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A SHORT REVIEW ON THE SYNTHESIS OF AZAMACROCYCLIC LIGAND: CONVENTIONAL AND NON-TEMPLATE METHODS

(Ulasan Pendek Sintesis Ligan Aza Makrosilik: Kaedah Konvensional dan Tanpa Templat)

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Abstract

Various methods have been developed for the synthesis of azamacrocyclic ligands and their derivatives, which varies from the selection of amino group, ionic compound, and solvent. Among the popular methods include the rigid group method, high dilution method, and the template metal effect method. Recently, researchers have considered the non-template method as a promising and effective approach to produce a higher yield of metal-free azamacrocyclic ligands compared to the conventional approaches. Hence, this review presented an overview of the synthesis and structure of azamacrocyclic compounds through conventional methods and the newly developed non-template method. The advantages and disadvantages related to each technique were also highlighted.

Keywords: azamacrocyclic ligand, non-template method, cyclisation, metal ion

Abstrak

Pelbagai kaedah dikembangkan untuk sintesis ligan aza makrosilik dan terbitannya yang berbeza daripada pemilihan kumpulan amino, sebatian ion dan pelarut. Antara pelbagai kaedah yang terkenal termasuklah kaedah kumpulan tegar, kaedah percairan tinggi, dan kaedah kesan templat logam. Baru-baru ini, penyelidik telah mengenal pasti kaedah tanpa templat sebagai pendekatan berkesan untuk menghasilkan ligan aza makrosilik yang bebas logam dengan hasil yang tinggi, berbanding dengan kaedah konvensional. Oleh itu, ulasan ini membincangkan sintesis dan struktur sebatian aza makrosilik dengan kaedah konvensional dan tanpa templat. Di samping itu, kelebihan dan kekurangan setiap teknik juga dibincangkan untuk penambahbaikan pada masa hadapan.

Kata kunci: ligan aza makrosilik, kaedah tanpa templat, perkitaran, logam ion

Introduction

A macrocyclic ligand is defined as a cyclic compound with a minimum of nine heteroatoms and consists of three or more potential donor atoms for ligating. To date, donor atoms found in macrocycles include nitrogen, oxygen, and sulphur. Since its discovery by Busch and

Curtis in the 1960s [1], studies on macrocyclic ligand has undergone tremendous development and progress in various field of application. The pioneering work has also been adopted in the synthesis of oxygen-based ligand for biological processes by Pedersen where cyclic polyether showed good interaction towards alkali and alkaline earth metal ions [2].

Macrocyclic ligands are classified based on their donor types (Figure 1) and chemical structures (Figure 2). The aza crowns class is the most diverse and studied macrocyclic compound compared to the crown ethers and thiacrowns [3]. This is because nitrogen is available naturally in many common groups, including pyridine, porphyrins, ammonium, thiourea, amino, and others, which forms the basic structure of azamacrocyclic ligands [4-10]. Moreover, ligand containing nitrogen atoms has a high possibility to interact and form a coordination bond with transition metal ion to produce complex compounds [11].

The utilisation of azamacrocyclic ligand has been studied by chemists thoroughly by focusing on its complexation towards a variety of metal ions [12]. In addition, they have been applied in various fields, such as biomimetics, the removal of heavy metal in waste treatment, as a contrasting agent in medical imaging, and also as an anti-cancer agent [13-15].

Realising the significance of azamacrocyclic ligand, various methods were proposed for the synthesis of macrocyclic compounds. The most crucial and difficult step in the synthesis of azamacrocyclic ligand is the assemblymen of the macrocyclic compound. As the research field expands, continuous efforts and progress have led to the establishment of simpler and cheaper methods with higher yield. Currently, there are three established methods for the synthesis of azamacrocyclic ligand [16]. The first approach, known as the rigid group method, restricts the rotation of the open-chain precursors [17]. Secondly, the high dilution method is performed under high temperature and inert atmosphere [18]. The third method is the selective metal template effect method, which introduces transition metal ions to promote the formation of macrocyclic compounds [19].

The non-template method is a newly introduced method to synthesis macrocyclic compounds in the absence of metal ions during cyclisation. Recently, Borisova et al. stated that the suitable selection of reaction conditions such as solvent, concentration, and temperature in the non-template method plays a vital role in obtaining the target product with various structures at a considerable yield [33]. Therefore, this study aimed to analyse and discuss the process and speciality of the non-template method for the synthesis of azamacrocyclic ligand compared to the conventional approaches. The fundamental understanding of the macrocyclisation process is important towards the synthesis of a diverse range of ligands as artificial cationic, anionic, and neutral guest receptors.

