Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **7** (1989), 183–191.

Chemistry and Functions of Recently Developed Macrocyclic Polyamines

EIICHI KIMURA
Department of Medicinal Chemistry, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima 734, Japan

(Received: 1 February 1988)

Abstract. New, functionalized macrocyclic polyamines **1**, **9**, **17**, and **20** have been synthesized for investigation of their metal and molecular inclusion.

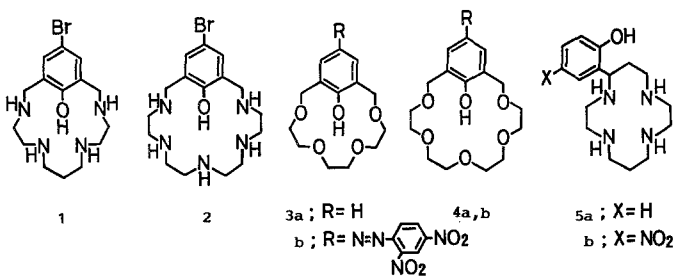
Key words. Macrocyclic polyamines, alkaline earth metals, cyclam, transition metal ion, cyclic voltammetry.

1. Introduction

Recently we have synthesized newly functionalized macrocyclic polyamines **1**, **9**, **17**, and **20** for the investigation of their metal and molecular inclusion.

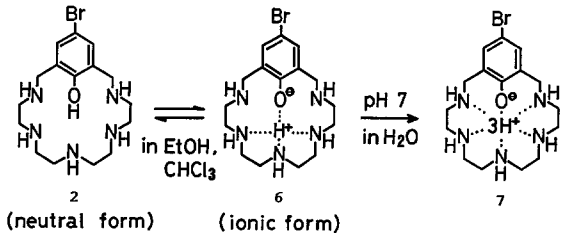
2. A New Mg^{2+} Ion Receptor. Macrocyclic Polyamines Bearing an Intraannular Phenolic Group [1]

To explore a new potential of macrocyclic polyamines, we now have synthesized intraannular phenol-containing derivatives **1** and **2**, which were discovered to possess novel uptake features for alkaline earth metal ions. The homologous bifunctional host molecules **3**, **4** [2, 3] and **5** [4] have recently been reported and comparison with those congeners sheds light on the unique properties of the present phenol azamacrocycles.



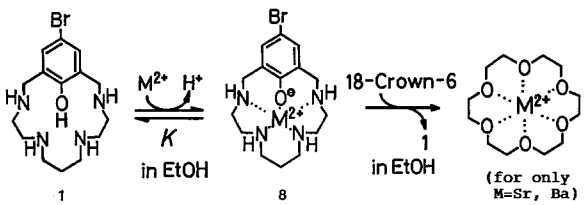
The azacrown rings here are efficient acceptors of the phenol protons. Both the neutral phenol (λ_{max} 294 nm) and ionic phenoxide absorptions (λ_{max} 301 and 250 nm) are observed in the electronic spectra of **1** and **2** in EtOH and $CHCl_3$ solutions. The ratios for the neutral phenol form **2** to ionic phenolate form **6** with

the pentaamine are estimated to be 1 : 1 in anhydrous EtOH and 1 : 0.75 in $CHCl_3$, on the basis of the UV absorptions for the sole phenol form (generated with CCl_3CO_2H, ε 2200 at 283 nm) and phenolate form (with NaOEt, ε 4400 at 301 nm and ε 8600 at 250 nm). Apparently, self dissociation of the phenol protons should be negligible with **3** and **4** in EtOH, and with **5a** in $CHCl_3$ and EtOH.



2 (neutral form) 6 (ionic form) 7

The phenol ionization in EtOH is further promoted by addition of *neutral alkaline earth metal salts* $MgCl_2$, $CaCl_2$, $SrCl_2$, *and* $Ba(SCN)_2$. In varying the [ligand]/[M^{2+}] ratio ([ligand] + [Mg^{2+}] = 1 mM), the total phenolate concentration reaches a maximum at [ligand]/[M^{2+}] = 1 with all the metals. Monovalent alkali metal salts (LiCl, NaCl, KCl, CsCl), on the other hand, do not dispel the phenolic protons of **1** and **2**. With crown homologues **3**, **4** basic conditions are needed to displace the phenol protons for M^+ and M^{2+}. The phenol-pendant N_4 homologues **5a**, **5b** do not interact with alkaline earth metal salts in EtOH solution.



