Dendrimers as Ligands: An Investigation into the Stability and Kinetics of Zn^{2+} Complexation by Dendrimers with 1,4,8,11-Tetraazacyclotetradecane (Cyclam) Cores

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Abstract: We have investigated the complexation of Zn^{2+} with 1,4,8,11-tetrakis(naphthylmethyl) cyclam (**1**; cyclam = 1,4,8,11-tetraazacyclotetradecane) and with two dendrimers consisting of a cyclam core with four dimethoxybenzene and eight naphthyl appendages (**2**), and twelve dimethoxybenzene and sixteen naphthyl appendages (**3**). An important, common feature of model compound **1** and dendrimers **2** and **3** is that their potentially fluorescent naphthyl units are quenched by exciplex formation with the cyclam nitrogen atoms. Complexation with Zn^{2+}, however, prevents exciplex formation and results in the appearance of an intense naphthyl fluorescence signal that can be used for monitoring the complexation process. Luminescence titration, together with competition experiments and ^{1}H NMR titration, have shown that 1:1 and 1:2 (metal/ligand) complexes are formed in the cases of **2** and **3**, whereas model compound **1** gives only a 1:1 complex. We have also investigated the 1:1 complexation kinetics by the stopped-flow technique. In the case of **1**, a second-order process ($k_1 = 44\times10^5\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$) is followed by two consecutive first-order steps ($k_2 = 0.53\,\mathrm{s}^{-1}$ and $k_3 = 0.10\,\mathrm{s}^{-1}$). For **2**, a slower second-order process ($k_1 = 4.9\times10^5\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$) is followed by a slow first-order step ($k_2 = 0.40\,\mathrm{s}^{-1}$). In the case of **3**, only a very slow second-order process was observed ($k_1 = 1.2\times10^5\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$). The different metal–ion incorporation rates for model compound **1** and dendrimers **2** and **3** have been discussed in terms of conformational changes of the dendron subunits affecting the chelating properties of the cyclam core. This work reports the first kinetic study on metal–ion coordination by dendrimers with a well-defined coordination site.

Keywords: cyclams · dendrimers · kinetics · luminescence · zinc

Introduction

Dendrimers[1,2] are currently attracting great attention due to their unusual and tunable chemical and physical properties, and the wide range of potential applications. An important feature of dendrimers is the presence of internal, dynamic cavities,[3] often containing moieties capable of coordinating metal ions. Research on dendrimer-based host–guest systems has been performed for a variety of purposes that include preparation of encapsulated metal nanoparticles,[4] dioxygen binding,[5] ion transportation,[6] ion sensing,[7] light harvesting,[8,9] and stepwise complexation.[10] Metal ions have also been used to assemble coordinating dendrons[11] and as branching centers in dendrimer synthesis.[12] However, dendrimers with a well-defined metal-coordinating core have seldom been reported,[13] the exception being porphyrin-based systems.[14]

1,4,8,11-Tetraazacyclotetradecane (cyclam) is one of the most extensively investigated ligands in coordination chemistry.[15] In aqueous solution, cyclam can coordinate

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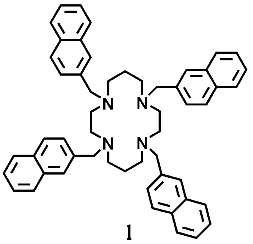
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Table S1 lists the rate constants for complex formation of ligands **1**, **2**, and **3** with Zn^{2+} in acetonitrile/dichloromethane 1:1 at 298 K with a Zn^{2+}-to-ligand ratio ranging from 3 to 10.

DOI: 10.1002/chem.200305255

metal ions such as Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+} to give 1:1 complexes with very large stability constants.[16] Currently, cyclam and its derivatives are extensively investigated in medicine for imaging applications[17] and as carriers of metal ions in antitumor[18] and anti-HIV[19] agents. For all these reasons, we thought that cyclam was a suitable and most interesting core for constructing dendrimers capable of coordinating metal ions. Therefore, we have synthesized[20] two dendrimers consisting of a cyclam core with four dimethoxybenzene and eight naphthyl appendages (**2**), and twelve dimethoxybenzene and sixteen naphthyl appendages (**3**). For comparison purposes, we have also prepared and investigated tetrakis(naphthylmethyl) cyclam[21] (**1**) as a model compound. In a previous paper,[20] we have shown that a common feature of **1** and dendrimers **2** and **3** is that their potentially fluorescent naphthyl units are quenched by exciplex formation with the cyclam nitrogen atoms. Complexation with Zn^{2+}, however, engages the nitrogen lone pairs and thereby prevents exciplex formation, with a resulting intense naphthyl fluorescence signal. This strong signal is quite suitable for monitoring the formation of complexes in ligand–metal titration experiments.[22]



