species in methanol.[18] On the other hand, **6a–c** are diamagnetic d^6 Co(III) complexes both in methanol and in CH_2Cl_2. The reactivity of (OEP)Co^{III} toward DMADC increases with decreasing electron donation from the axial ligand (Me > I > Br > Cl > H_2O), and consequently with increasing charge transfer interaction of the porphyrin ligand with Co(III). However, **1** is no longer a d^6 Co(III) complex in noncoordinating solvents, and thus the direction of attack of DMADC is changed. As a Co(III) complex of dibenzo[*b*,*i*]-5,7,12,14-tetramethyl-1,4,8,11-tetraaza[14]annulene reportedly[19] reacts analogously to **6**, the present reaction is remarkable since the metalloporphyrin is completely planar and rigid and biologically significant in relation to heme catabolism.[20] That is, a *C*^{5},*Fe*-peroxo-bridged iron 5*H*,21*H*-porphyrin structurally similar to **7** may be formed from Fe(II) porphyrin with dioxygen and converted into oxophlorins and eventually into biliverdins in vivo.

In summary, the reaction behaviors of Co(III) porphyrins are strongly dependent on the nature of their axial ligands to give novel organocobalt(III) porphyrins of biological interest.

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Biomimetic Ferric Ion Carriers. A Chiral Analogue of Enterobactin

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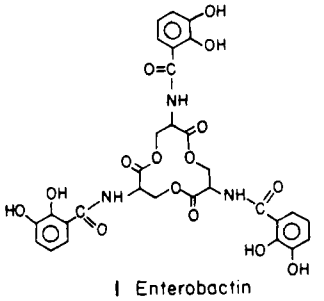
The potency of enterobactin **1**, the most powerful natural siderophore (ferric ion carrier),[1-3] has stimulated the synthesis of a large number of analogues,[2] with the triscatecholate **2** (MECAM) prepared and analyzed by Harris and Raymond[4] being the most efficient one. It has recently been shown that only the native enterobactin, but not its enantiomer, is taken up by *Escherichia coli*[5] and that the native molecule assumes a right-handed propellerlike conformation which is governed by its chirality and intramolecular hydrogen bonds (H bonds).[6] Similar arrangements stabilized by interchain H bonds have recently been obtained in C_3 symmetric molecules where three L-amino acids are attached to a mesitylene as common anchor.[7] Here we demonstrate that an extension of such amino acid derivatives by catecholates provides a binder **3b** and its protected precursor **3a** that mimic enterobactin: **3a** adopts a chiral structure circularly organized by interchain H bonds, and **3b** forms metal complexes of similar geometry and identical configuration, Δ-cis. Although still below enterobactin, the binding efficiency of **3b** is comparable and perhaps even better than that of Raymond's artificial binder **2**, the best so far prepared.[4]

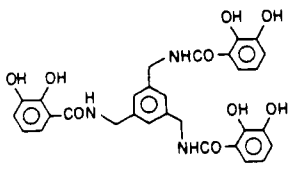
Table I. ^{1}H NMR Chemical Shift (δ) Values[a] of Ligands **1**, **3b**, and **2**[e]

proton	**1**[b]	**3b**	**2**
N*H*	9.06 (+2.66)	8.79 (+1.16)[c] 8.57 (+0.13)[d]	9.39 (+0.76)
o-catechol	7.34 (–0.50)	7.42 (–0.42)	7.29 (–0.28)
m-catechol	6.73 (–0.60)	6.67 (–0.33)	6.65 (–0.27)
p-catechol	6.98 (–0.54)	6.91 (–0.34)	6.91 (–0.32)

[a] In DMSO-d_6. Concentrations: **1**, ca. 0.045 M; **3b** and **2**, 0.033 M. Temperature: **1**, ca. 318 K; **3b** and **2** 298–300 K. δ values are expressed as ppm downfield from internal TMS. [b] Data taken from ref 12. [c] C*α*–N*H*. [d] CH_2NH. [e] Their induced changes (Δδ) upon Ga^{3+} binding are in parentheses.



