relationships, and as demonstrated above, none except CE can claim an intimate association as a basic coordinate of the table.

Historically, the need for configuration energy has been partially met by the concept of electronegativity, originally defined by Pauling 10 years after Bohr's contribution.[8] This concept has been the subject of much debate over many years, but a survey of textbooks and the research literature since 1932 shows that only two scales, those of Pauling[8,9] and of Allred and Rochow,[10] have been extensively used by experimental scientists. We have previously shown that eq 1 closely matches these two,[3] thus assuring that the information content of electronegativity is subsumed in CE. Since CE is a simpler, more general[4] quantity and since it is an inherent part of the periodic table rather than an ad hoc independent property, it is no longer necessary to retain electronegativity per se.[11]

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Supplementary Material Available: A tabulation of configuration energies for 57 atoms and a plot of CE versus group number (2 pages). Ordering information is given on any current masthead page.

(8) Pauling, L. *J. Am. Chem. Soc.* **1932**, *54*, 3570.
(9) Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215. Update of Pauling's scale.
(10) Allred, A. L.; Rochow, E. G. *J. Inorg. Nucl. Chem.* **1958**, *5*, 264.
(11) This communication has been concerned with the CE of free atoms and the periodic table; however, it is possible to carry the CE concept in situ to molecules and solids by defining a quantum mechanical operator, the energy index, EI_A: Allen, L. C.; Egolf, D. A.; Knight, E. T.; Liang, C. *J. Phys. Chem.* **1990**, *94*, 5602. An application to group electronegativity is given in Reed, L. H.; Allen, L. C. *J. Phys. Chem.* **1992**, *96*, 157.

A Receptor for the Enantioselective Recognition of Phenylalanine and Tryptophan under Neutral Conditions

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Molecular recognition of relevant biological targets constitutes a dynamic branch of organic chemistry. Recent work with model systems has led to a number of receptors for amino acids,[2,3] nucleic acid heterocyclic bases,[4] nucleotides,[5] and carbohydrates.[6]

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(2) (a) Peacock, S. C.; Walba, D. M.; Gaeta, F. C. A.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2043, and references therein. (b) Rebek, J., Jr.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738. (c) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432. (d) Pirkle, W. H.; Pochawski, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 5975. (e) Aoyama, Y.; Yamagishi, A.; Asagawa, M.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 4076. (f) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184.
(3) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994.
(4) (a) Hamilton, A. D.; van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035. (b) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (c) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245, and references therein. (d) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201. (e) Medina, J. C.; Li, C.; Bott, S. G.; Atwood, J. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 366.

Scheme I

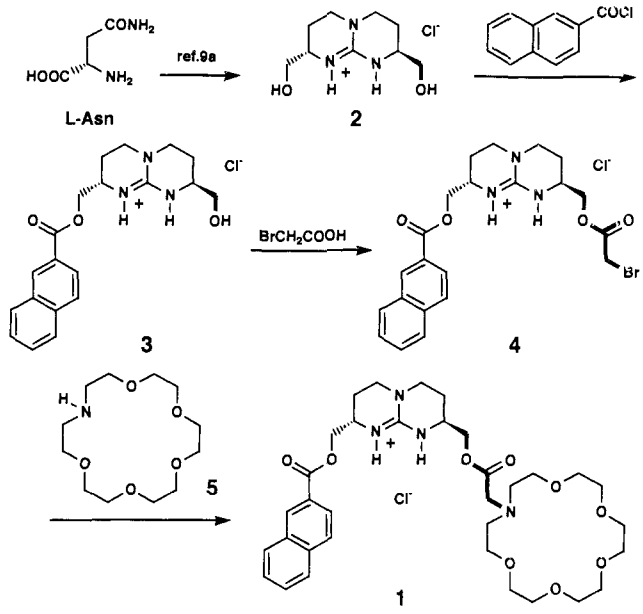

Table I. Single Extraction of a Mixture of 13 Amino Acids by Receptor **1**[a]

	total amount, μmol	ratio		total amount, μmol	ratio
Phe	2.61	100	Ala	0.09	3
Trp	1.20	46	Arg	0.05	2
Leu	0.73	28	Asp	0.05	2
Tyr	0.45	17	Pro	0.05	2
Ile	0.28	11	His	0.04	1
Gly	0.13	5	Asn	ND[b]	
Val	0.11	4			

[a] For explanation, see text and refs 14 and 15. [b] ND, not determined.