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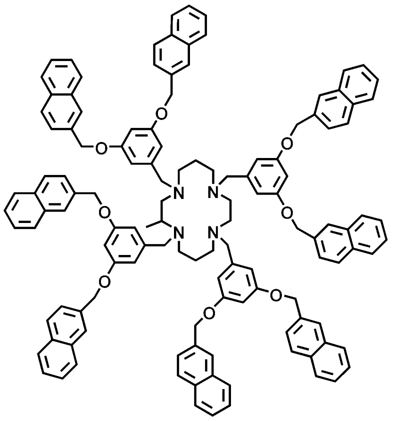

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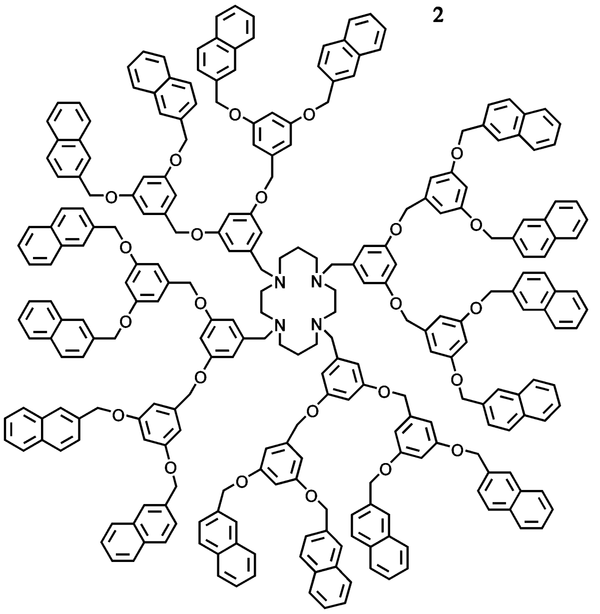

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Few kinetic studies have so far been performed on the incorporation of substrates into dendrimers.[13,23,24,25] Aida et al. reported a kinetic investigation on the oxidation of active centers encapsulated within aryl ether dendrimers of different sizes.[13,25] Kinetic investigations can provide useful information on the accessibility of coordination sites buried in the dendrimer structures. In this paper we report a systematic study of the complexation stoichiometry of model compound **1** and dendrimer ligands **2** and **3** with Zn^{2+} in a wide range of concentrations, and the kinetics of the complexation process investigated by the stopped-flow technique. It should be noted that kinetic investigations on metal–macrocyclic complexes are usually performed by monitoring changes in the d–d absorption bands. In the case of Zn^{2+}, however, this handle is not available. Instead, cyclam ligands **1**–**3** provide an opportunity to investigate the complex formation from the changes of the emission bands.

Experimental Section

Compound **1** and dendrimers **2** and **3** were synthesized as previously described.[20] $Zn(CF_3SO_3)_2$ was obtained from Aldrich. The acetonitrile and dichloromethane for spectroscopy were purchased from Merck. All the luminescence measurements were carried out in an air-equilibrated CH_3CN/CH_2Cl_2 1:1 v/v solution at 298 K with a Perkin Elmer LS50 spectrofluorimeter. Titration curves were obtained by evaluating the spectra with the SPECFIT software.[26]

^1H NMR experiments were carried out in CD_3CN/CD_2Cl_2 (1:1 v/v) at 298 K with Bruker AM 400 equipment (400 MHz).

Stopped-flow experiments were performed in a CH_3CN/CH_2Cl_2 mixture (1:1 v/v) at 298 K with Applied Photophysics SX 18-MV equipment. The complex formation between compounds **1**–**3** and Zn^{2+} (as the $CF_3SO_3^-$ salt) was monitored by the change in the fluorescence intensity above 305 nm, upon excitation at 275 nm. The experiments were performed with a moderate excess of metal salt, that is, with a $[Zn^{2+}]_0/[L]_0$ ratio lying in the range of 3 to 10. The rate constants were evaluated with the fitting software SPECFIT.[26] In the case of **3**, the kinetics of complexation was also studied under pseudo-first-order conditions ($[Zn^{2+}]_0 \geq 10[L]_0$), and the observed rate constant was computed by an iterative procedure, in which one exponential function was fitted to the fluorescence versus time data by using global analysis software. For each set of conditions, a series of four to six experiments were performed and the resulting data were averaged.