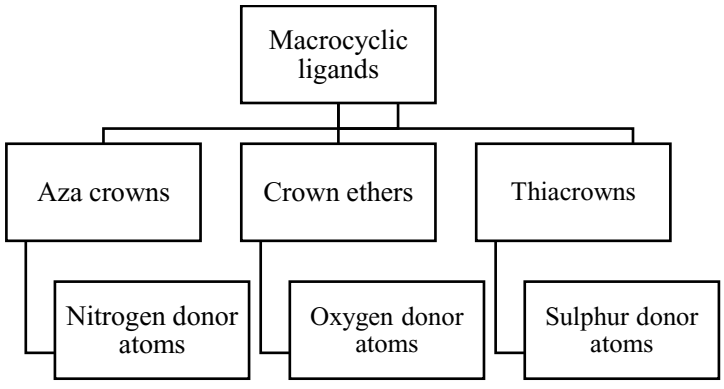


Figure 1. Classification of predominantly macrocyclic ligands

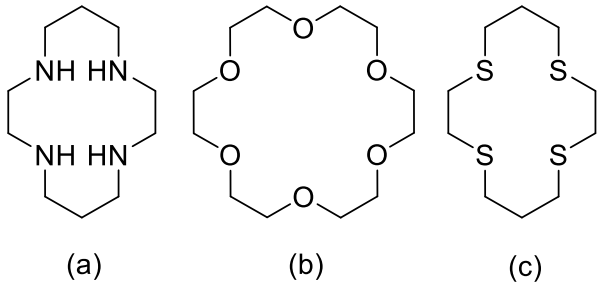


Figure 2. Chemical structures of a) azacrowns b) crown ethers c) thiacrowns

Rigid Group Method

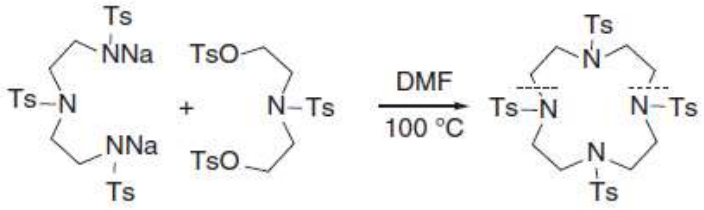
The Richman-Atkins reaction is reaction of dimetal salts of sulphonamide with a terminal dihalide in preparation of polyamines with a yield of up to 90% [20]. The cyclisation process is performed in a low dilution medium through the condensation of a tosylamide and tosylated alcohol in dimethyl formamide (DMF) (Scheme 1). Each precursor compound has two reactive functional groups at the end. The use of the tosyl group is more complicated because it requires the preparation of arduous reagents with a limited scope of substrates [21].

The rigid group method is used of condensation catalysts such as dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino) pyridine (DMAP) for the condensation of primary amines. Previously, this technique was applied using different rigid groups, including DCC and DMAP in Richman-Atkins reaction. The study reported the successful synthesis of 14-22-membered tetraoxomacrocyclic tetramines with 50% yield from dicarboxylic acids and primary diamines [22]. The presence of rigid groups serves as a good condensing agent to reduce the number of conformational degree of freedom by preventing bond rotation. Hence, minimising the condensation pathway allows the formation of macrocyclic compounds. This method is still widely used but only limited to the synthesis of macrocyclic polyamines and alkyl halides because sometimes difficult to obtain the desired pure product [23].

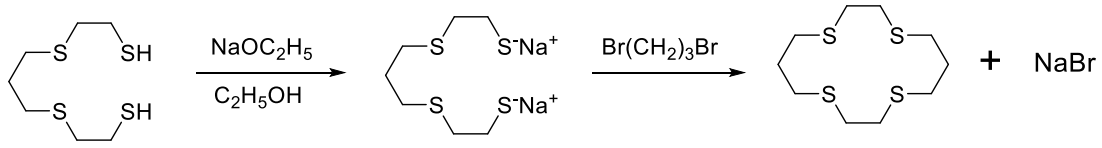
High Dilution Technique

The rate of formation of linear polymers is higher in a concentrated solution due to the presence of many active sites and frequent contacts between polymers and reagents. Therefore, diluting the solution to achieve an exceedingly low concentration of the reacting reagents subsequently reduces the rate of contact between polymers and additional reagent. This process, known as the high dilution technique, enhances intramolecular reactions and increases the possibility of the formation of macrocyclic ligands.

