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Overview on bismuth(III) and bismuth(V) complexes with activity against *Helicobacter pylori*

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Contents

Abstract

Helicobacter pylori, a chronic gastritis and peptic ulcer causing bacterium, was rediscovered by Warren in 1983. The therapy to eradicate the stomach bacterium includes antibiotics, bismuth compounds and proton pump inhibitors.

After the success of the classical substances bismuth subsalicylate and bismuth subcitrate, numerous efforts have been made to synthesize bismuth complexes with improved antibacterial activity. Bismuth(III) complexes with thiosemicarbazones and dithiocarbazonic methylester

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derivatives, and bismuth(III) and bismuth(V) tropolonato complexes have shown promising activity against *Helicobacter pylori* in an agar dilution test. © 1997 Elsevier Science S.A.

1. Introduction

Helicobacter pylori (*H.p.*) was first discovered about a hundred years ago, when German pathologists observed similar organisms, but they were not able to culture the bacteria. In 1983 B.J. Marshall and J.R. Warren reported the discovery of unidentified curved bacilli on gastric epithelium in active chronic gastritis and grew them in culture [1]. In an experiment, they infected themselves with some of the cultivated bacteria [2]. Within a short time, they were suffering from a painful gastritis. This was the first sign of a direct relationship between the appearance of gastritis and a bacterial infection of the stomach. The pathogenic germs were known as *Campylobacter pylori* until 1989. Results of investigations by C.S. Goodwin made it necessary to characterize them as *Helicobacter pylori* [3]. Many experiments followed and proved that *Helicobacter pylori* is the reason for many cases of chronic gastritis and peptic ulcers. Infection with the bacteria has also been linked to stomach cancer, most probably because stomach cancer is related with chronic peptic ulcers [4]. In contrast to the treatment with bismuth compounds, which are active even in the acid medium of the stomach, therapy with combinations of organic antibiotics requires the application of proton pump inhibitors in order to achieve a neutral medium in the stomach where the antibiotics can become effective. Today combination therapies are used to eradicate *H.p.* which are often referred to as triple therapy and which consist of proton pump inhibitors together with antibiotics with or without bismuth compounds [5].

1.1. Helicobacter pylori (H.p.)

1.1.1. Discovery of Helicobacter pylori

In accordance with the thesis that microorganisms cannot survive in the acidic medium of the gastric juice the microbiological investigation of the stomach was incomplete in the past. At the end of the 19th century microbiologists observed the existence of microorganisms in the stomach of animals but they did not continue their research [6]. In the 20th century Doenges reported spiral-shaped bacteria in nearly 50% of human stomachs from accident victims [7].

The discovery and cultivation of *Campylobacter pylori* bacteria by Marshall and Warren in 1983 finished a period with few investigations into the gastric microflora [1]. Their results and conclusions form the basic principles of an effective treatment of gastrointestinal diseases such as gastritis and peptic ulcers. For this feat, Warren and Marshall were awarded the Paul–Ehrlich-Prize 1997.

1.1.2. Properties of Helicobacter pylori

Helicobacter pylori (*H.p.*) is a gram-negative, spiral-shaped bacterium. It has a smooth outer coat with usually seven tail-like flagella at one end. The bacterium

was initially classified as *Campylobacter pylori* but several features were soon found to distinguish this microorganism from the Campylobacter species [3]. Its exceptionally strong urease production, atypical protein content and unique fatty acid profile, together with sequencing studies, resulted in *H.p.* being classified as part of a new genus. *H.p.* have only been found in the mucus layer in the stomach. The seven tail-like flagella increase the corkscrew-like movement of the bacteria [8].

The acid-sensitive bacteria would not be able to survive in the stomach [9] without the high urease production. Urease, a nickel-containing enzyme isolated and crystallized in 1926 from the jack bean plant [10], catalyzes the hydrolysis of urea to form ammonia and carbon dioxide at a rate approximately 10^{14} times the rate of the uncatalyzed reaction [11]. The ammonia from the urease production buffers the acid concentration around the bacteria and enables them to survive under acidic conditions.

The history of *Helicobacter pylori* is illustrative of the transitoriness of theories once thought irrefutable and treated almost as a dogma, such as the belief that the cause of peptic ulcers is an increased gastric acid production along with stress and other psychological reasons.

1.2. Bismuth compounds in the therapy of gastrointestinal diseases

Bismuth compounds have been used in the treatment of gastrointestinal diseases for about two centuries [12]. Compounds such as bismuth carbonates were at one time applied so carelessly that the intake of 10 g several times per day actually resulted in strong side-effects such as neurotoxicity [13]. These side-effects are not to be expected today, with a rational treatment measured into very small doses [14]. There are arguments in favour of giving the "traditional bismuth therapy", which is carried out with pharmaceuticals in appropriate doses and formulations, which is preferred over a combination of organic antibiotics and proton pump inhibitors [15]. Some studies with bismuth compounds report on longer intervals without any complaints and higher eradication rates; on the other hand, an important argument is probably also the fact that the treatment with bismuth compounds does not require maintenance of a practically neutral stomach pH, which involves the risk of intestinal infections with other bacteria that can no longer be destroyed by the acidic gastric juice [16]. Furthermore, bismuth compounds have the advantage that they are practically not resorbed, so that there is no systemic strain on the body.

1.2.1. Clinically used bismuth compounds

The compounds which are applied today include simple bismuth salts such as bismuth nitrate, the so-called "colloidal bismuth subcitrate" (CBS) or bismuth subsalicylate [17]. CBS is the preferred bismuth drug in the classical triple therapy [18]. Nothing is known about the mechanism of action of the active bismuth compounds. In 1991 W.A. Herrmann isolated crystals of "colloidal bismuth subcitrate" and resolved the crystal structure [19]. Syntheses and characterization of other bismuth complexes followed, e.g. bismuth lactate [20,21]. J. Reedijk published structural and spectroscopic data for bismuth(III) citrate compounds [22,23]. The

adduct of ranitidine, a proton-pump inhibitor, and bismuth(III) citrate was investigated in solutions of different pH values with the aid of NMR techniques by P.J. Sadler and H. Sun [24]. This adduct showed interesting results in the treatment of peptic ulcer and is now used in the clinic.

The biological and bacteriostatic activity of some bismuth(III) compounds has been known for a long time but there was no information on how bismuth(III) compounds or bismuth(III) cations can be transported or bound in biological systems. The X-ray crystal structure analysis of bismuth(III) malate monohydrate and bismuth(III) tartrate trihydrate characterized two bismuth complexes which have been suggested as models for the interaction of metal cations and organic acids of human metabolism [25]. (Penicillaminato-*O,S,N*) bismuth(III) chloride shows a stable *S,N*-complexation and may be an antidote in possible cases of bismuth poisoning [26].

