Synthesis of 1,4,7-triazacylononane derivative as a ligand for preparation of Fe(II) complex

MAINAK MITRA
Department of Chemistry, Burdwan Raj College, Purba Bardhaman, W.B. 713104, India

Abstract — 1,4,7-Triazacyclononane (tacn) is a promising ligand framework which has been used over two decades for chelating transition metal ions. In this work, tacn ligand framework is modified by introducing imidazolyl side arm to develop a new N4 donor tetradentate ligand. The synthetic routes to this new ligand are reported in the present work. The complexing ability of the ligand has also been investigated using Fe(II) salt and the corresponding Fe(II) complex containing the above ligand was also identified.

Index Terms — Tetradentate Ligand, Imidazole, Iron, Oxidation, Catalyst.

I. INTRODUCTION

Iron compounds provide a broad range of applications in organic synthesis. They can be used for addition reactions, cross couplings, cycloadditions and several enantioselective transformations.[2] Besides its versatility, iron, as a raw material is inexpensive because of its relatively high abundance on earth.[3] For these reasons many different iron salts (i.e. halides, chlorates and sulfates), elemental iron and simple iron complexes (i.e. carbonyl and bipyridyl complexes) were used.[2] More intricate ligands were applied as chelating agent for iron center in order to catalyze different oxidation reactions.[1] For tetradentate nitrogen containing compounds, which were used for these applications, a general rule has been observed: Two cis labile sites of the iron center are required for an active catalyst.[4] The chelating agent is of great significance for the reactivity of the metal complexes. Several different oxidation reactions can be achieved just by tuning the ligand framework.[4]

The aim of this work is to synthesize a tetradentate nitrogen donor containing ligand, which can be utilized for the preparation of earth-abundant transition metal complexes as potential oxidation catalyst. The ligand is based on 1,4,7-triazacyclononae (tacn) framework modified with an appended imidazolyl moiety. For the sake of its potential ligating property, a new Fe(II) complex has also been synthesized and reported in this work.

II. IRON IN ENZYME

Iron has many different functions in biological systems: for example the transport of oxygen, the transfer of energy by electron transport, as magnetosensor and geosensor for organisms and many oxidation or reduction reactions.[5] Redox active heme containing proteins are inter alia responsible for dioxygen transport and storage (globins), the transport of nitric oxide (nitrophorin) and several redox reactions (cytochrome P450).[6]

Beside porphyrins, several amino acids are able to bind iron ions to proteins. The most important ones are cysteine (Cys), histidine (His), the carboxylic group containing amino acids glutamate (Glu) and aspartate (Asp) and tyrosine (Tyr).[5] Rieske dioxygenases for example contain iron ions which are bound to a 2-His-1-carboxylate facial triad.[1] This type of enzymes is inter alia responsible for the first step in biodegradation of aromatic compounds by adding dioxygen to the molecule to form aromatic *cis*-diols.[7] In the last step these products are oxidized by catechol dioxygenases: The catechols are converted to nonaromatic, acyclic molecules by inserting both molecules of dioxygen in the aromatic double bond.[1] The iron ion of this class of enzymes is bound either similarly to the Rieske dioxygenases or by two His and two Tyr.[5]

In order to understand these enzymes, many different types of ligands were used as biomimetic system.[1] Several tetradentate tripods like tris(2-pyridylmethyl)amine (tpa)[8], BPMEN[9], 1,4,7-triazacyclononan derivatives[10] and many other compounds were used as ligands for model complexes for catechol dioxygenases.

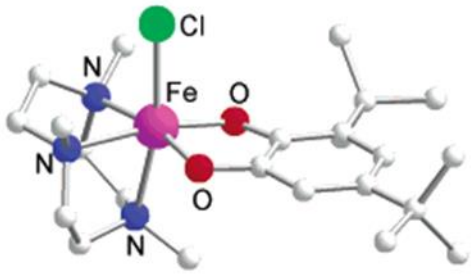


Figure 1. [Fe^{II} (Me_3tacn)] complex as a biomimetic system for catechol dioxygenase.[1]

Beside their function as model systems, these complexes can also be used in oxidation catalysis:

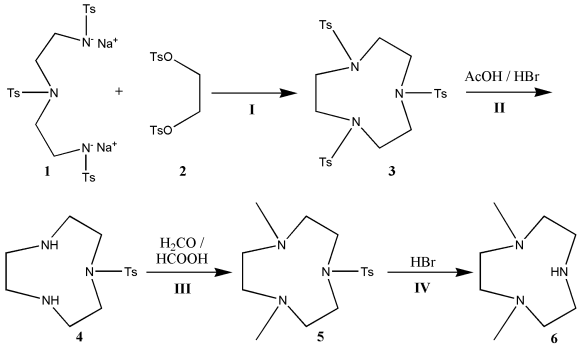
- The stereospecific hydroxylation of alkanes with hydrogen peroxide catalyzed by an iron-TPA complex for example offers a way to activate the strong CH-bond.[11]
- In order to avoid toxic and expensive oxidative compounds like osmium tetroxide iron-BPMEN complexes can be applied to catalyze the *cis*-hydroxylation of olefins.[9]
- As a "green" alternative to regular compounds N,N'-dimethyl-N,N'-bis(2-pyridylmethyl)-ethane 1,2-diamine complexes with iron can be used to epoxidize alkenes.[12]

Furthermore, there are some small industrial applications for iron complexes. For instance, iron-tacn complexes can be applied as catalyst for living radical polymerization of methacrylate or styrene. These compounds are safer, less expensive and more environment-friendly than the standard catalyzers.[13] Another iron complex can be deployed as a bleaching agent: The compound catalyzes the bleaching reaction with dioxygen, and no peroxy-based substances are used and the process is cost effective and more environment-friendly.

III. TACN AND ITS DERIVATIVES

1,4,7-Triazocyclononane is a heterocyclic, nitrogen containing compound, which has many different applications. The modified ligand itself can be used as a transfection agent in cytological or biochemical approach [14] or as a chelating agent for lead(II) in order to bind this environmental contaminant.[15] Furthermore complexes of different metals and tacn derivatives show various properties depending on the type of metal and the modification of the ligand. Gadolinium complexes for instance can be applied as MRI contrast agent[16] or copper compounds with immobilized tacn derivative are adaptable for IMAC (immobilized metal affinity chromatography) in order to purify proteins.[17] Beside copper and iron (see 2.1) manganese complexes have various application as catalyst for bleaching with hydrogen peroxide,[18] as a compound to catalyze the epoxidation of alkenes or the oxidation of carbon-hydrogen bonds.[19]

In literature several methods are known to synthesize tacn.[20] A common route of synthesis is the method of Richman and Atkins[21] (see **Error! Reference source not found.** step I): The disodium salt of *N,N',N''*-tritosylethylentriamine (1) is converted with ditosylated ethylene glycol (2) to the 1,4,7-tritosyl-1,4,7-triazacyclononane (3). In order to obtain 1,4-dimethyl-1,4,7-triazacyclononane (6; Me_2tacn), which was used in this report, Flassbeck and Wieghardt described the method shown in **Error! Reference source not found.** (step II to IV): After removing two of the protective groups at acidic conditions the secondary amino groups are methylated and 1,4-dimethyl-7-tosyl-1,4,7-triazacyclononane (5) is obtained. In order to gain the unprotected Me_2tacn the last tosyl group is removed by adding hydrobromic



acid.

Figure 2. The synthetic route to Me_2tacn ligand.

IV. RESULTS AND DISCUSSIONS

In order to obtain a tetradentate ligand to form an iron complex the route of synthesis shown in **Error! Reference source not found.** was chosen. 1-Methyl-

1*H*-imidazole-2-carbaldehyde (7) was selected as comparatively inexpensive starting material.

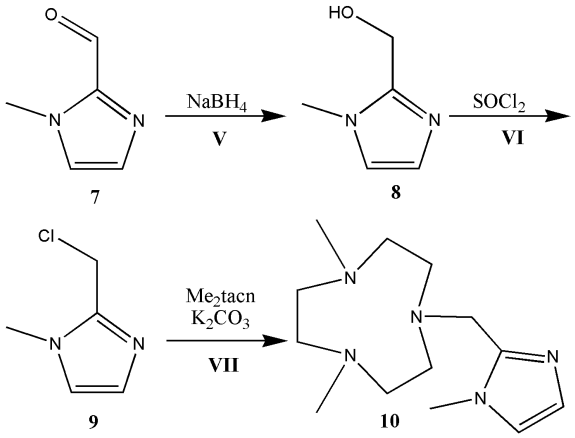


Figure 3. Route of synthesis for 1,4-dimethyl-7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane (10).