Rosen and Busch first reported the synthesis of 14-thiacrown-4 (14aneS_4) with a very low yield of 7.5% as a result of the competitive formation of polymeric compounds [24]. However, when Travis applied the high dilution technique, the yield recorded an increase up to 50% as more sulphur donor atoms were available in the reaction, as shown in Scheme 2 [25]. This remarkable discovery demonstrated that the production of the macrocyclic ligand was improved with the increasing dilution of the solution. However, certain drawbacks of the method remain a concern, particularly the long reaction time and the ability to synthesis many ring system [46]. For example, many-membered ring ketones should be synthesized on different reaction paths such as the dinitrile reaction and acyloin condensation [46].



Scheme 1. The Richman-Atkins reaction [20]



Scheme 2. High dilution method for the synthesis of 14-thiacrown-4 [25]

Metal Template Effect Method

The term template is broadly used in coordination chemistry to indicate a substance that acts as a mould to amplify the chemical reaction. The transition metal templates are commonly used as a guide for the cyclisation process and are a powerful tool in inorganic chemistry [26]. In this method, the synthetic route of macrocyclic ligands involves the use of a metal ion template to orient the reacting groups of ligands in the desired conformation for optimum ring closure. The favourable enthalpy for the formation of the metal-ligand bonds dominated over the unfavourable entropy from the ordering of the multidentate ligand around the metal ion, thereby enhancing the cyclisation reaction [27]. Hence, the synthesis of macrocyclic compounds through the template effect method is contributed by the combination of pre-ligand and metal ions, as illustrated in Scheme 3 [28]. The macrocyclic product is electrophilically alkylated with 1,2-bis(bromomethyl) benzene, while [Ni(L4)] acts as the template.

In terms of template synthesis, the macrocyclic complex can be useful to remove or replace the templated metal with different transition metal ions. The metal complex can be demetallated using specific reagents for the release of metal-free macrocyclic ligand [30]. For example, a hydrated hexaaza macrocyclic ligand was prepared through the demetallation of nickel [Ni(II)] complex of 6,6'-dihydrazino-2,2'-bipyridil using sodium cyanide in methanol to provide a free macrocyclic ligand, as presented in Scheme 4 [29].

However, the template cyclisation technique lacks the consistency to isolate azamacrocycles. The major drawback of the technique is contributed by the demetallation process in which the macrocycles become unstable in the uncoordinated state or the complex formation is too strong for the decomplexation process [31]. The high stability of the metal-ligand coordination and macrocyclic effect maintains the metal complex from releasing the free ligand. Thus, the direct synthesis or non-template method offers the best approach to overcome this problem.

Non-Template Method

In contrast to the metal template reaction, the ligand is synthesised first in the direct or non-template method, followed by the combination with a transition metal to form the complex compound. In 1971, Holm reported the first straightforward non-template synthesis of a basic macrocyclic 14-membered tetraaza ring system [32]. The moderate yield of 50% crystalline product from reaction of carbonyl-containing group and ketone group inspired other researchers to further explore this technique.

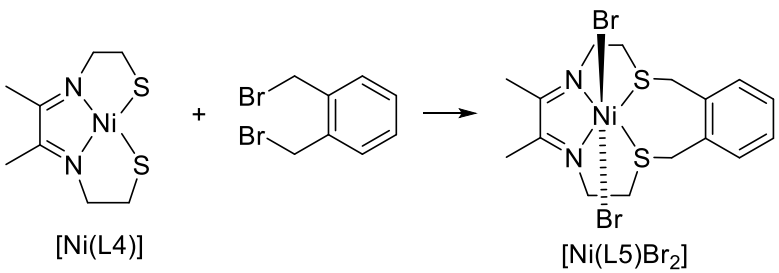
In 1980, Owston and co-workers proposed the preparation of a metal-free tetraaza macrocycle under various condensation conditions [34]. The selected solvents allowed the free ligands to separate from the solution and structure formation based on the stability of the imine bond during the cyclisation process. However, the reaction of dialdehyde group with 1,2-diaminoethane, 1,2-diaminobenzene, and 1,3-diaminopropane produced different arrangements of linear products instead of macrocyclic di-imines. This due to the absence of aniline-hydrogen in the reactant that affecting the stabilization of the imine bond by hydrogen-bonding.

Swamy et al. carried out further studies by reacting to different groups of amines with diacid chlorides and diesters in the presence of anhydrous sodium carbonate during the isolation of pure macrocycles [35]. The results obtained revealed the formation of 14-, 15-, or 16-membered rings with four amide nitrogen atoms in Figure 3 (left). In addition, the diamines-diamides also reacted with alkyl dichlorides to form two amide and two secondary amine nitrogen atoms in the ring in Figure 3 (right). The success of the cyclisation process indicates that the lone pair repulsions were reduced in the presence of at least two secondary amine hydrogen atoms, as shown in Figure 3 (right).

