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Participation of host 'spacer' atoms in carboxylic acid binding: implications for amino acid recognition

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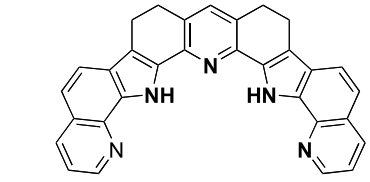
Abstract—Chiral 4,4′-diamido-2,2′-biimidazoles were synthesized and found to bind *N*-Boc protected amino acids in $CDCl_3$. The biimidazole that features (*R*)-tetrahydrofurfuryl units discriminates between *N*-Boc-L-Ser ($K_{assoc} = 120\ M^{-1}$) and its non-natural D-enantiomer ($270\ M^{-1}$). X-ray diffraction and computational analyses show that members of this receptor class adopt a cleft-like conformation, presenting a donor-spacer-donor-acceptor H-bonding array. Complexes of such biimidazoles with the –COOH unit of amino acids are stabilized by direct involvement of what is nominally a 'spacer' atom, unlike other D-Sp-D-A hosts.

1. Introduction

Biological recognition of amino acids is accomplished by macromolecules with binding sites that are complementary to their designated substrates. Each of the aminoacyl-*t*RNA synthetases, for example, presents a unique array of functional groups and hydrophobic surfaces to detect differences in the structures of amino acid side chains.[1] Selectivity arises from a combination of noncovalent interactions like hydrogen bonding and van der Waals contacts. Individually, such interactions are generally weak; cumulatively, several such interactions can be relatively strong. Complexes of synthetic hosts and amino acid guests[2] can therefore be quite robust if stabilized by multiple H-bonds, particularly in nonpolar solvents.[3–5]

In the design of artificial receptors for carboxylic acids, the donor-spacer-donor-acceptor arrays present in **1**[6] and **2**[7] offer several advantages. Binding occurs according to mode *A*, which places the most acidic proton of the guest close to the H-bond **A**cceptor, while the lone pair electrons of the carbonyl O are 'saturated' with hydrogen bonds from the **D**-H units.[8] Nitrogen or oxygen spacer atoms (**Sp**) help maintain receptor rigidity via intramolecular D-H···Sp interactions, but are not expected to directly bind to a carboxylic acid guest. As part of a program to evaluate the supramolecular chemistry of biheterocycles,[9] the present paper examines the factors that drive recognition between the –COOH unit of amino acids and D-Sp-D-A receptors. Comparing a new set of 2,2′-biimidazoles to other cleft-shaped hosts, we find that the spacer group can play an active role in the recognition process. This result calls into question the assumption that mode *A* is always operative, and may have practical consequences for the design of enantioselective sensors and chiral stationary phases.[10]



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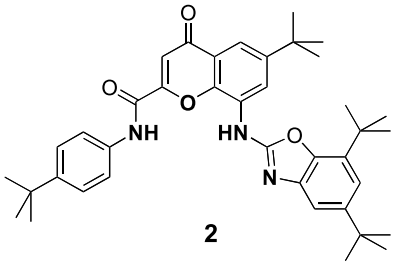

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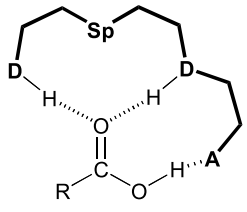

mode *A*

Keywords: Biimidazole; Amino acid recognition; Hydrogen bonding; DFT.
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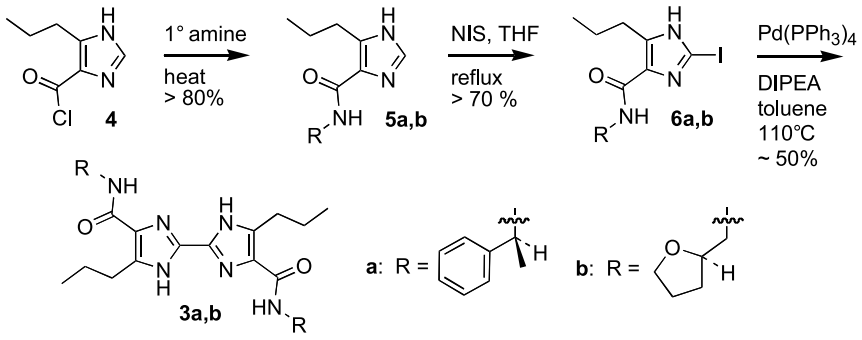

Scheme 1.