1.2.2. Requirements of therapeutically more effective bismuth compounds

In preparing new, more effective bismuth drugs, two aspects must be taken into account. First, an increase in antibacterial activity would make it possible to reduce the period of application while at the same time the eradication rate would be higher. In addition, the applied dose may be reduced and, with this, the share that is absorbed in the gastrointestine and which may be responsible for side-effects. Second, the physical properties should be optimal for interaction with the bacteria but should also ensure a low or negligible absorption rate.

The combination of bismuth with biologically active ligands provides bismuth complexes with a high degree of effectiveness against *H.p.* bacteria. This is particularly valid in the case of thiosemicarbazones and dithiocarbazonic acid esters.

Another aspect of bismuth drug design is the application of bismuth(V) compounds. Most of them are very unstable in aqueous (acidic) media, therefore there is a lack of antibacterial data sets. In an attempt to stabilize the high oxidation state of bismuth(V) by coordination of suitable ligands, bismuth(V) complexes could be obtained which are stable enough to be used in investigations into their biological and antibacterial activity.

2. Bismuth(III) and bismuth(V) tropolonato complexes

2.1. Bismuth(III) tropolonato complexes

The first bismuth complexes with tropolone, which is the basic structural constituent of colchicine, were synthesized and characterized through elemental analysis by Muetterties and Wright in 1964 [27–29] (Fig. 1).

No new bismuth(III) complexes with tropolone (Tr) or derivatives of tropolone as ligands were described in the literature until recently. The two new types of compound, bistropolonatobismuth(III) nitrate and phenylbistropolonatobismuth(III), shown in Fig. 2, have different chemical properties [30–32].

Reaction of bismuth(III) salts, e.g. $Bi(NO_3)_3 \cdot 5H_2O$ or $BiCl_3$ with tropolone (Tr),

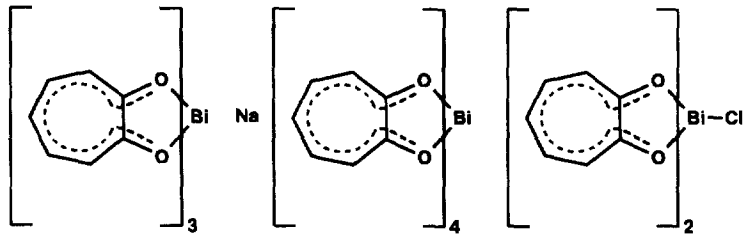


Fig. 1. Formal structures of tropolonato complexes synthesized by Muetterties and Wright.

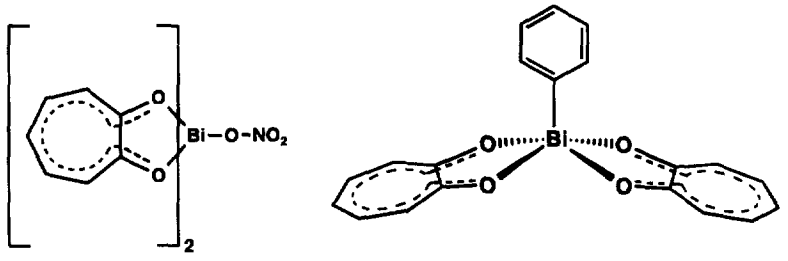


Fig. 2. Formal structures of new types of tropolonato complexes.

results in the formation of yellow coloured complexes. They have high melting points and a poor solubility in most solvents. Only $[(Tr)_2Bi]NO_3$ is soluble and shows a conductivity of a 1:1 electrolyte in DMSO/DMF, probably due to dissociation of the nitrate ion.

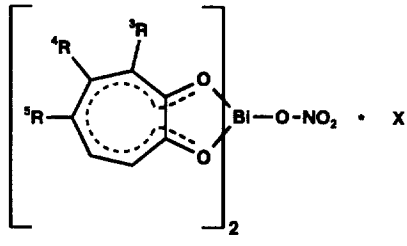
By crystal structure analysis of two representatives of the bis-tropolonatobismuth(III) nitrate group it was possible to resolve the structure of this class of complexes. In nitratobis(tropolonato)bismuth(III), the tropolonates are coordinated as bidentate ligands to the bismuth atom by two Bi–O bonds. There is a weaker interaction between the bismuth atom Bi(1) and the oxygen atom O(7) of the adjacent tropolonate, which is firmly coordinated to Bi(2). An analogous interaction can be observed between Bi(2) and O(2), which is probably caused by packing effects in the solid state. The bonding distances Bi(1)–O(7) (268.8 pm) and Bi(2)–O(2) (266.6 pm) are distinctly smaller than the sum of their van der Waals radii (360 pm) and can be treated as polar interactions [33]. This interaction, which may be termed Bi–O side interaction, influences Bi–O bond distances and angles, which differ depending on its presence or absence. One of the nitrate ions is coordinated to the bismuth atom *via* one oxygen atom, Bi(1)–O(1), the other is coordinated by two of the nitrate oxygen atoms, Bi(2)–O(14), Bi(2)–O(16). The coordination of the nitrate ion to the bismuth atom was confirmed by FD mass spectroscopy, where a molecular peak was be observed at $m/z = 513$. The bond lengths Bi(1)–O(11) (269.4 pm), Bi(2)–O(14) (266.2 pm) and Bi(2)–O(16) (274.0 pm) can also be classified as polar interactions. The tropolonate rings without a Bi–O side interaction lie in a plane spanned by the two bismuth atoms. Their

bond angles Bi–O–C are close to 120° (an ideal sp^2 hybrid). The Bi–O–C angles in the other two tropolonates which have Bi–O side interactions are further away from this value due to distortion. The coordination spheres of the two bismuth atoms differ, with Bi(1) surrounded by seven oxygen atoms and Bi(2) by six [32]. The inert 6s electron pair of the bismuth(III) cation is stereochemically active. The conductivity of nitratobis(tropolonato)bismuth(III) in DMF is 64.3 S cm^2 mol^{-1}, which corresponds to a 1:1 electrolyte [34].

Similar complexes with other derivatives of tropolone were synthesized for the first time. The complexes with the stoichiometric formula $[T_2Bi]NO_3$ (T = tropolone derivative) are shown in Fig. 3.

