Supplementary Material Available: Tables of bond distances, bond angles, and positional and thermal parameters for hydrogen and non-hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

Isolation and Unusual Stability of a New Macrocyclic Polyamine Containing a Phthalimidine

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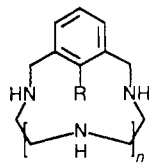
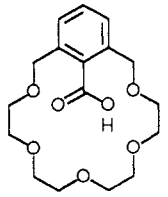
The host properties of macrocyclic polyamines containing a 2-hydroxy-1,3-xylyl unit as part of the large ring (**1** and **2**) are of great interest.[1] Effective uptake of alkaline-earth metal ions by them in MeOH has been achieved with the 1:1 complexation constants being in the order of $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$. Moreover, the simultaneous dissociation of the phenolic H^+ has allowed for the facile determination of complexation constants.



1: n = 2, R = OH
2: n = 3, R = OH
3: n = 3, R = COOH



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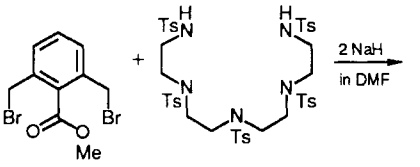
In order to develop further the chemistry of host polyamines, we have attempted to synthesize macrocycle **3**. This putative new compound **3** would be of interest in that its benzyl nitrogens could be close enough to the carboxyl substituent so that the lone pair of each benzyl nitrogen points toward the carbonyl carbon along the axis of its π system. Such overlap could conceivably lead to some unusual properties for the carbonyl group in **3**. In the polyether counterpart **4**,[2] for instance, the distances of the O···C=O bond were observed to be shorter than the usual van der Waals contacts, suggesting the presence of attractive dipole–dipole interactions.[3]

A new macrocycle (**6**) was prepared from dibromide **5** and tetraethylenepentamine pentatosylate in order to explore the above possibilities. Compound **6** was then heated at reflux in 48% HBr–acetic acid solution over a period of 48 h to complete the detosylation. Usual workup by anion exchange chromatography and recrystallization from acetonitrile then afforded a product as prismatic crystals, which on the basis of the reaction sequence was expected to be **3**. Elemental analysis, ^1H and ^{13}C NMR, IR, and UV spectra, and other physicochemical data for this product, however, did not fit to the anticipated structure **3**. This left some doubts about the structural assignment. The structure of this material was therefore



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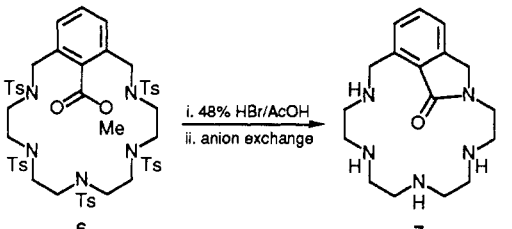
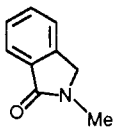


6 **7**



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determined by X-ray diffraction analysis and on this basis assigned unequivocally as compound **7** (Figure 1).

In addition to allowing for the structural assignment, the X-ray structure provides interesting details about the macrocyclic conformation, where the planar phthalimidine ring stands almost vertically to create a shielded cavity for guest ions.

The protonation constants (pK_a) were determined by pH (see Figure 2) to be 9.9, 9.2, 5.9, and 2.2 at I = 0.1 M ($NaClO_4$), 25 °C, indicating feasible accommodation of two protons into the macrocyclic cavity. The UV spectral absorptions (220–280 nm) of the phthalimidine are substantially increased in intensity in macrocycle **7**, as compared to *N*-methylphthalimidine itself (structure **8**). Moreover, in **7**, successive addition of protons affects the UV absorptions at 240–280 nm, whereas the UV absorption of **8**, as expected, is not subject to such proton dependence.

A similar significant UV absorption change was observed upon Zn^{2+} and Cu^{2+} uptake (up to 1:1 molar ratio). The pH–titration method has established 1:1 complexation with Zn^{2+} and Cu^{2+} (Figure 2). From the titration curve the modes of complexation of Cu^{2+} and Zn^{2+} are suggested to be as shown in Scheme I.

