Inorganica Chimica Acta xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Research paper

Dual properties of water-soluble Ru-PTA complexes of dendrimers: Catalysis and interaction with DNA

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ARTICLE INFO

Article history:
Received 3 February 2017
Received in revised form 19 April 2017
Accepted 22 April 2017
Available online xxxx

Dedicated to Prof. Dr. Carlo Mealli, on the occasion of his 70th birthday.

Keywords:
Dendrimers
Complexes
PTA phosphine
Homogeneous catalysis
DNA interaction

ABSTRACT

Phosphorhydrazone dendrimers ended by PTA (1,3,5-triaza-7-phosphaadamantane) derivatives are used for the complexation of ruthenium. The corresponding complexes, either isolated (synthesized *ex situ*, i.e. preformed) or generated *in situ* are used as catalysts for the hydration of phenylacetylene in various conditions (*ex situ* or *in situ*, quantities, temperature, duration, co-catalyst or not, recycling). The same preformed complexes are tested for their interaction with supercoiled DNA, to afford relaxed DNA.

1. Introduction

Dendrimers are hyperbranched macromolecules synthesized from a central core, using repetitive branching elements. Thanks to their step-by-step synthesis, they have a perfectly defined multifunctionalized structure, contrarily to that of polymers. The presence of multiple terminal functions, easily accessible, is certainly the most important characteristic of dendrimers, which enables their use in many different fields [1]. Different types of dendrimers exist, depending on the nature of their internal structure, which can be purely organic as for instance for PAMAM [2] and PPI [3] dendrimers, but also partly inorganic [4], such as carbosilane [5] and phosphorhydrazone [6] dendrimers. Specific terminal functions of dendrimers have to be chosen to fulfill specific properties. For instance in the case of phosphorhydrazone dendrimers, organometallic complexes [7] for catalysis [8–11], or water-solubilizing functions for biology [12–15] have been synthesized. The use of the same dendrimers in radically different fields is an exception, but organometallic dendrimers ended by coordination complexes are interesting candidates in this topic [16]. Indeed, we have previously reported that poly(phosphorhydrazone) dendrimers ended by analogous (but not strictly identical) copper complexes of pyridineimine terminal ligands have catalytic properties [17], and are able to fight *in vitro* against various cancer cell lines [18,19].

An important question to observe dual properties with a same dendrimer is the solubility, in particular the solubility in aqueous media if one of the properties concerns biology. Water solubility is generally attained with most dendrimers when having charges (positive or negative) on the terminal functions [20,21]. We have previously reported the synthesis of phosphorhydrazone dendrimers functionalized by PTA (1,3,5-triaza-7-phosphaadamantane [22–26]), and preliminary catalysis experiments with the corresponding Ru complexes, synthesized *ex situ* (preformed) [27]. The structure of the free and complexed compounds previously synthesized is shown in Fig. 1, from generations 1 to 3 of the dendrimers

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http://dx.doi.org/10.1016/j.ica.2017.04.044
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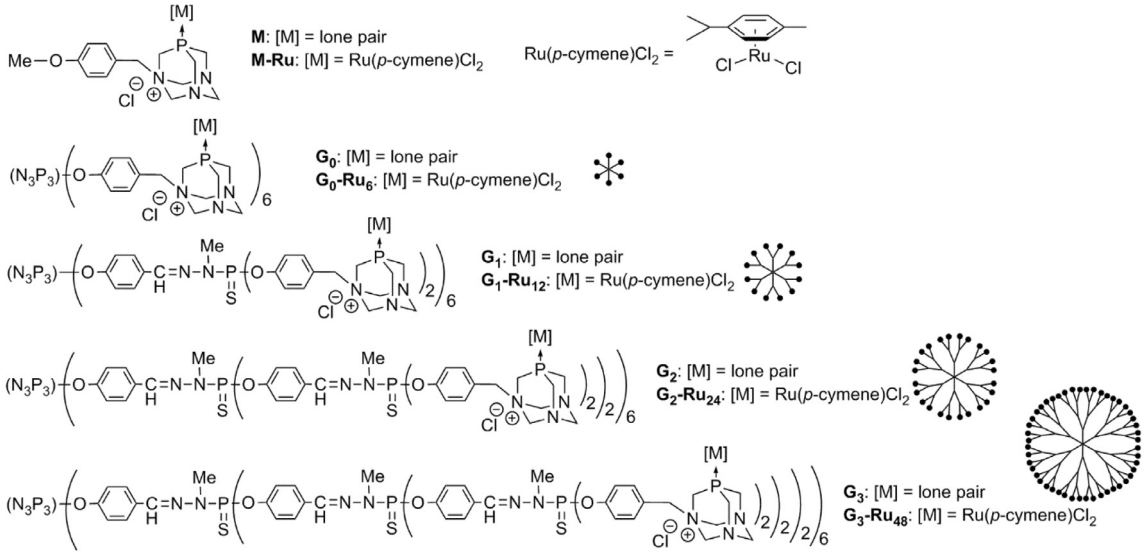

Fig. 1. Monomer and dendrimers functionalized by PTA (**M**, **G_0**, **G_1**, **G_2**, **G_3**), and the corresponding ruthenium complexes (**M-Ru**, **G_0-Ru_6**, **G_1-Ru_{12}**, **G_2-Ru_{24}**, **G_3-Ru_{48}**). The linear representation is used, but these compounds have a tridimensional branched structure, schematized on the right.