1 8

The apparent constants for the 1 : 1 complexation between **1** (or **2**) and M^{2+} in EtOH are calculable in terms of $K = [M^{2+}\text{-complex}]/[M^{2+}][H_{-1}L](M^{-1})$ (where $H_{-1}L$ is free ligand in phenolate anion form, and [M-complex] is [total phenolate anion]–$[H_{-1}L]$ using the UV spectral data. The results are summarized in Table I. As the M^{2+} size increases, complexation becomes more favorable with the larger macro ligand **2**. These size effects suggest that the metal inclusion into the size-fitted polyamine hole is a determining factor for the selective uptake. It is to be emphasized that the macrocyclic polyamine ligands are most appropriate for the smallest, Mg^{2+}, while crown ethers favor larger M^{2+} cations.

Furthermore, in EtOH the complexation of Mg^{2+} and Ca^{2+} with **1** or **2** is proved to be stronger than with 15-crown-5 or 18-crown-6, while that of Sr^{2+} and Ba^{2+} with **1** or **2** is weaker than with 18-crown-6. This is revealed by the change of the phenolate UV absorptions upon addition of crown ethers (1 eq.) to a 1 : 1 mixture of **1** (or **2**) and MX_2 in EtOH.

Table I. 1:1 Metal complexation constants (log K)

Metal Ion (Ionic Diameter, Å)	**1**[a] Cavity Size (1.4–2.0 Å)	**2**[a] (1.8–2.2 Å)	15-Crown-5[b] (1.7–2.2 Å)	18-Crown-6[b] (2.6–3.2 Å)
Mg^{2+} (1.30)	3.3	3.1	noncomplexation	unreported
Ca^{2+} (1.98)	2.9	2.9	2.1	3.9
Sr^{2+} (2.26)	2.3	2.6	2.6	>5.5
Ba^{2+} (2.70)	1.6	2.4	unreported	7.0

[a] $K = [M^{2+}\text{-complex}]/[M^{2+}][H_{-1}L](M^{-1})$ in EtOH at 25°C. Standard deviation is ±0.1.
[b] $K = [M^{2+}\text{–L}]/[M^{2+}][L](M^{-1})$ in MeOH at 25°C (R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, and J. J. Christensen: *Chem. Rev.* **85**, 271–339 (1985)).

Finally, the 1:1 complexation of **1** with Mg^{2+} was proved by isolation of its monoperchlorate salt, Mg^{2+}–$H_{-1}L{\cdot}ClO_4{\cdot}H_2O$ (as light yellow powder) from an aqueous EtOH solution.

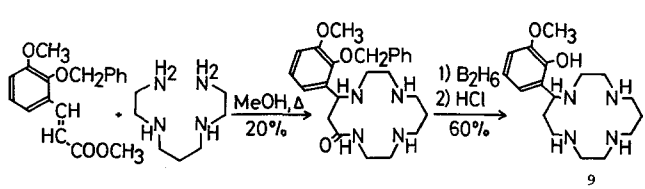
The present results have thus revealed new potentials of macrocyclic polyamines for selective receptors of hard metal ions.

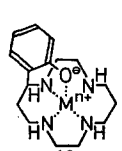
3. The *o*-Methoxyphenol-Pendent Cyclam Complexes 11. A Novel Molecule Designed for Intramolecular Redox-Coupling between Monodentate Catecholate and Metal Ions in a N_4 Macrocycle [5]

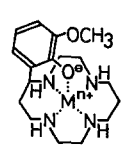
The coordination chemistry of bidentate catechol ligands (cat^{2-}) has long been a subject of chemical [6] as well as biochemical interest [7]. By contrast, the chemistry of monodentate catecholate ($catH^-$) complexes is virtually unknown. Recently, however, Fe^{3+}–$catH^-$ coordination was proposed as an active intermediate in catechol-cleaving dioxygenases, (e.g. protocatechuate 3,4-dioxygenase), whereupon the catechol becomes susceptible to O_2 attack [8].

