygen [Bi-O$_{nitrate}$ 3.004(6)Å; Bi-O$_{water}$



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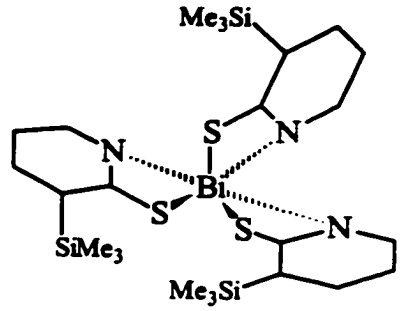
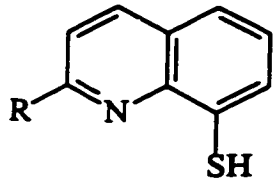


564

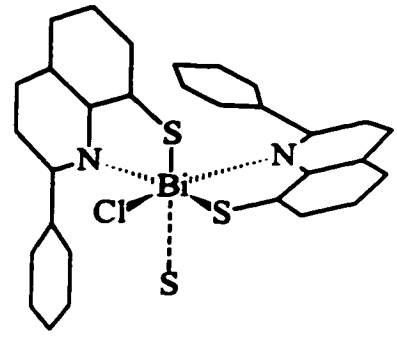
3.107(6)Å] bond distances suggest an increased stability for the bicyclic unit and decreased Lewis acidity of the bismuth center.

Related to these aminothiolate complexes are those containing ligands which incorporate a nitrogen donor into an aromatic ring. The tris(thiolate) compound [Bi(2-SC_5H_3N-3-$SiMe_3)_3$] **564**[446] has a distorted pentagonal pyramidal geometry around bismuth incorporating a pyramidal BiS_3 arrangement [Bi-S 2.544(6)-2.647(7); Bi-N 2.69(2)-2.83(2)Å]. The inverse relationship of the Bi-S and Bi-N bond distances suggests a greater ring strain for the resulting four membered -BiSCN- rings than the -BiSCCN- rings of **563**.

Bis(2-phenyl-8-mercaptoquinolinato) (pmq) bismuth chloride [Bi(pmq)$_2$Cl] **565**[447] shows bismuth in a five coordinate distorted square pyramidal environment. The axial and basal sulfur atoms [Bi-S 2.532(3) and 2.591(3)Å, respectively] and the chlorine atom [Bi-Cl 2.579(3)Å] are in a *fac* arrangement. The long bismuth-nitrogen distances [Bi-N 2.628(9) and 2.880(7)Å] may be a consequence of ring strain enforced by the sp^2 carbon backbone atoms of the -BiSCCN- rings, while the formation of the bis(thiolate) is a possible consequence of the induced decrease in Lewis acidity of the bismuth center by the imino nitrogen donor, as well as the steric bulk of the ligand. A long sulfur contact to the empty

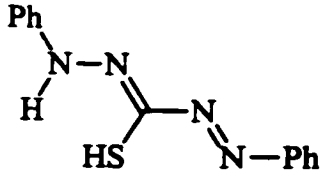


R = Me, Hmmq
= Ph, Hpmq

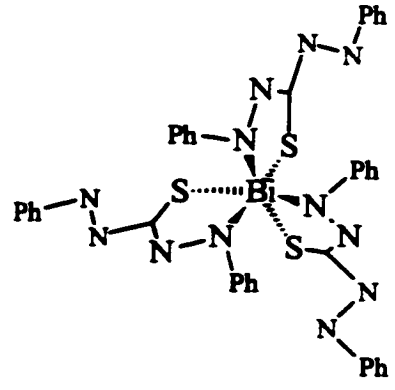


565

apical site [Bi---S 3.304(3)Å] dimerizes the compound and increases the coordination number of bismuth to six. The related tris(methyl-) analogue [Bi(mmq)$_3$] **566**[448] shows bismuth chelated by three 2-methyl-8-mercaptoquinolinate ligands [Bi-S 2.571(2)-2.623(3); Bi-N 2.689(4)-2.796(4)Å] in a *fac* arrangement with no intermolecular contacts, giving a six-coordinate distorted octahedral geometry for bismuth. A similar structure is observed for the 3-mercapto-1,5-diphenylformazan (dithizone) (H_2dz) compound Bi(Hdz)$_3$, **567**[449] [Bi-S 2.607(3)-2.613(3)Å; Bi-N 2.678(8)-2.746(10)Å], forming five membered -BiSCNN- rings.



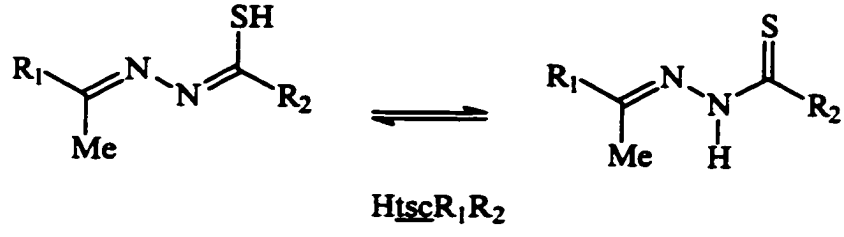
H_2dz



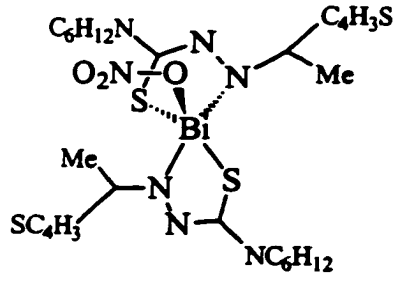
567

Examples of mono-, bis- and tris- complexes of various thiosemicarbazone derivatives (HtscR_1R_2) have been prepared.[450] The bis(tsc) complexes [Bi(tscR_1R_2)$_2$(NO_3)] **568** and [Bi(tscR_1R_2)(HtscR_1R_2)Cl_2] **569** (R_1 = C_4H_3S, R_2 = C_6H_{12}) both show the tsc ligand

chelating in an *S,N*-manner, while in **569** [Bi-$S_{thiolate}$ 2.527(3); Bi-N 2.518(8); Bi-Cl 2.605(4) and 2.630(4)Å] one of the ligands bonds the bismuth center in a monodentate fashion as the thione tautomer [Bi-S_{thione} 2.992(3)Å]. Compound **568** shows a similar bond arrangement to



$HtscR_1R_2$



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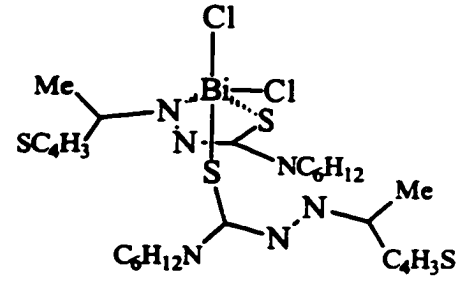
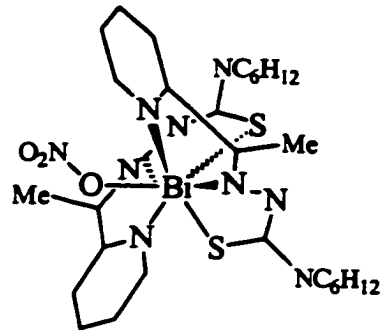


569

the aminothiolate **563**, with the absence of a bonded water molecule [Bi-S 2.561(3) and 2.565(4); Bi-N 2.438(10) and 2.445(11); Bi-O 2.889(11)Å]. The (R_1 = C_5H_4N, R_2 = NC_6H_{12}) derivatives [Bi(tscR_1R_2)$_2$(NO_3)] **570** and [Bi(tscR_1R_2)Cl_2] **571** both show the tsc ligand chelating in a tridentate *S,N,N'*-manner, forming -BiSCNN- and -BiNCCN- rings. Compound **570** shows a monodentate nitrate anion and a seven coordinate environment for bismuth [Bi-S 2.584(4) and 2.654(4); Bi-N_{azo} 2.471(8) and 2.581(8); Bi-N_{imine} 2.711(10) and 2.649(9); Bi-O 2.731(11)Å]. The mono(tsc) complex **571** dimerizes via bridging chlorine atoms, giving a total coordination number of six for bismuth [Bi-S 2.583(3); Bi-N_{azo} 2.355(8); Bi-N_{imine} 2.501(8); Bi-Cl 2.585(3); Bi---Cl 2.791(3)Å].



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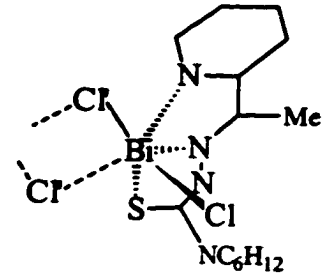

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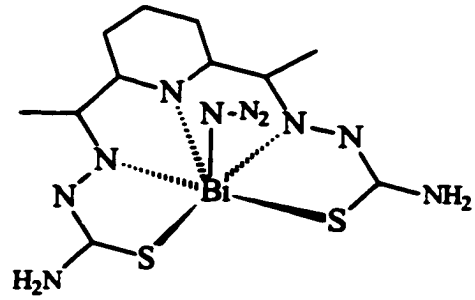
The 2,6-diacetylpyridine bis(thiosemicarbazone) (H_2dapts) compound [Bi(dapts)N_3] **572**[451] shows bismuth in a six coordinate distorted pentagonal pyramidal environment. All



572

basal sites are occupied by the *S,N,N',N'',S'*-pentadentate ligand [Bi-S 2.685(7) and 2.717(8); Bi-N_{azo} 2.46(2) and 2.58(2); Bi-N_{imide} 2.44(2)Å] with an azide nitrogen in the apical site [Bi-N 2.25(2)Å].

5.4 Thio- and Dithiocarboxylates

Bismuth thio- and dithiocarboxylates (Figure 1.1) are interesting species in that they may provide a useful link between thiolate chemistry and carboxylate chemistry. The thiophilicity of bismuth allows for the formation of hydrolytically stable complexes, while the group chelates and bridges bismuth in an analogous manner to the carboxylate functionality. While dithiocarboxylates have been extensively studied, there have been few

studies into thiocarboxylates of bismuth. The incorporation of both a hard oxygen atom and a soft sulfur atom or two sulfur atoms gives way to structural diversity and allows for the group to bond as a bifunctional ligand. As a result, examples of mono-, bis-, tris and tetra(dithiocarboxylate) species, as well as mixed ligand complexes, have been prepared. Characterization data for these compounds are included in Tables 5.6-5.7.

5.4.1 Thiocarboxylates

Table 5.6 Analytical data for thiocarboxylate compounds.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	IR	NMR
$[Bi(SOCC_6H_5)_3]$ **573**[452,453]	92-95 (31-33)	-	x	x	x	x	x
$[Bi(SOCC_6H_4$-*o*-$Me)_3]$ **574**[452]	98 (32)	x	x	x	x	x	x
$[Bi(SOCC_6H_4$-*p*-$Me)_3]$ **575**[452]	90 (32)	-	x	x	x	x	x

*Syntheses:

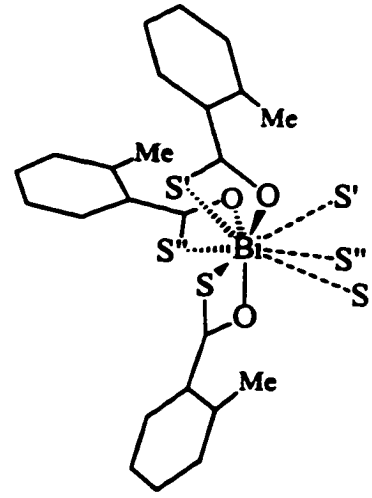
5.31) $Bi_2O_3 + 6\,RCOSH \rightarrow 2\,Bi(SOCR)_3 + 3\,H_2O$

5.32) $Bi(OOCCH_3)_3 + 3\,RCOSH \rightarrow Bi(SOCR)_3 + 3\,CH_3COOH$

5.33) $Bi(SPh)_3 + 3\,RCOSH \rightarrow Bi(SOCR)_3 + 3\,PhSH$

The series of tris(thiobenzoates) of the general formula $[Bi(SOCC_6H_4R)_3]$ **573-75**[452,453] are thermally stable, with **574** being much more soluble in organic solvents than the other derivatives. In **574**, all three thiocarboxylate ligands chelate to form four-membered -BiSCO- rings [Bi-S 2.630(3)Å], with quite long bismuth-oxygen bond distances [Bi-O

2.752(6)Å] and the three sulfur atoms in a pyramidal *fac* arrangement. Long contacts from the three sulfur atoms of a neighboring molecule [Bi---S 3.498Å] increases the coordination number of bismuth to nine.



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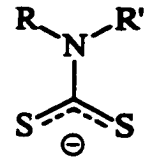
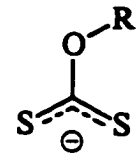
5.4.2 Dithiocarboxylates (Dithiocarbamates, Dithioxanthates)

The majority of dithiocarboxylate compounds that have been prepared are dithiocarbamates (R_2dtc), while there are also several examples of dithioxanthates (Rdtx). Both classes of compounds exhibit a variety of organic R groups. Mixed dithiocarbamate compounds **5110-117** include combinations of the following R (R') groups: Et, CH_2Ph, C_4H_8, C_5H_{10} and C_5H_8.



R_2dtc



Rdtx

Table 5.7 Analytical data for dithiocarboxylate compounds.

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	con	IR	UV	NMR	MS	TGA	CV	MW
$[Bi(Et_2dtc)_3]$ **576**[454-456,462,463]	63 (34)	x	x	x	x	-	x	-	-	-	x	-	-
$[Bi(\{HOCH_2CH_2\}_2dtc)_3]$ **577**[464]	- (35)	x	-	-	-	-	-	-	-	-	-	x	-
$[Bi(C_4H_8dtc)_3]$ **578**[465]	95 (36)	x	-	x	-	-	x	-	-	-	-	-	-
$[Bi(Et_2dtc)_2Br]$ **579**[466]	94 (37,38)	x	x	x	x	x	x	x	x	-	-	-	x
$[Bi(^tBu_2dtc)_2Br]$ **580**[466] $[Bi(\{CH_2Ph\}_2dtc)_2Br]$ **581**[466]	86-84 (37)	-	x	x	x	x	x	x	x	-	-	-	x
$[Bi(C_4H_8dtc)_2Br]$ **582**[466] $[Bi(C_5H_{10}dtc)_2Br]$ **583**[466]	91-95 (37)	-	x	x	x	x	x	x	-	-	-	-	x
$[Bi(Et_2dtc)_2I]$ **584**[467,468]	85 (37,38)	x	x	x	x	-	x	x	x	x	-	-	x
$[Bi(^tBu_2dtc)_2I]$ **585**[467,468] $[Bi(\{CH_2Ph\}_2dtc)_2I]$ **586**[467]	80, 75 (37)	-	x	x	x	-	x	x	x	-	-	-	x
$[Bi(C_4H_8dtc)_2I]$ **587**[467]	84 (37)	-	x	x	x	-	x	x	-	x	-	-	x
$[Bi(C_5H_{10}dtc)_2I]$ **588**[467]	88 (37)	-	x	x	x	-	x	x	-	-	-	-	x
$[Bi(C_4H_8dtc)_2Cl(tu)]$ **589**[465]	low (39)	x	-	x	-	-	x	-	-	-	-	-	-
$[Bi(Et_2dtc)_2(BF_4)]$ **590**[457] $[Bi(C_4H_8dtc)_2(BF_4)]$ **591**[457] $[Bi(C_5H_{10}dtc)_2(BF_4)]$ **592**[457]	~70 (40)	-	x	x	x	x	x	x	x	x	-	-	x
$[Bi(Et_2dtc)Cl_2]$ **593**[469]	60 (38)	x	x	x	-	-	x	-	x	-	-	-	-
$[Bi(Et_2dtc)X_2]$ (X = Br **594**, I **595**)[470]	- (38)	x	x	x	-	-	x	-	-	-	-	-	-
$[Bi_5(Et_2dtc)_8X_7(dmf)]$ (X = Cl **596**, Br **597**)[471]	- (41)	x	-	x	-	-	-	-	-	-	-	-	-
$[Bi_5(Et_2dtc)_8I_7(dmf)]$ **598**[471]	- (41)	x	-	-	-	-	-	-	-	-	-	-	-
$[NEt_4][Bi(Et_2dtc)I_3]$ **599**[472]	- (42)	x	-	x	-	-	-	-	-	-	-	-	-
$[NEt_4][Bi(Et_2dtc)I_2Br]$ **5100**[472]	- (42)	x	-	-	-	-	-	-	-	-	-	-	-
$[Hpy][Bi_4(Et_2dtc)_4Br_{10}]$ **5101**[471]	- (43)	x	-	-	-	-	-	-	-	-	-	-	-
$[Bi(Medtx)_3]$ **5102**[473-476]	- (44)	x	-	-	-	-	-	-	x	-	-	-	-

Table 5.7 Analytical data for dithiocarboxylate compounds (continued).