Results and Discussion

Stoichiometry of the complexes: Compound **1** exhibits a broad emission band with a maximum around 480 nm, which is assigned to the formation of exciplexes between the cyclam nitrogen atoms and excited naphthyl units (dotted line in Figure 1a). Dendrimers **2** and **3** (dotted lines in Figure 1b and c) exhibit three types of weak emission bands, assigned to naphthyl-localized excited states ($\lambda_{max} = 337$ nm), naphthyl excimers (λ_{max} ca. 390 nm), and naphthyl–amine exciplexes ($\lambda_{max} = 480$ nm).[20]

Titration of ligand **1** (2.93×10^{-5} M) with Zn^{2+} (as the $CF_3SO_3^-$ salt) causes the disappearance of the exciplex emission and the appearance of a strong naphthyl-localized fluorescence (solid line in Figure 1a). The titration plot (Figure 1a′) shows the formation of a stable 1:1 Zn/ligand spe-

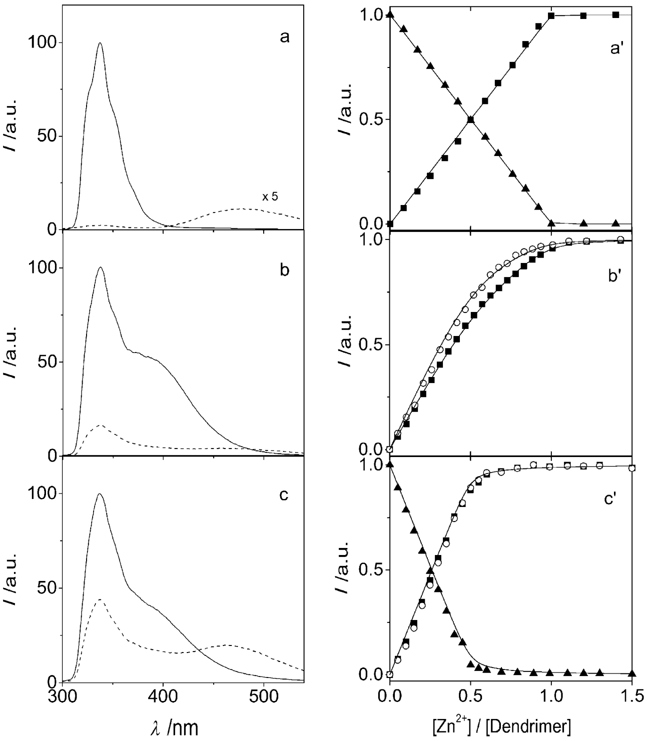

Figure 1. Graphs a), b), and c) show the luminescence spectrum of **1** (2.93×10^{-5} M), **2** (1.26×10^{-5} M), and **3** (6.65×10^{-6} M), respectively, before (dashed line) and after (full line) addition of a stoichiometric amount of $Zn(CF_3SO_3)_2$ in CH_3CN/CH_2Cl_2 (1:1 v/v) at 298 K with $\lambda_{exc} = 275$ nm. The normalized fluorescence intensity changes observed upon addition of $Zn(CF_3SO_3)_2$ to **1**, **2**, and **3** are depicted in graphs a'), b'), and c'), respectively (■ = 337 nm, ○ = 390 nm, ▲ = 480 nm).

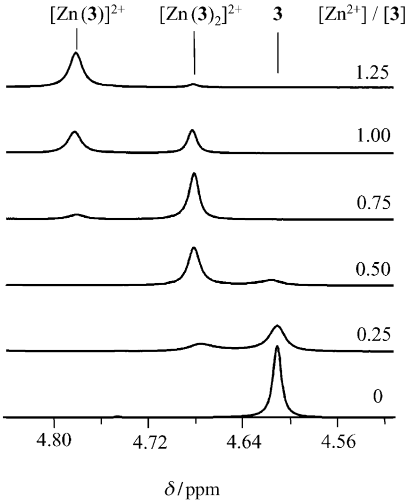

Figure 2. ^{1}H NMR titration of **3** (6.40×10^{-4} M) with $Zn(CF_3SO_3)_2$ in CD_3CN/CD_2Cl_2 (1:1 v/v) at 298 K. Spectral evolution of the Ar–CH_2–O–Ar resonance. The assignments of the observed peaks and the $[Zn^{2+}]/[\mathbf{3}]$ ratio are indicated.