With the intention of exploring the redox coupling between the monodentate catecholate and metal ions, we have designed a new cyclam ligand **9** that strategically places the N_4 macrocycle so as to hold metal ions during the course of the redox process close to the *o*-methoxyphenol, an equivalent of catechol. Earlier, we have reported the X-ray structure of the axial phenolate coordinating complexes (structure **10**), along with the mutually affected redox behavior of the phenolate ion and metal ions [4].

The new ligand **9** was synthesized as follows:







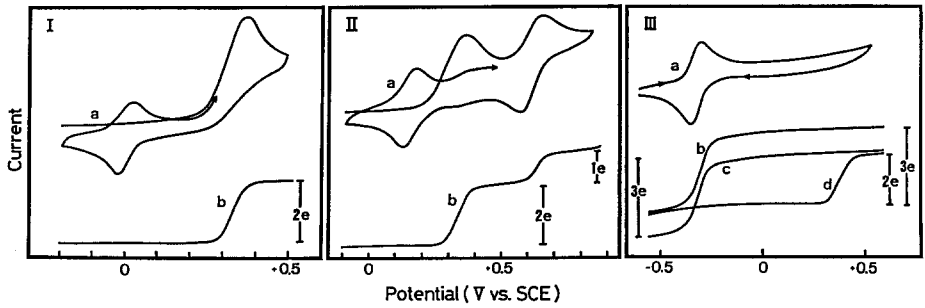


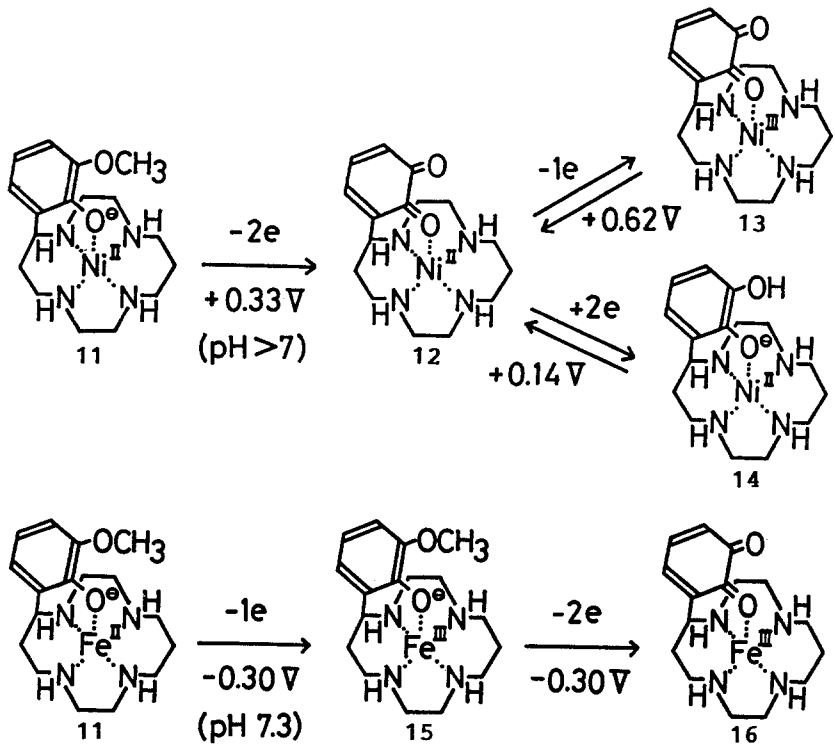
Fig. 1. Cyclic voltammograms (I-a, II-a, III-a) at a scan rate of 100 mV s^{-1} and RDE voltammograms (I-b, II-b, III-b, c, d) at an electrode rotation rate of 1000 rpm, and a scan rate of 10 mV s^{-1} on a glassy carbon disk electrode with 0.2 M Na_2SO_4 at 25°C. I for 1 mM Cu^{2+}-complex **3** at pH 10.0. II for 1 mM Ni^{2+}-complex at pH 7.3 (Tris buffer); curve *a* and *b* for Fe^{2+}-complex **3**, curve *c* for Fe^{3+}-complex **7** (aeration product of Fe^{2+}-complex **3**), curve *d* for free ligand **1**; no further oxidation wave was seen up to +0.5 V vs. SCE.