1 Enterobactin



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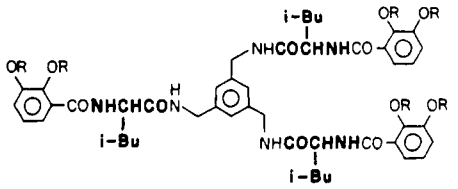
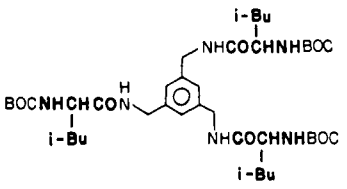


3a R = CH_2Ph
3b R = H



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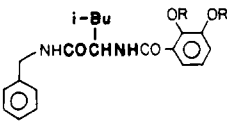

5 R = CH_2Ph

3b was prepared from 1,3,5-tris(*N*-Boc-leucylamido)benzene (**4**)[7] via deprotection, condensation with 2,3-bis(benzyloxy)benzoyl chloride,[8] and subsequent hydrogenolytic removal of the protecting groups. The IR spectrum of **3a** in dilute $CHCl_3$ (0.5 mM) showed only low-frequency NH absorptions at 3354 cm^{-1}. The NMR spectrum ($CDCl_3$, 5 mM) revealed nonequivalence of the diastereotopic $C_6H_3(CH_2NH\text{-})_3$ protons (Δδ = 0.56 ppm). The single chain reference molecule **5** shows higher NH frequencies (3437, 3361 cm^{-1}) and magnetic equivalence for the diastereotopic $PhCH_2NH$ protons. In DMSO-d_6 the NMR pattern of **3a** becomes similar to that of **5**.

[†] Department of Organic Chemistry.
[‡] Department of Chemical Physics.
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These observations demonstrate the occurrence of intramolecular H bonds between the chains in **3a** that restrict the conformational freedom of the molecule.[9] **3a** thereby simulates enterobactin in adopting a chiral, circularly organized conformation that is stabilized by intramolecular H bonds.[6,10]

Addition of $Ga_2(SO_4)_3$ to a DMSO-d_6 solution of **3b** resulted in the appearance of a second set of signals, due to its Ga^{3+} complex.[11] This set is characterized by a pronounced low field shift of the Cα-N*H* proton and high field shifts of the catecholate aromatic protons, relative to that of free **3b** (Table I). The low-temperature coefficient for the Cα-N*H* in **3b**-Ga^{3+} (ca. -0.0003 ppm/K) is compatible with H bonding to the catecholate, as earlier suggested on the same grounds for the Ga^{3+} enterobactin complex.[12] Such H bonds were also recently demonstrated by X-ray crystal analysis in artificial Fe^{3+} catecholates.[13] The electrostatically induced differences in chemical shifts observed in chiral **3b** are smaller than those reported for enterobactin[12] but still larger than those we found for the achiral analogue **2**. Since all three complexes contain the same metal ion and make use of identical binding sites, the electrostatically induced differences are determined mainly by their geometries.[14] If we assume that the induced differences are increasing with the strength of binding, then **3b** as a binder may be ranked somewhere between enterobactin and **2**.

CD measurements of the **3b**-Fe^{3+} complex showed Cotton effects close to those of the enterobactin-Fe^{3+} complex,[15] in respect to the location of the extremes, their absolute signs, and magnitudes ($\Delta\epsilon$ = -2.3 at 556 nm and +4.4 at 438 nm for **3b**-Fe^{3+} in 20% methanol-TRIS buffer pH 8.5 and $\Delta\epsilon$ = -4.0 at 535 nm and +4.0 at 420 nm for **1**-Fe^{3+} in 50% ethanol[15]). This demonstrates that the predominant configuration of the **3b**-Fe^{3+} complex is identical with that of the Fe^{3+}-enterobactin complex, namely Δ-cis.[2]

Competition between chiral **3b** and achiral **2** for binding Fe^{3+} was monitored by the Cotton effect of the Fe^{3+}-catecholate chromophore in **3b**. $Fe(ClO_4)_3$ (1 equiv) was added to a 20% methanol-TRIS buffer (pH 8.5) solution of **3b** and **2**, 1 equiv each. Approximately 80% of the circular dichroism of the full **3b**-Fe^{3+} was retained,[16] indicating that **3b** competes favorably with **2**. Although this advantage is small, it does not seem fortuitous as it is compatible with the NMR results on the related Ga^{3+} complexes (Table I).