cies $[Zn(\mathbf{1})]^{2+}$. This result is in agreement with previous investigations.[21]

Titration of dendrimer **3** (6.65×10^{-6} M) with Zn^{2+} causes the disappearance of the exciplex band, with a concomitant increase in the excimer and naphthyl-localized emissions (solid line in Figure 1c). In this case, monitoring the emission intensity at 337 nm (naphthyl emission) and 390 nm (excimer emission) yielded coincident linear plots (Figure 1c′) that reach a plateau for 0.5 equivalents of Zn^{2+}, showing the unexpected formation of a 1:2 Zn/ligand species, $[Zn(\mathbf{3})_2]^{2+}$. Fitting of the data yielded $\log\beta_{1:2} = 13.4 \pm 0.2$ for the formation constant of this complex. On increasing the Zn^{2+} concentration, it can be expected that the $[Zn(\mathbf{3})_2]^{2+}$ species is gradually replaced by a $[Zn(\mathbf{3})]^{2+}$ species. Although evidence of the formation of such a species is not apparent from the plot of Figure 1c′, it should be noted that $[Zn(\mathbf{3})_2]^{2+}$ and $[Zn(\mathbf{3})]^{2+}$ could have the same fluorescence response, since the metal ion could prevent formation of exciplexes in both species. This seems indeed to be the case, since formation of a $[Zn(\mathbf{3})]^{2+}$ species at more than 0.5 equivalents of Zn^{2+} is evidenced by NMR experiments, which have also fully confirmed the formation of a $[Zn(\mathbf{3})_2]^{2+}$ complex at lower Zn^{2+} concentration (Figure 2).

Titration of dendrimer **2** (1.26×10^{-5} M) causes the disappearance of the exciplex band, with a concomitant increase in the excimer and naphthyl-localized emissions (solid line in Figure 1b). In this case, as depicted in Figure 1b′, slightly different plots have been obtained on monitoring the emission intensity at 337 nm (naphthyl emission) or 390 nm (excimer emission). This point will be discussed below. In addition, both plots are nonlinear and reach a plateau after addition of about one equivalent of Zn^{2+}. This behavior shows that more than one species is formed. Implementation of the spectral changes in the SPECFIT software[26] yielded a fitting curve corresponding to the formation of 1:2 ($[Zn(\mathbf{2})_2]^{2+}$) and 1:1 ($[Zn(\mathbf{2})]^{2+}$) complexes, with association constants $\log K_1 = 5.7 \pm 0.4$ M^{-1} and $\log K_2 = 7.9 \pm 0.3$ M^{-1}, respectively.

All the complexes of cyclam and cyclam derivatives with metal ions reported so far have displayed 1:1 stoichiometry.[16] However, kinetic evidence for the formation of a 2:1 $[Ni(1{,}8\text{-dimethylcyclam})_2]^{2+}$ species has been reported.[27] The unexpected $[Zn(\mathbf{3})_2]^{2+}$ and $[Zn(\mathbf{2})_2]^{2+}$ species formed by the cyclam dendritic ligand **3** and **2**, respectively, show that the dendrimer branches not only do not hinder, but in fact favor coordination of cyclam to Zn^{2+}, with respect to the coordination of solvent molecules or counter ions.

Stability of the complexes: The results obtained show that: 1) model compound **1** forms a strong 1:1 complex with Zn^{2+}, 2) dendrimer **2** gives rise to both 1:1 and 2:1 complexes, with the former being more stable than the latter, and 3) dendrimer **3** forms both 1:1 and 2:1 complexes, with the latter being more stable than the former.

The formation of a stable $[Zn(\mathbf{3})_2]^{2+}$ species has been further confirmed by competition experiments.