The first sub-ordinate target of the synthesis was to get the chlorinated compound 9. Therefore 7 was reduced with sodium borohydride in methanol according to literature (step V).[22] The pure product (8) was obtained in good yield, so no further improvements of the synthesis were required. Afterwards the hydroxyl group of 8 had to be substituted by chlorine. For that reason, the compound was treated with thionyl chloride (step VI). In literature two different methods are known: with[23] or without[24] solvent. The favorite method should be the one without solvent to prevent impurities in the product, but unfortunately the reaction mixture is very viscous. Therefore, the reactants were not able to react completely and the obtained yield (78%) was not as good as for the reaction in dichloromethane (93 %).

For the last step of the synthesis of the ligand the given Me_2tacn had to be purified, because the compound was contaminated with small amounts of 5. Therefore, the pH is to be adjusted at 8, since the most of the tosylated compound is neutral and could be extracted with dichloromethane. After removing the impurities Me_2tacn could be extracted with CH_2Cl_2 at pH 14. In order to obtain 1,4-dimethyl-7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane (10) the chlorinated imidazole compound 8 was added to a solution of the purified Me_2tacn at basic conditions. Beside potassium hydroxide, triethylamine was tested at the same conditions (see 4.4), but lower yields were obtained (25%). Unfortunately, impurities were still detected after purification, which are probably decomposition products of tacn.

In order to test its complexing ability, iron(II) triflate was added to an acetonitrile solution containing the synthesized ligand. The slightly brown solution turned immediately to dark brown. After 20 hours of stirring at room temperature, a fine crystalline off-white residue was obtained and was identified as $[Fe^{II}(L)(CH_3CN)_2](OTf)_2$ (see Figure 4) by mass spectrometry. Experiments to obtain single crystals of this complex by vapor diffusion crystallization failed, but the fast complexation reaction was an indication, that the synthesized ligand can be used as a good chelating agent for iron metal ion.

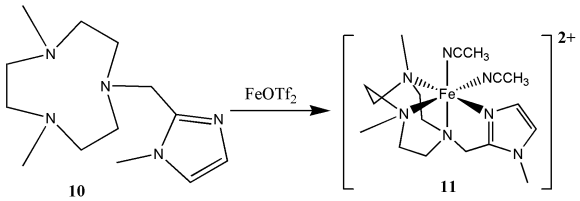


Figure 4. Synthesis of $[Fe^{II}(L)(CH_3CN)_2](OTf)_2$.

V. EXPERIMENTAL PART

A. Synthesis of (1-methyl-1H-imidazol-2-yl)methanol (8)

2.05 g (18.6 mmol) of 1-methyl-1*H*-imidazole-2-carbaldehyde were dissolved in 20 mL methanol. At 0° C 1.10 g (29.1 mmol) $NaBH_4$ were added portion wise. The reaction mixture was stirred for 22 h at room temperature. Than 10 mL water were added and the solution was stirred for additional 30 min. The methanol was removed in vacuum and the product was extracted four times with 10 mL chloroform. The solution was dried with $NaSO_4$ and the solvent was removed in vacuum. Appearance: Colourless crystalline solid. Yield: 1.74 g (15.5 mmol; 83.5%). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 3.72 (s, 3H), 4.63 (s, 2H), 6.81 (d, 1H), 6.87 (d, 1H).

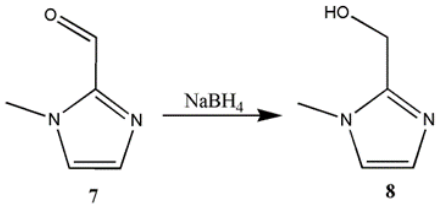


Figure 5. Synthesis of (1-methyl-1H-imidazol-2-yl)methanol.

B. Synthesis of 2-(chloromethyl)-1-methyl-1H-imidazole (9)

0.5 g (4.5 mmol) of (1-methyl-1*H*-imidazol-2-yl)methanol were added to 0.7 mL (9.6 mmol) thionyl chloride at 0 °C. The reaction mixture was stirred for 20 h at room temperature. The obtained solid was dissolved in 3 mL ethanol and filtered. After removing the solvent, the hydrochloride of the product was obtained. Appearance: Bright yellow crystalline solid. Yield: 0.59 g (3.5 mmol; 77.8%). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 3.97 (s, 3H), 5.16 (s, 2H), 7.16 (s, 1H), 7.34 (s, 1H).

