

to the α -carbon of the newly forming amino acid. Part of our evidence was the higher rate (Table I) of transamination by systems such as Id in which the chain was long enough to permit proton delivery compared with shorter chains (e.g., Ib, Ic).⁹ Of course, this mechanism was also the basis for our successful stereoselective transamination process.¹⁰

As a further check on these conclusions, we have now examined the effect of chain length in compounds Ia-g on the reaction with chloropyruvic acid. As in the previous study,⁹ reaction in methanol at pH 4.0 and addition of zinc acetate led to rapid ketimine formation (λ_{\max} 328 nm), and we followed the rate of the subsequent process. In this case HCl elimination formed the dehydroalanine derivative II, with λ_{\max} 414 nm,¹¹ which then reacted more slowly (presumably by adding solvent) to form an aldimine with λ_{\max} 380 nm.¹² Dehydroalanine-pyridoxal structures related to II are intermediates in a number of biochemical processes, including the condensation of serine with indole by tryptophan synthetase discussed above.

In the dimethylamino series (Ib-d) the HCl elimination rates (Table I) were fastest¹³ with the shorter chain of Ic, as expected for a process that requires only proton removal from the pyridoxamine 4'-CH₂ group. The contrast with the data for transamination (Table I), in which Id with the longer chain was the fastest, supports our previous contention^{9,10} that in transamination the catalytic group also performs the protonation at the amino acid α -carbon. In the imidazole series (Ie-g) the shortest chain system Ie was also fastest in HCl elimination. The striking contrast to the data for transamination fully supports the proposition that in our transamination studies the catalysis is sequential, with proton transfer by the catalytic group to the remote position of the intermediate.

(11) Cf.: Matsushima, Y.; Karube, Y.; Kono, A. *Chem. Pharm. Bull.* **1979**, *27*, 703-709 for a related compound with λ_{\max} 412 nm.

(12) This elimination apparently resembles Elcb, not E2, since with bromopyruvate the reaction is slightly slower.

(13) The six-atom transition state with Ib is too small, for stereoelectronic reasons; cf.: Hine, *J. Acc. Chem. Res.* **1978**, *11*, 1-7.

High-Dilution Synthesis of Macrocyclic Polycatecholates

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There exists a clear need for new iron chelating agents in medicine,¹ particularly for the treatment of the iron overload syndromes. The siderophores² are a class of microbially produced iron chelators that are powerful sequestering agents for Fe(III) and other trivalent (or tetravalent) metal ions of similar charge to ionic radius ratios. As such, the structures of siderophores serve as important models for the biomimetic design of new chelating agents. Synthetic polycatecholate ligands modeled on the siderophores enterobactin and agrobactin have been found to form strong Fe(III) complexes,³ to remove iron rapidly from the mammalian iron transport protein, transferrin,⁴ and to be effective

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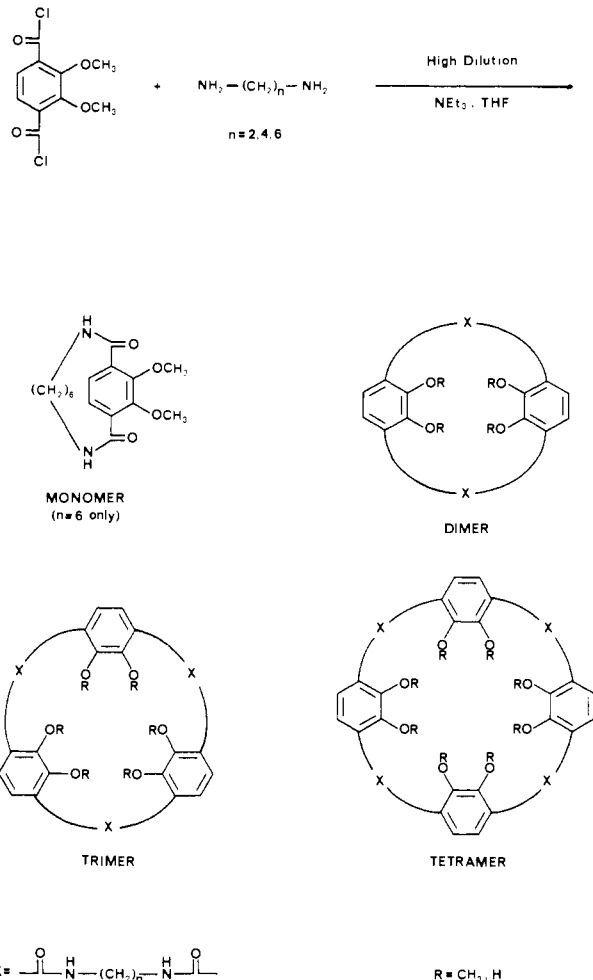


Figure 1. High-dilution synthesis of polycatecholate macrocycles.