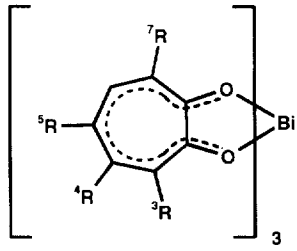
Investigations into the biological activity of the new type of compounds had promising results. The complexation of 3-isopropenyltropolones and 3-acetyltropolones to bismuth(III) cations gave compounds which could be divided into two complex classes, namely bis(3-isopropenyltropolonato)bismuth(III) nitrate and tris(3-acetyltropolonato)bismuth(III) [35]. The latter belongs to the group $[T_3Bi]$, representatives of which are shown in Fig. 4.

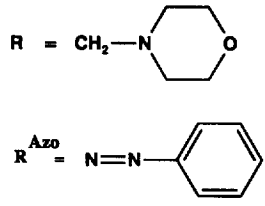
By crystal structure analysis of bis(3-bromotropolonato)chlorobismuth(III), the structure of the $[T_2BiCl]$ complex class (T = tropolone ligand) could be resolved. The crystals show long twisted Bi–Cl chains; the two 3-bromotropolonato rings coordinate as bidentate ligands to the bismuth(III) ion. The inert electron pair at the bismuth atom is stereochemically active and distorts the structure [35]. Other complexes of this class are shown in Fig. 5.



R^3	R^4	R^5	X	Ref.:	Compound
H	H	H	H_2O	[32]	$[(T_2Bi)]NO_3 * H_2O$
H	H	CH_3	-	[32]	$[(5\text{-}MT)_2Bi)]NO_3$
H	C_6H_4		H_2O	[32]	$[(4,5\text{-}BT)_2Bi)]NO_3 * H_2O$
H	C_6H_4		CH_3OH	[32]	$[(4,5\text{-}BT)_2Bi)]NO_3 * MeOH$
Isopropenyl	H	H	-	[35]	$[(DB)_2Bi)]NO_3$
Isopropenyl	H	CH_3	-	[35]	$[(IMT)_2Bi)]NO_3$

Fig. 3. Complexes with the stoichiometrical formula $[T_2Bi]NO_3$.



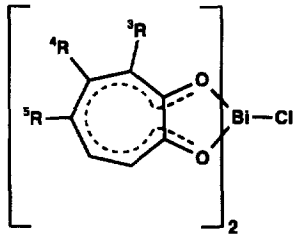


R^3	R^4	R^5	R^7	Ref.:	Compound
H	H	H	H	[32]	T_3Bi
H	CH_3	H	H	[32]	$(4\text{-}MT)_3Bi$
H	H	CH_3	H	[32]	$(5\text{-}MT)_3Bi$
CH_3	H	CH_3	CH_3	[32]	$(TMT)_3Bi$
H	C_6H_4	C_6H_4	H	[32]	$(4,5\text{-}BT)_3Bi$
H	H	NO_2	H	[32]	$(NT)_3Bi$
H	H	CHO	H	[32]	$(FT)_3Bi$
Br	H	H	H	[32]	$(BT)_3Bi$
Br	H	H	Br	[32]	$(BDT)_3Bi$
Br	H	Br	Br	[32]	$(TBT)_3Bi$
CH_2OH	H	CH_2OH	CH_2OH	[32]	$(THMT)_3Bi$
R	H	R	R	[32]	$(TMMT)_3Bi$
CH_3	H	$COCH_3$	H	[35]	$(AMT)_3Bi$
$COCH_3$	H	H	H	[35]	$(ACT)_3Bi$
H	H	R^{Azo}	H	[30]	$(PDT)_3Bi$

Fig. 4. Complexes with the stoichiometrical formula $[T_3Bi]$.

In all bismuth tropolonato complexes, the proton of the hydroxy group is dissociated and the seven-membered tropolone ring is bound to the bismuth(III) cation by the neighbouring oxygen atoms. The two equivalent carbon–oxygen bonds have partial double bond character. The three double bonds in the ring system are completely delocalized.

Reduction of the electron density in the coordinated tropolonato rings by the bismuth atom is proved by ^1H NMR and ^{13}C NMR spectra. The partial loss of the C=O double bond character after coordination to the bismuth atom was also confirmed by IR spectroscopy.



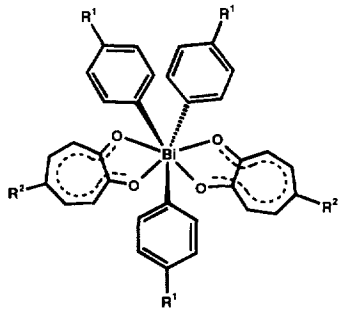
R^3	R^4	R^5	Ref.:	Compound
H	H	H	[32]	T_2BiCl
H	CH_3	H	[32]	$(4\text{-}MT)_2BiCl$
H	H	CH_3	[32]	$(5\text{-}MT)_2BiCl$
H	C_2H_5	H	[32]	$(4\text{-}ET)_2BiCl$
H	$CH(CH_3)_2$	H	[32]	$(4\text{-}IT)_2BiCl$
Br	H	H	[32]	$(BT)_2BiCl$
H	H	NH_2	[42]	$(AT)_2BiCl$

Fig. 5. Complexes with the formula $[T_2BiCl]$.

2.2. *Bismuth(V) tropolonato complexes*

Most known bismuth(V) complexes are not stable enough to be studied in biological systems. To increase the stability of bismuth(V) compounds, strong electronegative groups such as substituted aromatic rings, or similar aromatic systems, are necessary [36]. The good coordination abilities of tropolone ring systems were used to synthesize tri(aryl)tropolononatobismuth(V) complexes which are stable and not air-sensitive [37]. These have been characterized by elemental analysis, ^1H NMR, ^{13}C NMR and IR spectroscopy, and their structure is shown in Fig. 6.

Treatment of bisacetatotri(aryl)bismuth(V) compounds with tropolone derivatives results in the cleavage of the two acetate groups and their exchange for two tropolone rings. Thus, bisacetatotriphenylbismuth(V) and bisacetatotri(*p*-tolyl)bismuth(V) were synthesized and the crystal structure of the latter resolved. Tri(*p*-tolyl)bistropolonatobismuth(V) has a distorted pentagonal-bipyramidal structure; the base of the pyramid comprises a tolyl group (C(17)) and two tropolone rings (twist angle 11.7°). The remaining two tolyl groups occupy axial positions; the angle between them (C(32)–Bi(1)–C(20)) is 158.8° and thus deviates markedly from the expected 180° angle. The interaction between the oxygen atoms of the tropolone rings and the bismuth atom leads to Bi–O bonds of different lengths. The Bi–C distances range from 2.119–2.215 Å, differing at most by 4.5% from each other; the observed bond lengths are within the range of values previously reported for covalent Bi–C bonds. This finding provides conclusive evidence that the central bismuth atom



R^1	R^2	Ref.:	Compound
H	NO_2	[37]	$(NT)_2Bi(Ph)_3$
CH_3	H	[37]	$T_2Bi(To)_3$

Fig. 6. Structures of tri(aryl)tropolonatobismuth(V) complexes.

is seven-coordinate. The ligands completely surround the metal ion and prevent hydrolysis [35].

