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Review

Recent applications of high-performance liquid chromatography to the analysis of metal complexes

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Abstract

Interest in metal complexes in modern inorganic chemistry has resulted in increasing demands for the analysis of these compounds. This paper reviews the most recent applications of high-performance liquid chromatography (HPLC) to the analysis of metal complexes. The review centres on the use of the technique in metal complex syntheses, reactions, characterizations and complexations and retention behaviour of these compounds, as reported in the literature since 1994. © 1997 Elsevier Science B.V.

Keywords: Reviews; Metal complexes; Organometallic compounds

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1. Introduction

Apart from their importance in the materials and catalysis areas, metal ions and their complexes play an important role in the vital functions of living organisms. As a result, the reactivity, synthesis, stability, structure and formation of these compounds are studied by a variety of inorganic, organic,

analytical and physical techniques. Amongst these techniques, high-performance liquid chromatography (HPLC) is widely used for the separation, determination, and in the preparation of organometallic compounds and metal coordination compounds. Organometallic compounds, by definition, are those compounds characterized by the presence of metal–carbon bonds, possibly along with other metal–element bonds, while metal coordination compounds are those that contain “only” metal–oxygen, metal–

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sulfur, metal–nitrogen and/or other metal–donor bonds. However, such classification between organometallic and coordination compounds is not very clear-cut. In the context of this paper, we investigate the recent progress achieved in the HPLC analysis of both these types of compounds.

HPLC is characterized by high speed and efficiency, and can be coupled to many sensitive and selective detectors. The first reported use of HPLC for the separation of organometallic complexes was made by Veening et al. in 1969 [1]. Chromatographic analysis of metal complexes carried out by traditional gravity column chromatography (CC) and thin-layer chromatography (TLC) are usually complicated because of oxidative, hydrolytic, thermal or photochemical instability of some complexes during the long periods of such analyses. HPLC, however, can surmount these difficulties since the analysis is performed rapidly under ambient temperature and the system (stainless-steel columns, degassed mobile phases, inert solvents, etc.) can effectively prevent the metal complexes from contacting the atmosphere and light. For these reasons, HPLC has gained considerable popularity in this field [2,3]. During the past few years, the rapid developments of column and an increasing variety of detection techniques have made it suitable for the separation and determination of metal complexes.

This review includes applications that utilize most of the known HPLC separation modes. It does not cover those applications carried by so-called ion chromatography (IC). We have limited the review to the work that involves the complexation of metals with ligands before injection into the HPLC system. The applications with post-column derivatization of metal ions to form complexes are not covered. Those applications where metal complexes are formed during the separation by addition of metal ions or ligands to the mobile phases are also not included. Likewise, studies involving the use of HPLC for analysing non-metal-species by complexing them with metal ions, are excluded from this review.

2. Separation and determination

2.1. HPLC separation and detection techniques

In the field of metal complex analysis in the past

three years, reversed-phase (RP) HPLC has been more widely used than normal-phase (NP) HPLC. Among various RP-HPLC methods, ion-pair (IP) RP-HPLC is rapidly gaining in popularity. Other separation modes, such as ion-exchange HPLC (HPIEC) and size-exclusion HPLC have also been applied. Table 1 summarizes many of the HPLC applications in the analysis of metal complexes from 1994 to 1997.

Except for the widely used UV spectrophotometric detection (primarily photodiode array detection, PDA), fluorescence detection has been used extensively for the detection of metal complexes. Sutheimer and Cabaniss [89] separated soluble complexes of aluminum, including fluorides, citrates, acetates and silicates, from uncomplexed Al using gradient elution cation-exchange HPLC. After post-column reaction with lumogallion, the Al–lumogallion complexes were quantitated by fluorescence detection. An IP-RP-HPLC method with fluorimetric detection, using lumogallion as a ligand, has been successfully applied to the determination of aluminum in human serum by Wu et al. [90]. In a later work, a simple and sensitive HPLC method for quantifying aluminum in serum and urine by measuring the fluorescence of the Al–lumogallion complex was described [91]. Schuster and Sando [92] used RP-HPLC and fluorometric detection to analyze the chelates of heavy-metal ions with N-Dansyl-N'-ethylthiourea. Also presented were the first measurements of fluorescence decay times of the ligand as well as some complexes. Copper complexes with fulvic, caffeic, vanillic and salicylic acids were investigated by RP-HPLC with dual UV–Vis PDA and fluorescence detection using retention enrichment and direct complex introduction methods [93]. A RP-HPLC method with fluorescence detection to analyze free Gd^{3+} in ionic Gd chelates, $Gd(EDTA)^-$, $Gd(DTPA)^{2-}$ and $Gd(DOTA)^-$, was developed. In this method, free Gd^{3+} was complexed with cyclohexanediaminetetraacetic acid (CDTA) [94].