2. Results and discussion

Biimidazoles **3** were prepared by adapting previously described procedures,[9b] as shown in Scheme 1. Molecular diversity was provided by treating acid chloride **4** separately with (*S*)-α-methylbenzylamine and (*R*)-tetrahydrofurfurylamine; these arms were chosen for their potential to participate in π interactions[11] or H-bonds with aromatic or polar amino acids, respectively. Products **3a** and **3b** were judged to be enantiomerically pure by chiral HPLC (CH_3CN–H_2O gradient, monitoring 295 nm) and by ^1H NMR ($CDCl_3$, 500 MHz).

A solid-state structure was obtained for an achiral diastereomer of **3a** (Fig. 1).[12] As observed in other biimidazole diamides,[9b] *meso*-**3a** adopts an anti conformation in which the imidazole rings are nearly coplanar. Assuming that a planar orientation is retained in solution, two essentially identical chiral clefts (with N*H*···*H*N ≈ 4.2 Å) are available to bind carboxylic acid guests.

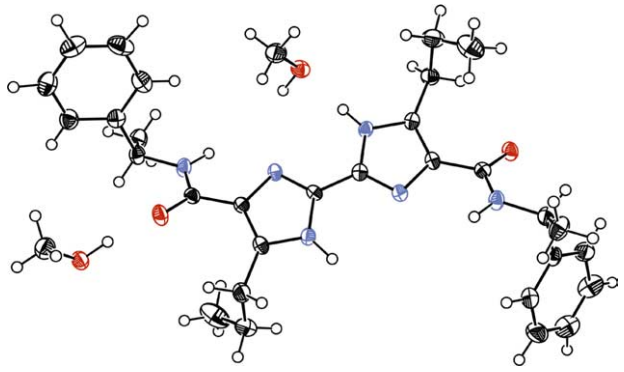

Figure 1. Structure of *meso*-**3a**·$(CH_3OH)_2$ in the crystal.

Computational modeling[13,14] of several biimidazole conformations and tautomers reveals that the anti structure observed in the crystal minimizes steric congestion while maximizing intramolecular N–H···N hydrogen bonding. Both the amide N*H* groups and the imidazole N and N*H* are involved in this stabilizing intramolecular interaction. The syn conformer, in its various tautomeric forms, disrupts the network of intramolecular hydrogen bonding and replaces these stabilizing interactions with steric clashes between adjacent N*H* atoms, increasing the energy anywhere from 5.6 to 21.3 kcal/mol (see the Supplementary data).

Table 1 shows the association constants, derived from ^1H NMR titrations in $CDCl_3$,[15] for **3a** and **3b** with both enantiomers of two different *N*-Boc amino acids. Downfield chemical shifts in the amide N*H* protons of the receptors occurred with increasing amino acid concentration, consistent with H-bond donation to the guests. Control experiments using an esterified amino acid (*N*-Boc-L-Phe-OMe) established that guest binding takes place largely at the –COOH group; although *N*-Boc-L-Phe is bound relatively strongly by **3a** ($K_{assoc} = 100\ M^{-1}$), *N*-Boc-L-Phe-OMe induced negligible shifts in the ^1H resonances of the same receptor ($K_{assoc} \approx 0\ M^{-1}$).

Table 1. Binding constants K_{assoc} (M^{-1})[a] for chiral biimidazoles with amino acid derivatives in $CDCl_3$ at 23 °C

Complex	K_{assoc}
3a·*N*-Boc-L-Phe, -D-Phe	100, 65
3a·*N*-Boc-L-Ser, -D-Ser	<60, 65
3b·*N*-Boc-L-Phe, -D-Phe	65, 65
3b·*N*-Boc-L-Ser, -D-Ser	120, 270

[a] Values represent averages of at least two replicate titrations, rounded to the nearest ±5 M^{-1}. Errors in individual fits were ≤15%.