The structure of bis(5-nitrotropolonato)triphenylbismuth(V) is different in two aspects: The two 5-nitrotropolone rings are twisted relative to each other by only 2° and with the phenyl ring collectively form the base of the pentagonal pyramid. In order to compensate the increased steric hindrance between the 5-nitrotropolone oxygen atoms and the Bi(1)–C(17) bond of the equatorial phenyl group, the Bi(1)–C(17) bond extends to a length of 2.390 Å making it one of the longest Bi–C bonds reported to date [37].

These new bismuth(V) compounds are stable enough for antibacterial tests against *H.p.* strains.

3. Bismuth(III) complexes with thiosemicarbazones and dithiocarbazonic acid methylester derivatives

3.1. Biological activity of thiosemicarbazones and dithiocarbazonic acid methylester derivatives

Thiosemicarbazones have a wide range of biological applications including antibacterial activities. Domagk demonstrated the activity of thiosemicarbazones against Streptococcus [38]. Other investigations by Klayman and Scovill followed (Fig. 7) [39,40]. Thiosemicarbazones, which have good chelating abilities ought to bring about an even higher antibacterial activity for complexes with bismuth.

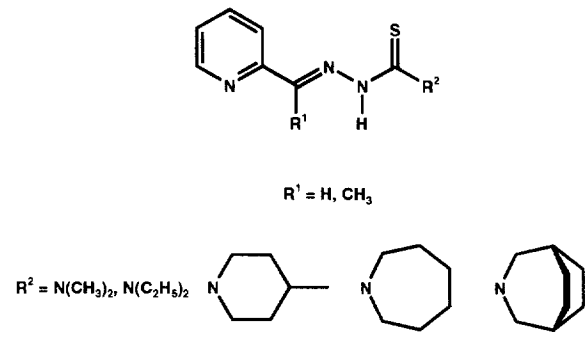


Fig. 7. Dithiocarbazonic acid methylesters synthesized by Klayman.

3.2. Bismuth(III) complexes with thiosemicarbazones and dithiocarbazonic acid methylester derivatives

The first bismuth(III) complexes with thiosemicarbazones were described by Tandon and Singh in 1992 [41]. Their formal structure is shown in Fig. 8. New complex types have now been synthesized and characterized by spectroscopic methods and X-ray crystal structure analysis.

A variety of thiosemicarbazones and derivatives of dithiocarbazonic acid methylester were used, which behave as bi-, tri- or pentadentate ligands. Reaction of these ligands with bismuth(III) salts such as $Bi(NO_3)_5^*5H_2O$, $Bi(CH_3COO)_3$ and BiX_3 (X=Cl, Br, I) resulted in the formation of bismuth(III) complexes with colours varying from yellow to red. Fig. 9 gives an example of coordination between bismuth(III) cations and a tridentate heterocyclic ligand.

Because of their molecular structure and stoichiometric properties, the new complexes can be divided into 9 groups A–I.

Group A – $[L_2Bi]NO_3$ (Figs. 10–12) [31,35,42,43].

Two ligands and the nitrate ion surround the bismuth(III) central atom. The ligands are bidentate or tridentate resulting in coordination numbers of 5 or 7. In DMF, these complexes show low conductivities of a 1:1 electrolyte.

Group B – $[L_2Bi(ac)]$ (Fig. 13) [35,42].

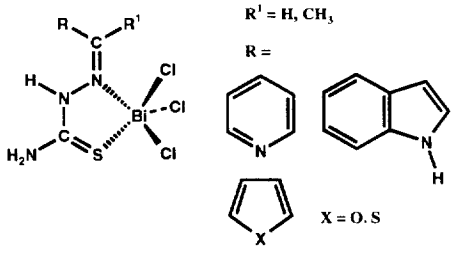


Fig. 8. Bismuth(III) complexes with thiosemicarbazones synthesized by Tandon and Singh.

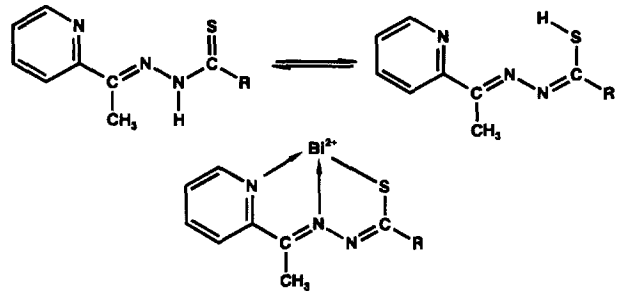
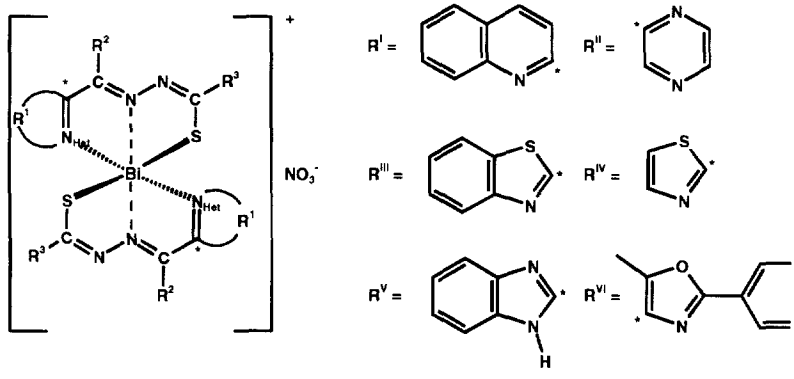
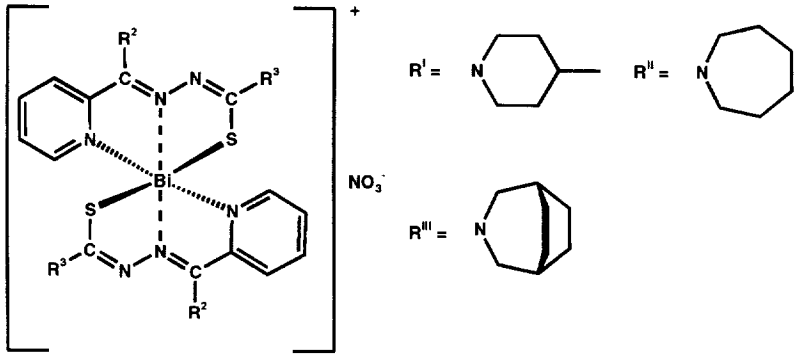


Fig. 9. Coordination between bismuth(III) ions and thiosemicarbazones.