Pu(IV) removal agents in vivo.⁵

Among the structures of the hydroxamate siderophores are examples of acyclic, endocyclic, and exocyclic ligands.² The beneficial entropic aspects of incorporating the chelating moieties within a macrocyclic ring can be seen in endocyclic hydroxamate siderophores (such as ferrioxamine E), which possess the highest Fe(III) formation constants⁶ of all the hydroxamate siderophores. A general theoretical discussion of the advantages of such complexes has been described, along with a number of proposed ligand structures, on the basis of these considerations.⁷ All catecholate siderophores isolated to date are either acyclic or exocyclic. The recent introduction^{8,9} of the symmetric 2,3-dihydroxyterephthalate moiety as a synthon for Fe(III) chelators makes possible the synthesis of a host of endocyclic polycatecholate chelators that have yet to be explored¹⁰ and that potentially could have even greater iron-binding properties than previously known ligands. We report here the synthesis of a new class of endocyclic polycatecholate ligands.

Under high-dilution conditions¹¹ a series of alkane diamines ($n = 2, 4, 6$) react with 2,3-dimethoxyterephthaloyl chloride¹² in

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Table I. Yields of the High-Dilution Reaction and FAB Mass Spectrum of Macrocyclus

		methyl protected		free ligand	
		ring size	% yield	FAB-MS ^a	FAB-MS ^a
ethane	trimer	30	17	751	667
	tetramer	40	8	1023 ^b	911 ^b
	pentamer	50	1	1251	
butane	hexamer	60	<1	1501	
	dimer	24	3	557	501
	trimer	36	10	835	751
	tetramer	48	4	1113	1001
	pentamer	60	<1	1391	
hexane	monomer	14	5	307	
	dimer	28	24	612	557
	trimer	42	9	919	835
	tetramer	56	2	1225	
	pentamer	70	<1	1531	

^aPositive FAB-MS run from a liquid matrix of glycerol or thio-glycerol. M + H peak reported. ^bM + Na peak only observed.

THF in the presence of NEt_3 to give a mixture of oligomers (Figure 1, R = Me). The relatively nonpolar cyclic oligomers, which separate easily from the linear oligomers and polymer, were separated from each other by flash chromatography.¹³ The cyclic structure of each oligomer was confirmed by the simplicity of the ^1H NMR: both the terephthalate protons and the methoxy protons appear as singlets, reflecting the symmetry of the molecules. The identity of each cyclic oligomer was revealed by FAB mass spectra (Table I). Precedent for the isolation of similar macrocycles based on unsubstituted terephthalic acid can be found in the polyamide and polyester literature¹⁴⁻¹⁷ and in the synthesis of crown ethers containing the terephthalate moiety.¹⁸

The yield of total cyclic oligomers isolated for each series ($n = 2, 4, 6$) was approximately 30%. Table I gives the yields of the cyclic oligomers obtained after separation from single 10-g dimethoxyterephthaloyl chloride high-dilution reactions, showing that gram quantities of these macrocycles can be prepared by this method. The relative yield of each oligomer within a series was found to vary depending on the overall ring size, reaching an apparent maximum for 30-membered rings. For instance, the ethane and butane diamine reactions yield predominately trimer whereas the hexane diamine reaction give predominately dimer. Higher molecular weight cyclic macrocycles such as pentamers and hexamers with ring sizes as large as 60 were isolated in small amounts (<1%) from the reaction mixtures. Presumably there is some ring strain associated with the 20-membered ring of the ethane dimer which precludes its formation in isolable amounts, a result that has been suggested in the synthesis of unsubstituted terephthalate-based polyesters.¹⁴

Within the hexane reaction mixture was isolated a small amount of a cyclic monomer, in which the hexane diamine bridges across the face of the terephthalate ring. This monomeric compound has radically different physical properties from the higher cyclic oligomers, in particular a ~ 0.5 ppm upfield shift of the methylene protons in the ^1H NMR due to the effect of the terephthalate ring current. The identity of this monomeric compound has been confirmed by X-ray crystallography.¹⁹

The methyl protecting groups of the isolated oligomers were removed by reaction with BBR_3 to give the free catecholate macrocycle (R = H) typically in 80% yield. The cyclic structures

of these macrocycles were again confirmed by ^1H NMR and FAB mass spectra.

