# Synthesis of Macropolycyclic Ligands Based on Tetraazacycloalkanes

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A versatile synthesis of spherical macrobicyclic and cylindrical macrotricyclic ligands is described using 1,4,8,11-tetraazacyclotetradecane (cyclam), 1,4,7,10-tetraazacyclododecane (cyclen), or dioxo macrocycles as precursors. Macrobicycles have been obtained by allowing cyclam, cyclen, or 5,12-dioxocyclam (1,4,8,11-tetraazacyclotetradecane-5,12-dione) to react with a bis-electrophilic spacer under high dilution conditions. A surprising selectivity has been observed for 2,6-dioxocyclen (1,4,7,10-tetraazacyclododecane-2,6-dione), which yields only macrotricycles under the same reaction conditions. Molecular modelling studies have been carried out to investigate the selectivity of the reactions, and good agreement has been observed between the theoretical predictions and experimental data. 1D- and 2D-NMR studies reveal a highly rigid structure in the case of macrobicycles. The macropolycyclic ligands show very different basicities, which demonstrates the influence of the cross-linker on the coordination properties of the ligands.

The quest for new macrocyclic ligands continues to be an active field of research owing to their use as models for metalloproteins in biological systems such as cytochrome *c* oxidase[1][2][3][4][5][6][7], cytochrome P-450[8], haemoglobin and myoglobin[9][10][11]. Moreover, polyazacycloalkanes selectively complex metal ions in solution[12][13][14][15][16][17] or in the solid state[18][19][20][21], exhibit host-guest interactions[22] and DNA cleavage properties[23][24][25], and find application in medicine as contrast-enhancing agents in magnetic resonance imaging (MRI)[22][26][27]. Furthermore, macropolycyclic ligands[28][29] have been extensively studied owing to their suitability as frameworks for many receptor sites[30][31][32][33][34][35]. Since the first reports on spherical macrobicyclic cryptates of the polyether series by Lehn et al.[36][37], many macrobicycles[38][39][40][41][42][43][44][45][46][47] as well as spherical and cylindrical macrotricycles[48][49][50][51][52] possessing various structural features have been synthesized. The chelating ligands delineate cavities into which a substrate can penetrate so as to form inclusion complexes. For example, the cylindrical macrotricycle ligands form dinuclear cryptates with metal cations. These ligands are formed by linking two macrocycles with two spacers, thereby defining three cavities: two lateral circular cavities and one central cavity. The distance between the two macrocycles can be finely tuned by changing the length of the bridges[32][34]. The corresponding dimetallic complexes exhibit redox or magnetic properties that are critically dependent on the structural features of the macrotricycle. Face-to-face dinuclear complexes, where the metal ions are separated by a distance of 4−6 Å, are particularly interesting because a substrate inside the cavity should be able to interact simultaneously with both metal ions.

Numerous studies on cage-type tetraazamacrobicycles[38][39][40][41][42][43][44][45][46] have shown the influence of the cavity size on the selectivity for coordination of alkali, alkaline earth, and ammonium ions when such systems are used as selective receptors. Thus, they are an important class of molecules in coordination and host-guest chemistry, with the coordination properties depending upon the design of the macrocyclic receptor. The chelating ring can be adjusted in order to elaborate catalysts or design selective recognizers of transition or heavy metals[14][15][16][53], or of anions[16][54]. Moreover, careful design of macropolycyclic ligands should favour the coordination of small molecules such as dioxygen or carbon monoxide to the central metal, thereby furnishing attractive models of metalloproteins which act as carriers of gaseous molecules[10][11][55][56][57][58] or which induce electron transfer[59]. The synthesis of new macropolycyclic polyamines is thus a major topic since these systems can exhibit unusual basicity, redox, and coordination properties.

Most of the macrotricyclic ligands described in the literature contain N,O- or N,S- donor atoms, but these polyether or polythia cryptands exhibit low affinity towards transition metals when compared to polyazacycloalkanes[16].

The cross-bridging of cyclam (1,4,8,11-tetraazacyclotetradecane) has been performed so as to form a macrobicyclic tetraamine, and in previous studies such cage-type

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macrocycles were obtained starting from a *trans*-diprotected macrocycle. The first cyclam-based macrobicycle synthesis was reported by Weisman et al.[60][61], but the synthesis of systems containing different cross-linkers cannot be realized by this method. New synthetic pathways have been elaborated more recently that allow the production of a large range of ligands starting from 1,7-dimethyl-1,4,7,10-tetraazacyclododecane[38][39][40][41][42][46][62] or 1,7-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane[43][63]. Most macrobicycles and macrotricycles[52] have been prepared according to a multi-step reaction scheme involving *trans*-diprotection of tetraazacycloalkanes, using tosyl[64], methyl[62] or *tert*-butyloxycarbonyl[65][66][67] as protective groups, but the yields of these syntheses are generally low.

In preliminary communications, we have described a versatile synthesis of spherical macrobicyclic[68][69] and cylindrical macrotricyclic[70][71] ligands starting from cyclam (1,4,8,11-tetraazacyclotetradecane) or dioxo macrocycles, in order to avoid the use of the usual protecting groups. We describe herein in detail the methods of synthesis of these new cylindrical macrotricycle ligands in a face-to-face arrangement based on a tetraazamacrocycle subunit, and two different ways of synthesizing spherical macrobicycles. The rigid architecture of these ligands allows the formation of well-defined cavities.

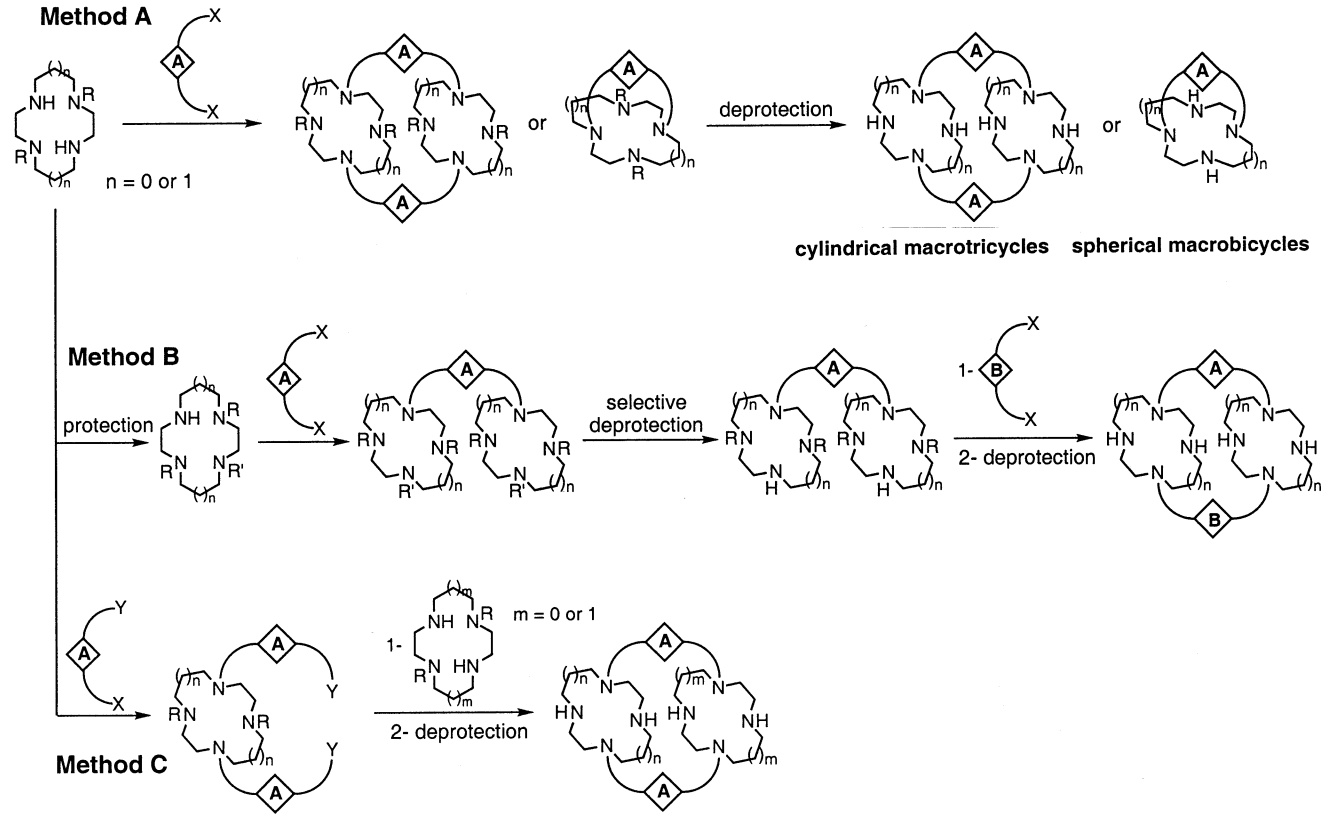
Moreover, in order to rationalize the new synthetic pathway we have undertaken a molecular simulation study in order to aid understanding of the reactivity of the macrocyclic ligands. The description of chemical reactivity is one of the ultimate goals of quantum chemistry. Whereas actual methods can be used to locate transition states for simple systems, it is still appealing for chemists to interpret or predict molecular reactivity in terms of descriptors of electronic distributions of the individual molecules. To this end, Molecular Electrostatic Potentials (MEPs) can explain the chemical reactivity of systems interacting mainly through electrostatic forces, and recently[72] interest in this property has grown considerably. The information contained in MEPs is used in a variety of classical and quantum chemical models and its topology is now considered as a standard tool in quantum chemistry for analyzing the reactivity of stable and intermediate species[73][74][75][76][77].