R^1	R^2	R^3	Ref.:	Compound
R^I	CH_3	SCH_3	[42]	$[(CDCM)_2Bi]NO_3$
R^{II}	CH_3	SCH_3	[35]	$[(PZDT)_2Bi]NO_3$
R^{III}	CH_3	SCH_3	[44]	$[(BEDM)_2Bi]NO_3$
R^{III}	C_6H_5	SCH_3	[44]	$[(BBDM)_2Bi]NO_3$
R^{III}	$(CH_2)_4$-CH_3	SCH_3	[44]	$[(BPDM)_2Bi]NO_3$
R^{IV}	CH_3	SCH_3	[44]	$[(TEDM)_2Bi]NO_3$
R^{IV}	C_6H_5	SCH_3	[44]	$[(TBDM)_2Bi]NO_3$
R^{IV}	$(CH_2)_4$-CH_3	SCH_3	[44]	$[(TPDM)_2Bi]NO_3$
R^V	C_6H_5	SCH_3	[44]	$[(BIDM)_2Bi]NO_3$
R^{VI}	CH_3	SCH_3	[44]	$[(OEDM)_2Bi]NO_3$

Fig. 10. Bismuth complexes of Group A.



R^2	R^3	Ref.:	Compound
H	NH_2	[43]	$[(PASC)_2Bi]NO_3$
CH_3	NH_2	[43]	$[(PTSC)_2Bi]NO_3$
CH_3	$N(CH_3)_2$	[43]	$[(DMPH)_2Bi]NO_3$
CH_3	$N(C_2H_5)_2$	[43]	$[(DEPH)_2Bi]NO_3$
CH_3	R^I	[43]	$[(PTPH)_2Bi]NO_3$
CH_3	R^{II}	[43]	$[(HMPH)_2Bi]NO_3$
CH_3	R^{III}	[43]	$[(ANPH)_2Bi]NO_3$
CH_3	SCH_3	[43]	$[(PDTC)_2Bi]NO_3$
C_6H_5	SCH_3	[44]	$[(PBDM)_2Bi]NO_3$

Fig. 11. Group A.

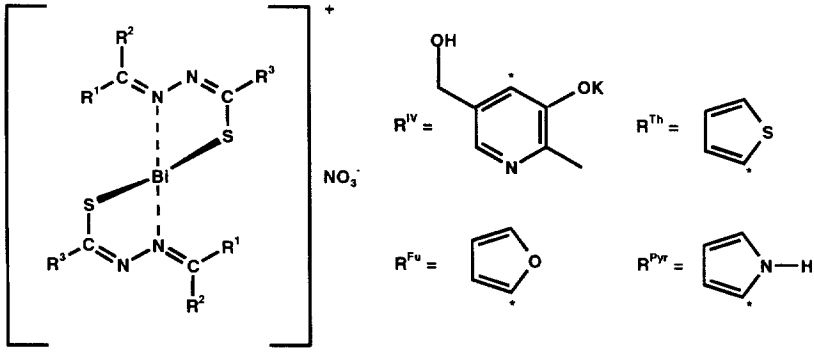
Two ligands and the acetate ion surround the bismuth(III) central atom. The acetate ion is bound *via* two oxygen atoms and the ligand is tridentate resulting in a coordination number of 8. In DMF, these complexes show conductivities of a neutral undissociated electrolyte. Conductivity measurements in MeOH have indicated that dissociation occurs.

Group C – $\{[LBi]Cl\}_2$ (Fig. 14) [31,43, 44].

This complex group contains a dimeric unit with dichloro-bridged bismuth atoms and two tridentate ligands, as shown by X-ray crystal structure analysis. In DMF, these complexes show conductivities of a neutral undissociated electrolyte.

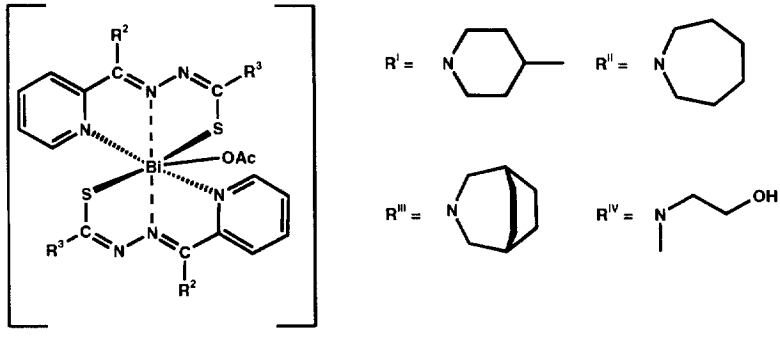
Group D – $[L_3Bi]$ (Fig. 15) [35].

Three bi- or tridentate ligands surround the bismuth(III) central atom. Steric hindrance and interactions between the coordinated ligand molecules cause a weakening in coordination. As a result, the thermal stability of these compounds decreases.



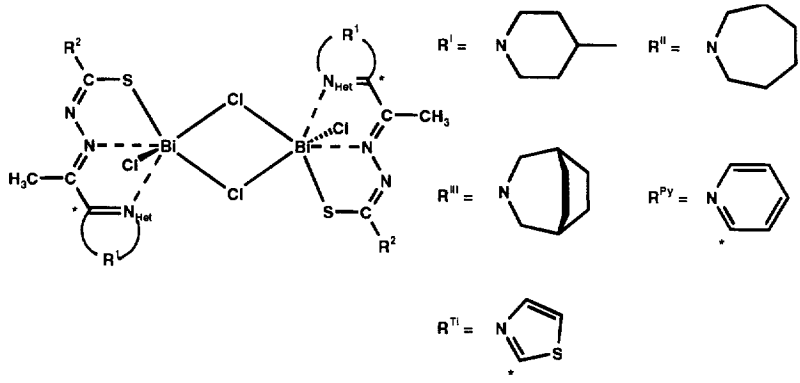
R^1	R^2	R^3	Ref.:	Compound
R^{Th}	CH_3	SCH_3	[43]	$[(TDTC)_2Bi]NO_3$
R^{Pyr}	H	SCH_3	[42]	$[(PTC)_2Bi]NO_3$
R^{Fu}	CH_3	SCH_3	[43]	$[(FDTC)_2Bi]NO_3$
R^{IV}	CH_3	SCH_3	[35]	$[(PDDT)_2Bi]NO_3$

Fig. 12. Group A.