Competition between dendrimer 3 and 2,2′-bipyridine for complexation of Zn^{2+}: We have found that under our experimental conditions, the absorption band of 2,2′-bipyridine with a maximum at 280 nm moves towards lower energies (305 nm) upon complexation with Zn^{2+}.[28] On addition of

2,2′-bipyridine to a solution containing **3** and Zn^{2+} in a 2:1 ratio, no increase in absorption was observed in the 305 nm region. This result shows that in such a solution all the Zn^{2+} ions are engaged in a stable $[Zn(\mathbf{3})_2]^{2+}$ species. For a solution containing **3** and Zn^{2+} in a 1:1 ratio, addition of 2,2′-bipyridine causes the formation of a band at 305 nm, showing that either the 1:1 $[Zn(\mathbf{3})]^{2+}$ species are labile or contain coordinatively unsaturated Zn^{2+} ions that can coordinate the 2,2′-bipyridine.

Competition between H^+ and Zn^{2+} for coordination to ***3***: We have previously reported that the addition of trifluoroacetic acid causes protonation of the cyclam core of **3**, thereby preventing the formation of exciplexes and causing an increase in the naphthyl-localized fluorescence,[20] as does metal–ion coordination. Addition of trifluoroacetic acid to a solution containing **3** and Zn^{2+} in a 2:1 ratio does not cause any increase in the naphthyl-localized fluorescence, showing that all the dendrimers are engaged with Zn^{2+}. Similar competition experiments performed on a solution containing **1** and Zn^{2+} in a 2:1 ratio showed that half of the ligand is in its free form.

Conformations of the complexes: Whereas cyclam usually gives 1:1 metal complexes, we have found that the presence of bulky dendritic substituents favors the coordination of two cyclam moieties to Zn^{2+}. This surprising result can be tentatively rationalized by considering two limiting structures for the 2:1 complexes: The first is an *inward* structure, stabilized by the intermeshing of the branches of the two coordinated dendrimers. The second is an *outward* structure in which the branches of the two coordinated dendrimers do not interact, but impose on the cyclam core a very specific coordination structure.

An *inward* structure for the 2:1 complex, stabilized by branch intermeshing, should increase the probability of excimer formation compared with the 1:1 species. In such a case, the intensity of the excimer band (λ_{max} ca. 390 nm) should increase more rapidly at the beginning of the titration, when formation of a 2:1 species is favored. This seems to be the case for dendrimer **2** (Figure 1b′), which gives rise to both $[Zn(\mathbf{2})_2]^{2+}$ and $[Zn(\mathbf{2})]^{2+}$ species from the beginning of the titration. For dendrimer **3**, however, which forms only a $[Zn(\mathbf{3})_2]^{2+}$ species at low Zn^{2+} concentrations, there is no evidence of a decreasing number of excimers on increasing the Zn^{2+} concentration (Figure 1c′). Therefore, it seems more likely that for $[Zn(\mathbf{3})_2]^{2+}$ the dendrimer branches extend outward. Furthermore, the two cyclam cores, to account for the coordination number (≤ 6) of Zn^{2+}, are likely forced to adopt a structure in which not all of the four N atoms are available for Zn^{2+} coordination, thereby favoring a 2:1 stoichiometry.

Kinetics of complex formation: Formation of a complex between a metal ion and a cyclic multidentate ligand involves, of course, a sequence of several steps.[27] Investigations performed on the kinetics of complex formation, between Ni^{2+} and Cu^{2+} metal ions and ligands of the cyclam family in dipolar aprotic solvents, have led to the identification of the general reaction sequence comprising two consecutive stages [Eq. (1)].[27,29]

$$\begin{array}{l} M^{2+} + L \rightarrow (ML^{2+})_{int} \rightarrow [ML]^{2+} \\ |\leftarrow \text{Fast stage} \rightarrow | \leftarrow \text{Slow stage} \rightarrow | \end{array} \tag{1}$$

In the first stage, a fast equilibrium is established between the solvated metal ion M^{2+} and a precursor complex $(ML)^{2+}$, in which the multidentate ligand is bonded with only one of the nitrogen atoms. This equilibrium is followed by a rate-limiting step leading to the coordination of a second nitrogen. A possible rate-limiting factor is supposed to be due to conformational changes of the ligand prior to a second metal–nitrogen bond formation. Subsequent coordination of the two remaining nitrogen atoms is thought to be very fast, since after coordination of the first two nitrogen atoms, the two remaining coordination sites are very close to the metal. The complex obtained, $(ML^{2+})_{int}$, is stereochemically and thermodynamically unstable and, depending on the pattern of substituents, may undergo up to three reorganization steps involving rearrangement of the carbon skeleton and metal–nitrogen inversion processes that finally lead to stereochemically and thermodynamically stable complexes.[27] The presence of N-substituents has, of course, an important effect on all these processes.