## Results and Discussion

### Synthesis

Several strategies for synthesizing cylindrical macrotricycles may be considered, and these are represented in Scheme 1. The *N*-bridging of tetraazacycloalkanes (cyclam: $n = 1$, or cyclen: $n = 0$) in a *trans* position, involving the *trans*-diprotection of the starting macrocycle, represents a crucial limiting factor for the synthesis of cage-type ligands in high yields. Various conditions have to be fulfilled for the successful operation of the protection reaction: the preparation of the diprotected tetraazacycloalkane has to be straightforward and the protective group must be removed without affecting the bridging arm. In most cases, methyl,

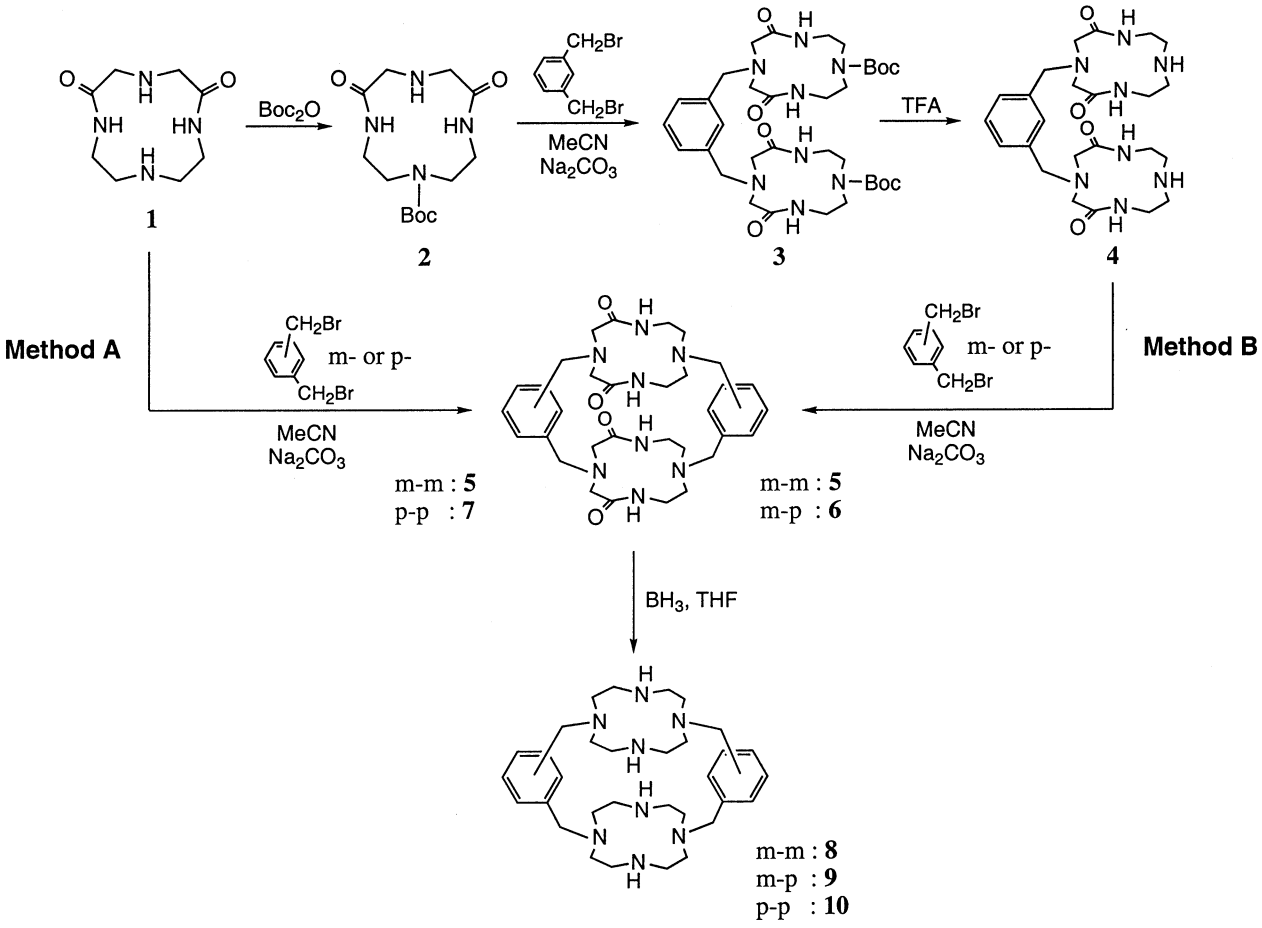
Scheme 1



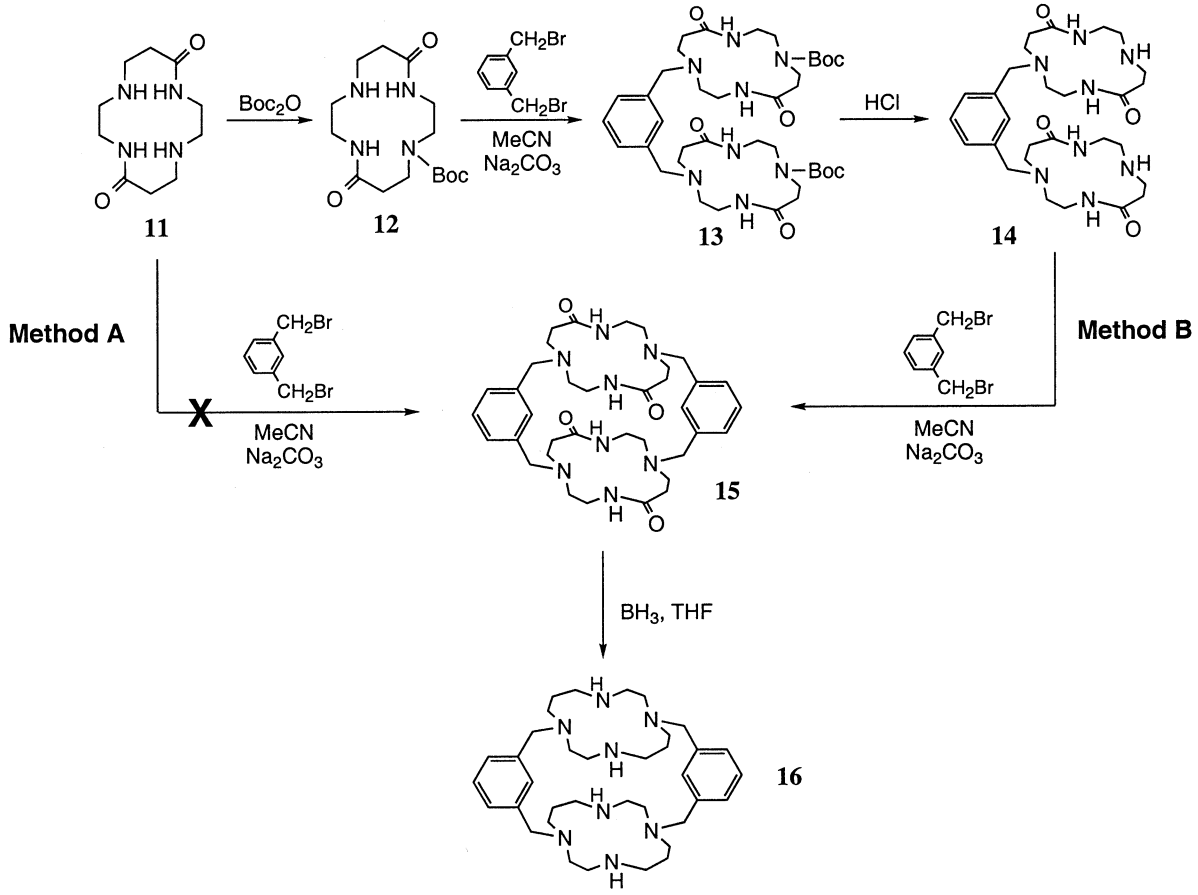
tosyl, and *tert*-butyloxycarbonyl (Boc) protective groups have been used in the preparation of macropolycyclic systems, but many problems are encountered. First, when methyl is used as protective agent, the deprotection is almost impossible and methylated macrocycles generally exhibit lower affinity towards transition metals than deprotected ones[14][62][78]. For *N*-tosyl and *N*-carbamate derivatives, the protection reaction leads simultaneously to monoprotected, *cis* and *trans* diprotected, tri- and tetraprotected macrocycles, and hence a laborious chromatographic purification step is necessary. Moreover, disubstituted tetraazacycloalkanes have previously been prepared according to the Richman and Atkins cyclization[62][79], but this methodology is far from optimal as many chemical functions cannot survive the harsh conditions required in the detosylation step. However, the diprotection reaction can proceed in high yields when various carbamates are used[67], although this selectivity is only observed for cyclen. Three different synthetic pathways can be followed to obtain cylindrical macrotricycles starting from a diprotected tetraazacycloalkane[28]: The tricyclic skeleton may be symmetrical (Method A), the spacers connecting the rings may be different in order to modulate the dimensions of the cavity (Method B), or the two macrocyclic rings may be different (Method C). Method A is rarely used to synthesize macrotricycles owing to the lack of selectivity generally observed, a macrobicycle being the major product in most cases.

In our opinion, the best synthetic approach for obtaining tetraazamacrocycle-based macropolycyclic ligands starts from the two dioxo macrocycles 2,6-dioxocyclen **1** (1,4,7,10-tetraazacyclododecane-2,6-dione)[80][81] and 5,12-dioxocyclam **11** (1,4,8,11-tetraazacyclotetradecane-5,12-dione)[82] (Schemes 2 and 3). Recently, an unusual and efficient synthesis of C-substituted 5,12-dioxocyclams and bis(dioxocyclams) was reported, based on acid-catalysed dimerization of azepenams[83][84]. However, the 2,6-dioxocyclen and 5,12-dioxocyclam starting materials can be obtained on a larger scale according to literature procedures, and only two nitrogens are available for connection to a bridging group, the two *trans*-amide groups inducing a *trans*-"autodiprotection" of the macrocycles. Method B was employed with **1** and **11** using *tert*-butyloxycarbonyl (Boc) as a protecting group and the yield of monosubstituted product was generally higher for **1** (83%) than for **11** (49%). Condensation of **2** and **12** with 0.5 equiv. of $\alpha,\alpha'$-dibromo-*m*-xylene in acetonitrile leads to bis(macrocycles) **3** and **13** in high yields, and treatment with acid (TFA or HCl) quantitatively cleaves the protective groups to yield the corresponding deprotected bis(macrocycles) **4** and **14**. The symmetrical and unsymmetrical macrotricycles **5**, **6**, and **15** are obtained in

Scheme 2



Scheme 3




63−80% yield, respectively, by reacting 1.1 equiv. of α,α′-dibromo-*m*-(or -*p*)-xylene with the bis(macrocycle) in acetonitrile. The reaction is carried out under high dilution conditions ($\leq$ 2 mmol·l$^{-1}$) so as to avoid the exclusive formation of oligomers. Finally, reduction of the tetraamide macrotricycles with borane in refluxing THF gives the desired cylindrical macrotricycles **8−10** and **16** in high yields.