R^2	R^3	Ref.:	Compound
CH_3	R^{II}	[35]	$(HMPH)_2Bi(ac)$
CH_3	R^{III}	[35]	$(ANPH)_2Bi(ac)$
CH_3	$N(C_2H_5)_2$	[35]	$(DEPH)_2Bi(ac)$
CH_3	R^{IV}	[35]	$(MEPH)_2Bi(ac)$

Fig. 13. Bismuth complexes of Group B.



R^1	R^2	Ref.:	Compound
R^{Py}	$N(CH_3)_2$	[43]	$[(DMPH)BiCl_2]_2$
R^{Py}	$N(C_2H_5)_2$	[43]	$[(DEPH)BiCl_2]_2$
R^{Py}	R^{I}	[43]	$[(PTPH)BiCl_2]_2$
R^{Py}	R^{II}	[43]	$[(HMPH)BiCl_2]_2$
R^{Py}	R^{III}	[43]	$[(ANPH)BiCl_2]_2$
R^{Py}	SCH_3	[43]	$[(PDTC)BiCl_2]_2$
R^{Ti}	SCH_3	[44]	$[(TEDM)BiCl_2]_2$

Fig. 14. Bismuth complexes of Group C.

A representative complex molecule has been analyzed by X-ray crystal structure analysis and exhibits a nine-coordinate central atom.

Group E – $[LBiX_2]$ (X=Cl, Br, I) (Fig. 16) [31,35,43].

Two halogenide ions and a bi- or tri-dentate ligand surround the central atom. The question whether these complexes exist in a monomeric, dimeric or oligomeric form has not yet been determined, as crystal structure analyses are not available for this group of complexes.

Group F – $BiCl_3^*L$ (Fig. 17) [31,41,43].

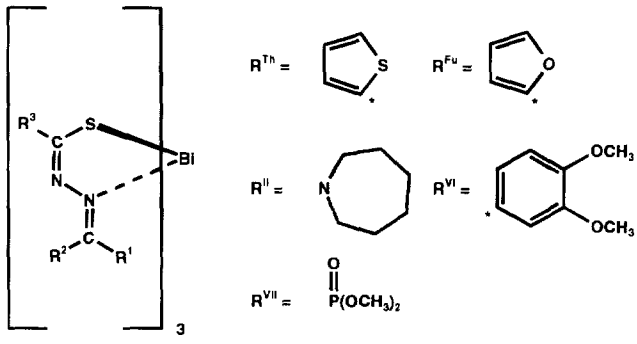
The ligand molecule is not deprotonated and coordinates *via* the thioketo and one azomethine group.

Group G – $[LBiCl_2]L^*$ (Fig. 18) [31,43].

In addition to two chlorine ions, the bismuth(III) cation is coordinated with a protonated and a deprotonated bidentate ligand.

Group H – $[LBi]NO_3$ (Fig. 19) [35,42].

The ligand molecule has two chelating arms. Both tridentate arms are deprotonated. The red-coloured complexes of this group show conductivities of 1:1 electrolytes.



R^1	R^2	R^3	Ref.:	Compound
R^{Fu}	CH_3	SCH_3	[35]	$(FDTC)_3Bi$
R^{Th}	CH_3	R^{II}	[35]	$(HMTH)_3Bi$
R^{IV}	CH_3	R^{VII}	[35]	$(DPVT)_3Bi$

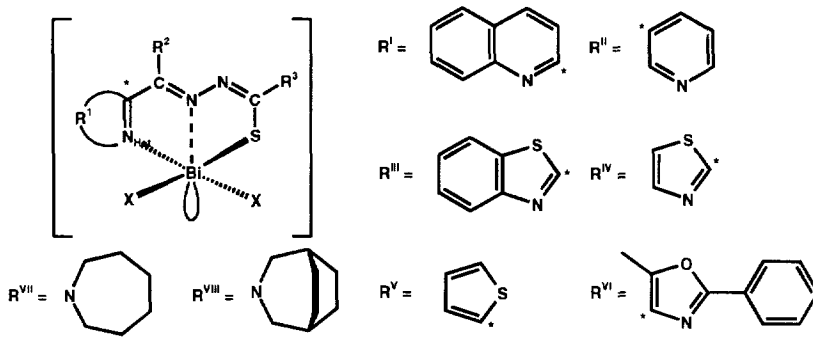
Fig. 15. Bismuth complexes of Group D.

Group I – $[LBiCl_2]$ (Fig. 19) [35,42].

The ligand molecule has two chelating arms. From the stoichiometric formula, only one of these arms should be deprotonated and the other should be protonated. IR and NMR spectra, however, failed to show the expected signals for two different chelating arms. The orange-coloured complexes show conductivities for non-electrolytes.

The inert electron pair of the bismuth(III) atom is stereochemically active in all investigated crystal structures and forces steric pressure on the coordination interaction between the ligand and metal ion. Variation of the ligand structure, e.g. replacement of the SCH_3 group by cyclic secondary amines, improves the solubility of the corresponding bismuth(III) complex and increases its antibacterial activity.

If $Bi(CH_3COO)_3$ is used in combination with tridentate ligands with pyridine as the heterocyclic element, only complexes of Group B $[L_2Bi(ac)]$ will form [35]. Bidentate ligands with furane or thiophene as heterocycles react with $Bi(CH_3COO)_3$ and form complexes of Group D. There is no interdependence between the chosen stoichiometric ratio ligand: bismuth(III) salt and the obtained complex. The nature of the heterocyclic element determines the formation of the respective complex: If a steric ability for coordination is given, the nitrogen atom of a pyridine heterocycle will interact with the bismuth(III) atom, two acetato ions will be replaced and a $[L_2Bi(ac)]$ compound will form. Without the possibility for an additional coordination *via* a heterocyclic atom, all of the acetato anions will be replaced and a $[L_3Bi]$ complex will form.



R^1	R^2	R^3	X	Ref.:	Compound
R^{II}	CH_3	R^{VII}	Br	[42]	$(HMPH)BiBr_2$
R^{II}	CH_3	R^{VII}	I	[42]	$(HMPH)BiI_2$
R^{I}	H	SCH_3	Cl	[42]	$(CDCM)BiCl_2$
R^{IV}	CH_3	SCH_3	Cl	[44]	$(TEDM)BiCl_2$
R^{IV}	C_6H_5	SCH_3	Cl	[44]	$(TBDM)BiCl_2$
R^{IV}	$(CH_2)_4CH_3$	SCH_3	Cl	[44]	$(THTM)BiCl_2$
R^{III}	CH_3	SCH_3	Cl	[44]	$(BEDM)BiCl_2$
R^{VI}	CH_3	SCH_3	Cl	[44]	$(OEDM)BiCl_2$
R^{V}	CH_3	SCH_3	Cl	[43]	$(TDTC)BiCl_2$

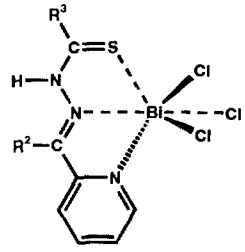
Fig. 16. Bismuth complexes of Group E.

