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Review

Template synthesis of azacyclam metal complexes using primary amides as locking fragments

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ABSTRACT

Nickel(II) and copper(II) azacyclam complexes can be obtained through a metal template procedure involving the pertinent open-chain tetramine, formaldehyde and a primary amide (either carboxy- or sulfonamide) as a locking fragment. Azacyclam complexes, which display the same properties and solution behavior of the corresponding cyclam analogues, can be obtained with any desired side-chain appended to the ligand's framework, by choosing the appropriate amide derivative, through a convenient one-pot synthesis. This opens the way to the design of multi centered redox systems, redox switches of fluorescence, and anion receptors of unusually high Brønsted acidity.

1. Metal template syntheses

Metal ions typically interact with molecules displaying binding tendencies (ligands) and place them in the space around themselves, according to a definite geometrical order. This property lies at the basis of coordination chemistry and, over the last 100 years, gave rise to thousands and thousands of compounds of interest for medical care, diagnostics, industrial catalysis, optics and electronics, solar energy harvesting, hydrometallurgical extraction, *et cetera* [1]. In some particular cases, metal coordinated ligands react with molecules coming from the solution to give a ligand of higher denticity, whose structure still satisfies the geometrical requirements of the metal center and which can reach a high level of sophistication. The metal addresses the synthetic pathway to a chemical object of a predetermined geometry and is said to act as a *template*. The term template was first used in chemistry by Busch and Thompson, to illustrate the role of nickel(II) in the synthesis of macrocyclic complexes like **2** (see Scheme 1) [2].

In fact, the Ni^{II} ion, which has a pronounced preference for square coordination, places and orientates the two thiolate sulphur atoms in positions favorable to the reaction with one molecule of 1,2-bis(bromomethyl)benzene, thus affording the synthesis of the macrocyclic complex **2** with a 60% yield. Notice that the cyclization process – which involves the stepwise nucleophilic attack of a thiolate sulphur atom on a $BrCH_2-$ group – is intrinsically irreversible. Things go better, and yields can become higher, when the cyclization process is reversible. One of the first examples in this sense was provided by Karn and Busch with the synthesis of the nickel(II) tetra-aza-macrocyclic complex, shown in Scheme 2 [3].

First, Ni^{II} forms a 1:1 complex with the open-chain triamine **3**, picking up one water molecule from the solution to achieve four-coordination according to a square geometry (**4**). Then, in step (ii), the sp^2 nitrogen atom of a 2,6-diacetylpyridine molecule displaces the labile water molecule and binds the Ni^{II} center, thus bringing the two carbonyl groups within reaction distance of the two primary amine groups of the coordinated triamine. At this stage,

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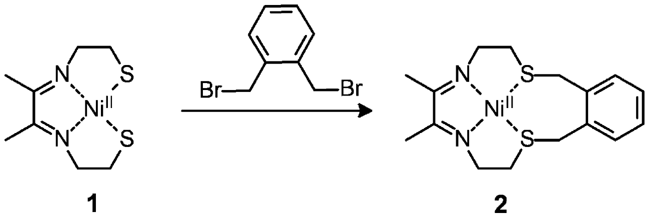
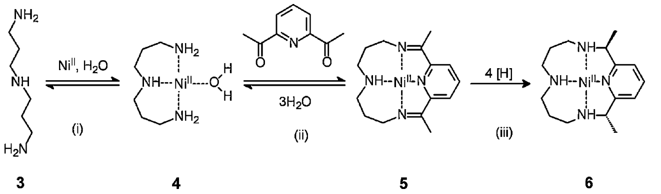


Scheme 1. The first metal template synthesis of a macrocycle. The Ni^{II} ion places the two thiolate sulphur atoms in positions suitable for cyclization, which involves the irreversible nucleophilic attack on the BrCH$_2$– groups of 1,2-bis(bromomethyl)benzene.



Scheme 2. The nickel(II) template synthesis of CR (**5**) and CRH (**6**) tetra-aza-macrocyclic complexes. The cyclization step (ii) involves the reversible Schiff base condensation of the carbonyl groups of 2,6-diacetylpyridine with the –NH$_2$ groups of the triamine **3**, preoriented through coordination to the metal.

a Schiff base condensation reaction takes place and a tetra-aza macrocycle is formed. The formation of the C=N imine bond is reversible, as it can undergo fast hydrolysis to give back the ketone and the amine. Reversibility guarantees, through a trial and error mechanism, the achievement of the most stable structural arrangement, in the present case the formation of the 14-membered tetra-aza macrocycle. The coordinative situation can be 'frozen' (i.e. the hydrolysis of the imine bond prevented) by hydrogenating the two C=N fragments [4], giving complex **6**. Complexes **5** and **6** are currently indicated as [Ni^{II}(CR)]$^{2+}$ and [Ni^{II}(CRH)]$^{2+}$, respectively [5]. Two diastereoisomers are formed, depending whether the two methyl substituents extend on either the same or opposite sides of the plane of the complex: *meso* (*R*,*S*) or racemic (*R*,*R* + *S*,*S*), respectively. The meso (red) and racemic (yellow) complexes are obtained according to a 10:1 ratio. Both complexes are diamagnetic, a spin state of Ni^{II} that corresponds to the formation of complexes of square coordination geometry. Structural features and configurational details of the two diastereoisomers were later made clear through the determination of crystal and molecular structures [8,9]. In particular, Fig. 1 shows the structures of the nickel(II) complexes with the *R*,*S* form and the *R*,*R* enantiomer of CRH. Both complexes can be demetalated with excess cyanide to give the free ligands.