It is worth noting that the coordination of Zn^{2+} into compound **1** and dendrimers **2** and **3** does not cause an appreciable change in the absorbance; thus, the kinetic investigations could not be performed by means of this detection method. In these compounds, however, the fluorescence of the naphthyl groups is strongly quenched by the formation of exciplexes involving the nitrogen lone pairs of the cyclam core.[20] Complexation of the cyclam unit with Zn^{2+} prevents exciplex formation and causes a strong increase in the fluorescence intensity of the naphthyl units. Therefore, the kinetics of complex formation can be followed by monitoring the change in the fluorescence intensity. Usually for a reaction sequence, only the slower processes can be experimentally evidenced. It should also be considered that some of the steps might not cause appreciable changes in the signal that is used for monitoring the process.

In preliminary experiments we have verified that under our experimental conditions: 1) the mixing of CH_3CN/CH_2Cl_2 1:1 solutions does not cause optical artefacts in the stopped-flow-observation cell and 2) both the dendrimers and their complexes are photo stable (see Figure 3). The experiments were performed with a moderate excess of metal ion in order to form only 1:1 complexes, a stoichiometry exhibited by all three ligands.

For the reaction of Zn^{2+} with **1**, a good fitting of the fluorescence intensity versus time plot (Figure 3) requires the presence of three consecutive steps, namely a second-order association step $k_1 = (44 \pm 1) \times 10^5\, \text{M}^{-1}\text{s}^{-1}$ with about 65% signal amplitude, followed by two first-order rearrangement steps (rate constants $k_2 = 0.53 \pm 0.04\, \text{s}^{-1}$ and $k_3 = 0.10 \pm 0.02\, \text{s}^{-1}$). The experiments performed with different concentrations of Zn^{2+} and **1** (Table S1 in the Supporting Informa-

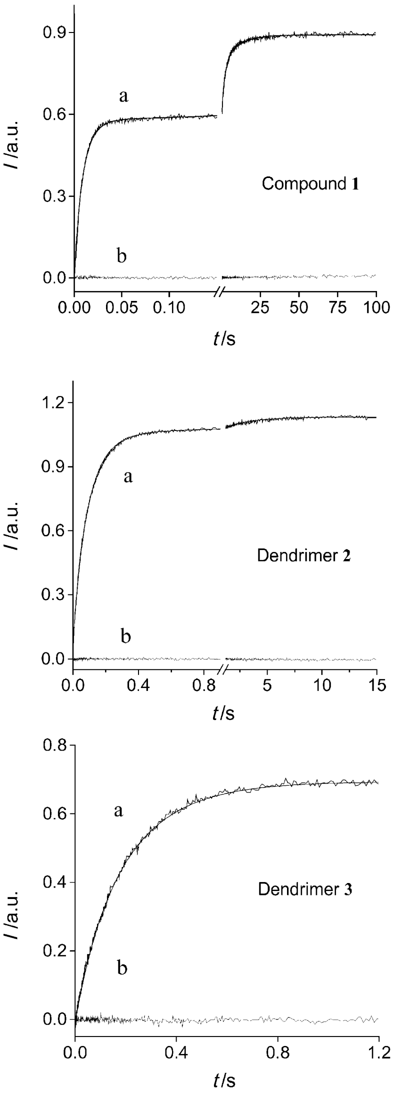

Figure 3. Variation of the fluorescence versus time for a) the reaction of **1**, **2**, and **3** (4.40×10^{-6} M) with 5.0 equivalents of Zn^{2+} and b) for the mixing with the solvent (CH_3CN/CH_2Cl_2 1:1). $T=298$ K, $\lambda_{exc}=275$ nm, $\lambda_{em}>305$ nm. The fitting of the kinetics was obtained by using the SPECFIT software according to the postulated reaction mechanism [see Eqs. (2)–(4)].

tion) gave very similar results, thereby supporting the postulated reaction mechanism given by Equation (2).