4. *In vitro* activity of selected bismuth(III) and bismuth(V) complexes

Most of the bismuth complexes discussed above have been tested against *Helicobacter pylori* in an agar dilution test. In this test, the bismuth complexes are dissolved in DMSO or ethanol and diluted with water in a geometric dilution series. These solutions are given to a brain–heart infusion agar in a dish with decreasing concentrations (512–2 $\mu g\,ml^{-1}$). The dishes are infected with *Helicobacter pylori*, and bacteria growth is evaluated after a three day incubation in a microaerophilic medium. In each case the compounds were tested against ten *Helicobacter pylori* strains. The complexes were compared to the standards bismuth citrate, bismuth salicylate and bismuth nitrate aluminate, which reached minimal inhibitory concentrations (*MIC*) of 16–64 $\mu g\,ml^{-1}$.

Table 1 gives a selection of the results with the bismuth complexes tested.

These *in vitro* tests are carried out under an almost neutral pH, which is necessary



R^2	R^3	Ref.:	Compound
H	NH_2	[41]	$(PASC)BiCl_3$
CH_3	NH_2	[41]	$(PTSC)BiCl_3$

Fig. 17. Bismuth complexes of Group F.

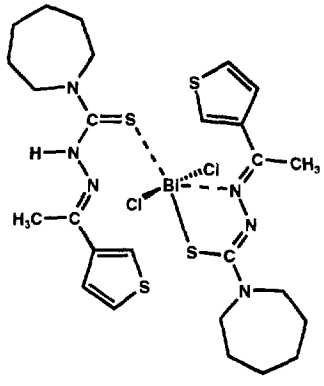


Fig. 18. Bismuth complexes of Group G.

to keep bacteria strains growing. So far it has not been possible to grow *H.p.* in an artificial stomach medium. Therefore the predictivity of such cell culture experiments for clinical activity is unknown. Today, new bismuth compounds with *MIC* values lower than those of the drugs which are clinically established can only be assumed to be more active than these. Such results have to be verified in predictive animal experiments and, finally, in clinical trials.

There is general evidence that some compounds among the bismuth tropolonato complexes and, in particular, the bismuth thiosemicarbazonato complexes are considerably more active in this test system than the clinically used standard drugs. There is no clear structure–activity relationship apart from the fact that in general tropolonates seem to be less active than the thiosemicarbazonates. There is the possibility that activity is considerably influenced by the physical parameters, surface properties, etc. of the barely soluble compounds. If an increase in activity by up to

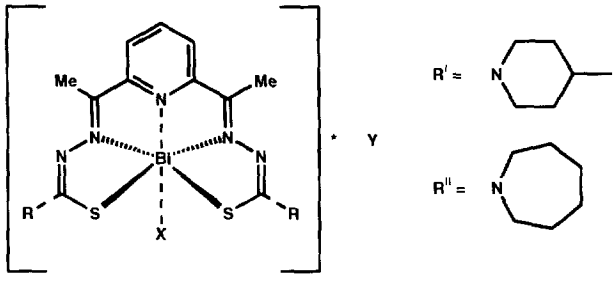
Table 1
Minimal inhibitory concentrations, *MIC* (in $\mu g\,ml^{-1}$), of bismuth(III) and bismuth(V) tropolonato complexes and of bismuth(III) thiosemicarbazones and dithiocarbazonic acid methylester complexes in an agar dilution test against eight *H.p.* strains

Compound (Solvent)	*Helicobacter pylori* strains							
	NCTC 11637	04713 8991	*H.p.* 0008	*H.p.* 0012	*H.p.* 0016	*H.p.* 0032	*H.p.* 0072	*H.p.* 0083
$(AMT)_3Bi$ (DMSO)	10	10	10	10	10	10	10	10
T_3Bi (DMSO)	16	–	–	–	–	-	–	–
$(4,5\text{-}BT)_3Bi$ (DMSO)	>512	–	–	–	–	–	–	–
$(NT)_3Bi$ (DMSO)	4	4	–	–	–	–	–	–
$(4\text{-}MT)_3Bi$ (DMSO)	16	16	–	–	–	–	–	–
$[DB)_2Bi)]NO_3$ (DMSO)	10	10	10	10	10	10	10	10
$[(IMT)_2Bi]NO_3$ (DMSO)	10	10	10	10	5	10	10	10
$[(AT)_2Bi]NO_3$ (DMSO)	16	8	8	16	–	4	8	8
T_2BiCl (DMSO)	8	8	–	–	–	–	–	–
$(4\text{-}MT)_2BiCl$ (DMSO)	8	–	–	–	–	–	–	–
$[(CDCM)Bi]NO_3$ (DMSO)	16	16	4	16	–	8	16	16
$[(PTC)Bi]NO_3$ (DMSO)	16	16	2	16	–	8	16	16
$[ANPH)_2Bi]NO_3$ (DMSO)	64	32	–	–	8	–	–	–
$[ANPH)_2Bi]NO_3$ (EtOH)	25	10	5	10	10	10	25	10
$[(ANPH)BiCl_2]_2$ (DMSO)	32	16	–	–	8	–	–	–
$[(ANPH)BiCl_2]_2$ (EtOH)	100	50	50	50	50	50	100	50
$(ANPH)_2Bi(ac)$ (DMSO)	128	128	32	128	–	64	128	64
$(ANPH)_2Bi(ac)$ (EtOH)	10	10	5	5	2.5	10	10	10
$(MEPH)_2Bi(ac)$ (DMSO)	10	25	5	10	5	10	10	10
$(DPVT)_3Bi$ (EtOH)	25	25	25	25	10	25	25	25
$(FDTC)_3Bi$ (DMSO)	25	25	10	25	10	10	25	25
$(CDCM)BiCl_2$ (DMSO)	32	32	16	32	–	16	32	32
$[(PDCH)Bi]NO_3$ (DMSO)	8	4	0.5	8	–	8	4	8
$[(PDHM)Bi]NO_3$ (DMSO)	10	10	10	5	2.5	10	5	5
$T_2Bi(To)_3$ (DMSO)	10	10	10	10	10	10	10	10
$(NT)_2Bi(Ph)_3$ (DMSO)	10	2.5	2.5	5	1	2.5	2.5	2.5

two decimal powers such as can be observed with some of the new compounds would also show *in vivo*, at least approximately, it might be possible to successfully eradicate *H.p.* in a monotherapy with bismuth compounds. There would also be the advantage that these compounds which are even more difficult to dissolve would be even less resorbed than those which are already used in the clinic.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft, DFG, Bonn, Germany. We would like to thank Prof. Dr. W. Opferkuch, Bochum, for carrying out the *in vitro* tests.