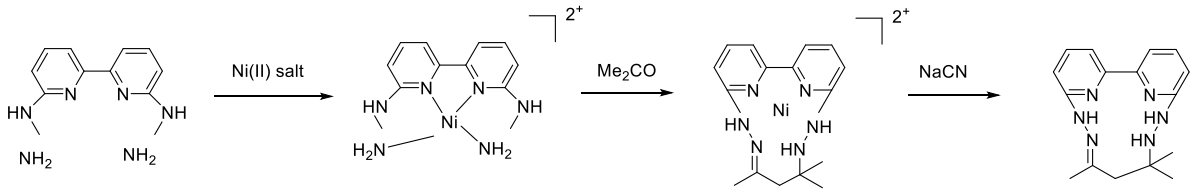
Alternative steps for the synthesis of novel tetraaza macrocyclic ligand were proposed by Swamy et al. through the non-template condensation reaction between ethylenediamine and ethyl acetoacetate, as in Scheme 5 [35]. The formation of crystalline ligand at an approximate yield of 75% was contributed by the effective coordination of amide nitrogen with metal chlorides from the *d*-block elements, including ruthenium [Ru(III)], platinum [Pt(II)], and palladium [Pd(II)] metal ions. These interactions were demonstrated through the presence of peaks of medium bands in the Infra-Red (IR) spectra around the region of 450–470 cm^{-1}, which were assigned to the metal-nitrogen vibrations.

Besides, Ni(II) complex was synthesised using the same non-template condensation technique in the presence of acetic acid [11]. Tetraaza cyclotetradeca ligand was obtained from the reaction of diaminoethane in ethanol with ethyl acetoacetate, resulting in a high yield of 75% crystalline product. Moreover, the presence of nitrogen with lone pairs in macrocyclic makes it a versatile coordinating agent with a high possibility to form stable complexes with transition metals. Hence, Ni(II) ion was able to fit in the centre of the ring while attached to the $(CH_3COO)_2$ groups in an octahedral configuration.

In addition, a tetraaza macrocyclic nitrogen donor ligand, $C_{24}H_{28}N_4$ was prepared by Chandra et al. [3] through a simple two-step synthesis. Firstly, the 2,3-hexanedione reacts with *m*-phenylenediamine in the presence of hydrochloric acid (HCl) to develop a macrocyclic moiety. This is followed by the complexation of Co(II), Cu(II), and Ni(II) complexes for antibacterial and antifungal screening activity. The study also used different types of counter anion, X = chloride (Cl^-), nitrate (NO^{3-}), and isothiocyanate(NCS^-), resulting in the formation of different geometry due to the metal-ligand interaction. The magnetic moment values corresponded to the high spin configuration, indicating the tetrahedral square pyramidal with anions occupied the axial positions and octahedral geometry of complexes (Figure 4).



Scheme 3. The preparation of $[Ni(L5)Br_2]$ through kinetic coordination template effect [28]



Scheme 4. Demetallation of Ni(II) to obtain metal-free macrocyclic ligand [29]

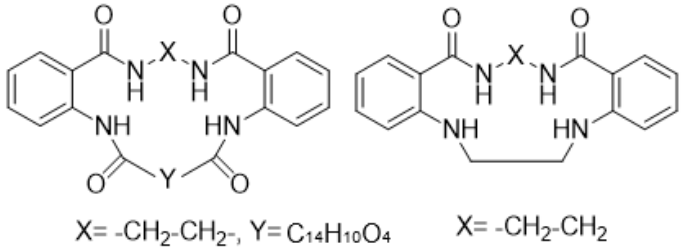
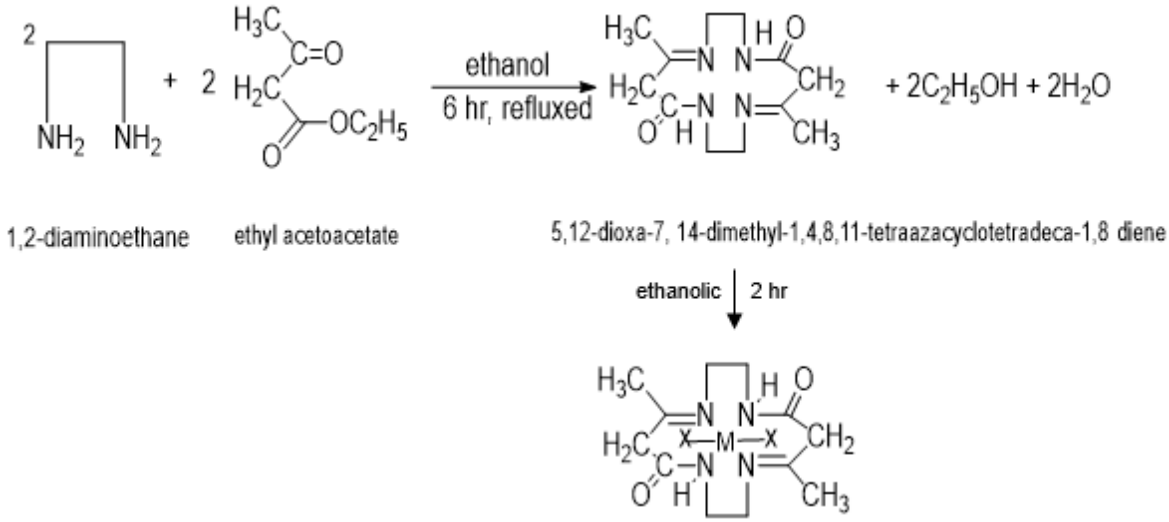


