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# A Novel Synthesis of Chiral Guanidinium Receptors and Their Use in Unfolding the Energetics of Enantiorecognition of Chiral Carboxylates

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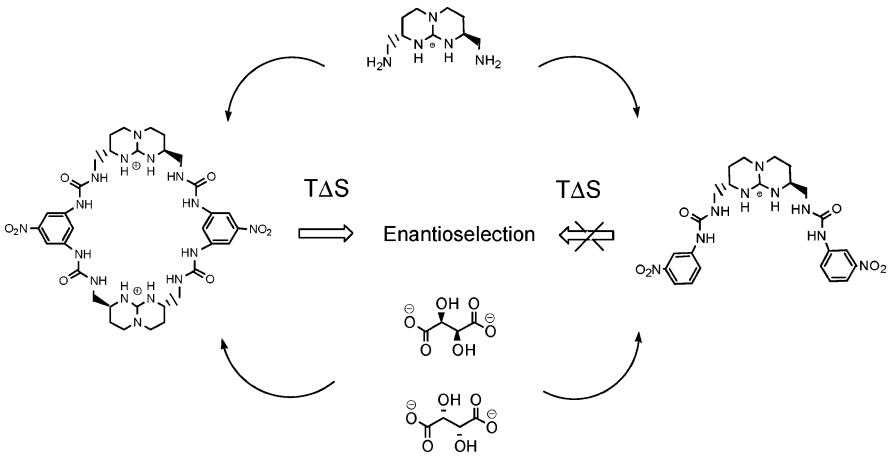


A novel synthetic route to the versatile chiral bicyclic guanidinium building block is described making use of L-methionine as a starting material from the natural chiral pool. Furthermore, the synthetic elaboration of this building block is shown in the construction of macrocyclic and open chain hosts, respectively. The host design employs urea functions as the connecting units and supplementary anchor groups for the complexation of anions. The binding studies of these hosts with various chiral and achiral oxoanions are performed by isothermal titration calorimetry. A trend analysis of the binding energetics in an ensemble of structurally similar guests discloses the importance of geometrical confinement of the guest. Association entropy rather than free energy (affinity) is identified as an indicator of structural uniqueness needed to distinguish configurational isomers in the recognition of enantiomeric carboxylates by the chiral guanidinium hosts.

## Introduction

Supramolecular interactions play a fundamental role in all living systems.[1−3] In order to mimic these interactions, a wide range of host−guest systems has been developed and successfully utilized to perform functions like catalysis, molecular recognition, and membrane transport. Among the various abiotic applications of supramolecular interactions the discrimination of enantiomers occupies a prominent position.[4−8] In this vein, the bicyclic guanidinium scaffold **1** has been widely adopted

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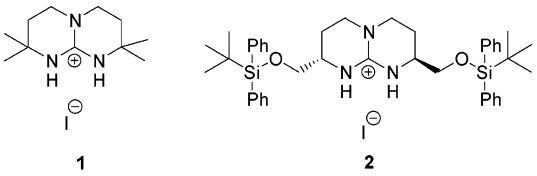
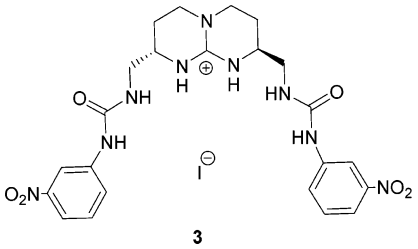
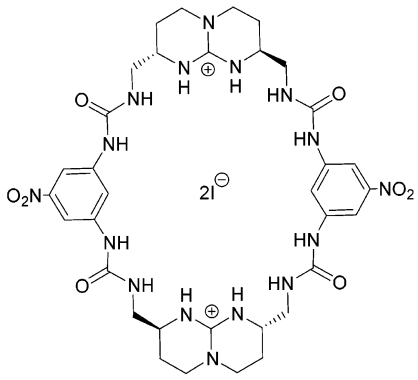
for the construction of dedicated molecular hosts for oxoanions.[9−11] As a chiral member of this class, the disubstituted compound **2** has been utilized as a building block in the construction of chiral hosts for anions.[12−16] In particular, open-chain[12,16−27] or macrocyclic[27−29] chiral receptors have been produced on this basis. Recently, we have elaborated the parent compound **2** into the chiral macrocyclic host **4**[28] and its open chain analogue **3**. In the design of these compounds, urea functionality was incorporated as a connecting element between the guanidinium units and as an additional anchor group. Urea functions have been widely employed in hosts for anionic species as neutral binding motifs based on their ability to form strong and directional hydrogen bonds.[30−36] The chiral host **4** was shown to effectively differentiate the antipodal tartrate and aspartate anions.[28]



**1** **2**



**3**



**4**

Despite its popularity, there are only a few synthetic routes known to target the building block **2**.[13,14,37] All strategies make use of readily available components of the natural chiral pool. The original two independent strategies made use of L-asparagine.[13,37] Although both approaches follow the same general strategy to construct the bicyclic skeleton via an open-chain triamine intermediate, they differ in many steps. Neither of these routes furnished more than an overall 20% yield. A much improved pathway was subsequently published by Schmidtchen et al.[38] and adopted by others[39] following a route starting from two different commercial chiral amino acids and passing through a thiourea key intermediate containing all carbon atoms to finally assemble the bicyclic guanidinium skeleton.

Here, we describe a novel route to the guanidinium building block **2** which avoids the low-yielding bimolecular cyclization step used in the earlier route. The novel pathway makes use of only one chiral building block from the chiral pool. The guanidinium target compound **2** is constructed by virtue of an intramolecular two-step, one-pot, double-cyclization process of a linear, yet branched, guanidinium precursor. This route adapts the previous ones with respect to the educt and the reliability of stereochemical outcome but is distinctly superior in terms of rapidity, manageable scale, experimental handling, and the total number of steps. In addition, we report on the synthetic elaboration of **2** into the macrocyclic host **4** and its open-chain analogue **3**, thus setting the stage for binding studies with some achiral and stereogenic organic carboxylates.

