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Kinetics and mechanism of metal complex formation with N_4-donor macrocycles of the cyclam type

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Abstract

The N_4-donor macrocyclic ligand cyclam (1,4,8,11-tetraazacyclotetradecane) forms very stable complexes with nickel(II) and copper(II). With regard to kinetics and mechanism of complex formation, tetraaza cyclic ligands such as cyclam represent an interesting type of chelate ligands in that they are less flexible than aliphatic open-chain N-donor ligands and less rigid than cyclic N-donor ligands of the porphyrin type. The Eigen–Wilkins mechanism provides an adequate description of the kinetics of complex formation of nickel(II) and copper(II) with monodentate ligands and allows to correlate the rate of complex formation with the rate of solvent exchange on the solvated cations NiS_6^{2+} and CuS_6^{2+} (S = solvent). This review focuses on the factors controlling the rate and mechanism as well as the stereochemistry of complex formation of nickel(II) and copper(II) with N_4-donor macrocyclic ligands of the cyclam type. The kinetic results obtained in aqueous solution are briefly reviewed, although their mechanistic interpretation is hampered by ligand protonation. The kinetic studies carried out in aprotic polar solvents such as *N*,*N*-dimethylformamide are reviewed and discussed in detail. In comparison to the Eigen–Wilkins mechanism and Eigen–Winkler mechanism, the aspect of metal-based rate control versus ligand-based rate control is emphasized.

Keywords: Macrocyclic ligand complexes; Kinetics of complex formation; Reaction mechanisms; Cyclam; Eigen–Wilkins mechanism; Eigen–Winkler mechanism

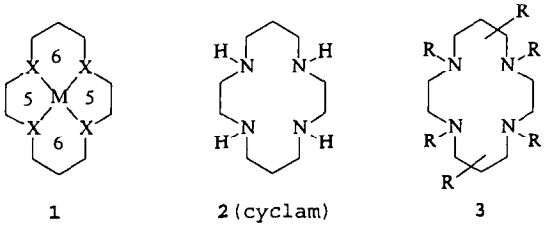
1. Introduction

Macrocyclic ligand complexes are part of a number of fundamental biological systems. The importance of such complexes has provided a motivation for investigation of the metal-ion chemistry of these biological systems as well as of cyclic ligand systems in general. The possibility of using synthetic macrocycles as models for biologically important ones has initiated a broad spectrum of research activities,

ranging from synthesis of new ring systems with pendant arms and studies on the properties and function of macrocyclic ligand complexes to their application in industry, medicine and other fields.

From the kinetic point of view, macrocyclic ligands represent an interesting class of ligands. Compared with linear multidentate ligands, cyclic ligands, especially substituted ones, are less flexible and less apt to folding. One can expect, therefore, that the process of metal coordination by cyclic ligands is more complex and not necessarily metal-controlled, as it is in the case of the Eigen–Wilkins mechanism. The steric constraints of the cyclic system may well lead to ligand-control in that the second (or a later) coordination step becomes rate-limiting.

The properties and structure of macrocyclic ligand complexes critically depend on ring size, number and type of donor atoms as well as on size and number of chelate rings formed upon coordination. Fourteen-membered rings with four donor atoms X, spaced as shown in **1**, provide a cavity large enough to allow the planar X_4 coordination of a range of metal ions. In particular, the N_4-donor macrocycle cyclam (1,4,8,11-tetraazacyclotetradecane), **2**, has been the subject of numerous investigations on the chemistry and structure of complexes with 3d transition metals such as nickel, copper and cobalt.



1 2 (cyclam) 3

The literature on the kinetics and mechanism of complex formation with a variety of macrocyclic ligands, as published up to the late 1980s, has been competently summed up by Lindoy [1] and Wilkins [2]. In a more specific way, the present contribution summarizes the results of studies on the kinetics of reaction (1), as studied in non-aqueous media with $M = Ni^{2+}$ (and, to a lesser extent, Cu^{2+}) and $L = \mathbf{3}$.

$$M + L \rightarrow ML \quad (1)$$

Ligands **3** are derivatives of cyclam(**2**), bearing a variable number of methyl groups R bound to the N-donor atoms and/or C atoms of cyclam. For comparison, the results describing the kinetics of complex formation of N_4-donor macrocyclic ligands in aqueous solution are reviewed briefly.

2. Background

The kinetics of complex formation with monodentate ligands can be described adequately and understood in terms of the Eigen–Wilkins mechanism. In the study

of complex formation with multidentate open-chain and cyclic chelate ligands, one of the key points of interest has been the question: do these reactions follow the Eigen–Wilkins mechanism or not?

The following sections give a brief summary of results pertinent to this question.

2.1. The Eigen–Wilkins mechanism

As described in detail by Burgess [3], the work of Eigen, Tamm and Wilkins [4,5] led to a simple hypothesis which was able to accomodate the results obtained for the kinetics of complex formation of a wide range of metal ions. What has become known as the Eigen–Wilkins mechanism is set out in reaction sequence (2) (M, metal ion; S, solvent; L, monodentate ligand, present in excess; charges omitted for clarity).

$$MS_x + L \overset{K_{os}}{\rightleftharpoons} \{MS_x, L\} \overset{k_i}{\rightarrow} MS_{x-1}L + S \tag{2}$$

The equilibrium constant K_{os} describes the rapid equilibration of the solvated metal ion MS_x and the ligand L to form the outer-sphere complex $\{MS_x, L\}$. The ligand L, outer-sphere bound in $\{MS_x, L\}$, enters the inner coordination sphere by an interchange process, i.e. L replaces a coordinated solvent molecule. The rate of this interchange, characterized by the first-order rate constant k_i, controls the rate of complex formation. The fundamentally important point is that the size of k_i is close to that of k_{ex}, as long as the mechanism of solvent exchange is dissociatively controlled (I_d-type). The rate constant k_{ex} describes the rate of solvent exchange on the solvated metal cation MS_x according to reaction (3).

$$MS_x + S^* \overset{k_{ex}}{\rightleftharpoons} MS_{x-1}S^* + S \tag{3}$$

Knowing k_{ex} for a given metal ion in a given solvent, one has a remarkably good measure for k_i. The size of K_{os}, which is determined mainly by the charges on M and L, can be calculated on the basis of electrostatic considerations. This means that the known values of k_{ex} [6] and calculated values of K_{os} allow one to predict (2) complex formation rates rather reliably for those metal ions, the solvent exchange of which is I_d-controlled.

2.1.1. The validity of the Eigen–Wilkins mechanism for complex formation with chelate ligands

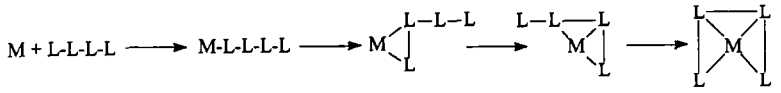
As shown in the reaction sequence (4) for an octahedrally solvated metal ion, changing from monodentate to bidentate ligands, L–L, introduces another step in which ring closure occurs.

$$MS_6 + L\text{-}L \overset{K_{os}}{\rightleftharpoons} \{MS_6, L\text{-}L\} \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} S_5M\text{-}L\text{-}L + S \xrightarrow{k_{rc}} S_4M\begin{smallmatrix}L\\|\\L\end{smallmatrix} + 2S \tag{4}$$

The ratio k_{rc}/k_{-i} dominates the kinetics in that, for $k_{rc} \gg k_{-i}$, the formation of the S_5M–L–L entity is rate-controlling whereas, for $k_{rc} \ll k_{-i}$, ring closure determines the rate.

It has been shown convincingly for the complex formation of Ni(II), Co(II) and Cu(II) with bidentate ligands L–L′ such as α-amino acids and β-amino acids [2,3] that the shift from rate-control through first-bond formation (based on k_{ex}) to rate-control through ring closure is determined by the size of the chelate ring formed and by steric factors, affecting the flexibility of L–L′. When the geometry and structure of L–L′ make chelate ring closure the rate-limiting step, reaction (4) is sometimes called a sterically controlled substitution (SCS mechanism) [3].

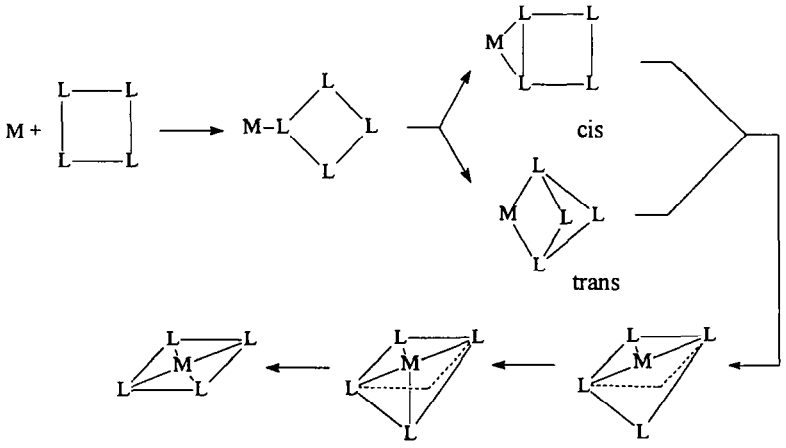
Reaction sequence (5) indicates schematically that, in the case of linear tetradentate ligands, L–L–L–L, the multiplicity of steps increases the difficulty in predicting the rate-determining step and understanding the mechanism.



(5)

In principle, the formation of the first M–L bond could still be rate-limiting (rate-control through solvent exchange on the metal; Eigen–Wilkins mechanism). There is a good chance, however, that one of the consecutive steps determines the rate of the overall process (rate-control through steric constraints of the ligand; SCS mechanism).

Compared with linear tetradentate ligands, cyclic tetradentate ligands are different in that they have no end and the cyclic structure keeps the four donor atoms in a rather close neighborhood. As indicated schematically in reaction sequence (6), second-bond formation can occur either with a *cis* or with a *trans* located donor atom.



(6)

With second-bond formation occurring, both the third and the fourth donor atom are being pulled close to the metal so that their coodination is favored strongly and expected to be fast, compared with second-bond formation.

2.2. Kinetics of complex formation with crown ethers—the Eigen–Winkler mechanism

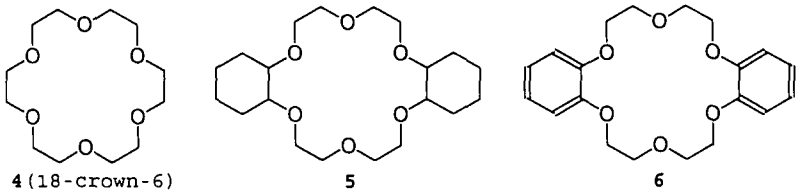
Crown ethers are all-oxygen donor macrocycles and, as hard ligands, they form stable complexes preferentially with alkali and alkaline earth cations. The studies on the kinetics of complex formation of a variety of synthetic and biological crown ethers with metal cations such as Na^+ and K^+ in different solvents [3] led to the general result that the formation rate constants are high and remarkably insensitive to ligand structure [7].

The work carried out by the groups of Eigen ([8]a–d), Petrucci ([9]a–e) and Eyring [10] revealed that, compared with the Eigen–Wilkins mechanism, complex formation with crown ethers (and cryptands) is mechanistically more complex. In addition to the formation of the outer-sphere complex and the first metal–ligand bond, as based on the rate of solvent loss from the metal, one or more ring closures with attendant changes in ligand conformation have to be considered. As an extension of the Eigen–Wilkins mechanism, the Eigen–Winkler mechanism emerged from the mechanistic discussion of complex formation with biological and synthetic crown ethers. According to this mechanism, which is set out in reaction sequence (7), without charges and the solvation number of the metal, diffusion-controlled formation of the outer-sphere complex {M, C} is followed by stepwise coordination of the i donor atoms of the crown ether C, until full coordination in MC_i is achieved.

$$M + C \overset{K_{os}}{\rightleftharpoons} \{M, C\} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MC_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} MC_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} MC_3 \ldots \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} MC_i \quad (7)$$

In each of the single steps, a metal-bound solvent molecule is successively replaced by another M–C bond, so that a balance of solvation and ligand-binding energy is always maintained.

As in the case of the Eigen–Wilkins mechanism, the condition $k_1 (\equiv k_i) \approx k_{ex}$ should be fulfilled. This could mean that, for a very flexible crown ether C forming a very stable complex MC_i, only one reaction step is observed and, due to $k_1 \approx k_2 \approx k_3 \approx k_i$, the overall complex formation rate constant k_f is close to k_{ex}. On the other hand, increasing ligand rigidity should make one of the subsequent steps slower and thus observable. Convincing proof for the latter expectation comes from the kinetic investigation of the crown ethers **4–6** reacting with Na^+ ions in *N*,*N*-dimethylformamide [10].