Figure 3. 14-, 15-, or 16-membered rings with four amide nitrogen atoms (left) with two amide and two secondary amine nitrogen atoms in the ring (right) [35]



Scheme 5. Synthesis of tetraaza macrocyclic ligand and its complexes where M= Ru(III), Pt(II) and Pd(II) and X= Cl^- [35]

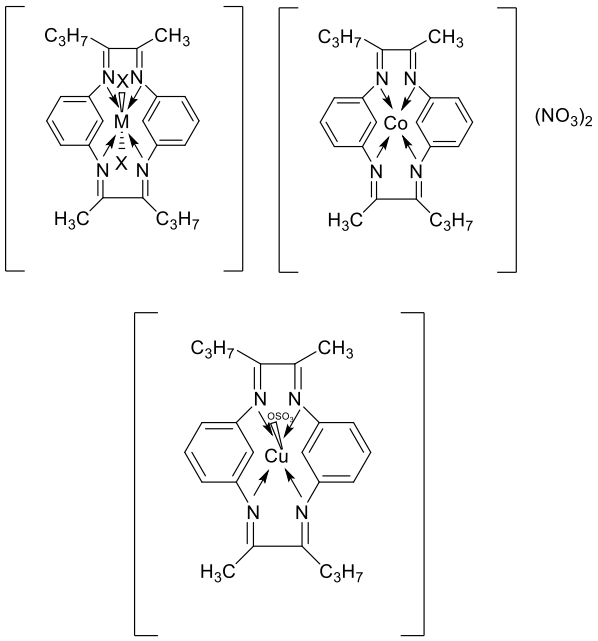


Figure 4. Structures of the tetradentate macrocyclic nitrogen donor ligand complexes where M = Co(II), Ni(II), and Cu(II) and X = Cl^-, NO_3^-, and NCS^- [3]

The successful development in the previous research [3] has facilitated other studies to investigate different diamines groups for the synthesis of tetraaza macrocyclic ligands. Recently, a hot ethanolic solution of benzyl was mixed with 2,6-diaminopyridine, *o*-phenylenediamine, and ethylenediamine, respectively [45]. An IR band corresponding to C=N at a range of 1650–1660 cm^{-1} in the ligands, which was referred to as the azomethine linkage, was observed to shift to the lower band due to the complex formation [30]. The ligands provided the binding sites towards the Pd(II) and Pt(II) metal ions through four nitrogen atoms of the azomethine groups. The structure of the complexes was diamagnetic and exhibited a square-planar geometry of *N,N,N,N*-pattern.

In another study, the reaction between *o*-phenylenediamine and benzoylacetone in ethanolic solution led to the formation of tetraazacyclotetradecine [36]. The Hydrogen-1 Nuclear Magnetic Resonance (^{1}H-NMR) spectrum confirmed the existence of imine methyl and methylene protons of benzoyl acetone ranging at 2.20–2.64 ppm, suggested the free ligand is formed. The antifungal screening action was evaluated by performing complexation with Co(II), Ni(II), and Cu(II) metal ions attached to four nitrogen donor. Co and Cu atoms were formulated as $[M(L)Cl_2]$, while Ni atoms were formulated as $[M'(L)]Cl_2$ due to their non-electrolytic and electrolytic nature, respectively. Based on the spectral studies, each metal complex displayed different coordination, as depicted in Figure 5. The Co(II) complex exhibited octahedral geometry with chlorine atoms at the axial position, whereas Ni(II) and Cu(II) complexes were arranged in a square-planar and tetragonal geometry, respectively.