## Results and Discussion

Recently, guanidinylation of primary or secondary amines using di(1*H*-imidazol-1-yl)methanimine **5** as a reagent was

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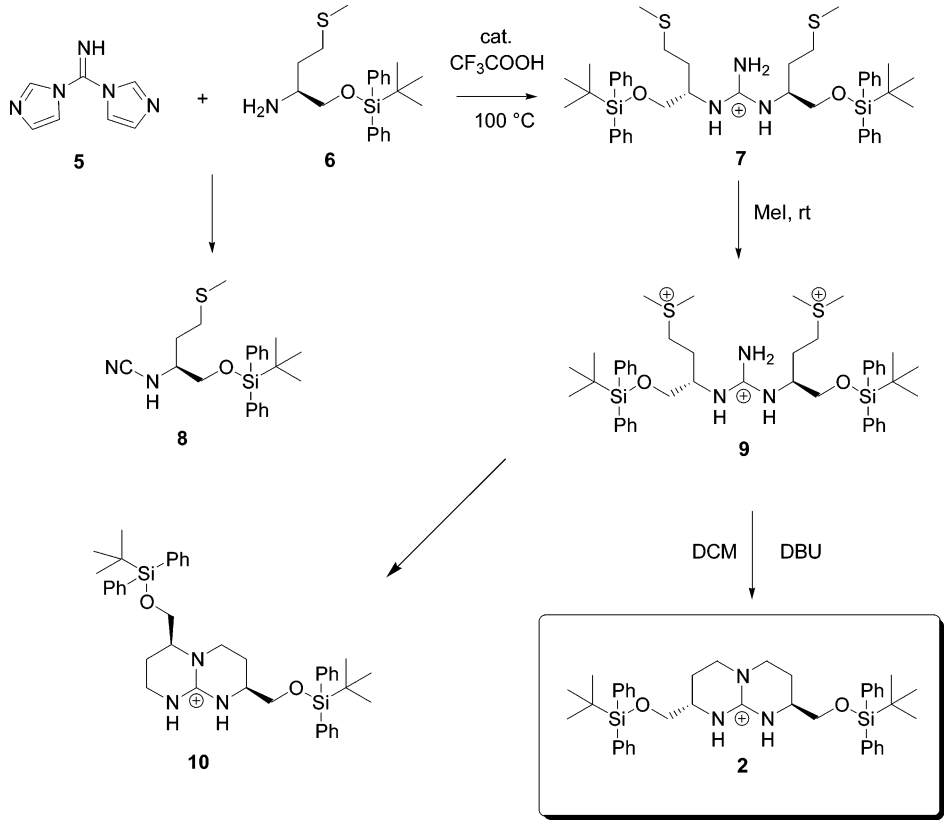
**SCHEME 1. Synthetic Approach to Guanidinium Compound 2 (Iodide as a Counteranion)**




demonstrated by Wu, et al.[40,41] Under similar conditions, the reaction of **5** with the protected methioninol **6** was expected to yield the guanidinium compound **7**. Based on this key conversion, a strategy for the quick preparation of guanidinium compound **2** was devised (Scheme 1). The coupling partners **5** and **6** were prepared according to literature procedures.[38,40] Their reaction applying an excess of amino compound **6** over reagent **5** under the same conditions used by Wu et al.,[40,41] however, did not furnish the guanidinium product **7** but exclusively formed cyanamide **8**. Careful tuning of reaction conditions was necessary to redirect the pathway toward the desired compound **7**. Best results were obtained on a small scale (<1 g) on heating a mixture of the neat compounds **5** and **6** with a catalytic amount of trifluoroacetic acid to 100 °C for 4 h. Thereafter, the bis-sulfonium compound **9** was obtained in quantitative yield by stirring the guanidinium compound **7** in neat methyl iodide at room temperature overnight. To afford the final bicyclization step bis-sulfonium compound **9** was initially treated with tetramethylguanidine (TMG). This treatment expectedly resulted also in the formation of the undesired regioisomer **10** along with the desired target compound **2**, however, in the ratio of **10**/**2** = 60:40, respectively. Several attempts to favor the formation of the desired isomer **2** including a change of the base to DBU finally furnished a 65:35 (**2**:**10**) preference of this target compound.

The refining of the mixture of isomers so obtained employed crystallization from acetonitrile at −18 °C. Under such conditions, the desired bicyclic guanidinium compound **2** crystallized preferentially to give, after supplementary chromatographic purification of the mother liquor, a 45% yield. Thus, the versatile[12−14,16] and much desired guanidinium building block **2** was accessible in an overall 30% yield in a straightforward four-step sequence from commercial chiral compounds.

**Synthesis of Macrocyclic Compound 4.** The preparation of the macrocyclic compound **4** was planned as a one-pot process by 2 + 2 addition of synthons **11** and **12** as shown in the retrosynthetic Scheme 2. The bisaminomethylguanidinium compound **11** was prepared by the series of steps shown in Scheme 3. The bishydroxy compound **13** obtained from silyl ether deprotection of **2** using polymer-supported fluoride was converted to the bismesylate **14** under standard conditions followed by nucleophilic displacement with sodium azide in DMF (90 °C). The bis(azidomethyl)guanidinium compound **15** was thus obtained in 60% yield referring to the last three steps. Finally, hydrogenation over Pd/C furnished the bisaminomethyl derivative **11** from **15** in quantitative yield.

**Synthesis of the Bisisocyanato Reagent 12.** The bisisocyanato reagent **12** was prepared by a modification of the literature procedure[42] as shown in Scheme 4. 5-Nitroisophthalic acid **16** was converted to the dichloride derivative **17** by using oxalyl