Compound	yield (rxn 5.*n*)*	XR	mp	EA	sol	coon	IR	UV	NMR	MS	TGA	CV	MW
[Bi(Et<u>dtx</u>)$_3$] **5103**[474-477]	- (44)	x	-	x	-	x	x	x	x	-	-	-	x
[Bi(^{i}Pr<u>dtx</u>)$_3$] **5104**[474-476,478]	- (44)	x	x	-	-	-	x	-	x	-	-	-	-
[Bi(R<u>dtx</u>)$_3$] (R = *c*-C_6H_{11} **5105**, CH_2Ph **5106**)[474-476,479]	- (44)	x	-	-	-	-	x	-	-	-	-	-	-
[Bi(Et<u>dtx</u>)$_2$X] (X = Cl **5107**, Br **5108**)[458]	- (37,45)	-	-	x	-	-	x	x	-	-	-	-	x
[NEt_4][Bi(Et<u>dtx</u>)$_4$] **5109**[474,480]	- (46)	x	-	x	-		x	-	-	-	-	-	-
[Bi(R_2<u>dtc</u>)$_2$(R'_2<u>dtc</u>)] **5110-117**[459]	58-90 (47,48)	-	x	x	x	-	x	x	x	x	-	-	x
[Bi(Et<u>dtx</u>)$_2$(Me<u>dtx</u>)] **5118**[460]	- (48)	-	x	-	-	-	x	-	x	-	-	-	-
[Bi(R_2<u>dtc</u>)$_2$(Et<u>dtx</u>)][459] (R = Et **5119**; $\{CH_2\}_2$ **5120**)	58-97 (48)	-	x	x	x	-	x	x	x	x	-	-	x
[Bi(Et_2<u>dtc</u>)(Et<u>dtx</u>)$_2$] **5121**[460]	- (48)	-	x	-	-	-	x	-	x	-	-	-	-
[Bi(<u>eacd</u>)$_3$] **5122**[461]	98,90 (49,50)	x	-	-	-	-	-	-	-	-	-	-	-

*<u>Syntheses:</u>

5.34) $BiCl_3 + 3\,CS_2 + 3\,NHR_2 \rightarrow Bi(S_2CNR_2)_3 + 3\,HCl$

5.35) $BiONO_3 + 3\,HS_2CR + (n+1)\,NH_3 + n\,HCl \rightarrow Bi(S_2CR)_3 + H_2O + NH_4NO_3 + n\,NH_4Cl$

5.36) $BiCl_3 + 3\,NH_4(S_2CR) \rightarrow Bi(S_2CR)_3 + 3\,NH_4Cl$

5.37) $Bi(S_2CR)_3 + X_2 \rightarrow Bi(S_2CR)_2X$ + by-products

5.38) $m\,BiX_3 + n\,Bi(S_2CR)_3 \rightarrow (m+n)\,Bi(S_2CR)_nX_m$

5.39) $BiCl_3 + 2\,NH_4(S_2CR) + L \rightarrow [Bi(S_2CR)_2Cl(L)] + 2\,NH_4Cl$

5.40) $Bi(S_2CR)_3 + BF_3 \rightarrow Bi(S_2CR)_2(BF_4)$ + by-products

5.41) $Bi(S_2CR)X_2 + L \rightarrow [Bi_5(S_2CR)_8X_7(L)]$ + by-products

5.42) $Bi(S_2CR)I_2 + [NEt_4]X \rightarrow [NEt_4][Bi(S_2CR)I_2X]$

*Syntheses: (continued)

5.43) $Bi(S_2CR)Br_2 + L \rightarrow [HL][Bi_4(S_2CR)_4Br_{10}]$ + by-products

5.44) $BiCl_3 + 3\,Na(S_2CR) \rightarrow Bi(S_2CR)_3 + 3\,NaCl$

5.45) $2\,Bi(S_2CR)_3 + CuX_2 \rightarrow 2\,Bi(S_2CR)_2X + Cu(S_2CR)_2$

5.46) $Bi(S_2CR)_3 + NEt_4(S_2CR) \rightarrow [NEt_4][Bi(S_2CR)_4]$

5.47) $Bi(S_2CNR_2)_2I + CS_2 + 2\,NHR'_2 \rightarrow [Bi(S_2CNR)_2(S_2CNR'_2)] + NH_2R'_2I$

5.48) $Bi(S_2CR)_2X + M(S_2CR') \rightarrow [Bi(S_2CR)_2(S_2CR')] + MX$

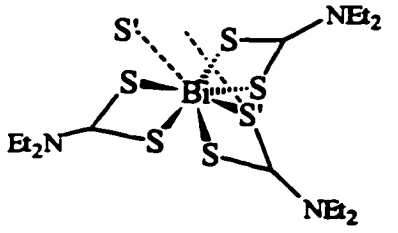
5.49) $BiCl_3 + 3\,HS_2CR \rightarrow Bi(S_2CR)_3 + 3\,HCl$

5.50) $BiOCl + 3\,HS_2CR \rightarrow Bi(S_2CR)_3 + H_2O + HCl$

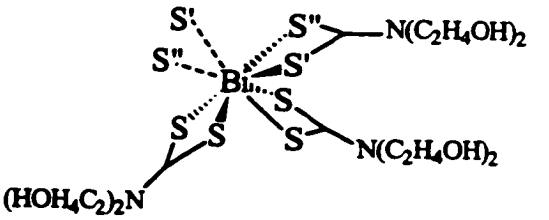
Several methods have been used to prepare mono-, bis-, tris- and tetra- examples of dithiocarboxylates. These complexes exhibit varying degrees of solubility and stability toward hydrolysis, oxidation and thermolysis. The dithiocarbamate $[Bi(Et_2\underline{dtc})_3]$ **576**[454-456] is soluble in chloroform, carbon disulfide and carbon tetrachloride, monomeric in solution, and fairly air stable. The bis(dithiocarbamate) tetrafluoroborate salts $[Bi(R_2\underline{dtc})_2(BF_4)]$ **590-92**[457] react with water, while the bis(dithioxanthate) halides $[Bi(Et\underline{dtx})_2X]$ (X = Cl **5107**, Br **5108**)[458] are thermally stable but susceptible to hydrolysis. Mixed-ligand complexes have also been synthesized, which incorporate two different dithiocarbamate or xanthate ligands, or both a dithiocarbamate and a dithioxanthate ligand. These include mixed dithiocarbamate complexes $[Bi(R_2\underline{dtc})_2(R'_2\underline{dtc})]$ **5110-117**,[459] a mixed dithioxanthate complex $[Bi(Et\underline{dtx})_2(Me\underline{dtx})]$ **5118**,[460] and mixed dithiocarbamate-dithioxanthate complexes $[Bi(R_2\underline{dtc})_2(Et\underline{dtx})]$ **5119-120**[459] and $[Bi(Et_2\underline{dtc})(Et\underline{dtx})_2]$ **5121**.[460] Compounds **5110-117** and **5119-120** are air and solution stable, while the mixed ligand complexes **5119-120** are more stable than tris(*O*-ethyldithioxanthate). An analogue of the

2-ethylamino derivative complex [Bi(eacd)$_3$] **5122**[461] involving the unsubstituted ligand is reported without a formula designation or characterization data.

There are several examples of tris(dithiocarbamate) compounds, all of which contain three asymmetrically *S,S'*-chelated ligands, forming four-membered -BiSCS- rings. In each case, the shorter Bi-S contacts are in a *fac* arrangement, and varying degrees of intermolecular Bi---S bonding create dimeric structures. The structure[462,463] of the diethyl analogue [Bi(Et$_2$dtc)$_3$] **576**[454-456] [Bi-S 2.595(5)-2.964(4)Å] shows bismuth in a seven coordinate environment, with a single long sulfur contact from a neighbouring molecule [Bi-S 3.210(4)Å]. The structure of the diethanol analogue

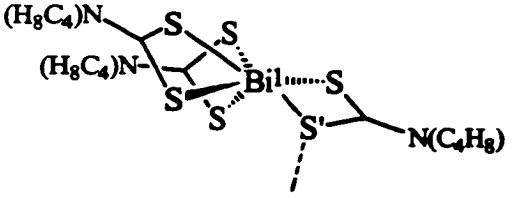


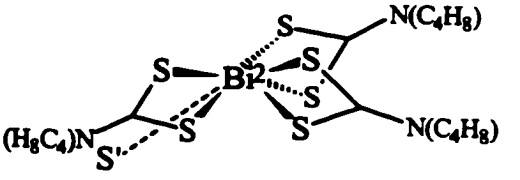
576



577

[Bi({HOCH$_2$CH$_2$}$_2$dtc)$_3$] **577**[464] shows bismuth in an eight coordinate distorted square antiprism bonding environment [Bi-S 2.669(7)-2.885(7)Å]. In this case, dimerization is through four bridging sulfur atoms of two ligands [Bi---S 3.076(9)-3.179(9)Å]. The pyrrolidine analogue [Bi({CH$_2$}$_4$dtc)$_3$] **578**[465] shows two unique bismuth atoms in both six and seven coordinate environments [Bi-S 2.612(7)-3.017(8)Å]. Here, only one of the



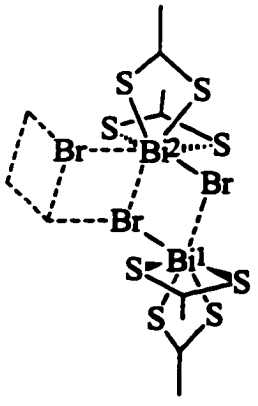


578

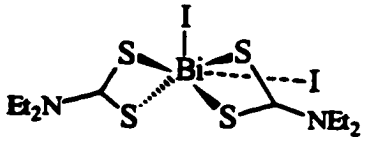
bismuth centers receives a long Bi---S contact from a neighbouring molecule [Bi---S 3.163(6)Å].

A number of bis(dithiocarbamate) halide complexes have also been prepared and conductance measurements of the bromo analogues [Bi(R_2dtc)$_2$Br] **579-83**[466] suggest that these compounds are non-electrolytes in nitrobenzene, while molecular weight measurements of both the bromide and iodide analogues [Bi(R_2dtc)$_2$I] **584-88**[467] suggests that they are dimers in solution. Spectroscopic data for the iodo complexes suggest that the dithiocarbamate ligands function as bidentate ligands.

The bismuth centers of **579**, **584**[468] and **589**[465] are each coordinated to two asymmetrically bound *S,S'*-dithiocarbamate ligands. Intermolecular halide and sulfur contacts again allow for varying degrees of polymerization. Compound **579** (NEt_2 omitted from drawing) shows tetramer-based polymeric network with two unique bismuth environments. One bismuth center (Bi^1) [Bi-S 2.657(4)-2.843(7)Å] coordinates two *cis* bridging μ_2- and μ_3-bromine atoms [Bi-S 3.066(2) and 3.004(2)Å, respectively], while a second bismuth center (Bi^2) [Bi-S 2.641(5)-2.814(5)Å] is coordinated to three *fac* bridging μ_2- and μ_3-bromine atoms [μ_2: Bi-S 3.104(2); μ_3: Bi-S 3.232(2) and 3.390(3)Å].

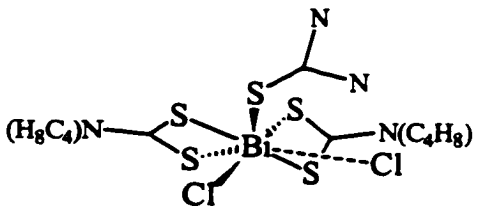


579



584

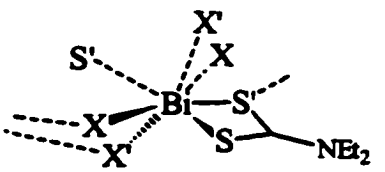
The structure of **584**[468] shows a one-dimensional polymeric structure with a -Bi-I-Bi-I- backbone, facilitated by two *cis* bridging μ_2-iodine atoms [Bi-I 3.257(2) and 3.354(1)Å], and bismuth in a six coordinate environment [Bi-S 2.646(4)-2.860(5)Å]. The bis(dithiocarbamate) thiourea adduct [Bi({CH_2}$_4$dtc)$_2$Cl(tu)] **589**[465] shows bismuth in a seven coordinate environment [Bi-S_{dtc} 2.624(4)-2.805(3)Å; Bi-$S_{thiourea}$ 3.017(4)Å]. A dimeric structure is formed through two *cis* μ_2-chlorine atoms [Bi-Cl 2.911(4) and 3.187(4)Å].



589

Conductivity data for the tetrafluoroborate salts [Bi(R_2dtc)$_2$(BF_4)] **590-92**[457] suggest that the compounds are univalent-electrolytes in nitrobenzene, while molecular weight measurements in dichloromethane suggests the compounds are monomeric in solution.

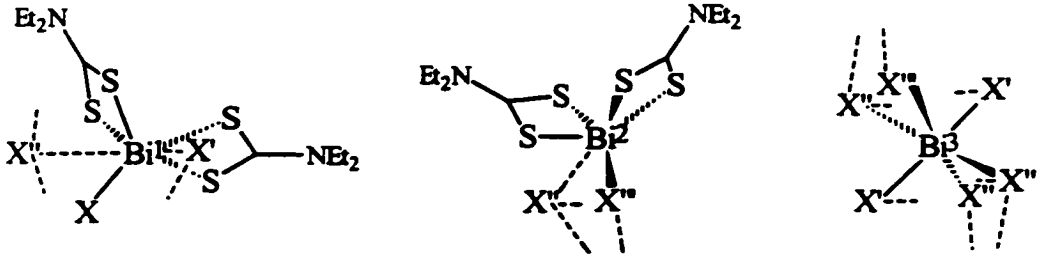
Examples of mono(dithiothiocarbamate) dihalides have also been prepared. The ethyl derivatives [Bi(Et_2dtc)X_2] **593**[469,481]**-95**[470 482]are isostructural and show a one-dimensional polymer with bismuth in a seven coordinate environment.[483] The



593-95

coordination spheres are occupied by an *S,S'*-dithiocarbamate ligand [Bi-S 2.594(3)-2.690(5)Å], two pairs of *cis* μ_2-halogen atoms which bridge to two neighbouring bismuth centers [Bi-X: Cl 2.673(3)-3.165(3); Br 2.820(2)-3.305(2); I 3.032(2) and 3.501(2)Å], and a bridging sulfur atom from a neighboring molecule [Bi---S 3.378(3)-3.462(5)Å].

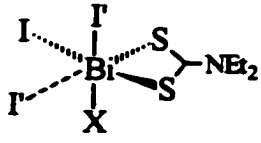
The intermediate mono-/bis- complexes of empirical formula $[Bi_5(Et_2\underline{dtc})_8X_7(\underline{dmf})]$ **596-98**[471] are also isostructural and show a pentanuclear unit with two six and one seven coordinate unique bismuth environments. One bismuth atom (Bi^1) is coordinated by two *S,S'*-dithiocarbamate ligands [Bi-S 2.60(1)-2.81(1)Å], a terminal halogen atom [Bi-X: Cl 2.89(1); Br 3.050(2); I 3.278(3)Å], a bridging μ_2-halogen atom [Bi-X: Cl 3.42(1); Br 3.515(3); I 3.706(4)Å], and a bridging μ_3-halogen atom [Bi-X: Cl 3.43(1); Br 3.533(3); I 3.680(3)Å]. A second bismuth center (Bi^2) is in a similar bonding environment [Bi-S 2.61(1)- 2.80(1)Å; Bi-(μ_2-X): Cl 3.04(1); Br 3.194(3); I 3.421(4)Å; Bi-(μ_3-X): Cl 3.42(1); Br 3.469(3); I 3.582(3)Å], but with the absence of the terminal halogen atom. A third bismuth center (Bi^3) is coordinated to bridging μ_2-halogen atoms [Bi-X: Cl 2.68(1) and 2.74(1); Br 2.860(3) and 2.862(3); I 3.070(3) and 3.053(3)Å] and μ_3-halogen atoms [Bi-X: Cl 2.71(1); Br 2.855(2); I 3.079(3)Å] only.



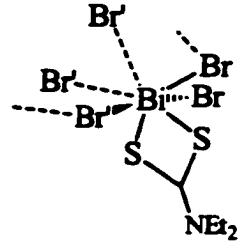
596-98

Several anionic complexes have also been prepared, including the monoanionic complex $[NEt_4][Bi(Et_2\underline{dtc})I_3]$ **599** and the partially brominated $[NEt_4][Bi(Et_2\underline{dtc})I_2Br]$

5100,[472] and the dianion $[Hpy]_2[Bi_4(Et_2dtc)_4Br_{10}]$ **5101**.[471] The dimeric anions of **599** and **5100** are isostructural and show bismuth in a six coordinate distorted octahedral environment. In addition to the *S,S'*-dithiocarbamate ligand [Bi-S 2.649(5)-2.770(6)Å], the bismuth coordination sphere is occupied by axial and equatorial terminal halogen



599-5100

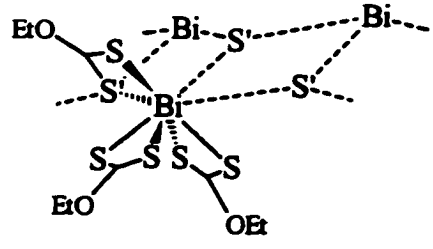


5101

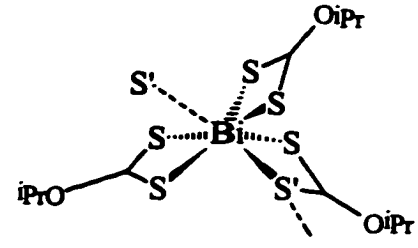
atoms [**599**: Bi-I 2.965(1) and 3.091(1); **5100**: Bi-Br 2.813(2)Å and Bi-I 3.006(2)Å] and axial and equatorial bridging iodine atoms [Bi-I **599**: 3.190(1), 3.291(1); **5100**: 3.115(2), 3.244(2)Å]. The anion of **5101** shows a tetranuclear unit with bismuth in a six coordinate environment. The coordination sphere contains one terminal [avg. Bi-Br 2.94(1)Å] and three bridging bromine atoms [Bi-Br 3.24(1)-3.34(1)Å], and an *S,S'*-dithiocarbamate ligand [Bi-S 2.68(3)-2.73(3)Å]. There is also one very long contact to the empty site on each bismuth center [avg. Bi---Br 3.74(1)Å].

A number of dithioxanthates have also been prepared, including the tris- products $[Bi(Rdtx)_3]$ **5102-106**,[474-476] and have structures similar to the tris(dithiocarbamate) analogues. Conductivity measurements suggest that the ethyl derivative $[Bi(Etdtx)_3]$ **5103** dissociates in ethanol solution. The structure of $[Bi(Medtx)_3]$ **5102**[473] [Bi-S 2.596(3)-2.998(4)Å] shows a dimeric unit analogous to $[Bi(Et_2dtc)_3]$ **576**, where the reciprocation of a long Bi---S contact [Bi---S 3.405(1)Å] from a neighbouring molecule creates a dimeric arrangement. The cyclohexyl- and benzyl- analogues **5105** [Bi-S 2.599(2)-3.063(2); Bi---S

3.210(2)Å] and **5106** [Bi-S 2.597(1)-3.025(1); Bi---S 3.375(1)Å] have analogous structures.[479] The one-dimensional polymeric arrangement of **5103**[477] [Bi-S 2.605(8)-2.99(1)Å] involves two long sulfur contacts from two neighbouring molecules [Bi---S 3.352(8)-3.627(9)Å], giving a bismuth-sulfur "ladder"-type polymeric backbone. The



5103

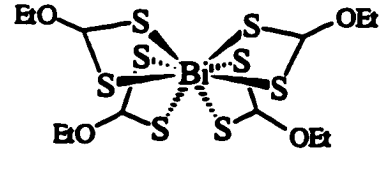


5104

structure of [Bi(ⁱPrdtx)$_3$] **5104**[475,478] is similar to that of **5102**, but in this case the long bismuth sulfur contacts of the molecular unit are to two separate neighbouring molecules, forming a one-dimensional coordination polymer [Bi-S 2.682(2)-3.175(2); Bi---S 2.842(2)Å].

Spectroscopic data of the bis(dithioxanthate) halides [Bi(Etdtx)$_2$X] (X = Cl **5107**, Br **5108**)[458] suggests solid state polymeric structures, while molecular weight measurements suggest that they are monomeric in solution.

The monomeric anion of the tetrakis(dithioxanthate) [NEt$_4$][Bi(Etdtx)$_4$] **5109**[474] shows an eight coordinate bismuth center bound by three asymmetrically bound [Bi-S 2.803(11)-2.972(10)Å] and one symmetrically bound [Bi-S 2.833(6) and 2.859(9)Å] *S,S'*-

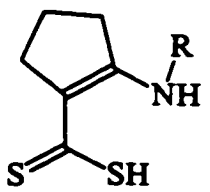


5109

dithioxanthate ligand.[480]

Although there are no examples of structurally characterized dithiocarbamate and dthioxanthate mixed ligand complexes, infrared data for [Bi(R_2dtc)$_2$(Etdtx)] **5119-120**[459] and [Bi(Et_2dtc)(Etdtx)$_2$] **5121**[460] suggest that dithiocarbamate ligands are more strongly bound than dithioxanthate ligands due to $^{2-}S_2C{=}N^+$ resonance.

In addition to the dithiocarbamate and dithioxanthates, 2-aminocyclopent-1-ene-1-dithiocarboxylic acid (Hacd) derivatives have been employed as ligands for bismuth. The 2-ethylamino derivative complex [Bi(eacd)$_3$] **5122**[461] shows a six coordinate distorted



R = H, Hacd
R = Et, Heacd

trigonal antiprismatic environment for bismuth, with three asymmetrically bound *S,S'*-dithiocarboxylate ligands [Bi-S 2.617(2)-3.108(2)Å]. A long bismuth sulfur contact [Bi---S 3.689Å] creates a weakly bound dimeric structure similar to **576**.