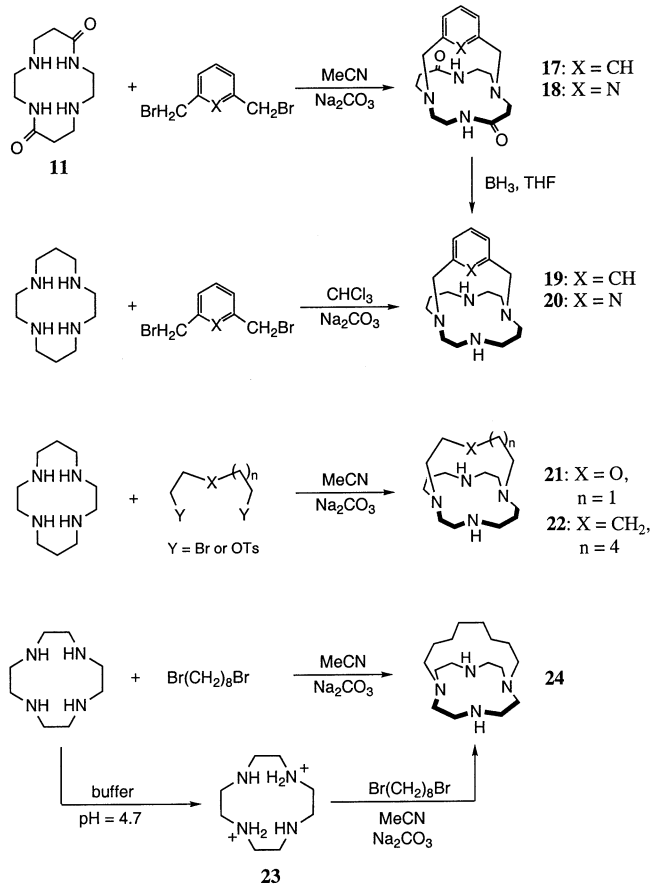
Moreover, Method A was explored as a means of synthesizing in two steps symmetrical macrotricycles with *m*- or *p*-xylene bridges. A high dilution procedure was envisaged for providing the cylindrical cryptands, and indeed only a 2:2 cyclization reaction occurs leading to ligands **5** and **7** in the case of 2,6-dioxocyclen **1**. After reduction, the cyclen-based macrotricycles **8** and **10** are then obtained in overall yields of 36−42%. Furthermore, no spherical macrobicycle is formed and a high selectivity is thus observed. This synthetic method can be employed to prepare a large variety of cyclen-based cryptands using a one-pot procedure.

In contrast, when the reaction is performed starting from 5,12-dioxocyclam **11**, only macrobicyclic ligands are formed in high yields when *m*-xylylene and 2,6-pyridinedimethylene are used as cross-linkers (Scheme 4). It is thus possible to induce a 1:1 or 2:2 cyclization to prepare a macrobicycle or macrotricycle by using dioxocyclam or dioxocyclen, respectively.

Moreover, we have prepared macrobicyclic ligands[69] of the cyclam or cyclen series using the corresponding nonprotected macrocycle as a starting material (Scheme 4). The reaction proceeds by mixing cyclam or cyclen with a bis-electrophilic cross-linker under high dilution conditions. We have used aromatic and aliphatic spacers, and we have varied the nature of the donor atom of the spacers (nitrogen or oxygen) in order to modify the coordination properties of the cage ligands towards metal ions. Surprisingly, the condensation reaction leading to **21** does not occur when 5,12-dioxocyclam is used as starting material, probably due to the length of the spacer and the rigidity of the dioxo macrocycle in comparison to cyclam. Starting from cyclen, yields are often low, but ligand **24** can be obtained in moderate yield following an indirect procedure (Scheme 4). Cyclen is first solubilized in an acetate buffer and the *trans*-diprotonated species thus formed (log $K_2$ = 9.49 and log $K_3$ = 1.6 for cyclen)[14][67] is reacted with 1,8-dibromooctane to yield **24** in 61% yield.

These synthetic procedures thus represent versatile methods for preparing macrobicyclic and macropolycyclic ligands in the tetraazacycloalkane series. The most appealing features of such methods are that use of the usual protective groups in the synthetic scheme is avoided and that the starting materials are readily available on a large scale. Furthermore, a surprising selectivity was observed for each macro-

Scheme 4




cycle. When cyclam, cyclen, and 5,12-dioxocyclam are reacted with a bis-electrophilic reagent under high dilution conditions, only macrobicyclic compounds are obtained. On the other hand, the same reaction conditions yield only macrotricyclic derivatives when 2,6-dioxocyclen is used as starting material. However, a five step procedure has to be envisaged for the synthesis of dissymmetrical macrotricycles.

Final and intermediate products were characterized by $^1$H-NMR, $^{13}$C-NMR, and IR spectroscopies, as well as by microanalysis (see Experimental Section). In particular, the latter two techniques have shown that most of the macrocyclic ligands are obtained in hydrated form. However, the IR spectrum and microanalytical data of ligand **20** show that this cryptand is isolated in its monoprotonated form, indicating a high basicity of this cage-macrocycle (vide infra).

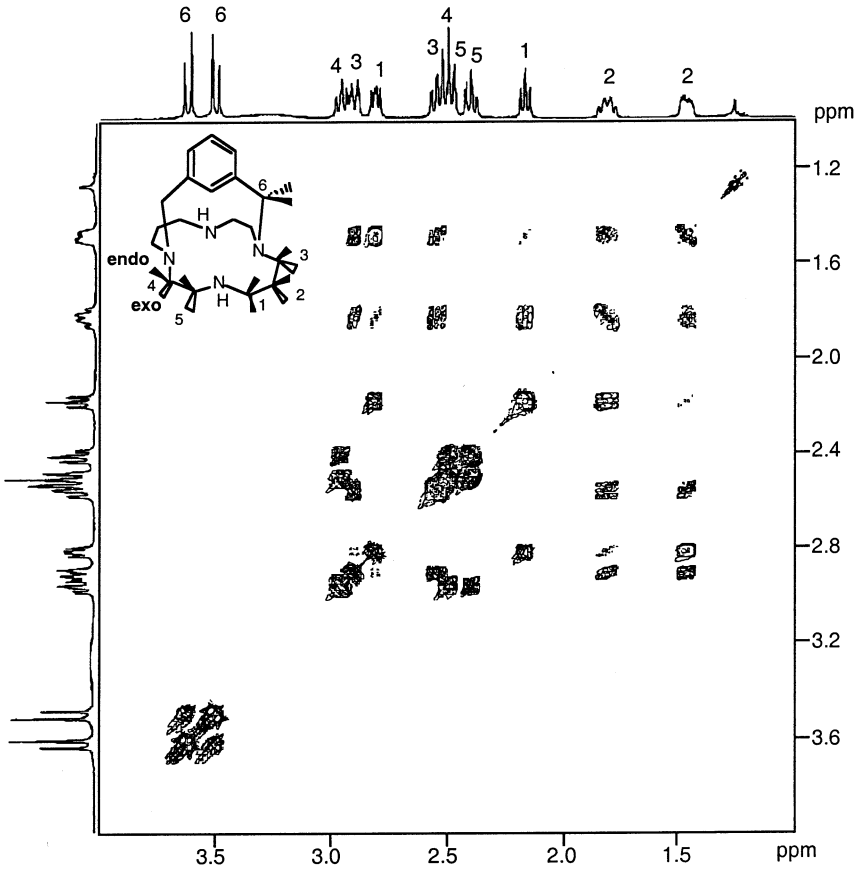
### Physicochemical Characterization

$^1$H- and $^{13}$C-NMR spectra of cyclam, cyclen, and dioxotetraazacycloalkanes used as starting materials reveal the symmetry of the macrocycles, in spite of the existence of conformers in solution. This is due to exchange between conformers that is too fast to be detected on the NMR time scale. Likewise, macrotricycles and the intermediate bis(macrocycles) exhibit the expected number of signals when a fast conformational exchange occurs. However, macrobicycles **17**−**21** show a remarkable behaviour. $^1$H-NMR spectra of these cage-tetraazamacrocycles reveal a lower symmetry than observed for the precursors, the geminal protons of each methylene site being diastereotopic due to the magnetic anisotropy induced by the cross-linker[85]. Moreover, the resolution of $^1$H-NMR spectra is qualitatively higher when the spacer is shorter, which is due to a higher rigidity of the structural arrangement inducing a slow interchange between conformers. The $^{13}$C-NMR spectra of **17**−**21** each show five different signals for the macrocycle, and one signal for the methylene of the aromatic spacer (**17**−**20**), indicative of their apparent $C_2$ symmetries. The low symmetry of these ligands induces an AB spin system for each proton site of the macrocycle, as well as for the geminal methylene protons of the aromatic spacer in **19** and **20** (Figure 1). When compared with spectra of macrobicycles containing a longer spacer (**22** and **24**), the spectra show higher equivalence of protons within each methylene group, suggesting less rigidity of the ligand. $^1$H-$^1$H COSY and $^1$H-$^{13}$C HETCOR 2D spectra were recorded for macrobicycles **17**−**20** to assign the one-dimensional $^1$H- and $^{13}$C-NMR spectra, and $^1$H-$^1$H correlations in **19** are shown in Figure 1. The combination of the 2D NMR techniques has allowed an unequivocal assignment of all carbon resonances, but we cannot unambiguously assign diastereotopic protons within each methylene group (*exo* and *endo* protons). The two multiplets at $\delta = 1.44$ and 1.77 are attributed to the β-$CH_2$ (C-2) protons, each of them being correlated with five protons. Benzylic methylene sites (C-6) appear as two doublets ($J = 15$ Hz), typical of an AB system, in the range $\delta = 3.5-4.0$.

### Protonation Measurements

The protonation equilibria of the macropolycycles **8**, **10**, **19**, **20**, and **21** were studied in 0.1 mol·l$^{-1}$ aqueous KCl solution at 298 ± 0.2 K by potentiometric measurements. The basicity constants for the three macrobicycles **19**, **20**, **21**, and the two macrotricycles **8**, **10** are reported in Table 1. By using the equilibrium data, the distribution diagrams of the protonated species of ligands formed as a function of the pH were calculated. Cage-macrocycles **19** and **21** behave as triprotic bases, while the pyridine cage compound **20** exhibits only two measurable basicities. The first protonation constant of **20** is unmeasurable because this constant is very high in aqueous solution and the isolated ligand after standard work-up is monoprotonated. Compound **20** can thus be considered as a proton sponge, like many other cyclen-based cages[38][39][40][41][42][43][44][45][46][62][85][86]. These features indicate that the hydrogen ion interacts very strongly with the nitrogen atoms in forming the monoprotonated species, suggesting that the proton is bound inside the macrocyclic cavity and stabilized by a hydrogen bond network. In the second protonation step, **20** exhibits a high basicity, while the macrobicycles **19** and **21** are seen to be more moderately basic. The low basicity of

Figure 1. COSY spectrum of **19**




**19** and **21** is rather surprising, because it is well-known that cage-macrocycles generally possess higher basicities than the analogous non-cage macrocycles. However, unsubstituted macrocycles show higher basicities when compared to 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam)[14][87] or other fully substituted macrocycles[88]. It seems that the increase of log $K_1$ and log $K_2$ due to the cage effect is balanced by the *N*-substitution effect, which decreases the basicity of the ligands. These three ligands show very different basicities, which demonstrates the strong influence of the nature of the cross-linker in modifying the basicity and consequently the coordination properties. Macrotricycle **10** exhibits a high basicity in the first protonation step, while for **8** this basicity is lower (log $K < 10$). The other basicities are rather similar and the sixth protonation process of **10** is detectable in the studied pH range (2−12). We note that the two first basicity constants measured for **10** are similar to those observed for cyclen and disubstituted cyclen[62], which certainly indicates a low cage effect for the macrotricycle containing the longest spacer.