Although spectrophotometric detection has been most popular, electrochemical, pulsed amperometric and other detection methods have also been applied to metal complex analysis. Weber [95] used triple-step pulsed amperometry to detect selectively metal complex species after HPLC separation in the presence of coeluting matrix compounds. The method is

Table 1

Recent applications of HPLC to some metal complexes (RP=reversed-phase, IP=ion-pair, NP=normal-phase)

HPLC mode or column	Metal complexes	Remarks	Ref.
IP-RP	Metal chelates of 4,2-(pyridylazo)resorcinol and 4-(2-thiazodylazo)resorcinol	water samples	[4]
RP	<i>trans</i> -[RuCl ₄ (imidazole) ₂]		[5]
Size-exclusion	In-111-immunoglobulin(Ig)G	Liver	[6]
	Metal ions with 2-hydroxy-5-sulfoaniline-N-salicylidene		[7]
RP	Cu(II), Co(II) and Ni(II) chelates with diethyldithiocarbamic acid	Many types of samples, including alloys	[8]
NP	Vanadium with N-phenylbenzohydroxamic acid (PBHA)	Clam tissue (<i>Cititerea</i> Sp.)	[9]
RP	Metal chelates of 3-mercapt-1,5-diphenylformazane		[10]
RP	Metal-cyanide complexes [PtCl ₂ (dach)]	Gold mill solution [12]	[11]
RP	Nb-(4-2-pyridyl(azo)resorcinol) (PAR) chelate [PtCl ₂]	Rocks	[13]
	Metal dithiocarbamate complexes	Plasma	[14]
	1,2-Diaminocyclohexane platinum(IV)		[15]
NP	Silver, nickle, zinc and palladium complexes of tetra(pentafluorophenyl)porpholactone (TFPL)		[16]
	Iron(III) complex of 1,2-diethyl-3-hydroxypyridin-4-one	Serum and urine of thalassaemic patients	[18]
	Chelate of Ni(II) and 2-pyridylaldehydebenzoylhydrazone (PAB)	Coal fly ash samples	[19]
	Metal-polypeptides (phytochelatins)		[20]
RP	Pd(II), Rh(III), Ru(III) and Pt(II) complexes of 4-(5-nitro-2-pyridylazo)resorcinol (5-NO ₂ -PAR)		[21]
RP	Chelates of Ru, Os and Pd with 4-(2'-thiazolylazo)resacetophenone oxime	Anode slime	[22]
RP	Dichloro (1,2-diarylethylenediamine) platinum(II)		[23]
	Ruthenium(II) diimine complex		[24]
IP-RP	Platinum with 4,4'-bis(dimethylamino)thiobenzophenone	Analysis of cisplatin or carboplatin	[25]
RP	Cobalt and nickel with diethyldithiocarbamic acid	Many types of samples, including alloys	[26]
RP	Metal α , β , γ , δ -tetrakis(4-carboxyphenyl)porphine (TCPP)	Water samples	[27]
RP	Titanium, vanadium, niobium and tantalum ternary complexes with hydrogen-peroxide and 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol	Water samples and human hair	[28]
	Metal complexes with ligands from soil and water	Soil and water	[29]

(Continued on p. 440)

Table 1 (continued)

HPLC mode or column	Metal complexes	Remarks	Ref.
RP	Chromium(II)- β -nicotinamide adenine-dinucleotide phosphate	Yeast extracts	[30]
	Magnetic microsphere-methotrexate conjugates	Drug	[31]
	Cd-Zn peptides complex	Leaf extracts	[32]
RP	Th and U complexes with α -hydroxy-isobutyric acid (HIBA)	Rock	[33]
	Platinum complexes (cisplatin, carboplatin, oxaliplatin, oxoplatin and tetraplatin)	Plasma and urine of rabbits	[34]
RP	Cu(II), Co(II) and Fe(II) complexes with 2-acetylphridine-4-phenyl-3-thiosemicarbazone (APPT)	Pharmaceutical preparations	[35]
RP	Zinc and copper pyrithione	Cosmetic preparations	[36]
IP-RP	Palladium and gold with 4, 4'-bis(dimethylamino)thiobenzophenone	Gold recovery solution and anode mud from copper smelters	[37]
	Low-molecular-mass copper complexes	Ultrafiltrates of rheumatoid synovial fluid	[38]
RP	Iron complex of 1,2-dimethyl-3-hydroxy-pyrid-4-one	Serum and urine	[39]
	Polymetallic complexes of rhodium(III), iridium(III) and ruthenium(II) with 1,4,5,8,9,12-hexaazatriphenylene		[40]
Cation exchange	Pentaamminemethylcobalt(III)		[41]
	Fe(III) citrate		[42]
	PtC ₁₂ [<i>meso</i> -1,2-bis(2,6-dichloro-4-hydroxyphenyl)ethylenediamine]		[43]
	Dinuclear chromium(III) complexes		[44]
NP	Oxovanadium(IV) complex of bis(salicylaldehyde)tetramethylethylene diimine (H ₂ SA ₂ Ten)	A coin	[45]
	Ni(II), Co(II) and Cu(II) as diethyl dithiocarbamate complexes	Nickel and copper in real samples	[46]
RP	Pt-195m-radiolabeled <i>cis</i> -diammine (1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin)		[47]
RP	(pheophytin)mercury(II)		[48]
	Cobalt complexes		[49]
	<i>cis</i> -Dichlorodiammineplatinum(II), platinum and nickel complexes with diethyldithiocarbamate	Plasma	[50]
Narrow-bore and RP	Gadolinium chelates	human serum and urine	[51]
RP	Nb(V), V(V), Co(II), Fe(III), Ni(II), Ru(III) and Pd(II) chelates of 4-(5-nitro-2-pyridylazo) resorcinol	Rain and liquor	[52]
Sephadex G-50	Cu-binding peptides	Non-inoculated and inoculated roots of Cu-treated plants	[53]