R	X	Y	Ref.:	Compound
SCH_3	NO_3	-	[42]	$[(PDCH)Bi]NO_3$
SCH_3	Cl	-	[42]	(PDCH)BiCl
R''	NO_3	-	[35]	$[(PDMP)Bi]NO_3$
R'	NO_3	H_2O	[35]	$[(PDCH)Bi]NO_3 * H_2O$
R''	NO_3	HCl	[35]	(PDHM)BiCl * HCl

Fig. 19. Groups H and I.

References

[1] J.R. Warren, B. Marshall, Lancet 1 (1983) 1273.
[2] B. Marshall, J. Armstrong, D. McGechie, R. Glancy, Med. J. Austr. 142 (1985) 436.
[3] C.S. Goodwin, J.A. Armstrong, T. Chilvers, M. Peters, M.D. Collins, L. Sly, W. McConnell, W.E.S. Harper, Int. J. Syst. Bacteriol. 39 (1989) 397.
[4] M.J. Blaser, Gastroenterology 102 (1992) 720.
[5] A. Burette, Y. Glupczynski, C. Depres, D. Jacobs, Infect. Dis. Ther. 18 (1995) 520.
[6] J.P. Rappin, Bergey's Manual of Determinative Bacteriology, 6th ed., Wiliams and Wilkins Co, Baltimore, 1881, p. 68.
[7] J.L. Doenges, Arch. Pathol. Lab. Med. 27 (1939) 469.
[8] H.C. Wolfsen, N.J. Talley, in: C.S. Goodwin, B.W. Worsley (Eds.), *Helicobacter pylori*: Biology and Clinical Practice, CRC Press, Boca Raton, FL, 1993, p. 365.
[9] M. Tsuda, M. Karita, T. Mizote, M.G. Morshed, K. Okita, T. Nakazawa, Eur. J. Gastroenterol. Hepatol. 6 Suppl. 1 (1994) 49.
[10] J.B. Sumner, J. Biol. Chem. 69 (1926) 435.
[11] R.P. Hausinger, Biochemistry of Nickel, Plenum Press, New York, 1993, ch. 3.
[12] G. Börsch, Med. Klinik 83 (1988) 605.
[13] P. Lechat, R. Kisch, Gastroent. Clin. Biol. 10 (1986) 562.
[14] G.D. Bell, K. Powell, S.M. Burridge, A. Pallecaros, P.H. Jones, P.W. Gant, G. Harrison, J.E. Trowell, Aliment. Pharmacol. Ther. 6 (1992) 427.
[15] G. Börsch, Med. Monatsschr. Pharm. 11 (1988) 301.
[16] Y. Glupczynski, A. Burette, Am. J. Gastroenterol. 85 (1990) 1545.
[17] A.J. Wagstaff, P. Benfield, J.P. Monk, Drugs 36 (1988) 132.
[18] G.N.J. Tytget, Aliment. Pharmacol. Ther. 8 (1994) 359.
[19] W.A. Herrmann, E. Herdtweck, L. Pajdla, Inorg. Chem. 30 (1991) 2579.
[20] P. Kiprof, W. Scherer, L. Pajdla, E. Herdtweck, W.A. Herrmann, Chem. Ber. 125 (1992) 43.

[21] W.A. Herrmann, P. Kiprof, W. Scherer, L. Pajdla, Chem. Ber. 125 (1992) 2657.
[22] E. Asato, W.L. Driessen, R.A.G. de Graaff, F.B. Hulsbergen, J. Reedijk, Inorg. Chem. 30 (1991) 4210.
[23] E. Asato, K. Katsura, M. Mikuriya, U. Turpeinen, I. Mutikainen, J. Reedijk, Inorg. Chem. 34 (1995) 2447.
[24] P.J. Sadler, H. Sun, J. Chem. Soc. Dalton Trans. (1995) 1395.
[25] W.A. Herrmann, E. Herdtweck, W. Scherer, P. Kiprof, L. Pajdla, Chem. Ber. 126 (1993) 51.
[26] W.A. Herrmann, E. Herdtweck, L. Pajdla, Chem. Ber. 126 (1993) 895.
[27] E.L. Muetterties, C.M. Wright, J. Am. Chem. Soc. 86 (1964) 5132.
[28] E.L. Muetterties, C.M. Wright, J. Am. Chem. Soc. 86 (1965) 21.
[29] E.L. Muetterties, C.M. Wright, J. Am. Chem. Soc. 88 (1966) 4856.
[30] R. Diemer, Diploma Thesis, University of Heidelberg, 1990.
[31] R. Diemer, PhD Thesis, University of Heidelberg, 1993.
[32] R. Diemer, B.K. Keppler, U. Dittes, B. Nuber, V. Seifried, W. Opferkuch, Chem. Ber. 128 (1995) 335.
[33] G. Smith, A.N. Reddy, K.A. Byriel, C.H.L. Kennard, Austr. J. Chem. 47 (1994) 1413.
[34] W.J. Geary, Coord. Chem. Rev. 7 (1971) 110.
[35] U. Dittes, PhD Thesis, University of Heidelberg, 1995.
[36] P.R. Wells, Prog. Phys. Org. Chem. 6 (1968) 111.
[37] U. Dittes, B.K. Keppler, B. Nuber, Angew. Chem. Int. Ed. Engl. 35 (1996) 67.
[38] G. Domagk, R. Behnisch, F. Mietzsch, H. Schmidt, Naturwissenschaften 33 (1946) 315.
[39] D.L. Klayman, J.F. Bartosevich, J.P. Scovill, C.J. Mason, J. Med. Chem. 22 (1979) 855, 1367; 25 (1982) 1261; 26 (1983) 35.
[40] D.L. Klayman, J.F. Bartosevich, J.P. Scovill, C.J. Mason, Eur. J. Med. Chem. 16 (1981) 317.
[41] K. Singh, J.P. Tandon, Monatsh. Chem. 123 (1992) 315.
[42] U. Dittes, Diploma Thesis, University of Heidelberg, 1993.
[43] R. Diemer, U. Dittes, B. Nuber, V. Seifried, W. Opferkuch, B.K. Keppler, Metal Based Drugs 2 (5) (1995) 271.
[44] O. Lenz, PhD Thesis, University of Heidelberg, 1996.