The type and ring size of macrocyclic ligands are very useful in the application of biological process, which is termed as the metalloenzymes. Previously in 2010, Patil and Akkasali reported the non-template synthesis of tetraaza macrocyclic compound with variable ring sizes and higher yield [37]. The starting materials were prepared by reacting diketone with ethylenediamine, *o*-phenylenediamine, and diaminopropane. As a result of the ring closure reaction, 14- and 16-membered nitrogen groups of tetraaza macrocycles were successfully

isolated. All the free ligands exhibited moderate biological activity, thus, signifying the stability and effectiveness of this method.

Furthermore, Sen et al. synthesised a novel tetraaza macrocyclic ligand ranging from 14 to 15 rings [38]. The study involved the reaction of diethyl malonate with three different amino groups comprising 1,2-Bis{(2-aminobenzoyl)amino}propane, 2-amino-N-[3-(2-aminobenzoilamino)propil] benzamide, and 1,4-Bis{(2-aminobenzoil)amino}butane. The results were in agreement with Swamy et al. where three ligands with particular macrocyclic members were obtained through the non-template condensation reaction [35]. The reaction between various amino groups is summarized in Table 1.

Recently, the metal complexes comprising Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) were reported to exhibit as ionic compounds in the presence of chloride ions [39]. The tetraaza macrocyclic ligands were synthesised from *N,N'*-bis(2-aminoethyl)hexanediamide, which served as the starting material that originated from the reaction between adipic acid and ethylenediamine, followed by diethyloxalate and diethylmalonate, respectively (Scheme 6). This new approach was focused on antimicrobial activity against various microorganisms. The results showed that all metal complexes displayed efficient functionality compared to their parent ligands under the same experimental conditions due to the polarity of the metal ion.

According to Scheme 7, the cyclocondensation of ethylenediamine with acetone produced isomeric macrocyclic compounds [40]. The isomeric macrocycles were formed when ethylenediamine reacted with methyl ethyl ketone, which was 2a and 2b. Further reactions of 1a and 1b with monoperchlorate salt of ethylenediamine and acetone produced the stable free ligand in addition to the perchlorate salt. Further studies were performed based on the insights of this study, which involved the synthesis of an 18- and 22-membered azamacrocyclic compound containing two azomethine and amine nitrogen atoms in the ring. The ability of α,ω-diamine to develop azamacrocyclic mixture depended on the length of the carbon chain since the 16-membered compound only recorded a low yield of 25% [41]. In contrast, the reaction of 1,3-diaminopropane with acetone achieved a 100% yield.

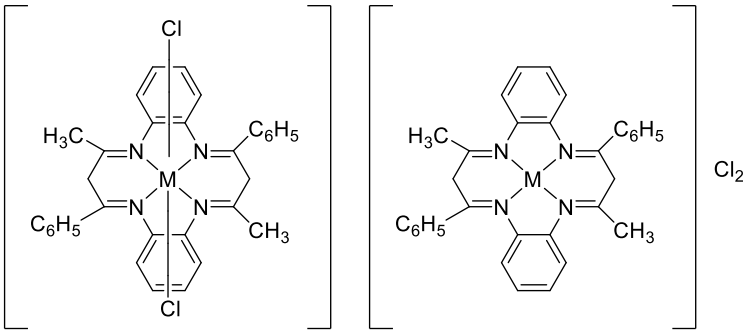
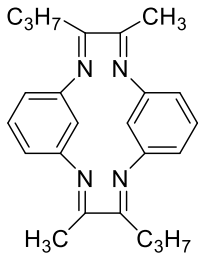
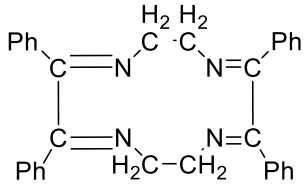
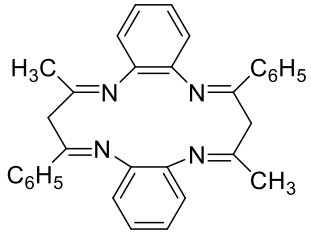
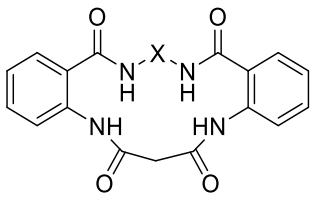
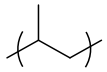
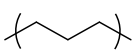
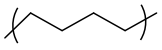
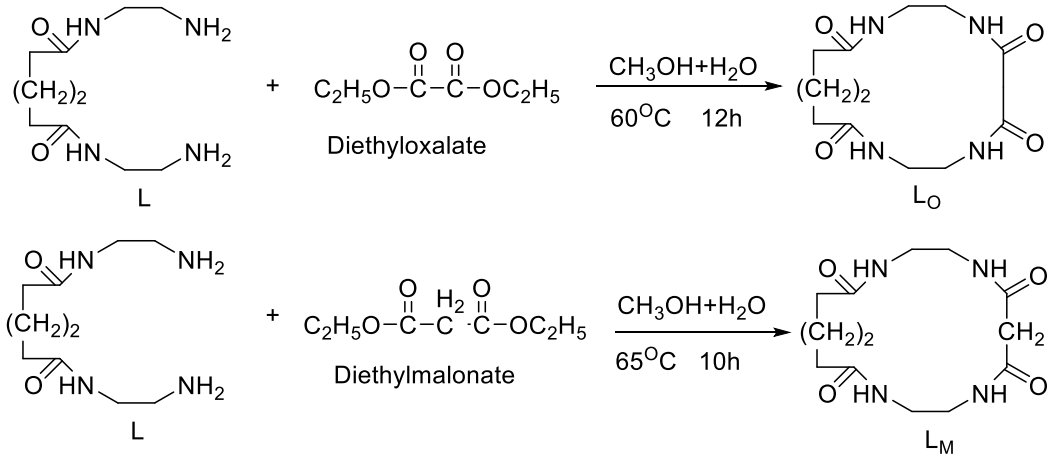