5.5 Summary and Conclusions

In summary, the data for bismuth-thiolate compounds presented in this chapter (see Figure 5.1) is intended as an introduction to the synthetic and structural chemistry of bismuth thiolates and as a platform for discussions regarding bifunctional thiolate chemistry in Chapters 6 and 7. For the most part, the database for the thiolate chemistry of bismuth is extensive, but is composed of examples which represent unique complexes

for a particular ligand, rather than series of related compounds establishing fundamental synthetic guidelines and illustrating general chemical properties. For monothiolate ligand complexes, the high thiophilicity of bismuth routinely imposes multithiolation and results in tris- thiolation in most cases. The introduction of an electron-withdrawing fluorinated R group increases the Lewis acidity of the bismuth center and facilitates the isolation of

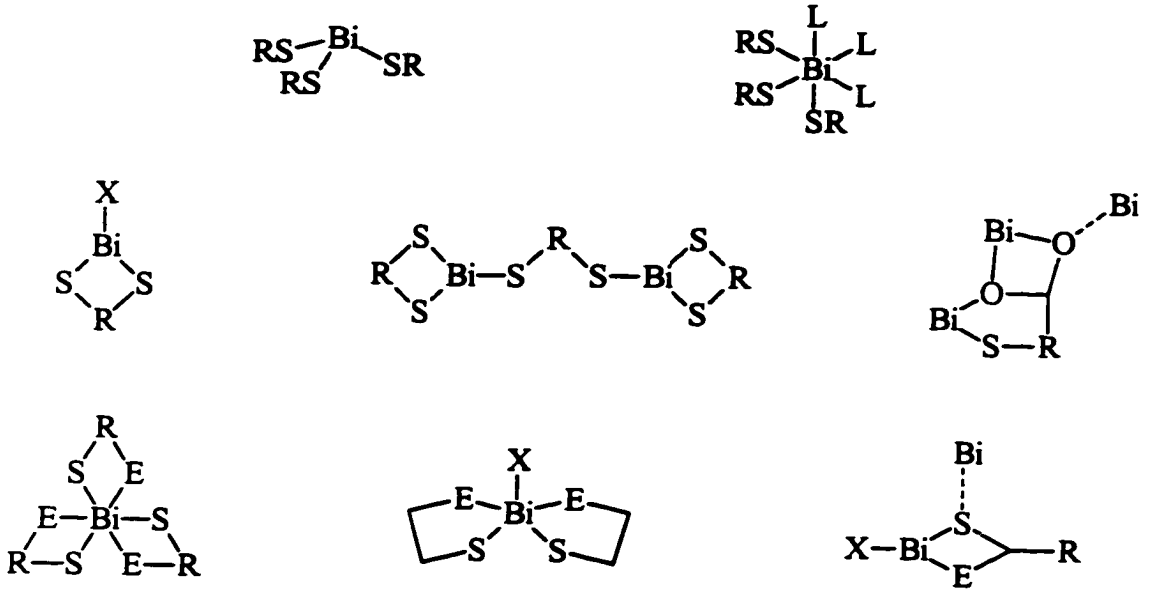


Figure 5.1 Bonding situations observed for bismuth thiolate complexes.

pentathiolate dianion and a series of Lewis base adducts, all of which exhibit octahedral-based geometries. The thiophilicity of bismuth is further demonstrated by the formation of highly coordinated and stable monocyclic bis(thiolate) and "tethered" tris(thiolate) complexes from dithiolate ligands. Few bismuth thiolatocarboxylate complexes have been prepared and show the ligand chelating bismuth in both *S,O* and *O,O* capacities, resulting in extensive intermolecular bonding typical of the carboxylate functionality. Although there are tris(thiolate) examples of complexes incorporating bifunctional

ketone-, imino- and azathiolate ligands, the introduction of secondary electron-donating functionalities allows for a potential decrease in Lewis acidity for bismuth and control of thiolation. This is demonstrated by the preference for a bicyclic bis(thiolate) arrangement of bismuth hydroxy- and amino-ethanethiolates, as well as the isolation of bis- and monothiolate complexes of the thiosemicarbazone ligand. Mono- and dithiocarboxylates chelate and intermolecularly bond with bismuth analogously to the carboxylate functionality, and may be viewed as bifunctional thiolates, incorporating a secondary ketone or thione donor. Only tris(monothiocarboxylate) complexes have been reported, while dithiocarboxylates currently represent the most varied coordination number for bismuth with examples of mono-, bis-, tris- and tetra- complexes known, but involve a range of ligands and a variety of synthetic procedures.

Chapter 6. Defining and Controlling the Aminoethanethiolate Chemistry of Bismuth(III): Synthesis and Comprehensive Characterization of Homologous Thiolatobismuth Series

6.1 Introduction

Difficulties associated with isolation and characterisation of bismuth compounds have precluded comprehensive assessment of their relative stability. Isolation yields are often not reported or are low, and are rarely evaluated in terms of other possible reaction products. Nevertheless, the synthesis and chemistry of these compounds remains superficially understood in that most compounds have been isolated under specific conditions and without investigation of other possible reaction products. Moreover, there are few examples[6,484] of studies into the reproducible interchange between derivatives or related compounds, and variation in antimicrobial bioactivity[485,486] among the members of systematic series of structurally simple compounds[2,3] suggests a structure/activity relationship for the bismuth environment.[4] Such realizations highlight the need for universally applicable synthetic procedures which enable control of the coordination chemistry for heavy elements. Comprehensive structural and spectroscopic characterisation of systematic series of compounds represents the most reliable fundamental foundation for rational chemical development.

The potential utility of chelating bifunctional ligands, containing one thiolate moiety and an auxiliary donor to mediate the thiophilicity of bismuth is demonstrated by isolation of the bicyclic bis(hydroxyethanethiolato)bismuth complexes **550-51**, **553** and **555**[3,435,436] as most readily isolated products.[437] Further, the analogous

bis(aminoethanethiolato) bismuth nitrate complex **563** [hereafter denoted **6B**$(NO_3)\bullet H_2O$] is the only reported product of the reaction between $Bi(NO_3)_3$ and aminoethanethiol in acetic acid.[445] The penicillamine compound **549** represents a unique example of a mono(thiolate), but is facilitated through the introduction of an anionic carboxylate functionality.[434]

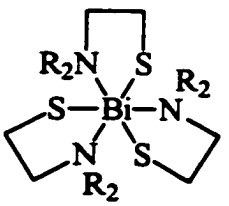
In addition to the examples presented in Chapter 5 (**561-63**), there are rare examples of spectroscopically characterized organobismuth aminobenzenethiolate (abt) complexes. The preparation of both the mono- and bis(thiolate) compounds $[BiPh_2(abt)]$[487] and $[BiPh(abt)_2]$[443] from Habt and $BiPh_3$ represent the only reports of variable thiolation from common starting materials. However, it is odd that the formation of the monothiolate product involves a greater stoichiometry of thiol reactant [1:1 vs. excess $BiPh_3$ for the bis(thiolate)] and heating, both conditions which would be expected to promote maximum metathesis. The methyl bis(thiolate) analogue $[BiMe(abt)_2]_n$[487] and a series of dimethyl thiolate compounds Me_2BiSR,[488] were R is a nitrogen substituted organic ring, are prepared from metathesis reactions involving alkali metal thiolates and organobismuth halides.

To exploit the realization of variable and minimal thiolate coordination, a comprehensive assessment of the reactions involving $BiCl_3$ or $Bi(NO_3)_3$ with aminoethanethiol or dimethylaminoethanethiol was performed at various stoichiometries, in the presence of KOH. Addition of base serves to activate the thiol (to a thiolate), and thereby provides a reliable and direct control of the extent of metathesis. In this manner, this chapter defines the conditions to prepare and characterize homologous series of tris- (**6A**), bis- (**6B**) and mono(aminoethanethiolato)bismuth complexes (**6C** and **6D**),[489] and the solid state structure of at least one example of each has been confirmed, thereby

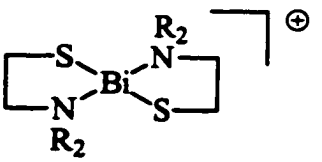
clarifying and expanding the limited preliminary conclusions arising from previous spectroscopic[434,440,441,444,445,490,491] and structural studies.[434,445]

6.2 Results and Discussion

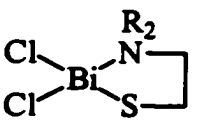
The aminoethanethiolate and dimethylaminoethanethiolate anions react rapidly with $BiCl_3$ or $Bi(NO_3)_3$ to give yellow solutions from which crystalline materials have been isolated by various solution concentrating procedures. Isolates from reactions of the dimethylaminoethanethiolate anion with $BiCl_3$ reflect the respective reaction stoichiometry [3:1 gives **6A(Me)**, 2:1 gives **6B(Me)**, 1:1 gives **6C(Me)**]. In contrast, tris-thiolation to give **6A** can only be achieved with the parent aminoethanethiolate ligand by introducing a heavy excess (5:1) of the anionic ligand, and the precise 3:1 stoichiometry affords **6B**Cl.



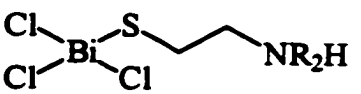
6A



6B



6C



6D

R = H for compounds labeled ***6N***
R = Me for compounds labeled ***6N*(Me)**

The apparent impedance of complete metathesis for the parent ligand is likely due to coordinative interactions from the pendant amines, which inevitably mediate the Lewis

acidity of the bismuth center. The apparent weaker donor ability of the dimethylamino-functionality (pK_b of NMe_3 4.13) over that of the amino- group (pK_b of NH_2Me 3.35) is counterintuitive and is accredited to the relative increase in steric restrictions, as observed in the methylated (amine) derivative [**6B**(Me)Cl]. Also, the excess ligand is anomalously soluble in the reaction mixture to give **6A**, and **6B**Cl shows an enhanced solubility in the presence of excess ligand. This may be interpreted as indications of the incipient formation of anionic poly-thiolates of the type $[Bi(SCH_2CH_2NR_2)_4]^-$ and $[BiX(SCH_2CH_2NR_2)_3]^-$, respectively, the lability of which may be responsible for the broad signals observed in NMR spectra (*vide infra*), and the existence of which contributes to the incompleteness of thiolation.

Reactions involving $Bi(NO_3)_3$ with the methylated ligand typically give oils on evaporation of solvent, so that **6B**(Me)NO_3 and **6C**(Me)NO_3 have not been isolated, and an insignificant yield of **6A**(Me) (identified by Raman spectroscopy) was obtained from a 3:1 reaction stoichiometry. Further, the lability of the nitrate counterion[492] suggests that the monothiolate compound **6C**(Me)NO_3 is not likely to be isolated. Nevertheless, the parent compound **6B**NO_3 is readily obtained both as the previously reported hydrated form,[445] and as an unsolvated solid. The former is isolated from relatively dilute solutions containing excess ligand (3:1 stoichiometry), by slow crystal growth over a number of days. Rapid crystal growth from preconcentrated solutions of appropriate stoichiometry give **6B**NO_3. These synthetic routes may be viewed as improvements over the literature preparation,[445] which could not be repeated despite several attempts and of which the original reaction conditions are questionable. The reaction involves similar reactants but is performed in acidic media, and would be expected to give ammonium salts.

Reactions of BiX_3 with dimethylaminoethanethiol or dimethylaminoethanethiol hydrohalide give **6D(Me)X** (X = Cl, Br) as an essentially quantitative precipitate, independent of stoichiometry.[493] This dramatic thermodynamic preference for coordination of the ammoniumethanethiolate tautomer of the thiol is confirmed by the high yield substitution of nitrate for chloride/ bromide observed in the 3:1 reaction of $HSCH_2CH_2NMe_2 \bullet HX$ with $Bi(NO_3)_3$. Moreover, precipitate mixtures containing **6C(Me)Cl** and KCl produce **6D(Me)Cl** when washed with water, illustrating the labile and basic nature of the amine chelate interaction.

Except in the case of **6D(Me)X** [obtained as a analytically pure powder in 97 (Cl) and >95% (Br) yield], the isolated yields do not generally illustrate quantitative reactions, that are sometimes observed for thiolate-bismuth systems,[2] and each reaction mixture may contain all of the metathetical products that have been isolated over the range of stoichiometric conditions. Nevertheless, it is clear that the imposed stoichiometries conveniently and sufficiently enhance formation of one complex over the others to allow for isolation by crystal growth. Compound **6C(Me)**$\bullet$¼HCl is reproducibly obtained (each sample characterized by X-ray crystallographic analysis) as Pasteur isolated crystals from a powder mixture.

Bismuth thiolates typically exhibit low solubilities in most solvents and strong donor solvents are required to enable any appreciable solvation, usually with the formation of a resilient solvent coordination complex (eg. **522**$\bullet$2py, **532**$\bullet$2py and **533**$\bullet$2py).[2,428,432] Complexes involving the bifunctional chelate ligands aminoethanthiolate and hydroxyethanethiolate have substantially higher solubility,

perhaps due to the presence of the auxiliary donor site on the ligand, which mimics the role of the donor solvent and occupies possible intermolecular coordination sites. As a result, these complexes are more routinely recrystallised and are amenable to solution NMR spectroscopic characterization. ^{1}H and ^{13}C NMR spectra are consistent with the compounds retaining their topological solid state structures in solution, but signals are generally broad, implicating exchange processes, possibly due to the formation of hypervalent anionic complexes and consequential ligand lability.

As is typical for thiolatobismuth compounds, these complexes are thermally sensitive and, except for compound **6A** and **6A(Me)**, all decompose (dramatic color change) before melting. Each compound exhibits a number of useful features in the IR spectra, but the Raman spectra show very distinctive and intense bands below 400 cm^{-1}, which can be conveniently used as a reliable "fingerprint" identification of crystalline or powder materials.

While electron impact mass spectra of thiobismuth compounds are generally uninformative as a result of their thermal instability, the APCI technique[3] provides characteristic fragments, the most prominent of which are the bis-thiolates **6B**$^{+}$ and **6B(Me)**$^{+}$ (m/z 361, 417), and atomic bismuth (m/z 209). Other fragments include the bismuthenium monocycle $[Bi(SC_2H_4NH)]^{+}$ (m/z 284), $[Bi(SC_2H_4NH_2)Cl]^{+}$ (m/z 320) and $[Bi(SC_2H_4NH_2)Cl + (dmf)]^{+}$ (m/z 393) for **6B**Cl and $[Bi(SC_2H_4NMe_2)Cl]^{+}$ (m/z 348) for **6B(Me)**Cl. A protonated molecular ion is also readily observed for **6B(Me)**Cl (m/z 453) and **6C(Me)** (m/z 384). In addition to other fragments also observed for **6A(Me)** and **6B(Me)**, spectra of both compounds show a solvent adduct peak $[Bi(SC_2H_4NMe_2)Cl +$

(dmf)]$^+$ (m/z 421). Interestingly, **6D(Me)Cl** displays the m/z 417 fragment, suggesting that ligand lability allows for rearrangement to a bicyclic configuration.

The solid state structures of compounds **6A**, **6A(Me)**, **6B**NO_3, **6B**$NO_3 \cdot H_2O$, **6B**Cl, **6B(Me)Cl**, **6C(Me)**$\cdot$¼HCl and **6D(Me)Cl** have been confirmed by X-ray crystallography (Table 6.1), although the crystal structure of **6A(Me)** involves positional disorder which precludes detailed structural discussion.[a] As representatives of each type of complex, crystal structure views of compounds **6A**, **6B**Cl, **6B(Me)Cl**, **6C(Me)**$\cdot$¼HCl and **6D(Me)Cl** are shown in Figures 6.1-6.5, respectively (H atoms are omitted for clarity). The chelate motif of the ligand is evident in all structures except for that of **6D(Me)Cl**, in which the pendant amine is protonated rather than coordinated to the Lewis acidic bismuth centre. As observed for the dithiolate[2] and hydroxythiolate[3] heterocycles, polymeric packing arrays are made possible by intermolecular Bi---Cl and/or Bi---S interactions,[493] which are distinctively long. **6C(Me)** adopts a 4:1 hydrochloride cluster array (Figure 6.4) in which the unique chloride anion acquires a tetragonal site, engaging four bismuth centers and representing the third Bi-Cl (Bi---Cl) interaction for each molecule of **6C(Me)**.

Bis(thiolate) complexes involving the parent ligand, **6B**NO_3 and **6B**Cl, are best interpreted as ionic materials composed of the cation **6B**$^+$, on the basis of their relatively long Bi-O [3.05(2)Å] and Bi-Cl [3.121(3) Å] distances, respectively. These interactions are responsible for their polymeric lattice arrays, and the structure of **6B**NO_3 only differs from the hydrated solid **6B**$NO_3 \cdot H_2O$[445] in that water adopts one of two anion contacts

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[a] Crystal data for **6A(Me)**: $C_{12}H_{30}BiN_3S_3$, FW 521.55, trigonal, space group R3 (#146), a = 16.2626(8)Å, c = 6.579(2)Å, V = 1506.9(2)Å, Z = 3.

Table 6.1 Selected bond distances (Å) for aminoethanethiolates (Bi---Cl and Bi---S are intermolecular contacts).