Detailed computational analysis of the experimental curves has allowed the values of the complexation constants to be determined as log K_{CuHL} = 12.2 (K_{CuHL} = $[Cu^{II}HL]/[Cu^{II}][HL]$), log K_{CuL} = 15.3 (K_{CuL} = $K_{CuHL} \times K'_{CuL}/K_1$, where $K' = [Cu^{II}L] \times a_{H^+}/[Cu^{II}HL]$), and log K_{ZnL} = 8.1 ($K_{ZnL} = [Zn^{II}L]/[Zn^{II}][L]$).[4] The considerably smaller K values observed here relative to those for unsubstituted N_4 macrocyclic ligands[5] may indicate that the stretched N_4 ring conformation present in **7** is unfavorable for metal incorporation (due to lack of flexibility).

The amide bond in macrocyclic **7** strongly resists hydrolysis in acid (e.g., refluxing 6 N HCl) and use of Zn^{2+} or Cu^{2+} ions (which were tried in an effort to activate the

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(4) The titration data of **7** in the presence of each metal ion (see dots on lines (b) and (c) in Figure 2) were treated by the Schwarzenbach method for the 1:1 complexation [Schwarzenbach, G. *Helv. Chim. Acta* **1950**, *33*, 947]. The metal hydrolysis was taken into account, where K_{OH} (= $[M(OH)^+]/([M^{2+}]a_{OH^-})$) values are 4.6×10^6 for Cu^{II} and 1.1×10^5 for Zn^{II} [Iitaka, Y.; Koike, T.; Kimura, E. *Inorg. Chem.* **1986**, *25*, 402].
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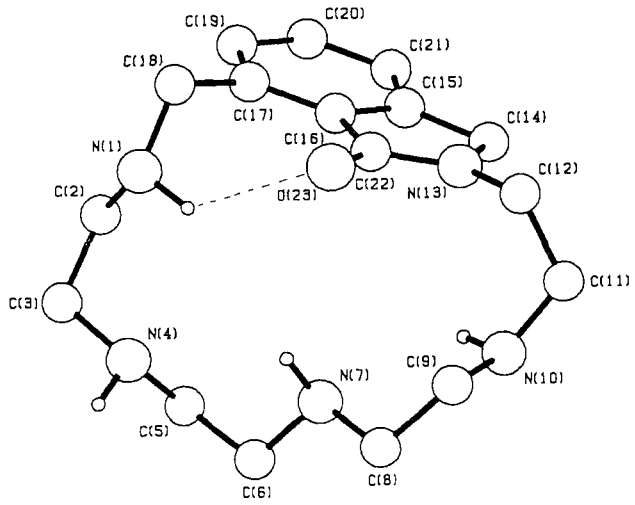
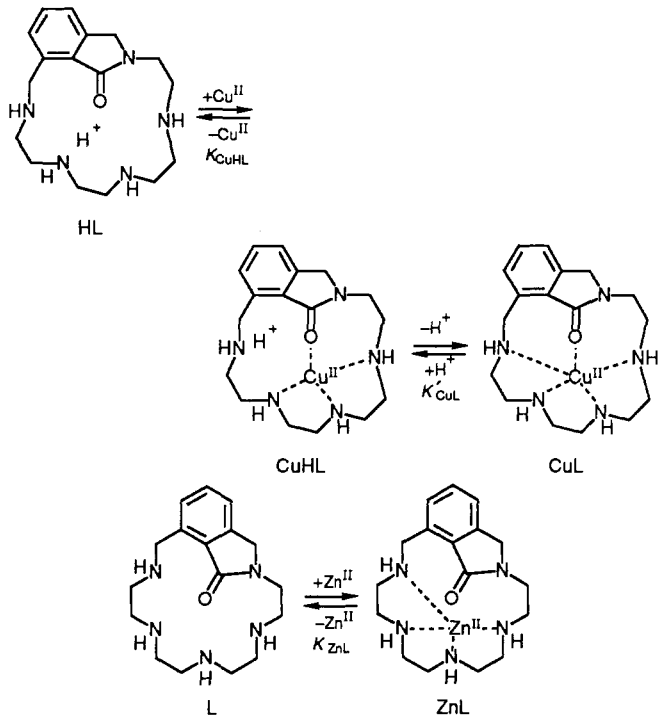