4 (18-crown-6) **5** **6**

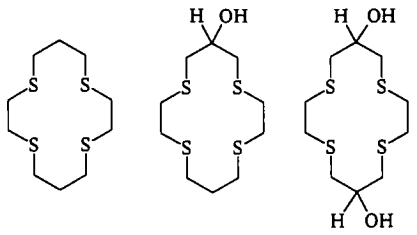
By fusing cyclohexane rings (**5**) or benzene rings (**6**) into the crown, ligand flexibility is reduced. Two steps are observed, the first one with k_f between 4 and 6×10^8 M^{-1} s^{-1} for these three ligands, and the second one with $k = 3.5 \times 10^6$ s^{-1}

(**4**), 2×10^6 s^{-1} (**5**) and $< 1 \times 10^6$ s^{-1} (**6**) at 313 K. This example shows that, after first-bond formation, there are subsequent slower steps which are obviously affected by the dynamics of conformational change in the ligand.

2.3. Kinetics of complex formation with sulfur-donor macrocycles

Macrocycles containing sulfur atoms as donors possess several properties which are relevant to the study of their complex formation kinetics, namely, (i) S-donor macrocycles are soft ligands and only metal ions such as Cu(II), Pd(II), Ag(I) and Hg(II) show a significant affinity for these ligands, (ii) copper(II) complexes with S_4-donor macrocycles absorb strongly in the visible reagion, which facilitates spectrophotometric monitoring, (iii) in contrast to N-donor macrocycles, S-donor macrocyclic ligands are free of protonation, and (iv) the solubility of unsubstituted S-donor macrocycles in water is very limited. As a result, copper (II) has been the metal of choice for the investigation of complex formation with S-donor macrocycles and methanol–water mixtures have been used as medium.

The kinetics of formation and dissociation of Cu(II)–cyclic polythiaether complexes have been studied extensively by Rorabacher and coworkers ([11]a–e). With regard to complex formation kinetics, the work of this group concentrates on $Cu(H_2O)_6^{2+}$ cations reacting with a variety of S_4-donor macrocyclic ligands. In view of multi-step scheme (7), one of the important overall results is that, for complex formation of Cu(II) with a wide spectrum of cyclic S_4-donor ligands, only one reaction step is observed, leading to a single second-order formation rate constant k_f.

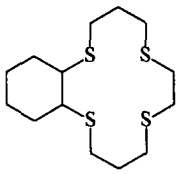


7 **8** **9**

The variation of ring size, as studied with the ligand series [12]aneS_4 → [13]aneS_4 → [14]aneS_4(**7**) → [15]aneS_4 → [16]aneS_4, showed that k_f^{298} is lowest for the 12-membered ring [12]aneS_4 (0.65×10^4 M^{-1} s^{-1}) and highest for the 15-membered one, [15]aneS_4 (23.50×10^4 M^{-1} s^{-1}), with a steady increase upon going from [12]aneS_4 to [13]aneS_4 and [14]aneS_4 (13×10^4 M^{-1} s^{-1}) ([11]a). The authors conclude that second-bond formation, i.e. closure of the first chelate ring (see sequence (6)), is the probable rate-controlling step for all of the ligands studied. The corresponding experiments with the OH-derivatized series of ligands, ranging from [12]aneS_4-ol via [14]aneS_4-ol(**8**) to [16]aneS_4-ol, led to the result that the relative change in k_f with ring size is the same. The k_f values are by a factor of 5–8 smaller though ([11]e).

The introduction of two –OH groups led to the *cis*- and *trans*-isomer of ligand **9**. Again, a reduction in rate constant k_f was observed according to [14]aneS$_4$: [14]aneS$_4$-ol : *trans*-[14]aneS$_4$-diol : *cis*-[14]aneS$_4$-diol = 13:1.4:0.6:0.13 at 298 K ([11]b).

The study of complex formation kinetics for solvated copper(II) reacting with substituted polythiaethers was extended to a series of ligands in which one or both of the ethylene bridging groups in [14]aneS$_4$(**7**) were replaced by *cis*- or *trans*-1,2-cyclohexanediyl, to yield two stereoisomers of **10** and five stereoisomers of **11** ([11]d). These seven ligands were compared to the unsubstituted parent [14]aneS$_4$ ligand **7**.



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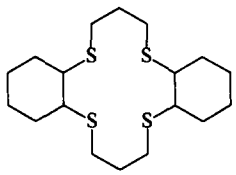

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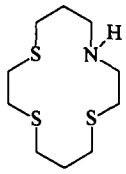


12

The complex formation rate constants k_f were found to lie within the narrow range of $(2-5) \times 10^4$ M^{-1} s^{-1}. This means that the cyclohexandiyl substituents do not induce significant steric effects relative to the first two bond formation steps, which is surprising.

Substantial rate effects were observed when the four sulfur-donor atoms in **7** were successively replaced by nitrogen, according to the series [14]aneS$_4$(**7**) → [14]aneNS$_3$(**12**) → [14]aneN$_2$S$_2$ → [14]aneNSSN → [14]aneNSNS → [14]aneN$_3$S → [14]aneN$_4$ (**2** = cyclam) ([11]c). For the reaction of aquocopper(II) with these ligands, each N-donor replacing a S-donor increases the thermodynamic stability of the complex formed considerably and the complex formation rate constant k_f markedly. For [14]aneNSNS, k_f arrives at 2.0×10^9 M^{-1} s^{-1} at 298 K, which is in line with the interpretation that formation of the first coordinate bond is the rate-determining step.

The mechanistic information resulting from the work of Rorabacher and coworkers on copper(II) complex formation with type **7** S$_4$-donor macrocycles can be summarized as follows, (i) the size of complex formation rate constant k_f suggests that formation of the second Cu–S bond (i.e. closure of the first chelate ring) is rate-determining, (ii) the introduction of sterically demanding groups, such as in **10** and **11**, does not induce significant rate effects, and (iii) for all of the cyclic S$_4$-donor ligands studied, only one second-order reaction step is observed, which means that the mechanistic assignment of this step is difficult.

3. Kinetics of complex formation with N$_4$-donor macrocycles in aqueous solution

3.1. General

As pointed out, the 14-membered N$_4$-donor macrocyclic ligand cyclam(**2**) provides a cavity most properly sized for the planar coordination of 3d transition metal

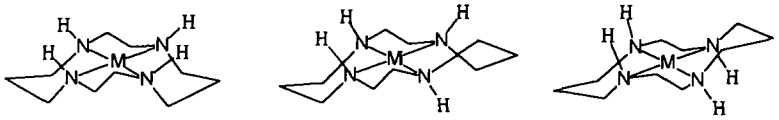
cations M^{2+} according to reaction (8).

$$M^{2+} + \text{cyclam} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} M(\text{cyclam})^{2+} \quad (8)$$

Complex formation constants $K = k_f/k_d$ of the species $[Ni(cyclam)]^{2+}$ ($\log K = 20.1$) and $[Cu(cyclam)]^{2+}$ ($\log K = 26.5$) are large [12], due to very small dissociation rate constants k_d. This means, that even under 1:1 conditions, complex formation according to reaction (8) with M = Ni, Cu proceeds to completion and the reverse reaction can be neglected.

In contrast to oxygen-donor and sulfur-donor macrocycles, cyclic polyamines are much more basic and subject to protonation. In the case of cyclam, for example, the pH has to be raised to pH > 12 to generate the non-protonated neutral ligand. Under these conditions, metal hydroxide precipitation or hydroxo complex formation occurs. This means that, at low pH, complex formation of hydrated transition metal cations $M(H_2O)_6^{2+}$ with N_4-donor macrocycles is complicated by protonation and deprotonation equilibria.

Finally, the four nitrogen atoms in N_4-donor type ligands such as cyclam are prochiral centers. Upon metal coordination, they become chiral centers which, according to Bosnich et al. [13], leads to the stereoisomers *trans*-I (RSRS) to *trans*-V (RRRR). In the solid state, most of the cyclam complexes prefer the *trans*-III arrangement, whereas the *trans*-I configuration is often observed in the case of substituted cyclam ligands L, forming five-coordinate complexes MLX (X = monodentate ligand)[1].



trans-I (RSRS) trans-II (RSRR) trans-III (RRSS)

The overall process of complex formation with N_4-donor ligands of the cyclam type thus will be strongly affected by stereochemical factors.

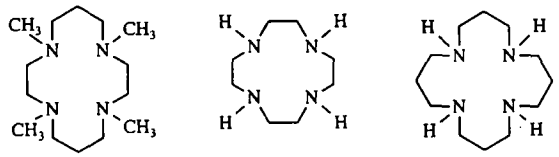
3.2. Kinetic studies with non-functionalized N_4-donor macrocycles

As indicated above, in aqueous solution the kinetics of complex formation of N_4-donor macrocycles according to reaction (8) are very much pH-affected in that, at high pH, the hydrated metal M^{2+}, unless precipitating as hydroxide, forms hydroxometalates and, at low pH, the ligand is protonated. The kinetic information obtained in aqueous solution is therefore valuable as such but not necessarily informative with regard to the basic mechanistic question of complex formation by metal-control (Eigen–Wilkins mechanism) or ligand-control.

In 1970, Kaden was the first to study the kinetics of complex formation with a N_4-donor macrocycle in aqueous solution [14]. He compared the systems Ni^{2+}/cyclam and Ni^{2+}/trien (trien = triethylenetetraamine) and found that the hydrated

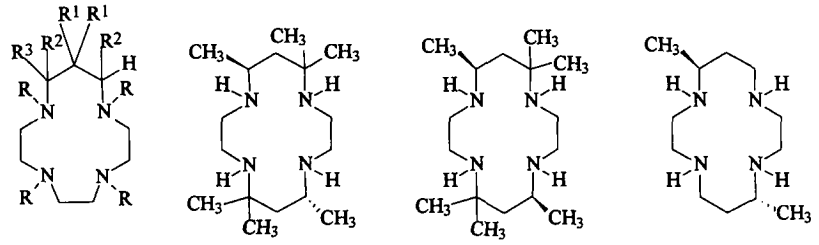
[1] See Ref.[1] and the original literature cited therein.

Ni^{2+} cation reacts 3×10^4 times faster with the open-chain N_4-donor trien than with the cyclic N_4-donor cyclam. He concluded that, in the reaction with the more rigid ligand cyclam, formation of the second Ni–N bond is rate-limiting. Later on, Kaden and coworkers showed that the rates observed for the reaction of protonated tetramethylcyclam **13**(TMC), with divalent transition metal cations follow the order $Cu^{2+} > Zn^{2+} > Co^{2+} > Ni^{2+}$, which parallels the order found for the rate of water exchange on these cations [15].



13 (TMC) **14** **15**

The rate of complex formation is by a more or less constant factor of 10^{-3}–10^{-4} slower than the rate of water exchange, which was attributed to a conformational change of the ligand TMC. Analogous results were obtained in a study on ring size effects, carried out with six macrocyclic N_4-donor ligands, ranging from 12-membered, **14**, to 16-membered, **15**. Again, the rate of water exchange on Cu^{2+}, Zn^{2+}, Co^{2+} and Ni^{2+} paralleled the (slower) rate of complex formation with a given protonated species of these ligands [16]. Another interesting finding was that *C*-methylation and/or *N*-methylation of the 13-membered macrocycle **16** has a rate-reducing effect on the complexation with Cu^{2+} and Ni^{2+} [17]. The number as well as the position of the methyl groups was found to be important.



16 **17a**(tet-a) **17b**(tet-b) **18**(5,12-DMC)

More specifically, within the series of methylated ligands **16** studied, the *N*-methylated derivative of **16** ($R = CH_3$; $R^1 = R^2 = R^3 = H$) is slowest in complex formation. Complexation kinetics were also studied with 14-membered N_4-donor macrocycles in which one aliphatic N-donor function was replaced by a pyridine unit [18]. This substitution led to a decrease in complexation rate, most probably due to increased ligand rigidity, as induced by the pyridine ring.

The results obtained by Wu and Kaden for the reaction of partially complexed, hydrated metal species NiX^z and CuX^z ($z = +2, +1, 0, -1$) with mono-protonated cyclam are very interesting from the mechanistic point of view [19]. For NiX^z, going from $z = +2$ (X = water) to $+1$ (X = acetate), 0 (X = oxalate) and -1 (X = tricarballylate) leads to an increase in rate by a factor of ca. 10. This rate

enhancement is explained on electrostatic grounds. For the series of nickel species $NiX^{2+} = Ni(H_2O)_6^{2+}$, $Ni(H_2O)_5NH_3^{2+}$, $Ni(H_2O)_4en^{2+}$ and $Ni(H_2O)_3dien^{2+}$, the change in complexation rate with cyclam was found to be very minor. The authors present a quantitative relationship which correlates the thermodynamic stability of a series of copper(II) species CuX^z with the reactivity of the species CuX^z towards mono-protonated cyclam and explains the results of earlier studies [20,21] in a more general way. With regard to the mechanism, Wu and Kaden [19] conclude that, for the reaction of the species NiX with mono-protonated cyclam, formation of the first Ni–N bond is not the rate-limiting step.