Table 1 (continued)

HPLC mode or column	Metal complexes	Remarks	Ref.
RP	Platinum metal and co-existing metal complexes with 2-(6-methyl-2-benzothiazolylazo)-5-diethylaminophenol (MBTAE)		[54]
RP	V(V), Nb(V) and Ta(V) with 2-(5-nitro-2-pyridylazo)-5-diethylaminophenol	Mineral	[55]
RP	Co(II), Co(III) and Fe(II) complexes with bis(salicylaldehyde)tetramethylethylene	Pharmaceutical preparations	[56]
	Metal complexes		[57]
	Platinum complex (cisplatin)	Rat kidney and liver	[58]
Size-exclusion	Organic low-molecular-mass aluminum complexes	Soil solution	[59]
RP	Co(II), Ni(II), Cu(II) and Pd(II) with ammonium pyrrolidine dithiocarbamate (PDC)	Waste-, well- and river-water samples	[60]
RP	Bi, Cd, Cu, In, Ni and Pb with hexamethylenedithiocarbamate (HMDC)	High-purity aluminum	[61]
RP	Cu, Ni and V with 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino)phenol (5-Br-PAPS)	Sea water	[62]
IP-RP	Metal–EDTA species	Many kinds of water samples, suspended particles and sediment cores	[63]
	Gadolinium(III) sodium calcium, Zn and Cu complexes with diethylenetriaminepentaacetic acid bis-methylamide (DTPA-BMA)		[64]
	Cobalt(III) complexes containing a sulfinate-S ligand		[65]
	2,2'-Bipyridyl-6-carbothioamide copper(II) complex [BPYTA Cu(II)]		[66]
RP	Hg(II) binding with phytochelatin		[67]
	Diethyldithiocarbamate (DDTC)–Cu ²⁺		[68]
	[Bis(acetato)ammine-dichloro (cyclohexylamine)platinum(IV)]	Human plasma	[69]
RP	Cobalt(II), copper(II), iron(II) and vanadium(IV) complexes of bis(acetyl-pivalylmethane)ethylenediamine	Crude petroleum oils	[70]
IP-RP	Cu(II), Fe(II) and U(VI) complexes of [M(H ₂ PO ₄) ₃] [−] and their neutral complexes	Synthetic mixtures and Standard Reference Materials	[71]
	Chromium(III)–diphenylcarbazone	Geological samples	[72]
	Al ³⁺ (III) complex of siderophore desferriferrithiocin (DFFTH ₂) and Cr(III) complex of nordesferriferrithiocin (NDFFFTH ₂)		[73]
	Rhenium(V) complex with 3-diphenylphosphinopropionylglycyl-L-(S-benzyl) cysteinyl methyl-ester-ligand		[74]
RP	Mo(VI) and Mn(II) with 8-hydroxyquinoline	Sea water	[75]
	Cobalt(III)–polyamine complexes of aminopolyphosphonates		[76]
NP	Zinc dialkyldithiophosphates	Lubricating oil additives	[77]

(Continued on p. 442)

Table 1 (continued)