Figure 1. Perspective view of **7** with atom-numbering system. Hydrogen atoms except those bound to nitrogen atoms are not drawn for clarity. Important bond lengths (Å) (average standard deviation, 0.003 Å) and bond angles (deg) (average standard deviation, 0.2°) are as follows: C (12)–N(13) 1.456, N(13)–C(14) 1.453, C(16)–C(22) 1.487, N(13)–C(22) 1.362, C(22)–O(23) 1.224, C(17)–C(18) 1.513, C(18)–N(1) 1.455; N(1)–C(18)–C(17) 116.0, C(16)–C(17)–(18) 122.3, C(17)–C(16)–C(22) 129.1, C(16)–C-(22)–O(23) 128.4, N(13)–C(22)–C(16) 105.9, C(12)–N(13)–C(14) 123.8, C(14)–C(15)–C(16) 109.4, N(13)–C(14)–C(15) 102.5.

Scheme I



amide function for hydrolysis) also failed to facilitate the cleavage. On the other hand, the nonmacrocyclic *N*-methylphthalimidine (**8**) is readily hydrolyzed in acid. Finally, macrocycle **7** is barely hydrolyzed to **9** (identified by thin layer chromatography, IR, and NMR spectra), after being refluxed with equivalent KOH in an aqueous solution for 44 h. Indeed, **9** is in rapid equilibrium with **7** and rapidly reverses to this form on protonation. In particular, it is important to note that attempts to convert the alkaline salt **9** to free form **3** in neutral to weak acidic solution always failed and ended in production of **7**. These observations suggest that the location of the carbonyl in **7** unusually close to the benzyl nitrogens in the macrocyclic

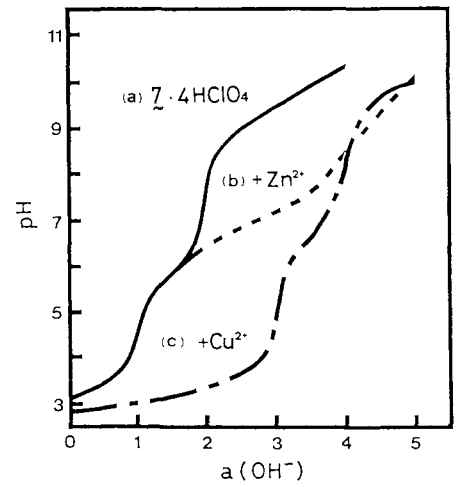
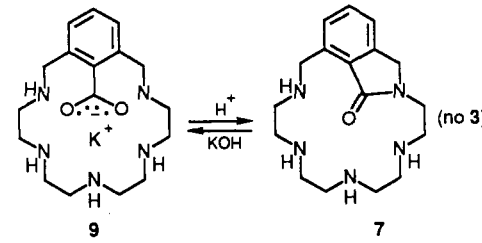


Figure 2. Potentiometric titration curves of **7**·4$HClO_4$ (a, —) and in the presence of equimolar Zn^{2+} (b, - - -) or Cu^{2+} (c, – – –). Curve a: 1 mol of base per mol of ligand.

cavity destabilizes **3** and favors the alternative intramolecular amidation of **7**. More elaborate work on the properties of various salts of **9** is continuing.



Experimental Section

^1H NMR spectra were obtained on a Hitachi R-40 high-resolution NMR spectrometer (90 MHz, 35 °C, Me_4Si reference) and a JEOL GX-400 spectrometer (400 MHz, 35 °C, Me_4Si reference). IR and mass spectra were obtained on Shimadzu FTIR-4200 and JEOL JMS-O1SG-2 instruments, respectively. Column chromatography was carried out on silica gel (Wakogel C-300). pH was measured with an Orion Research Model 811 pH meter. Potentiometric titrations were conducted in the usual manner as described before.[6] UV spectra were recorded on a Hitachi U-3200 double-beam spectrophotometer at 25 °C.