### Molecular Modelling

In order to help explain the selectivity of the condensation reaction, a molecular modelling study was carried out. The calculated MEPs of the four starting macrocycles are shown in Figure 2. The minimum potential values are

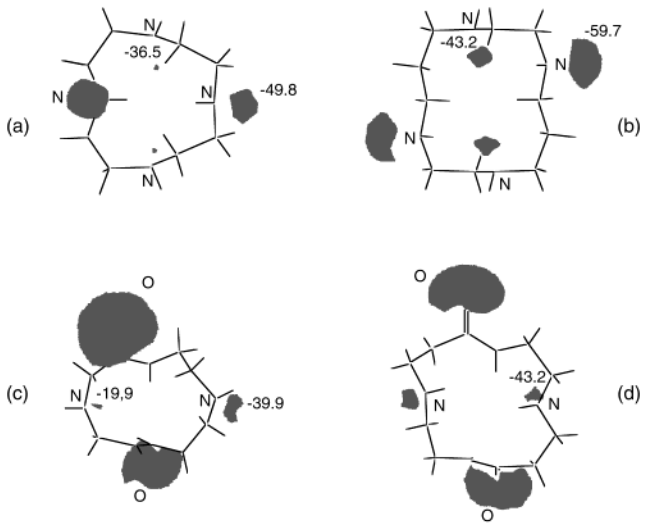
Table 1. Logarithms of the protonation constants of macrobicycles and macrotricycles in 0.1 mol·l$^{-1}$ aqueous KCl solution at 298 K

| Protonations | log *K* | | | | | | |
|---|---|---|---|---|---|---|---|
| | **19** | **20** | **21** | **8** | **10** | cyclam[a] | cyclen[b] |
| $L + H^+ = LH^+$ | 10.57 | >13 | 9.60 | 9.77 | 10.51 | 11.29 | 10.51 |
| $LH^+ + H^+ = LH_2^{2+}$ | 7.65 | 10.36 | 8.65 | 9.25 | 9.47 | 10.19 | 9.49 |
| $LH_2^{2+} + H^+ = LH_3^{3+}$ | 1.43 | 1.48 | 2.31 | 7.37 | 8.14 | 1.61 | 1.6 |
| $LH_3^{3+} + H^+ = LH_4^{4+}$ | | | | 6.39 | 6.01 | 1.91 | 0.8 |
| $LH_4^{4+} + H^+ = LH_5^{5+}$ | | | | 3.21 | 2.87 | | |
| $LH_5^{5+} + H^+ = LH_6^{6+}$ | | | | | 2.62 | | |

[a] From R. J. Motekaitis, B. E. Rogers, D. E. Reichert, A. E. Martell, M. J. Welch, *Inorg. Chem*. **1996**, *35*, 3821−3827. − [b] From A. Bianchi, M. Micheloni, P. Paoletti, *Coord. Chem. Rev.* **1991**, *110*, 17−113.

expressed in kcal·mol$^{-1}$. On the basis of these calculated values, it is not difficult to establish a sequence of reactivity towards an electrophilic substrate for each tetraazamacrocycle. The cyclam showing experimentally the greatest reactivity has the greatest minimal value (−59.7 kcal·mol$^{-1}$) on the two *trans* nitrogen atoms. However, for cyclen, the lower corresponding values (−49.8 kcal·mol$^{-1}$) reflect a lower reactivity towards electrophilic reactants. Moreover, their location on the opposite faces of the macrocycle sterically hinders the reactivity of rigid cross-linkers having a short spacer length such as *m*-xylylene, 2,6-pyridinedimethylene, or an aliphatic chain possessing less than six atoms. Thus, the reaction of cyclen with such a spacer cannot furnish a macrobicyclic ligand. To rationalize the reactivity pattern of a tetraazacycloalkane towards a bridging group, we have to consider parameters other than the MEP values, mainly the location and the stereochemical fit between the two reacting nitrogen atoms and the spacer length, as well as the flexibility of the spacer group. For dioxocyclam, the observed yields are higher than for cyclam when *m*-xylylene or 2,6-pyridinedimethylene are used as cross-linkers and evaluation of the *trans* N−N distance for cyclam, 5,12-dioxocyclam, and the resulting product **19** shows a better fit for 5,12-dioxocyclam than for cyclam. In contrast, for dioxocyclen the electrostatic potential values on the amine functions are non-equivalent. This result is not surprising if we consider the dissymmetry of dioxocyclen and the withdrawing inductive effect of carbonyl groups, which decreases the electronic density on the nearer amine group. This finding readily explains the fact that only a macrotricyclic ligand is formed with dioxocyclen when different spacer groups are used. Considering that N4 is less nucleophilic that N10 in dioxocyclen, the first reaction step most likely corresponds to the formation of a bis(macrocycle) linked by a xylylene unit, which is followed by the cyclization reaction leading to the macrotricycle.

Figure 2. Negative molecular electrostatic potentials [kcal·mol$^{-1}$] of (a) cyclen, (b) cyclam, (c) 2,6-dioxocyclen, and (d) 5,12-dioxocyclam




## Conclusion

In the present work we have reported a new convenient synthesis of macrobicyclic and macrotricyclic ligands using the non-protected tetraazacycloalkanes cyclam and cyclen, and "autodiprotected" dioxotetraazacycloalkanes as starting materials. The versatility of the method allows us to prepare various macropolycycles by changing the cross-linker size and its hydrophobic character. A rather surprising selectivity was observed when we compared the reactivity of 2,6-dioxocyclen with that of the other macrocycles. The reactivity of all the precursors was studied by calculating their Molecular Electrostatic Potentials, and a good agreement with the experimental data was found. The titration data have shown different basicities for each ligand, indicating a strong influence of the nature of the bridging chain on the coordination properties. Thus, the design of the ligand should favour a selective coordination of transition, alkali, alkaline earth, or heavy metals in the central cavity. Moreover, we have shown that macrobicycles exhibit higher rigidity than macrotricycles, and this demonstrates that one or two cross-linkers are able to modify the rigidity of the ligands and therefore their selectivity towards metal ions. In the macrobicycle series, the steric hindrance of one side of the tetraazacycloalkane should assist in this respect. Moreover, one or several donor atoms present in the spacer, essentially nitrogen or oxygen, can bind a metal ion located in the tetraazamacrocyclic cavity in order to complete its coordination sphere.

## Experimental Section

*Materials and Equipment:* The $^{1}$H- and $^{13}$C-NMR spectra were recorded at 200 MHz on a Bruker AC 200 for 1D spectra, or at 500 MHz on a Bruker DRX 500 spectrometer for 2D experiments, at the Centre de Spectroscopie Moléculaire de l'Université de Bourgogne. Chemical shifts are referenced to $CHCl_3$ at $\delta$ = 7.24 and $\delta$ = 77.4 for $^{1}$H- and $^{13}$C-NMR spectra, respectively. − IR spectra were recorded as KBr pellets or nujol dispersions from 4000 to 400 cm$^{-1}$ on a Bruker IFS 66v spectrometer. − Microanalyses were performed on a Fisons EA 1108 CHNS instrument.

*Potentiometric Measurements:* All the potentiometric measurements were carried out in 50 ml solutions with 0.1 mol·dm$^{-3}$ ionic strength (KCl) at 298 ± 0.2 K in the range pH 2−12. The titration curves were obtained with a Schott TPC 2000 automatic titrimeter controlled by an IBM PC. The glass electrode was calibrated as a hydrogen-concentration probe with three buffer solutions (pH = 4, 7, and 10) from Acros, and p$K_w$ = 13.77 under the conditions of ionic strength and temperature used[42]. The determination of the protonation constants was performed using the HYPERQUAD computer program.

*Molecular Modelling:* Unlike many of the other parameters used as reactivity indices, MEP is an observable which can be measured experimentally by X-ray and electron diffraction methods[89][90][91] or calculated from the wavefunction. It is straightforward to calculate the V(*r*) (MEP) of a molecular system if one knows the electron density $\rho(r)$, the nature of nuclei, and their respective positions, using the expression (Eq. 1):

$$V(r) = \Sigma\, Z_i/(R_i - r) - \int \rho(r')dr'/(r' - r) \quad (1)$$

where $Z_i$ is the charge on nucleus *i* located at $R_i$ and $\rho(r)$ is the electronic charge density function of the molecule. This equation contains a summation over the point charges of the nuclei and an integration over the "continuous" negative electron distribution. The sign of $V(r)$ at any point near the molecule depends on whether the effect of the nuclei or the electrons is dominant there. The derivatives of the MEP, the electric field and the electric field gradient, are also important from the chemical reactivity point of view. These parameters are also needed for determining the MEP's topography and its critical points. In addition to the conventional ab initio methods for computing molecular properties, there is increasing use of Density Functional Theory. An important feature of this approach is that it takes into account the electron correlation, while requiring much less computer time and space than the ab initio methods. It is clear from Eq. 1 that the MEP strongly depends on the exact positions of the nuclei. Considering that tetraazacycloalkanes are very flexible and adopt a large variety of dynamically interconverting geometries, it was imperative to explore the conformational energy hypersurface in order to locate the local minima and the global minimum, prior to quantum chemical calculations of the MEP. In the present study, Molecular Mechanics and Molecular Dynamics (DISCOVER module of the MSI[92] Molecular Modelling Package on a Silicon Graphics Indigo2 workstation) have been used to perform an exhaustive search to identify the low energy conformers of cyclam, cyclen, and the respective dioxotetraazamacrocycles. Molecular dynamics calculations have been carried out using the CVFF[92] force field within a Verlet leapfrog integrating procedure. The Steepest Descent method has been used for the final optimization of the selected conformers. The respective MEPs have been obtained from DFT (Density Functional Theory, Dmol[92]) calculations using the non-local spin density functional BLYP (B = Becke gradient corrected exchange functional and LYP = Lee, Yang, and Parr gradient corrected correlation). It should be noted that in our approach the MEP does not typically take into account the changes such as polarization charge transfer or geometry distortion occurring when the two reactants approach and begin to interact. Moreover, the MEP does not reflect the nature of the approaching species. Because of these inherent limitations, it is most useful as a guide to study the early stages of a reaction where these effects are relatively minor. It is important to note that all the calculations have been carried out on isolated (gas phase) ligands. Introduction of solvent effects in the MEP by means of mixed QM/MM methods, the solvent being represented by empirical force fields, is an attractive approach since using this methodology the calculated electrostatic potential would be more realistic. Unfortunately, the application of these techniques is limited to very small systems due to large CPU time requirements. However, the order of the local minima is well reproduced even if the calculations are performed on isolated species, indicating that this technique may be used for estimation of unknown p*K* values from DFT calculations.