The kinetics of complex formation of non-protonated N_4-donor macrocyclic and open-chain ligands with copper(II) in strongly basic aqueous solution (pH $\approx$ 13) was studied first by Margerum and coworkers [22,23]. Under these conditions, the copper is present as $Cu(OH)_3^-$ and $Cu(OH)_4^{2-}$, with $Cu(OH)_3^-$ being the more reactive species. In contrast to the systems Ni^{2+}/cyclam and Ni^{2+}/trien, as studied by Kaden [14], the rate-reducing effect of ligand cyclization was found to be very small for the reaction of $Cu(OH)_3^-$ with cyclam and 2,3,2-tet (= 1,4,8,11-tetraazaundecane), respectively. The species $Cu(OH)_4^{2-}$ reacts with cyclam by approximately two orders of magnitude slower than with 2,3,2-tet. The comparison of the ligands 2,3,2-tet, Et_2-2,3,2-tet (= 1,11-diethyl-1,4,8,11-tetraazaundecane), cyclam, **17a**(tet-a) and **18**(5,12-DMC) showed convincingly, that in addition to the effect of cyclization, alkylation at the N-donor atoms or on the carbon backbone has a strong rate-reducing effect on the complexation with the species $Cu(OH)_3^-$ and $Cu(OH)_4^{2-}$. Second-bond formation was suggested as the rate-controlling step for the $Cu(OH)_4^{2-}$ reaction with the macrocyclic ligands and the more sterically hindered open-chain polyamines. Similar kinetic and mechanistic results were obtained by Chung and coworkers [24] for the reaction of $Cu(OH)_3^-$ and $Cu(OH)_4^{2-}$ with **17b**(tet-b).

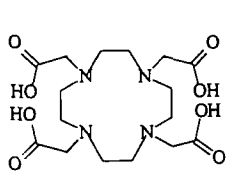
The kinetics of complex formation of Zn^{2+} and Cu^{2+} with the macrocyclic ligand **18** in aqueous solution was studied by Choi [25].

3.3. Kinetic studies with N_4-donor macrocycles with pendant functional groups

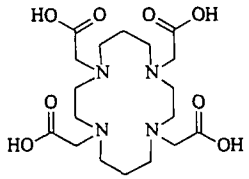
There has been an increasing number of kinetic studies on complex formation with N_4-donor macrocycles bearing pendant functional groups, such as carboxylate groups. Compared to non-functionalized macrocycles, complex formation with this sort of ligand is different in the sense that, in general, bonding to the pendant arms initiates the process of metal coordination.

In macrocyclic ligands with pendant arms, obtained by the attachment of coordinating groups to the donor atoms or carbon skeleton of the macrocycle, the properties resulting from the more rigid cyclic structure are combined with those of more flexible open-chain ligands. As pointed out by Kaden in an early review [26], the increasing interest in this sort of ligands is based on a variety of different objectives. In view of possible applications in analytical chemistry and medical diagnosis, additional ligating groups were introduced into macrocycles in order to modify ligand and/or complex properties such as specificity, thermodynamic stability, kinetic stability, solubility in organic media, redox potential, etc. [27].

Ligands **19** and **20** are examples of *N*-functionalized N_4-donor macrocyclic ligands H_4L with pendant acetate groups.



19 (DOTA)



20 (TETA)

Kasprzyk and Wilkins investigated the kinetics of complex formation of **19** and **20** with a series of hydrated M^{2+} ions [28]. They found that the monoprotonated ligand species HL^{3-} is the reactive one and that complex formation is 10^3–10^4 times faster than with the corresponding non-functionalized macrocycles. In addition to more favorable electrostatic conditions, the acetate groups, working in cooperation with the non-protonated nitrogen atoms, help to enhance the rate of complexation by rapid intermediate formation which brings the metal close to the macrocyclic ring. Further kinetic studies, especially on complex formation of lanthanide ions Ln^{3+} with various N-donor macrocycles with pendant acetate groups, confirmed that, compared to the non-functionalized parent macrocyclic ligands, there is a change in mechanism. The metal ion is initially captured by one of the pendant acetate groups, which occurs in cooperation with the N-donor atoms of the macrocycle and facilitates fast formation of protonated intermediates. Deprotonation of these intermediate complexes controls the rate of product formation [29].

Pendant hydroxyl groups are also affecting the rate of metal entry into N_4-donor macrocycles. This was shown for complex formation with derivatives of the ligand cyclam, bearing either 2-hydroxyethyl groups [30] or 2-hydroxypropyl groups [31] on the four nitrogen atoms. As in the case of acetate groups, the hydroxy groups, in cooperation with the nitrogen atoms, are supposed to initiate complex formation by fast adduct formation. In support of this mechanistic interpretation, it was found [32] that a minimum of two 2-hydroxyethyl groups, located on adjacent nitrogen atoms, is required to achieve the facilitation of metal coordination.

4. Kinetic investigation of complex formation with N_4-donor macrocycles in organic media

4.1. Introductory remarks

The general discussion of mechanisms of complex formation focuses on reactions of solvated metal cations with solvated ligands, the chemical form of which is identical in the free and coordinated state. More clearly, the Eigen–Wilkins scheme, as based on the parameters k_{ex} and K_{os} (see Section 2.1), is able, for example, to predict satisfyingly the rate of formation of the complex species $Cu(H_2O)_5X^+$ as the product of $Cu(H_2O)_6^{2+}$ ions reacting with hydrated X^- ions. It fails to predict the rate of formation of $Cu(H_2O)_5X^+$ as the product of the reaction of

$Cu(OH)_4^{2-}$ ions with X^- ions because there are no data describing the kinetic lability of the OH^- ions in $Cu(OH)_4^{2-}$. Also, the rate of $Cu(H_2O)_6^{2+}$ ions reacting with HX to form $Cu(H_2O)_5X^+$ can be accordingly treated only if the pK_a of HX is known and if the reaction of copper with HX can be excluded. In other words, in the case of macrocyclic ligands L, an adequate check for the operation of the Eigen–Wilkins mechanism should be made only for solvated, non-complexed metal ions reacting with solvated, non-protonated ligands L.

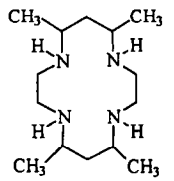
As pointed out (see Section 3.2), the study of complex formation of nitrogen-donor macrocycles L in aqueous solution is hampered by the fact that these ligands are protonated at the low pH necessary to prevent deprotonation of the hydrated metal ions M. The mechanistic interpretation of the formation kinetics of complexes ML via partially protonated intermediates $M(LH_x)$ is in most cases difficult.

As a result of these limitations, dipolar aprotic organic solvents S can be considered as an interesting alternative to the medium water. Taking into account that these solvents should be polar enough to dissolve and dissociate metal salts sufficiently, one can think, for example, of nitriles, sulfoxides and dialkylformamides. Another condition is, of course, that the corresponding k_{ex} data (see reaction (3)) for the solvated metal species, MS_x, are known. For the divalent 3d transition metal cations Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+}, the rate of solvent exchange has been measured for the species $M(DMF)_6^{2+}$ and $M(MeCN)_6^{2+}$ (DMF = *N*,*N*-dimethylformamide, MeCN = acetonitrile) [6]. Systems such as $Ni(DMF)_6(ClO_4)_2/N_4$-macrocycle/DMF or $Cu(DMF)_6(ClO_4)_2/N_4$-macrocycle/DMF should therefore be suitable systems for the study of complex formation of hexasolvated nickel(II) and copper(II) with non-protonated N_4-donor macrocycles.

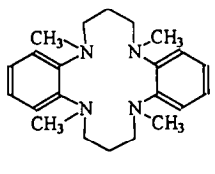
Oxygen-donor and sulfor-donor macrocycles are free of protonation in aqueous solution. The mechanistic results obtained for complex formation of crown ethers (Section 2.2) and S_4-donor macrocycles, reacting with hexasolvated copper(II) in methanol–water mixtures (Section 2.3), can be used for a powerful comparison with the results obtained for complex formation of non-protonated N_4-donor macrocycles in media such as DMF and acetonitrile. This comparison should reflect the difference in the kinetic effects of sulfur and nitrogen as donor in macrocyclic ligands of equal size and structure.

4.2. Results of earlier studies

Hay and Norman were the first to study the kinetics of metal incorporation into N_4-donor macrocyclic ligands in a dipolar aprotic solvent [33]. They investigated the reactions of nickel(II) with **2**(cyclam) and *C*-methylated cyclam derivatives, **18**(5,12-DMC), **21**, **17a**(tet-a) and **17b**(tet-b), in acetonitrile.



21



22 (TMBC)

In all cases, they observed a fast incorporation step (first-order in both nickel and ligand), followed by one or two slower isomerisation steps. The second-order rate constant for nickel incorporation was found to be more or less the same for all of the macrocyclic ligands and even open-chain tetra-amines studied (see Table 1).

*4.2.1. Cyclam(**2**) in comparison with tetramethylcyclam(**13**)*

Hertli and Kaden investigated the kinetics of complex formation of nickel(II) with cyclam(**2**) and TMC(**13**) in dimethylsulfoxide (DMSO) and DMF [34]. In both solvents and for both ligands, an initial second-order reaction was observed, leading to electronic spectra typical for nickel(II) in a square-planar N_4-coordination

Table 1
Rate constants for complex formation of N_4-donor macrocycles L with nickel(II) and copper(II) in aprotic dipolar solvents according to reaction scheme (9)

Ligand	Metal	Solvent	T (K)	$10^{-2}k$ (M^{-1} s^{-1})	10^3k_{int} (s^{-1})	Ref.
2	Ni	MeCN	298	7.6		[33]
18	Ni	MeCN	298	7.3		[33]
21	Ni	MeCN	298	7.9		[33]
17a	Ni	MeCN	298	9.2		[33]
17b	Ni	MeCN	298	8.3		[33]
2	Ni	DMSO	298	16	2300	[34]
2	Ni	DMF	298	18	320	[34]
13	Ni	DMSO	298	0.052		[34]
13	Ni	DMF	298	0.8		[34]
22	Cu	DMF	298	0.39	71	[35]
2	Ni	DMF	303	79	260	[36]
23	Ni	DMF	303	23	0.19	[36]
24	Ni	DMF	303	13	0.9	[36]
25	Ni	DMF	303	5.5	0.1	[36]
13	Ni	DMF	303	0.61	0.58	[36]
13	Cu	DMF	303	870[a]	5.4	[36]
17a	Ni	DMF	303	2.0	0.30	[37]
17b	Ni	DMF	303	9.8	0.080	[37]
18	Ni	DMF	303	10	0.41	[37]
22	Ni	DMF	303	0.00057	0.18	[37]
26	Ni	DMF	303	1.1		[37]
27	Ni	DMF	303	3.7	1.5	[37]
13	Cu	DMF	218	73	5.4[b]	[37]
17a	Cu	DMF	218	3.1	2.8[b]	[37]
17b	Cu	DMF	218	14	3.4[b]	[37]
18	Cu	DMF	218	4.8	0.54[b]	[37]
22	Cu	DMF	218	2.8	84[c]	[37]
26	Cu	DMF	218	1.3		[37]
27	Cu	DMF	218	1.7	7.8[b]	[37]

[a] Extrapolated to 303 K on the basis of measurements at 215–230 K.
[b] $T = 303$ K.
[c] $T = 298$ K.

sphere. The second-order rate constant k for the complexation with TMC was smaller than with cyclam by a factor of 300 (DMSO) and 23 (DMF). As shown in two-step reaction scheme (9), for the reaction of nickel(II) with L = cyclam in both DMF and DMSO a slow subsequent first-order step was observed.

$$Ni^{2+} + L \xrightarrow{k} (NiL^{2+})_{int} \xrightarrow{k_{int}} NiL^{2+} \quad (9)$$

This step was interpreted to describe a rearrangement of the coordinated ligand in the intermediate $(NiL^{2+})_{int}$ to form the thermodynamically most stable stereoisomer NiL^{2+}.

For the system Ni^{2+}/cyclam/DMF, the second-order rate constant for the incorporation step was found to be $k = 1.8 \times 10^3$ M^{-1} s^{-1} at 298 K (see Table 1). Within the framework of the Eigen–Wilkins mechanism (see Section 2.1), the assumption of an outer-sphere complex formation constant $K_{os} = 0.1$–0.5 M^{-1} leads to $k_i = k/K_{os} = (3.6$–$18) \times 10^3$ s^{-1} for the interchange step. In view of the very comparable rate of solvent exchange in $Ni(DMF)_6^{2+}$ ($k_{ex} = 3.8 \times 10^3$ s^{-1} [6]), Hertli and Kaden concluded that for the systems Ni^{2+}/cyclam/DMF and Ni^{2+}/cyclam/DMSO the substitution of the first solvent molecule (i.e. formation of the first Ni–N bond) is rate-controlling. The substantial drop in rate observed for the tetra-*N*-methylated ligand TMC(**13**) was ascribed to steric effects.

