

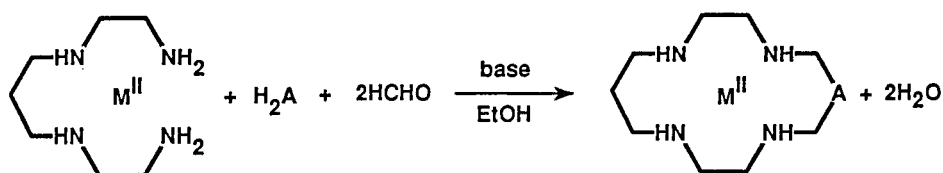
Novel routes to functionalized cyclam-like macrocycles

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Abstract Amides and sulphonamides act as molecular padlocks in closing an open-chain tetramine around a Ni^{II} or a Cu^{II} ion, in presence of formaldehyde and triethylamine. Through the above template procedure and using the appropriate RCONH₂ or RSO₂NH₂ locking fragments, cyclam-like macrocycles carrying the desired R functional group can be obtained in a one-pot synthesis.

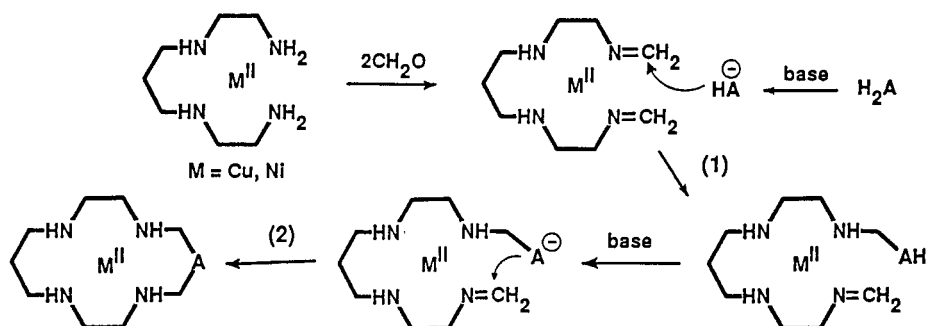
1,4,8,11-tetraazacyclotetradecane, *cyclam*, forms the most stable complexes with transition metal ions from both a thermodynamic and a kinetic viewpoint, among cyclic polyamines of varying ring size and denticity (ref. 1). Moreover, it promotes the redox activity of the encircled metal centre, in particular favouring the access to unusually high oxidation states (Ni^{III}, Cu^{III}, Ag^{II}, Ag^{III}) (ref. 2). Cyclam can be conveniently prepared through the Ni^{II} template reaction between the open-chain tetramine 3.2.3-tet and glyoxal, followed by hydrogenation of the C=N double bonds which form in the Schiff-base condensation (ref. 3). The [Ni^{II}(cyclam)]²⁺ complex, which is obtained in high yield, can be demetallated in a boiling cyanide solution to give the free ligand. Interestingly, the reactivity of a cyclam incorporated metal centre can be further controlled or made richer by appending to the ligand's framework chosen functionalities: coordinating groups, redox active fragments, acidic subunits. Such a functionalization typically involves: (i) the selective protection of the uncomplexed macrocycle, e.g. through the tosylation of all but one the secondary amine nitrogen atoms (ref. 4), (ii) the reaction with a molecule RX carrying the wanted functionality R, (iii) the deprotection and (iv) the metal complexation, a multi-step procedure which may substantially lower the overall yield. Alternatively, the RX synthon can be reacted with a large excess of cyclam, to avoid the formation of poly-substituted derivatives. In this case, tedious separation of the mono-substituted macrocyclic derivative from the unreacted cyclam is required. We report now a convenient template synthesis in which a cyclam-like system, already carrying the wanted functionalization, is obtained in a one-pot reaction. Such a synthetic procedure is based on the general template reaction illustrated in the Scheme below. In particular, the AH₂ fragment should be a diprotic acid, the acidic hydrogen atoms being bound to a *carbon* atom, e.g. nitroethane, CH₃CH₂NO₂ (ref. 5) or diethylmalonate, CH₂(COOC₂H₅)₂ (ref. 6), or to a *nitrogen* atom, e.g. a primary amine, RNH₂ (refs. 7, 8).