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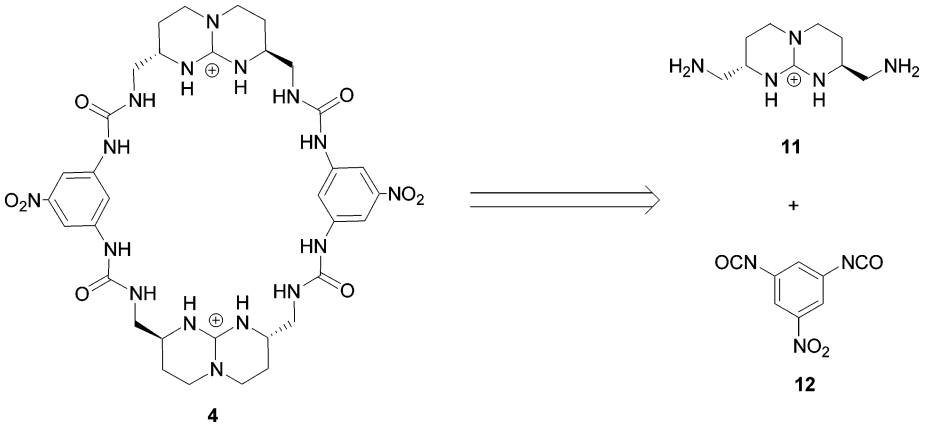
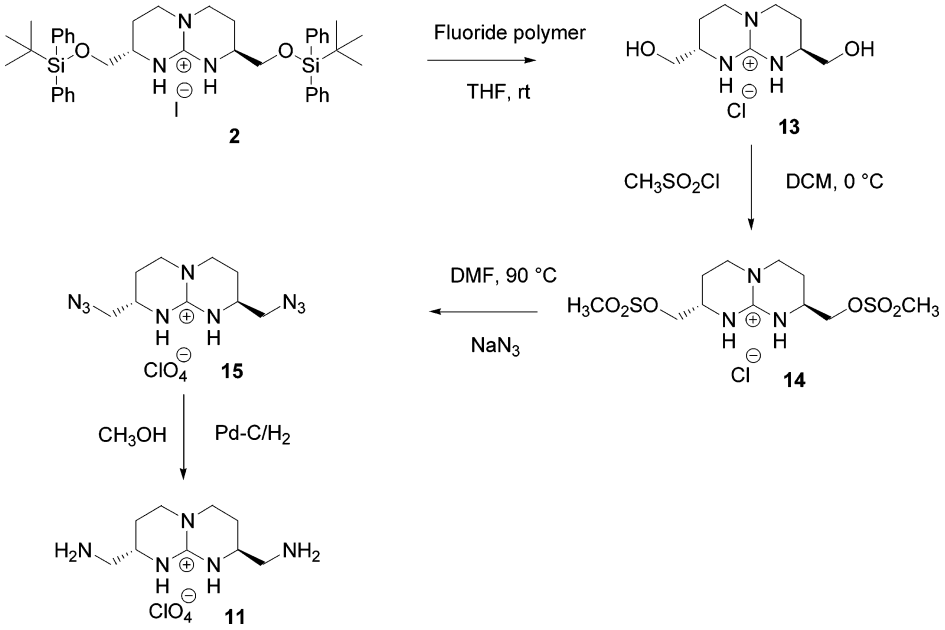
**SCHEME 2. Retrosynthetic Approach for Macrocyclic Compound 4**




**SCHEME 3. Synthetic Approach to the Bisaminoguanidinium Compound 11a[a]**

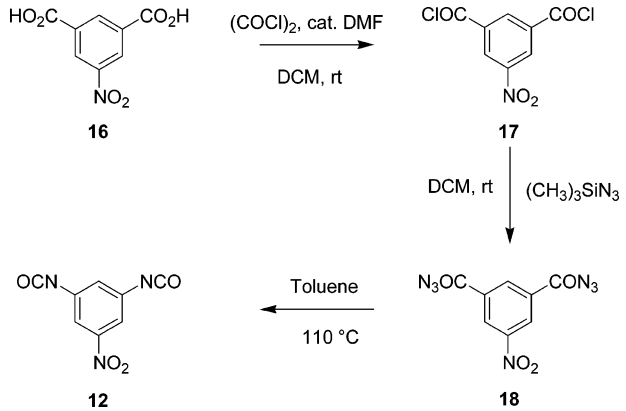



[a] Counterions may be exchanged for the isolated compounds, which eventually require anion exchange as discussed in the Experimental Section.

chloride in the presence of a catalytic amount of DMF. The 5-nitroisophthalic acid azide **18** in turn was prepared from **17** by reaction with an excess of trimethylsilyl azide. The acid azide **18** was thermally labile as expected and underwent a Curtius rearrangement at 110 °C in toluene to afford bisisocyanato reagent **12** in 70% yield.

The final addition of synthons **11** and **12** to form macrocycle **4** was conducted in a pilot reaction by adding **12** to the solution of bisamino compound **11** and triethylamine in acetonitrile at 60 °C monitoring the reaction by HPLC−MS analysis. Only traces of the desired macrocycle **4** could be detected along with a major portion of polymers. Freshly sublimed isocyanate **12** and slow reagent addition using a syringe pump into a diluted solution of the amino compound **11** and base finally furnished the desired chiral macrocyclic host **4** in 10% yield after chromatographic purification.

**SCHEME 4. Synthetic Strategy for the Compound 12**




**Binding Studies of the Macrocycle 4 with Different Oxoanions.** The complexation characteristics of the chiral macrocycle **4** with a series of simple oxodianions of varying dimensions were carried out by isothermal titration calorimetry (ITC) in acetonitrile (Chart 1). Complexation studies by NMR titration were not feasible due to the poor solubility of the host.