*4.2.2. Studies with TMBC(**22**)*

The kinetics of complex formation of copper(II) with the highly substituted N_4-donor macrocycle **22**(TMBC) in DMF was studied by Elias and coworkers [35]. The kinetic pattern observed was the same as the one found for the system Ni^{2+}/cyclam/DMF [34], namely, fast second-order intermediate formation and slow first-order rearrangement according to reaction scheme (9). Compared with the fast solvent exchange in $Cu(DMF)_6^{2+}$ ($k_{ex} = 9.1 \times 10^8$ s^{-1} ([6]b)), the size of second-order rate constant $k = 39$ M^{-1} s^{-1} (see Table 1) for the reaction of copper(II) with TMBC is too small to be possibly indicative of the operation of the Eigen–Wilkins mechanism. TMBC is a sterically very much hindered ligand. It was suggested therefore that, according to reactions (10–12) (solvation shell of Cu^{2+} omitted for clarity), fast first-bond formation has occurred before the observation on the stopped-flow time scale begins.

$$Cu^{2+}(solv) + TMBC \rightleftharpoons \{Cu, TMBC\}^{2+} \rightleftharpoons Cu\text{–}(TMBC)^{2+} \quad K_1 \quad (10)$$

$$Cu\text{–}(TMBC)^{2+} \rightleftharpoons Cu\text{-}(TMBC')^{2+} \quad K_{con} \quad (11)$$

$$Cu\text{–}(TMBC')^{2+} \rightarrow Cu(TMBC)^{2+}(int) \quad k'_{ex} \quad (12)$$

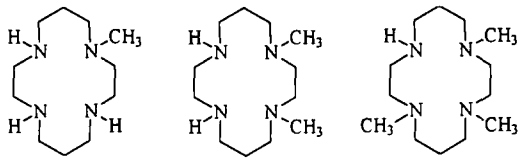
$$Cu(TMBC)^{2+}(int) \rightarrow Cu(TMBC)^{2+} \quad k_{int} \quad (13)$$

To explain the low rate of copper incorporation into TMBC, Elias et al. argue that the formation of the second bond (and of further bonds) according to reaction (12) can take place only when the singly bonded N_4-macrocycle in the species $Cu\text{–}(TMBC)^{2+}$ finds itself in a suitable conformation and spatial arrangement, relative to the copper, to allow closure of the first chelate ring and, subsequently,

full N_4-coordination. The intermediate $Cu(TMBC)^{2+}$(int) finally isomerizes according to reaction (13) to optimize its stereochemistry. According to equilibrium (11), this mechanistic interpretation invokes the dynamics of conformational change in a partially coordinated macrocyclic ligand as possible rate-limiting factor. It implies that the experimentally obtained second-order rate constant $k = 39\ M^{-1}\ s^{-1}$ corresponds formally to $k = K_1 \cdot K_{con} \cdot k'_{ex}$. The small size of k relative to k_{ex} for the solvated copper, $Cu(DMF)_6^{2+}$, would thus be due to a small value of K_{con} and, possibly, of K_1.

4.2.3. The kinetic effect of stepwise N-methylation of cyclam on intermediate formation

The kinetics of complex formation of nickel(II) and copper(II) with a series of five increasingly *N*-methylated ligands L (**2**(cyclam) → **23** → **24**(1,4-DMC) → **25** → **13**(TMC)) in DMF was investigated by Röper and Elias [36]. The overall kinetic pattern observed corresponds to the two-step scheme (9).



23 **24** (1,4-DMC) **25**

Even at the reduced temperature of 218 K, the initial second-order reaction of copper(II) with ligands **2**, **23**, **24** and **25** was too fast to be monitored by the stopped-flow technique. Only with fully *N*-methylated TMC(**13**), the coordination of copper(II) could be followed at 215–230 K. Extrapolation to 303 K yielded $k = 8.7 \times 10^4\ M^{-1}\ s^{-1}$ (see Table 1), which means that copper(II) reacts with TMC(**13**) by three orders of magnitude faster than with TMBC(**22**). As in the case of TMBC, the coordination of copper(II) by TMC is nevertheless too slow to be controlled by the rate of solvent exchange in $Cu(DMF)_6^{2+}$.

Second-order rate constants k for the reaction with nickel(II) were found to follow sequence (I).

$$k(\mathbf{2}):k(\mathbf{23}):k(\mathbf{24}):k(\mathbf{25}):k(\mathbf{13}) = 130:38:21:9:1 \quad \text{(I)}$$

The drop in rate with increasing number of methyl groups on the N-donor atoms obviously reflects the stepwise reduced flexibility of the macrocyclic ligands L. Mechanistically, sequence (I) points to a changeover in rate-control from first-bond formation (L = **2** = cyclam) to second-bond formation (L = **25**, **13**). The rate of rearrangement of the intermediates formed was found to be much less affected by the *N*-methyl groups. With the exception of $k_{int}(\mathbf{2}) = 256 \times 10^{-3}\ s^{-1}$, rate constants k_{int} all lie in the narrow range $(0.1–0.9) \times 10^{-3}\ s^{-1}$ (see Table 1). The relative pK_a values of the species LH^+ ($pK_a(1)_r$) and LH^{2+} ($pK_a(2)_r$), as determined in DMF for L = **2**, **23**–**25** and **13**, provided a valuable mechanistic information. Increasing *N*-methylation (**2** → **23** → **24** → **25** → **13**) does not affect the size of $pK_a(1)_r$, but reduces the size of $pK_a(2)_r$. Interestingly, a LFE relationship was found to exist between second-order rate constant k and $pK_a(2)_r$, which suggests that formation of

Table 2
Comparison of rate constants for complex formation of *C*-substituted and *N*-substituted ligands L with copper(II) and nickel(II) in DMF according to reaction scheme (9) [37]

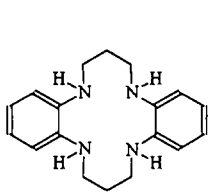
Ligand L	$10^{-3} \times [k(\mathrm{Cu})/k(\mathrm{Ni})]$ at 303 K	$k_{int}(\mathrm{Cu})/k_{int}(\mathrm{Ni})$ at 303 K
13	1.7	9.3
26	3.4	
22	0.73	4.7×10^2 [a]
17a		9.3
17b		43
18	1.0	1.3
27	1.4	5.2

[a] Rate constant $k_{int}(\mathrm{Cu})$ used to calculate this value refers to 298 K instead of 303 K.

the second Ni–N bond is indeed involved in the rate-controlling step of intermediate formation.

4.2.4. The kinetic effect of C-methylation of cyclam on intermediate formation

Ligands **17a**, **17b**, **18**, **22**, **26** and **27** were chosen by Röper and Elias [37] to investigate the influence of substituents on the carbon skeleton of cyclam on the kinetics of complex formation with nickel(II) and copper(II) in DMF.



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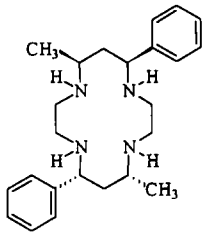


27

Again it was found that complex formation according to reaction (1) follows the two-step scheme (9). Compared with the effect of stepwise *N*-methylation on second-order rate constant k (see sequence (I)), the effect of *C*-methylation is less pronounced. For M = Ni, the k values obtained for **18** (two methyl groups), **17a**/**17b** (six methyl groups) and **27** (two methyl and two phenyl groups) are all of the same order ($(2-10) \times 10^2$ M^{-1} s^{-1} at 303 K; see Table 1). For M = Cu, the results are similar ($k = (2-14) \times 10^4$ M^{-1} s^{-1} at 218 K). One can conclude, therefore, that methyl or phenyl groups on the propylene bridge of cyclam have a minor effect only on the rate of metal incorporation. The addition of ring systems, however, as in **26** (dibenzocyclam), has a much more pronounced rate-reducing effect (for M = Cu, $k = 1.3 \times 10^2$ M^{-1} s^{-1} at 218 K) and the combination of *N*-methylation and added ring systems, as in **22**, lets the rate of metal coordination drop by a factor of ca. 10^4 (nickel) and 10^6 (copper) [37].

The comparison of the second-order rate constants k obtained for the reaction of ligands **13**, **17a**, **17b**, **18**, **22**, **26** and **27** with nickel(II) and copper(II), respectively, leads to an interesting result. As shown in Table 2, the ratio $k(\mathrm{Cu})/k(\mathrm{Ni})$,

describing the difference in the rate of intermediate formation according to reaction (9), is of the order of 10^3 for all of the differently substituted ligands studied. Considering the rate of DMF exchange on $Cu(DMF)_6^{2+}$ and $Ni(DMF)_6^{2+}$, it is not surprising to see copper reacting faster than nickel. It is very remarkable and instructive, however, to find a factor of only 10^3 instead of ca. 10^5, as expected on the basis of the corresponding k_{ex} data [6]. This general finding indicates clearly, that even in the case of sterically very hindered N_4-donor macrocycles such as **22**, the kinetic lability of the solvent bound to the metal affects the rate of intermediate formation, but does not control it. In other words, the incorporation of the metal into the planar N_4-donor cavity of cyclic ligands of the cyclam type is obviously metal-controlled as well as ligand-controlled, which has to be discussed in detail.

4.2.5. The nature of the slow step following metal incorporation

The kinetic information on complex formation of N_4-donor macrocyclic ligands L of the cyclam type with divalent 3d transition metal ions M^{2+}, as obtained in dipolar aprotic media, can be summarized by reaction scheme (14).

$$\begin{array}{ccccccc} M^{2+} & + & L & \xrightarrow{k} & (ML^{2+})_{int} & \xrightarrow{k_{int}} & ML^{2+} \\ | & \text{<— fast stage —>} & | & & \text{<— slow stage —>} & & | \end{array} \qquad (14)$$

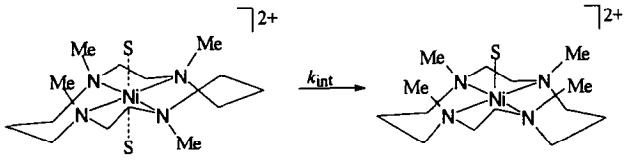
The overall process of complexation has two stages. The initial stage, accompanied by substantial spectral changes, is fast and second-order. The second stage, associated with only minor spectral changes, is considerably slower and first-order. The data obtained for second-order rate constant k in the case of *N*- and/or *C*-substituted cyclam derivatives suggest that formation of the second M–N bond (i.e. closure of the first chelate ring) is determining the rate of the first stage (as an exception, the size of k for the non-substituted ligand L = cyclam(**2**) is compatible with rate-control through first M–N bond formation). The absorption spectra of the intermediates present at the end of the first stage confirm planar N_4-coordination of the metal. This means that, compared with second-bond formation, formation of the third and fourth M–N bond is a fast consecutive process.

As pointed out earlier (see Section 3.1), the four nitrogen atoms of a N_4-donor macrocycle become chiral upon coordination. It is well conceivable that, in the course of fast consecutive coordination of the third and fourth N-donor atom, there is not enough time for the cyclic ligand to accommodate the metal in the stereochemically most favorable configuration. It has been suggested therefore [33–35] that first-order rate constant k_{int} describes a stereochemical reorganization of the intermediate $(ML^{2+})_{int}$, leading to a thermodynamically more stable stereoisomer ML^{2+} as product.

It is very informative to analyze the data obtained for rate constant k_{int} (see Table 1). In DMF and for M = Ni, the rearrangement of the intermediate $(NiL^{2+})_{int}$ with L = cyclam(**2**) occurs with $k_{int} = 0.26\ s^{-1}$ at 303 K. The introduction of one *N*-methyl group (L = **2** → L = **23**) is sufficient to let k_{int} drop from 0.26 s^{-1} to $0.19 \times 10^{-3}\ s^{-1}$, i.e. by three orders of magnitude. Further *N*-methylation and *C*-methylation or even addition of benzene rings (as in **22**) has a minor effect

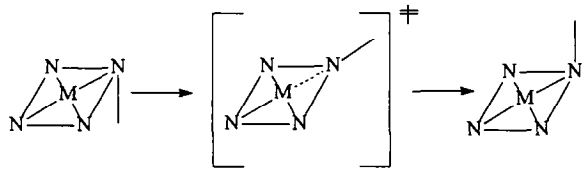
only in that the data for k_{int} lie in the rather narrow range of $(0.08-1.5) \times 10^{-3}$ s^{-1} for all of the substituted ligands (**13**, **18**, **17a**, **17b**, **18**, **22–27**). Considering the fact that, for example, $k(\mathbf{23})/k(\mathbf{22}) = 4 \times 10^4$ and $k_{int}(\mathbf{23})/k_{int}(\mathbf{22}) = 1.1$, one recognizes that, mechanistically, intermediate formation (rate constant k) and inter-mediate reorganization (rate constant k_{int}) are fundamentally different. One should also note that the copper intermediate $Cu(TMC)^{2+}_{int}$ (TMC = **13**) reacts only ten times faster than the analogous nickel intermediate (see Table 2) and that the corresponding enthalpies of activation, $\Delta H^{\neq}$, agree within the limits of error (67 kJ mol^{-1} for nickel and 65 kJ mol^{-1} for copper [36]). These findings support the plausible interpretation that the second slow stage of the overall process of complexation describes ligand-specific stereochemical rearrangement steps.