HPLC mode or column	Metal complexes	Remarks	Ref.
NP	Triphenylphosphine(pph(3))-substituted homo- and hetero-dinuclear metal carbonyl complexes		[78]
RP	Uranium, iron, nickel and copper complexes with N,N'-ethylenebis(salicylalimine)	Mineral ore samples and phosphate rock residues	[79]
IP-RP	Cu(II) complexes of oxidized chlorophylls		[80]
RP	Amino acid-copper complexes	Valine fermentation samples	[81]
RP	Iron(III) chlorophyllin		[82]
RP	Pptide oxorhenium complexes and Tc-99m complexes		[83]
RP	Platinum metals complexes with 2-(6-methyl-2-benzothiazolylazo)-5-diethylaminophenol		[84]
IP	Iron complexes of mugineic acid, 2'-deoxymugineic acid and 3-hydroxymugineic acid		[85]
RP	Dioxouranium(VI), oxavanadium(IV), iron(III), copper(II), cobalt(II), nickel(II) and palladium(II) complexes with bis(salicylaldehyde)-tetramethylethylenediamine	Mineral ore samples	[86]
RP	Rh-nucleotide bound peptides		[87]
RP	Fe(III) complexes	Pooled serum	[88]

applied to detect platinum complexes in a grass extract and iron(II)-lactate in fruit juice. Optimised pulse parameters enable accurate and selective detection of some metal complexes even in the presence of electroactive compounds such as phenols or sulfur-containing peptides [95]. A sensitive RP-HPLC method with electrochemical detection has been developed for the determination of vanadium(V) by complexation with N-phenylbenzohydroxamic acid. The method has been applied to the determination of vanadium(V) in two river water samples and one mussel homogenate [96]. Yamamoto et al. [97] described a split-type flow cell for polarized spectrophotometric detection (PPD) and discussed its utility as a universal polarimetric detector for HPLC for the detection of coloured amino acid-copper(II) complexes.

Of the more novel detection techniques, HPLC coupled with inductively-coupled plasma-atomic

emission spectrometry (ICP-AES), inductively coupled plasma isotope-dilution mass spectrometry (ICP-IDMS) and particle beam mass spectrometry (PB-MS) are of increasing interest to analytical researchers. RP-HPLC coupled with PB-MS detection was used to separate and characterise some dinuclear iron derivatives of general formula $[\text{Fe}_2(\text{CO})_5(\text{Ph}_2\text{PXEPPh}_2\text{-p})(\text{Et}_2\text{C}_2(\text{CO})\text{C}_2\text{Et}_2)]$ ($\text{X} = \text{CH}_2$ or CH_2CH_2 , $\text{E} = \text{P}$ or As) [98]. The NP-HPLC-PB-MS technique was used in the elucidation of the structure of polar organometallic compounds, such as the chromium-carbene complexes [99]. A HPLC system with a size-exclusion column was coupled with ICP-MS to get specific distribution patterns of the heavy metal complexes in natural aquatic systems. Accurate results were obtained by the application of isotope dilution mass spectrometry (IDMS) [100,101]. Ion-pair and ion-exchange HPLC coupled with ICP-MS and ICP-OES (optical emission spec-

trometry) were applied for the separation of metal–EDTA and metal–peptide complexes [102]. HPLC–ICP–AES (atomic emission spectrometry) for the determination of trace amounts of metallorganic compounds in marine ecosystem has been reported by Mazzucotelli and Rivaro [103]. Cairns et al. [104] used the RP–HPLC–ICP–MS system to determine organometallic species in tea. Suzuki et al. [105] applied HPLC with ICP–MS to determine the binding of Cu–thiomolybdate complex to albumin. HPLC–ICP–MS was also used in the separation of *cis*-dichlorodiammineplatinum(II) (cisplatin or CDDP) in aqueous and biological media. The HPLC conditions in which mobile phases of formic or phosphoric acids interact with CDDP were investigated [106]. Another application of HPLC–ICP–MS was demonstrated by Suzuki et al. [107] when they investigated the distribution profile of externally provided Se among biological constituents and its effect on endogenous Se in rats. Se, monomethylselenol and trimethylselenonium ion were separated and detected. Ebdon et al. [108] have compared HPLC–ICP–MS and HPLC with UV detection in the analysis of nickel geoporphyris from Julia Creek and Serpiano oil shales. Good agreement between these two techniques was obtained.

As a survey of the analytical literature of the past three years, we found that much work has been done in the separation of technetium complexes. Most of the technetium complexes were prepared for radiopharmaceuticals as brain imaging agents. HPLC has demonstrated its applicability in such applications, as shown in Table 2.

