



The effect of chain size on the modeling of second sphere effects in biomimetic complexes



Bernardo de Souza, Renata Heying, Adailton J. Bortoluzzi, Josiel B. Domingos, Ademir Neves*

Departamento de Química, Laboratório de Bioinorgânica e Cristalografia (LABINC), Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina 88040-900, Brazil

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ABSTRACT

In this paper, we describe a new method for the systematic synthesis of catalytic dinuclear Zn(II) hydrolyses incorporating second coordination sphere effects by using a polyamidoamine dendrimer as a secondary chain model. Six complexes bearing different dendrimer generations were studied in the hydrolysis of 2-hydroxypropyl-4-nitrophenyl-phosphate (HPNP) and sets of kinetic data were compared in order to better understand the effect of the chain model on the reactivity. The results indicate that a chain of 4000 g mol⁻¹ is sufficient to represent the second sphere effect in our model. Although the activation entropy ΔS^\ddagger was significantly increased, the k_{cat} value was not increased, due to unfavorable changes in ΔH^\ddagger . The dinuclear catalytic center remained intact, acting through the same mechanism, which opens new possibilities for the rational functionalization at this chain length to further increase the complex activity.

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1. Introduction

Over the past decade, the focus on biomimetic modeling has been expanded by the introduction of second sphere effects [1]. It has been shown that these effects play a major role in the activity of the catalyst, particularly in relation to metalloenzyme model complexes. Many systems have demonstrated the need to model more than just the active site in order to obtain higher catalytic constants which are attractive from a practical point of view. Phosphatases [2,3], nucleases [4], peroxidases [5] and hydrogenases models [6,7], among others, have been previously subjected to second coordination sphere effect studies and in some cases a significant improvement in the reaction rate was obtained.

In fact, such results arise from the well-known fact that, in the case of enzymes, the microenvironment of the catalytic site determines the activity, pH, substrate binding and reaction rates [8,9]. In principle, based on the Eyring model of transition state energetics, a few correctly positioned hydrogen bonds from the second sphere to the activated complex (~ 10 kcal mol⁻¹) can increase the k_{cat} by factors of millions [10] and this is very attractive in relation to synthetic catalysts. Many model complexes present spectroscopic and

redox characteristics similar to those of their parent enzymes, but their activity differs considerably from that of actual complexes due to the lack of second sphere effects [11].

Common approaches toward modeling the second sphere include the development of ligands with non-innocent arms [3,12], the binding of catalysts to nanostructures [4] and the use of polymers/dendrimers in order to model the protein chain [7,11,13]. Although success has been achieved through all of these possibilities, the polymer/dendrimer approach appears to be a promising way to improve these effects because of its similarity with the real problem. In addition, the systematic modification of these models has been shown to be a promising strategy for catalyst development. Hollfelder and co-workers [14] have recently demonstrated that through the rational functionalization of a polyethyleneimine (PEI) chain it is possible to enhance the reaction rate of phosphate transfer by a factor as high as 10⁸.

When studying these polymeric systems some questions arise including: how big does the secondary chain need to be in order to model second sphere effects and how does the size of this chain influence the mechanism and the transition state energies? These are probably the most important questions which need to be answered in order to develop model catalysts where a systematic functionalization approach is taken. In principle, the secondary chain should be as small as possible and with minimal polydispersity in order to reduce the costs, to facilitate the synthesis and to simplify the characterization.

* Corresponding author. Tel.: +55 48 3721 3605; fax: +55 48 331 9711.
E-mail address: ademir.neves@ufsc.br (A. Neves).