^{1}H-NMR monitoring of the reaction $(Ni(TMC)^{2+})_{int} \rightarrow Ni(TMC)^{2+}$ with TMC = **13** in DMF-d_7 allowed a more detailed description of the rearrangement taking place [36]. In agreement with earlier studies on the stereoisomers of $Ni(TMC)^{2+}$ [38–40], it was confirmed that this step corresponds to the stereochemical isomerization *trans*-II(RSRR) → *trans*-I(RSRS) according to reaction scheme (15). The participation of the solvent S = DMF follows from the paramagnetic shift of the NMR spectra.



trans-II (RSRR) trans-I (RSRS) (15)

The rearrangement of the intermediate $(Ni(TMC)^{2+})_{int}$ according to reaction (15) is the only one which is stereochemically well-characterized. As a matter of fact, for both nickel and copper the data for k_{int} lie in the rather narrow range of $(0.1-8) \times 10^{-3}$ s^{-1} for all of the substituted ligands studied (see Table 1; as the only exception, intermediate $(CuL^{2+})_{int}$ with L = **22** rearranges faster). It is therefore reasonable to assume that the first-order rearrangement of all of these intermediates corresponds to an inversion of configuration of one of the chiral N-donor atoms, as schematically shown in reaction sequence (16).

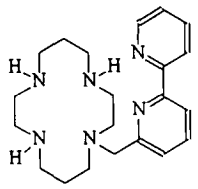


(16)

The low rate of reorganization is due to the high energy barrier for the transition state of such inversion processes. The stereochemical details of the various isomerization steps have yet to be studied.

4.2.6. The role of pendant coordinating groups

The kinetic investigation of the complex formation of ligand **28** with divalent metal ions M^{2+} (M = Zn, Ni, Co, Cu) in DMSO, as carried out by Moore et al. [41], is an example to show as to how ligand functionalization affects the mechanism of metal incorporation.



28

As in the case of the medium water (see Section 3.3), the pendant donor group initiates complex formation by catching the metal. The overall process, schematically described by reaction sequence (17), has two stages.

$$M(DMSO)_6^{2+} + L \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_3} \text{product} \tag{17}$$

The rapid first stage is second-order and reversible, leading to an intermediate with the metal bound to the bipyridyl group. The slower second stage is first-order and practically irreversible, involving chelation by the macrocyclic ring.

4.3. Recent results

4.3.1. General

Due to the fact that the synthesis of substituted N_4-donor macrocycles is mostly laborious, many of the earlier studies described in Section 4.2 were carried out under stoichiometric conditions in order to save material. When pseudo-first-order conditions were applied, they were established with an excess of metal, not with an excess of ligand. In the meantime, the synthetic procedures have improved and, in addition, the experimental techniques for monitoring reactions in the UV–vis range have become more sophisticated. The availability of diode arrays has led from conventional stopped-flow spectrophotometry (with monitoring at a single wavelength) to rapid scan stopped-flow spectrophotometry. This technique provides series of complete absorption spectra at time intervals of a few milliseconds. The computer-aided multi wavelength analysis of such series of spectra leads to more accurate rate constants and allows the detection and spectroscopic characterization of intermediates.

Based on more powerful experimental techniques, recent studies on the kinetics of complex formation of N_4-donor cyclic ligands have revealed a greater kinetic complexity of the overall process of metal complexation. The kinetic pattern described by the two-step reaction sequence (14) has to be refined. Novel experimental results allow and demand to describe the initial fast stage of metal incorporation as well as the consecutive slower stage of reorganization in greater detail.

4.3.2. More detailed information on intermediate formation in the reaction of nickel(II) with cyclam(2) and tet-a(17a) in DMF

Multi wavelength analysis of the data obtained for the reaction of L = cyclam(**2**) with an excess of nickel(II) in DMF revealed that the experimental rate constant describing the initial fast stage of the reaction, k_{obs1}, is not just linearly depending on $[Ni^{2+}]$ according to $k_{obs1} = k \cdot [Ni^{2+}]$. The data obtained for k_{obs1} at variable concentration of nickel follow relationship (II) instead [42].

$$k_{obs1} = a \cdot b \cdot [Ni^{2+}]/(1 + b \cdot [Ni^{2+}]) \quad \text{(II)}$$

This sort of dependence indicates the existence of a fast equilibrium according to reaction (18a) ($M \equiv Ni^{2+}$), preceding the formation of the intermediate $(ML)_{int}$ according to reaction (18b).

$$M + L \rightleftharpoons \{ML\} \quad K \quad \text{(18a)}$$

$$\{ML\} \rightarrow (ML)_{int} \quad k_1 \quad \text{(18b)}$$

The parameters a and b in (II) correspond to $a \equiv k_1 = 27 \pm 1\ s^{-1}$ and $b \equiv K = 210 \pm 20\ M^{-1}$ at 298 K (see Table 3). With regard to the chemical nature of the species {ML}, the size of equilibrium constant K is such that the assumption of {ML} being an outer sphere complex can be ruled out. It is much more plausible to suggest instead that {ML} is sort of a precursor complex, M–L, with singly bonded cyclam, which forms the species with doubly bonded cyclam, M=L, with first-order rate constant k_1. The conversion of the species M=L into the fully N_4-coordinated intermediate $(ML)_{int}$ is a fast process, not detected by stopped-flow technique at ambient temperature (see Section 4.2).

The results obtained for complex formation of the ligand tet-a(**17a**) with an excess of nickel in DMF are in line with the kinetic pattern described for complex formation with cyclam(**2**) [42]. The fast stage of intermediate formation with tet-a can be broken down into three steps, characterized by the experimental rate constants k_{obs1}, k_{obs2} and k_{obs3}. The nickel dependence of rate constant k_{obs1} follows

Table 3
Rate and equilibrium constants for complex formation of the N_4-donor macrocyclic ligands L = cyclam(**2**), tet-a(**17a**) and 5,12-DMC(**18**) with nickel(II) in DMF at 298 K ($M \equiv Ni^{2+}$)

Reaction scheme: $M + L \overset{K}{\rightleftharpoons} \{ML\} \overset{k_1}{\rightarrow} (ML)_{int} \overset{k_{int1}}{\longrightarrow} A \overset{k_{int2}}{\longrightarrow} B \overset{k_{int3}}{\longrightarrow} ML$

L	K (M^{-1})	k_1 (s^{-1})	k_{int1} (s^{-1})	k_{int2} (s^{-1})	k_{int3} (s^{-1})[a]	Ref.
Cyclam(**2**)	210	27			1.2	[42]
Tet-a(**17a**)	8.9	41	2.1	0.28	0.3×10^{-3}	[42]
5,12-DMC(**18**)	10.5	78	2.4[b]		0.84×10^{-3} [b,c]	[42]

[a] Rate constant k_{int3} describes the rate of formation of the final product complex ML.
[b] Base catalyzed step.
[c] Upon prolonged observation under anaerobic conditions, another slow first-order rearrangement step can be detected, $k_{int4} = 0.018 \times 10^{-3}\ s^{-1}$ at 298 K.

relationship (II), whereas k_{obs2} and k_{obs3} are independent of $[Ni^{2+}]$. As shown in reaction sequence (19a–d) ($M \equiv Ni^{2+}$), the consecutive first-order steps (19c) and (19d) are fast steps.

$$M + L \rightleftharpoons \{ML\} \quad K = 8.9\ M^{-1} \tag{19a}$$

$$\{ML\} \rightarrow (ML)_{int} \quad k_1 = 41\ s^{-1} \tag{19b}$$

$$(ML)_{int} \rightarrow A \quad k_{int1} = 2.1\ s^{-1} \tag{19c}$$

$$A \rightarrow B \quad k_{int2} = 0.28\ s^{-1} \tag{19d}$$

The intermediate $(ML)_{int}$ formed initially according to reaction (19b) rearranges quickly via an intermediate A to an intermediate B, which finally isomerizes slowly with rate constant $k_{int3} = 0.30 \times 10^{-3}\ s^{-1}$ (see Table 3). The size of equilibrium constant $K = 8.9 \pm 1.7\ M^{-1}$ again suggests that in the species {ML} the ligand tet-a is singly bonded.

Compared with the parent ligand cyclam, hexa *C*-methylated tet-a is less flexible. Reduced flexibility of the N_4-donor ligand causes obviously a greater kinetic complexity of the initial fast stage of intermediate formation, which makes sense. It is also plausible to see that the equilibrium constant K for the formation of the precursor complex {ML} with singly bonded ligand is considerably smaller for the substituted ligand tet-a than for cyclam.

As outlined in Section 4.2, in the earlier work intermediate formation according to reaction sequence (14) was kinetically treated as a simple second-order reaction with rate constant k (see Table 1). For $b \cdot [Ni^{2+}] \equiv K \cdot [Ni^{2+}] \ll 1$, relationship (II) takes the form (III) with $k_1 \cdot K$ corresponding to second-order rate constant k of reaction (14)

$$k_{obs1} \approx a \cdot b \cdot [Ni^{2+}] \equiv k_1 \cdot K \cdot [Ni^{2+}] \tag{III}$$

For L = cyclam(**2**) and L = tet-a(**17a**), the product $k_1 \cdot K$ amounts to $55 \times 10^2\ M^{-1}\ s^{-1}$ and $3.7 \times 10^2\ M^{-1}\ s^{-1}$, respectively, at 298 K, which differs from the data obtained for k (see Table 1) by less than a factor of two.

In summary, the investigation of the reaction of cyclam(**2**) and tet-a(**17a**) with an excess of nickel reveals that the rate-controlling step of intermediate formation is preceded by a fast equilibrium in which species with (most probably) singly bonded N_4-donor ligands are formed.

*4.3.3. Refinement of the course of complex formation of 5,12-DMC(**18**) with nickel(II) in DMF*

The kinetic investigation of the the formation of $Ni(5,12\text{-}DMC)^{2+}$ in the presence of an excess of nickel or ligand L is revealing in a two-fold sense [43].

The results obtained with excess nickel confirmed that, as in the case of tet-a(**17a**), intermediate formation is not a simple second-order process. The fast stage can be broken down into a fast initial equilibrium followed by two steps according to the sequence (20a–c) ($M \equiv Ni^{2+}$).

$$M + L \rightleftharpoons \{ML\} \quad K = 10.5\ M^{-1} \tag{20a}$$

$$\{ML\} \rightarrow (ML)_{int} \quad k_1 = 78\ s^{-1} \tag{20b}$$

$$(ML)_{int} \rightarrow A \quad k_{int1} = 2.4\ s^{-1} \tag{20c}$$

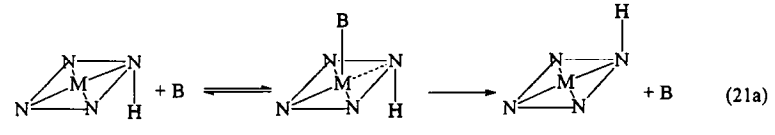
The mechanistic interpretation is analogous to the one given for reaction sequence (19a–c). The precusor complex {ML} is again assumed to be one with singly bonded 5,12-DMC. It reacts with rate constant k_1 to form the fully N_4-coordinated intermediate $(ML)_{int}$. The latter one rearranges quickly with rate constant k_{int1} to an intermediate A, which finally isomerizes slowly in two first-order steps (see Table 3) to form the thermodynamically most stable product $Ni(5,12\text{-DMC})(DMF)_2^{2+}$.