In an argon atmosphere **9** forms 1 : 1 complexes *in situ* having structure **11** with Ni^{2+} (pH > 7), Cu^{2+} (pH > 9) and Fe^{2+} (pH > 6), as established by pH-metric titration. The UV absorptions [λ_{max} 293 nm (ε 3600) and 247 nm (ε 8600) for Ni^{2+} (pH 8.2), 288 nm (ε 5700, *sh*) and 246 nm (ε 12 000) for Cu^{2+} (pH 10.0), and 287 nm (ε 3700) and 243 nm (ε 7600) for Fe^{2+} (pH 8.3)], being similar to each one of **10**, support the phenolate coordination in **11**. In electrochemical behavior, the Cu^{2+} complex **11** displays an identical CV (at pH 10.0, Figure 1-I) with that of the uncoordinated ligand, indicating little influence of Cu^{2+} on oxidation of the axial *o*-methoxyphenolate. Cu^{2+} is not oxidized in the measured potential range.

The CV and rotating disk electrode (RDE) voltammogram of the Ni^{2+} complex **11** (Figure 1-II) indicate the 2*e* oxidation (to **12**) at +0.33 V (pH > 7), followed by 1*e* oxidation (to **13**) at +0.62 V; in the subsequent CV sweep the reversible *o*-quinone/catechol (**12**⇌**14**) wave appears at +0.14 V, as was seen with the free ligand.

The most unusual synergistic oxidation behavior was revealed by the definite 3*e oxidation of* Fe^{2+} *complex* **11** *simultaneously at* −0.30 *V (pH* 7.3 *Tris buffer) on RDE* (see Figure 1-IIIb). The CV of **11** in Figure 1-IIIa shows no other redox wave up to +0.5 V. The potential of −0.30 V is too low for the 2*e* oxidation of free or mere polycation (such as Cu^{2+}, Ni^{2+})-binding *o*-methoxyphenolate. The 1*e* oxidation potential for Fe^{2+}/Fe^{3+} in **10** was −0.16 V [4]. We are thus tempted to conclude that Fe^{2+} is initially oxidized to Fe^{3+} (**15**) at the lower potential of −0.30 V under the influence of the stronger σ-donor, *o*-methoxyphenolate, and thereupon Fe^{3+} catalytically drains 2*e* out of this ligand to a possible quinone pendant **16**. All the attempts to prepare **16** in a large enough quantity for further identification by electrochemical oxidation at −0.10 V resulted in failure, mostly due to the immediate halt of the electric current. Mild aeration (20 min) of **11** initially oxidizes Fe^{2+} to Fe^{3+} [**15**, deep violet, λ_{max} 278 nm (ε 5500), 518 nm (ε 2150) at pH 7.0, in analogy to Fe^{3+} complex of **10** [4], which undergoes further 2*e* oxidation to **16** at −0.30 V (curve *c*).

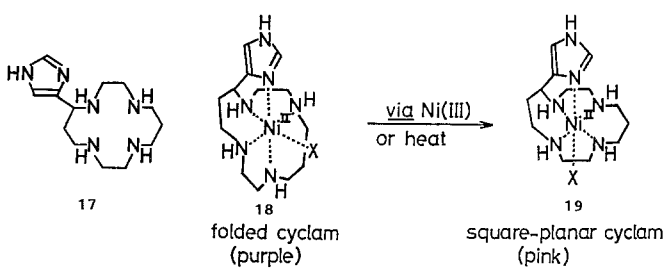
Although the final product structure **16** remains open to question, the present Fe macrocyclic complexes **11** and **15** have offered the first prototype for synergistic



intramolecular redox coupling between monodentate catecholate and metal ions to render the catechol unusually vulnerable to oxidation. Further modification of metal ions or the macrocyclic structure with a catechol pendant would find a novel redox system. Moreover, the reactivity of the remaining 6th axial position would be extremely interesting as a catalytic site.