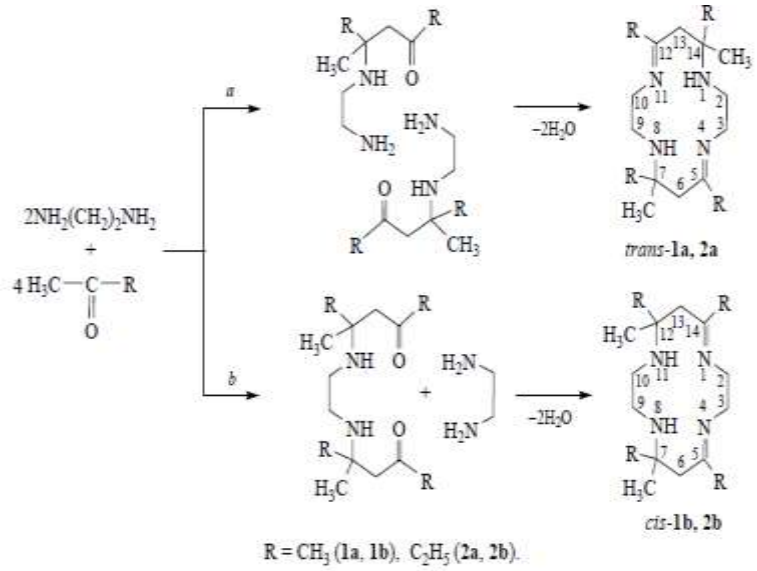
Figure 5. Proposed structures of the metal complexes, where M = Co(II), Cu(II) and M' = Ni(II) [36]

Table 1. Structural compounds of tetraaza macrocyclic ligand by non-template synthesis

Structural Compounds	Experiment Condition	Wavenumber (cm^{-1})	References
	Hot ethanolic solution of 2,3-hexanedione and hot ethanolic solution of *m*-phenylenediamine were mixed at 75°C for 9 hr in the presence of few drops of concentrated hydrochloric acid (pH~3)	1618 730-768 1441-1590	[3]
	Hot ethanolic solution of benzil and hot ethanolic solution of ethylene diamine were mixed at 75 °C for 8 hr in the presence of few drops of concentrated hydrochloric acid (pH~3)	1650-1660	[45]
	Hot ethanolic solution of benzoylacetone and hot ethanolic solution of *o*-phenylenediamine were mixed at 85 °C for 15 hr in the presence of few drops of concentrated hydrochloric acid (pH~3)	1594 1566	[36]
 -X- =  -X- =  -X- = 	Diethyl malonate in methanol was mixed with three different amino groups: 1,2-Bis{(2-aminobenzoyl)amino}propane,2-amino-N-[3-(2-aminobenzoilamino)propil] benzamide, 1,4-Bis{(2-aminobenzoil)amino}butane respectively at 60-70 °C for 4-5 hr	3468-3480 3292-3053 1603-1626 1532-1579 1433-1489	[38]



Scheme 6. The final step of synthesis of macrocyclic ligands [39]



Scheme 7. *Trans*- and *cis*-isomers of tetraaza macrocycles [40]

Furthermore, the condensation between 1,4-diaminobutane and 1,6-diaminohaxane with acetone obtained a 75-85% yield of *trans*-azamacrocyclic compound [41]. In comparison with the cyclocondensation process, the outcome of the experiment was similar in the reaction of α, ω-diamine using acetone or hydrated/dehydrated alcohol and ketone. Nonetheless, an exothermic effect was detected when anhydrous alcohol and ketone reacted with the α, ω-diamine.

