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Review

Platinum complexes containing adenine-based ligands: An overview of selected structural features

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ABSTRACT

This work offers an overview of the platinum(II,IV) complexes involving adenine or its derivatives coordinated to platinum through *N*- or *C*-donor atom(s) of the adenine moiety. This large group of coordination compounds is reviewed with respect to the oxidation state of the platinum central atom(s), the nuclearity of the complexes and the coordination mode(s) of the adenine-based ligands. The important structural features, such as selected bond lengths and angles in the vicinity of the platinum atom as well as those around the adenine coordination sites, are summarized for a total of 122 crystallographically characterized complexes. Among them, complexes containing monodentate *N7*-coordinating adenine-based ligand(s) are the most numerous, while the monodentate *N6*-, *N9*- or *C8*- and bidentate *N1,N6*-coordination modes are rare. Numerous adducts of the platinum complexes with nucleotides, nucleosides and nucleic acids coordinated to the metal center through the adenine moiety are also discussed. The review of the structural features of platinum complexes with adenine-based ligands is completed with a brief summary of the biological activities of the complexes known to date.

Contents

Abbreviations: 1,9dimeade, 1,9-dimethyladenine; 1mecyt, 1-methylcytosine; 1methy, 1-methylthymine; 1meura, 1-methyluracil; 2,4diOMecba, 2-chloro-*N6*-(2,4-dimethoxybenzyl)-9-isopropyladenine; 2aade, 2-aminoadenine; 2OMecba, 2-chloro-*N6*-(2-methoxybenzyl)-9-isopropyladenine; 3meade, 3-methyladenine; 6,9dimeade, 6,9-dimethyladenine; 6aeade, *N6*-aminoethyladenine; 6etade, *N6*-ethyladenine; 6et-6,9dimeade, *N6*-ethyl-methyl-9-methyladenine; 6heade, *N6*-hydroxyethyladenine; 6meheade, *N6*-methyl-hydroxyethyladenine; 9etade, 9-ethyladenine; 9etgua, 9-ethylguanine; 9meade, 9-methyladenine; 9megua, 9-methylguanine; 9mehx, 9-methylhypoxanthine; acet-9meade, *N*-(9-methyl-1,9-dihydro-purin-6-ylidene)-acetamidine; acramtu, 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea; ade, adenine; ado, adenosine; adp, adenosinediphosphate; ala, alanine; amp, adenosine 5′-monophosphate; atp, adenosinetriphosphate; benz-9meade, *N*-(9-methyl-1*H*-purin-6(9*H*)-ylidene)benzimidamide; boh, 2-(3-hydroxypropylamino)-N6-benzyl-9-isopropyladenine (bohemine); cba, 2-chloro-N6-benzyl-9-isopropyladenine; cbdc, cyclobutane-1,1-dicarboxylate dianion; dach, 1,2-diaminocyclohexane; dado, deoxyadenosine; damp, 2-deoxy-adenosine 5′-monophosphate; dguo, deoxyguanosine; dien, diethylenetriamine; dmso, coordinated dimethyl sulfoxide; en, ethylene-1,2-diamine; ESI, electrospray ionization; gly, glycine; guo, guanosine; his, histidine; *n*ade, adenine-based ligands in general; *n*am, amine in general; *n*pur, purine-based ligands in general; *n*pyr, pyrimidine-based ligands in general; ox, oxalate dianion; PBu_3, tri-*n*-butylphosphane; PEt_3, triethylphosphane; ph, phenanthridine; PMe_3, trimethylphosphane; PPh_2Me, diphenylmethylphosphine; pyz, pyrazine; ros, 2-(1-ethyl-2-hydroxyethylamino)-N6-benzyl-9-isopropyladenine (roscovitine); ssn_2, 1-(N9-adenine)-4,7-octane; taado, triacetyladenosine; tmeade, *N6,N6,N9*-trimethyladenine; tmen, tetramethylethylene-1,2-diamine.