The AH₂ fragment, in presence of formaldehyde and triethylamine, acts as a very efficient *molecular padlock*, closing the open-chain tetramine 2.3.2-tet around a labile metal centre, prone to a tetragonal type of symmetry (e.g. Ni^{II}, Cu^{II}). We have found that also *amides*, both carboxyamides and sulphonamides, aliphatic or aromatic in nature, work well as locking fragments in the above template synthesis. In general, reactions are carried out under very mild conditions: an ethanolic solution 5 x 10⁻² M in the NiCl₂ or Cu(NO₃)₂ salt, in the 2.3.2-tet tetramine, in the AH₂ padlock and in triethylamine, and 0.5 M in formaldehyde, is kept at 50°C for 5-7 days. In some cases, a silky precipitate of the macrocyclic metal complex forms during the course of the reaction; in other cases, precipitation of the complex is achieved through concentration or after addition of concentrated perchloric acid. The obtained complexes display the genuine macrocyclic properties of the corresponding cyclam species: inertness toward demetallation, even in strongly acidic solutions; easy access to the trivalent state, in the case of nickel complexes. When the AH₂ fragment is an amine or an amide, a penta-aza-macrocycle is obtained, which is called *azacyclam*. In fact, in this macrocycle, a tertiary amine nitrogen atom replaces the middle -CH₂-group of one of the trimethylenic chains of cyclam. X-ray evidences and studies of the solution behaviour have demonstrated that this tertiary amine nitrogen atom is not involved in coordination to the metal centre (ref. 8). On the contrary, it plays a purely structural role and does not disturb the cyclam-like coordination tendencies of the four secondary amine nitrogen atoms.

KINETIC ASPECTS OF THE TEMPLATE REACTION

A possible mechanism of the template reaction is outlined in the Scheme below.



First, two formaldehyde molecules react with the terminal primary amine groups of the open-chain tetramine coordinated to the metal, according to a Schiff-base condensation. Second, in a very crucial step, the monodeprotonated species AH⁻ makes a nucleophilic attack on one of the two C=N double bonds (step 1, in the Scheme). Subsequently, the pendant -AH group further deprotonates and attacks the second C=N double bond (step 2, in the Scheme). It is possible that step (2), due to the chelate effect, is faster than step (1), which probably remains the rate determining step of the overall template reaction.

Reactions involving Cu^{II} as a templating centre have been investigated in their dynamic aspects. In particular, portions of the aqueous ethanolic solution, containing

the reagents as described in the previous section and kept at 50°, were syringed out a predetermined time intervals (3 hrs or more) and treated with a fixed volume of a 3 M HCl solution. All the non-cyclized complex species decompose in presence of strong acid, whereas the macrocyclic complex remains intact and persists in solution. As a matter of fact, the d-d spectrum of the acidified portion presented the typical absorption band, centred at *ca* 520 nm, of a cyclam or cyclam-like Cu^{II} complex. Through comparison with the spectrum of the preformed and analysed corresponding complex in the same conditions, the percent yield of the macrocyclic complex at varying time was obtained. A typical profile, referring to the template reaction involving benzenesulphonamide as a locking fragment, is shown in Figure 1.

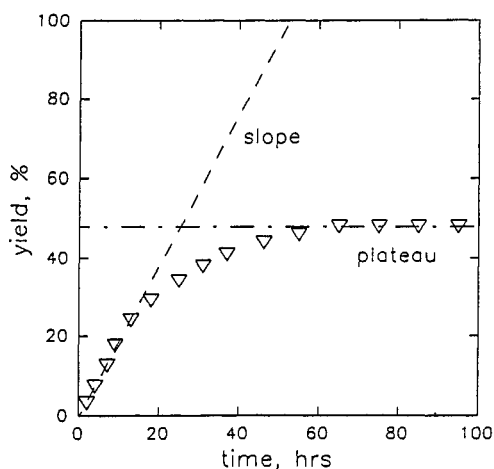


Fig. 1. Time dependent profile of the Cu^{II} template reaction involving C₆H₅SO₂NH₂ as a locking fragment