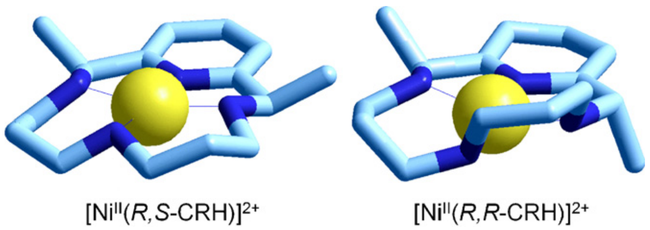
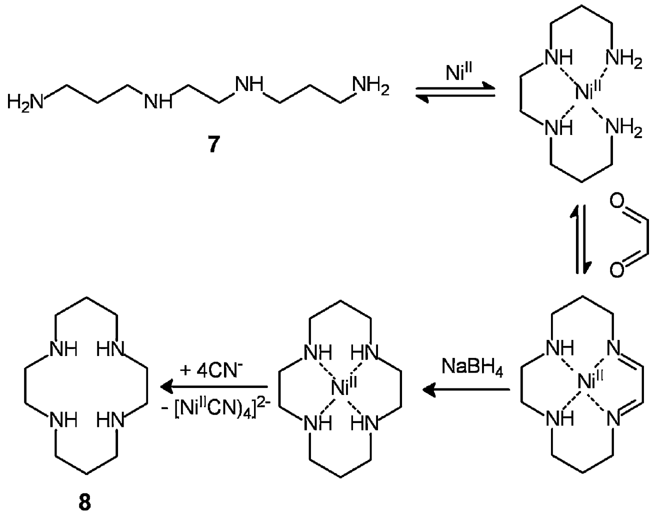


Fig. 1. The molecular structure of the Ni^{II} complexes of CRH (2,12-dimethyl-3,7,11,17-tetra-azabicyclo1[1.3.1]heptadeca-1(17),13,15-triene). Due to the presence of two asymmetric carbon atoms, the tetra-aza ligand gives rise to two diastereoisomers: the (*R*,*S*) meso form, with the two methyl groups on the same side of the plane of the complex and the racemic (*R*,*R* + *S*,*S*) form, with the methyl groups in the opposite sides. The *R*,*S* (meso) configuration allows the establishing of stronger metal–ligand interactions, according to a less distorted square geometry, which accounts for the higher thermodynamic stability. Structures redrawn from data deposited at the Cambridge Crystallographic Data Centre: *R*,*R*, Ref. [8]; *R*,*S* Ref. [9].



Scheme 3. The nickel(II) template synthesis of cyclam, 1,4,8,11-tetra-aza-cyclotetradecane (**8**) [10]. The cyclization step involves the reversible Schiff base condensation of the carbonyl groups of glyoxal with the –NH$_2$ groups of the linear tetramine **7**, preoriented through coordination to the metal.

CRH transition metal complexes profit from the benefits of the coordination by a 14-membered tetra-aza-macrocycle: high thermodynamic and kinetic stability, which is expressed for instance by a high resistance to the demetalation by strong acids. However, the most pronounced macrocyclic properties are observed with cyclam (**8**), which possesses four secondary amine nitrogen donor atoms and, on complexation, gives an alternating sequence of five- and six-membered chelate rings. Cyclam is obtained through a Ni^{II} template synthesis [10], and, also in this case, the cyclization step involves a Schiff base condensation, as illustrated in Scheme 3.

Cyclam has a pronounced tendency to stabilize unusually high oxidation states of the encircled metal [11]. For instance, the stable yellow [Cu^{III}(cyclam)]$^{3+}$ complex can be obtained through chemical (with S$_2$O$_8$$^{2-}$) or electrochemical oxidation of the corresponding Cu^{II} complex in a strongly acidic solution [12]. The [Ag^{II}(cyclam)]$^{2+}$ complex has been isolated in a crystalline form and its structure has been elucidated through X-ray diffraction experiments [13]. Moreover, [Ag^{II}(cyclam)]$^{2+}$ undergoes reversible oxidation in water to give the stable [Ag^{III}(cyclam)]$^{3+}$ species [14]. [Hg^{III}(cyclam)]$^{3+}$ has been electrochemically generated as a red transient and characterized in the cavity of an ESR spectrometer [15]. However, the most investigated uncommon oxidation state among transition metal cyclam complexes is Ni^{III}, d^7 low-spin, showing a preference towards axially elongated octahedral geometry [16]. Indeed, Ni^{III} cannot be any longer regarded as a rather uncommon oxidation state, if one considers that the Ni^{III}(cyclam)]$^{3+}$/Ni^{II}(cyclam)]$^{2+}$ couple in 1 M HCl has an electrode potential of 0.71 V vs. NHE, i.e. less positive than that corresponding to the Fe^{3+}/Fe^{2+} couple under the same conditions (0.77 V vs NHE) [17]. For this reason, the Ni^{II}(cyclam)$^{2+}$ moiety has been used as a redox active unit in the design of multicomponent systems, as a sort of inorganic analogue of ferrocene (Fc, easily oxidizable to Fc$^+$), and it has been appended to a variety of organic substrates in order to generate functional systems (simple molecular devices [18], electrochemical sensors [19], and anion carriers through liquid membranes [20]). The design of the pertinent multicomponent systems requires the derivatization of the redox subunit, a task easily performed in the case of ferrocene, prone to substitution reactions at the aromatic ring. On the contrary, in the case of cyclam, derivatization has to be carried out at one of the amine nitrogen atoms of the demetalated ligand and requires selective protection, functionalization, deprotection, then complex formation. Moreover, the obtained Ni^{II}