*Chemicals:* Cyclam[93][94], cyclen[95], 2,6-dioxocyclen[80], and 5,12-dioxocyclam[82] were synthesized according to literature procedures. All other commercial chemicals (Acros or Aldrich) were used as received without further purification.

*Syntheses: 10-tert-Butyloxycarbonyl-1,4,7,10-tetraazacyclododecane-2,6-dione* (**2**): 2,6-Dioxocyclen (7.0 g, 35 mmol) was dissolved in 500 ml of MeOH and 300 ml of methanolic solution of di-*tert*-butyl dicarbonate (7.25 g, 33.2 mmol) was added dropwise at room temperature over a period of 3 h. The mixture was then stirred for an additional 3 h and the crude compound was adsorbed onto silica by evaporation of the solvent in presence of 20 g of silica. The product was chromatographed on silica gel ($CH_2Cl_2$/MeOH, 88:12 to 80:20) to give **2** as a white solid (8.75 g, 83%). − IR (KBr): $\tilde{\nu}$ = 3310 $cm^{-1}$ (NH), 3270 (NH), 1686 ($CO_{Boc}$), 1655 ($CO_{macrocycle}$). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 3.29 (m, 4 H), 3.39 (s, 4 H), 3.55 (m, 4 H), 7.28 (broad, 2 H). − $^{13}$C NMR (50 MHz, [$D_6$]DMSO): δ = 29.0 ($CH_3$), 53.5, 53.9 ($CH_2N$), 56.5 (NH*C*$H_2$CO), 79.7 [C(*t*Bu)], 156.3 ($CO_{Boc}$), 172.3 (CO). − $C_{13}H_{24}N_4O_4$ (300.3): calcd. C 52.0, H 8.0, N 18.7; found C 51.8, H 8.0, N 18.7.

*4,4′-m-Xylylenebis[10-tert-butyloxycarbonyl-1,4,7,10-tetraazacyclododecane-2,6-dione]* (**3**): To 3.5 g of **2** (11.65 mmol) in 90 ml of acetonitrile were added 1.54 g of α,α′-dibromo-*m*-xylene (5.83 mmol) and 1.5 g of anhydrous sodium carbonate. The mixture was refluxed for 10 h and then the hot solution was filtered. After adsorption of the crude compound on silica, the product was chromatographed on silica gel ($CH_2Cl_2$/MeOH, 92:8) to give **3** as a white solid (3.6 g, 82%). − IR (KBr): $\tilde{\nu}$ = 3480 $cm^{-1}$ ($H_2O$), 3363 (NH), 1659 ($CO_{Boc+macrocycle}$). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 18 H), 3.17 (broad, 16 H), 3.36 (broad, 8 H), 3.70 (s, 4 H), 7.15 (d, 2 H), 7.24 (m, 2 H), 7.54 (t, 4 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 29.0 ($CH_3$), 39.7, 53.2, 61.3, 63.4 ($CH_2$), 80.8 [C(*t*Bu)], 129.5, 131.1, 138.2 (Ar), 157.0 ($CO_{Boc}$), 171.0 (CO). − $C_{34}H_{54}N_8O_8 \cdot 3\ H_2O$ (756.9): calcd. C 53.9, H 7.1, N 14.8; found C 53.8, H 7.4, N 14.7.

*4,4′-m-Xylylenebis[1,4,7,10-tetraazacyclododecane-2,6-dione]* (**4**): The bis(macrocycle) **3** (3.55 g, 4.69 mmol) was stirred in 35 ml of trifluoroacetic acid for 2 h at room temperature. After evaporation of the solvent, the oily residue was dissolved in 10 ml of water, the pH was adjusted to 10 with triethylamine, and the water was evaporated. The crude product was taken up in a mixture of $CH_2Cl_2$/pentane/EtOH, 40:40:20, and the resulting suspension was filtered to give **4** as a white solid (2.51 g, 94%). − IR (KBr): $\tilde{\nu}$ = 3480 $cm^{-1}$ ($H_2O$), 3315 (NH), 3283 (NH), 1649 (CO). − $^1$H NMR (200 MHz, $D_2O$): δ = 2.94 (q, 8 H), 3.19 (s, 8 H), 3.38 (t, 8 H), 3.83 (s, 4 H), 7.38 (broad, 3 H), 7.43 (broad, 1 H). − $^{13}$C NMR (50 MHz, $D_2O/D_2SO_4$): δ = 35.7, 45.2, 55.9, 61.6 ($CH_2$), 129.5, 131.1, 134.1, 138.0 (Ar), 166.5 (CO). − $C_{24}H_{38}N_8O_4 \cdot 3.5\ H_2O$ (565): calcd. C 50.9, H 6.7, N 19.8; found C 50.7, H 7.0, N 19.5.

*4,4′,10,10′-Bis[m-xylylene-1,4,7,10-tetraazacyclododecane-2,6-dione]* (**5**). − *a) Method A:* To 2.35 g of 2,6-dioxocyclen (11.75 mmol) suspended in 2.5 l of acetonitrile was added 3.1 g of anhydrous sodium carbonate. After refluxing, a solution of α,α′-dibromo-*m*-xylene (3.41 g, 12.92 mmol) in 20 ml of acetonitrile was added dropwise over a period of 12 h, and then the stirred mixture was kept under reflux for a further 24 h. After filtration, the solvent was evaporated from the filtrate, the residue was adsorbed on alumina, and chromatographed (alumina, $CH_2Cl_2$/MeOH, 96:4) to give **5** as a white solid (1.88 g, 50%). − IR (KBr): $\tilde{\nu}$ = 3480 $cm^{-1}$ ($H_2O$), 3336 (NH), 1655 (CO). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.61 (t, 8 H), 3.22 (broad, 16 H), 3.76 (s, 4 H), 3.89 (s, 4 H), 7.06 (t, 4 H), 7.18−7.70 (m, 8 H). − $^{13}$C NMR (50 MHz, $D_2O/D_2SO_4$): δ = 40.2, 59.8, 62.6, 66.9, 68.7 ($CH_2$), 133.0, 135.4, 135.8, 136.3, 140.3, 141.0 (Ar), 170.0 (CO). − $C_{32}H_{44}N_8O_4 \cdot 1.5\ H_2O$ (631): calcd. C 60.8, H 7.4, N 17.7; found C 60.8, H 7.5, N 17.8.

*b) Method B.* The above procedure was carried out using 1.0 g of **4** (1.76 mmol), 476 mg of α,α′-dibromo-*m*-xylene (1.80 mmol), 530 mg of anhydrous sodium carbonate, and 1 l of acetonitrile, to yield **5** as a white solid (730 mg, 66%).

*4,4′-m-Xylylene-10,10′-p-xylylenebis[1,4,7,10-tetraazacyclododecane-2,6-dione]* (**6**): The procedure described for **5** was carried out with 1.4 g of **4** (2.47 mmol), 686 mg of α,α′-dibromo-*p*-xylene (2.60 mmol), 740 mg of anhydrous sodium carbonate, and 1.4 l of acetonitrile, to yield **6** as a white solid (1.00 g, 63%). − IR (KBr):

$\tilde{\nu}$ = 3480 $cm^{-1}$ ($H_2O$), 3319 (NH), 1656 (CO). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.49 (m, 8 H), 2.87 (m, 4 H), 3.10–3.57 (m, 12 H), 3.63 (s, 4 H), 3.80 (s, 4 H), 7.13 (m, 8 H), 7.54–7.66 (m, 4 H). – $^{13}C$ NMR (50 MHz, $D_2O/D_2SO_4$): δ = 38.8, 59.0, 62.5, 63.8 ($CH_2$), 132.2, 133.2, 133.9, 134.7, 136.7 (Ar), 170.0 (CO). – $C_{32}H_{44}N_8O_4 \cdot 2\ H_2O$ (640.8): calcd. C 60.0, H 6.9, N 17.5; found C 60.6, H 6.9, N 17.0.

*4,4′,10,10′-Bis[p-xylylene-1,4,7,10-tetraazacyclododecane-2,6-dione]* (**7**): Method A described for **5** was carried out using 1.0 g of 2,6-dioxocyclen (5 mmol), 1.45 g of α,α′-dibromo-*p*-xylene (5.5 mmol), 1.3 g of anhydrous sodium carbonate, and 1 l of acetonitrile, to yield **7** as a white solid (732 mg, 44%). – IR (KBr): $\tilde{\nu}$ = 3480 $cm^{-1}$ ($H_2O$), 3337 (NH), 1655 (CO). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.63 (m, 8 H), 3.01–3.09 (m, 8 H), 3.34–3.43 (m, 8 H), 3.70 (s, 4 H), 3.84 (s, 4 H), 7.35–7.49 (m, 12 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 37.3, 52.4, 60.0, 61.6, 63.3 ($CH_2$), 129.4, 129.6, 138.4, 138.9 (Ar), 170.7 (CO). – $C_{32}H_{44}N_8O_4 \cdot 3\ H_2O$ (658.8): calcd. C 58.3, H 7.6, N 17.0; found C 58.2, H 7.2, N 16.5.

*1,1′,7,7′-Bis[m-xylylene-1,4,7,10-tetraazacyclododecane]* (**8**): The tetraamide **5** (1.6 g, 2.53 mmol) was suspended in 10 ml of THF under argon and 40 ml of a 1 M borane solution in THF was slowly added at 0°C. The mixture was stirred at room temperature for 6 h, and then refluxed for 12 h. After cooling, the excess borane was hydrolyzed with a 1:1 mixture of water/MeOH (5 ml) and the solvents were evaporated. The residue was then refluxed in 20 ml of a 6 M aqueous HCl solution for 2 h and the mixture was neutralized by the addition of NaOH pellets (pH > 11). Extraction of the aqueous solution with chloroform, followed by drying and concentration of the organic phase, yielded **8** as a white solid (1.33 g, 84%). – IR (KBr): $\tilde{\nu}$ = 3420 $cm^{-1}$ ($H_2O$), 3319 (NH), 2950–2793 (CH). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.59–2.73 (m, 32 H), 3.80 (s, 8 H), 7.09–7.30 (m, 8 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 47.4, 53.6, 61.4 ($CH_2$), 127.6, 128.7, 129.4, 140.6 (Ar). – $C_{32}H_{52}N_8 \cdot 4.5\ H_2O$ (629.8): calcd. C 61.0, H 8.2, N 17.8; found C 61.1, H 8.4, N 17.4.