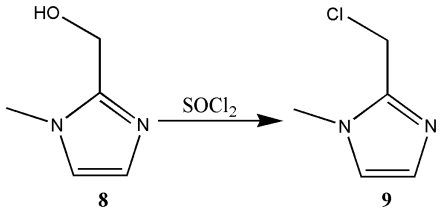


Figure 6. Synthesis of 2-(chloromethyl)-1-methyl-1H-imidazole.

C. Purification of 1,4-dimethyl-1,4,7-triazacyclononane (6; Me_2tacn)

0.31 g of the raw reactant was dissolved in 10 mL water. The pH value was set with 10 M sodium hydroxide solution and 1 M hydrochloric acid to 8. Afterwards the impurities were extracted three times with 10 mL dichloromethane. Then the aqueous phase was set to pH 14 and the product was extracted five times with 10 mL dichloromethane. The solution was dried with sodium sulfate and after removing the solvent in vacuum the purified product was obtained. Appearance: Colourless oil. Yield: 0.10 g (0.64 mmol). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 2.43 (s, 6H), 2.52 (s, 4H), 2.65 (t, 4H), 2.91 (t, 4H).

D. Synthesis of 1,4-dimethyl-7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane (10)

99 mg (0.63 mmol) of Me_2tacn were dissolved in 12 mL dry acetonitrile. 82 mg (0.49 mmol) of 2-(chloromethyl)-1-methyl-1H-imidazole, 0.44 g (3.18 mmol) of potassium carbonate and 0.14 g (0.85 mmol) of potassium iodide were added. The reaction mixture was stirred for 68 h at room temperature and then heated under reflux for additional 23 h. After removing the solvent in vacuum, the obtained brown residue was dissolved in 20 mL dichloromethane. The impurities were extracted with 20 mL water and four times with 10 mL 1 M sodium hydroxide solution. After drying the organic layer with sodium sulfate the solvent was removed in vacuum and brown oil was obtained. The raw product was dissolved in mixture of 5 mL dichloromethane and 20 mL hexane. After 24 h a dark brown, highly viscous residue has been formed. The solution was transfused, and the solvent was removed in vacuum. Appearance: Slight yellow oil. Yield: 51 mg (0.20 mmol; 41.4%). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 2.32 (s, 6H), 2.61 (t, 4H), 2.71 (s, 4H), 2.77 (t, 4H), 3.70 (s, 2H), 3.74 (s, 3H), 6.84 (d, 1H), 6.91 (d, 1H).

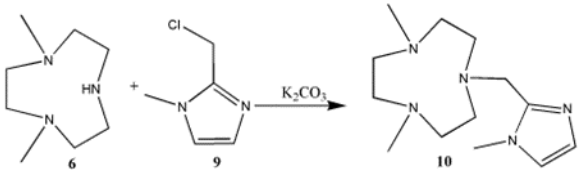


Figure 7. Synthesis of 1,4-dimethyl-7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane (L).

E. Synthesis of $[Fe^{II}(L)(CH_3CN)_2](OTf)_2$ (10)

38 mg (0.15 mmol) of L were dissolved in 1 mL dry acetonitrile. A dispersion of 120 mg (0.29 mmol) of iron(II) triflate in 1 mL acetonitrile were added. The mixture was stirred for 20 h at room temperature. The brown solution was overlaid with 10 mL diethyl ether and reddish-brown residue was obtained.

V. SUMMARY AND PERSPECTIVE

Iron containing compounds can be used for many applications: simple substances like halide salts are involved in many reactions in organic chemistry, whereas several highly intricate enzymes in nature contain iron in their active center. In order to imitate these natural compounds and to obtain similar synthetic catalysts a number of iron complexes were synthesized. One possibility for a ligand is 1,4,7-triazacyclononane (tacn), which was already used as biomimetic and as chelating agent.

The ambition of this work was to develop and synthesize a suitable N4 donor tetradentate ligand, which can be used as chelating agent in order to

achieve an active oxidation metal catalyst. Therefore, a tacn derivative was synthesized, which was modified with an imidazole group. Imidazole group is basic in nature and can stabilize high-valent oxidation state of transition metals. Also, the π-acidic character can help to stabilize low-valent state.

For the synthetic purpose 1-methyl-1*H*-imidazole-2-carbaldehyde was converted in two steps first with sodium borohydride to (1-methyl-1*H*-imidazol-2-yl)methanol than with thionyl chloride to 2-(chloromethyl)-1-methyl-1*H*-imidazole. Afterwards the chlorinated species was added to a solution of 1,4-dimethyl-1,4,7-triazacyclononane (Me_2tacn) and 1,4-dimethyl-7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane was obtained. The complexing ability was investigated using simple iron(II) triflate salt and a brown fine crystalline Fe(II) complex containing the imidazolyl derivatized tacn ligand was obtained.