X-ray Crystal Study. Intensities of 2961 unique reflections in the region of $0.2 < 2\theta < 130$ were measured on a Rigaku AFC-5 diffractometer, using Cu–K_α radiation, and were corrected for absorption effects by use of North's method.[7] The structure was solved by the direct method and refined by a block-diagonal least-squares technique on a FACOM M-340R computer to R and R_W = 0.051 and 0.078, respectively, for 2631 observed reflections with $|F_o| > 3\sigma(F_o)$. Crystal data for **7**: $C_{17}H_{27}N_5O_1$, M = 317.4, monoclinic, space group $P2_1/c$, a = 9.431 (1), b = 24.684 (3), and c = 7.917 (1) Å, γ = 109.24 (1)°, V = 1740.1 Å^3, Z = 4, D_{calcd} = 1.212 g cm^{-3}.

Synthesis: *N*-Methylphthalimidine (8). *N*-Methylphthalimidine was synthesized according to the literature.[8]

Macrocycles 6 and 7. Synthesis of **6** involves cyclization of methyl 2,6-bis(bromomethyl)benzoate[2b,9] (5.0 g, 15.5 mmol) with the corresponding pentamine pentatosylate (14.9 g, 15.5 mmol) in the presence of ca. 2 equiv of NaH (>55%, 1.43 g) in DMF (600 mL) at 100 °C for 24 h. The solvent was evaporated in vacuo

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and the residue was dissolved in CH_2Cl_2 and washed with water. After drying of the organic phase over anhydrous sodium sulfate and filtration, removal of solvent under reduced pressure yielded a viscous yellow oil, which was purified by silica gel column chromatography (eluent, hexane/ethyl acetate = 3:1 in volume). A white powder of **6** (12.2 g, 70% yield) was obtained: mp 123–128 °C; IR (KBr pelet) $\nu_{C=O}$ 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3–2.7 (m, 15 H, $ArCH_3$), 2.7–3.4 (m, 16 H, NCH_2CH_2N), 3.81 (s, 3 H, CO_2CH_3), 4.11 (d, J = 16 Hz, 2 H, $ArCH_aH_bN$), 4.48 (d, J = 16 Hz, 2 H, $ArCH_aH_bN$), 7.2–7.5 (m, 13 H, Ar*H*, Ar*H* (Ts)), 7.5–7.9 (m, 10 H, Ar*H* (Ts)).

The detosylation of the pentatosylate **6** (1.0 g, 0.89 mmol) was achieved in 50 mL of AcOH–48% aqueous HBr (3:2 in volume) at 140 °C for 48 h. After the removal of solvent, the residue was dissolved in 50 mL of water and washed with three portions of CH_2Cl_2. The water phase was evaporated and the residue was passed through a strong anion exchange resin column (Amberlite IRA-400). The free **7** was obtained as colorless prisms (80 mg, 28% yield), recrystallized from CH_3CN: mp 134.0 °C; MS M^+ (m/e) 317; IR (KBr pelet) $\nu_{C=O}$ 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5–2.9 (m, 12 H, $HNCH_2CH_2NH$), 2.9–3.1 (m, 2 H, $HNCH_2CH_2NC{=}O$), 3.7–3.9 (m, 2 H, $HNCH_2CH_2NC{=}O$), 4.10 (s, 2 H, $ArCH_2NH$), 4.40 (s, 2 H, $ArCH_2NC{=}O$), 7.2–7.6 (m, 3 H, Ar*H*). Anal. Calcd for $C_{17}H_{27}H_5O_1{\cdot}0.2H_2O$: C, 63.60; H, 8.60; N, 21.82. Found: C, 63.64; H, 8.57; N, 21.64.