	6A	**6B**NO_3	**6B**NO_3 •H_2O[445]	**6B**Cl	**6B**(Me)Cl	**6C**(Me) •¼HCl	**6D**(Me)Cl
Bi(1)-S(1)	2.748(7)	2.575(8)	2.549(2)	2.608(3)	2.538(9)	2.530(7)	2.669(3)
Bi(1)-S(2)	2.567(5)		2.589(2)	2.569(3)	2.572(9)		
Bi(1)-S(3)	2.654(5)						
Bi(1)-N(1)	2.81(2)	2.48(2)	2.462(5)	2.528(9)	2.84(2)	2.52(2)	
Bi(1)-N(2)	2.83(2)		2.455(6)	2.398(8)	2.67(3)		
Bi(1)-N(3)	2.64(2)						
Bi(1)-O(1)		3.05(2)	3.107(6)				
Bi(1)-O(3)			3.004(6)				
Bi(1)-Cl(1)				3.121(3)	2.618(9)		2.776(4)
Bi(1)-Cl(2)						2.672(7)	2.615(4)
Bi(1)-Cl(3)						2.548(8)	2.636(3)
Bi(1)---Cl(1)						3.109(1)	3.001(4)
Bi(1)---S(1)	3.686(9)	3.331(10)	3.550(2)	3.479(3)	3.494(9)	3.534(8)	2.927(3)
Bi(1)---S(2)			3.517(2)				

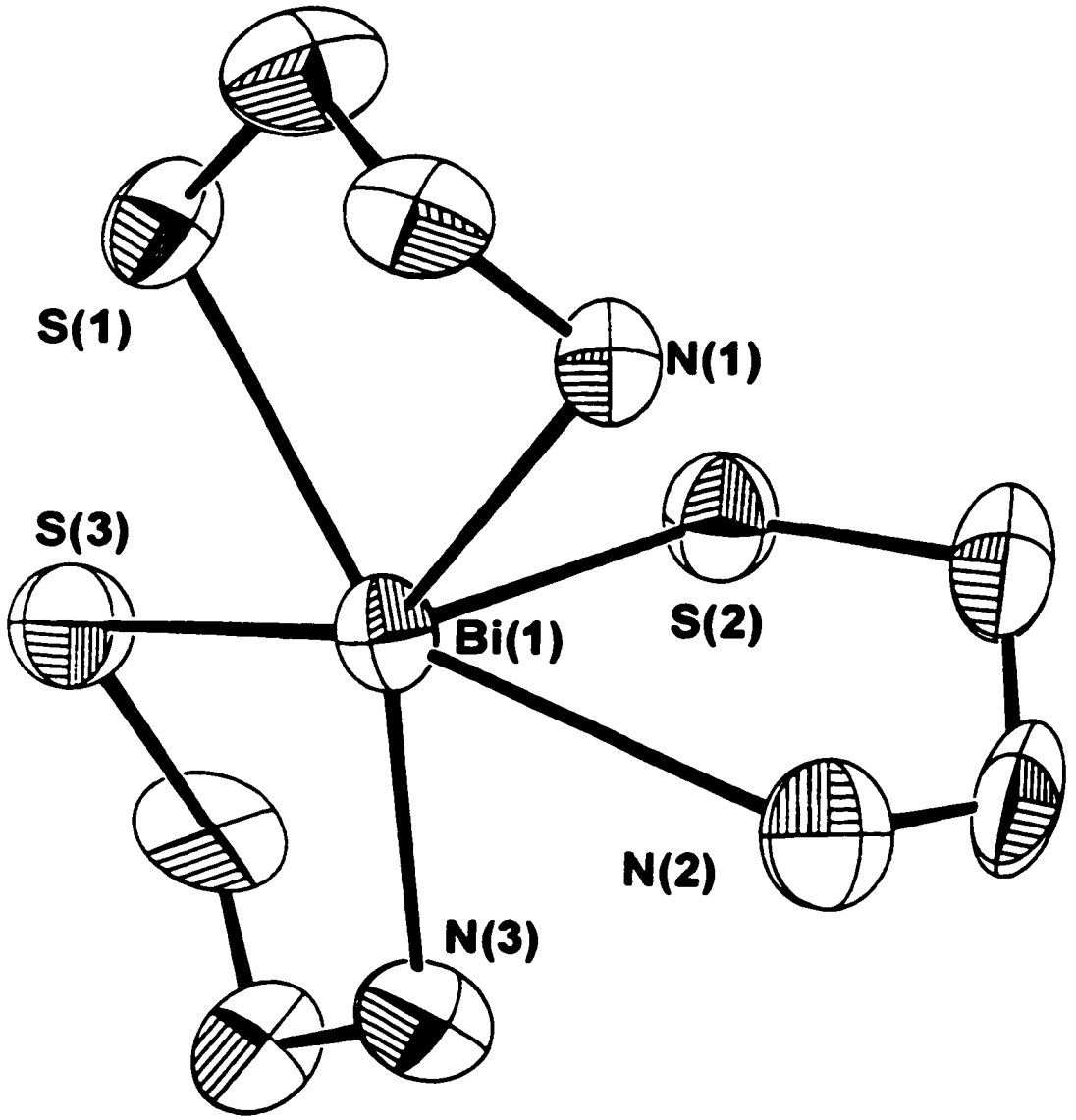


Figure 6.1 Crystallographic view of $Bi(SCH_2CH_2NH_2)_3$, 6A.

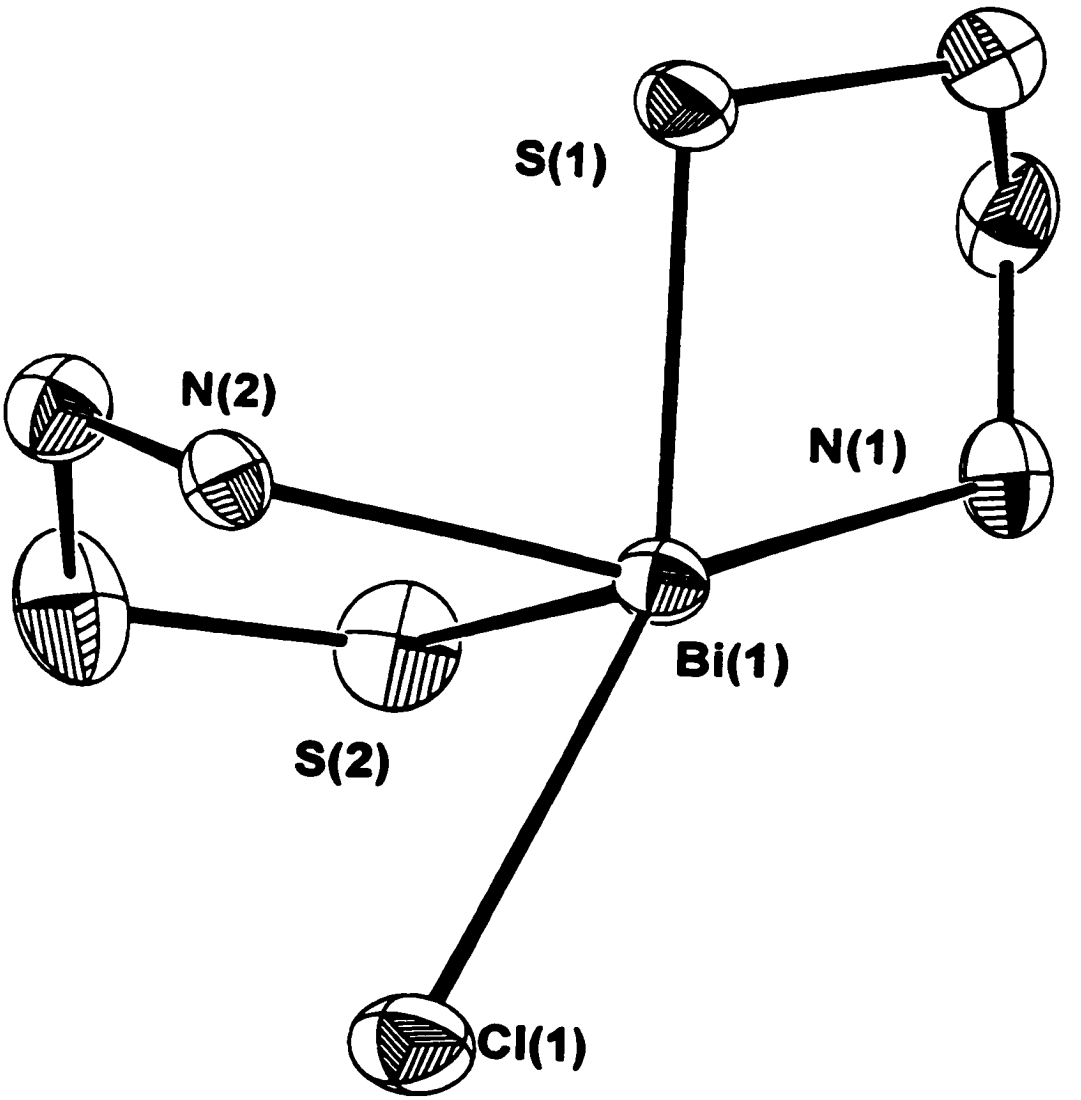


Figure 6.2 Crystallographic view of $Bi(SCH_2CH_2NH_2)_2Cl$ 6BCl.

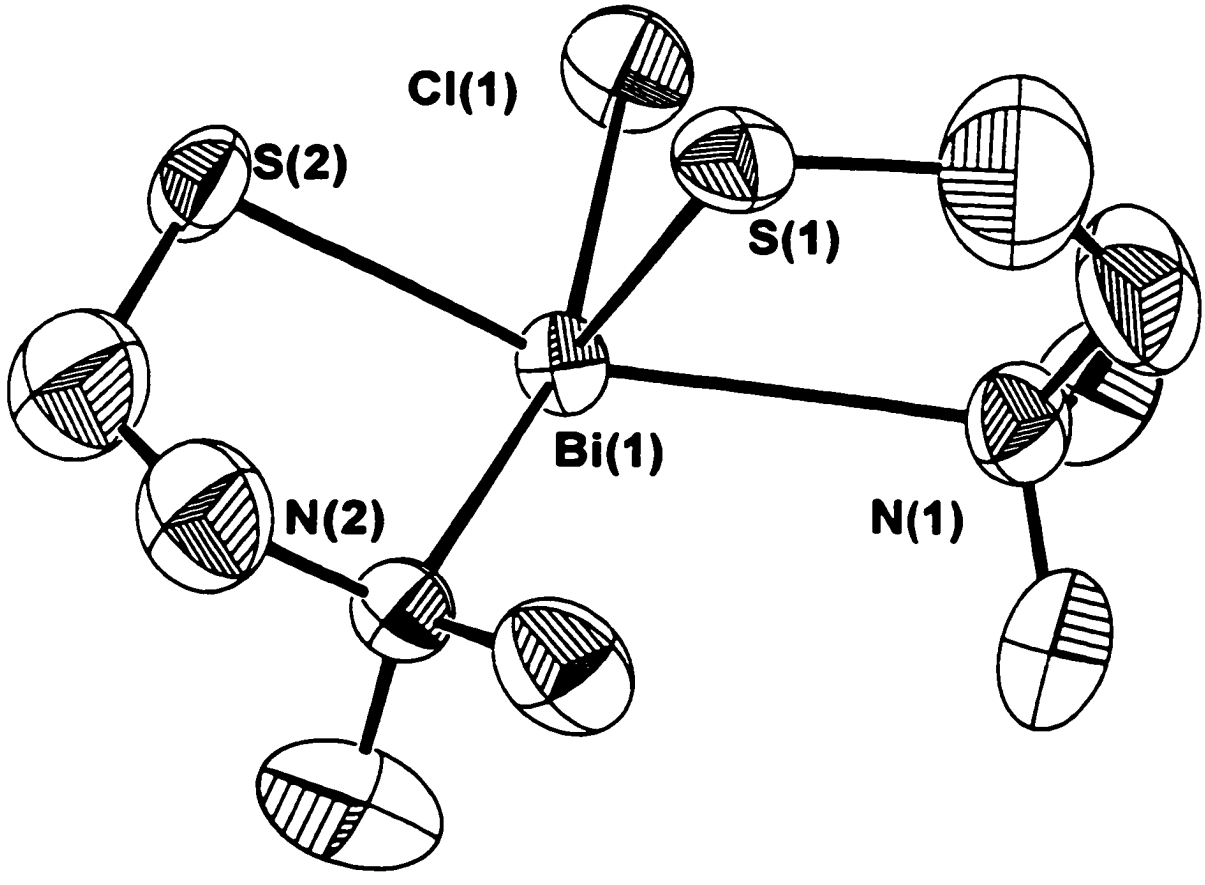


Figure 6.3 Crystallographic view of $Bi(SCH_2CH_2NMe_2)_2Cl$ ⊆B(Me)Cl.

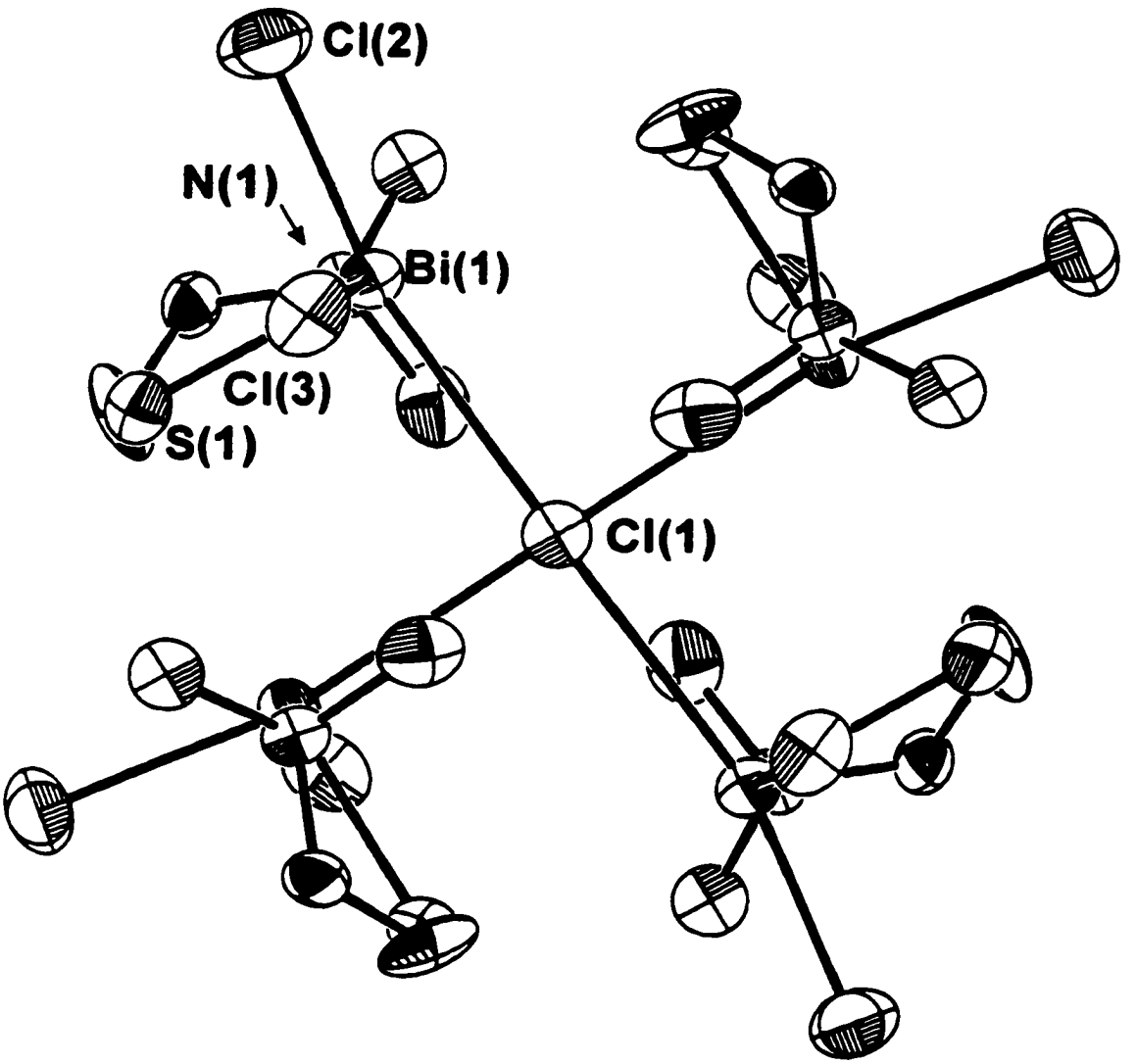


Figure 6.4 Crystallographic view of the tetramer of $Bi(SCH_2CH_2NMe_2)Cl_2$ 6C(Me)•¼HCl.

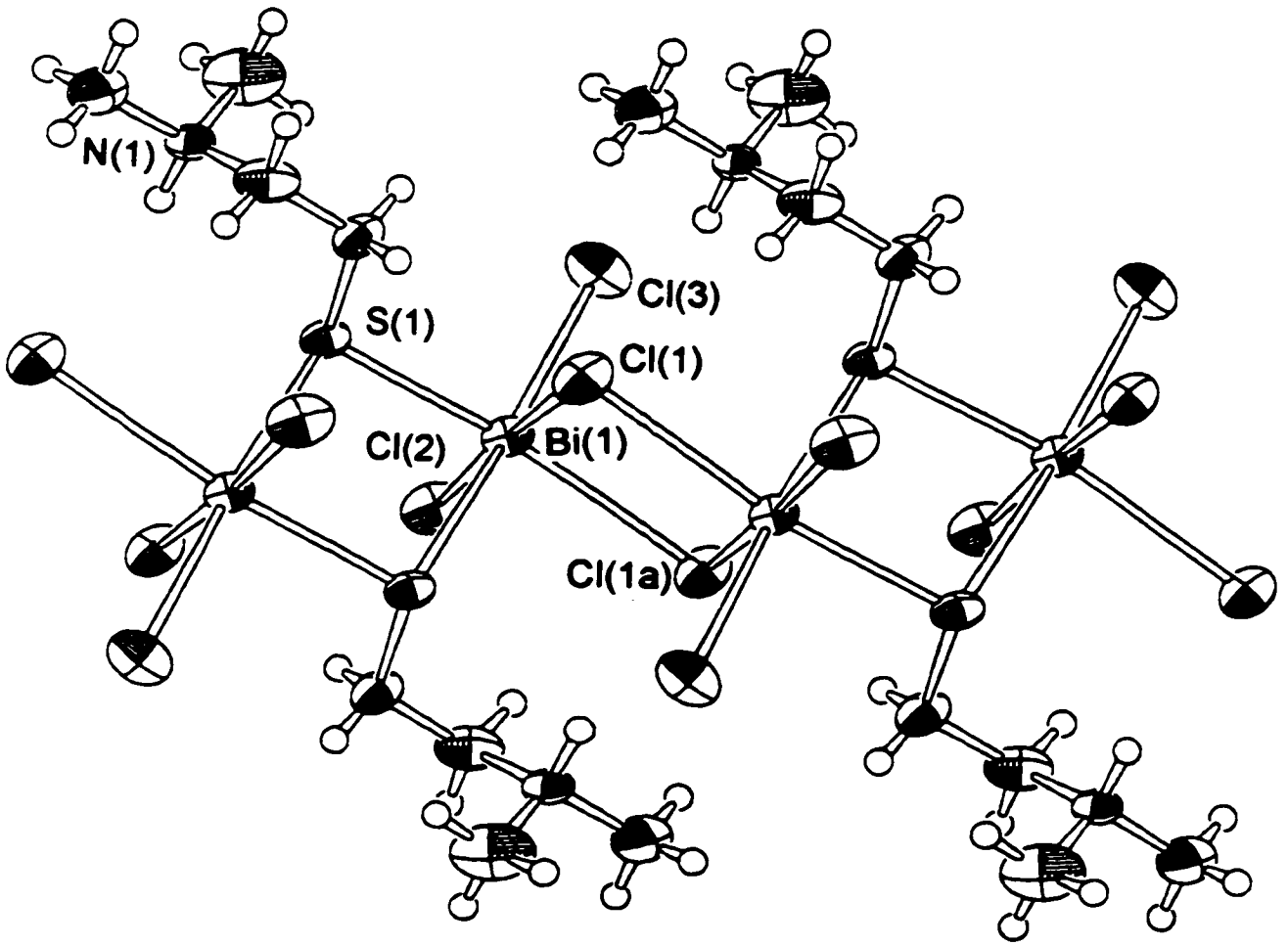


Figure 6.5 Crystallographic view of $Bi(SCH_2CH_2NHMe_2)Cl_3$, 6D(Me)Cl.

observed in the solvent free structure. In surprising contrast to **6B**Cl, **6B**(Me)Cl has a substantially shorter (more covalent) Bi-Cl interaction [2.618(9)Å], and is best considered molecular in the solid state aside from the intermolecular Bi---S contacts. These structural differences may be rationalized in terms of the steric hindrance borne by the pendant amines in **6B**(Me)Cl relative to those of the parent ligand. The restricted access of the amines in **6B**(Me)Cl is evident in the Bi-N bond distances [**6B**(Me)Cl: 2.84(2)Å, 2.67(3)Å; **6B**NO_3: 2.48(2)Å; **6B**Cl: 2.528(9) Å, 2.398(8) Å], and the correspondingly weaker auxiliary amine donation in **6B**(Me)Cl enabling a more competitive coordination of Cl^-. The relative withdrawal of the pendant amines in **6B**(Me)Cl may be associated with the distorted *cis* configuration of the cation moiety, which contrasts the *trans* configuration adopted in both **6B**NO_3 and **6B**Cl.