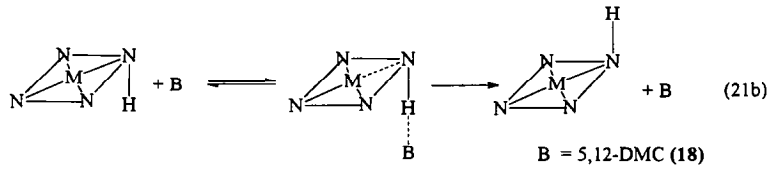
In the presence of an excess of the ligand 5,12-DMC(**18**), three comparatively fast steps are observed, as characterized by rate constants k_{obs1}, k_{obs2} and k_{obs3} [43]. Surprisingly, all three of these rate constants increase linearly with [5,12-DMC]. Accepting equilibrium (20a) with $K = 10.5\ M^{-1}$, as resulting from the studies with an excess of nickel, one would expect to find this equilibrium in the presence of an excess of 5,12-DMC as well. In other words, relationship (II) should apply in the form of (IIa).

$$k_{obs1} = k_1 \cdot K \cdot [L]/(1 + K \cdot [L]) \tag{IIa}$$

The solubility of the ligand 5,12-DMC in DMF is, however, limited to 0.02 M. For this maximum concentration and $K = 10.5\ M^{-1}$, the term $K \cdot [L]$ amounts to 0.105 and contributes to the denominator in relationship (IIa) only very weakly. This means that (IIa) takes the form $k_{obs1} \approx k_1 \cdot K \cdot [L]$ and the dependence of k_{obs1} on [5,12-DMC], as observed experimentally, is linear with a slope of $k_1 \cdot K = 644\ M^{-1}\ s^{-1}$. On the basis of $K = 10.5\ M^{-1}$, rate constant k_1 is calculated to be $61\ s^{-1}$. This number compares satisfactorily to $k_1 = 78\ s^{-1}$, as obtained with an excess of nickel.

According to this interpretation of the ligand dependence of k_{obs1}, the first step of complex formation leads to the intermediate $(ML)_{int}$ which is expected to isomerize slowly in two steps (see above and Table 3). As a matter of fact, this is not observed. The product *trans*-III-Ni(5,12-DMC)$(DMF)_2^{2+}$ is formed instead in two surprisingly fast steps and the corresponding rate constants k_{obs2} and k_{obs3} increase linearly with [5,12-DMC]. Sanzenbacher and Elias give a plausible explanation for this observation by assuming that the last two steps of the overall process are stereochemical rearrangement steps, which are subject to base catalysis by 5,12-DMC (and, less efficiently, by triethylamine). As schematically suggested in reaction sequence (21) ($M \equiv Ni^{2+}$), the base B = 5,12-DMC might add to the nickel and thus facilitate the process of N–H bond inversion according to reaction (21a).

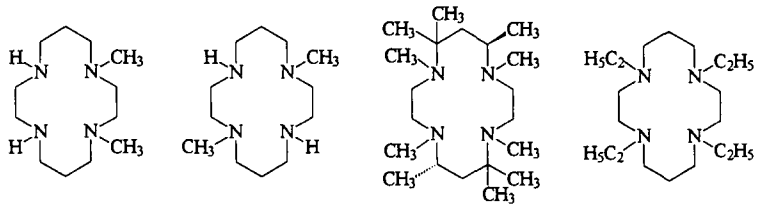




Alternatively and possibly additionally, hydrogen bond formation between coordinated 5,12-DMC and bulk 5,12-DMC according to reaction (21b) might contribute to lower the energy barrier for the inversion process. This sort of interaction between $(ML)_{int}$ and 5,12-DMC would mean that, at high concentrations of the free ligand, rate constants k_{obs2} and k_{obs3} should show saturation behavior according to relationship (IIa). Unfortunately, the solubility of 5,12-DMC in DMF is too limited to prove this.

*4.3.4. Complex formation of 1,4-DMC(**24**), 1,8-DMC(**29**) and tmtet-a(**30**) with nickel(II) and copper(II) in DMF*

The N_4-donor macrocycles **24**, **29** and **30** were chosen by Schwamberger and Elias [44] as ligands for the study of reaction (1) in order to provide further kinetic information on how the specific position and number of methyl groups on the parent ligand cyclam(**2**) affect the course of complex formation with nickel and copper.



Ligands **24** and **29** differ only in the relative positions of the two *N*-bound methyl groups (*cis* and *trans*, respectively), whereas ligand **30**, bearing four *N*-bound and six *C*-bound methyl groups, should allow an interesting comparison to ligands **17a** (six *C*-bound methyl groups) and **13** (four *N*-bound methyl groups).

The X-ray structure analysis of the product complexes shows that in Ni(1,8-DMC)$(ClO_4)_2$, Ni(tmtet-a)$(ClO_4)_2$ and Cu(tmtet-a)$(ClO_4)_2$ the ligand configuration is *trans*-III(RRSS). In the complex Ni(1,4-DMC)$(ClO_4)_2$ the ligand has the *trans*-I(RSRS) configuration [44] and the ethylene bridge located *trans* to the two methyl substituents is disordered.

As found earlier under stoichiometric conditions [36], the overall process of complex formation of 1,4-DMC(**24**) with nickel(II) in DMF can be split into two stages. The investigation with an excess of either nickel or ligand reveals however that, as found for the ligands tet-a(**17a**) (see Section 4.3.2) and 5,12-DMC(**18**) (see Section 4.3.3), both stages can be kinetically resolved in greater detail than before.

As shown schematically in reaction sequence (22) ($M \equiv Ni^{2+}$, $L \equiv$ 1,4-DMC), the first (fast) stage begins with an equilibrium, leading to the species {ML} with (most probably) singly bonded L, and ends with a fully N_4-coordinated, stereochemically (and thermodynamically) unstable intermediate $(ML)_{int}$.

$$\text{1st stage:}\quad M + L \overset{K=4\ M^{-1}}{\rightleftharpoons} \{ML\} \xrightarrow{k_1 = 240\ s^{-1}} (ML)_{int} \qquad (22)$$

According to reaction sequence (23) (A, B ≡ intermediates), the second (slower) stage comprises three stereochemical rearrangement steps and leads finally to the

stereochemically (and thermodynamically) stable product ML ≡ *trans*-I-Ni(1,4-DMC)$^{2+}$.

$$\text{2nd stage:}\quad (\text{ML})_{\text{int}} \xrightarrow[1.2\ \text{s}^{-1}]{k_{\text{int1}}=} \text{A} \xrightarrow[4.3\times10^{-2}\ \text{s}^{-1}]{k_{\text{int2}}=} \text{B} \xrightarrow[4.7\times10^{-4}\ \text{s}^{-1}]{k_{\text{int3}}=} \text{ML} \qquad (23)$$

Rate constants k_{int1}, k_{int2} and k_{int3} are independent of the concentration of the excess partner.

One might argue that outer-sphere complex formation should be considered as step preceding first-bond formation. In the case of macrocyclic ligands such as cyclam, this argument is, however, questionable. There is good reason to assume that, due to the dynamics of conformational change of the cyclic molecule, its effective dipole moment is close to zero and the outer-sphere complex formation is, therefore, negligibly small.

Equilibrium constant $K = 4\ \text{M}^{-1}$ for the formation of the complex species {Ni(1,4-DMC)}$^{2+}$ with the singly bonded ligand is of the same order of magnitude as in the case of the systems nickel(II)/tet-a(**17a**) and nickel(II)/5,12-DMC(**18**) (see Table 3). In view of the fact that the product complex Ni(1,4-DMC)$^{2+}$ has the *trans*-I configuration [44], Schwamberger and Elias suggest that, mechanistically, rearrangement steps k_{int1} and k_{int2} refer to the conversions $(\text{ML})_{\text{int}} \rightarrow$ *trans*-II and *trans*-II → *trans*-I, respectively (see Fig. 1). The corresponding activation enthalpies, $\Delta H^{\neq}$,are found to be 72 kJ mol^{-1} (k_{int1}) and 110 kJ mol^{-1} (k_{int2}) (see Table 4). The last step (rate constant k_{int3}) is assigned to the conversion of the *trans*-I isomer with a parallel arrangement of the two ethylene bridges (*trans*-I(p)) into the *trans*-I isomer with antiparallel ethylene bridges (*trans*-I(ap)), which is reported to be energetically more favored [45]. The possible course of the overall reaction is schematically shown in Fig. 1.

For the reaction of the ligand 1,8-DMC(**29**) with nickel(II), equilibrium constant K is obviously rather small, so that $K\cdot[\text{L}]_{\text{max}}$ (and $K\cdot[\text{Ni}^{2+}]_{\text{max}}$) < 0.1. As a consequence (see Eq. (IIa)), the experimental rate constant k_{obs1} increases linearly with the concentration of the excess partner and leads to the parameter $k_1\cdot K = 770\ \text{M}^{-1}\ \text{s}^{-1}$ (see Table 4). In the presence of excess nickel, two first-order rearrangement steps are observed. The corresponding rate constants k_{int1} and k_{int2}, which are independent of the concentration of the excess nickel, are close to those obtained with the ligand 1,4-DMC(**24**) (see Table 4). In the presence of an excess of the ligand 1,8-DMC, the data obtained for K, k_{int1} and k_{int2} agree satisfyingly with those obtained in the presence of an excess of nickel. It is noteworthy, however, that the k_{int2} step is followed by a another step, which is linearly depending on the concentration of the excess ligand with second-order rate constant $k_{\text{int3}} = 0.13\ \text{M}^{-1}\ \text{s}^{-1}$ (see Table 4). The spectral changes associated with this final step suggest that the complex Ni(1,8-DMC)$_2^{2+}$ with six-coordinate nickel in a {N_4(folded),*cis*-N_2} environment is formed, as shown in Fig. 1. This complex has not been isolated yet.

Compared to the *N*-dimethylated ligands 1,4-DMC and 1,8-DMC, the ligand tmtet-a(**30**), bearing four *N*-methyl groups and six *C*-methyl groups, is expected to be much more rigid. The loss in flexibility is reflected by the corresponding rate data (see Table 4). The pseudo-second-order rate constant $k_1\cdot K$ is by three orders of magnitude smaller and so are first-order rate constants k_{int1} and k_{int2}. In

Table 4
Rate and equilibrium constants for complex formation of the N_4-donor macrocyclic ligands L = 1,4-DMC(**24**), 1,8-DMC(**29**), and tmtet-a(**30**) with nickel(II) and copper(II) in DMF at 298 K [44]

Ligand	Metal	First stage			Second stage		
		$k_1 \cdot K$(M^{-1} s^{-1}) {E_a}[a]	K (M^{-1}) {$\Delta H°$}[a]	k_1 (s^{-1}) {$\Delta H^{\neq}$}[a]	k_{int1} (s^{-1}) {$\Delta H^{\neq}$}[a]	k_{int2} (s^{-1}) {$\Delta H^{\neq}$}[a]	k_{int3} (s^{-1}) {$\Delta H^{\neq}$}[a]
1,4-DMC(**24**)	Ni	920 {53}	4.0 {−23}	230 {73}	1.2 {72}	4.3×10^{-2} {110}	4.7×10^{-4}
1,8-DMC(**29**)	Ni	770 {107}			1.2 {100}	1.9×10^{-2} {57}	0.13[b] {54}
tmtet-a(**30**)	Ni	0.50 {56}			2.2×10^{-4} {73}	5.0×10^{-5}	6.2×10^{-6} {91}
tmtet-a(**30**)	Cu	6400 {33}			1.0×10^{-2} {72}	5.3×10^{-3}	

[a] In kJ mol^{-1}.

[b] Second-order rate constant (M^{-1} s^{-1}) for the reaction of intermediate B (see reaction scheme (23)) with excess ligand 1,8-DMC to form $Ni(1,8\text{-DMC})_2^{2+}$ (see Fig. 1).

