ELSEVIER

Progress in Nuclear Magnetic Resonance Spectroscopy 49 (2006) 65–98

PROGRESS IN NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

www.elsevier.com/locate/pnmrs

Insights into the mechanism of action of platinum anticancer drugs from multinuclear NMR spectroscopy

Susan J. Berners-Price [a,*], Luca Ronconi [b], Peter J. Sadler [b,*]

[a] *School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Crawley, Perth, WA 6009, Australia*
[b] *School of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK*

Received 28 March 2006
Available online 28 July 2006

Keywords: NMR; Platinum drugs; ^{195}Pt NMR; ^{15}N NMR; [^{1}H,^{15}N] NMR; Proteins; Glutathione; DNA; Aquation; Kinetics

Contents

* Corresponding authors. Tel.: +61864883258; fax: +61864881005 (S.J. Berners-Price).
E-mail addresses: sbp@chem.uwa.edu.au (S.J. Berners-Price), pjs01@staffmail.ed.ac.uk (P.J. Sadler).

0079-6565/$ - see front matter
doi:10.1016/j.pnmrs.2006.05.002

Abbreviations: AMP, adenosine monophosphate; CBCDA, cyclobutane-1,1-dicarboxylato; CMP, cytidine monophosphate; CSA, chemical shift anisotropy; CysH, cysteine; DACH, 1*R*,2*R*-diaminocyclohexane; DEPT, distortionless enhancement by polarization transfer; dGMP, deoxyguanosine monophosphate; dien, diethylenetriamine; en, ethylenediamine; DQFCOSY, double quantum filtered correlation spectroscopy; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; ESI-MS, electrospray ionization-mass spectrometry; GARP, globally optimized alternating phase rectangular pulse; GMP, guanosine monophosphate; GSH, glutathione; GSSG, glutathione disulfide; GTP, guanosine triphosphate; His-MetH, histidylmethionine; HMBC, heteronuclear multiple bond coherence; HMG proteins, high-mobility-group proteins; HMQC, heteronuclear multiple quantum coherence; HPLC, high performance liquid chromatography; HSQC, heteronuclear single quantum coherence; HSA, human serum albumin; HEPES (buffer), *N*-(2-hydroxyethyl)-piperazine-*N*′-2-ethanesulfonic acid; ICP-MS, inductively-coupled plasma-mass spectrometry; INEPT, insensitive nuclei enhancement by polarization transfer; IXL, interstrand cross-link; L-MetH, L-methionine; L-MeCysH, *S*-methyl-L-cysteine; NOE, nuclear Overhauser effect; NOESY, nuclear Overhauser effect spectroscopy; ox, oxalate; 2-pic, 2-picoline (2-methylpyridine); 3-pic, 3-picoline (3-methylpyridine); rHA, recombinant human albumin; ROESY, rotating frame nuclear Overhauser effect spectroscopy; RPMI, culture media developed at Roswell Park Memorial Institute; L-Se-MetH, L-selenomethionine; TMP, thymidine monophosphate; TOCSY, total correlated spectroscopy; Tris (buffer), tris-hydroxymethylaminoethane; Ub, ubiquitin.

1. Introduction

Platinum complexes are now amongst the most widely used drugs for the treatment of cancer. The three platinum anticancer drugs in current worldwide clinical use are shown in Chart 1. The first and second generation compounds cisplatin (*cis*-[$PtCl_2(NH_3)_2$]) and carboplatin (*cis*-[Pt(CBDCA-*O*,*O*′)$(NH_3)_2$]) are in widespread use to treat a variety of cancers, either as single agents or in combination with other drugs [1–3]. Oxaliplatin, ([Pt(ox)(-DACH-*N*,*N*′)]), introduced into the clinic in 2002 has become an important option for the treatment of colorectal cancer and its possible use in the treatment of other cancers is a focus of intense investigation [1–3].

The search for improved platinum drugs continues with the goals of reducing the toxic side effects and broadening the spectrum of activity to tumours resistant to cisplatin. A major focus of current research is in the investigation of ''non-classical'' platinum antitumour compounds that act by a different mechanism to that of cisplatin to achieve a different profile of activity. Current knowledge of the mechanism of action of platinum drugs has been summarised in several recent books and review articles [4–10].

NMR methods have proved useful in the investigation of platinum drugs from the time that cisplatin was first introduced into the clinic more than 30 years ago. Both ^{195}Pt [11,12] and ^{15}N NMR [12] were used in early studies and made a major contribution in the understanding of the molecular mechanism of action from model studies involving reactions with amino acids (proteins) and nucleotides (DNA). However, these NMR studies were limited by the inherent insensitivity of these nuclei until the introduction of 2D [^1H,^{15}N] NMR techniques in the early 1990s [13] made it possible to follow the reactions of cisplatin and related platinum anticancer complexes under physiologically relevant conditions.

Over the past decade [^1H,^{15}N] NMR studies have provided unique insight into the molecular mechanism of action of platinum drugs including investigations of simple aquation reactions, protein binding and the kinetics and sequence selectivity of DNA binding interactions. The early applications of the [^1H,^{15}N] NMR method have been the subject of several review articles [14–17]. In this article, emphasis is given to more recent [^1H,^{15}N] NMR studies, in particular the kinetics and mechanism of DNA platination reactions, the detection of platination sites on proteins and studies of new platinum drugs under investigation including the trinuclear platinum complex [{*trans*-$PtCl(NH_3)_2$}$_2$-{μ-*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$ (BBR3464), *cis*-[$PtCl_2(NH_3)$ (2-pic)] (AMD473/ZD0473), *trans*-Pt(II) complexes and photoactivatable Pt(IV) diazido complexes. We have not included here NMR structural studies of platinated DNA adducts, which have been reviewed recently elsewhere [18,19] or related NMR studies of retro models of the cisplatin–DNA cross-link (see for example Refs. [20–22]).

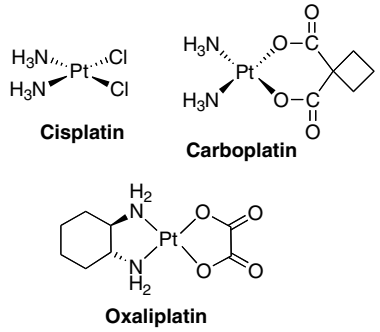

Chart 1. Platinum anticancer drugs in worldwide clinical use.

2. ^{195}Pt NMR spectroscopy

^{195}Pt NMR is a reasonably sensitive nucleus for NMR detection having a natural abundance of 33.8% and receptivity relative to ^1H of 3.4×10^{-3}. However, the limit of detection (5–10 mM) precludes observation of natural