4. New Cyclam with an Appended Imidazole. The First Biomimetic Ligation of Imidazole for Axial π-Interaction with Metal Ions [9]

We now have succeeded in synthesizing the first cyclam (**17**) bearing an appended imidazole that acts as an ideal axial donor for effective imidazole → metal π-interaction. Our synthetic procedure is simple and versatile, serving also for pyridyl [10] and phenol-appended cyclams [4].



Purple and pink crystals were precipitated when equimolar amounts of $NiSO_4$ and **17** were treated at 50°C for 10 min in an aqueous solution (pH = 8) in the presence of $NaClO_4$. The purple product is a kinetic one, which by longer treatment in warmer (>70°C) aqueous solution is completely converted to the pink as the ultimate thermodynamic product. The purple **18** and pink **19** crystals were subjected to X-ray structure analysis.

In six-coordinate **18** ($X = OClO_3^-$), the cyclam moiety is in a folded configuration with the imidazole nitrogen N_{16} and a perchlorate oxygen O_1 occupying the remaining two *cis* sites. The metal-macrocyclic nitrogen bond Ni—N_1, —N_4, —N_8, and —N_{11} lengths are 2.090(4), 2.087(5), 2.108(4), and 2.091(5) Å, respectively, which are in the normal range 2.05–2.10 Å for high-spin Ni^{II}—N bonds. The Ni—N(imidazole) bond length is extremely short at 2.067(5) Å. The Ni—O(perchlorate) bond length is 2.219(5) Å, to complete the octahedron.

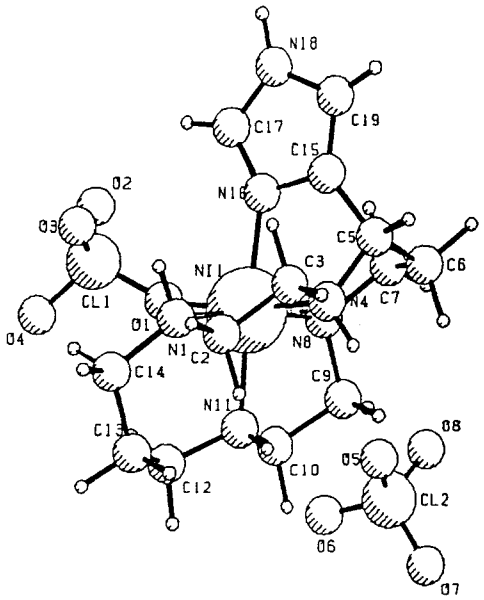
Pink crystals of **19** ($X = CH_3CN$) were grown in CH_3CN—H_2O solution. The coordinate structure (Figure 2) reveals high-spin Ni^{II} in a planar cyclam ('chair form') with imidazole N_{16} and acetonitrile N_{20} at the axial positions. The bond lengths for Ni—cyclam N_1 2.060(11), —N_4 2.058(12), —N_8 2.121(12), and —N_{11} 2.046(12) of the 'metal-in' complex **19** are a little shorter than the corresponding ones of the 'metal-out' complex **18**. The imidazole ring stands vertically to the cyclam N_4 plane to become an axial donor. Moreover, the imidazole plane bisects (by 20°) the $N_4(N_1)$—Ni—$N_8(N_{11})$ angles, which, coupled with short Ni—N_{16}(Im) distance of 2.098(9) Å, may facilitate the imidazole → metal π-donation. Similar bond lengths (2.06–2.1 Å) [11] and orientations of the imidazole ring of the proximal histidine onto the porphyrin plane (20–22.5°) [11] are recognized in hemes or their models to serve Im–Fe^{II} π-interaction for the *trans* O_2 binding. Our new cyclam (**17**) is thus proved to be equipped with an ideal imidazole ligand for axial coordination.