(**G_1**, **G_2**, **G_3**, and **G_1-Ru_{12}**, **G_2-Ru_{24}**, **G_3-Ru_{48}**) and the monomers (**M** and **M-Ru**), together with the newly synthesized **G_0** and **G_0-Ru_6**. The PTA is linked to the dendrimers through the alkylation of one nitrogen atom, thus affording dendrimers which, are soluble in water media, in particular in the water/isopropanol mixtures in which the catalytic experiments were carried out [27].

In this paper, we will report more insights in the catalytic properties of these dendrimers (the preformed complexes, or the free PTA-dendrimers to which the ruthenium is added *in situ*), and a preliminary biological experiment, concerning their interaction with supercoiled DNA, in comparison with cisplatin.

2. Experimental

2.1. General

All reactions were carried out under argon, using standard Schlenk techniques. All solvents were distilled (toluene over sodium, THF and ether over sodium/benzophenone, pentane over phosphorus pentoxide, and CH_2Cl_2 over CaH_2), and degassed when phosphines were used. ^1H, ^{13}C, ^{31}P NMR spectra were recorded with Bruker AC 200, AM 250, or DPX 300 spectrometers. References for NMR chemical shifts are 85% H_3PO_4 for ^{31}P NMR, $SiMe_4$ for ^1H and ^{13}C NMR. The numbering used for NMR assignments is depicted in Fig. 2. Monomers **M** and **M-Ru**, dendrimers **G_1**, **G_2**, **G_3**, **G_1-Ru_{12}**, **G_2-Ru_{24}**, and **G_3-Ru_{48}** were synthesized as published [27], as well as compound **1-G_0** [28].

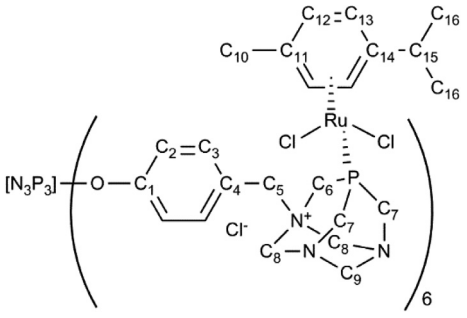

Fig. 2. Numbering used for NMR assignment.

2.2. Synthesis and characterization of *2-G_0*

A solution of borane dimethyl sulfide-complex 1.0 M in dichloromethane (7 mL, 7 mmol) was added to a solution of **1-G_0** (2 g, 2.32 mmol) in dichloromethane (80 mL) at 0 °C and the mixture was left stirring overnight. When there was no more aldehyde, solvent was removed in vacuum and methanol was added till all solid was solubilized, and then was again evaporated. This procedure was repeated two times more to afford **2-G_0** (2 g, 2.3 mmol, 99% yield) as a white powder. ^1H NMR (250 MHz, DMSO-d_6) δ (ppm): 4.47 (d, J_{HH} = 5.5 Hz, 12H, CH_2), 5.24 (t, J_{HH} = 5.5 Hz, 6H, OH), 6.8 (d, J_{HH} = 8.4 Hz, 12H, C_2H), 7.20 (d, J_{HH} = 8.4 Hz, 12H, C_3H). $^{31}P\{^1H\}$ NMR (81 MHz, DMSO-d_6) δ ppm: 12.3 (s). $^{13}C\{^1H\}$ NMR (62.9 MHz, DMSO-d_6) δ (ppm): 62.17 (s, CH_2OH), 120.01 (s, C_2H), 127.59 (s, C_3H), 139.36 (s, C_4), 148.53 (s, C_1). MS (DCI/NH_3, positive, MeOH) m/z for $C_{42}H_{42}N_3O_{12}P_3$: 874.3 [M+1].

2.3. Synthesis and characterization of *3-G_0*

Thionyl chloride (8 mL, 0.109 mol) was added dropwise to dendrimer **2-G_0** (1.058 g, 1.2 mmol) in solid state under stirring on an ice bath till dendrimer was dissolved and the mixture was left overnight. Toluene was added to the mixture and the excess of thionyl chloride was co-evaporated (3 times). The dendrimer was precipitated in THF:pentane (1:10) to afford **3-G_0** (1.09 g,1.1 mmol, 92% yield) as a white powder. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 4.59 (s, 12H, CH_2Cl), 6.94 (d, J_{HH} = 8.4 Hz, 12H, C_2H), 7.25 (d, J_{HH} = 8.4 Hz, 12H, C_3H). $^{31}P\{^1H\}$ NMR (81 MHz, $CDCl_3$) δ (ppm): 12.2 (s). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$) δ (ppm): 45.59 (s, CH_2Cl), 121.20 (s, C_2H), 129.92 (s, C_3H), 134.31 (s, C_4), 150.31 (s, C_1). MS (DCI/NH_3, positive, $CDCl_3$) m/z for $C_{42}H_{36}Cl_6N_3O_6P_3$: 984.2 $[M+1]^+$.

2.4. Synthesis and characterization of *G_0*

A solution of PTA (471 mg, 3 mmol) in MeOH (48 mL, degassed) was added to a solution of dendrimer **3-G_0** (420 mg, 0.427 mmol) in THF (15 mL, degassed) and the mixture was let stirring at room temperature (^{31}P-NMR monitoring, 1 day). Solvents were removed in vacuum and the residue was washed with degassed THF (3 times) to afford **G_0** (820 mg, 0.425 mmol, 99% yield) as a white powder. ^1H NMR (250 MHz, DMSO-d_6) δ (ppm): 3.72 (dd, J_{HH} = 14 Hz,