Participation of the imidazole NH groups in guest binding could not be established from the experiments described above, because the heterocycle N*H* signals disappeared upon addition of the amino acids in Table 1. However, complexes of 'half biimidazoles' **5a** and **5b** were significantly less robust than those formed from the corresponding full receptors; K_{assoc} for **5a**·*N*-Boc-L-Phe and **3a**·*N*-Boc-L-Phe in $CDCl_3$ were 15 and 100 M^{-1}, respectively, while **5b**·*N*-Boc-D-Ser and **3b**·*N*-Boc-D-Ser had values of 80 and 270 M^{-1}. That the imidazole N*H* groups make a significant contribution, two possible amino acid binding modes were examined with DFT computational methods.[13,14] Using receptor **3b** for illustration, Figure 2a shows an interaction analogous to mode *A* described above. Alternatively, the carboxylic acid proton can interact with the imidazole nitrogen (Fig. 2b), an atom which is several orders of magnitude more basic than the ethereal oxygen. To highlight the direct involvement of so-called spacer atoms in such complexes, we describe them as occurring by mode *S*.

Although all of the complexes listed in Table 1 are weak, modest enantioselectivity was observed between **3b** and the *N*-Boc-serines. This result is difficult to rationalize within the context of mode *A*, which places the stereogenic α carbon of the amino acid far from the chiral arm of the receptor. Both the relatively high K_{assoc} values and degree of

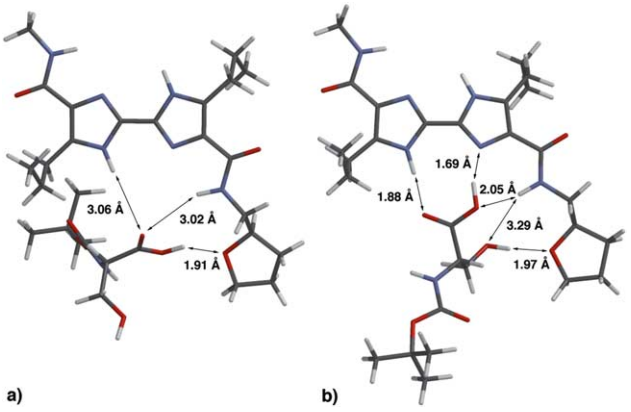

Figure 2. Model complexes of **3b**·*N*-Boc-L-Ser, optimized at the BOP/DNP level of theory. (a) Mode *A*; (b) Mode *S*. Binding energies are given in Table 2.

stereodifferentiation are better explained if complexation occurs predominantly by mode *S*,[16] which allows a tetrahydrofuranyl ring in **3b** to accept a hydrogen bond from the $-CH_2OH$ side chain. Computational studies of serine complexes predict small enhancements (-2 to -3 kcal/mol) in binding energies for **3b** relative to **3a**, consistent with weak $O–H_{Ser}\cdots O_{\mathbf{3b}}$ interactions (Table 2).

Unlike biimidazole **3b**, the groups Sp and A in molecule **1** are electronically similar (i.e., both are nitrogen atoms from substituted pyridines). As such, this host allows for more direct assessment of the geometric factors that influence guest binding, divorced from effects arising from differences in the basicities of the groups Sp and A. Gas phase calculations indicate that *N*-Boc-L/D-Phe and *N*-Boc-L/D-Ser prefer to associate with **1** via traditional mode *A*, with the intrinsic helicity of the host giving rise to small energy differences between complexes of enantiomers (Table 2). However, calculations using acetic acid as a model guest show that mode *S* can be competitive with mode *A* as the binding cleft of the host becomes less concave. Parent **1** favors mode *A* over mode *S* by -5.9 kcal/mol, largely because its 'pinched' binding pocket prevents host–guest coplanarity in mode *S* (Fig. 3a). Removal of a bridging methylene group yields the hypothetical **1**-pent, which features a greater N*H*···*H*N separation and a mode *A* bias of just -2.7 kcal/mol (Fig. 3b). This analysis was extended to determine the optimal placement of donor pyrroles and spacer/acceptor pyridine, in the absence of a receptor scaffold. In Figure 3c, the heterocycles were allowed to move independently of each other, with the single constraint that the three host nitrogen atoms and the carboxyl carbon of the acid guest remain planar. Under these conditions, mode *S* is favored by 0.7 kcal/mol. At the opposite extreme, the tiny cleft in receptor **2** (calcd N*H*···*H*N <3 Å) precludes approach of acid guests in mode *S*.

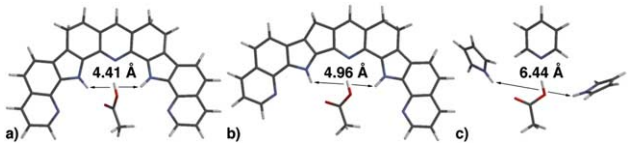

Figure 3. Comparison of acetic acid complexes derived from (a) **1**, (b) model receptor **1**-pent, and (c) their 'free floating' donor–acceptor fragments. As the D*H*···*H*D distance increases (from (a) to (c)), the O–C═O unit of the guest becomes more nearly coplanar with the D-'Sp'-D atoms.