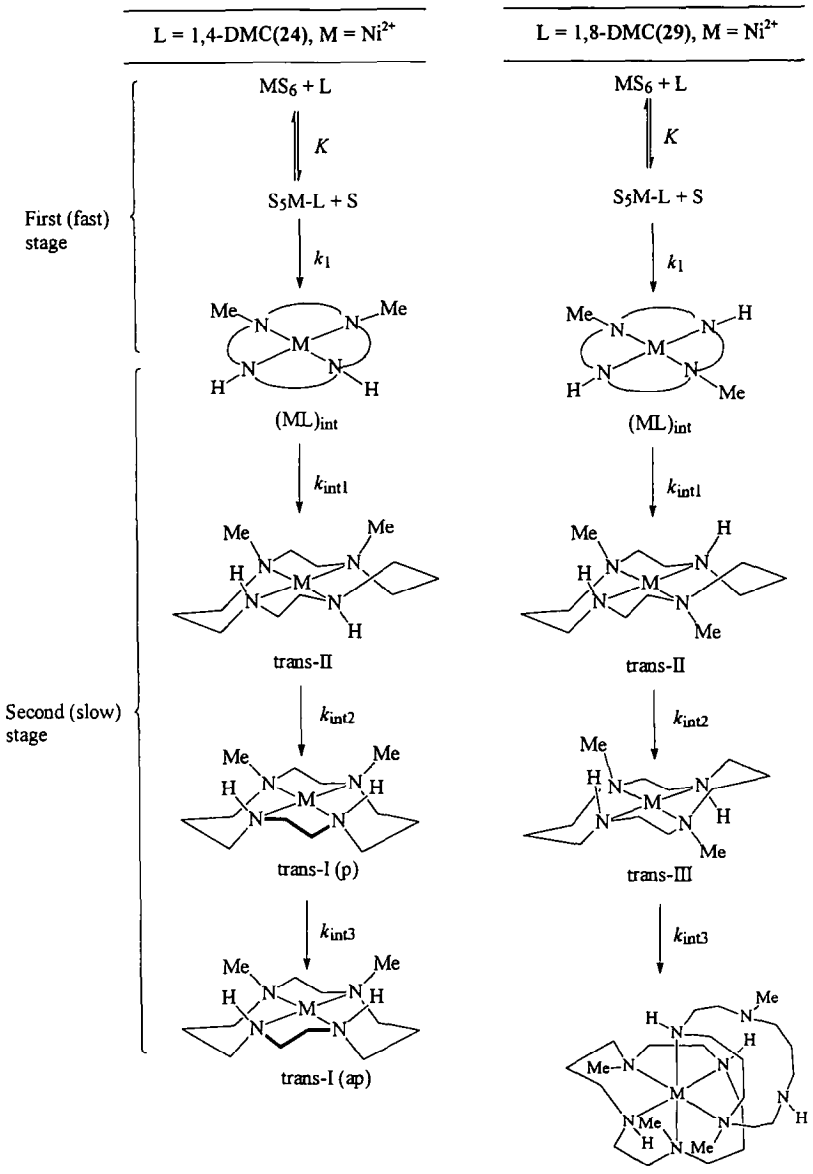


Fig. 1. Reaction scheme suggested for the course of complex formation of ligands **24** and **29** with nickel(II) in DMF.

addition, there is another very slow rearrangement step, characterized by $k_{int3} = 6.2 \times 10^{-6}$ s^{-1}. As expected, copper(II) reacts with tmtet-a(**30**) faster than nickel(II). The difference in rate is given by a factor of ca. 10^4 for the first stage and ca. 10^2 for the second stage (see Table 4).

Fig. 2 shows schemes suggested for the course of the reactions of tmtet-a(**30**) with nickel and copper. The assignment of specific ligand configurations to the various steps (as well as the corresponding assignments in Fig. 1) is based (i) on the known ligand configuration of the product complex ML, (ii) on vis-spectroscopic information and (iii) on the results of a molecular mechanics study on nickel(II) complexes

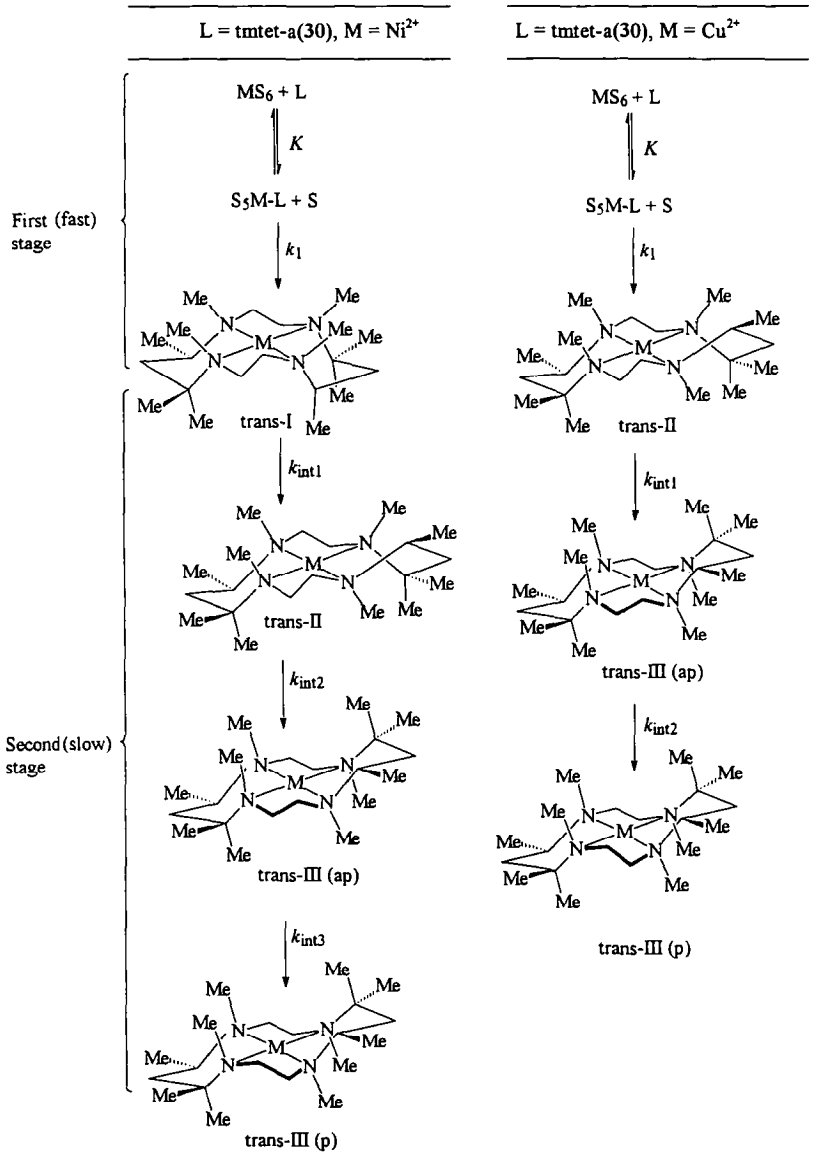


Fig. 2. Reaction scheme suggested for the course of complex formation of ligands **30** with nickel(II) ar copper(II) in DMF.

with N_4-donor macrocycles [45]. It follows from the latter study that, in the case of Ni(cyclam)$^{2+}$, the *trans*-I and *trans*-III isomer are the lowest in relative strain energy. The *trans*-II isomer, somewhat less favored than the *trans*-I and *trans*-III isomer, is calculated to be much more stable than the *trans*-IV and *trans*-V isomer. One has to keep in mind, however, that any *N*- or *C*-methylation of cyclam will affect the relative stabilities of the various configurational isomers.

4.3.5. Solvent and anion effects on the kinetics of complex formation with N_4-donor macrocycles of the cyclam type

Most of the results reported in Section 4 refer to studies carried out in the aprotic solvent DMF. As clearly shown by the work of Hertli and Kaden [34], the rate data obtained for the reaction of nickel(II) with cyclam(**2**) and TMC(**13**) in DMF differ substantially from those obtained in the aprotic solvent DMSO (see Table 1). In principle, these solvent effects can originate in the solvation of the metal cation as well as in the solvation of the ligand. One would expect, however, that the solvated metal cation plays a major role. It is well-documented for the medium water that the lability of the coordinated water in nickel complexes such as $Ni(H_2O)_6^{2+}$, $Ni(H_2O)_5(NH_3)^{2+}$, $Ni(H_2O)_4(NH_3)_2^{2+}$, $Ni(H_2O)_3(NH_3)_3^{2+}$ and $Ni(H_2O)_5Cl^+$ varies with the nature and composition of the first coordination sphere ([6]a). A variation of the inner solvation shell of the metal can be achieved most simply by changing the solvent S. Alternatively, the introduction of, for example, coordinating anions X^- generates species such as NiS_5X^+ in the case of nickel(II). Compared with the fully solvated cation, NiS_6^{2+}, these species should differ in the lability of the coordinated solvent and, as a consequence, in reactivity towards macrocyclic ligands.

*4.3.6. Kinetics of complex formation of 5,12-DMC(**18**) with nickel(II) in DMF containing an admixture of a less coordinating solvent*

The absorption spectrum of a solution of Ni(5,12-DMC)$(ClO_4)_2$ in nitromethane clearly proves the presence of the four-coordinate planar species Ni(5,12-DMC)$^{2+}$. In DMF, however, the spectrum indicates the formation of the six-coordinate species Ni(5,12-DMC)$(DMF)_2^{2+}$ [43]. These facts show that, compared with DMF, the solvent nitromethane is much less coordinating.

The reaction of 5,12-DMC(**18**) with nickel(II) in DMF, as described in detail in Section 4.3.3, leads to the intermediate $(Ni(5,12\text{-DMC}))_{int}^{2+}$ in the first step. In the presence of excess nickel, the corresponding experimental rate constant, k_{obs1}, depends on $[Ni^{2+}]$ according to Eq. (II). Interestingly, the size of k_{obs1} increases when the medium DMF is diluted with nitromethane [42]. In pure DMF (i.e. [DMF] = 12.9 M), rate constant k_{obs1} is found to be 7.3 s^{-1} under given conditions of concentration and temperature. Keeping these conditions constant, one observes a considerable increase in k_{obs1} upon stepwise admixture of nitromethane. At the very low concentration of [DMF] = 0.5 M in the solvent mixture, rate constant k_{obs1} has increased to 165 s^{-1}. The dependence of k_{obs1} on [DMF] is of the type $k_{obs1} \sim [DMF]^{-1}$. Admixture of the non-coordinating solvent 1,2-dichloroethane to the medium DMF has an analogous rate-enhancing effect.

These preliminary results demonstrate the significance of the solvent. The kinetic interpretation of the observed effects is difficult. It is reasonable to assume that the less coordinating solvent nitromethane (NM) partially enters the inner solvation shell of the nickel ion to form species such as $Ni(DMF)_5(NM)^{2+}$, $Ni(DMF)_4(NM)_2^{2+}$ and $Ni(DMF)_3(NM)_3^{2+}$. In these species the lability of the coordinated solvent molecules is probably increased. In the case of the non-coordinating solvent 1,2-dichloroethane (DE) partial dissociation of the cation $Ni(DMF)_6^{2+}$ and changes in coordination number and coordination geometry according to equilibria (24) are also conceivable.

$$Ni(DMF)_6^{2+} \rightleftharpoons Ni(DMF)_5^{2+} + DMF \rightleftharpoons Ni(DMF)_4^{2+} + 2DMF \quad (24)$$

Compared with the cation $Ni(DMF)_6^{2+}$, species such as $Ni(DMF)_5^{2+}$ and $Ni(DMF)_4^{2+}$ with a reduced coordination number are probably much more reactive with regard to complex formation with N_4-donor macrocyclic ligands.

4.3.7. The kinetic effect of coordinating ligands such as chloride

The reaction of TMC(**13**) with nickel(II) in DMF, as studied by Röper and Elias under 1:1 conditions at $I = 0.1$ M ($NaClO_4$) [36], follows reaction scheme (14) (see Section 4.2 and Table 1). Fast second-order intermediate formation is followed by slow first-order rearrangement of the *trans*-II isomer to the *trans*-I isomer $Ni(TMC)(DMF)^{2+}$ according to reaction (15).

In the presence of chloride ions ($[Cl^-]/[Ni^{2+}] = 1.3:1$, $[TMC]/[Ni^{2+}] = 1:1$), the fast incorporation step, as characterized by the second-order rate constant k, is accelerated by a factor of 117 (see Table 5) [46]. Interestingly, the consecutive isomerization step, as characterized by the first-order rate constant k_{int}, is practically not affected. As following from the vis spectra, the intermediate complex is $Ni(TMC)Cl_{int}^+$ (instead of $Ni(TMC)_{int}^{2+}$) and the product complex is $Ni(TMC)Cl^+$ (instead of $Ni(TMC)(DMF)^{2+}$).

Ishiguro et al. [47] have reported the equilibrium constants for the stepwise formation of nickel chloro complexes in DMF according to equilibria (25).

$$Ni^{2+} + 4Cl^- \overset{K_1}{\rightleftharpoons} NiCl^+ + 3Cl^- \overset{K_2}{\rightleftharpoons} NiCl_2 + 2Cl^- \overset{K_3}{\rightleftharpoons} NiCl_3^- + Cl^- \overset{K_4}{\rightleftharpoons} NiCl_4^{2-} \quad (25)$$

One can thus calculate that, under the given conditions for the system $TMC/Ni^{2+}/Cl^-$ (see Table 5), the monochloro species $Ni(DMF)_5Cl^+$ is dominating (61% $Ni(DMF)_5Cl^+$, 38% $Ni(DMF)_6^{2+}$, 1% $Ni(DMF)_xCl_2$). It is therefore reasonable to assume, that the more than 100-fold increase in the rate of intermediate formation has to be ascribed to the greater reactivity of this species compared to that of the hexasolvated cation $Ni(DMF)_6^{2+}$. As in the case of the monochloro aqua species $Ni(H_2O)_5Cl^+$ ([6]a), the inner solvent shell is labilized by the coordinated chloride, due to *cis*- and *trans*-effects and the reduction of the overall charge from +2 to +1.