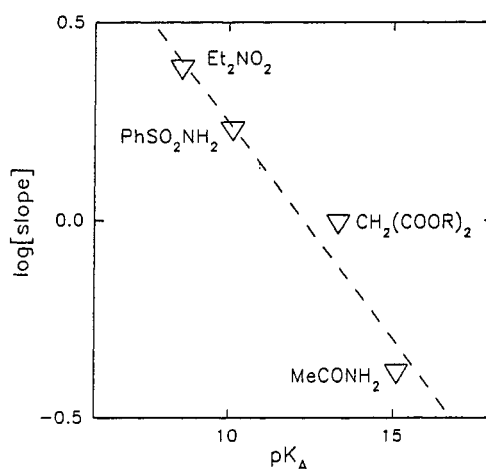


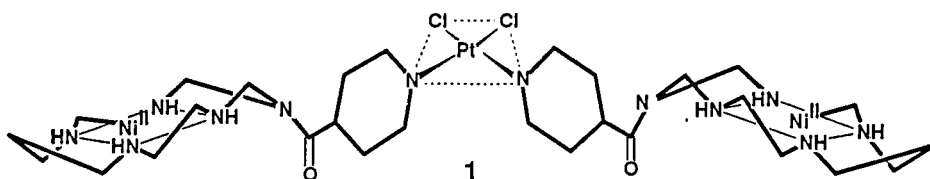
Fig. 2. Relationship between the acidity constant of the AH₂ locking fragment and the slope of the reaction profile, as shown in Fig.1

As a general behaviour, the concentration of the cyclam-like complex linearly increases to reach a *plateau*. Interesting parameters of the profile are: (a) the *slope* of the initial straight-line, which has a kinetic meaning and should be related to the rate of the slowest step of the overall reaction, and (b) the *plateau* value, which indicates the effective yield of the cyclam-like metal complex formed in solution, in absence of exotic effects (e.g. the more or less pronounced tendency of the salt to crystallize). Quite interestingly, for the limited number of locking fragments whose pK_A values are known (in aqueous solution), a reasonable linear correlation exists between the acidity constant and the slope. Such a relationship is illustrated in Figure 2, where the two envisaged quantities are reported in log units, for sake of clarity. In particular, the stronger the AH₂ acid, the faster the cyclization process. Such a finding reinforces the hypothesis that step (1) of the mechanistic scheme determines the rate of the template reaction. In fact, the concentration of the attacking fragment AH⁻ is proportional to K_A: the greater [AH⁻], the faster the process.

The interpretation of the trend of the *plateau* values, which are related to the stability of the formed poly-aza ring, is less straightforward: yields in solution range from 58% to 27% and decrease along the series CH₃CH₂NO₂ > C₃H₇NH₂ > C₆H₅SO₂NH₂ > C₆H₅CONH₂ > CH₃CONH₂ > C₆H₅NH₂ ≡ CH₂(COOC₂H₅)₂. Reactions with some H₂A groups (e.g. CH₃SO₂NH₂) could not be followed in their dynamic aspects, as described above, due to the precipitation of the macrocyclic metal complex in the course of the reaction.

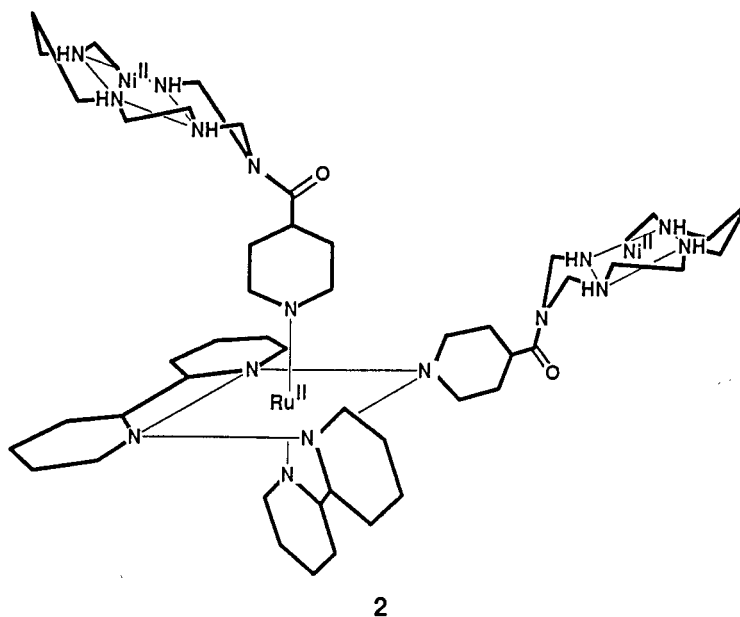
**PYRIDINES WITH AN APPENDED METALLO-AZACYCLAM SUBUNIT:
CONVENIENT BUILDING BLOCKS TO SUPRAMOLECULAR COORDINATION
COMPOUNDS**