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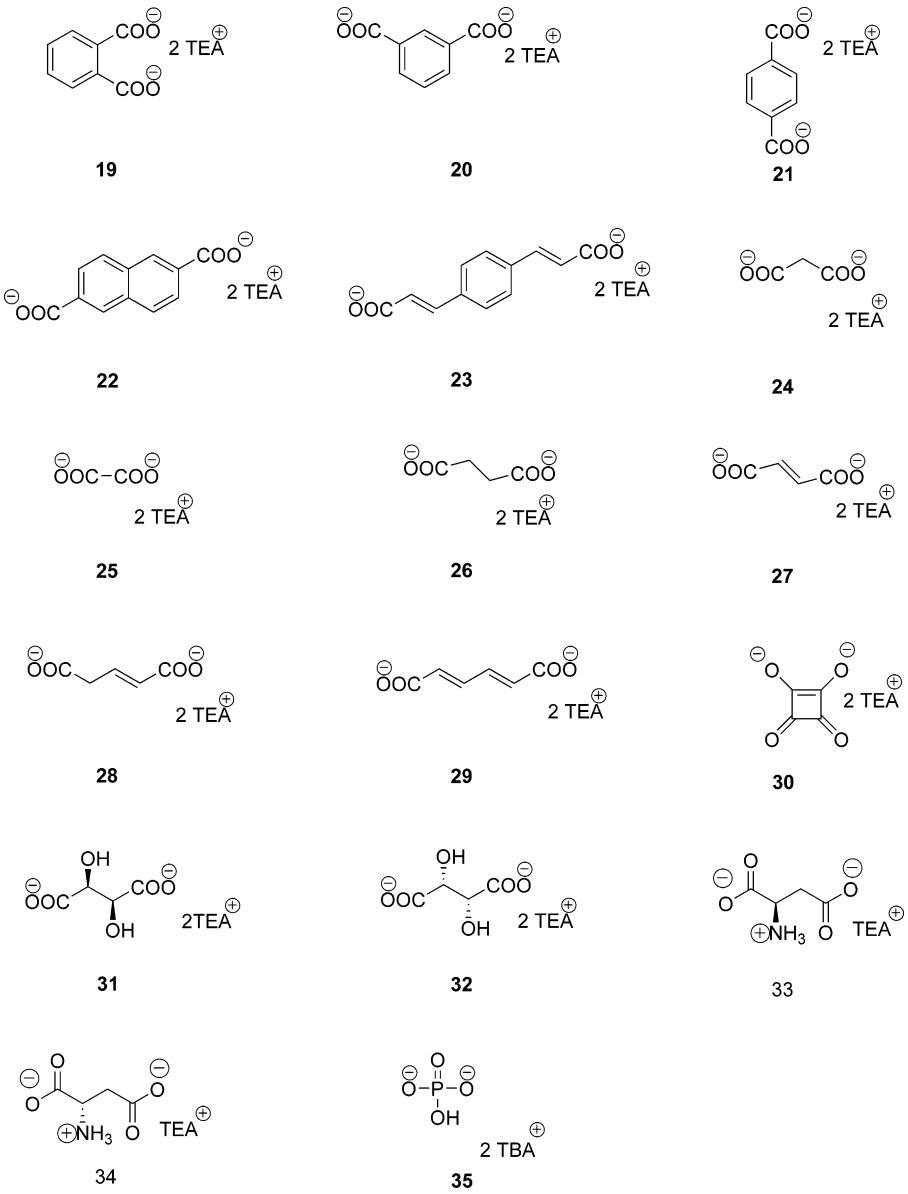
**CHART 1**




The ITC titrations were performed by addition of the solution of the macrocyclic host (as the iodide salt) into the solution of guest dianions (as tetraethylammonium salts) at submillimolar concentrations to ensure best dissociation of the salts.[51] In some cases, the titrations gave clear evidence of the formation of higher order complexes in addition to ordinary 1:1 host−guest binding. The energetics of complexation derived from applying the best fitting binding model (as provided by the software of the calorimeter) is collected in Table 1. A crude overview of the binding data reveals the notion that there are subtle differences clearly emerging from the various guest structures, yet no sensible overall size correlation is obvious. Similar studies of host−guest binding of carboxylic dianions to hydrogen bond donor macrocycles generally report clear correlations of the molecular sizes of these hosts and guests.[43−47]

A trend analysis of the binding energetics unfolds some unexpected observations. Excluding malonate **24**, which did not give a sufficient heat response for analysis, three different energetic patterns can be found for the series of guests (see Figure 1) which all add up to very similar averages in free energies. In the first series, A, comprising phthalate **19**, succinate **26**, squarate **30**, and one binding step each of fumarate **27** and glutaconate **28** (Table 1, entries 4, 7, 10, 12, and 13), small negative enthalpies are found accompanied by huge positive entropic contributions to give high affinities ($K_{assoc}$, $\Delta G$). In essence, this kind of energetic signature resembles unspecific ion-pairing which mainly arises from minute structuring in the host−guest complex.[48−50]

The next class, B, comprising terephthalate **21**, hydrogen phosphate **35**, naphthalenedicarboxylate **22**, oxalate **25**, and *trans,trans*-muconate **29** (Table 1, entries 1, 5, 6, 8, and 15), exhibits a somewhat diminished entropy of association in combination with more negative enthalpies, suggesting improved

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**TABLE 1. Energetics of Dianion Binding (Tetraethylammonium Salts) to Macrocycle 4 (as the Iodide Salt)[51] in Acetonitrile at 298 K[a]**

| entry | guest | model[b] | $K_{assoc}$ ($M^{-1}$) | $\Delta G°$ (kJ $mol^{-1}$) | $\Delta H°$ (kJ $mol^{-1}$) | $T\Delta S°$ (kJ $mol^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | terephthalate$^{2-}$ **21** | A | $7.17 \times 10^6$ | −39.1 | −35.7 | +03.4 |
| 2 | pCVC$^{2-}$ **23** | A | $4.33 \times 10^6$ | −37.9 | −41.9 | −04.1 |
| 3 | isophthalate$^{2-}$ **20** | A | $7.18 \times 10^5$ | −33.4 | −38.5 | −05.0 |
| 4 | phthalate$^{2-}$ **19** | C | $1.65 \times 10^5$ | −29.8 | −03.1 | +26.7 |
| | | C | $1.82 \times 10^5$ | −30.0 | −12.3 | +17.7 |
| 5 | hydrogen phosphate$^{2-}$ **35** | A | $9.00 \times 10^5$ | −33.9 | −32.4 | +01.6 |
| 6 | naphthalene dicarboxylate **22** | A | $2.76 \times 10^5$ | −31.0 | −28.0 | +02.6 |
| 7 | squarate$^{2-}$ **30** | A, $n = 2$ | $6.5 \times 10^6$ | −38.9 | −14.2 | +24.6 |
| 8 | oxalate$^{2-}$ **25** | A, $n = 2$ | $6.4 \times 10^5$ | −33.1 | −21.4 | +11.9 |
| 9 | malonate$^{2-}$ **24** | no sufficient heat effect | | | | |
| 10 | succinate$^{2-}$ **26** | B, $n = 1$ | $1.8 \times 10^6$ | −35.8 | −07.0 | +28.8 |
| 11 | fumarate$^{2-}$ **27** | C, $n = 1$ | $1.7 \times 10^7$ | −41.2 | −52.8 | −11.5 |
| 12 | | C, $n = 2$ | $8.7 \times 10^4$ | −28.1 | −08.3 | +19.8 |
| 13 | glutaconate$^{2-}$ **28** | C, $n = 1$ | $5.0 \times 10^5$ | −32.5 | −05.2 | +27.3 |
| 14 | | C, $n = 2$ | $2.9 \times 10^4$ | −25.4 | −50.9 | −25.4 |
| 15 | *t*,*t*-muconate$^{2-}$ **29** | A, $n = 2$ | $3.8 \times 10^5$ | −31.8 | −26.7 | +05.2 |