3. Conclusions

For receptors with D-Sp-D-A topology, binding of carboxylic acids may occur at 'spacer' atoms with good accessibility/basicity. If close contact between the stereogenic centers of a chiral receptor and chiral analyte is desired (e.g., as a means to enantioselective recognition), the binding pocket of the host should be carefully engineered to control the preference for mode *A* or mode *S*.

4. Experimental

4.1. (*S*)-5-Propyl-1*H*-imidazole-4-carboxylic acid (1-phenylethyl)amide (5a)

Under N_2, a stirring mixture of freshly prepared acid chloride **4**[9b] (0.92 g, 5.3 mmol) and neat (*S*)-α-methylbenzylamine (4.2 mL, 33 mmol) was warmed with a heat gun for 15 min. Upon cooling, the green-gold syrup was dissolved in 100 mL of EtOAc, and the precipitated hydrochloride salt was filtered off. The filtrate was evaporated and purified by flash column chromatography on silica gel using EtOAc as the eluent to afford 1.25 g (92%) of the product as a viscous brown oil. TLC (EtOAc): $R_f=0.32$; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7.2$ Hz, 3H), 1.57 (d, $J=6.9$ Hz, 3H), 1.64 (m, 2H), 3.01 (m, 2H), 5.25 (m, $J=7.2$ Hz, 1H), 7.20–7.38 (m, 6H), 7.45 (d, $J=7.2$ Hz, 1H), 10.21 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.6, 26.9, 48.4, 126.0, 127.2, 128.6, 129.7, 132.5, 136.2, 143.8, 163.1; Anal. Calcd for $C_{15}H_{19}N_3O\cdot0.5(H_2O)$: C 67.64, H 7.57, N 15.78. Found: C 67.99, H 7.51, N 15.46.

4.2. (*R*)-5-Propyl-1*H*-imidazole-4-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide (5b)

Under N_2, a biphasic stirring mixture of acid chloride **4**[9b] (1.55 g, 9.8 mmol), (*R*)-tetrahydrofurfurylamine (1.00 g,

Table 2. Calculated binding energies (kcal/mol) for complexes of amino acid derivatives

Complex	Mode *A*	Mode *S*
1·*N*-Boc-L-Phe, -D-Phe	−8.2, −7.3	+0.1, −2.3
1·*N*-Boc-L-Ser, -D-Ser	−9.1, −11.7	−5.3, −6.1
3a·*N*-Boc-L-Phe, -D-Phe	ND,[a] ND[a]	−7.1, −5.7
3a·*N*-Boc-L-Ser, -D-Ser	ND,[a] ND[a]	−7.8, −7.6
3b·*N*-Boc-L-Phe, -D-Phe	−4.5, ND	−7.3, −7.1
3b·*N*-Boc-L-Ser, -D-Ser	−4.6, ND	−9.5, −10.4

[a] The α-methylbenzyl groups of receptor **3a** lack classical H-bond acceptor atoms like O or N. See Ref. 11. ND, not determined.

9.9 mmol), and *N*,*N*-diisopropylethylamine (6.8 mL) was warmed with a heat gun for 10 min. Upon cooling, the top layer was decanted away, and the bottom layer was treated with 100 mL of EtOAc. The precipitated hydrochloride salt was removed by filtration, and the filtrate was evaporated. Flash column chromatography on silica gel using EtOAc–MeOH (9:1, v:v) as the eluent provided 1.89 g (81%) of the product as a yellow oil which solidified upon standing. Mp 98–100 °C; TLC (EtOAc–MeOH, 9:1) R_f=0.31; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.2 Hz, 3H), 1.64 (m, 3H), 1.85–2.05 (m, 3H), 2.98 (t, J=7.2 Hz, 2H), 3.37 (m, 1H), 3.60 (m, 1H), 3.75 (q, J=6.9 Hz, 1H), 3.88 (q, J=6.3 Hz, 1H), 4.06 (m, 1H), 7.44 (s, 1H), 7.53 (t, 1H), 11.76 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.6, 25.7, 26.9, 28.6, 42.5, 68.0, 77.8, 129.5, 133.0, 136.2, 164.2; Anal. Calcd for $C_{12}H_{19}N_3O_2$: C 60.74, H 8.07, N 17.71. Found: C 60.58, H 8.06, N 17.34.