In neutral aqueous solutions, amino acids exist largely as strongly solvated zwitterionic structures. The electronic densities at the carboxylate and ammonium functions are greatly affected by their mutual vicinity, causing the binding forces of complementary groups of the receptor to be less effective for the complexation. Thus, the design of a model receptor for amino acids in zwitterionic form is still a challenging problem, and most work so far has been performed with single-charged substrates, under acidic (amino acid or amino ester salts)[2a] or basic (carboxylate salts)[7] conditions.[8] We describe herein the preparation and properties of compound **1**, a receptor for amino acids featuring the following: (i) non-self-complementary binding sites for carboxylate (a guanidinium function) and ammonium (a crown ether), preventing the receptor from internal collapse; (ii) an aromatic planar surface (the naphthalene ring) for an additional selective stacking interaction with the side chain of aromatic amino acids; (iii) a chiral structure (*S,S*-isomer shown) for enantioselective recognition.

The synthesis of **1** was achieved in three steps (Scheme I) from the chiral bicyclic guanidine salt **2**, readily available in optically pure form from L-asparagine.[9] Condensation with 2-naphthoyl

(5) (a) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493. (b) Hosseini, M. W.; Blacker, A. J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 3896. (c) Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978. (d) Galán, A.; Pueyo, E.; Salmerón, A.; de Mendoza, J. *Tetrahedron Lett.* **1991**, *32*, 1827.
(6) (a) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349. (b) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407.
(7) Behr, J.-P.; Lehn, J.-M. *J. Am. Chem. Soc.* **1973**, *95*, 6108.
(8) For earlier examples of nonchiral recognition of zwitterionic amino acids under neutral conditions, see refs 2b, c, and e.
(9) (a) Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 685. (b) Kurzmeier, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, *55*, 3749.

0002-7863/92/1514-1511$03.00/0

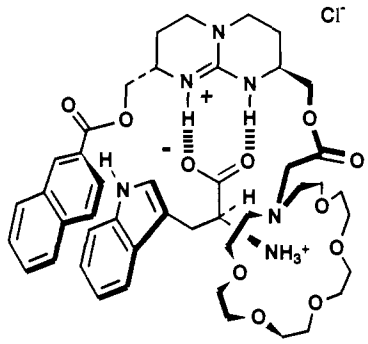

Figure 1. Proposed structure for a 1:1 complex between (*S,S*)-**1** and L-tryptophan.

chloride (1.7 equiv, DMF, Et_3N) afforded the monosubstituted naphthoyl ester **3**[10] in 50% yield. Reaction of **3** with bromoacetic acid (1,3-dicyclohexylcarbodiimide, CH_2Cl_2) gave **4** (82%), which upon reaction with monoazacrown ether **5**[11] (CH_2Cl_2, reflux, 4 days) afforded **1** in 87% yield.[12]

Despite its ionic structure, receptor **1** is scarcely soluble in water, but almost freely soluble in common organic solvents. The affinity of **1** toward amino acids was therefore determined by liquid–liquid single-extraction experiments, in which 0.5 mL of an aqueous solution of L-Trp, L-Phe, or L-Val (0.2 M) was extracted into 2 mL of a CH_2Cl_2 solution of **1** (5.5×10^{-3} M). The extraction efficiencies (i.e., fraction of receptor molecules occupied by substrate) in the organic phase, determined by NMR integration, were ca. 40% for L-Trp and L-Phe, but L-Val, without any aromatic side chain, was not detected.[13] A competition experiment with a mixture of all three amino acids (0.2 M each) resulted in 100:97:6 Phe/Trp/Val ratios.[14] The results of the extraction of a 2-mL aqueous solution of a more complex mixture of 13 amino acids (4.9×10^{-2} M each) by a 3-mL CH_2Cl_2 solution of receptor **1** (9.7×10^{-3} M) are shown in Table I.[15] In this case, selectivity for phenylalanine was enhanced, and some lipophilic substrates, like leucine, were also extracted to a significant extent.

Chiral recognition was confirmed by the observation (NMR) that the corresponding D-enantiomers were not extracted. Reciprocally, use of (*R,R*)-**1** allowed the extraction of D-Phe or D-Trp, but not of the L-enantiomers. A more precise account of the selectivity was achieved by HPLC analysis of diastereomeric dipeptides prepared from extracts of racemic samples of Phe or Trp and a suitable optically pure L-Leu derivative.[16] The amount of D-isomer in the extracts was lower than 0.5% for D-Trp (determined as L-Leu-D-Trp) and 2% or less for D-Phe (as L-Leu-D-Phe). This high degree of chiral recognition can be explained by the three simultaneous[2c] noncovalent interactions of the substrate with the flexible and foldable receptor. ^{1}H-NMR data (upfield shifts for the naphthoyl protons) support the binding model illustrated in Figure 1 for a 1:1 complex of (*S,S*)-**1** with L-Trp. No similar model can be assembled (CPK) for the D-enantiomer.[17]

Full NMR studies of the complexes, and development of related amino acid receptors with enhanced side-chain recognition features, are currently underway.