[a] The stoichiometry *n* refers to the number of stepwise association constants. (For the error range of ITC titrations, see ref 52). [b] A = titration mode: host into guest solution; one-site-model; ligand-in-cell; guest/host stoichiometry $n = 1$ unless indicated otherwise; entries 7, 8, and 15 refer to two identical sites. B = titration mode: guest into host solution; one-site-model; guest:host stoichiometry $n = 1$. C = titration mode: host into guest solution; 2 sequential-site-model; ligand-in-cell. pCVC = *p*(carboxyvinyl)cinnamate.

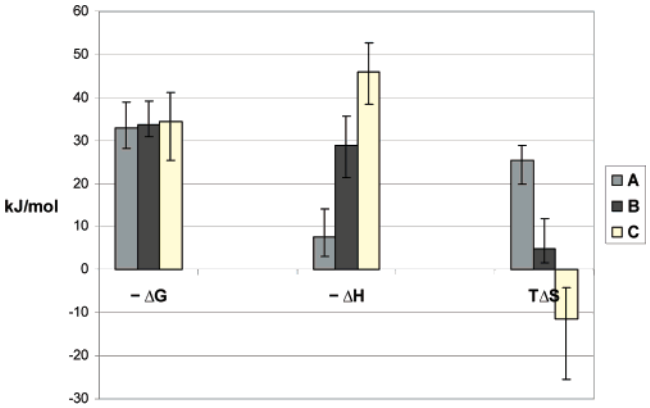


**FIGURE 1.** Binding energetics comparison for different guests with macrocycle **4**: (A) entries 4, 7, 10, 12, and 13 from Table 1; (B) entries 1, 5, 6, 8, and 15 from Table 1; (C) entries 2, 3, 11, and 14 from Table 1.

structuring of the respective complexes. Yet, overall 1:2 host-to-guest stoichiometries are maintained supporting the notion that macrocycle **4** can offer two independently acting binding sites.

The last class, C, comprising the more rigid olefinic carboxylates fumarate **27**, glutaconate **28**, *p*-carboxyvinylcinnamate **23**, and aromatic isophthalate **20**, features dramatic changes in the energetic signature. All of these guests reveal a huge exothermic binding step ($-\Delta H°$) that is accompanied by a strong negative entropy of association

The combination of both components flags fumarate **27** as the example of highest affinity in the entire series, while its congener glutaconate **28** possessing one more methylene group shows dramatically lower affinity (factor of ∼1000). Among the three benzenedicarboxylic regioisomers, isophthalate **20** is bound with the most negative entropy and enthalpy values suggesting a strongly dedicated correspondence of structural moieties of host and guest.

Such a relationship is less distinct for terephthalate **21**, yet the compensating character of enthalpy and entropy contributions seen for isophthalate **20** is lost, leaving terephthalate **21** as the highest affinity example of this series. The calorimetric analysis allowed a disclosure of two steps in the complexation of phthalate dianion **19**. Both of them profit from rather positive entropy contributions supplemented by weak attractive enthalpies. Obviously, the fixed directionality of the anionic guest functions generates quite different binding modes with the structurally restricted host skeleton that are hardly apparent from the magnitude of the binding constants, but are unfolded on inspection of the energetic signatures.

Comparing the energetics of fumarate **27** and glutaconate **28** with its closest congener succinate **26** leads to the conclusion that the differences in the entropies of association found do not correlate with the size of the guest surfaces. As it is well established[53] that solvation entropy scales with the buried surface in the host−guest complex (polar and nonpolar regions both contribute linearly, but to different extent) plain solvation effects cannot explain the severe variations observed. It is plausible to presume a basic interaction mode of host **4** with all three guest species characterized by moderately negative enthalpies and large positive entropies as is usually found in the pairing of ions of opposite charge in polar solvents.[48−50] Such an energetic signature reflects extensive desolvation of host and guest on unspecific contact ion-pair formation and does not lead to great differentiation. In contrast, the olefinic substrates fumarate **27**, glutaconate **28**, and pCVC **23** apparently specifically address the sticky hydrogen-bonding sites of the host in a way that gives rise to strong enthalpic interaction concomitant with a strong decrease in entropy. Such a scenario diminishes the internal mobility leading to very restricted structural variability of the complex. It is important to realize that this binding mode describing the structuredness of the host−guest complex does not correlate with affinity (compare entries 11 and 12 or 13 and 14) and cannot be read from the absolute magnitude of binding constants (compare entries 11 and 14). In fact, the binding step with best structuredness (fit) according to this enthalpy/entropy criterion (entry 14) has the weakest affinity (lowest binding constant).

Take the example of fumarate **27**, which shows structural dedication in both host guest partners as indicated by a substantial negative entropy of association and a large binding enthalpy resulting in the highest association constant in the series (entry 11). Interestingly, glutaconate **28** (entry 14), the slightly

(53) Luque, I.; Freire, E.; Gary, K. A. a. M. L. J. *Methods of Enzymology*; Academic Press: New York, 1998; Vol. 295, p 100.