A unique axial imidazole coordination in **19** affects the $Ni^{III/II}$ redox potential. Cyclic voltammetry (CV) shows a quasi-reversible voltammogram at $E_{1/2}$ of +0.54 V vs. saturated calomel electrode (SCE) (0.5 M Na_2SO_4, pH = 7.0, 25°C), which goes between +0.61 V of the pyridyl coordinate homologue [10] and +0.35 V of the phenol coordinate (**10**, M = Ni) [4], but is near to +0.50 V of the cyclam (without pendant) complex.

Another remarkable effect of the destined axial coordination of the imidazole is shown in the O_2 binding of its Co^{II} complex at room temperature in aqueous solution. The brown solid 1:1 Co^{II}–O_2 complex precipitated as the diperchlorate salt. Its ESR parameters in a frozen aqueous solution at 77 K are $g_\perp = 2.01$, $g_\parallel = 2.08$, $A_\perp^{Co} = 13.3$ G, $A_\parallel^{Co} = 20.0$ G, being identical to those reported for paramagnetic 1:1 Co^{II}–O_2 adducts [12]. Without the pendant imidazole, Co^{II}(cyclam) yields only diamagnetic 2:1 O_2 adducts (μ-peroxo complex). In the Fe complex of **17**, the $Fe^{III/II}$ redox potential (pH = 7, I = 0.1 M, $NaClO_4$, 25°C) is +0.00 V vs. SCE, to be compared with −0.16 V of (**10**, M = Ni) and +0.12 V of (pyridyl homologue). The Fe^{II}–**17** complex also forms an O_2 adduct with appearance of the O_2 → Fe CT band at 344 nm, which is currently under investigation.

5. A New Ditopic Receptor Molecule for Ionic Guest Molecules [13]

Macrocyclic polyethers (crown ethers) bind with cationic guests (e.g. primary ammonium cations) [14]. Meanwhile, anionic substrates (e.g. carboxylates) or

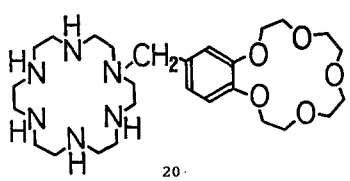


Ni - N_1	2.090	Å
Ni - N_4	2.087	Å
Ni - N_8	2.108	Å
Ni - N_{11}	2.091	Å
Ni - N_{16} (Im)	2.067	Å
Ni - O_1	2.219	Å

Fig. 2. Crystal structure of imidazole-pendant cyclam.

electron donor substrates (e.g. catechols) are recognized by macrocyclic polyamine cations [15]. However, receptor molecules that can simultaneously recognize both cations and anions are very rare. Such ditopic hosts would offer efficient and selective recognition sites for ionic molecules by concerted binding actions.

Herein we report the first ditopic receptor molecule **20** composed of a macromonocyclic polyamine and crown ether, which indeed forms 1 : 1 complexes with ionic substrates such as amino acids **22**–**25**, peptides **26**, or catecholamine **27** in neutral aqueous solutions.



20

A measurement of host–guest interaction has been made with an anodic wave polarography in the same manner as those previously applied to the complexation of polycarboxylate [15] and catechols with [18]aneN_6 [16]. The final results along with the K_i values used for calculation are summarized in Table II.

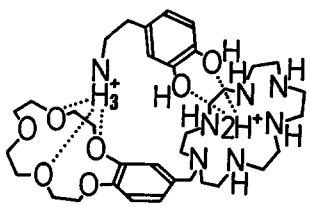
The strong interaction of **20** with dopamine **27** is noteworthy. [18]aneN_6·3 H^+ alone binds with the catechol moiety of dopamine **27** with a β_L value of 1.1×10^3 M^{-1} [16]. Addition of 10 eq. of benzo-15-crown-5 has not affected its polarographic behavior at all. However, when covalently attached as in **20**, the crown ether moiety interacts complementarily with the primary ammonium cation part of dopamine **27**, as depicted in **21**, resulting in a β_L value that is greater by a factor of ten. Since the