The small advantage of chiral **3b** over **2** may imply that the **3b** complex is less strained than the **2** complex or that less conformational entropy is lost in **3b** upon binding. Both these factors have been estimated to contribute to the superiority of enterobactin relative to **2**.[6] If and to which extent the similarities between this analogue and genuine enterobactin are reflected in its chiral recognition by the outer membrane receptor[17] has still to be established.

Acknowledgment. We thank the US-Israel Binational Science Foundation for support.

(9) Such interchain H bonds may point either clockwise or counterclockwise, which would result in two diastereomeric conformations, since the chains are chiral. The observation of a single set of signals in the NMR spectra suggests predominance of one of the two possible arrangements. A similar situation was observed in **4** (ref 7).

(10) **3a** rather than **3b** was selected for detailed structural analysis because of the insolubility of the latter in apolar solvents.

(11) The complex with Ga^{3+} was selected for these experiments since it is amenable to NMR analysis and structurally very close to that of Fe^{3+}. See: Borgias, B. A.; Barclay, S. J.; Raymond, K. N. *J. Coord. Chem.* **1986**, *15*, 109-123.

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Biomimetic Ferric Ion Carriers. Chiral Ferrichrome Analogues

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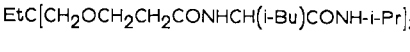
Among the natural siderophores (Fe^{3+} carriers), the hydroxamate-based binders are the most abundant,[1-4] and much effort has been devoted to the synthesis of artificial analogues.[5] The microbial ferrichrome Fe^{3+} carriers resemble the enterobactin siderophore by being macrocyclic molecules composed of L-amino acids and three ligating side chains.[3,4] They, however, differ from the latter by lacking its C_3 symmetry, by using hydroxamates instead of catecholates as binding sites, and by forming Fe^{3+} complexes of opposite configuration, Λ-cis. In the preceding communication[6] we showed that the conformation and ion-binding configuration of enterobactin may be mimicked by simple tripodlike molecules whose chains are interlinked through "circular" H bonds. In this communication we demonstrate that the same principle of design provides artificial hydroxamate carriers that adopt a propellerlike conformation and simulate the ferrichromes in respect to their ion-binding configuration (Λ-cis) and in their capability to act as growth promoters of ferrichrome dependent bacteria. These carriers are tripod structures composed of natural L-amino acids that are attached to a tricarboxylate anchor via their N terminals and flanked by ion-binding sites at their C terminals.

The tripods **1-4** were synthesized by condensation of the trisphenolate $EtC(CH_2OCH_2CH_2COOC_6Cl_5)_3$[7] with the respective amino acid derivatives. Tripods **1** and **2** were used as structural



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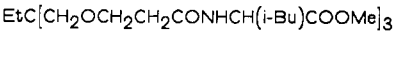

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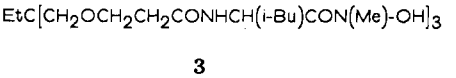

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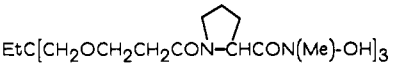

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models for establishing the conformational properties of this family of compounds. IR of **1** in $CHCl_3$ solution (0.6 mM) revealed mainly bonded NH (3303 cm^{-1}), with only a trace of free NH (3429 cm^{-1}). NMR showed two distinct signals for each of the diastereotopic $-CH_2-O$ and $-CH_2CO-$ protons in $CDCl_3$ (Figure 1b) but single peaks in CD_3OD. The single chain molecule **5**

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(4) Hider, R. C. *Structure and Bonding* **1984**, *58*, 25-87.

(5) For recent examples of artificial hexadentate hydroxamates, see: (a) Emery, T.; Emery, L.; Olsen, R. *Biochem. Biophys. Res. Commun.* **1984**, *199*, 1191-1197. (b) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem.* **1985**, *28*, 317-323, 323-327. (c) Shimizu, K.; Nakayama, K.; Akiyama, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2421-2424.

(6) Tor, Y.; Libman, J.; Shanzer, A.; Lifson, S. *J. Am. Chem. Soc.*, preceding paper in this issue.

(7) The trisphenolate was prepared by cyanoethylation of 1,1,1-tris(hydroxymethyl)propane, subsequent acid-catalyzed hydrolysis, and condensation with pentachlorophenol. A full account of the synthesis of these compounds and their spectral properties will be given in a full paper.

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