**TABLE 2. Energetics of Enantioselective Binding of Chiral Tartrate Dianions 31 and 32, and Aspartate Monoanions 33 and 34 (as Tetraethylammonium Salts) to Macrocycle 4 (as the Iodide Salt)[51] in Acetonitrile at 298 K[a]**

| entry | guest | model | $K_{assoc}$ ($M^{-1}$) | $\Delta G°$ (kJ $mol^{-1}$) | $\Delta H°$ (kJ $mol^{-1}$) | $T\Delta S°$ (kJ $mol^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | (*S*,*S*)-tartrate$^{2-}$ **31** | A, $n = 1.0$ | $3.1 \times 10^6$ | −37.0 | −40.5 | −03.4 |
| 2 | (*R*,*R*)-tartrate$^{2-}$ **32** | A, $n = 1.0$ | $8.8 \times 10^5$ | −33.9 | −45.0 | −11.0 |
| 3 | *S*-aspartate$^{1-}$ **34** | A, $n = 2.8$ | $4.1 \times 10^5$ | −32.0 | −34.5 | −02.5 |
| 4 | *R*-aspartate$^{1-}$ **33** | A, $n = 3.0$ | $3.9 \times 10^5$ | −31.9 | −30.1 | +01.8 |

[a] Abbreviations are the same as in Table 1. For the fidelity of ITC titrations, see ref 52.

larger analogue, displays an even more negative entropy of association in one of the binding steps confirming the requirement that more degrees of freedom must be lost to reach a similar level of host−guest structural correspondence as fumarate **27**. Merging of the enthalpy and entropy components furnishes a smaller affinity in the specific step than even seen in the ion-pair mode of succinate (entry 10). This simple comparison of the stepwise constants not only relates and unfolds incompatible binding modes of both olefinic guests, but also allows the quite amazing assignment of the structurally best defined complex as the one of the *weakest* affinity.

Whether or not a host−guest complex under study complies with the ultimate model of structural uniqueness, i.e., the lock-and-key picture, is of prime importance for addressing the various goals of molecular recognition.[9,11] The singularity of the binding mode plays a predominant role in all supramolecular applications targeting a peculiar geometrical identity as in assembly processes or in catalyses depending on a specific stereoelectronic disposition of the interaction partners. In contrast, supramolecular interactions aiming at maximum affinity for, e.g., two-phase extraction or rigorous blocking of a receptor site have less demand for structural uniqueness. The discrimination between two structures that exclusively differ in their geometry as it occurs in enantiorecognition clearly belongs to the former domain. The energetics of enantiodiscrimination comparing the binding of the macrocyclic host **4** with the optical antipodes of tartrates **31** and **32** and aspartates **33** and **34**, respectively, is shown in Table 2.

Enantiorecognition represents a particularly fortuitous case to separate the energetic effects arising from the mutual interaction of the binding partners from all changes attributable to solvation. The initial states before binding for both enantiomers are exactly alike and also the diastereomeric host−guest complexes formed on association do not differ with respect to the number and nature of functional groups nor in the overall dimensions. Thus, the contribution of differential solvation on the energetic outcome is at a minimum and any differences observed must result from the direct interactions of the antipodal guests with the chiral host. As a corollary, the observable entropy preponderantly consists of the configurational term. The differences in the structural fidelity of the complex species can thus be directly read from experiment. Traditionally, the diastereomeric host−guest pair is considered to form matched or mismatched configurations merely based on the observed affinity ($\Delta G°$).[54] The situation before complexation for both of the enantiomers is identical and also the complexed states are alike due to the identical chemical nature, number of functional groups and overall sizes of host and guests. Thus, the differences in the observed entropies of association would reflect changes in the configurational entropy in the diastereomeric complexes and consequently address the bilateral structuredness. From this point of view, tartrate exhibits an appreciable effect, the difference in association entropy component reaching 7.6 kJ $mol^{-1}$. This difference in the entropic contribution to binding would translate to a differentiation factor of 20. But the ubiquitous enthalpy−entropy compensation[55,56] almost annihilates this entropic factor leaving behind a factor of 3.5 in terms of the association constant (Table 2, entry 1 vs 2).

Entropy remains the decisive factor in this enantiodiscrimination. Some unexpected observations add to this picture: The complex with better geometrical fit, i.e., the matched pair having the more negative entropy of association, displays *weaker* affinity compared to the mismatched one. One is led to conclude that affinity is disqualified as the evaluation criterion in enantiodiscrimination and should be replaced by the proper appreciation of the entire energetic signature of the process. A similar effect is observed in case of the titration of aspartate monoanions **33** and **34** with the macrocycle **4**. The observed 1:2 host−guest stoichiometry for either enantiomer proves that both diastereomeric complexes consist as ternary species. Most probably this is due to the lack of charge complementarity of the host with a single aspartate anion. The uptake of another guest into the complex, however, opens additional ways to satisfy all binding needs leading to easier structural compromises as reflected by more positive entropy contributions than found for tartrate. On top, a leveling of the enantiomeric distinction (Table 2, entries 3 and 4) is realized emphasizing the presumption that clearly defined and geometrically unique host−guest complex structures are required for optimal enantiodifferentiation.

The macrocycle **4** shows high affinity binding in the highly competitive solvent DMSO ($K_{assoc}$ in the range of $10^4-10^6$ $M^{-1}$) with all guests probed (for a concrete example, see the Supporting Information). The calorimetric analyses, however, unveil quite different binding modes in individual cases allowing an intimate view on structural relationships that reach far beyond common ion pairing. Thus, it was of interest to learn about the consequences of structural relaxation.

Toward this end, the host **3**, representing an open-chain analogue of the macrocyclic host **4**, was prepared according to Scheme 5. The isocyanato compound **36** was obtained from the reaction of 3-nitroaniline with triphosgene following a standard recipe.[57] Condensation of **36** with the chiral bisaminoguanidinium compound **11** gave the desired host **3** in 85% yield.

For the direct comparison of the chiral discrimination capacity between the macrocyclic host **4** and its open-chain analogue **3**, the enantiomeric tartrates **31** and **32** and aspartates **33** and **34** along with some other common chiral carboxylates were examined in acetonitrile under the same conditions as before, and the results are collected in Table 3.