*1,1′-m-Xylylene-7,7′-p-xylylenebis[1,4,7,10-tetraazacyclododecane]* (**9**): The procedure described for **8** was carried out using 960 mg of **6** (1.50 mmol), to yield **9** as a white solid (500 mg, 52%). – IR (KBr): $\tilde{\nu}$ = 3429 $cm^{-1}$ ($H_2O$), 2925, 2814 (CH). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.39–2.75 (m, 32 H), 3.49 (s, 8 H), 6.97–7.48 (m, 8 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 45.2, 45.5, 46.2, 46.4, 52.4, 52.6, 53.5, 53.9, 60.9, 62.4 ($CH_2$), 128.8, 129.2, 129.5, 138.3, 138.8, 141.3 (Ar). – $C_{32}H_{52}N_8 \cdot 5\ H_2O$ (638.9): calcd. C 60.2, H 8.1, N 17.5; found C 60.3, H 8.4, N 17.1.

*1,1′,7,7′-Bis[p-xylylene-1,4,7,10-tetraazacyclododecane]* (**10**): The procedure described for **8** was carried out using 700 mg of **7** (1.06 mmol), to yield **10** as a white solid (533 mg, 83%). – IR (KBr): $\tilde{\nu}$ = 3429 $cm^{-1}$ ($H_2O$), 3326 (NH), 2949, 2812 (CH). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.25–2.58 (m, 32 H), 3.37 (s, 8 H), 7.20–7.32 (m, 8 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 45.1, 52.0, 59.1 ($CH_2$), 128.7, 139.1 (Ar). – $C_{32}H_{52}N_8 \cdot 3\ H_2O$ (602.9): calcd. C 63.8, H 9.7, N 18.6; found C 63.3, H 9.9, N 18.0.

*1-tert-Butyloxycarbonyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione* (**12**): The procedure described for **2** was carried out using 6.0 g of 5,12-dioxocyclam (26.3 mmol), 5.2 g of di-*tert*-butyl dicarbonate (23.8 mmol) and 3 l of MeOH, to yield **12** as a white solid (3.8 g, 48%). – IR (KBr): $\tilde{\nu}$ = 3317 $cm^{-1}$ (NH), 1698 ($CO_{Boc}$), 1652 ($CO_{macrocycle}$). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 2.05 (t, 2 H), 2.34 (t, 2 H), 2.46 (t, $CH_2N$), 2.61 (t, 2 H), 3.13 (m, 8 H), 6.43 (m, 1 H), 8.21 (m, 1 H), 8.98 (m, 1 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 28.6 ($CH_3$), 36.0, 36.7, 38.2, 38.9, 45.0, 45.1, 48.8, 48.9 ($CH_2$), 80.4 [C(*t*-Bu)], 157.4 ($CO_{Boc}$), 171.9, 172.7 (CO). – $C_{15}H_{28}N_4O_4$ (328.4): calcd. C 54.9, H 8.5, N 17.0; found C 54.9, H 8.6, N 17.0.

*1,1′-m-Xylylenebis[8-tert-butyloxycarbonyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione]* (**13**): The procedure described for **3** was carried out using 3.0 g of **12** (9.13 mmol), 1.2 g of α,α′-dibromo-*m*-xylene (4.56 mmol), 3 g of anhydrous sodium carbonate and 100 ml of acetonitrile, to yield **13** as a white solid (2.98 g, 84%). – IR (KBr): $\tilde{\nu}$ = 3297 $cm^{-1}$ (NH), 1694 ($CO_{Boc}$), 1670 ($CO_{macrocycle}$). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 18 H), 2.26 (t, 4 H), 2.41 (t, 4 H), 2.55 (t, 4 H), 2.68 (t, 4 H), 3.33–3.43 (m, 16 H), 3.57 (s, 4 H), 6.50 (m, 2 H), 7.14–7.36 (m, 4 H), 7.77 (m, 2 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 29.1 ($CH_3$), 34.8, 38.0, 40.4, 46.6, 51.2, 53.2, 59.1 ($CH_2$), 81.2 [C(*t*-Bu)], 129.3, 129.5, 131.7, 138.5 (Ar), 157.8 ($CO_{Boc}$), 172.2, 173.3 (CO). – $C_{38}H_{62}N_8O_8 \cdot H_2O$ (777): calcd. C 58.7, H 8.3, N 14.4; found C 58.6, H 8.3, N 14.2.

*1,1′-m-Xylylenebis[1,4,8,11-tetraazacyclotetradecane-5,12-dione]* (**14**): The bis(macrocycle) **13** (2.5 g, 3.22 mmol) was dissolved in 6 M HCl (100 ml) and the mixture was stirred for 1 h at room temperature. The solution was then concentrated and the residue was purified on a basic ion-exchange resin (Dowex 1X8-100) to yield **14** as a white solid (1.65 g, 83%). – IR (KBr): $\tilde{\nu}$ = 3291 $cm^{-1}$ (NH), 1649 (CO). – $^1H$ NMR (200 MHz, $D_2O$): δ = 2.49–3.07 (m, 28 H), 3.37 (m, 4 H), 3.80 (s, 4 H), 7.22–7.43 (m, 4 H). – $^{13}C$ NMR (50 MHz, $D_2O$): δ = 30.7, 31.8, 38.5, 38.9, 45.0, 49.6, 52.2, 57.9, 61.2 ($CH_2$), 133.1, 133.5, 135.6, 136.5 (Ar), 177.1, 177.9 (CO). – $C_{28}H_{46}N_8O_4 \cdot 3\ H_2O$ (612.7): calcd. C 54.9, H 8.5, N 18.3; found C 55.1, H 8.8, N 18.1.

*1,1′,8,8′-Bis[m-xylylene-1,4,8,11-tetraazacyclotetradecane-5,12-dione]* (**15**): The procedure described for **5** was carried out using 1.65 g of **14** (2.69 mmol), 780 mg of α,α′-dibromo-*m*-xylene (2.95 mmol), 2 g of anhydrous sodium carbonate and 1 l of acetonitrile, to yield **15** as a white solid (1.47 g, 80%). – IR (KBr): $\tilde{\nu}$ = 3405 $cm^{-1}$ ($H_2O$), 2931, 2809 (CH), 1649 (CO). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.93–3.98 (m, 40 H), 7.16–7.36 (m, 6 H), 8.51 (broad, 2 H), 8.77 (broad, 4 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 32.5, 37.5, 48.2, 53.4, 60.7 ($CH_2$), 129.6, 129.9, 132.4, 137.9 (Ar), 172.8 (CO). – $C_{36}H_{52}N_8O_4 \cdot H_2O$ (678.9): calcd. C 63.7, H 8.0, N 16.5; found C 63.5, H 7.8, N 16.1.

*1,1′,8,8′-Bis[m-xylylene-1,4,8,11-tetraazacyclotetradecane]* (**16**): The procedure described for **8** was carried out using 500 mg of **15** (0.74 mmol), to yield **16** as a white solid (430 mg, 96%). – IR (KBr): $\tilde{\nu}$ = 3401 $cm^{-1}$ ($H_2O$), 3285 (NH), 2944, 2808 (CH). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.64 (m, 8 H), 1.97–3.87 (m, 32 H), 6.96 (d, 4 H), 7.14 (t, 2 H), 7.39 (s, 2 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 26.3, 48.0, 51.6, 52.2, 53.8, 56.6 ($CH_2$), 128.0, 130.5, 132.5, 137.2 (Ar). – $C_{36}H_{60}N_8$ (604.9): calcd. C 71.5, H 10.0, N 18.5; found C 71.3, H 10.2, N 18.4.

*1,8-m-Xylylene-1,4,8,11-tetraazacyclotetradecane-5,12-dione* (**17**): To 2.0 g of 2,9-dioxocyclam (8.77 mmol) in 1.7 l of acetonitrile were added 2.55 g of α,α′-dibromo-*m*-xylene (9.64 mmol) and 2.4 g of anhydrous sodium carbonate. The mixture was refluxed for 24 h and then the hot solution was filtered. After purification on silica gel ($CH_2Cl_2$/MeOH, 99:1), the title compound was obtained as a white solid (2.6 g, 90%). – IR (KBr): $\tilde{\nu}$ = 3338 $cm^{-1}$, 3301 (NH), 2791 (CH), 1674 (CO), 1616 (aromatic C=C). – $^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.14 (m, 2 H), 2.36 (m, 2 H), 2.62 (m, 2 H), 2.82 (m, 2 H), 3.00 (m, 4 H), 3.10 (m, 2 H), 3.42 (m, 2 H), 3.63 (s, 4 H), 6.35 (broad, 2 H), 6.88 (d, 2 H), 7.07 (dd, 2 H), 8.20 (s, 1 H). – $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 37.9, 39.5, 54.4, 56.6, 60.9, 125.1, 128.1, 132.0, 142.6, 173.7. – $C_{18}H_{26}N_4O_2$ (330.4): calcd. C 65.4, H 7.9, N 17.0; found C 65.0, H 7.9, N 16.9.

*1,8-(2,6-Pyridinedimethylene)-1,4,8,11-tetraazacyclotetradecane-5,12-dione* (**18**): The procedure described for **17** was carried out using 2.0 g of 2,9-dioxocyclam (8.77 mmol), 2.55 g of 2,6-pyridinedimethyl bromide (9.64 mmol), and 2.4 g of anhydrous sodium carbonate, the reaction being performed in refluxing acetonitrile. Purification on silica gel ($CH_2Cl_2$/MeOH, 99:1) yielded the title compound (2.44 g, 84%). − IR (KBr): $\tilde{\nu}$ = 3224 $cm^{-1}$, 3181 (NH), 2814 (CH), 1655 (CO). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.26 (m, 4 H), 2.44 (m, 2 H), 2.78 (m, 4 H), 2.97 (m, 2 H), 3.13 (m, 2 H), 3.30 (m, 2 H), 3.71 (d, 2 H), 3.90 (d, 2 H), 6.97 (d, 2 H), 7.54 (t, 2 H), 9.64 (broad, 2 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 34.6, 37.7, 51.0, 54.8, 58.3, 120.1, 137.9, 158.7, 172.0. − $C_{17}H_{25}N_5O_2$ (331.4): calcd. C 61.5, H 7.6, N 21.1; found C 61.2, H 7.8, N 21.0.

*1,8-m-Xylylene-1,4,8,11-tetraazacyclotetradecane* (**19**). − *a) Procedure A:* Cyclam (7.00 g, 35 mmol) was dissolved in 3.5 l of chloroform in the presence of 9.3 g of anhydrous sodium carbonate. A solution of α,α′-dibromo-*m*-xylene (12.7 g, 48.1 mmol) in 500 ml of chloroform was added dropwise over a period of 12 h and then the mixture was stirred at room temperature for an additional 24 h. The solvent was then evaporated and the oily residue was purified on an alumina column ($CH_2Cl_2$/MeOH, 97:3). After evaporation of the solvents from the appropriate fraction, the product was dissolved in 200 ml of chloroform and washed with 50 ml of a 1 M KOH aqueous solution. The organic phase was dried over magnesium sulfate and the solvent was evaporated to yield **19** as the monohydrate (4.1 g, 37%). − IR (nujol): $\tilde{\nu}$ = 3470 $cm^{-1}$ ($H_2O$), 3296 (NH), 1612, 1588 (aromatic C=C). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.52 (m, 2 H), 1.9−3.3 (m, 18 H), 3.57 (d, 2 H), 3.67 (d, 2 H), 6.97 (d, 2 H), 7.15 (dd, 2 H), 8.45 (s, 1 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 26.2, 49.3, 51.6, 52.5, 59.2, 60.5 ($CH_2$), 124.4, 128.3, 131.3, 143.8 (Ar). − $C_{18}H_{30}N_4 \cdot H_2O$ (320.5): calcd. C 67.5, H 10.0, N 17.5; found C 68.0, H 9.9, N 17.4.