2.2. Separation of isomers

Recent papers focusing on the analysis of the isomers of the metal complexes include that by Akama and Kajitani [131]. They have confirmed by HPLC that the Fe(III) complex of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone is a mixture of two isomers. Papadopoulos et al. [132] separated syn- and anti-oxorhenium complexes, $\text{ReO}–[(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{S}_2)_2][\text{SC}_6\text{H}_4\text{OCH}_3]$, by HPLC. Westmeyer et al. [133] analyzed the isomers of iron sulfide derivatives of the fullerenes C_{60} and C_{70} by using HPLC. *Cis*- and *trans*-

$\text{Cr}(\text{NH}_3)_4(\text{pyridine})(\text{H}_2\text{O})^{3+}$ were separated by HPLC by Riccieri and Zinato [134]. Rotational isomers of the group-6 metal tetracarbonyl complexes of 3,4-diphosphinidenecyclobutenes protected with the 2,4-di-*tert*-butyl-6-methylphenyl group were analyzed by a chiral column by Yoshifuji et al. [135]. Nowotnik et al. [120] have compared three columns (the Resolvosil BSA-7, Chiracel OD and Chiralpak AD) for their suitability in the separation of technetium-99m complex of hexamethyl-propyleneamine oxime (HM-PAO). They pointed out that the OD column could be used for HPLC analysis of Tc-99m complexes of HM-PAO stereoisomers.

In the past three years, the importance of the role played by optically active metal complexes for the elucidation of reaction mechanisms and the dynamic behaviour of chiral metal complexes has been demonstrated to be significant. Separation of enantiomers by HPLC needs specific conditions that differ from separations of any other compounds. Recent advances in HPLC have made available several classes of columns in which the active solid-phase is chiral. Following on from their previous work, Plesek et al. [136] achieved the separation of enantiomers of cobaltacarborane complexes $[4,8'\text{-Mu-R}_2\text{N-commo}(1,2\text{-C}_2\text{B}_9\text{H}_{10})_2\text{-3-Co}]$ ($\text{R}=\text{H}$ and Me) on the β -cyclodextrin HPLC column. Cole et al. [137] shown that chiral gallium(III) complex may be resolved by preparative HPLC. Diastereomers of $[\text{RuCl}_2(\text{eta}(6)\text{-C}_6\text{H}_5\text{CHMeET})]$ (NMDPP) and $[\text{RuCl}_2(\text{eta}(6)\text{-C}_6\text{H}_5\text{CHMe}(\text{tert.})\text{Bu})]$ (NMDPP) (NMDPP = neomenthyl-diphenylphosphine) can be separated by HPLC as investigated by Pertici et al. [138]. Linder et al. [118] resolved a technetium(V)oxo nitroimidazole complex into its two enantiomers by chiral HPLC (using Chiracel OD). RP–HPLC chromatographic data for five dihydropyridine calcium antagonists (Cas) were obtained on a β -cyclodextrin column by Tesarova et al. [139]. It was shown that several types of inclusion complexes were energetically possible and contributed to the retention simultaneously. Molecular modelling studies were shown to be a useful tool for explaining the enantioselectivity and predicting the elution order of enantiomers. On a recently developed chiral stationary phase which contains “active sites” comprising of clefts formed by the perpendicular disposition of π -acidic 3,5-dinitrobenzamide groups relative to π -

Table 2

Recent applications of HPLC to Tc complexes (RP=reversed-phase, IP=ion-pair, radio=radioactivity detection)

HPLC mode or column	Complexes	Remarks	Ref.
RP	Bis(1-ethoxy N-ethyl)dithiocarbamato nitrido technetium(V)	Heart tissue of rat	[109]
	N-Acetyl anthranilic acid (NAA)-Tc(V)		[110]
	Bis(amine-phenol)nitroimidazole-Tc-99m		[111]
	Tc-99m-labeled amine phenols		[112]
Cation exchange	Tc-99m complexes	Radiopharmaceuticals	[113]
	Tc-99m complexes		[114]
	Tc-99m-MAG3		[115]
	Tc-99m complexes		[116]
RP	Tc-99(V)-2-thiohydantoin		[117]
Chiracel OD	Technetium(V) oxo nitroimidazole		[118]
	Technetium(V)-oxo complexes with mercaptoacetylglycylglycylglycine		[119]
Resolvosil BSA-7, Chiralpak OD and Chiralpak AD	Tc-99m complexes of hexamethyl-propyleneamine oxime (HM-PAO)	Separation of stereoisomers	[120]
RP	Tc-99m chelate with (MeO) ₂ P(S)N MeNHCH ₂ C ₆ H ₄ SH and (MeO) ₂ P(S)N MeNHC(O)C ₆ H ₄ SH	Radiopharmaceuticals	[121]
RP	Tc-99m complexes with bisaminoethanethiol (Bat)	Radiopharmaceuticals	[122]
RP	Tc-99m complexes with <i>cis</i> -4,5-dimethoxycyclohexane-1,2-dionedioxiime (DMCDO)	Liver, renal clearance, heart and brain of rats	[123]
Radio-HPLC	[Tc-99m]chelator complexes		[124]
Radio-HPLC	Tc-99m complexes		[125]
	Tc(III) complexes	Heart, liver of rats	[126]
IP-RP	Tc-99m(V)-oxo and Tc-99m(V)-nitrido complexes of L,L-enthylene dicycstene (L,L-EC) and its di-ester derivative L,L-ethylcysteinate dimer (L,L-ECD)		[127]
	Tc-99m complex with tris (hydroxymethyl)phosphine (THMP)	Radiopharmaceuticals	[128]
	Tc-99m and Tc-99g complexes	Radiopharmaceuticals	[129]
Size-exclusion	Tc complexes		[130]