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**SCHEME 5. Synthetic Approach for Open-Chain Host 3**

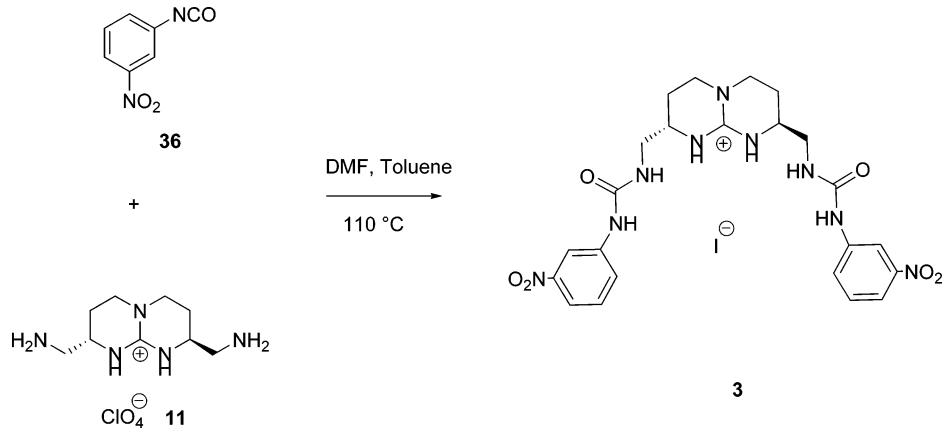


**TABLE 3. Energetics of Anion Binding (Tetraethylammonium Salts) to Open-Chain Host 3 (as the Iodide Salt)[51] in Acetonitrile at 298 K[a]**

| guest | model[b] | $K_{assoc}$ ($M^{-1}$) | $\Delta G°$ (kJ $mol^{-1}$) | $\Delta H°$ (kJ $mol^{-1}$) | $T\Delta S°$ (kJ $mol^{-1}$) |
|---|---|---|---|---|---|
| (*R*,*R*)-tartrate$^{2-}$ **32** | B, $n_1 = 1.2$ | $3.8 \times 10^4$ | −26.1 | −30.7 | −04.5 |
| | B, $n_2 = 0.9$ | $2.8 \times 10^6$ | −36.8 | −66.3 | −29.4 |
| (*S*,*S*)-tartrate$^{2-}$ **31** | B, $n_1 = 0.9$ | $1.7 \times 10^6$ | −35.5 | −68.3 | −32.8 |
| | B, $n_2 = 1.0$ | $4.4 \times 10^4$ | −26.5 | −32.4 | −05.9 |
| *S*-aspartate$^{1-}$ **34** | A, $n = 1.4$ | $3.5 \times 10^5$ | −31.6 | −67.5 | −35.8 |
| *R*-aspartate$^{1-}$ **33** | A, $n = 1$ | $4.7 \times 10^5$ | −32.35 | −68.9 | −36.5 |
| *R*-phenylglycine$^{1-}$ **37** | C, $n_1 = 0.5$ | $6.5 \times 10^7$ | −44.6 | −40.5 | +04.1 |
| | C, $n_2 = 0.9$ | $8.6 \times 10^5$ | −33.9 | −30.9 | +02.9 |
| *S*-phenylglycine$^{1-}$ **38** | C, $n_1 = 0.6$ | $6.4 \times 10^7$ | −44.5 | −42.4 | +02.2 |
| | C, $n_2 = 0.9$ | $9.9 \times 10^5$ | −34.2 | −32.3 | +02.0 |

[a] For the fidelity of ITC titrations, see ref 52. [b] A = titration mode: host into guest solution; one-site-model; ligand-in-cell; guest/host stoichiometry = *n*. B = titration mode: host into guest solution; two-site-model; guest/host stoichiometry = *n*. C = titration mode: guest into host solution; two-site-model; guest/host stoichiometry = *n*.

In general, the calorimetric analyses revealed no significant differential effects in enantiomer binding. The affinities ($\Delta G°$) as well as the component entropies ($\Delta S°$) and enthalpies ($\Delta H°$) were identical within experimental error. The lack of enantiodiscrimination ($\Delta\Delta G°$) in these cases does not arise from enthalpy−entropy compensation that is commonly observed in supramolecular interactions[55,56] but is seen in the energetic components, too. The chiral centers in host and guest seem too remote in the complexes to influence each other. A similar effect was observed in the interaction of tetra-substituted bicyclic guanidinium hosts with benzoates.[51]

With tartrate dianions, the open-chain host **3** shows stepwise binding (Table 3), again demonstrating the effect of charge matching. Titrating the guest into the host solution the initial phase shows clean low-affinity host−guest 2:1 complex formation caused by the excess of the host in this concentration regime. On continuation the ternary complex dissociates to form the high affinity 1:1 host−guest complex (see the Supporting Information). In the case of aspartate introduced as the monoanion, a clean high-affinity 1:1 host−guest complexation was observed, too, the more negative entropy of association presumably reflecting the more effective restriction of motion of the hosts's urea substituents by the hydrogen-bonding side chain of the guest. Similar arguments can be advanced to rationalize the energetic outcome for phenylglycine; however, here again the enantioselectivities elude a serious evaluation.

Despite the identical binding motif occurring in the parent guanidinium compound **3** which formally is a building block of macrocycle **4**, the outcome in the differentiation of tartrate and aspartate anions is different. Though showing a similar magnitude in overall complex affinity only the macrocycle **4** brings out countable differences in the diastereomeric complexes with chiral carboxylates. The calorimetric results indicate the mandatory requirement for an preponderantly populated and geometrically unique binding mode in order to differentiate between enantiomeric carboxylate anions effectively. Such conditions are the more easily met the more restricted the accessible conformational space of the receptor is. The energetic analysis here corroborates the general guideline for enantiorecognition, however, replacing the binding constant (Gibbs free energy) by the observable association *entropy* as a more reliable indicator of structuredness.

## Conclusion

We report on a fast and convenient access route to the versatile chiral guanidinium building block **2** starting from the chiral amino acid methionine. Furthermore, we have also elaborated **2** into the chiral macrocyclic host **4** and its open-chain analogue **3**. The comparison of these very similar compounds by means of isothermal titration calorimetry emphasizes the role of spatial confinement in distinguishing between configurational isomers. A trend analysis of the binding energetics depending on restricted structural variation supports the view that a dedicated structural disposition of host and guest as can be read from the pattern of energetic components ($\Delta H°$ and $T\Delta S°$) is more important to enantiorecognition (in, e.g., kinetic resolutions) than global affinity.