Supplementary Material Available: NMR data for new compounds and details for the amino acid analyses (3 pages). Ordering information is given on any current masthead page.

(10) Some dinaphthoyl ester was also obtained, but both compounds were easily separated and purified by column chromatography.[3]

(11) Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6659. (b) Gokel, G. W.; Garcia, B. J. *Tetrahedron Lett.* **1977**, 317.

(12) All new compounds were characterized by a full complement of high-resolution spectra.

(13) No Phe and Trp extraction was observed when the dinaphthoyl guanidinium derivative was employed as receptor.

(14) For the analysis of amino acid mixtures the organic layer was washed twice with water and the aqueous solution evaporated. The resulting amino acid extract was dissolved in 1 mL of buffer (Beckman Na-S) and determined in a Beckman 6300 analyzer (ion-exchange column, postcolumn ninhydrin reaction).

(15) For the 13-amino acid mixture, a 50-μL aliquot was first injected to determine residues present at low concentrations. The sample was next diluted 1:10 for more accurate analysis of residues at higher concentration (Leu, Phe, Trp).

(16) Mitchell, A. R.; Kent, S. B. H.; Chu, I. C.; Merrifield, R. B. *Anal. Chem.* **1978**, *50*, 637.

(17) With the data available, the more hindered 2:1 complexes could not be ruled out, however.

Structural and Spectroscopic Characterization of Chiral Ferric Tris-Catecholamides: Unraveling the Design of Enterobactin

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Enterobactin, a siderophore of *Escherichia coli*, is remarkable not only in forming the most stable known complex of iron[1] but also in preferentially forming a specific tris-chelate isomer with labile metal ions.[2] Efficient iron accumulation, including recognition at the cell receptor,[3] depends on these features. Furthermore, the Δ conformation assigned to [Fe(enterobactin)]$^{3-}$ ($\mathbf{Ent}_{Fe}$)[4] is unusual among siderophores.[5,6] The source of stereospecific chelation has been ascribed to nonbonded interactions rather than steric strain within the chiral backbone.[7] Similar interactions between peripheral appendages in tris-bidentate metal chelates have been identified as important energetic contributors to the diastereomeric distributions[8,9] and the thermodynamic stability[10] of kinetically labile metal complexes. The role of these weakly polar interactions,[11] especially between aromatic groups packed in a herringbone fashion, has only recently been appreciated in stabilizing protein structures and metal complexes.[12] Moreover, ligands incorporating aromatic rings which stereospecifically ligate labile metals have potential application in asymmetric induction in organic transformations.[13] A group of ferric and gallium complexes have been synthesized and structurally characterized that provide insights into enterobactin's

(1) Loomis, L. D.; Raymond, K. N. *Inorg. Chem.* **1991**, *30*, 906 and references therein.

(2) Isied, S. S.; Kuo, G.; Raymond, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 1763.

(3) Lodge, J. S.; Emery, T. *J. Bacteriol.* **1984**, *160*, 801.

(4) Labeling scheme: The bold names or numbers refer to the ligand(s) of a complex with the subscript indicating the appropriate metal.

(5) The metal chirality of $\mathbf{Ent}_{Fe}$ has been assigned as Δ through spectroscopic comparisons of kinetically inert metal complexes (ref 2). We have very recently structurally characterized the first metal complex of enterobactin, [V(enterobactin)]$^{2-}$, which has the expected Δ chirality: Karpishin, T. B.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.*, in press.

(6) Matzanke, B. F.; Müller-Matzanke, G.; Raymond, K. N. *Iron Carriers and Iron Proteins*; Loehr, T. M., Ed.; VCH Publishers: New York, 1989; p 1.

(7) Lennard Jones and electrostatic interactions: Shanzer, A.; Libman, J.; Lifson, S.; Felder, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 7609.

(8) The diastereomeric relationship of the Δ and Λ isomers results from the chirality of the ligands.

(9) Okawa, H. *Coord. Chem. Rev.* **1988**, *92*, 1.

(10) Garrett, T. M.; Miller, P. W.; Raymond, K. N. *Inorg. Chem.* **1989**, *28*, 128.

(11) (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *23*, 229. (b) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995. (c) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem.* **1988**, *39*, 125.

(12) Sigel, H.; Tribolet, R.; Yamauchi, O. *Comments Inorg. Chem.* **1990**, *9*, 305.

(13) (a) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296 and references therein. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.

0002-7863/92/1514-1512$03.00/0