$$Zn^{2+} + \mathbf{1} \xrightarrow[44\times10^{5}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}]{k_1} (Zn^{2+}\cdot\mathbf{1})_{\mathrm{int},1} \xrightarrow[0.53\,\mathrm{s}^{-1}]{k_2} (Zn^{2+}\cdot\mathbf{1})_{\mathrm{int},2} \xrightarrow[0.10\,\mathrm{s}^{-1}]{k_3} [Zn(\mathbf{1})]^{2+} \quad (2)$$

In the case of **2**, the change in the fluorescence intensity with time (Figure 3) indicates biphasic kinetics, as shown in Equation (3), with the incorporation rate constants $k_1=(4.9\pm0.2)\times10^5\,\mathrm{M}^{-1}\mathrm{s}^{-1}$ followed by a first-order process $k_2=0.40\pm0.02\ \mathrm{s}^{-1}$. The second-order process contributes to 95% of the total change in fluorescence.

$$Zn^{2+} + \mathbf{2} \xrightarrow[4.9\times10^{5}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}]{k_1} (Zn^{2+}\cdot\mathbf{2})_{\mathrm{int}} \xrightarrow[0.40\,\mathrm{s}^{-1}]{k_2} [Zn(\mathbf{2})]^{2+} \quad (3)$$

For the reaction of Zn^{2+} with **3**, the observed changes in the fluorescence intensity (Figure 3) can be accounted for by a second-order process alone, with $k_1=(1.2\pm0.1)\times10^5\,\mathrm{M}^{-1}\mathrm{s}^{-1}$. No subsequent rearrangement step was observed under our experimental condition ($[Zn^{2+}]_0/[L]_0$ ratio of 3–10). Figure 3 shows that no process occurs during the instrumental mixing time for ligand **3**. The reaction of Zn^{2+} with **3** is, in fact, slow enough to be investigated by using the stopped-flow technique, under pseudo-first-order conditions ($[Zn^{2+}]_0=10[L]_0$). The formation of the complex under these conditions can be fitted by a single exponential function, and the observed rate constants show a linear dependence on the Zn^{2+} concentration (Figure 4), as expected for a pseudo-first-order process. We have also checked the validity of the pseudo-first-order condition by keeping constant the Zn^{2+} concentration and varying the dendrimer concentration (with at least a tenfold excess of Zn^{2+}). The results obtained showed that the rate constant does not depend on the dendrimer concentration. Regardless of the experimental conditions, the rate constant for the formation of the complex, k_1, was $(1.0\pm0.1)\times10^5\,\mathrm{M}^{-1}\mathrm{s}^{-1}$, in agreement with the value obtained from the kinetics using a slight excess of metal [Eq. (4)].

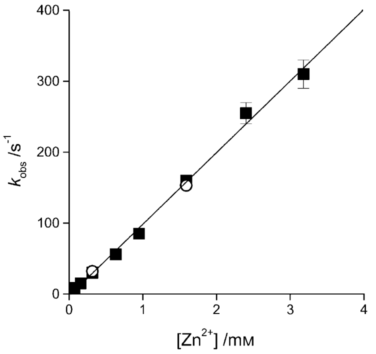

Figure 4. Dependence of k_{obs} [s^{-1}] on the concentration of $Zn(CF_3SO_3)_2$ with $[\mathbf{3}]_0=3.18\times10^{-6}$ M (■) and 6.36×10^{-6} M (○). The rate constant $k_1=(1.0\pm0.1)\times10^5\,\mathrm{M}^{-1}\mathrm{s}^{-1}$ was derived from the fit of the observed rate constants as a function of $[Zn^{2+}]$ using equation $k_{obs}=k_1[Zn^{2+}]$.

$$Zn^{2+} + \mathbf{3} \xrightarrow[1.2\times10^{5}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}]{k_1} [Zn(\mathbf{3})]^{2+} \quad (4)$$

Dendrimer dynamics: It has been shown that the value of the second-order rate constant, for Ni^{2+} incorporation into cyclam in a dipolar aprotic solvent (CH_3CN, DMSO, DMF), can be predicted by the Eigen–Wilkins mechanism schematized in Equation (5) (S = solvent).[30,31]

$$L + M^{2+}(S)_n \overset{K_{OS}}{\rightleftharpoons} \{L, M^{2+}(S)_n\} \xrightarrow{k_{ex}} L\cdot M^{2+}(S)_{n-1} + S \quad (5)$$