basic naphthyl groups, Villani and Pirkle [140] studied the enantiodiscrimination of thirty-four disubstituted tricarbonyl (eta(6)-arene)-chromium complexes having planar chirality. Thirty of these compounds showed different retention factors for their enantiomers. Using Bakerbond Chiralcel OD columns, most of the chiral arenechromium tricarbonyl complexes could be successfully resolved with good

to excellent results [141]. Aldrichwright et al. [142] developed two DNA-immobilized chromatographic stationary phases and optically resolved [Ru(dipyrido[6,7-d:2',3'-f]-quinoxaline)₃]²⁺ and [Ru(1,10-phenanthroline)₃]²⁺ complex ions. Racemic planar tricarbonyl(eta(4)-diene)iron complexes were separated into their enantiomers by chiral HPLC on β-cyclodextrin columns by Knolker et al.

[143]. A new type of optically active organic–inorganic composite was prepared by a sol–gel method by Mizukami et al. [144] and compared in the optical resolution of tris(2,4-pentanedionato)metal complexes with conventional silica composites.

2.3. Studies on retention behaviour

Solutes retention and selectivity are the basic controlling factors for their separation in HPLC. Parameters such as stationary phase and solvent composition can affect solutes retention, and consequently their separation. There have been several recent papers that discussed the retention behaviour of metal complexes and the factors affecting their separations. In their paper, Tan et al. [145] reported and discussed NP-HPLC of a series of group-6 dimetal decacarbonyl complexes, of the form $(OC)_5M(PCH_2)_nP(CO)_5$, where $M=Cr, Mo$ and W , and $P(CH_2)_n$, P =diphenylphosphinyl bridge with $n=2-6$, and the retention behaviour of these homometallic complexes. Kumar et al. [146] used a C_{18} RP (Nucleosil) column to determine the HPLC capacity factors (k') and the partition coefficients ($\log P$) of some Gd(III) complexes of linear and macrocyclic polyamino carboxylates. The partition coefficients ($\log P$) were measured in *n*-butanol–water and *n*-octanol–water and the capacity factors in 28 and 4% acetonitrile and aqueous buffered mobile phase [146]. Careri et al. [98] studied the behaviour of binuclear flyover-bridged iron compounds by HPLC–MS. It was found that the chromatographic behaviour of these compounds depended strongly on the substituents in the ligands. In a recent study, the IP-RP-HPLC behaviour of several metal complexes with 5-sulphoquinidine-8-ol (HQS) was investigated. The effects of the eluent pH, HQS concentration, the nature of anions in the eluent and the column temperature on the retention behaviour of the aluminum complex were discussed [147]. In their work, Tesarova et al. [139] studied the correlation between the structure of dihydropyridine calcium-antagonists and their retention behaviour and enantioseparation on the β -cyclodextrin stationary phase under RP conditions. The retention behaviour of platinum metal-complexes on RP-HPLC was studied recently [148]. The effects of methanol concentration in the mobile phase, column tempera-

ture, total flow-rate and foreign ions on the separation have been investigated. It was found that $\ln k'$ was linearly related to the methanol concentration and the reciprocal of the column temperature. Nesterenko et al. [149] studied the RP-HPLC chromatographic behaviour of a series of acid-sensitive cationic alkylcobalt(III) chelates with both $[N_2O]$ Schiff base and ethylenediamine and developed optimal conditions for RP-HPLC quantitative analysis of these labile organocobalt complexes. In another paper, the HPLC retention behaviour on an ODS column of rhenium complexes with phosphorus and 2,2'-bipyridine-derivative ligands was examined. Linear correlations were observed between the capacity factors of the mono-phosphorus complexes and Fujita's organicity–inorganicity ratios for the phosphorus ligands, showing that Fujita's organicity–inorganicity parameters are useful for evaluating the retention of these metal complexes [150]. In their work, Zheng et al. [151] studied the HPLC separation of gallium and indium complexes of bis(amino thiol) ligands. It was shown that the lipophilicity of the ligand determined the retention time of the complexes. The HPLC behaviour of six complexes of Ph_3P -substituted selenido carbonyl iron were investigated by Baistrocchi et al. [152]. The elution order was depended on the degree of phosphine substitution and the kind of cluster framework.

