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.

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Biomimetic Ferric Ion Carriers. Chiral Ferrichrome Analogues

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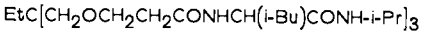
Among the natural siderophores (Fe^{3+} carriers), the hydroxamate-based binders are the most abundant,[1-4] and much effort has been devoted to the synthesis of artificial analogues.[5] The microbial ferrichrome Fe^{3+} carriers resemble the enterobactin siderophore by being macrocyclic molecules composed 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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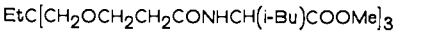

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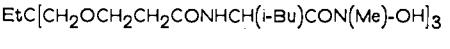

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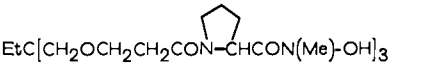

4

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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(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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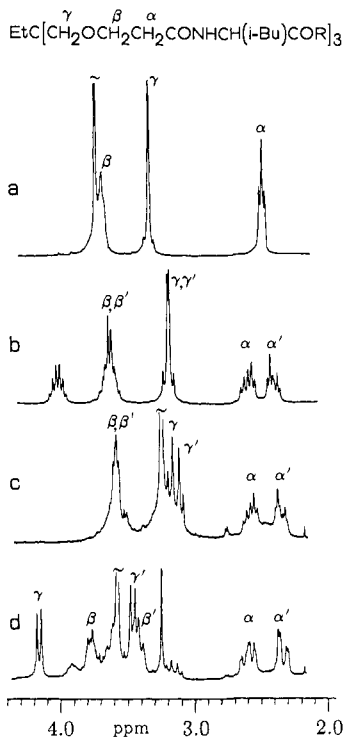

Figure 1. 270 MHz ^{1}H NMR traces of compound **2** (R = OMe, trace a), **1** (R = NH-*i*-Pr, trace b), **3** (R = N(Me)OH, trace c), and **3**–Ga^{3+} (trace d) in $CDCl_3$ solution (10 mM), 298 K. Residual signals of **3** in trace d (ca. 20%) indicate slow exchange under these conditions.

[*n*-$BuOCH_2CH_2CONHCH(i\text{-}Bu)CONH\text{-}i\text{-}Pr$] showed almost identical chemical shifts for its diastereotopic protons and little solvent dependence ($CDCl_3$ versus CD_3OD). All this indicated restricted conformational freedom due to interchain H bonds in **1**. A priori, H bonds may involve equivalent or nonequivalent amides of adjacent chains. In order to distinguish between these two possibilities compound **2** with only one type of amide group was examined. The IR spectrum of ester **2** showed two NH absorptions (3435 and 3371 cm^{-1}, 0.65 mM $CHCl_3$) and its NMR spectrum (Figure 1a) single signals for the diastereotopic protons $-CH_2-O$ and $-CH_2-CO$ in $CDCl_3$, indicating weak H bonds that do not impair the molecule's conformational freedom. The H bonds in amide **1** thus involve nonequivalent amides. This ultimately causes a tilt of the side chain to generate a propellerlike arrangement.[8]

Replacement of the isopropylamine in **1** by methyl hydroxylamine provided the Fe^{3+} binder **3**. **3** adopted a H bonded propellerlike conformation like the parent molecule **1** according to its bonded NH (3284 cm^{-1} in $CDCl_3$) in the IR spectrum and the nonequivalence of its diastereotopic protons in the NMR (Figure 1c). Titration showed a 1:1 stoichiometry for Fe^{3+} binding, and CD ($\Delta\epsilon$ = +3.4 at 450 nm and −6.8 at 365 nm in MeOH) established predominance of the Λ-cis isomer[3] (see Figure 2). This coordination isomer proved to be stabilized by H bonding (NH absorption at 3353 cm^{-1} in $CDCl_3$). The Fe^{3+} complex of the proline binder **4** which is incapable of forming such H bonds showed significantly smaller Cotton effects ($\Delta\epsilon$ = +1.27 at 465 nm and −4.3 at 378 nm in MeOH).

NMR analysis of the Ga^{3+} complex of **3** (which is structurally close to the Fe^{3+} complex[9] but amenable to NMR measurement) showed a single set of signals with a pattern close to that of the free ligand (Figure 1d). This establishes the isomeric purity of the complex and its structural similarity to the uncomplexed molecule. In contrast, the Ga^{3+} complex of the proline binder **4** showed a complex NMR pattern, indicative of isomeric mixtures.

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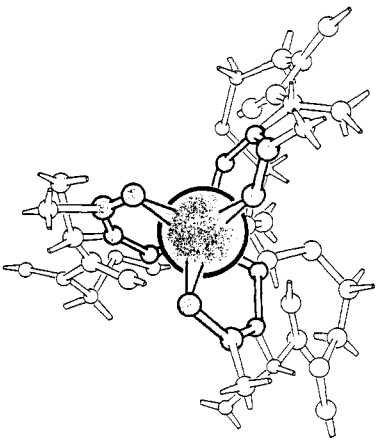

Figure 2. Schematic representation of the Λ-cis Fe^{3+} complex of **3**.

These biomimetic tripodlike binders functioned as growth promoters of *Arthrobacter flavescens*.[10] This mutant still contains ferrichrome receptors but lacks the capability to produce ferrichrome. Therefore, its growth depends on externally added siderophores. Although the activity observed for some of these compounds described above was only around 1% of that of ferrichrome, this result is significant and suggestive of specific recognition. No synthetic compound tested so far on this very system, except for synthetic retrohydroxamate ferrichrome, has shown any activity. If and to which extent the chemistry of the natural ferrichromes is governed by some preorientation of conformation that favors certain pathways of complexation, as in the artificial carriers, remains a topic of future research.

Acknowledgment. We thank Prof. S. Lifson for stimulating discussions, R. Lazar for skillful technical assistance, and the US–Israel Binational Science Foundation and the National Council for Research and Development for support.

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The First [4 + 3] Cycloaddition of a 1,3-Dipole with a 1,3-Diene

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1,3-Dipolar cycloaddition reactions are usually considered to proceed via concerted [$_\pi4_s + _\pi2_s$] mechanisms[1] though arguments for the stepwise nature have been presented.[2] The nonstereospecific cycloaddition of an electron rich thiocarbonyl ylide with dimethyl dicyanofumarate, an electron deficient dipolarophile, has just been reported as the first unequivocal example of a nonconcerted 1,3-dipolar cycloaddition.[3]

In accordance with the orbital symmetry rules,[4] 1,3-dipoles have been found to react with 1,3-dienes to give vinyl-substituted five-membered rings exclusively.[5] Corresponding [4 + 3] cycloadditions have only been observed in the ozonation of anthracenes[6] and in one case as an intramolecular variant.[7]

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