In future the iron complex will be further characterized structurally. Furthermore investigations will be directed towards the activity of this Fe(II) complex in C-H oxidative catalysis.

ACKNOWLEDGMENT

The author acknowledges infrastructural facilities provided by Burdwan Raj College and the University of Burdwan. The author is thankful to Udita Ghosh for fruitful discussions.

REFERENCES

[1] M. Costas, M. P. Mehn, M. P. Jensen, L. Que, *Chem. Rev.*, 2004, 104, 939-986.

[2] C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.*, 2004, 104, 6217-6254.

[3] E. Riedel, C. Janiak, *Anorganische Chemie*, Walter de Gruyter, Berlin, New York, 2007, 7,

[4] K. Chen, M. Costas, L. Que Jr, *Journal of the Chemical Society, Dalton Transactions*, 2002, 672-679.

[5] I. Bertini, H. Gray, E. Stiefel, *Biological Inorganic Chemistry: Structure and Reactivity*, University Science Books, 2006.

[6] M. Sono, M. P. Roach, E. D. Coulter, J. H. Dawson, *Chem. Rev.*, 1996, 96, 2841-2888.

[7] D. T. Gibson, R. E. Parales, *Curr. Opin. Biotech.*, 2000, 11, 236-243.

[8] T. Funabiki, T. Yamazaki, A. Fukui, T. Tanaka, S. Yoshida, *Angew. Chem. Int. Ed.*, 1998, 37, 513-515.

[9] M. Costas, A. K. Tipton, K. Chen, D.-H. Jo, L. Que, *J. Am. Chem. Soc.*, 2001, 123, 6722-6723.

[10] D. H. Jo, L. Que Jr, *Angew. Chem. Int. Ed.*, 2000, 112, 4454-4457.

[11] C. Kim, K. Chen, J. Kim, L. Que, *J. Am. Chem. Soc.*, 1997, 119, 5964-5965.

[12] M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, 123, 7194-7195.

[13] H. Kai, A. Hamada, H. Hayakawa; Process for Production of Polymers with Iron Complex Catalyst; EP 2 269 995 A1. 05.01.2011.

[14] Q.-F. Zhang, W.-H. Yang, W.-J. Yi, J. Zhang, J. Ren, T.-Y. Luo, W. Zhu, X.-Q. Yu, *Bioorg. Med. Lett.*, 2011, 21, 7045-7049.

[15] M. Di Vaira, F. Mani, P. Stoppioni, *Dalton Trans.*, 1998, 3209-3214.

[16] Y. Miyake, Y. Kimura, S. Ishikawa, H. Tsujita, H. Miura, M. Narazaki, T. Matsuda, Y. Tabata, T. Yano, A. Toshimitsu, *Tetrahedron Lett.*, 2012, 53, 4580-4583.

[17] B. Graham, P. Comba, M. T. Hearn, L. Spiccia, *J. Biol. Inorg. Chem.*, 2007, 12, 11-21.

[18] R. Hage, J. E. Iburg, J. Kerschner, J. H. Koek, E. L. Lempers, R. J. Martens, U. S. Racherla, S. W. Russell, T. Swarthoff, M. R. P. van Vliet, *Nature*, 1994, 369, 637-639.

[19] K. F. Sibbons, K. Shastri, M. Watkinson, *Dalton Trans.*, 2006, 645-661.

[20] J. Huang, Z. Zhou, T. H. Chan, *Synthesis*, 2009, 2009, 2341-2344.

[21] J. E. Richman, T. J. Atkins, *J. Am. Chem. Soc.*, 1974, 96, 2268-2270.

[22] C. Robinson, J. Zhang, D. Garrod, T. Perrior, G. Newton, K. Jenkins, R. Beevers, M. Major, M. Stewart; Pyruvamide Compounds as Inhibitors of Dust Mite Group 1 Peptidase Allergen and their Use; US 2012/0322722 A1. 21.01.2011.

[23] E. Alcalde, M. Alemany, M. Gisbert, *Tetrahedron*, 1996, 52, 15171-15188.

[24] C. Liao, X. Zhu, X.-G. Sun, S. Dai, *Tetrahedron Lett.*, 2011, 52, 5308-5310.