3. Applications to synthesis, reaction, characterization and complexation

The applications of HPLC in the synthesis and reaction of metal complexes and then the characterization of the products have been reported by many research workers. HPLC has become a powerful tool in monitoring the increase of the peak areas or heights of the products and the decrease of those of the reactants. Liao et al. [153] applied RP-HPLC in the synthesis, characterization of the rhenium(V) complexes of N,N' -ethylenebis(2-mercaptopropanamide). Toma and Bergstrom [154] employed HPLC in the synthesis and characterization of (penta-carbonyl)tungsten(0) nucleoside phosphites. Grummon et al. [119] have demonstrated the application of HPLC to the synthesis, characterization of tech-

netium(V)-oxo complexes in nuclear-medicine. Zheng et al. [155] used HPLC in the syntheses and characterization of the chloride and iodide ion complexes of a set of isomeric hydrophobic tetraphenyl mercuracarborand-4 hosts having sterically encumbered cavities. Anderson et al. [156] employed HPLC in the study of the synthesis, antitumor activity and chemical properties of silaplatin and related platinum(II) and platinum(IV) complexes derived from β -silylamines. Marmion et al. [129] synthesised and characterized sixteen novel $N_3O_3^-$ Schiff base complexes of Tc-99g and studied the in vivo imaging with analogous Tc-99m complexes. They showed the equivalence of the Tc-99m and Tc-99g complexes by HPLC techniques. The synthesis of the complex $[(bpy)_2Ru(Im)_2]^{2+}$ (bpy=2,2'-bipyridine; Im=imidazole) as a reaction intermediate has been monitored by RP-HPLC by Moreira and Santiago [157]. The authors have shown that the use of HPLC has enabled complete analytical control of the synthesis of the $[(bpy)_2RuL_2]^{2+}$ class of compounds, enabling the identification and isolation of reaction intermediates. Pirmettis et al. [158] used HPLC in the synthesis and characterization of oxotechnetium(V) mixed-ligand complexes containing a tridentate N-substituted bis(2-mercaptoethyl)amine and a monodentate thiol. Ricciari and Zinato [134] applied HPLC in the synthesis and characterization of (pyridine)pentaamminechromium(III). Sen et al. [159] synthesised platinum(II) complexes with *trans*-3,4-diamino-2,2,6,6-tetramethylpiperidine-1-oxyl and characterized the complexes by means of HPLC. Gaucheron et al. [160] used HPLC when they studied the preparation, physicochemical characterization and stability of iron-supplemented caseins.

The efficacy of preparative HPLC has been reported, in the synthesis and purification of Pt-95m-radiolabeled *cis*-diammine(glycolato)platinum(II) [161]. Kerr et al. [162] prepared the alkynepenta-carbonyldicobalt complexes containing the chiral (*R*)-(+)-glyphos ligand and obtained these complexes by preparative HPLC. Altmann et al. [163] have employed preparative HPLC in the synthesis of linear oligomers of [1,3-diethynyl-2,4-bis(trimethylsilyl)cyclobutadiene]cyclopentadienylcobalt dimer to nonamer.

The reaction between the cation (1,4,7-triazacyclononane)(3-thiapentane-1,5-diamine)cobalt(III),

Co(tacn)(daes)³⁺, and hydroxide at 59°C has been studied with HPIEC by Larsen et al. [164]. By using HPIEC as one of the analytical tools, the equilibration reaction between the mononuclear species *cis*-[Ir(NH₃)₄-(H₂O)₂]³⁺ (and its deprotonated forms) and the dinuclear species *cis,cis*-[(H₂O(NH₃)₄Ir(OH)Ir(NH₃)₄(OH₂)]⁵⁺ (and deprotonated forms) and [(NH₃)₄Ir(OH)₂Ir(NH₃)₄]⁴⁺ has been studied at 60–100°C in 1 M (Na,H)ClO₄ at pH=7, by Galsbol et al. [165]. Springborg et al. [166] studied the thermodynamic and kinetics of the equilibration between the sulfur-bonded and carbon-bonded forms of a cobalt(III) complex with the ligands 2-aminoethyl-3-aminopropyl-sulfide and 1,1,1-tris(aminomethyl)ethane. In a later paper, Song et al. [167] carried out a similar study on the thermodynamic and kinetics of the equilibration between the sulfur-bonded and carbon-bonded forms of the cobalt(III) complex with the ligands 1,4,7-triazacyclononane and 1,4-diaza-7-thiacyclodecane by using HPLC as one of the analytical tools. Wu et al. [168] investigated the transformation of the low-molecular-mass cadmium-binding complexes to the higher-molecular-mass complexes.