According to this mechanism, the rate constant of the second-order processes is controlled by the rate of solvent exchange on the metal ion, $k=K_{OS}\times k_{ex}$, in which K_{OS} is the equilibrium constant for the outer-sphere complex.[32] The solvent-exchange rate constant for Zn^{2+} in acetonitrile is reported to be $7.5\times10^7\ \mathrm{s}^{-1}$ at 298 K.[33] The equilibrium constant (K_{OS}) for Zn^{2+} and amine derivatives in acetonitrile is not known. Incorporation studies[30] of Ni^{2+} into linear and macrocyclic tetramines in acetonitrile at 25 °C led to $K_{OS} \sim 0.45\,\text{M}^{-1}$, a value close to the theoretical estimation of $0.3\,\text{M}^{-1}$ obtained by the Fuoss relationship.[34,35] It seems reasonable that a similar value can be used for Zn^{2+} complexes. On this basis, the second-order rate constant should be $\sim 3 \times 10^{7}\,\text{M}^{-1}\text{s}^{-1}$, which is much higher than the values found for complexation with **1**, **2**, and **3**. Furthermore, the rate constant of the second-order process leading to complex formation decreases with increasing dendrimer size ($k_1/10^{5}\,\text{M}^{-1}\text{s}^{-1} = 44$, 4.9, and 1.2 for **1**, **2**, and **3**, respectively). Therefore, we can conclude that the rate-limiting step does not correspond to the simple desolvation of Zn^{2+}.

This trend can be accounted for by a decrease (on increasing size of the branches) of either cyclam flexibility, which affects the rate constant for coordination of the second nitrogen atom, or accessibility to the dendrimer core due to efficient hydrophobic shielding. Incorporation of Zn^{2+} into dendrimers of different generations could indeed involve structural changes resulting in slow kinetics.[27,35,36] Conformational changes in the dendron subunits are probably necessary for the closure of the chelate ring and it is likely that the reorganization of the dendron subunits becomes slower on increasing dendrimer size, because of steric congestion.[37]

Hydrophobic protection has been suggested to delay the H^{+} (H_2O)-driven autoxidation of iron–porphyrin–dioxygen adducts.[25] It is also worth mentioning a recent study of proton protection of porphyrin cores encapsulated in phospholipid lyposome.[38] In contrast to these cases, our results indicate that the cyclam core is accessible to the incorporation of the metal ion; thus, dendron subunits probably do not adopt a rigidly folded structure around the coordination site. We have also found that the protonation (CF_3COOH) of **1**, **2**, and **3**, which leads to a strong increase of the emission intensity, is very fast and occurs during the instrumental mixing time of the stopped-flow process (ca. 1 ms).

Finally, it should be noted that for **1** and **2** there is a substantial fluorescence intensity change in the first stage of the process (Figure 3). The subsequent first-order steps observed by the stopped-flow technique cause only smaller changes in the fluorescent intensity, which is consistent with the occurrence of isomerization reactions that may involve inversion of the chiral nitrogen centers of the complex.[27,28] The absence of isomerization steps in the complex with dendrimer **3** could be related to a very high energy barrier for the inversion process. Alternatively, it may be that the large separation distance between the core and the peripheral luminescent units prevents any further change in the luminescence intensity when isomerization takes place.

Conclusion

We have investigated the complexation of Zn^{2+} by dendritic ligands containing a cyclam core and found that both the metal–ligand stoichiometry and the kinetics of complex formation depend on the size of the dendrimer branches.

The observed dendrimer effect may play an important role in various fields in which cyclam–metal complexes and metal-containing dendrimers are currently employed, including abiological applications (e.g., catalysis), and medical diagnosis and therapy. A further motif of interest is offered by the possibility, currently under investigation in our laboratory, of assembling different cyclam-based dendrons around a metal ion to obtain mixed-(dendritic)ligand complexes that might be very interesting for light harvesting and multiredox processes.

Acknowledgement

This work has been supported in Italy by MURST (Supramolecular Devices Project), University of Bologna (Funds for Selected Topics), and CNR (Sensori Fluorescenti Supramolecolari). C.S. acknowledges the Swiss National Science Foundation for financial support. We would also like to acknowledge the generous support from the European LIMM (Light Induced Molecular Motion, IST-2001-35503) and SUSANA (SUpramolecular Self-Assembly of Nanostructures, HPRN-CT-2002-00185) projects. We are also grateful to COST D11/0007 for support.

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Received: June 20, 2003 [F5255]