An alternative route to these macrocycles would be the multistep elongation of a linear oligomer followed by a final high-dilution cyclization reaction to give a single oligomeric product. However, the ease of the chosen route coupled with the potential interest of all of the compounds isolated makes this a practical route into such macrocycles.

Examination of CPK models indicates that all the trimers, including the shorter chain length ethane trimer, are capable of complexing Fe(III) in an octahedral arrangement. Preliminary studies of the ethane trimer²⁰ have shown that these ligands do form very stable Fe(III) complexes.²¹ The six phenolic $\text{p}K_a$'s of the ligand were found to be 11.61 (2), 11.18 (2), 10.83 (2), 7.98 (3), 6.97 (3), and 6.33 (5). The presence of two carboxamide substituents on the catechol ring substantially lowers the phenolic $\text{p}K_a$'s compared with the monosubstituted catecholate siderophores. Above pH 9 the deep burgundy Fe(III) ethane trimer complex exhibits two shoulders in the visible at 440 and 520 nm. The metal ligand complex protonates in two, sequential one-proton steps, yielding $\log K_{\text{MHL}} = 7.63$ (4) and $\log K_{\text{MHL}} = 4.80$ (10) by the Schwarzenbach method.²² From potentiometric data the same protonation constants were found to be 7.55 and 4.85, respectively. Competition experiments with excess EDTA at low pH (where EDTA can effectively compete with this ligand) yielded the overall formation constant $\log K_{\text{ML}} = 38.7$ (7). The $\text{p}M$ of this ligand defined as $-\log [\text{Fe}]$ at pH 7.4, $1 \mu\text{M}$ Fe(III), and $10 \mu\text{M}$ ligand is 28.2. These values attest to the great stability of the Fe(III) complexes of this new ligand. However, by analogy with the endocyclic hydroxamate siderophores, the ethane trimer would be anticipated to have an even greater formation constant with Fe(III) than the exocyclic siderophore enterobactin (estimated $K_{\text{ML}} = 10^{52}$). The cause of this 13 orders of magnitude difference in stability constants is, in part, a direct consequence of the lower cumulative basicities of the ethane trimer donor groups compared to enterobactin. The possible involvement of steric effects, reflected in the variation of the Fe(III) formation constants as a function of chain length, is under investigation.

Thus we have prepared a new class of macrocyclic polycatecholates which have a high affinity for Fe(III) and which should also have a high affinity for metal ions of similar charge to ionic radius ratios. The trimeric catecholates are intended to encapsulate Cr(III), Al(III), and Ga(III) whereas the tetramers can completely encapsulate eight-coordinate Ce(IV), Pu(IV), and other actinides. Further studies on the metal coordination chemistry of these ligands are in progress.

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Registry No. $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, 107-15-3; $\text{NH}_2(\text{CH}_2)_4\text{NH}_2$, 110-60-1; $\text{NH}_2(\text{CH}_2)_6\text{NH}_2$, 124-09-4; 2,3-dimethoxyterephthaloyl chloride, 7169-12-2; ethane trimer (R = Me), 96363-42-7; ethane trimer (R = H), 96363-54-1; ethane tetramer (R = Me), 96363-43-8; ethane tetramer (R = H), 96394-13-7; ethane pentamer (R = Me), 96363-48-3; ethane hexamer (R = Me), 96363-49-4; ethane trimer (Fe³⁺ complex), 96363-41-6; butane dimer (R = Me), 96363-44-9; butane dimer (R = H), 96363-55-2; butane trimer (R = Me), 96363-45-0; butane trimer (R = H), 96363-56-3; butane trimer (Fe³⁺ complex), 96363-39-2; butane tetramer (R = Me), 96394-12-6; butane tetramer (R = H), 96363-57-4; butane pentamer (R = Me), 96363-50-7; hexane monomer (R = Me), 96363-51-8; hexane dimer (R = Me), 96363-46-1; hexane dimer (R = H), 96363-58-5; hexane trimer (R = Me), 96363-47-2; hexane trimer (R = H), 96363-59-6; hexane trimer (Fe³⁺ complex), 96363-40-5; hexane tetramer (R = Me), 96363-52-9; hexane pentamer (R = Me), 96363-53-0; iron(III), 20074-52-6.

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(20) ^1H NMR (200 MHz, $\text{Me}_2\text{SO}-d_6$) δ 3.50 (br m, 12 H), 7.19 (s, 6 H), 8.83 (m, 6 H), 12.62 (br s, 6 H); ^{13}C NMR (50.8 MHz, $\text{Me}_2\text{SO}-d_6$) δ 37.83, 115.52, 117.25, 150.08, 169.15. Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_6\text{O}_{12}\cdot\text{H}_2\text{O}$ (C, H, N).

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