The use of HPLC in bioinorganic chemistry has been especially significant in recent years. The following summarizes the most recent studies. Using concentration measurements based on HPLC, Gonnet et al. [169] have investigated the kinetics of the reaction between single-stranded oligonucleotides containing a d(GpG) sequence d(TGG), d(TGG), d(TTGG) and d(CTGGCTCA) and the platinum complexes *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ and [Pt(NH₃)₃(H₂O)]²⁺. Bednarski [170] investigated the kinetics and the products of the reactions of the cisplatin analogue [*meso*-1,2-bis(2,6-dichloro-4-hydroxyphenyl)-ethylenediamine]-dichloroplatinum(II){PtCl₂(LL)} with L-cysteine, D,L-homocysteine, L-methionine and glutathione (GSH) by means of RP-HPLC. Billadeau and Morrison [171] studied the photoaquation of *cis*-dichlorobis(1,10-phenanthroline)chromium(III) and the photochemical and thermal-reactions of this complex with native calf-thymus DNA. Hambley et al. [172] have shown that the reaction of [Pt(hpip)Cl₂] (hpip=homopiperazine, 1,4-diazacycloheptane) with d(GpG) yields two isomers which were separable by HPLC. Sugden and Wetterhahn [173] employed HPLC as an analytical

tool to investigate the potential biologically relevant oxidation reaction of chromium(V) complex, sodium bis(2-ethyl-2-hydroxybutyrate)oxochromate(V) ($\text{Na}[\text{Cr}(\text{ehba})_2\text{O}]$), with the spin traps 5,5-dimethylpyrroline N-oxide (DMPO) and phenyl-N-tert.-butylnitron (PEN). Mailhot et al. [174] studied the photodegradation of copper(II) iminodiacetate (CuIDA) at 20°C onochromatic excitation at various pH. HPLC characterization of the reaction between antitumor platinum agents and the phosphorothioate chemoprotective agent S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR-2721) was performed by Thompson et al. [175]. Novakova et al. [176] studied the DNA interactions of antitumor platinum(IV) (oxoplatin) complexes by means of HPLC, amongst other techniques. Adams et al. [177] reported the use of ozone, hydrogen-peroxide ozone and UV ozone oxidant systems for the treatment (decolorization and metal release) of chromium-complex and copper-complex dyes. By using HPLC as one of the experimental approaches, Brabec et al. [178] studied the interaction of *trans*- $[\text{PtCl}_2(\text{E-imino ether})_2]$ complex with DNA. Navia et al. [179] studied the selectivity of benzylation of metal-chelates of sucrose by HPLC. Normann and Hals [180] investigated the biotransformation of Gd–diethylenetriaminepentaacetic-acid-bis-methylamide in rats. Solinas et al. [181] used HPLC as one of the analytical tools to study the reduction of the Fe(III)–desferrioxamine-B complexes by caffeic acid. Inagaki and Sawaki [182] investigated the reaction of (1*R*,2*S*,3*S*)-3-methylcyclohexanediamineplatinum(II) with DNA by means of HPLC and NMR.

During the period of review, there were several HPLC studies of the kinetics and mechanism of the complexation of the metal complexes. Mikola and Arpalahti [183] studied the kinetics of the complexation of *trans*- $[\text{PtCl}_2(\text{NH}_3)_2]$ and its hydrolysis products *trans*- $[\text{PtCl}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$ and *trans*- $[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$ in aqueous solution at 318.2 K (pH=2.8–3.4, $I=0.1\text{ M}$) by HPLC. Later, they investigated the kinetics of complexation of *trans*- $[\text{PtCl}(\text{NH}_3)_2(\text{H}_2\text{O})]^+$ with inosine and its 1-methyl derivative at 298.2 K in aqueous solution at different pH values [184,185]. Chellquist et al. [186] determined the binding constant of Win-22169 (a novel polymeric ligand) with Gd^{3+} , Ca^{2+} , Zn^{2+} and Cu^{2+} , and Dallavalle et al. [187] determined the formation

constants of ternary copper(II) complexes with (*S*)-amino acid amides and (*R*)-histidine or (*S*)-histidine and (*R*)-tyrosine or (*S*)-tyrosine in aqueous solution. Finally, Zhang and Bruice [188] used HPLC in the study of the kinetics of the stepwise Zn^{2+} incorporation into cofacial bis-porphyrin (IIIH_4) leading to III Zn_2 .

4. Conclusions

A review of the recent applications of HPLC to the metal complexes, including organometallic compounds and metal coordination complexes, from 1994 is presented. The review covers the retention, separation, determination, reaction, synthesis and complexation studies of the metal complexes by HPLC. About 190 papers on this subject are included in the review, in which the applicability of HPLC to inorganic and bioinorganic problems is clearly evident. The technique has been shown to be an effective tool in many such applications and is expected to play an even greater role in the future. More novel approaches are likely to be developed; for instance, a recent paper reported the use of a column packed with porous graphitic carbon particles to separate several diphosphine-bridged Au–Mn and Au–Re complexes, after conventional packings were found to lack the selectivity to do so [189].

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