The intermolecular interactions (Bi---S) are longest in **6A**, enabling an essentially molecular structure in the solid state, with a distorted pentagonal pyramidal geometry at bismuth imposed by two *cis* equatorial sulfur sites, one apical sulfur site and three equatorial nitrogen sites, and perhaps implicating a stereochemically active lone pair in the other apical position.

The acyclic structure of **6D**(Me)Cl contains a six-coordinate, near octahedral bonding environment for bismuth. A one dimensional spirocyclic polymeric arrangement results from the association of the bismuth centres by alternating chlorine and sulfur coordinative bridges. The two Bi-$Cl_{terminal}$ bonds [2.615(4) and 2.636(3)Å] are shorter than the Bi-$Cl_{bridging}$ bonds [2.776(4) and 3.001(4)Å]. Likewise, the Bi-S bond [2.669(3)Å] which is *trans* to the Bi-$Cl_{bridging}$ is significantly shorter than that which is *trans* to a Bi-

$Cl_{terminal}$ [2.927(3)Å].[493] These bond distance comparisons can be interpreted in terms of the bismuth center engaging four covalent bonds (three chlorine and one sulfur) (Figure 6.5) and two coordinative bonds (one chlorine and one thioether) from a neighboring molecule.

As a demonstration of the potential broad utility of the established synthetic methods, the antimony analogue (**6E**Cl) of complex **6B**Cl has been isolated[b] from an analogous reaction of aminoethanethiolate with antimony chloride in ethanol and structurally characterized (Figure 6.6). A similar bicyclic arrangement is observed as for the bismuth complex, but with the complete removal of the chlorine atom from the antimony coordination sphere, giving a rare example of a stibenium cation.

6.3 Conclusions and Future Directions

The homologous series of mono-, bis- and tris- thiolated bismuth complexes presented above establish the coordinative flexibility of bismuth(III) with aminoethanethiolates and illustrates the ease of stoichiometrically controlling thiolate coordination chemistry. The pendant amine moieties mediate the high thiophilicity of bismuth even in the presence of thiolate moieties (rather than thiols) by coordinatively engaging the bismuth center, so that the stoichiometry of the reaction mixture governs the degree of thiolation in the isolated product, thereby overcoming the astoichiometric multithiolation, typically encountered in reactions of bismuth salts with thiols. The degree of thiolation by the aminoethanethiolate ligand can be further tuned by manipulating the coordination of the auxiliary amine in two ways: the steric imposition of

[b] Prepared in the Chemistry 3101 undergraduate laboratory, Dalhousie University.

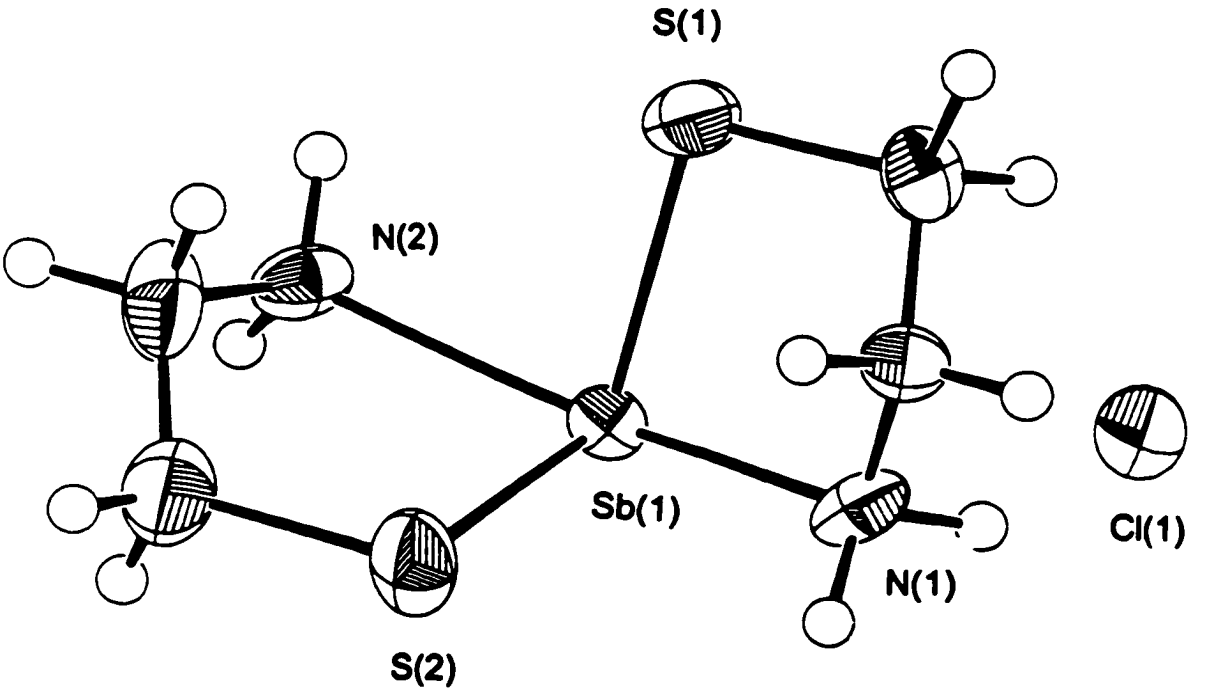
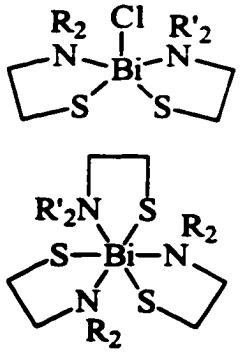


Figure 6.6 Crystallographic view of $Sb(SCH_2CH_2NH_2)Cl$ 6ECl. Selected bond lengths [Å]: Bi(1)-S(1) 2.470(6); Bi(1)-S(2) 2.440(6); Bi(1)-N(1) 2.37(2); Bi(1)-N(2) 2.35(2); Bi(1)-Cl(1) 3.577(6).

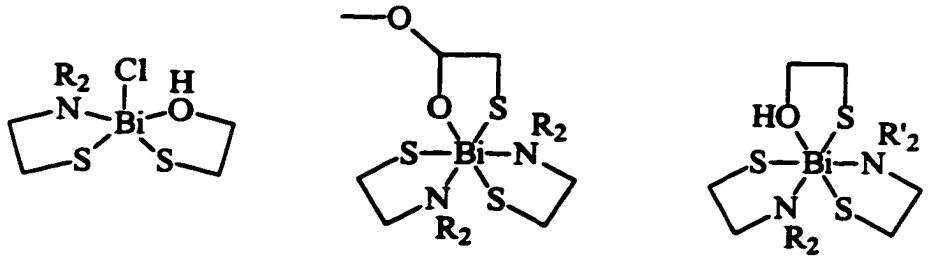
methyl substituents on nitrogen allows for a slightly higher degree of thiolation than the parent ligand, and the amine can be entirely uncoupled from bismuth by protonation, with retention of a monothiolatobismuth complex. These results provide a systematic and comprehensive series of structurally simple thiolatobismuth complexes and the synthetic approach is likely applicable to heavy metals in general. The potential widespread utility of the established synthetic methods has been demonstrated in the preparation of an antimony analogue and the novel bismuth (methylester)methanethiolates discussed in Chapter 7.

To date, studies into mixed-thiolate bismuth complexes have not been reported. Compounds of mixed dithiocarboxylate ligands have been prepared (Chapter 5.4), including mixed dithiocarbamate, dithioxanthate, as well as dithiocarbamate-dithioxanthate complexes. The controlled thiolation demonstrated by the synthesis of the first homologous aminothiolate series suggests a potential for sequential thiolation using various substituted amine functionalities:

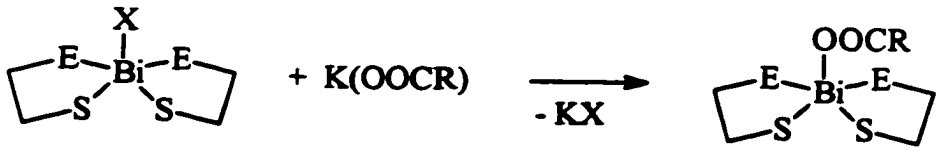
$$[Bi(SCH_2CH_2NR_2)_mCl_{3-m}] + n\,K(SCH_2CH_2NR'_2) \xrightarrow[-\,n\,KCl]{}$$



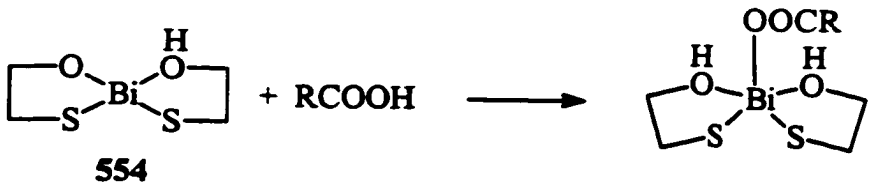
In addition, the aminothiolate ligands could be substituted for other bifunctional thiolate ligands (e.g. ester-, hydroxy-) to produce mixed functionality compounds:



Bis(bifunctional thiolate) bismuth sources have been isolated from aqueous media [e.g. bis(hydroxy-/aminothiolato)bismuth nitrates **550**/6BNO_3] and are potential intermediates to water stable bismuth carboxylate complexes. One possible reaction pathway involves ligand exchange reactions, such as those employed to prepare [$Bi(SCH_2CH_2OH)_2X$] (X = Cl, Br) **551-52** from the nitrate salt **550**:



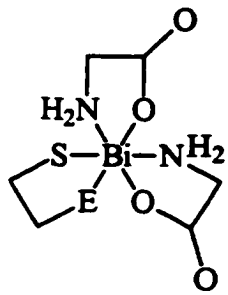
Also, as bis(hydroxyethanethiolato) bismuth acetate **555** is prepared by recrystallization of the hydroxythiolate-alkoxythiolate complex **554** from acetic acid, similar methods may be employed to prepare other carboxylate analogues:

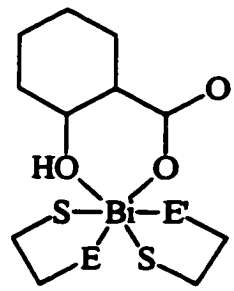


554

The high pK_a's and weak chelate abilities of α-amino acids, hydroxycarboxylates and other simple bifunctional carboxylates promote hydrolysis reactions of bismuth in aqueous media. The above outlined reactions may be expanded and employed to investigate the structural, spectroscopic and reaction chemistry of mixed water stable

bifunctional carboxylate/thiolate complexes, incorporating biologically and medicinally interesting ligands such as glycinate and salicylate:





Chapter 7. (Methylester)methanethiolates: The First Ester Complexes of Bismuth(III) as a Step Toward Modeling 'Colloidal Bismuth Subcitrate'

7.1 Introduction

This chapter describes the preparation of the first ester complexes of bismuth(III), which adopt intermolecular arrangements analogous to the ubiquitous dimer structure observed for citrate complexes of bismuth in CBS **209-15**.[234,235] In the absence of bismuth-ester complexes in the literature, section 7.2 introduces the established chemistry of bismuth-carbonyl compounds. As a backdrop for structural discussions, a molecular orbital model for bismuth complexes is presented in section 7.3.

7.2 Synthesis and Structure of Bismuth-Organocarbonyl Complexes

There are few examples of bismuth compounds containing *O*-carbonyl bound ligands in the literature, the majority of which are bifunctional and involve ketone and alkoxide donors. The dipivaloylmethanate compound [Bi(dpm)$_3$(Hdpm)] **705** is an analogue of the ketothiolate [Bi(PhCH{S}CH$_2$C{O}Ph)$_3$]$_2$[CH$_2$Cl$_2$] **558**, which was discussed in Chapter 5.3. Other structurally characterized compounds include mono- and polydentate Lewis base adducts. Characterization data is presented in Table 7.1.

Lewis base adducts of bismuth trihalides are prepared by direct addition of the ligand, while bifunctional alkoxides are isolated from metathesis reactions between bismuth alkoxides and titanium alkoxides, as well as other common bismuth reactants. Organobismuth halide adducts [PhBiBr$_2$(dmpu)] and [PhBiBr$_2$(dmpu)$_2$] have also been prepared and structurally characterized.[423]

Table 7.1 Analytical data for organocarbonyl compounds.

Compound	yield (rxn 7.*n*)*	XR	mp	EA	sol	con	IR	Ram	UV	NMR	MS
[Bi(dmpu)$_6$][Bi$_3$I$_{12}$] **701**[494]	36 (1)	x	-	x	-	-	-	-	-	-	-
[Bi(emal)$_3$] **702**[495]	- (2)	x	-	-	-	-	-	-	-	-	-
[Bi(bzt)$_2$(NO$_3$)] **703**[496]	57 (3)	x	x	x	-	x	x	-	-	x	x
[Bi$_2$(μ-OPr^i)$_2$(OPr^i)$_2$-(η^2-acac)$_2$]$_\infty$ **704**[497]	73.5 (4,5)	x	-	-	x	-	x	-	-	x	-
[Bi(dpm)$_3$(Hdpm)] **705**[498]	-(6)	x	-	-	-	-	-	-	-	-	-
[Bi(cfh)$_3$Cl$_3$] **706**[499]	- (1)	x	-	x	-	-	x	-	x	-	-

*Syntheses:

7.1) $BiX_3 + n\,L \rightarrow BiX_3(L)_n$

7.2) $BiX_3 + 3\,HL + 3\,MOH \rightarrow BiL_3 + 3\,MX + 3\,H_2O$

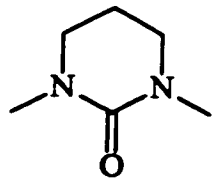
7.6) $Bi(NO_3)_3 + HL \rightarrow [Bi(L)_2(NO_3)] + 2\,HNO_3$

7.3) $Bi(OR)_3 + HL + Ti(OR')_4 \rightarrow Bi(L)(OR')_2 + Ti(OR)_2(OR')_2 + HOR$

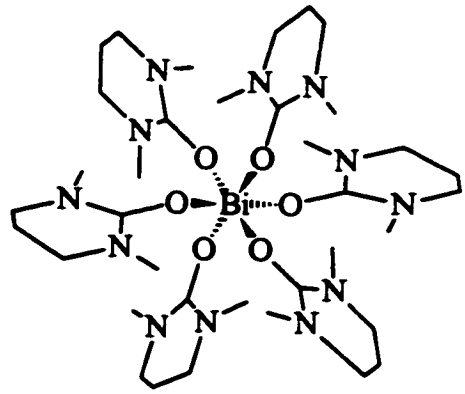
7.4) $Bi(OR)_3 + HL \rightarrow Bi(L)(OR)_2 + HOR$

7.5) $BiPh_3 + 3\,HL \rightarrow BiL_3 + 3\,PhH$

The structure of the cation of the dmpu complex [Bi(dmpu)$_6$][Bi$_3$I$_{12}$] **701**[494] shows bismuth in a six coordinate near octahedral environment, with all six coordination sites occupied by *O*-dmpu ligands [Bi-O 2.312(8)Å; Bi-O-C 155.7(8)°]. A bismuth thiolate dmpu adduct [Bi(SC$_6$F$_5$)$_3$(dmpu)$_2$] **518**[421] has also been structurally characterized, and was discussed in Chapter 5.

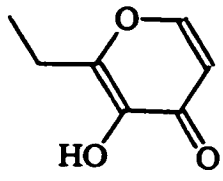


dmpu

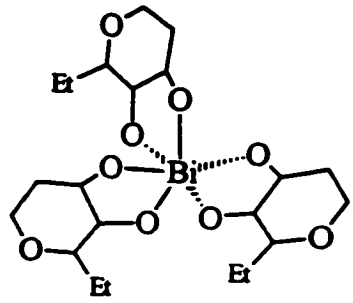


701

The monomeric structure of bismuth ethylmaltolate [Bi(emal)$_3$] **702**[495] shows a six-coordinate distorted pentagonal bipyramidal environment for bismuth, with all three *O,O'*-bidentate ligands forming five-membered -BiOCCO- rings [Bi-$O_{alkoxide}$ 2.124(7)-2.250(7)Å; Bi-O_{ketone} 2.420(8)-2.518(7)Å]. The facial alkoxide oxygen arrangement incorporates the apical site.

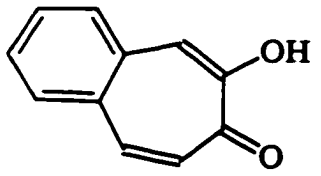


Hemal

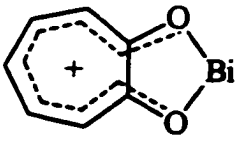


702

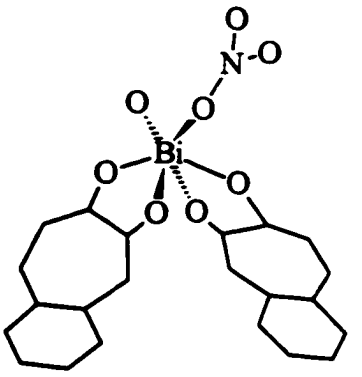
The aromatic character of the condensed benzene ring of the 4,5-benzotropolonato (bzt) anion prevents delocalization of the double bonds in the tropolonate ring (structure IX), allowing the ligand to chelate bismuth in a ketone-alkoxide manner. The bis(bzt) complex [Bi(bzt)$_2$(NO$_3$)(H$_2$O)] **703**[496] shows a six coordinate distorted environment for bismuth incorporating two *O,O'*-tropolonate ligands [Bi-O_{ketone} 2.323 and 2.311; Bi-



Hbzt



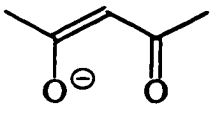
IX



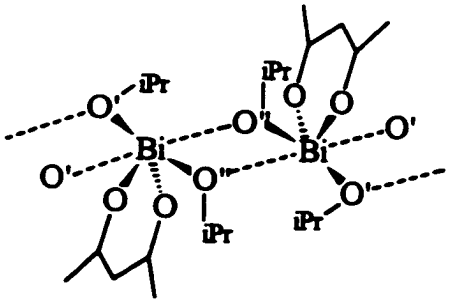
703

$O_{alkoxide}$ 2.263 and 2.130Å], an *O*-water molecule [Bi-O 2.621Å] and a weakly coordinated monodentate nitrate group [Bi-O 2.795Å].

