Novel Bifunctional Macrocyclic Ligands With Phosphorus-Based Side Arms

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Abstract. The main aim of this study was preparation of macrocyclic ligand based on 1,4,8,11-tetraazacyclotetradecane skeleton (cyclam), which is suitable for selective complexation of copper(II). Cyclam macrocycle bears one coordinating aminobenzylphosphinate pendant arm. During the synthesis, the skeleton was asymmetrically protected in positions 1, 4 and 8. Introduction of phosphinate pendant arm was done by Mannich-type reaction. In the frame of this work, the synthesis of the targeted product was developed. Reproducibility was also verified for synthesis of cyclam and its asymmetrical protection in three positions. Furthermore, a study of the kinetics of deprotection of cyclam skeleton and pendant arm using basic and acid hydrolysis was performed.

Keywords: Cyclam; Phosphinates; Nuclear medicine; Copper(II) complexes.
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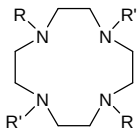
INTRODUCTION

Chemistry of complexes of macrocyclic ligands, in particular polyazamacrocycles, is a vital part of inorganic chemistry [1]. Polyazamacrocycles with coordinating pendant arms form very stable complexes with a wide range of metal ions. The ligands encapsulate metal ions in the macrocyclic cavity and the complexes often exhibit both thermodynamic stability and kinetic inertness [2]. The metal complexes of these ligands have found use in several areas, e.g. as contrast agents (CA) in magnetic resonance imaging (MRI) [3] or for labelling of biomolecules with metal radioisotopes for both diagnostic and therapeutic purposes [4].

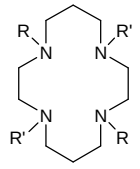
The ligands are often derivatives of cyclen (1,4,7,10-tetraazacyclododecane) and cyclam (1,4,8,11-tetraazacyclotetradecane) [5]. The study of the polyazamacrocycles with pendant arms has been focused mainly on acetates [5], phosphonates [6], phosphinates [6] or carboxamides [7]. Besides these groups, the ligands could contain also other pendant groups, for example, alcohol, phenol, or esters of carboxylate, phosphinate or phosphonate.

Cyclam (fourteen-membered tetraamine macrocycle) shows the ability to complex first-row transition metal cations, especially copper(II) [8]. There is a wide spectrum of copper isotopes (^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu and ^{67}Cu with half lives in range from 0.16 and 62 h), which can be used for in vivo applications. The mostly used copper isotopes are ^{64}Cu and ^{67}Cu [9].

However, the complexation of copper(II) with cyclam itself is very slow; fortunately, introduction of coordinating pendant arms generally leads to increase of the rate of complex formation. In addition, the suitable complexes should be highly soluble in water and rather hydrophilic to ensure their elimination through urinary pathway [10].



R = R´ = H	cyclen
R = R´ = CH_2CO_2H	H_4dota
R = R´ = $CH_2PO_3H_2$	H_8dotp
R = H, R´ = CH_2CO_2H	H_2do2a
R = H, R´ = $CH_2PO_3H_2$	H_4do2p



R = R´ = H	cyclam
R = R´ = CH_2CO_2H	H_4teta
R = R´ = $CH_2PO_3H_2$	H_8tetp
R = H, R´ = $CH_2PO_3H_2$	H_4te2p^{1,8}

FIGURE 1. Examples of ligands mentioned in the text.

EXPERIMENTAL PART

Synthesis

Goal of this synthesis was the ligand based on 1,4,8,11-tetraazacyclotetradecane (cyclam) with one 4-aminobenzylphosphinic pendant arm. Target ligand is shown in Fig. 2.

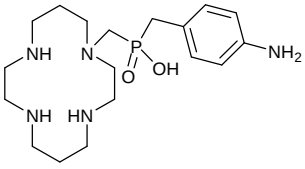


FIGURE 2. Targeted ligand.

Synthesis of the ligand starts from 1,5,8,12-tetraazadodecane (20.0 g; 110 mmol). It reacts with glyoxal (12.0 g; 57 mmol) forming a macrocycle with assistance of Ni(II) ion as template (27.3 g; 110 mmol; $NiCl_2 \cdot 6H_2O$). After reduction ($NaBH_4$ or RaNi) and removal of Ni(II) ion using excess of KCN in hydroxide solution, the macrocycle cyclam is extracted to chloroform and crystallized on concentration and addition of acetonitrile [11]. In the next step, cyclam (1.00 g; 5.0 mmol) was triprotected by reaction with ethyl trifluoroacetate (ETFA; 2.4 ml; 20 mmol) in presence of triethylamine (0.7 ml; 5 mmol) [12], Fig. 3.