4.3. (*S*)-2-Iodo-5-propyl-1*H*-imidazole-4-carboxylic acid (1-phenylethyl)amide (6a)

Reaction of **5a** (1.02 g, 4.0 mmol) with *N*-iodosuccinimide (95%; 1.10 g, 4.6 mmol) under conditions previously described[9b] afforded 1.07 g (70%) of iodide **6a** as a light yellow oil after flash column chromatography on silica gel using EtOAc as the eluent. TLC (EtOAc): R_f=0.61; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J=7.5 Hz, 3H), 1.51 (m, 2H), 1.54 (d, J=6.9 Hz, 3H), 2.85 (m, 2H), 5.21 (m, J=7.2 Hz, 1H), 7.15–7.35 (m, 5H), 7.45 (d, J=8.1 Hz, 1H), 11.62 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.4, 26.9, 48.5, 81.4, 126.0, 127.2, 128.5, 133.5, 141.4, 143.3, 162.0.

4.4. (*R*)-2-Iodo-5-propyl-1*H*-imidazole-4-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide (6b)

Reaction of **5b** (1.08 g, 4.6 mmol) with *N*-iodosuccinimide (95%; 1.19 g, 5.0 mmol) under conditions previously described[9b] afforded 1.60 g (97%) of iodide **6b** as a faintly yellow syrup. TLC (EtOAc): R_f=0.49; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=7.5 Hz, 3H), 1.63 (m, 3H), 1.85–2.05 (m, 3H), 2.97 (t, J=7.5 Hz, 2H), 3.35 (m, 1H), 3.59 (m, 1H), 3.79 (m, 1H), 3.91 (m, 1H), 4.12 (m, 1H), 7.37 (s, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.6, 25.7, 26.9, 28.8, 42.7, 68.0, 77.9, 81.3, 133.6, 140.9, 162.7.

4.5. (*S*,*S*)-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(1-phenylethyl)amide] (3a)

Homocoupling of **6a** (1.00 g, 2.6 mmol) using tetrakis-(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) under conditions previously described[9b] afforded 0.36 g (54%) of biimidazole **3a** as a tan solid after flash column chromatography on silica gel using CH_2Cl_2–EtOAc (2:1, v:v) as the eluent. Mp 165 °C dec.; TLC (CH_2Cl_2–EtOAc, 2:1) R_f=0.36; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J=7.0 Hz, 6H), 1.58 (d, J=6.5 Hz, 6H), 1.68 (m, J=7.5 Hz, 4H), 3.04 (m, 4H), 5.27 (m, J=7.5 Hz, 2H), 7.23–7.37 (m, 12H), 9.96 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.1, 22.2, 26.9, 48.4, 125.9, 127.1, 128.5, 130.7, 135.7, 137.6, 143.2, 162.6; UV/vis (CH_2Cl_2): λ_{max} (ε M^{-1} cm^{-1})=291 (32,000), 299 (33,000), 314 (19,000); Anal. Calcd for $C_{30}H_{36}N_6O_2$: C 70.29, H 7.08, N 16.39. Found: C 70.39, H 7.30, N 16.20.

4.6. *meso*-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(1-phenylethyl)amide] (*meso*-3a)

The reactions described above (Scheme 1, **4**→**3**) were repeated using racemic α-methylbenzylamine instead of (*S*)-α-methylbenzylamine. Product *meso*-**3a** was isolated as a tan solid after flash column chromatography on silica gel using CH_2Cl_2–EtOAc (2:1, v:v) as the eluent. TLC (CH_2Cl_2–EtOAc, 2:1) R_f=0.43; ^{1}H NMR (CD_3OD) δ 0.94 (t, J=7.5 Hz, 6H), 1.55 (d, J=7.0 Hz, 6H), 1.68 (m, 4H), 2.98 (m, 4H), 5.17 (m, J=7.0 Hz, 2H), 7.23–7.40 (m, 12H); ^{13}C NMR (CD_3OD) δ 14.0, 22.7, 24.0, 27.8, 127.1, 128.2, 129.6, 139.4, 145.2; Anal. Calcd for $C_{30}H_{36}N_6O_2$: C 70.29, H 7.08, N 16.39. Found: C 70.15, H 7.11, N 16.48.