The addition of bromide instead of chloride increases the rate of formation of the intermediate $Ni(TMC)Br_{int}^+$ by a factor of four only (see Table 5). An explanation for this comparatively small rate effect could lie in a smaller formation constant for

Table 5
Rate constants for complex formation of ligands TMC(13) and TEC(31) with nickel(II) in DMF according to *reaction scheme* (9) in the presence of halide ions X^- (298K, $I = 0.3$ M)

Ligand	$[Ni^{2+}] = [Ligand]$ ($M \times 10^{-3}$)	Halide X	$[X^-]$ ($M \times 10^{-3}$)	k ($M^{-1} s^{-1}$)	k_{int1} ($10^{-4} s^{-1}$)	k_{int2} ($10^{-4} s^{-1}$)	Ref.
TMC(13)[a]	2			40	7.3		[46]
TMC(13)[a]	3	Cl	4	4700	3.6		[46]
TMC(13)[a]	3	Br	4	160	5.6		[46]
TEC(31)[b]	1			47	400	65	[48]
TEC(31)[b]	1	Cl	1	220	350	72	[48]

[a] Ionic strength I adjusted with tetra-*n*-butylammonium hexafluorophosphate.
[b] Ionic strength I adjusted with tetra-*n*-butylammonium perchlorate.

the species $Ni(DMF)_5Br^+$ in the system nickel(II)/bromide/DMF. Alternatively, it is also conceivable that the stability of the halo species $Ni(TMC)X^+$ (as expressed by equilibrium constant $K(X)$ for reaction (26)) is essential.

$$Ni(TMC)^{2+} + X^- \overset{K(X)}{\rightleftharpoons} Ni(TMC)X^+ \quad (26)$$

In DMF solution, $K(Cl)$ is very high an can only be estimated ($K(Cl) > 10^6\ M^{-1}$), whereas $K(Br)$ is found to be considerably smaller ($K(Br) = 2.4 \times 10^4\ M^{-1}$) [46].

As pointed out above, the spectra obtained for the reaction of TMC(**13**) with nickel(II) in the presence of chloride ions clearly show that chloride is bound to the nickel in the rapidly formed intermediate as well as in the final product. In view of the Ni–N bond inversion mechanism suggested for the isomerization of $Ni(TMC)^{2+}_{int}$ (see reaction (15)), it is surprising to find that the intermediates $Ni(TMC)Cl^+_{int}$ and $Ni(TMC)^{2+}_{int}$ isomerize at practically the same rate (see data for k_{int1} in Table 5). Another puzzling finding is that, compared with the ligand TMC(**13**), the reaction of the tetra *N*-ethylated ligand TEC(**31**) with nickel(II) is only weakly accelerated by chloride ions (see Table 5).

In summary, the rate of complex formation of N_4-macrocyclic ligands of the cyclam type with nickel(II) in DMF is rather specifically affected by admixtures of less coordinating or non-coordinating solvents and by coordinating anions. It is obvious that this sort of solvent and anion effects needs to be studied in greater detail.

5. Summary and conclusions

The early work on the kinetics of complex formation of N_4-donor macrocycles L of the cyclam type with nickel(II) and copper(II) in aprotic organic media according to reaction (a) led to the two-stage reaction pattern (b).

$$M^{2+} + L \rightleftharpoons ML^{2+} \quad (a)$$

The initial second-order intermediate formation is followed by slow first-order product formation.

$$M^{2+} + L \xrightarrow{k\ (M^{-1}s^{-1})} (ML^{2+})_{int} \xrightarrow{k_{int}\ (s^{-1})} ML^{2+} \quad (b)$$

$$|\leftarrow \textit{initial (fast) stage} \rightarrow|\leftarrow \textit{second (slow) stage} \rightarrow|$$

The size of second-order rate constant k was found to depend critically on the position, number and nature of substituents on L. In contrast to k, first-order rate constant k_{int} was found to be much less affected by substituents on L. In the intermediate complex $(ML^{2+})_{int}$ the metal has achieved planar N_4-coordination geometry.

With regard to the mechanism, it was suggested that formation of the second M–N bond controls the rate of intermediate formation. The consecutive first-order step (rate constant k_{int}) was interpreted to be a stereochemical rearrangement reaction.

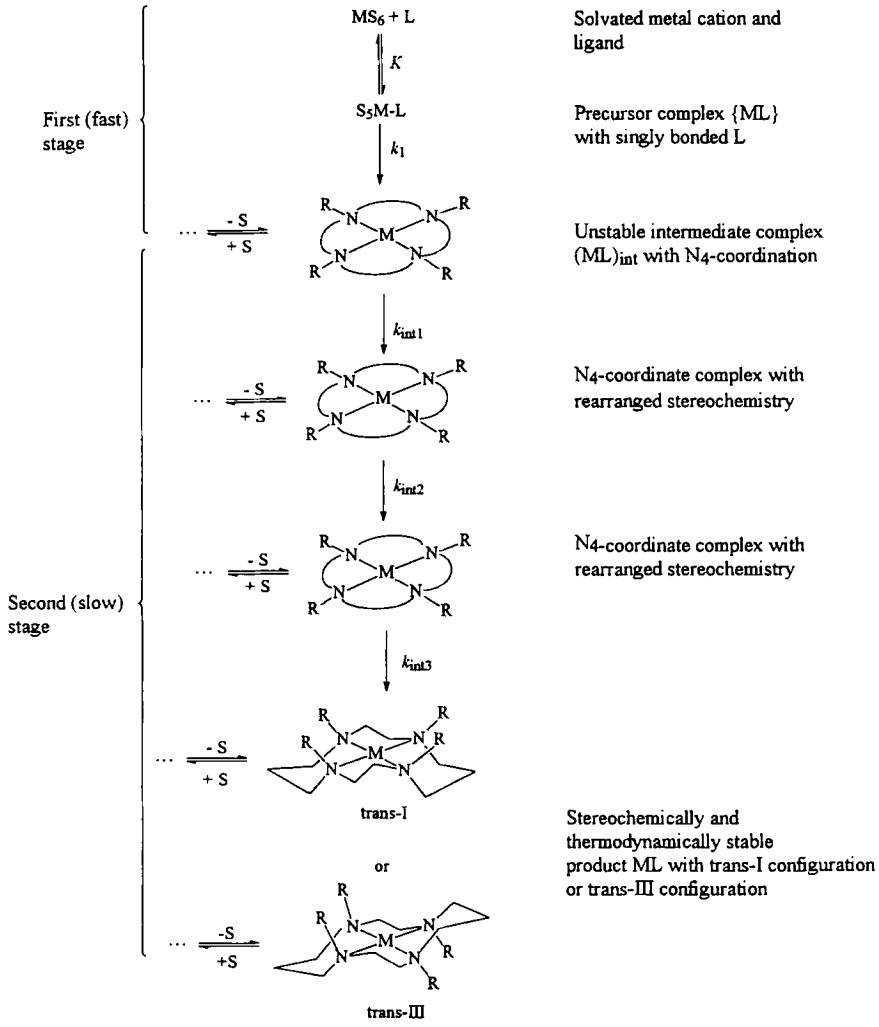


Fig. 3. General reaction scheme suggested for the course of complex formation of N_4-donor macrocyclic ligands L of the cyclam type with divalent metal cations in aprotic solvents S such as DMF (charges omitted).

More recent studies show that the two-stage reaction pattern (b) is basically correct, but for most ligands not detailed enough. As suggested schematically in Fig. 3, both stages have to be refined. In the first stage, rate-limiting formation of the second M–N bond (i.e. closure of the first chelate ring), is preceded by a fast equilibrium between the solvated metal cation and a precursor complex with (most probably) singly bonded L. The equilibrium constant K and first-order rate constant k_1 control the rate of intermediate formation (formation of the third and fourth M–N bond is too fast to be observed on the stopped-flow time scale). The first stage of the overall reaction leads to a stereochemically (and thermodynami-

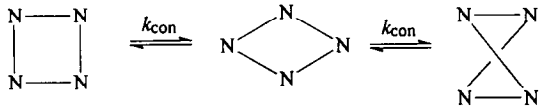
cally) unstable intermediate complex with planar N_4-coordination of the metal. Depending on the pattern of substituents on the ligand L, the second stage is found to consist of up to three first-order reorganization steps. In these steps, rearrangement of the carbon skeleton and M–N bond inversion occurs, which finally leads to the stereochemically and thermodynamically most stable *trans*-I or *trans*-III configurated product complex. Within the series of first-order rearrangement steps, the *trans*-II isomer plays probably a major role. It is important to note that, in the presence of bases (such as, for example, excess ligand) the rearrangement steps can be subject to base catalysis. In addition, all of the intermediate complexes and also the final product complex are subject to ligand-specific solvation of the metal site.

The reaction sequence suggested in Fig. 3 is general in the sense that intermediate formation and subsequent intermediate rearrangement is typically found for complex formation of nickel(II) and copper(II) with all of the N_4-macrocyclic ligands L studied. Ligand specificity expresses itself in the size of K and k_1 (first stage) and in the number of rearrangement steps following intermediate formation (second stage).

The Eigen–Wilkins mechanism correlates the rate of complex formation with the rate of solvent exchange on the metal, whereas the Eigen–Winkler mechanism allows for the rate of conformational change of the ligand L to become rate-limiting. Does the mechanistic scheme in Fig. 3, as suggested for intermediate formation, correspond to one of these two mechanisms? The answer to be given is obviously yes and no.

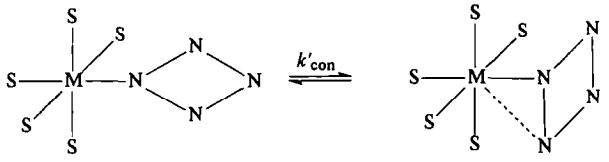
As a matter of fact, a highly substituted cyclam derivative such as tmtet-a(**30**) forms the intermediate complex with copper(II) and nickel(II) at such a low rate that the idea of rate control by solvent exchange on these metals has to be rejected. On the other hand, intermediate formation of this ligand with copper is by more than four orders of magnitude faster than with nickel, which reflects the greater lability of the solvated copper cation, as expressed by $k_{ex}(Cu(DMF)_6^{2+})/k_{ex}(Ni(DMF)_6^{2+}) = 2.4 \times 10^5$.

The consideration of ligand rigidity as well as of metal lability provides a reasonable explanation for the fact that, even in the case of very rigid cyclam derivatives, the reaction with copper is considerably less slow than the reaction with nickel. As schematically shown by reaction (c), the ligand L is subject to fast conformational change (rate constant k_{con}).



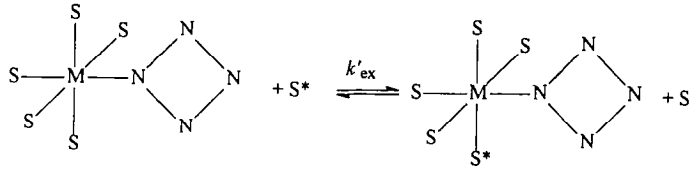
(c)

The rate of this conformational change will be reduced, when L is singly bonded to the metal in the precursor complex (see reaction (d); $k'_{con} < k_{con}$).



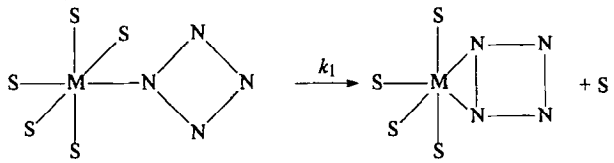
(d)

As schematically shown in reaction (e), in the precursor complex the rate of solvent exchange on the metal will also be changed ($k_{ex} \neq k'_{ex}$).



(e)

If formation of the second M–N bond according to reaction (f) is controlling the rate of intermediate formation, the rate of this step (rate constant k_1) will depend on both k'_{con} and k'_{ex}.



(f)

The rate constant k'_{con} determines the rate at which the partially coordinated ligand offers the second N-donor atom in a spatial arrangement close enough to the metal. On the other hand, rate constant k'_{ex} determines the rate at which the metal in the precursor complex offers a vacant site (or labilized solvent molecule) on the metal. Due to $k'_{ex}(Cu) \gg k'_{ex}(Ni)$, even with very rigid ligands L (for which k'_{con} is small) the copper will catch a properly positioned second N-donor atom of L faster than the nickel. In the case of a comparatively flexible ligand L such as non-substituted cyclam (for which k'_{con} is large), rate constant k_1 may well be close to rate constant k_{ex} for solvent exchange on the metal. Intermediate formation may thus appear to be metal-controlled (Eigen–Wilkins mechanism).

Unfortunately, data for k'_{con} and k'_{ex} are not available (and hard to determine).

In conclusion, the present results confirm that substituted N_4-donor macrocyclic ligands of the cyclam type represent indeed a special type of chelate ligand. In order to describe the mechanism of metal complex formation of these ligands plausibly one has to invoke elements of the metal-based Eigen–Wilkins mechanism as well as elements of the ligand-based Eigen–Winkler mechanism.

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