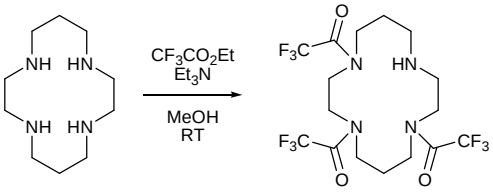


FIGURE 3. Synthesis of triprotected cyclam.

Phosphorus precursor was synthesized in inert Ar atmosphere starting from ammonium hypophosphite (10.0 g; 120 mmol). It was converted to bis(trimethylsilyl) ester using hexamethyldisilazane (50.0 ml; 237 mmol) [13] and in situ treated with 4-nitrobenzyl bromide (11.8 g; 55 mmol) in dry dichloromethane. Resulting 4-nitrobenzylphosphinic acid (3.7 g; 15 mmol) was isolated after hydrolysis in methanol and crystallization from hot aqueous HCl. The phosphinic acid was converted to ethyl ester in order to allow working Mannich-type reaction under anhydrous conditions. The ester was prepared through reaction of phosphinic acid with dicyclohexyl-carbodiimide (3.7 g; 18 mmol) in anhydrous ethanol in presence of catalytic amount of *N*,*N*-dimethylamino-pyridine (30 mg; 0.2 mmol), Fig. 4.

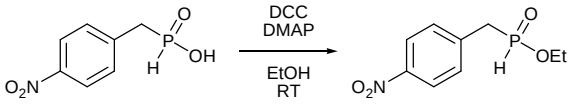


FIGURE 4. Synthesis of ethyl 4-nitrobenzylphosphinate.

Triprotected 1,4,8,11-tetraazacyclotetradecanemet-hylene-4-nitrobenzylphosphinic acid was prepared by a Mannich-type reaction between triprotected cyclam (0.90 g; 1.8 mmol), paraformaldehyde (0.60 g; 20 mmol) and ethyl ester of 4-nitrobenzylphosphinic acid (3.0 g; 12 mmol), when the pendant arm was attached to the macrocycle. The reaction was performed in refluxing toluene-ethanol mixture; the Dean-Stark trap was used for removal of water that is formed during the reaction. This synthesis is shown in Fig. 5.

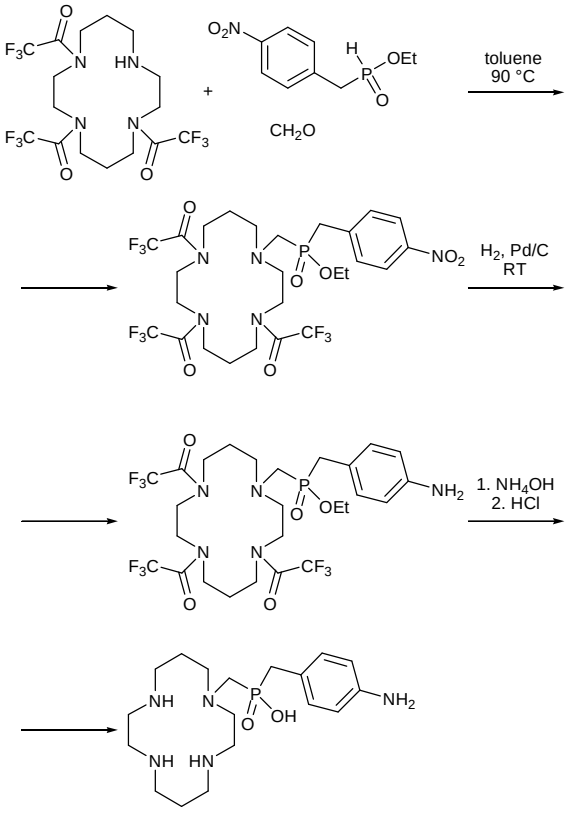


FIGURE 5. Mannich-type reaction.

The nitrobenzyl group was reduced using hydrogen in presence of palladium catalyst leading to 4-aminobenzyl group. Protecting trifluoroacetyl groups were removed by reaction with ammonium hydroxide. Removal of ethylester group on 4-aminobenzyl phosphinic pendant arm in mixture of conc. hydrochloric acid and water (1:1, 80 °C) afforded the target compound (Fig. 5).

RESULTS AND DISCUSSION

New macrocyclic ligand was synthesized. Critical step in the synthesis was removal of the protecting groups. The pendant arm with 4-nitrobenzyl phosphinic group shows limited stability – in aqueous acids and bases, retro-Mannich reaction was observed and whole methylenephosphinic arm is cleaved from the macrocycle. Therefore, its reduction to 4-aminobenzylphosphinate had to be performed first. In the next step, trifluoroacetyl groups were removed in NaOH. In the final step, ethyl ester phosphinate moiety was hydrolyzed using aqueous hydrochloric acid.

Preliminary results show that the ligand forms thermodynamically stable and kinetically inert complexes with copper(II) with high selectivity over other transition metal ions.

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