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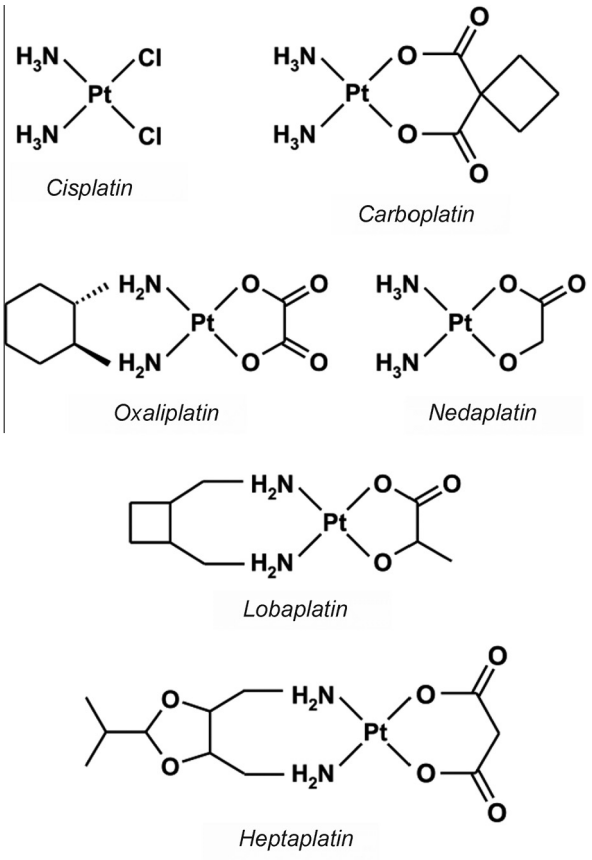
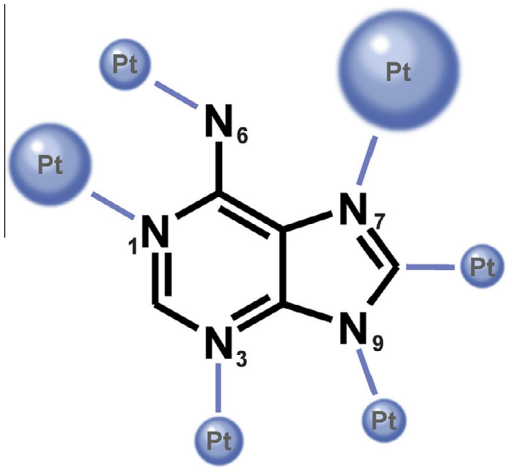
1. Introduction

Since the late 1970s, several platinum complexes have been marketed worldwide (*cisplatin*, *carboplatin*, *oxaliplatin*) or locally (*nedaplatin*, *lobaplatin*, *heptaplatin*) as chemotherapeutic agents for the treatment of various tumor diseases (Scheme 1) [1–3]. The mechanism of action of these complexes, also known as platinum-based drugs, is based on hydrolysis connected with the replacement of so-called "*leaving groups*" (*i.e.,* chlorido ligands of *cisplatin*) by water molecules under physiological conditions. Positively charged mono- or diaqua species can covalently bind to nuclear DNA leading to changes in its secondary structure, which subsequently result in the inhibition of both DNA and RNA synthesis [1,4,5]. Since adenine is one of the target nucleobases in DNA, the study of the interactions of various platinum complexes with adenine and its derivatives has been of great interest to many scientists.



Scheme 1. Structural formulas of the clinically used platinum-based anticancer drugs.

Adenine (ade; Scheme 2) is one of two purine nucleobases involved in nucleic acids (DNA and RNA) and other biomolecules, such as adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD). From the chemical point of view, the structure of ade involves four imino nitrogens within the purine ring and one exocyclic amino group [6], allowing versatile metal ion coordination [*e.g.,* [7,8]]. In 2000, Lippert [7] reviewed the binding modes of nucleobases (including adenine and its derivatives) to various transition metals. Two other reviews overviewed *a*) the binding modes of deaza- and aza-adenines (*e.g.,* 7-azaindole or 8-aza-adenine) and adenine isomers (*e.g.,* 2-aminopurine) in transition metal complexes [9], and *b*) the intramolecular interligand interactions within the transition metal complexes containing the purine nucleobases including the *N*9-derivatives of adenine [10].



Scheme 2. Structural formula of the adenine moiety as well as the nitrogen atom numbering. The sizes of the blue spheres correspond to the frequency of the platinum complexes containing the adenine moiety coordinated through the appropriate nitrogen atoms.