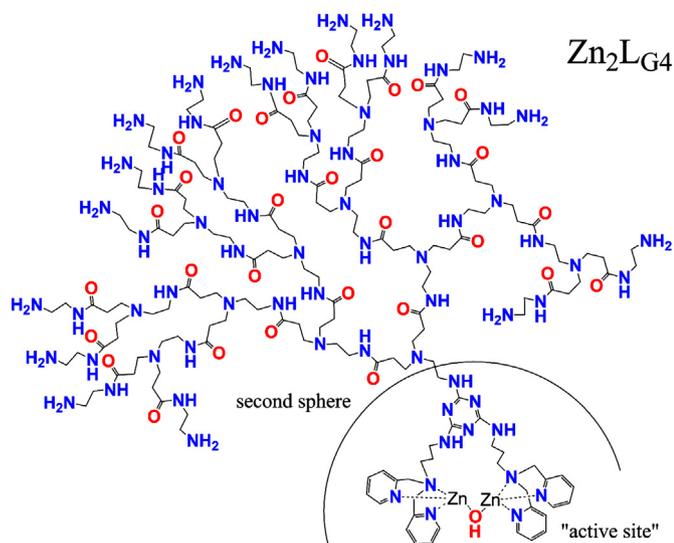


Fig. 1. Representation of the Zn_2L_{G4} structure, displaying a discrete active site and a second coordination sphere structure.

In this study, these questions were addressed by formulating a new approach to the development of second coordination sphere models using the polyamidoamine (PAMAM) dendrimer bound to a catalytic complex. PAMAM is currently used in many applications and it was chosen because of its ease of synthesis and characterization, and also because it presents minimal polydispersity and good water solubility [15,16]. In existing dendritic metal complex catalysts the active sites are generally positioned at the periphery, leading to cooperation between active units, which is termed the “dendrimer effect” [17]. Herein we describe a method for catalyst synthesis where only one catalytic unit is present at the dendrimeric center. This procedure offers the possibility of growing new generations of the dendrimer with a discrete “active site”, allowing the effect of the chain length on the catalytic activity to be evaluated (Fig. 1).

1,3,5-triazine bound to two *N,N'*-bis(pyridylmethyl)-1,3-propanediamine units was chosen as the ligand from which the synthesis of a dinuclear Zinc(II) complex as a model complex for HPNP transesterification was carried out. Similar dinuclear Zn^{II} systems have been studied in depth, both experimentally and theoretically [18–22]. This model has the advantages of avoiding too much complexity and it covalently binds to PAMAM. Five PAMAM generations were grown around the catalyst and detailed studies relating the chain size to the mechanism and activity are described.

2. Experimental

2.1. Measurements and materials

IR spectra were recorded on a Perkin-Elmer FTIR-S100 spectrometer from 500 to 4000 cm^{-1} in KBr pellets. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 200 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectrometry was carried out on a Bruker Micro QTOF with ESI ionization in positive mode for which all ligands were diluted in water. Kinetic measurements were obtained on a Cary Bio 50 UV/vis spectrophotometer with a thermostatic bath at $25 \pm 0.1^\circ C$. All solvents and reagents were purchased from commercial sources and used as received. The substrate barium 2-hydroxypropyl-4-nitrophenyl-phosphate (HPNP) and the proligand bis-(pyridylmethyl)amine (bpma) were prepared according

to procedures described in the literature [23,24]. The k_{uncat} value for the substrate under the experimental conditions was obtained from plots of the initial rate of hydrolysis versus $[S]_0$ without any catalyst. Purifications through dialysis were carried out using Spectra/Por[®] 7 membranes with a 1000 $g\ mol^{-1}$ cutoff.

2.2. Synthesis of *N,N'*-bis(pyridylmethyl)-1,3-propanediamine (bpmaNH₂)

This synthesis required two steps, a Michael addition of acrylonitrile to bis-(pyridylmethyl)amine (bpma) with subsequent reduction. Firstly, 5.97 g of bpma (30 mmol, 199.2 $g\ mol^{-1}$) were dissolved in 50 mL of MeOH and 3.97 mL of acrylonitrile (60 mmol, 53.06 $g\ mol^{-1}$, $d = 0.810\ g\ mL^{-1}$) were added to it. The solution was heated to $50^\circ C$ and maintained at this temperature for 24 h under stirring. After this time, the solvent and excess of nitrile were removed under reduced pressure and 6.98 g of bpmaCN (27.6 mmol, 252 $g\ mol^{-1}$) were obtained with 92% yield as a yellow oil and used without further purification.