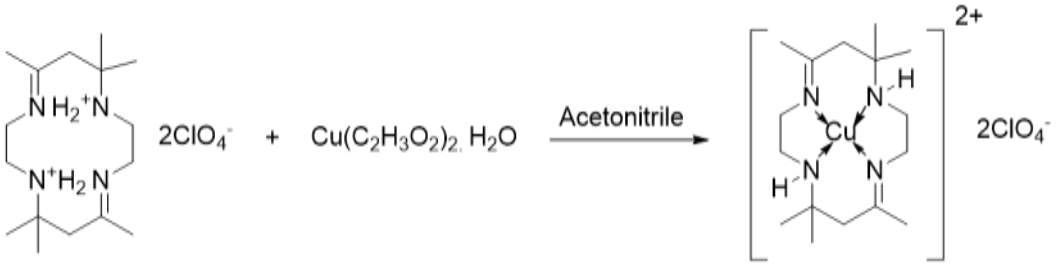
A preliminary study conducted by Yamin et al. [42] showed that tetraaza macrocyclic ligands were successfully synthesised via the non-template method at a higher yield. Scheme 8 shows the path of synthesis of the Cu(II) complex from its macrocyclic ligand. The technique to produce the tetraaza ligand and non-template complexation was considered a novel approach through the application of ammonium perchlorate that reacts with ethylenediamine to produce a free ionic tetraaza ligand and ClO_4^- counter anion. In addition, the

utilisation of this new method for the synthesis of ligand demonstrated a potentially simple and cheap alternative pathway for large scale production of macrocyclic ligand since the yield was recorded at 78%.

Based on the results from the magnetic moment, electronic spectral studies, and X-ray crystallography, the Cu(II) complex exhibited a square-planar geometry. However, when the same method was applied in the ionic liquid [Bmim] [PF_6], which is a different solvent, the complex displayed a different structural agreement where the Cu(II) complex exhibited an octahedral geometry bonded to two ethylenediamine ligands and two oxygen from the perchlorate ion with 79% yield [43]. These phenomena were strongly associated with the interaction or mechanism between metal/ligands during the synthesis reaction.

The discovery of new and simple method of preparation of 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclo tetradeca-7,14-dienium salts ligand has enabled the detailed study on the complexation reaction with various transition metal ions such as copper, nickel, and zinc complexes were carried out [44]. The analytical and physical data showed that up to 88% yield of the complexes were generated. In addition, the ultraviolet (UV)-visible spectrometric analysis indicated the existence of the azomethine chromophore and the *d-d* transition intensely indicate that the metal complex was successfully maintained in its original tetraaza ligand structure. The biological activity studies of the complexes were also reported.

The emerging non-template method using the various reaction of amino groups under several conditions shows significant results where free neutral and ionic ligands with their complexes are successfully synthesized. The presence of at least two secondary amine hydrogen atoms help to alleviate the lone pair repulsion on nitrogen donor atoms during cyclisation process. Apart from that, the cyclisation process of the tetraaza macrocyclic ligand has advantages which are inexpensive starting materials, high overall yield and desired product can be obtained easily since not involving difficult process of removing nitrogen-protecting groups [35].



Scheme 8. Synthetic route of Cu(II) complex from metal-free tetraaza ligand [42]

Conclusion

Several modifications and improvements have been conducted to prepare and provide an efficient mechanism for the synthesis of tetraaza macrocyclic ligand and its complexes. Based on the brief comparison of conventional method synthesis and the elaborative discussion on the new direct technique for the preparation of free tetraaza macrocyclic ligand, this paper highlighted the non-template method as the efficient method for the production of tetraaza macrocyclic ligands in the absence of metal ions during cyclisation with significantly high yield. In addition, the response between amide nitrogen atoms and alcohol functional group with the solvent provided a guideline for various ring size and ligand/complex nature. Given the limited studies of complexation reaction in the non-template method, future studies should focus on investigating the effect of various metal salts in the

complexation reaction at different conditions for a potential application such as catalyst in industrial activity and biomedical application.

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