Using the amide of 4-pyridinecarboxylic acid (isonicotinamide) as a locking fragment affords the synthesis of a metallo-azacyclam complex carrying a pendant pyridine subunit (indicated as: $\{M^{II}L\}$ -py). Steric features prevent from the binding of the pyridine heteroatom to the azacyclam metal centre, according to a *scorpiand* coordinative mode. Thus, the pyridine subunit can bind further metal centres. For instance, reaction of two equivalents of $\{M^{II}L\}$ -py with $[Pt^{II}Cl_4]^{2-}$ gave the *cis*- $[(\{M^{II}L\}$ -py) $_2Pt^{II}Cl_2]^{4+}$ system, **1**, whose hypothesized structure is sketched below. Such a system, in which two metal azacyclam complexes are held together through coordinative interaction, can be defined as a *supramolecular coordination compound*, or a *supercomplex*. The *cis*- $[(\{Ni^{II}L\}$ -py) $_2Pt^{II}Cl_2]^{4+}$ supercomplex in a DMSO solution undergoes a two-electron oxidation process, according to two consecutive one-electron reversible steps, whose potentials are separated by the statistical term ($E_2 - E_1 = 36$ mV). The oxidation process has to be ascribed to the Ni^{II}/Ni^{III} change, taking place in the two metallocyclam subunits. The Pt^{II} centre is not redox active in the present circumstances and plays a merely architectural role.



On the other hand, reaction of two equivalents of $\{M^{II}L\}$ -py with *cis*- $[Ru^{II}(bipy)_2Cl_2]$ (bipy = 2,2'-bipyridine) gave *cis*- $[(\{M^{II}L\}$ -py) $_2Ru^{II}(bipy)_2]^{6+}$, **2**. The oxidation behaviour of the nickel containing supercomplex: *cis*- $[(\{Ni^{II}L\}$ -py) $_2Ru^{II}(bipy)_2]^{6+}$ is especially interesting.

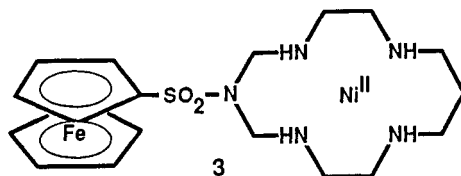
As a matter of fact, the ruthenium centre is redox active (through the Ru^{II}/Ru^{III} couple) and adds intriguing features to the redox behaviour of the supramolecular system.



In particular, electrochemical investigation in an MeCN solution made 0.1 M in Bu_4NClO_4 , showed that the one-electron oxidation process involving ruthenium takes place first, followed by the statistically controlled two-electron oxidation of the nickel-azacyclam subunits, at a potential *ca* 300 mV more positive. However, if Bu_4NCl is used as a supporting electrolyte, the *opposite* oxidation sequence is observed: the two-electron oxidation occurs first and the $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$ redox change takes place at potential 250 mV more positive. This unusual behaviour reflects the different stereochemical nature of the Ni and Ru centres. The Ni-azacyclam system is open to the axial coordination and can benefit from the Ni^{III} stabilization exerted by the chloride ions. Such a favourable effect cannot be experienced by the ruthenium centre, which is coordinatively saturated. $\text{cis}-[(\text{Ni}^{\text{II}}\text{L})\text{-py}]_2\text{Ru}^{\text{II}}(\text{bipy})_2]^{6+}$ is an interesting three-electron redox system, whose mode of electron release, (1+2) or (2+1), can be controlled through the background electrolyte.

TEMPLATE SYNTHESIS OF A METALLOCYCLAM/FERROCENE CONJUGATE

Reaction of ferrocenesulphonamide with NiCl_2 , 2,3,2-tet, formaldehyde and triethylamine under the usual conditions gave in good yield the conjugate system **3** in which the Ni-azacyclam subunit and the ferrocene moiety are linked through an $-\text{SO}_2-$ bridge.



Cyclic voltammetry investigation in non-aqueous solutions showed that **3** undergoes two consecutive one-electron oxidation processes. The less anodic process corresponds to the oxidation of the organometallic subunit, the more anodic one to the $\text{Ni}^{\text{II}}/\text{Ni}^{\text{III}}$ change inside the appended azacyclam ring. Again, a coordinatively saturated centre (ferrocene) and a coordinatively unsaturated centre (Ni-azacyclam) are coupled. This generates a unique sensitivity of the two-electron redox system **3** to the solvent donor tendencies. In particular, the $E_{\text{Ni}} - E_{\text{Fc}}$ difference decreases moving from poorly donating solvents (550 mV in MeNO_2) to strongly donating solvents (80 mV in DMSO).

Acknowledgments

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