Following the first reaction, the product was dissolved in 50 mL of EtOH and 7.2 g of Raney-Nickel and 3.6 g of LiOH were added to it. The solution was hydrogenated under 40 PSI of H_2 for 15 h at room temperature. It was then filtered and the solvent was removed under reduced pressure. The resultant oil was dissolved in $CHCl_3$, filtered to remove the excess of LiOH and washed three times with 100 mL of a saturated $NaHCO_3$ solution. The organic phase was dried with Na_2SO_4 and the solvent removed again to give 6.58 g of the product bpmaNH₂ (25.67 mmol, 256.35 $g\ mol^{-1}$) in 93% yield as an amber oil. IR with KBr in cm^{-1} : $\nu(N-H)$ 3285; $\nu(C-H_{ar}$ and $C-H_{alif})$ 2820–3050; $\nu(C=N$ and $C=C)$ 1475–1570; $\delta(C-H_{ar})$ 760. 1H NMR δH (200 MHz, $CDCl_3$, see SD): 1.68 (q, 2 H_{CH_2}); 2.17 (N–H); 2.58 (t, 2 H_{CH_2}); 2.71 (t, 2 H_{CH_2}); 3.78 (s, 4 H_{CH_2}); 7.15 (t, 2 H_{py}); 7.48 (d, 2 H_{py}); 7.64 (t, 2 H_{py}); 8.54 (d, 2 H_{py}).

2.3. Synthesis of 2,4-[*N,N'*-bis(pyridylmethyl)-1,3-propanediamine]-6-chloro-1,3,5-triazine – L_{Cl}

To a solution of 2.56 g of bpmaNH₂ (10 mmol, 256.35 $g\ mol^{-1}$) in 20 mL of acetone, 1.74 mL of diisopropylethylamine (DIPEA, 10 mmol, 129.24 $g\ mol^{-1}$, $d = 0.742\ g\ mL^{-1}$) were added and the mixture was cooled in an ice bath to around -5 to $0^\circ C$. Next, 0.922 g of 2,4,6-trichloro-1,3,5-triazine (5 mmol, 184.41 $g\ mol^{-1}$) were slowly added over a period of 1 h under stirring. The solvent was removed under reduced pressure at a maximum temperature of $40^\circ C$, the oil was redissolved in CH_2Cl_2 and the organic phase was washed five times with 50 mL of water and five times with 50 mL of saturated $NaHCO_3$. The organic phases were dried with Na_2SO_4 , the solvent removed and the product purified through column chromatography in MeOH/ CH_2Cl_2 20/80 v:v ($R_f \sim 0.5$). An amount of 1.96 g of the ligand L_{Cl} (3.14 mmol, 624.18 $g\ mol^{-1}$) was obtained in 63% yield as a yellow oil. IR with KBr in cm^{-1} : $\nu(N-H)$ 3260; $\nu(C-H_{ar}$ and $C-H_{alif})$ 2815–2950; $\nu(C=N$ and $C=C)$ 1435–1580; $\delta(C-H_{ar})$ 760. 1H NMR δH (200 MHz, $CDCl_3$, see SD): 1.61 (m, 4 H_{CH_2}); 2.43 (m, 4 H_{CH_2}); 3.20 (m, 4 H_{CH_2}); 3.59 (s, 8 H_{CH_2}); 4.30 (N–H); 6.90 (t, 4 H_{py}); 7.39 (d, 4 H_{py}); 7.54 (t, 4 H_{py}); 8.34 (d, 4 H_{py}).

2.4. Synthesis of 2,4-[*N,N'*-bis(pyridylmethyl)-1,3-propanediamine]-6-ethylenediamine-1,3,5-triazine – L_{G0}

To 5 mL of ethylenediamine, 3.12 g of L_{Cl} (5 mmol, 624.18 $g\ mol^{-1}$) were added at room temperature and the mixture was kept under stirring for 16 h. After this time, 40 mL of CH_2Cl_2 were added and the organic phase was extracted five times with 50 mL of a saturated solution of $NaHCO_3$. The solvent was

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