4.7. (*R*,*R*)-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(tetrahydrofuran-2-ylmethyl) amide] (3b)

Homocoupling of **6b** (1.60 g, 4.4 mmol) using tetrakis-(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol) under conditions previously described[9b] afforded 0.47 g (45%) of biimidazole **3b** as a white crystalline solid after flash column chromatography on silica gel using EtOAc–MeOH (9:1, v:v) as the eluent. Mp >260 °C; TLC (EtOAc–MeOH, 9:1) R_f=0.54; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J=7.5 Hz, 6H), 1.62 (m, 2H), 1.72 (m, J=7.5 Hz, 4H), 1.92 (m, 4H), 2.01 (m, 2H), 3.07 (t, J=7.5 Hz, 4H), 3.26 (m, 2H), 3.73 (m, 2H), 3.79 (q, J=6.0 Hz, 2H), 3.88 (q, J=7.0 Hz, 2H), 4.08 (m, 2H), 7.40 (t, J=7.0 Hz, 2H), 10.28 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 25.8, 27.0, 28.8, 42.6, 78.2, 130.9, 135.8, 137.3, 163.4; UV/vis (CH_2Cl_2): λ_{max} (ε M^{-1} cm^{-1})=290 (29,000), 298 (31,000), 313 (18,000); Anal. Calcd for $C_{24}H_{36}N_6O_4$: C 61.00, H 7.68, N 17.78. Found: C 60.89, H 7.82, N 18.05.

4.8. ^{1}H NMR binding studies

A sample of **3a** or **3b** was dissolved in 1.0 mL of $CDCl_3$ such that its concentration was near 0.01 M, then the solution was transferred to an NMR tube. Solid amino acid was added to a concentration of approximately 0.005 M, the tube was vigorously shaken, and a proton NMR spectrum was acquired. Successive additions of amino acid were made, and spectra recorded, until [amino acid] was at least five times [biimidazole]. During several titrations with **3a**, aryl proton peaks obscured the amide N*H* resonances, preventing their use in derivations of K_{assoc}. In these cases, chemical shifts of the benzylic C*H* were followed instead. Control experiments confirmed that using data for either the amide N*H* or benzylic C*H* gave the same K_{assoc} values within $\pm$5 M^{-1}. Binding curves (i.e., plots of $\delta_{NH/CH}$ vs [amino acid]) were fit using the program WinEQNMR.[15]

During ^{1}H NMR titration with *N*-Boc-L-Phe, the benzylic C*H* nuclei of biimidazole **3a** experienced a small upfield shift ($\Delta\delta$=−0.015 ppm) which was not observed with any other amino acids in Table 1. This phenomenon was examined using computational methods (see the Supplementary data).

^{1}H NMR titrations were also performed for **3a** and **3b** with *N*-Boc-L/D-Pro, but a reliable association constant could

only be derived in one case (**3a**·*N*-Boc-D-Pro, $K_{assoc}=30\ M^{-1}$). Binding curves for **3a**·L-Pro and **3b**·L/D-Pro were not strictly hyperbolic, but instead featured an initial region in which δ_{NH} moved upfield. Exclusion of these 'inverted' regions from the curve fits allowed for calculation of K_{assoc} values, but with errors of >20%. The anomalous binding curves may reflect the presence of competing equilibria involving weakly self-associated biimidazole oligomers.[9] A ^{1}H NMR dilution experiment[17] using **3b** in $CDCl_3$, in which the chemical shift of the imidazole N*H* was monitored as a function of [**3b**], gave $K_{dimer}=25\ M^{-1}$.

4.9. Computational methods

Preliminary geometry optimizations were performed using Gaussian 03[18] with a restricted Hartree–Fock (RHF) wave function and a 3-21G basis set.[19] These structures were subsequently refined using the density functional theory[20] package DMol3[13] with the Becke–Tsuneda–Hirao gradient-corrected exchange-correlation functional[14] (BOP) and a double numerical plus polarization (DNP) basis set.

To avoid overwhelming the available computational resources, truncated models of host–guest complexes involving **3** were necessary and involved replacing the chiral arm of the distal amide with a methyl group. Several initial host–guest geometries, including those with secondary H-bonding to the guest Boc group, were evaluated in an effort to probe all relevant regions of the potential energy surface, because algorithms for the systematic conformational search of such complex systems were not available.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.096

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