Hydrolysis of 7. Alkaline hydrolysis of the amide **7** was achieved by reflux with equivalent KOH in aqueous solution for 44 h. The reaction was monitored by silica gel TLC (eluent, CH_2Cl_2/CH_3OH/aqueous NH_3 = 25:10:1; R_f values are 0.2 for **7** and 0.5 for **9**). After evaporating the reaction mixture in vacuo, the crude product was obtained as the mixture of **7** and **9** (main product), which was supported by ^1H NMR (an equivalent benzylic protons at δ 4.35 (s) for **9**) and IR (an absorption at 1686 cm^{-1} for **9**) spectra. Attempts to neutralize the alkaline salt **9** with weak acidic solution always resulted in the formation of **7** (monitored by TLC).

Registry No. CuL, 124177-78-2; ZnL, 124199-98-0; TsN-$((CH_2)_2NTs(CH_2)_2NHTs)_2$, 99142-42-4; **5**, 56263-51-5; **6**, 124199-97-9; **7**, 124177-76-0; **9**, 124177-77-1.

Supplementary Material Available: Atomic coordinates, temperature factors, bond lengths and bond angles for **7**, and UV absorption spectral data (6 pages). Ordering information is given on any current masthead page.

Osmium Tetraoxide Catalyzed Vicinal Hydroxylation of Higher Olefins by Using Hexacyanoferrate(III) Ion as a Cooxidant

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The oxidation of olefins with osmium tetraoxide to give *cis*-diols is a well-established reaction.[1] Criegee showed that osmium tetraoxide in a stoichiometric amount could be used for effective cis hydroxylation of the olefins and that this method is more reliable than other diol syntheses,[2,3] despite its high cost and toxicity. Subsequently, a catalytic amount of osmium tetraoxide has been successfully used in the presence of suitable cooxidants like hydrogen peroxide (Milas' reagent),[4-6] metal chlorates,[7-9] *tert*-butyl hydroperoxide,[10-12] and amine *N*-oxides (such as *N*-methylmorpholine *N*-oxide, NMO).[13] These catalytic hydroxylation reagents, however, have disadvantages due to appreciable overoxidation or inertness toward hindered olefins. We report here a modification of catalytic vicinal hydroxylation using hexacyanoferrate(III) ion as a cheap and convenient cooxidant for osmium(VI).

Although hexacyanoferate(III) ion has previously been used in examining the kinetics of osmium tetraoxide oxidations,[14-17] these studies were limited to the oxidation of lower molecular weight organic compounds in an aqueous strong alkaline medium. The higher molecular weight olefins do not react with an entirely aqueous solution of hexacyanoferrate(III) ion in the presence of OsO_4. In the present study we have found that, by employing an aqueous *tert*-butyl alcohol, it is possible to obtain vicinal diols in good yields (Table I). We also examined acetone and acetonitrile as a cosolvent, but both were inferior to *tert*-butyl alcohol. In addition, this procedure gives only a low yield of the dihydroxylation product from cholesterol. It has been reported that this may be due to the formation of a stable osmate ester.[12] It was also reported by Criegee that the rate of formation of the osmate ester could be enhanced by the addition of an excess of tertiary amine, such as pyridine,[3] and more recently, by Sharpless that dihydroquinidine ester accelerated the catalytic dihydroxylation of styrene using NMO as cooxidant.[18] Accordingly, we have tried the osmium tetraoxide catalyzed oxidation of cholesterol by our procedure in the presence of various tertiary amines (Table II).

Addition of an equimolar amount (1.7×10^{-2} M) of quinuclidine or 1,4-diazabicyclo[2.2.2]octane (DABCO) to cholesterol dramatically accelerated the catalytic hydroxylation, resulting in an increased yield of diol (**6**). In order to make a qualitative measurement of the acceleration of the reaction, we chose 1-decene as a substrate instead of cholesterol and studied the rate enhancement of the hydroxylation of these added amines. Consequently, it was found that quinuclidine and DABCO accelerated the half-life rate by 13- and 7.8-fold, respectively. These results indicate a striking contrast with those of Sharpless. They reported that, although dihydroquinidine ester could accelerate the reaction, quinuclidine strongly retarded catalysis.[18,19] They argued that the rate acceleration in

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