$[Bi_2(\mu\text{-}OPr^i)_2(OPr^i)_2(\eta^2\text{-}\underline{acac})_2]_\infty$ **704**,[497] a rare example of a mixed anionic ligand complex, shows a dimer based one-dimensional polymer in the solid state. The six coordinate bonding environment for bismuth is occupied by two pairs of asymmetrically bridging alkoxide oxygen atoms [Bi-O 2.19(2) and 2.12(3); Bi---O 2.50(2) and 2.69(3)Å], and an <u>acac</u> ligand [Bi-$O_{alkoxide}$ 2.27(3); Bi-O_{ketone} 2.43(4)Å], forming a six-membered -BiOCCCO- ring. The increased coordination results in very low volatility and thermal instability of the compound compared to other bismuth alkoxides. Bismuth



<u>acac</u>



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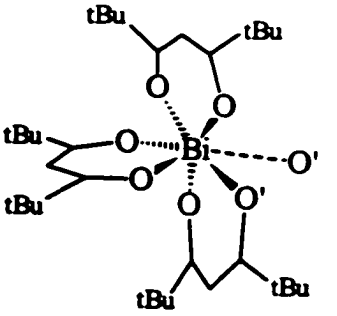
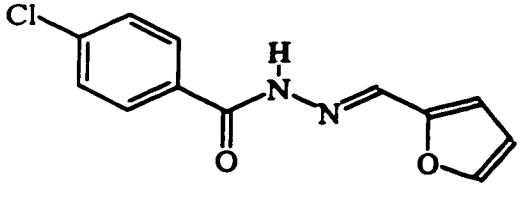


705

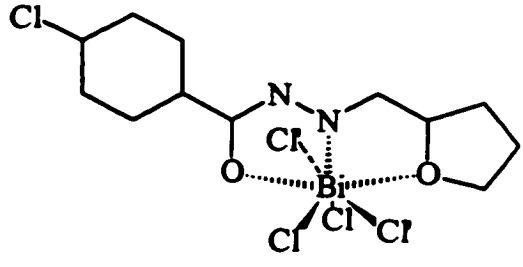
tris(dipivaloylmethanate) (<u>dpm</u>) [Bi(<u>dpm</u>)$_3$(H<u>dpm</u>)] **705**[498] shows two unique bismuth atoms each chelated by three *O,O'*-<u>dpm</u> ligands [Bi-O 2.133(7)-2.455(8)Å]. A long contact from a

neighbouring molecule [Bi---O' 3.070(8)Å] creates a dimeric structure and gives a seven coordinate pentagonal bipyramidal geometry for bismuth. In this case, however, Bi-O and C-O bond distances do not render an obvious distinction between the alkoxide and ketone functionalities in all cases.

The trifunctional *O,N,O'*-furaldehydohydrazone Lewis base adduct complex [Bi(cfh)$_3$Cl$_3$] **706**[499] [Bi-O$_{ketone}$ 2.424(8) ; Bi-N 2.654(10); Bi-O$_{ether}$ 2.986(9) Å] is based on a facially arranged $BiCl_3$ unit [Bi-Cl$_{bridging}$ 2.771(3); Bi-Cl$_{terminal}$ 2.562(5) and 2.510(4)Å]. A long chlorine contact [Bi---Cl' 2.909(5)Å] to the empty axial site creates a one-dimensional polymeric arrangement.



cfh

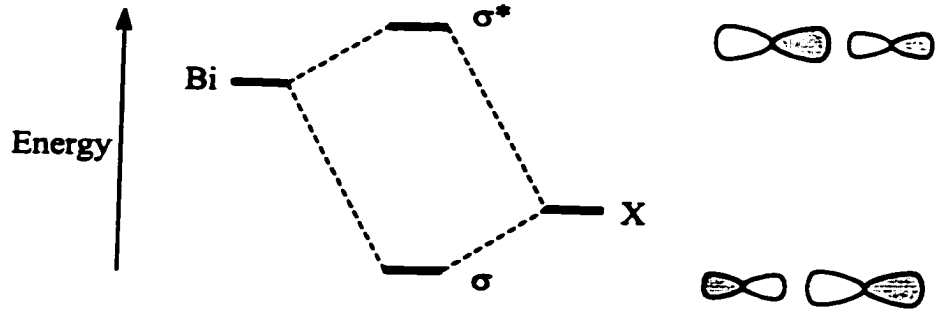


706

7.3 Secondary Bonding and the *trans* Effect: the Role of σ* Orbitals

The structural features of many bismuth compounds, including the bismuth ester-thiolates described below, may be rationalized in terms of secondary bismuth bonding[500] which warrants a brief definition. The Lewis acidity and pronounced expansion of the coordination sphere of bismuth, as well as that of the other heavier p-block elements, was believed to occur through low energy empty d-orbitals. However, calculations suggest they are too high in energy to enable significant involvement in bonding,[501] while an alternative model enlists the participation of Bi-X σ* orbitals. When X is more

electronegative than Bi, the antibonding σ* orbital will be polarized toward the bismuth atom:

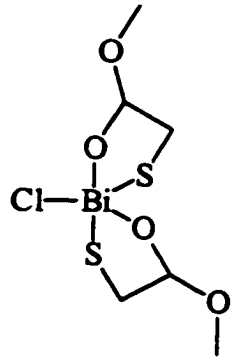


If this orbital is sufficiently low in energy it may act as an acceptor. The low electronegativity of bismuth means a higher atomic orbital energy and poorer orbital overlap with X, resulting in a low energy σ* orbital. This model requires a nearly linear L-Bi-X geometry, and a lengthening of the Bi-X bond as the L-Bi interaction increases, due to increased occupation of the σ* orbital. This model has been at least qualitatively useful in rationalizing the structures of a number of Lewis base adducts of bismuth phenylbismuth dihalides,[422-426] as well as the octahedral-based structures of $[Bi(SC_6F_5)_5]^{2-}$ **513**[416] and the $[Bi(SC_6F_5)_3(L)_n]$ adducts **514-21**[421] (Chapter 5.2).

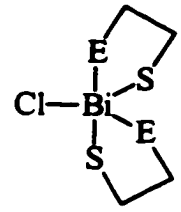
7.4 Results and Discussion

Reactions of potassium (methylester)methanethiolate with bismuth(III) chloride in 95% ethanol at the appropriate stoichiometry give bis[(methylester)methanethiolato]-bismuth(III) chloride **7A** (2:1) and tris[(methylester)methanethiolato]bismuth(III) **7B** (3:1), respectively. Reactions of (methylester)methanethiol with bismuth(III) chloride also give **7A**, which was identified by its distinctive Raman spectrum as the dominant product, independent of reaction stoichiometry (4:1, 3:1, 2:1).

Compound **7A** adopts a one-dimensional polymeric array in the solid state (Figure 7.1), with hepta-coordination for bismuth imposed by four equatorially disposed sulfur centers, two oxygen centers (carbonyl) and one chlorine center. The long and essentially equivalent Bi-S distances result from the strong *trans* influence[500] induced by intermolecular Bi-S contacts [S(1)-Bi-S(2a) 154.5(2)° and S(2)-Bi-S(1a) 170.3(1)°]. Although a molecular unit represented by drawing **7A** is indistinguishable in the polymeric solid state structure, the analogy with the more molecular hydroxy/thio **551**[3] and amino/thio **6B(R)Cl**[3,445,445,489] derivatives is important. The more polymeric structure of **7A** may be attributed to the restrictions imposed by the backbone sp^2 hybridized carbonyl carbon center and the consequential chelate ring strain.



7A



551: E = OH
6B(R)Cl: E = NR_2

The structure of the tris(esterthiolato)bismuth complex **7B** (Figure 7.2) may, at first glance, be viewed as two tris-chelated bismuth centers, as observed for the keto/thiolate **558**[439] and aminothiolate complexes **6A(R)**.[489] However, closer inspection of the Bi-S bond distances [i.e. Bi---S(2a), 3.331(2) is substantially longer than Bi-S(2), 2.608(2), Table 7.2] reveals that one of the ligands clearly functions as an internuclear

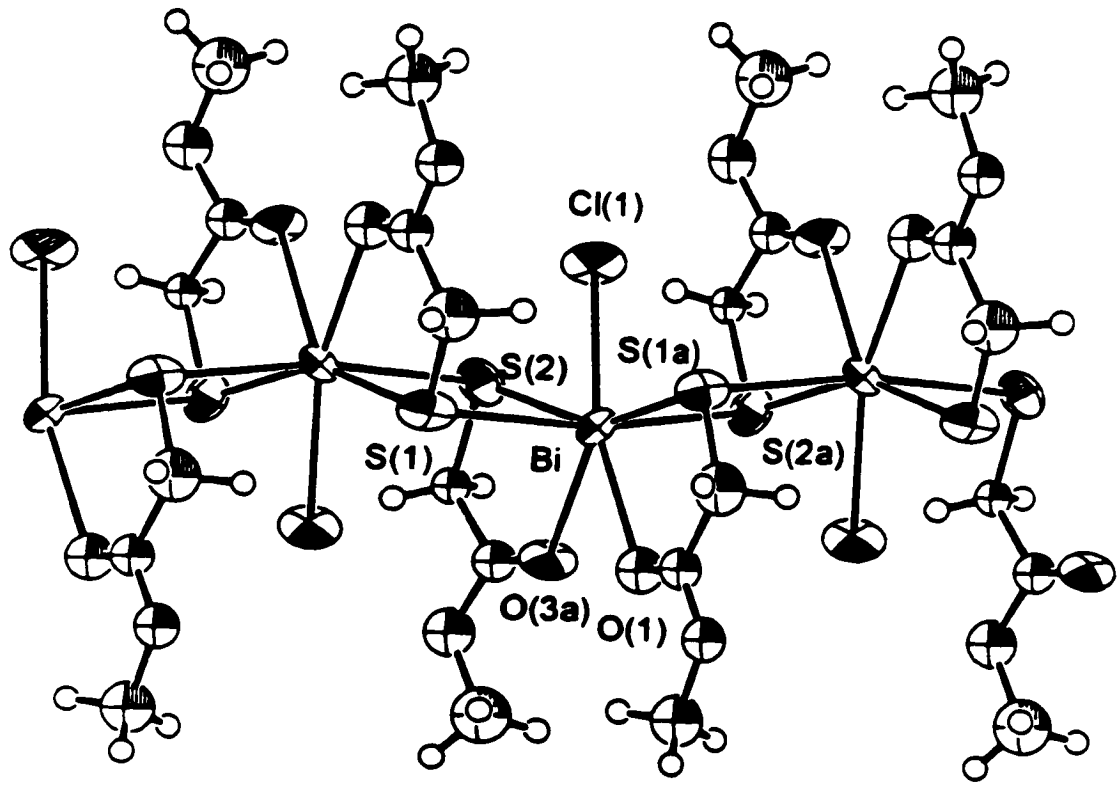


Figure 7.1 Crystallographic view of polymeric arrangement of $[Bi(SCH_2COOCH_3)_2Cl]$ **7A**.

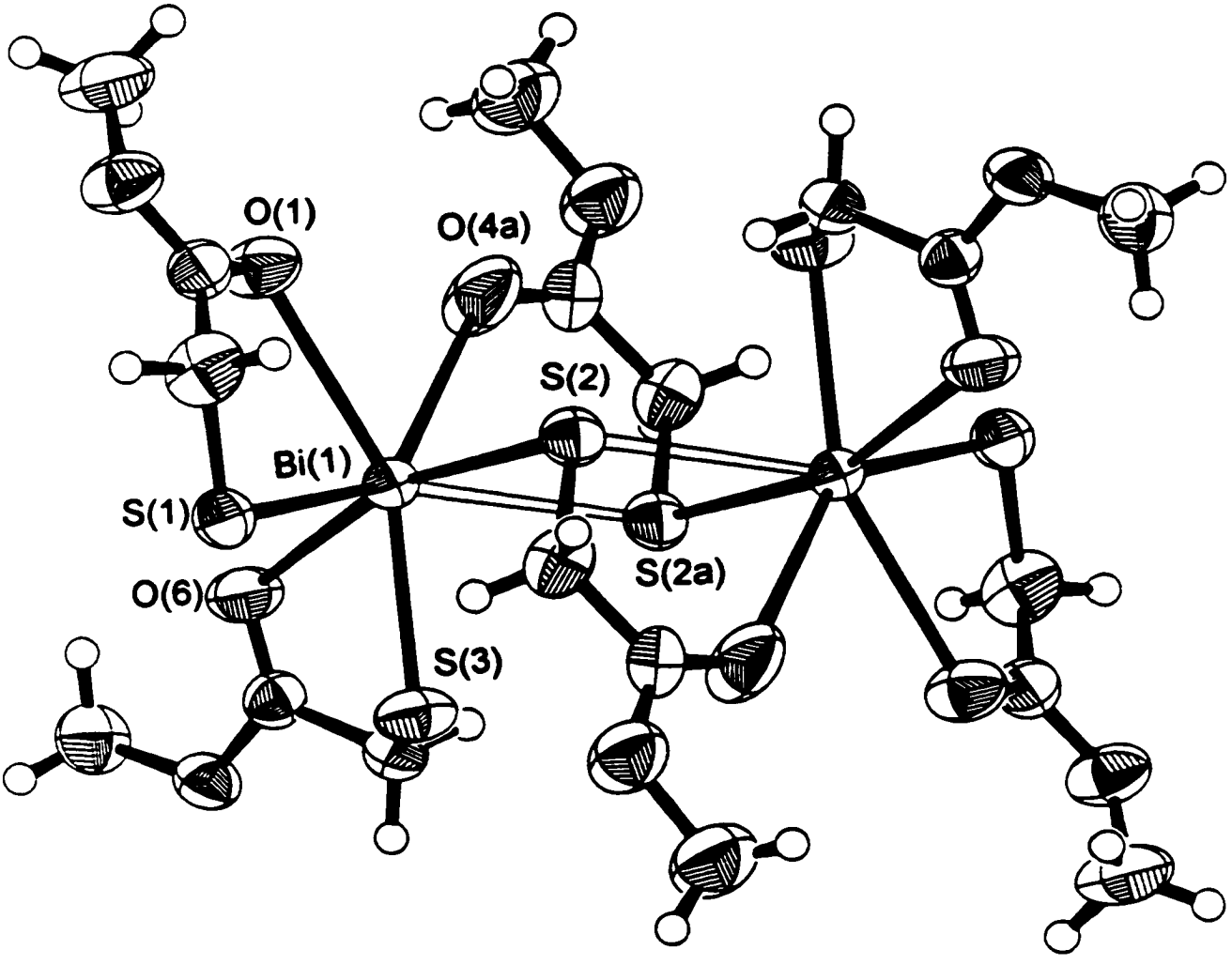


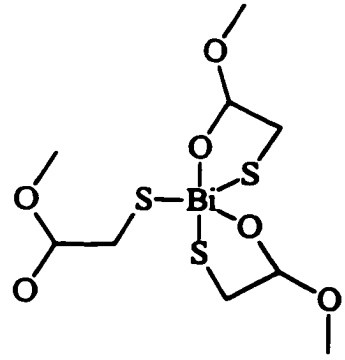
Figure 7.2 Crystallographic view of the dimeric arrangement of $[Bi(SCH_2COOCH_3)_3]$ **7B**.

Table 7.2 Comparison of selected bond lengths (Å) in bismuth-esterthiolate and related complexes.

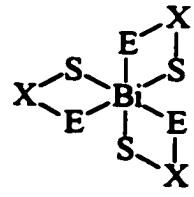
7A		**7B**		**511**[3]		**558**[439]		**CBS (209-15)** 234,235,238,241,242	
Bi-O(1)	2.68(2)	Bi-O(1)	2.807(5)	Bi-O	2.80(1)	Bi-O*	2.575(11)		
Bi-O(3a)	2.77(2)	Bi-O(6)	2.861(5)		2.86(1)		2.614		
							2.537(10)		
		Bi---O(4a)	3.071(7)					Bi---O	2.4-2.6
Bi-S(1)	2.849(7)	Bi-S(1)	2.568(2)	Bi-S	2.595(3)	Bi-S*	2.724(3)		
Bi-S(2)	2.884(6)	Bi-S(2)	2.608(2)		2.558(4)		2.581(4)		
Bi-S(1a)	2.963(7)	Bi-S(3)	2.574(2)				2.659(5)		
Bi-S(2a)	2.861(9)								
		Bi---S(2a)	3.331(2)	Bi---S	3.124(4)	Bi---S	3.494(5)		
Bi-Cl(1)	2.535(6)			Bi-Cl	2.589(3)		3.551(5)		
				Bi---Cl	3.488(4)				

* Average bond distances for two unique molecules.

(Bi---Bi) bridge, rather than a chelating ligand, imposing a distinct dimer structure (**7B**)$_2$.



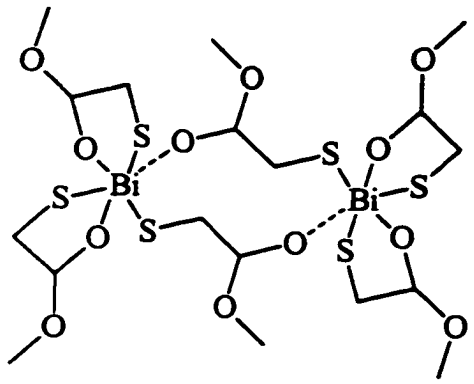
7B



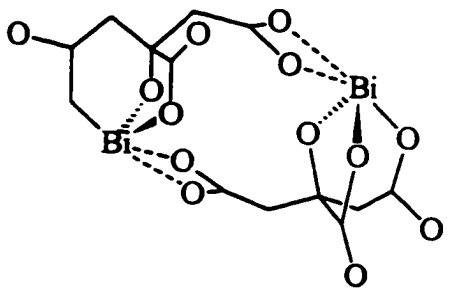
558: E = O, X = $PhCHCH_2CPh$

6A: E = NH_2, X = CH_2CH_2

In comparison with the polymeric structure of **7A**, substitution of the chloride for a third thiolate is manifested in the dislocation of the ...S_2BiS_2Bi... chain with consequential enhancement (shortening) of the three facial thiolate interactions (Table 7.2). The resulting centrosymmetric dimer **(7B)$_2$** mimics the dimeric arrangement evident in citrate complexes (CBS) **209-15**, which is made possible by pendant carboxylate moieties.



(7B)$_2$



209-15

However, the multiple intermolecular interactions observed among dimer units in the carboxylate complexes are precluded by formal introduction of the methyl group to the carboxylate functionality (to give the ester). The resulting molecular simplicity highlights the ester functionality as an important stepping stone to understanding and controlling the carboxylate chemistry of bismuth.

Preliminary studies have afforded the isolation and structural characterization of a thiolactate (thiolate-carboxylate) complex of bismuth through similar procedures. The stoichiometric reaction of $BiCl_3$ with thiolactic acid and two equivalents of KOH in ethanol gave a small crop of crystals of $K[Bi\{SCH(CH_3)COO\}Cl_2]$ **7C** (see Figure 7.3). As with the ester-thiolate complexes, the ligand chelates the bismuth center in an *S,O*-bidentate manner, however, the carboxylate group also bridges a second bismuth atom in an *O,O'* fashion, giving three coordination contacts for the functionality. As with

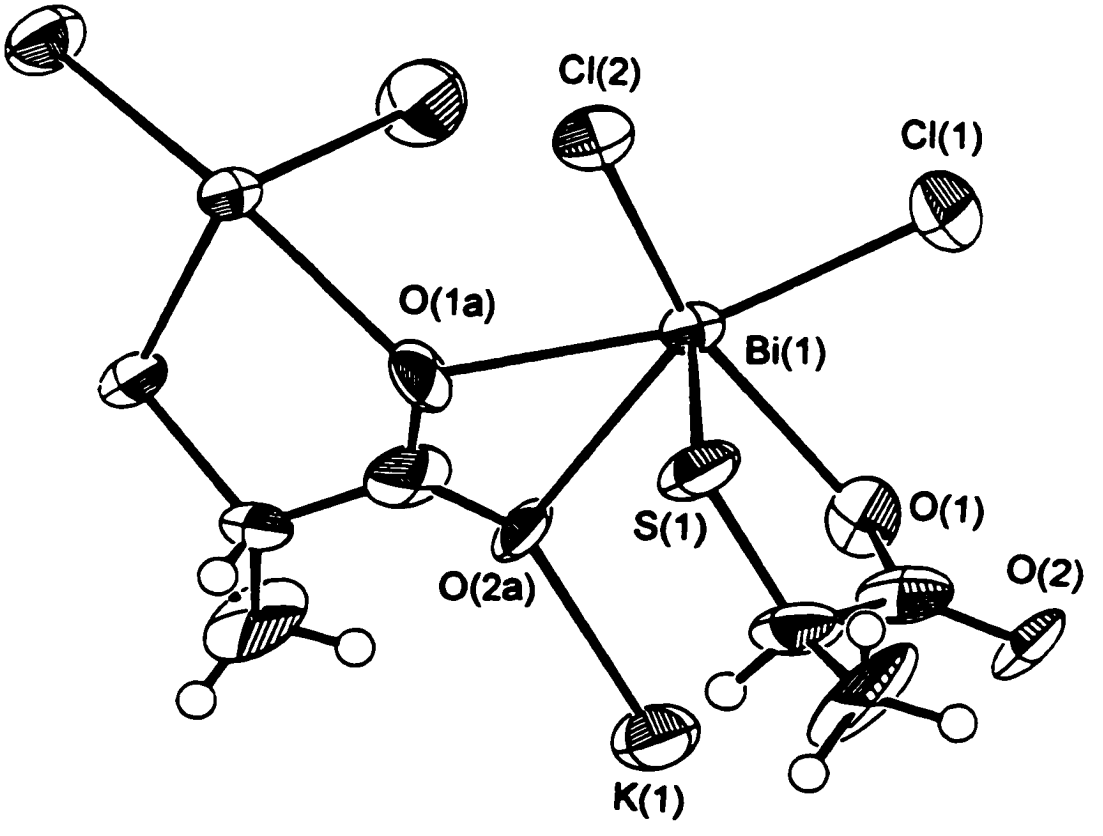


Figure 7.3 Crystallographic view of the polymeric arrangement of $K[Bi\{SCH(CH_3)COO\}Cl_2]$ 7C. Selected bond lengths [Å]: Bi(1)-S(1) 2.514(8); Bi(1)-Cl(1) 2.647(8); Bi(1)-Cl(2) 2.643(7); Bi(1)-O(1) 2.41(2); Bi(1)-O(1a) 2.51(2); Bi(1)-O(2a) 2.74(2); K(1)-O(2a) 2.70(2).

the thiosalicylate complex **548**, intermolecular bonding occurs solely through the carboxylate group, with no long sulfur or chlorine contact.