Table II. 1:1 Association constants β_L for (**20**)[a] with ionic substrates at 25°C and $I = 0.20$ M ($NaClO_4$)

Ionic Substrate	β_L, M^{-1}	Measured pH in Tris buffer
glycine (**22**)	1.50×10^2	6.5–8
β-alanine (**23**)	1.10×10^2	7–8
GABA (**24**)	1.02×10^2	7–8
6-amino-hexanoic acid (**25**)	1.05×10^2	7–8
diglycine (**26**)	6.87×10^1	7–8.5
dopamine (**27**)	2.92×10^4	7–8
catechol (**28**)	1.50×10^2	7–8

[a] $pK_a = 9.66, 9.13, 7.75, 4, \sim 2, \sim 1$.

experiment indicates involvement of $(i+j) = 5$ protons in this complexation, we assign $2\,H^+$ to the [18]aneN$_6$ part and $3\,H^+$ to the dopamine part. On the other hand, catechol **28**, a monotopic guest of [18]aneN$_6$·$3\,H^+$, does not enjoy affinity enhancement by the attachment of the crown ether moiety: the β_L value of 1.5×10^2 with **20** is almost the same, 1.6×10^2, as with [18]aneN$_6$.



21

In view of the versatility and simplicity of the present synthetic method, the macromonocyclic polyamine linked with a crown ether forms a promising prototype for the design of a variety of polytopic recognition receptors that should find a number of applications.

References

1. E. Kimura, Y. Kimura, T. Yatsunami, M. Shionoya, and T. Koike: *J. Am. Chem. Soc.* **109**, 6212 (1987).
2. G. M. Browne, G. Fergeson, M. A. McKervey, D. L. Mulholland, T. O'Connov, and M. Parvez: *J. Am. Chem. Soc.* **107**, 2703 (1985).
3. K. Nakashima, S. Nakatsuji, S. Akiyama, T. Kaneda, and S. Misumi: *Chem. Pharm. Bull.* **34**, 168 (1986), and references therein.
4. E. Kimura, T. Koike, K. Uenishi, M. Hediger, M. Kuramoto, S. Joko, Y. Arai, M. Kodama, and Y. Iitaka: *Inorg.* Chem. **26**, 2975 (1987), and references therein.
5. E. Kimura, S. Joko, T. Koike, and M. Kodama: *J. Am. Chem. Soc.* **109**, 5528 (1987).
6. L. A. deLearie and C. G. Pierpont: *J. Am. Chem. Soc.* **108**, 6393 (1986), and references therein.
7. C.-W. Lee, D. J. Ecker, and K. N. Raymond: *J. Am. Chem. Soc.* **107**, 6920 (1985), and references therein.

8. T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto, and S. Yoshida: *J. Am. Chem. Soc.* **108**, 2921 (1986), and references therein.
9. E. Kimura, M. Shionoya, T. Mita, and Y. Iitaka: *J. Chem. Soc., Chem. Commun.*, 1712 (1987).
10. E. Kimura, T. Koike, H. Nada, and Y. Iitaka: *J. Chem. Soc., Chem. Commun.*, 1322 (1986).
11. G. B. Jameson, F. S. Molinaro, J. A. Ibers, J. P. Collman, J. I. Brauman, E. Rose, and K. S. Suslick: *J. Am. Chem. Soc.* **102**, 3224 (1980).
12. E. Kimura, M. Kodama, R. Machida, and K. Ishizu: *Inorg. Chem.* **21**, 595 (1982), and references cited therein.
13. E. Kimura, H. Fujioka, and M. Kodama: *J. Chem. Soc., Chem. Commun.*, 1158 (1986).
14. D. J. Cram and J. M. Cram: *Science* **183**, 803 (1974).
15. E. Kimura: *Top. in Curr. Chem.* **128**, 113 (1985).
16. E. Kimura, A. Watanabe, and M. Kodama: *J. Am. Chem. Soc.* **105**, 2063 (1983).