*b) Procedure B:* To a suspension of 2.0 g of **17** (6.05 mmol) in 5 ml of THF under argon, 60 ml of a 1 M borane solution in THF was slowly added at 0°C. The mixture was then refluxed for 24 h and cooled in an ice bath. The excess borane was hydrolysed with a 1:1 mixture of water/MeOH (5 ml) and the solvents were evaporated. The residue was then refluxed in 20 ml of a 3 M aqueous HCl solution for 2 h and the mixture was neutralized by addition of NaOH pellets (pH > 11). Extraction of the aqueous solution with chloroform, followed by drying and concentration of the organic phase, yielded **19** as a sticky oil (1.12 g, 56%). − $C_{18}H_{30}N_4 \cdot 1.5\ H_2O$ (329.5): calcd. C 65.6, H 10.0, N 17.0; found C 65.4, H 9.6, N 16.5.

*1,8-(2,6-Pyridinedimethylene)-1,4,8,11-tetraazacyclotetradecane* (**20**). − *a) Procedure A:* The above procedure *A* for **19** was carried out using 2.0 g of cyclam (10 mmol), 2.8 g of 2,6-pyridinedimethyl dibromide (10.5 mmol), and 2.7 g of anhydrous sodium carbonate, to give after purification on alumina ($CH_2Cl_2$/MeOH, 95:5) compound **20** as the monoprotonated salt (530 mg, 14%). − IR (nujol): $\tilde{\nu}$ = 2948 $cm^{-1}$ (CH), 2425 ($NH^+$), 1594, 1578 (aromatic C=C). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.71 (m, 2 H), 2.08 (m, 2 H), 2.5−3.1 (m, 16 H), 3.55 (d, 2 H), 4.04 (d, 2 H), 6.94 (d, 2 H), 7.49 (dd, 1 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 25.6, 48.6, 50.3, 54.1, 55.0, 56.5 ($CH_2$), 120.1, 137.3, 156.7 (Ar). − $C_{17}H_{29}N_5 \cdot HBr$ (384.4): calcd. C 53.1, H 7.9, N 18.2; found C 53.3, H 7.9, N 18.0.

*b) Procedure B:* The above procedure *B* for **19** was used to obtain the title compound starting from 2.0 g of **18** (6.04 mmol). After refluxing in 20 ml of a 3 M aqueous HCl solution and concentration to dryness, the residue was dissolved in water and purified on a basic ion-exchange resin (Dowex 1X8-100) to yield the title compound as the diprotonated salt (1.20 g, 53%). − $C_{17}H_{29}N_5 \cdot 2$ HCl (376.4): calcd. C 54.2, H 8.3, N 18.6; found C 54.4, H 8.3, N 18.7.

*4-Oxa-1,7,10,16-tetraazabicyclo[6.6.5]nonadecane* (**21**): The procedure described for **17** was carried out using 2.0 g of cyclam (10 mmol), 4.5 g of diethylene glycol ditosylate (11 mmol), and 2.7 g of anhydrous sodium carbonate in refluxing acetonitrile. After purification on alumina ($CH_2Cl_2$/MeOH, 97:3) and washing with 50 ml of a 1 M aqueous KOH solution, the title compound was obtained as an oil (860 mg, 30%). − IR (nujol): $\tilde{\nu}$ = 3431 $cm^{-1}$ ($H_2O$), 3272 (NH), 2812 (CH). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.51 (m, 2 H), 1.73 (m, 2 H), 2.1−2.8 (m, 20 H), 3.34 (ddd, 2 H), 3.50 (ddd, 2 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 27.2 ($\beta_N$-$CH_2$), 49.2, 52.4, 54.7, 55.4, 59.0 ($\alpha_N$-$CH_2$), 69.1 ($\alpha_O$-$CH_2$). − $C_{14}H_{30}N_4O \cdot H_2O$ (288.4): calcd. C 58.3, H 11.1, N 19.4; found C 58.1, H 11.0, N 19.1.

*1,10,13,19-Tetraazabicyclo[8.6.6]dicosane* (**22**): The procedure described for **17** was carried out using 2.0 g of cyclam (10 mmol), 3.5 g of 1,8-dibromooctane (13 mmol), and 2.7 g of anhydrous sodium carbonate in refluxing acetonitrile. After purification on alumina ($CH_2Cl_2$/MeOH, 98:2) and washing with 50 ml of a 1 M aqueous KOH solution, the title compound was obtained as an oil (1.08 g, 35%). − IR (nujol): $\tilde{\nu}$ = 3315 $cm^{-1}$ (NH). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.28−2.95 (m, 36 H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 24.7, 25.1, 26.1, 26.8, 49.1, 53.8, 56.2, 56.7, 57.5. − $C_{18}H_{38}N_4$ (310.5): calcd. C 69.6, H 12.3, N 18.0; found C 70.0, H 12.2, N 17.5.

*1,10,13,18-Tetraazabicyclo[8.5.5]eicosane* (**24**). − *a) Direct Method:* The procedure described for **17** was carried out using 350 mg of cyclen (2.03 mmol), 775 mg of 1,8-dibromooctane (2.85 mmol), and 540 mg of anhydrous sodium carbonate in refluxing acetonitrile. After purification on alumina ($CH_2Cl_2$/MeOH, 99:1) and washing with 50 ml of a 1 M aqueous KOH solution, the product **24** was obtained as an oil (97 mg, 17%).

*b) Two-Step Method:* To 200 mg of cyclen (1.16 mmol) was added 25 ml of 0.5 M acetate buffer and the solution was stirred at room temperature for 1 h. After evaporation of water and drying, the solid residue was suspended in 100 ml of refluxing acetonitrile and 10 ml of a solution of 1,8-dibromooctane (443 mg, 1.63 mmol) in acetonitrile was added dropwise over a period of 12 h. After refluxing for 24 h and filtration, the solvent was evaporated and the residue was taken up in 50 ml of chloroform. The product was then deprotonated by washing with 50 ml of a 1 M KOH aqueous solution and purified on an alumina column ($CH_2Cl_2$/MeOH, 99:1) (200 mg, 61%). − IR (nujol): $\tilde{\nu}$ = 3200 $cm^{-1}$ (NH). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.33 (m, 12 H), 2.43−2.72 (m, 20 H, $\alpha_N$-$CH_2$). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 26.1, 27.2, 28.7, 47.3, 54.4, 57.3. − $C_{16}H_{34}N_4$ (282.5): calcd. C 68.0, H 12.1; found C 68.0, H 11.9.

[1] J. A. Ibers, R. H. Holm, *Science* **1980**, *209*, 223−235.
[2] G. Malmström, *Chem. Rev.* **1990**, *90*, 1247−1260.
[3] S. C. Lee, R. H. Holm, *J. Am. Chem. Soc.* **1993**, *115*, 11789−11798.
[4] K. D. Karlin, A. Nanthakumar, S. Fox, N. N. Murthy, N. Ravi, B. H. Huynh, R. D. Orosz, E. P. Day, *J. Am. Chem. Soc.* **1994**, *116*, 4753−4763.
[5] J. P. Collman, P. C. Herrmann, B. Boitrel, X. M. Zhang, T. A. Eberspacher, L. Fu, J. L. Wang, D. L. Rousseau, E. R. Williams, *J. Am. Chem. Soc.* **1994**, *116*, 9783−9784.
[6] R. Guilard, S. Brandès, C. Tardieux, A. Tabard, M. L′Her, C. Miry, P. Gouerec, Y. Knop, J. P. Collman, *J. Am. Chem. Soc.* **1995**, *117*, 11721−11729.
[7] S. Ferguson-Miller, G. T. Babcock, *Chem. Rev.* **1996**, *96*, 2889−2907.
[8] T. J. McMurry, J. T. Groves, in *Cytochrome P-450, Vol. 1* (Ed.:

P. R. Ortiz de Montellano), Plenum Press, New York, **1986**, p. 1−29.
[9] T. D. Smith, J. R. Pilbrow, *Coord. Chem. Rev.* **1981**, *39*, 295−383.
[10] D. H. Busch, N. W. Alcock, *Chem. Rev.* **1994**, *94*, 585−623.
[11] M. Momenteau, C. A. Reed, *Chem. Rev.* **1994**, *94*, 659−698.
[12] H. Handel, F. R. Muller, R. Guglielmetti, *Helv. Chim. Acta* **1983**, *66*, 514−521.
[13] R. D. Hancock, A. E. Martell, *Chem. Rev.* **1989**, *89*, 1875−1914.
[14] A. Bianchi, M. Micheloni, P. Paoletti, *Coord. Chem. Rev.* **1991**, *110*, 17−113.
[15] A. E. Martell, R. D. Hancock, R. J. Motekaitis, *Coord. Chem. Rev.* **1994**, *133*, 39−65.
[16] R. M. Izatt, K. Pawlak, J. S. Bradshaw, R. L. Bruening, *Chem. Rev.* **1995**, *95*, 2529−2586.
[17] A. E. Martell, R. D. Hancock, *Metal Complexes in Aqueous Solutions*, Plenum Press, New York, **1996**.
[18] S. Blain, P. Appriou, H. Chaumeil, H. Handel, *Anal. Chim. Acta* **1990**, *232*, 331−336.
[19] R. M. Izatt, R. L. Bruening, M. B. Borup, *Water Sci. Technol.* **1991**, *23*, 301−308.
[20] H. Tsukube, T. Yoden, T. Iwachido, M. Zenki, *J. Chem. Soc., Chem. Commun.* **1991**, 1069−1070.
[21] C. Gros, F. Rabiet, F. Denat, S. Brandès, H. Chollet, R. Guilard, *J. Chem. Soc., Dalton Trans.* **1996**, 1209−1214.
[22] V. Alexander, *Chem. Rev.* **1995**, *95*, 273−342.
[23] G. C. Silver, W. C. Trogler, *J. Am. Chem. Soc.* **1995**, *117*, 3983−3993.
[24] N. E. Dixon, R. J. Geue, J. N. Lambert, S. Moghaddas, D. A. Pearce, A. M. Sargeson, *J. Chem. Soc., Chem. Commun.* **1996**, 1287−1288.
[25] E. L. Hegg, J. N. Burstyn, *Inorg. Chem.* **1996**, *35*, 7474−7481.
[26] S. Aime, N. Botta, S. G. Crich, G. B. Giovenzana, G. Jommi, R. Pagliarin, M. Sisti, *J. Chem. Soc., Chem. Commun.* **1995**, 1885−1886.
[27] W. D. Kim, G. E. Kiefer, F. Maton, K. McMillan, R. N. Muller, A. D. Sherry, *Inorg. Chem.* **1995**, *34*, 2233−2243.
[28] H. An, J. S. Bradshaw, R. M. Izatt, *Chem. Rev.* **1992**, *92*, 543−572.
[29] B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*, VCH, Weinheim, **1993**.
[30] J. -M. Lehn, J. Simon, *Helv. Chim. Acta* **1977**, *60*, 141−151.
[31] R. Louis, Y. Agnus, R. Weiss, *J. Am. Chem. Soc.* **1978**, *100*, 3604−3605.
[32] J.-M. Lehn, *Pure Appl. Chem.* **1980**, *52*, 2441−2459.
[33] E. Graf, J.-M. Lehn, *Helv. Chim. Acta* **1981**, *64*, 1040−1057.
[34] A. Kumar, S. Mageswaran, I. O. Sutherland, *Tetrahedron* **1986**, *42*, 3291−3302.
[35] S. Quici, A. Manfredi, L. Raimondi, A. Sironi, *J. Org. Chem.* **1995**, *60*, 6379−6388.
[36] B. Dietrich, J.-M. Lehn, J.-P. Sauvage, *Tetrahedron Lett.* **1969**, 2889−2892.
[37] B. Dietrich, J.-M. Lehn, J.-P. Sauvage, J. Blanzat, *Tetrahedron* **1973**, *29*, 1629−1645.
[38] A. Bencini, A. Bianchi, A. Borselli, M. Ciampolini, E. Garcia-España, P. Dapporto, M. Micheloni, P. Paoli, J. A. Ramirez, B. Valtancoli, *Inorg. Chem.* **1989**, *28*, 4279−4284.
[39] M. Ciampolini, N. Nardi, B. Voltaconi, M. Micheloni, *Coord. Chem. Rev.* **1992**, *120*, 223−236.
[40] A. Bencini, A. Bianchi, C. Bazzicalupi, M. Ciampolini, P. Dapporto, V. Fusi, M. Micheloni, N. Nardi, P. Paoli, B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2* **1993**, 715−720.
[41] C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, P. Paoletti, B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2* **1994**, 815−820.
[42] C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, L. Mazzanti, P. Paoletti, B. Valtancoli, G. Golub, H. Cohen, D. Meyerstein, *J. Chem. Soc., Dalton Trans.* **1995**, 2377−2384.
[43] V. Jacques, M. Mesbahi, V. Boskovic, J. F. Desreux, *Synthesis* **1995**, 1019−1026.
[44] J. Springborg, P. Kofod, C. E. Olsen, H. Toftlund, I. Sotofte, *Acta Chem. Scand.* **1995**, *49*, 547−554.
[45] J. Springborg, C. E. Olsen, I. Sotofte, *Acta Chem. Scand.* **1995**, *49*, 555−563.
[46] A. Bencini, V. Fusi, C. Giorgi, M. Micheloni, N. Nardi, B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2297−2302.
[47] B. Dietrich, B. Dilworth, J.-M. Lehn, J.-P. Souchez, *Helv. Chim. Acta* **1996**, *79*, 569−587.
[48] J.-M. Lehn, J. Simon, J. Wagner, *Nouv. J. Chim.* **1977**, *1*, 77−84.
[49] I. O. Sutherland, *Pure Appl. Chem.* **1989**, *61*, 1547−1554.
[50] C. D. Hall, I. P. Danks, P. D. Beer, S. Y. F. Chu, S. C. Nyburg, *J. Organomet. Chem.* **1994**, *468*, 193−198.
[51] K. E. Krakowiak, J. S. Bradshaw, X. Kou, N. K. Dalley, *J. Heterocycl. Chem.* **1995**, *32*, 931−935.
[52] M. Lachkar, R. Guilard, A. Atmani, A. De Cian, J. Fischer, R. Weiss, *Inorg. Chem.* **1998**, *37*, 1575−1584.
[53] R. D. Hancock, H. Maumela, A. S. Desousa, *Coord. Chem. Rev.* **1996**, *148*, 315−347.
[54] L. Fabbrizzi, P. Pallavicini, L. Parodi, A. Taglietti, *Inorg. Chim. Acta* **1995**, *238*, 5−8.
[55] R. Machida, E. Kimura, M. Kodama, *Inorg. Chem.* **1983**, *22*, 2055−2061.
[56] E. C. Niederhoffer, J. H. Timmons, A. E. Martell, *Chem. Rev.* **1984**, *84*, 137−203.
[57] J. P. Collman, X. M. Zhang, K. Wong, J. I. Brauman, *J. Am. Chem. Soc.* **1994**, *116*, 6245−6251.
[58] D. Chen, R. J. Motekaitis, I. Murase, A. E. Martell, *Tetrahedron* **1995**, *51*, 77−88.
[59] G. Costa, C. Tavagnacco, *Gazz. Chim. Ital.* **1995**, *125*, 243−261.
[60] G. R. Weisman, M. E. Rogers, E. W. Wong, J. P. Jasinski, E. S. Paight, *J. Am. Chem. Soc.* **1990**, *112*, 8604−8605.
[61] G. R. Weisman, E. H. Wong, D. C. Hill, M. E. Rogers, D. P. Reed, J. C. Calabrese, *J. Chem. Soc., Chem. Commun.* **1996**, 947−948.
[62] M. Ciampolini, M. Micheloni, N. Nardi, P. Paoletti, P. Dapporto, F. Zanabini, *J. Chem. Soc., Dalton Trans.* **1984**, 1357−1362.
[63] J. Springborg, P. Kofod, C. E. Olsen, I. Sotofte, *Acta Chem. Scand.* **1995**, *49*, 564−570.
[64] A. Dumont, V. Jacques, Q. X. Peng, J. F. Desreux, *Tetrahedron Lett.* **1994**, *35*, 3707−3710.
[65] B. Boitrel, B. Andrioletti, M. Lachkar, R. Guilard, *Tetrahedron Lett.* **1995**, *36*, 4995−4998.
[66] S. Brandès, C. Gros, F. Denat, P. Pullumbi, R. Guilard, *Bull. Soc. Chim. Fr.* **1996**, *133*, 65−73.
[67] Z. Kovacs, A. D. Sherry, *Synthesis* **1997**, 759−763.
[68] F. Denat, S. Lacour, S. Brandès, R. Guilard, *Tetrahedron Lett.* **1997**, *38*, 4417−4420.
[69] S. Brandès, S. Lacour, F. Denat, P. Pullumbi, R. Guilard, *J. Chem. Soc., Perkin Trans. 1* **1998**, 639−641.
[70] S. Brandès, P. Cocolios, R. Guilard, *C. R. Acad. Sci., Série II b* **1996**, *322*, 827−833.
[71] F. Rabiet, F. Denat, R. Guilard, *Synth. Commun.* **1997**, *27*, 979−987.
[72] G. Naray-Szabo, G. G. Ferenczy, *Chem. Rev.* **1995**, *95*, 829.
[73] P. Politzer, D. G. Truhlar, *Chemical Applications of Atomic and Molecular Potentials*, Plenum Press, New York, **1981**.
[74] J. Tomasi, R. Bonaccorsi, R. Cammi, in *Theoretical Models of Chemical Bonding, Vol. IV* (Ed.: Z. Maksic), Springer Verlag, New York, **1991**, p. 229.
[75] J. S. Murray, T. Brinck, M. E. Grice, P. Politzer, *J. Mol. Struct.* **1992**, *256*, 29.
[76] J. Korchowiec, H. Gerwens, K. Jug, *Chem. Phys. Lett.* **1994**, *222*, 58.
[77] P. C. Mishra, A. Kumar, *Top. Curr. Chem.* **1995**, *174*, 27.
[78] B. S. Nakani, J. J. B. Welsh, R. D. Hancock, *Inorg. Chem.* **1983**, *22*, 2956−2958.
[79] J. E. Richman, T. J. Atkins, *J. Am. Chem. Soc.* **1974**, *96*, 2268−2270.
[80] L. Fabbrizzi, T. A. Kaden, A. Perotti, B. Seghi, L. Siegfried, *Inorg. Chem.* **1986**, *25*, 321−327.
[81] T. Koike, T. Watanabe, S. Aoki, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 12696−12703.
[82] D. A. Tomalia, L. R. Wilson, *United States Patent, 4 517 122*, **1985**.
[83] S. Dumas, E. Lastra, L. S. Hegedus, *J. Am. Chem. Soc.* **1995**, *117*, 3368−3379.
[84] Y. Hsiao, L. S. Hegedus, *J. Org. Chem.* **1997**, *62*, 3586−3591.
[85] A. Bianchi, M. Ciampolini, M. Micheloni, N. Nardi, B. Valtancoli, S. Mangani, E. Garcia-España, J. A. Ramirez, *J. Chem. Soc., Perkin Trans. 2* **1989**, 1131−1137.
[86] M. Ciampolini, M. Micheloni, P. Orioli, F. Vizza, S. Mangani, F. Zanobini, *Gazz. Chim. Ital.* **1986**, *116*, 189−192.
[87] M. Micheloni, A. Sabatini, P. Paoletti, *J. Chem. Soc., Perkin Trans. 2* **1978**, 828−830.
[88] A. Bencini, A. Bianchi, E. Garcia-España, V. Fusi, M. Mich-

eloni, P. Paoletti, J. A. Ramirez, A. Rodriguez, B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1059−1065.
[89] C. Lecomte, in *Adv. in Mol. Struct. Research, Vol. 1* (Ed.: M. a. I. Hargittai), Jai Press, Greenwich, Connecticut, **1995**, p. 261.
[90] N. E. Ghermani, C. Lecomte, N. Bouhmadia, *Z. Naturforsch.* **1993**, *48a*, 91.
[91] N. E. Ghermani, N. Bouhmadia, C. Lecomte, A.-L. Paper, A. Marsura, *J. Phys. Chem.* **1994**, *98*, 6287.
[92] *MSI Inc.*, San Diego CA, **1996** (Release 400).
[93] E. K. Barefield, F. Wagner, A. W. Herlinger, A. R. Dahl, S. Holt, *Inorg. Synth.* **1976**, *16*, 220−225.
[94] E. K. Barefield, F. Wagner, K. D. Hoges, *Inorg. Chem.* **1976**, *15*, 1370−1377.
[95] G. R. Weisman, D. P. Reed, *J. Org. Chem.* **1996**, *61*, 5186−5187. [98175]