7.5 Conclusions and Future Direction

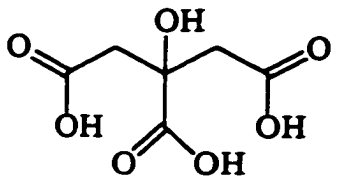
Despite the relatively low basicity of the ester (carbonyl) (pK_b 21.5; cf. OH pK_b 16.5, NR_2 pK_b 9.2, CO_2^- pK_b 9.2), the pendant donor intermolecular arrangement observed for 'colloidal bismuth subcitrate' has been modeled by anchoring the ligand on bismuth via a thiolate tether. In this way, bifunctional ligands offer synthetic versatility to study the interaction of bio-relevant functional groups with bismuth, and the hydrolytic stability of the thiobismuth unit allows for manipulations and observations in aqueous media.

Additionally, the ester functionality provides a simpler bonding model for the carboxylate group, which typically chelates bismuth in an *O,O'*-manner. In monodenate carboxylate bonding situations, exocyclic carbonyl oxygen atoms are typically involved in intermolecular bridging, as observed for **7C**, bismuth aminocarboxylates (Chapter 4) and CBS. The introduction of an organic group in the neutral ester functionality deters the second (ether) oxygen atom from possible intra- and intermolecular bonding, and allows for limited intermolecular coordination.

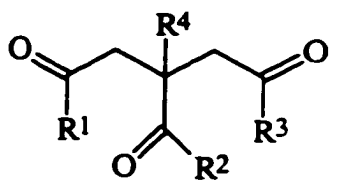
The amide [$C(O)NR_2$] functionality has the potential to accommodate an intermediate number of intermolecular interactions between those of the carboxylate and ester complexes. Replacement of a carboxylate oxygen atom with an amine group allows for both monodentate and *N,O*-chelating bonding situations, with limited (one) coordination to the amine fragment. As with ester-thiolate complexes, bifunctional

amide-thiolate ligands[502] are a rational route to the preparation of bismuth-amide complexes. Establishing bonding relationships between carboxylate, ester and amide functionalities is crucial when derivatization of more complex carboxylates are considered.

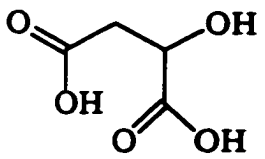
The solubilization of bismuth citrate under basic conditions is likely due to deprotonation of the hydroxy- group of the $(H_3cit)^{3-}$ ligand (to form the alkoxide) and the subsequent tridentate chelation of the ligand to the bismuth center (Chapter 2). Further, the solubility of the resulting structure may be enhanced by the negatively charged pendant carboxylate group. A comprehensive assessment of the role of individual functional groups of citric acid on determining the physical properties of CBS may be possible through sequential derivatization (structure **X**: R^1, R^2, R^3 = OMe, NH_2), replacement (structure **X**: $R^4 = NH_2$) or removal (e.g. malic acid, tricarballylic acid). Further, and as described in Chapter 4, mass spectrometry may be employed to study soluble species.



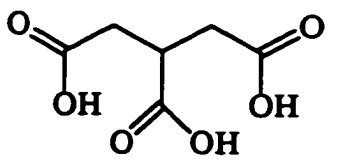
citric acid



X

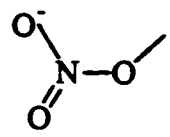


malic acid

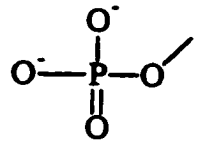


tricarballylic acid

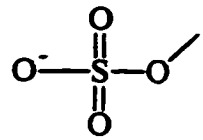
The focus of this thesis lies in the interaction of bismuth with organic functional groups outlined in Chapter 1, however, there are several "inorganic" functionalities which are commonly encountered in biological systems. The established bifunctional ligand approach may be extended to incorporate highly oxidized main group atoms such as nitrogen (nitrate), phosphorus (phosphate, phosphonate) and sulfur (sulfate, sulfonate).



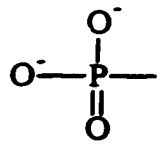
nitrate



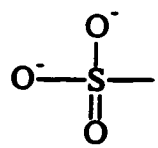
phosphate



sulfate

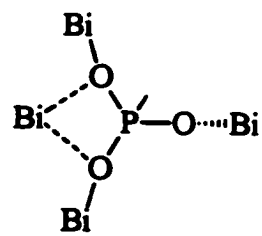


phosphonate



sulfonate

The highly acidic nature of these functionalites permits sufficiently low pH conditions to deter bismuth hydrolysis reactions and suitable media for simple metathesis reactions in aqueous media. The utility of these ligands has been demonstrated by the reaction of bismuth nitrate and the bifunctional phosphonato-carboxylate in water to give $[Bi(O_3PC_2H_4CO_2)(H_2O)]$ **707** or acetone to give the protonated $[BiH(O_3PC_2H_4CO_2H)_2(H_2O)]$ **708**.[503] Structural studies of **707** reveals the phosponate



707

functionality bridging three bismuth centers and weakly chelating a fourth. Similar structural studies may unveil novel bonding situations and intriguing structural arrangements.

Chapter 8. Experimental

8.1 General Procedures

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded as Nujol mulls on CsI plates using a Nicolet 510P spectrometer. Raman spectra were obtained for powdered and crystalline samples on a Bruker RFS 100 spectrometer. Chemical analyses were performed by Canadian Microanalytical Service Ltd., Delta, British Columbia. Solution ^{1}H and ^{13}C NMR data were recorded on a Bruker AC-250 spectrometer. Chemical shifts are reported in ppm relative to tms and are calibrated to the internal dmso solvent signal. Mass spectra were obtained using a VG Quattro triple quadrupole mass spectrometer (VG Organic).

Atmospheric pressure chemical ionization (APCI) samples were saturated solutions in 95% ethanol [**6A**, **6B**NO_3], acetonitrile [**550-52**, **555**, **6A**(Me), **6B**(Me)Cl], dimethylformamide [**6B**Cl, **6C**(Me)•¼HCl, **6D**(Me)] or dimethylsulfoxide [**7A**, **7B**]. Solvent flow [100% acetonitrile (95% ethanol for **6A**, **6B**NO_3) at 300μL/min] used a Shimadzu LC-10AT liquid chromatograph pump with a Rheodyne syringe loading sample injector.

8.2 Synthetic Procedures

Bismuth chloride, bismuth oxychloride, bismuth nitrate pentahydrate, antimony chloride, 2-aminoethanethiol hydrochloride, *N,N*-dimethylaminoethanethiol hydrochloride, methylthioglycolate, glyoxylic acid and thiolactic acid were used as received from Aldrich. Aminoethanethiol (cysteamine) was used as received from Fluka.

Oxalic acid was used as received from Fisher. *N,N,N',N'*-ethylenediaminetetraacitic acid and potassium hydroxide were used as received from BDH. All reactions involving thiols were performed under an atmosphere of N_2 (to prevent the oxidation of thiols to disulfides) using standard Schlenk techniques, with the exception of the preparation of compound **6D(Me)Cl** and **6D(Me)Br**. All compounds are air stable, although **6B(Me)Cl** changes colour over a period of weeks and **6BCl** is light sensitive. For compound **6D(Me)Br**, the dimethylaminoethanethiol hydrobromide salt is prepared *in situ* by reaction the chloride salt with $AgNO_3$ in the appropriate reaction solvent, filtration to remove AgCl, addition of NaBr and filtration (in the case of the ethanol reaction) to remove undissolved materials.

The syntheses of $[Bi_2(C_2O_4)_3]\bullet 8H_2O$ **3A**, which has been prepared by various methods, $Sb(SCH_2CH_2NH_2)Cl$ **6ECl** and $K[Bi\{SCH(CH_3)COO\}Cl_2]$ **7C** are preliminary results and have been attempted only once. Characterization of each is limited to single crystal X-ray diffraction data, which is of poor quality for **6ECl**. Samples of **3A** contained crystals of varying habit (needles, blocks), not all of which were identified.

Thiolate Complexes

The thiolate compounds described below were prepared by a general procedure, with the specific conditions for isolation presented in Table 8.1. Between 3 and 10 mmol of solid bismuth reagent [$BiCl_3$, $BiBr_3$, $Bi(NO_3)_3\bullet 5H_2O$ or $SbCl_3$] was added to a solution of an aminoethanethiol (parent or dimethyl derivative), an aminoethanethiol hydrochloride, an aminoethanethiol hydrobromide (generated *in situ*) or a mixture of an aminoethanethiol, methylthioglycolate or thiolactic acid with KOH, in 95% ethanol,

acetone or water (150 mL), or glacial acetic acid/water (6mL/14mL). Most reactions are instantaneous giving yellow solutions (colorless for **6E**Cl), which were stirred overnight, filtered and reduced in volume on a rotary evaporator (95% ethanol or acetone) or a hot water bath (water), until precipitation began. The solution was then re-filtered and cooled on ice, in the refrigerator (4°C) or freezer (<0°C), or left to evaporate slowly to give crystalline materials (Table 8.1). Isolated samples were washed with ethanol, acetone and ether (25mL each) and dried under vacuum for one hour. Characterization and spectroscopic data are presented in Tables 8.2-8.4.

Equimolar reaction mixtures of $BiCl_3$ with $KSCH_2CH_2NMe_2$ (7mmol, prepared *in situ*) in 95% ethanol (150mL) gave a low solubility powder, which was extracted from the reaction precipitate with dmf and recrystallized by removal of solvent *in vacuo*. Crystals of **6C**(Me)•¼HCl were reproducibly Pasteur separated from a crystalline mixture and were characterized by X-ray crystallography, but data for the bulk sample were not reproducible. Although the solubility of compound **6D**(Me)Cl is very low, small samples were crystallized from aqueous solution and shown to have the same identity as the bulk reaction mixture precipitate by a variety of techniques. The bromide analogue **6D**(Me)Br was isolated as a powder only. Compound **7A** was isolated as a powder from the reaction mixture and recrystallized from dmf under vacuum (yellow needles).

Table 8.1 Reaction and isolation conditions for thiolate complexes.

Compound	Reagents, solvents and amounts (g, mmol)	Crystal isolation and period	Comments
6A	$BiCl_3$ (1.06, 3.35) $HSCH_2CH_2NH_2 \bullet HCl$ (1.90, 16.7) KOH (1.88, 33.5) 95% ethanol (150 mL)	4°C, 4 days	
6A(Me)	$BiCl_3$ (2.10, 6.64) $HSCH_2CH_2NMe_2 \bullet HCl$ (2.83, 19.9) KOH (2.24, 39.9) 95% ethanol (150 mL)	4°C, 3 days	
6BNO_3	$Bi(NO_3)_3 \bullet 5H_2O$ (2.44, 5.03) $HSCH_2CH_2NH_2$ (0.78, 10) KOH (0.56, 10) water (150 mL)	ice, 2 hours	
6BNO_3 $\bullet H_2O$	$Bi(NO_3)_3.5H_2O$ (2.52, 5.20) $HSCH_2CH_2NH_2$ (1.20, 15.6) KOH (0.875, 15.6) water (150 mL)	evaporation, 4 days	light excluded no preconcentration of reaction filtrate
6BCl	$BiCl_3$ (3.02, 9.57) $HSCH_2CH_2NH_2 \bullet HCl$ (3.26, 28.7) KOH (3.22, 57.4) 95% ethanol (150 mL)	evaporation, 4 days	light excluded
6B(Me)Cl	$BiCl_3$ (2.09, 6.64) $HSCH_2CH_2NMe_2 \bullet HCl$ (1.88, 13.3) KOH (1.49, 26.6) acetone (150 mL)	4°C, 1 day	

Table 8.1 Reaction and isolation conditions for thiolate complexes (continued).

Compound	Reagents, solvents and amounts (g, mmol)	Crystal isolation and period	Comments
6D(Me)Cl	$BiCl_3$ (2.10, 6.64)	precipitation	$BiCl_3$ dissolved in THF and added dropwise to ligand solution
1)	$HSCH_2CH_2NMe_2 \bullet HCl$ (1.88, 13.3) 95% ethanol (150 mL), thf (50mL)		
2)	$Bi(NO_3)_3.5H_2O$ (2.43, 5.01) $HSCH_2CH_2NMe_2 \bullet HCl$ (2.13, 15.0) water (14 mL)/ acetic acid (6mL)	precipitation	ligand added to solution of $Bi(NO_3)_3 \bullet 5H_2O$ bulk sample isolated as powder
3)	crystals from water wash of reaction mixture precipitate of (2)	evaporation, 12 days	
6D(Me)Br	$BiBr_3$ (2.98, 6.64)	n/a	$HSCH_2CH_2NMe_2 \bullet$ HBr generated *in situ*
1)	$HSCH_2CH_2NMe_2 \bullet HCl$ (1.89, 13.3) $AgNO_3$ (2.50, 14.7) NaBr (1.51, 14.7) 95% ethanol (150 mL), thf (50mL)		
2)	$Bi(NO_3)_3 \bullet 5H_2O$ (2.43, 5.01) $HSCH_2CH_2NMe_2 \bullet HCl$ (2.13, 15.0) $AgNO_3$ (3.00, 17.7) NaBr (1.82, 17.7) water (14 mL)/ acetic acid (6mL)	n/a	$HSCH_2CH_2NMe_2 \bullet$ HBr generated *in situ*
6ECl	$SbCl_3$ (0.91, 4.0) $HSCH_2CH_2NH_2 \bullet HCl$ (1.36, 12.0) KOH (1.36, 24.2) 95% ethanol (150 mL)	<0°C	

Table 8.1 Reaction and isolation conditions for thiolate complexes (continued).

Compound	Reagents, solvents and amounts (g, mmol)	Crystal isolation and period	Comments
7A	$BiCl_3$ (1.67, 5.28) $HSCH_2COOMe$ (1.12, 10.6) 95% ethanol (150 mL)	from DMF under vacuum	light excluded
7B	$BiCl_3$ (1.65, 5.23) $HSCH_2COOMe$ (1.67, 15.7) KOH (0.88, 16) 95% ethanol (150 mL)	4°C, 1 day	
7C	$BiCl_3$ (1.00, 3.16) $HSCH(CH_3)COOH$ (0.30, 2.8) KOH (0.33, 5.9) 95% ethanol (150 mL)	4°C, 1 day	

Bismuth Oxalate Octahydrate $[Bi_2(C_2O_4)_3]\bullet 8H_2O$ **3A**

$BiCl_3$ (0.53g, 1.7mmol) and oxalic acid (4.51g, 50.1mmol) in water (40mL) were refluxed for 11 hours then hot filtered to remove unreacted material. Colorless needles of **3A** appeared on cooling in air and were collected after 2 days. Also prepared by a similar reaction, replacing BiOCl for $BiCl_3$(1.00g, 3.84mmol); oxalic acid (3.00g, 33.3mmol); water (100mL); reflux period 7 hours; crystallization period <1 day; crystals remained under reaction solution until X-ray data collection. Also prepared by a similar reaction, replacing glyoxylic acid for oxalic acid(5g, $5x10^{-2}$mol); $BiCl_3$ (0.51g, 1.6mmol); water (10mL); reflux period 12 hours; crystallization period 6 days; crystals remained under reaction solution until X-ray data collection.

Hydrogen Bis(Bismuth Hydrogen N,N,N',N'-ethylenediaminetetraacetate) Chloride Dihydrate $\{[Bi(HEDTA)]_2H\}Cl\bullet 2H_2O$ **4A**

$BiCl_3$ (1.08g, 3.42mmol) added to ethylenediaminetetraacetic acid (1.00g, 3.42mmol) and KOH (0.57g, 10mmol) in water (150mL) was allowed to stir overnight. The solution was filtered and concentrated to ~40mL over a hot water bath. Colorless needles of **4A** appeared on cooling, collected after one day evaporation in air.

Table 8.2 Yields and elemental analyses for all compounds.

Compound	Yield [g, mmol, %]	Elemental analysis [% calc (found)]
4A	1.30, 2.43, 71	C: 22.47 (22.70) H: 2.92 (2.65) N: 5.24 (5.19)
6A	0.55, 1.3, 38	C: 16.47 (16.45) H: 4.15 (4.08) N: 9.61 (9.50)
6A(Me)	0.75, 1.4, 22	C: 27.63 (27.74) H: 5.80 (5.63) N: 8.06 (7.99)
6BNO_3	0.48, 1.5, 23	C: 11.35 (11.40) H: 2.86 (2.84) N: 9.93 (9.96)
6B$NO_3 \bullet H_2O$	0.79, 2.4, 35	not determined
6BCl	0.64, 1.6, 17	C: 12.11 (12.28) H: 3.05 (3.00) N: 7.06 (6.86)
6B(Me)Cl	0.94, 2.1, 31	C: 21.22 (21.16) H: 4.45 (4.36) N: 6.19 (6.04)

Table 8.2 Yields and elemental analyses for all compounds (continued).

Compound		Yield [g, mmol, %]	Elemental analysis [% calc (found)]
6D(Me)Cl	1)	2.72, 6.47, 97	C: 11.42 (11.98)
			H: 2.62 (2.77)
			N: 3.33 (3.42)
	2)	1.41, 3.35, 67	C: 11.42(11.52)
			H: 2.62 (2.64)
			N: 3.33 (3.32)
	3)	0.05, 0.1, 2	C: 11.42 (11.57)
			H: 2.62 (2.79)
			N: 3.33 (3.32)
6D(Me)Br	1)	>95%	C: 8.67 (9.19)
			H: 2.00 (2.07)
			N: 2.53 (2.57)
	2)	2.49, 4.50, 90	C: 8.67 (8.94)
			H: 2.00 (2.04)
			N: 2.53 (2.62)
7A		1.10, 2.42, 46	C: 15.85 (16.08)
			H: 2.22 (2.26)
7B		0.71, 1.3, 26	C: 20.61 (20.71)
			H: 2.88 (2.84)

Table 8.3 Complete vibrational data for all compounds.

Compound	IR data (cm^{-1})	Raman data (cm^{-1})
4A	444m, 472w, 496w, 516w, 542w, 562w, 592w, 608w, 660w, 696w, 770w, 856m, 922s, 958m, 980m, 1002w, 1040w, 1054w, 1094m, 1110w, 1170w, 1224w, 1254w, 1302w, 1318w, 1598s, 1634s, 1726m	81s, 95vs, 136s, 152s, 172s, 204s, 228m, 275w, 293w, 361m, 380m, 407m, 448m, 485m, 581w, 639w, 667w, 715w, 734w, 830w, 920w, 973w, 998w, 1037w, 1054w, 1098w, 1167w, 1225w, 1250m, 1302w, 1324m, 1340w, 1383m, 1437m, 1472m, 1593w, 1629m, 2852w, 2910s, 2937s, 2958s, 2984m
6A	290vs, 315vs, 411s, 487s, 505m, 658m, 722w, 821w, 832m, 904w, 940w, 1020w, 1065w, 1106m, 1208m, 1264w, 1289w, 1301w, 1579m, 1609w	100vs, 123vs, 177vs, 211s, 256m, 286s, 321s, 663m, 832w, 902w, 944w, 976w, 1021w, 1065w, 1108w, 1210w, 1267w, 1298w, 1378w, 1419w, 1449m, 2818w, 2849m, 2900s, 2913s, 2924s, 3153w, 3244m, 3294w
6A(Me)	232w, 266vs, 346m, 415s, 437w, 522w, 662m, 723w, 762vs, 893vs, 951m, 1002s, 1038m, 1060m, 1098w, 1125w, 1154s, 1215m, 1245w, 1265w, 1291s, 1401w	70w, 112s, 162s, 233w, 270vs, 352m, 417w, 437w, 523w, 663m, 764w, 894w, 953w, 1003w, 1040w, 1062w, 1126w, 1156m, 1218w, 1248w, 1292m, 1367w, 1402w, 1432m, 1448m, 1467w, 2575w, 2648w, 2709w, 2785s, 2800m, 2816m, 2850m, 2919s, 2943m, 2980m

Table 8.3 Complete vibrational data for all compounds (continued).

Compound	IR data (cm^{-1})	Raman data (cm^{-1})
6BNO$_3$	264vs, 300w, 329m, 469s, 618s, 666m, 703w, 723w, 822m, 839m, 919m, 968s, 1035s, 1074m, 1221w, 1268w, 1319m, 1426w, 1573s	114vs, 192m, 216s, 268vs, 282s, 350vs, 475w, 667w, 712w, 841w, 921w, 1037s, 1066w, 1223w, 1273w, 1381w, 1424w, 1454w, 1572w, 1645w, 2661w, 2737w, 2828w, 2874m, 2911m, 2932s, 2948m, 3233w, 3308w
6BCl	244s, 281m, 317s, 330m, 370w, 461s, 477m, 589w, 657m, 664w, 675w, 722vs, 831w, 840w, 918m, 964s, 1011m, 1050m, 1082m, 1109w, 1155w, 1170w, 1215w, 1226w, 1275w, 1289w, 1307w, 1412w, 1585w	66vs, 90vs, 106vs, 124vs, 172s, 212vs, 246vs, 279vs, 322vs, 371vs, 462w, 591w, 664m, 831w, 845w, 921w, 963w, 1008w, 1054w, 1081w, 1103w, 1118w, 1214w, 1232w, 1273w, 1289w, 1372w, 1388w, 1412w, 1426w, 1450w, 1587w, 2728w, 2755w, 2830w, 2850m, 2909s, 2919s, 2935m, 2947m, 2956m, 3098w, 3229w, 3314w
6B(Me)Cl	221vs, 291vs, 358s, 411s, 426s, 435s, 520s, 661s, 723s, 753vs, 761vs, 894vs, 940s, 951w, 992s, 1026m, 1039m, 1050w, 1097w, 1119m, 1152m, 1159w, 1210m, 1245m, 1263w, 1291m, 1400w	88m, 103s, 125s, 171m, 218s, 299vs, 360s, 412w, 438w, 457w, 521w, 664m, 762w, 895w, 942w, 995w, 1122w, 1160m, 1213w, 1245w, 1297m, 1370w, 1403w, 1428m, 1448m, 2723w, 2787m, 2805m, 2833s, 2869s, 2910s, 2923s, 2953s, 2987m

Table 8.3 Complete vibrational data for all compounds (continued).

Compound	IR data (cm^{-1})	Raman data (cm^{-1})
6D(Me)Cl	303w, 335m, 411w, 513w, 662w, 722m, 756w, 835w, 885w, 926s, 967w, 1011m, 1035w, 1048w, 1117w, 1149w, 1211w, 1226w, 1256w, 1305w, 1404w, 1429m	107vs, 127vs, 172s, 220s, 247vs, 334s, 412w, 446w, 514w, 663m, 757m, 885w, 927w, 967w, 1011w, 1037w, 1050w, 1213w, 1229w, 1258w, 1305w, 1365w, 1385m, 1431m, 1451m, 2896w, 2939s, 2955s, 2991m, 3020m, 3032m
6D(Me)Br	513s, 588m, 658w, 721w, 752w, sh, 774s, 834m, 866m, 893w, 922m, 965w, 1007m, 1031w, 1045w, 1117w, 1145w, 1180m, 1226w, 1256w, 1321s, 1340m, 1425w, 1513vs, 1570vs, 1623vs, 1639w, 3402vs	75vs, 101m, 119vs, 144m, 162vs, 210vs, 300w, 328s, 408w, 444w, 513m, 660m, 753m, 878m, 924w, 967w, 1008w, 1033m, 1045w, 1117w, 1147w, 1212w, 1227w, 1257w, 1302w, 1359m, 1377m, 1394w, 1427m, 1451m, 1464w, 1475w, 2841w, 2893w, 2932w, 2947s, 2960s, 2983w, 3020m, 3074w
6BNO_3 •H_2O	258vs, 285vs, 347m, 481s, 662m, 688w, 722w, 823s, 839m, 921m, 966m, 1045s, 1082m, 1112w, 1223s, 1425vs, 1602s, 1636s, 1755w	86vs, 117s, 153w, 187m, 210s, 268vs, 287vs, 359vs, 478w, 665w, 713w, 840w, 922w, 961w, 1045s, 1076w, 1112w, 1222w, 1280w, 1294w, 1338w, 1385w, 1423w, 1451w, 1598w, 2744w, 2860w, 2924m, 2964w, 3154w, 3237w, 3297w
7A	555w, 681w, 770w, 874s, 886w, 986m, 994m, 1161m, 1206m, 1296m, 1318m, 1676s, 1707s	95vs, 117s,sh, 147s, 187s, 227vs, 260vs, 350m, 399w, 561w, 686w, 768w, 888m, 984w, 1181w, 1204w, 1325w, 1376w, 1392w, 1428w, 1673w, 2903s, 2940m, 2959m, 3044w

Table 8.3 Complete vibrational data for all compounds (continued).

Compound	IR data (cm^{-1})	Raman data (cm^{-1})
7B	569m, 583m, 681w, 711m, 772w, 864m, 880w, 889m, 899w, 909w, 992s, 1021w, 1141m, 1204s, 1287s, 1308s, 1397m, 1434s, 1558w, 1579w, 1605w, 1623w, 1691m, 1735m	95vs, 146m, 195m, 221m, 266vs, 292vs, 334m, 402w, 580w, 714w, 769w, 885w, 908w, 990w, 1151w, 1181w, 1296w, 1397w, 1435w, 1696w, 2886s, 2956m, 2976m, 2988m, 3034w

Table 8.4 Melting points, prominent APCI-MS peaks, and ^{1}H and ^{13}C NMR data for all compounds.

Compound	mp [dp]* (°C)	NMR (DMSO-d_6)** ^{1}H	NMR (DMSO-d_6)** ^{13}C	APCI-MS [Cone Voltage: m/z (% rel. intensity)]
4A	[297]	-	-	-
6A	87	2.24, 3.00, 3.57	31.0, 47.6	5V: 209(100), 361(48) 30V: 209(24), 361(100)
6A(Me)	140	2.31, 2.80, 3.53	25.3, 44.9, 65.8	5V: 209(100), 417(7) 30V: 209(23), 417(100)
6BNO_3	[158]	3.78, 3.96, 4.13	30.3, 49.1	5V: 361(100)
6BNO_3 •H_2O	[173]	ref. [445]	-	-
6BCl	[191]	3.77, 3.96	30.3, 49.0	10V: 209(89), 320(54), 393(100) 30V: 284(75), 320(100), 393(7)
6B(Me)Cl	[125]	2.76, 3.50, 4.32	26.1, 44.9, 66.9	5V: 209(100), 417(2), 453(2) 30V: 209(25), 348(100), 417(51), 453(2)
6D(Me)Cl	[205]	2.77, 3.30, 4.98, 9.02	23.2, 42.7, 60.8	10V: 209(100), 348(79), 384(9), 417(4), 421(57), 453(4) 30V: 209(10), 348(100), 384(4), 417(3)

* Decomposition occurs over a broad range and the temperature given represents the onset of blackening.

** Signals are generally poorly resolved.

Table 8.4 Melting points, prominent APCI-MS peaks, and ^{1}H and ^{13}C NMR data for all compounds (continued).

Compound	mp [dp]* (°C)	NMR (DMSO-d_6)** ^{1}H	NMR (DMSO-d_6)** ^{13}C	APCI-MS [Cone Voltage: m/z (% rel. intensity)]
6D(Me)Br	[195]	2.78, 3.30, 5.04, 8.99	24.2, 42.7, 60.9	
7A	128	3.62, 4.69	29.6, 52.3, 176.3	20V: 313(2), 349(100), 419(32)
7B	65	3.63, 4.46	29.4, 52.3, 175.8	20V: 313(4), 419(100)

* Decomposition occurs over a broad range and the temperature given represents the onset of blackening.

** Signals are generally poorly resolved.

Table 8.5 Peak assignments of the APCI mass spectra of bis(hydroxyethanethiolato)-bismuth salts $[Bi(SCH_2CH_2OH)_2X]$.

X	cone voltage 10V		cone voltage 30V	
	m/z (%)	assignment	m/z (%)	assignment
NO_3	285 (9)	$[-BiSC_2H_4O-]^+$	241 (3)	$[BiS]^+$
550	326 (33)	$[-BiSC_2H_4O- + NCCH_3]^+$	285 (100)	$[-BiSC_2H_4O-]^+$
	363 (100)	$[M-NO_3]^+$	363 (9)	$[M-NO_3]^+$
Cl	285 (9)	$[-BiSC_2H_4O-]^+$	241 (3)	$[BiS]^+$
551	321 (89)/ 323 (30)	$[M-SC_2H_4OH]^+$	285 (100)/ 287 (5)	$[-BiSC_2H_4O-]^+$
	326 (22)	$[-BiSC_2H_4O-+NCCH_3]^+$	321 (5)	$[M-SC_2H_4OH]^+$
	362 (100)/ 364 (42)	$[HOC_2H_4SBiCl+NCCH_3]^+$		
	363 (87)	$[M-Cl]^+$	363 (4)	$[M-Cl]^+$
	399 (6)/ 401 (5)	$[M+H]^+$		
Br	326 (34)	$[-BiSC_2H_4O-+NCCH_3]^+$	285 (100)	$[-BiSC_2H_4O-]^+$
552	363 (100)	$[M-Br]^+$	363 (7)	$[M-Br]^+$
CH_3COO	285 (7)	$[-BiSC_2H_4O-]^+$	241 (3)	$[BiS]^+$
555	326 (24)	$[-BiSC_2H_4O- + NCCH_3]^+$	285 (100)	$[-BiSC_2H_4O-]^+$
	363 (100)	$[M-CH_3COO]^+$	363 (9)	$[M-CH_3COO]^+$

Table 8.6 MS/MS assignments for bis(hydroxyethanethiolato)bismuth(III) salts $[Bi(SCH_2CH_2OH)_2X]$.

X	Daughters of (m/z)	cone voltage (V)	m/z (%)	assignment
NO_3	285	30	209 (46)	Bi^+
550			241 (58)	$[BiS]^+$
			285 (100)	$[-BiSC_2H_4O-]^+$
NO_3	326	10	209 (18)	Bi^+
550			241 (78)	$[BiS]^+$
			285 (100)	$[-BiSC_2H_4O-]^+$
			326 (32)	$[-BiSC_2H_4O-+NCCH_3]^+$
NO_3	363	10	209 (22)	Bi^+
550			241 (43)	$[BiS]^+$
			285 (100)	$[-BiSC_2H_4O-]^+$
			363 (33)	$[M-NO_3]^+$
Cl	321	10	209 (28)	Bi^+
551			241 (49)	$[BiS]^+$
			285 (100)	$[-BiSC_2H_4O-]^+$
			321 (73)	$[M-SC_2H_4OH]^+$
Cl	362	10	209 (12)	Bi^+
551			241 (45)	$[BiS]^+$
			285 (100)	$[-BiSC_2H_4O-]^+$
			321 (48)	$[M-SC_2H_4OH]^+$
			361 (26)	$[HOC_2H_4SBiCl + NCCH_3]^+$

Table 8.7 Crystallographic data for all complexes.

	3A	**4A**
empirical formula	$C_6H_{16}Bi_2O_{20}$	$C_{10}H_{15.50}BiCl_{0.50}N_2O_9$
Formula Weight	826.14	534.45
crystal description	yellow, needle	colorless, needle
crystal system	triclinic	monoclinic
space group	P-1 (#2)	C2/c (#15)
a (Å)	9.370(3)	25.203(6)
b (Å)	11.106(3)	8.979(4)
c (Å)	9.146(3)	12.897(2)
α (deg)	101.90(2)	90
β(deg)	105.95(3)	97.36(2)
γ(deg)	101.26(3)	90
V/Å^3	862.8(6)	2894(1)
Z value	2	8
D_{calc} (g/cm^3)	3.180	2.453
R; R_w	0.037; 0.040	0.036; 0.040
Goodness of Fit Indicator	1.44	1.64

$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $R_w = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma wFo^2]^{1/2}$

Table 8.7 Crystallographic data for compounds (continued).

	6A	**6B**NO_3	**6B**Cl
empirical formula	$C_6H_{18}BiN_3S_3$	$C_4H_{12}BiN_3O_3S_2$	$C_4H_{12}BiClN_2S_2$
Formula Weight	437.39	423.26	396.71
crystal description	yellow, needle	needles	light yellow, needle
crystal system	monoclinic	trigonal	triclinic
space group	$P2_1/n$ (#14)	$P3_121$ (#152)	P-1 (#2)
a (Å)	5.69(1)	8.9331(10)	8.747(2)
b (Å)	11.614(9)	8.9331(10)	9.636(2)
c (Å)	19.562(3)	12.156(4)	5.980(1)
α (deg)	90	90	90.83(2)
β(deg)	91.15(4)	90	101.85(2)
γ(deg)	90	120	91.15(2)
V/Å^3	1292(2)	840.1(3)	493.1(2)
Z value	4	4	2
D_{calc} (g/cm^3)	2.249	2.510	2.671
R; R_w[a]	0.043; 0.050		0.037; 0.045
R1; wR2[b] [I>2σ(I)]		0.0669; 0.1526	
R1; wR2[b] (all data)		0.0683; 01527	
Goodness of Fit Indicator	1.23	5.157	1.07

[a] $R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $R_w = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma wFo^2]^{1/2}$

[b] $R1 = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $wR2 = \{\Sigma[w(Fo^2-Fc^2)2] / \Sigma[w(Fo^2)^2]\}^{1/2}$

Table 8.7 Crystallographic data for all compounds (continued).

	6B(Me)Cl	**6C**(Me)•¼HCl	**6D**(Me)Cl
empirical formula	$C_8H_{20}BiClN_2S_2$	$C_4H_{10.25}BiCl_{2.25}NS$	$C_4H_{11}BiCl_3NS$
Formula Weight	452.81	393.19	420.54
crystal description	long yellow, blocks	yellow, square- plate	needle-like
crystal system	monoclinic	tetragonal	monoclinic
space group	$P2_1$ (#4)	I-4 (#82)	$P2_1/c$ (#14)
a (Å)	8.122(3)	15.082(5)	6.850(2)
b (Å)	10.107(2)	15.082(5)	13.977(2)
c (Å)	9.295(2)	9.609(7)	11.720(1)
α (deg)	90	90	90
β(deg)	107.3470	90	106.14(1)
γ(deg)	90	90	90
V/Å^3	728.3(3)	2186(1)	1077.8(4)
Z value	2	8	4
D_{calc} (g/cm^3)	2.065	2389	2.591
R; R_w	0.037; 0.044	0.049; 0.054	0.044; 0.050
Goodness of Fit Indicator	1.14	2.81	4.31

$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $R_w = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma wFo^2]^{1/2}$

Table 8.7 Crystallographic data for all compounds (continued).

	6ECl*	**7A**
empirical formula	$C_4H_{12}ClN_2S_2Sb$	$C_6H_{10}BiClO_4S_2$
Formula Weight	309.48	454.70
crystal description	colorless, needle	light yellow, needle
crystal system	monoclinic	monoclinic
space group	$P2_1/n$ (#14)	Pa (#7)
a (Å)	5866(2)	8.092(2)
b (Å)	9.634(2)	9.13(1)
c (Å)	17.605(1)	8.128(3)
α (deg)	90	90
β(deg)	92.0920(3)	102.90(2)
γ(deg)	90	90
V/Å^3	994.2(2)	585.5(6)
Z value	8	2
D_{calc} (g/cm^3)	3.131	2.579
R; R_w	0.082; 0.080	0.036; 0.027
Goodness of Fit Indicator	4.94	1.57

$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $R_w = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma wFo^2]^{1/2}$

Table 8.7 Crystallographic data for all complexes (continued).

	7B	7C
empirical formula	$C_9H_{15}BiO_6S_3$	$C_3H_4BiCl_2KO_2S$
Formula Weight	524.36	423.11
crystal description	yellow, needle	colorless, needle
crystal system	triclinic	monoclinic
space group	P-1 (#2)	$P2_1/c$ (#14)
a (Å)	9.340(1)	7.822(3)
b (Å)	11.553(3)	14.475(2)
c (Å)	8.168(1)	8.629(2)
α (deg)	109.81(2)	90
β(deg)	92.98(2)	109.17(2)
γ(deg)	103.38(2)	90
V/Å^3	798.4(3)	922.8(4)
Z value	2	4
D_{calc} (g/cm^3)	1.993	3.053
R; R_w[a]	0.0297; 0.0293	
R1; wR2[b]		0.055; 0.180
Goodness of Fit Indicator	1.60	1.18

* Preliminary structure.

[a] $R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $R_w = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma wFo^2]^{1/2}$

[b] $R1 = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$; $wR2 = \{\Sigma[w(Fo^2-Fc^2)2] / \Sigma[w(Fo^2)^2]\}^{1/2}$

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