## Experimental Part

**General Methods and Materials.** The general methods and materials are described in the Supporting Information.

**Di(1*H*-imidazol-1-yl)methanimine 5.**[40] To a solution of imidazole (6.8 g, 100 mmol) in dry dichloromethane (500 mL) under inert atmosphere was added a solution of cyanogen bromide (3.7 g, 33 mmol) in dichloromethane (20 mL), and the resultant reaction mixture was heated at reflux temperature for 30 min. The mixture was then cooled to room temperature, the obtained white precipitate was removed by filtration, and the filtrate was further concentrated to 50 mL and cooled to 0 °C for 2 days to obtain a crystalline solid. This solid was filtered, washed with cold dichloromethane, and dried to afford **5** (3.8 g, 70%) as a white crystalline substance.

**5**: $C_7H_7N_5$ (MW 161.2). HPLC analysis: $R_v$ = 3 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer. Mp: 102−103 °C (dichloromethane) (lit.[58] mp 103 °C). MS-ESI: *m*/*z* = 162.1 [(M + H)$^+$, 100]. Anal. Calcd for C, 52.17; H, 4.38; N, 43.45. Found: C, 51.91; H, 4.24; N, 43.96. $^1$H NMR (360 MHz; DMSO-$d_6$): $\delta$ = 10.19 (s, 1H, −N*H*), 8.09 (d, *J* = 14.8 Hz, 1H, C*H*), 7.60 (d, *J* = 22.7 Hz, 1H, C*H*), 7.11 (s, 1H, C*H*). $^{13}$C NMR (90.56 MHz; DMSO-$d_6$): $\delta$ = 140.9; 137.4; 129.6; 118.9.

**(2*S*)-2-Amino-1-[(*tert*-butyldiphenylsilyl)oxy]-5-thiahexane 6.**[38] To a well-stirred suspension of L-methionine (29.8 g, 200 mmol) in dry THF (500 mL) was added borane dimethyl sulfide complex (40 mL, 400 mmol). After being stirred for 1 h, the reaction mixture was refluxed for a period of 16 h to give a clear solution. After the reaction mixture was cooled, 10% aqueous HCl solution (150 mL) was added, and then the mixture was further refluxed for 30 min. Evaporation of solvent in vacuo left an oily residue, which was taken up in water (100 mL) and made basic by addition of 4 N NaOH (70 mL). The resultant emulsion formed was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and distilled at 100 °C/13 Pa to give amino alcohol (23 g, 85%) as a colorless oil.

The amino alcohol obtained above (23 g, 170 mmol) and imidazole (23 g, 340 mmol) were taken up in dry $CH_3CN$ (190 mL) under nitrogen. To this mixture was added a solution of *tert*-butyldiphenylchlorosilane (60.8 g, 220 mmol) in $CH_3CN$ (30 mL) while the temperature was maintained at 20 °C. After standing overnight, the solvent was evaporated and the residue was distributed at 50 °C between 1 N NaOH (600 mL) and hexane (500 mL), the aqueous phase was extracted again with hexane (200 mL), and the combined organic phases were washed with water (3 × 200 mL).

Separation from the silanol byproduct was achieved by extraction of the hexane layer with $CH_3CN/H_2O/CH_3COOH$ (40:60:2) (300 mL, 3 × 100 mL). The combined aqueous phases were made basic by addition of anhydrous $Na_2CO_3$ (25 g) and concentrated to half of its volume in vacuo. This aqueous phase was extracted with hexane (6 × 150 mL), and the combined phases were dried over magnesium sulfate. Evaporation in vacuo furnished **6** (58 g, 78%) as a colorless viscous oil.

**6.** $C_{21}H_{31}NOSSi$ (MW 373.6). HPLC analysis: $R_v$ = 7 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer. MS-ESI: *m*/*z* = 374.3 [(M + H)$^+$, 100]. $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 7.66−7.69 (m, 4H, aromatic), 7.38−7.41 (m, 6H, aromatic), 3.59−3.63 (dd, *J* = 4.3 Hz, 1H, −C*H*$_2$OSi−), 3.45−3.49 (dd, *J* = 6.5 Hz, 1H, −C*H*$_2$OSi−), 2.92−3.01(m, 1H, H$_2$NC*H*−), 2.54−2.58 (m, 2H, −C*H*$_2$SCH$_3$), 2.07 (s, 3H, −SC*H*$_3$), 1.68−1.78 (m, 1H; −CHC*H*$_2$−), 1.52−1.60 (m, 1H, −CHC*H*$_2$−), 1.09 (s, 9H, *tert*-butyl C*H*$_3$). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$ = 135.4, 133.3, 129.6, 127.6 (aromatic carbons), 68.8 (−*C*H$_2$OSi−); 52.0 (H$_2$N*C*H−), 33.0 (−*C*H$_2$SCH$_3$); 30.9 (−CH*C*H$_2$−), 26.8 (*tert*-butyl *C*H$_3$), 19.1 (quaternary carbon); 15.3 (−S*C*H$_3$).

**1,3-Bis[(*S*)-1-(*tert*-butyldiphenylsilyl)oxy-4-(methylthio)butan-2-yl]guanidine Hydroiodide 7.** Four reaction vials, each containing a mixture of guanidylating reagent **5** (80.5 mg, 0.5 mmol), amino reagent **6** (392 mg, 1.05 mmol), and trifluoroacetic acid (30 $\mu$L), were placed and stirred in an oil bath at 105 °C. After being stirred for 4 h, the reaction mixture was cooled, and a gummy substance obtained from each vial was dissolved in 3 mL of DMSO. To the combined DMSO solutions was added acetic acid (40 $\mu$L). This solution was then washed with ether/isooctane (3:1) (4 × 8 mL) to remove excess of **6**. The DMSO layer was diluted with water, and the emulsion obtained was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with a nearly saturated aqueous NaI solution (2 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo to give a gummy compound **7** (1.4 g, 77%) which was used in the next step without any further purification.

**7.** $C_{43}H_{61}N_3O_2Si_2$·HI (MW 900.2). HPLC analysis: $R_v$= 16 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer. MS-ESI *m*/*z* = 772.6 [(M + H)$^+$, 100]. $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 9.04 (bs guanidinium-1*H*), 8.57 (bs, guanidinium-1H), 7.51−7.57 (m, 8H, aromatic), 7.38−7.41 (m, 12H, aromatic), 6.7 (bs guanidinium, 2H), 3.66−3.72 (m, 6H, −C*H*$_2$OSi− + −C*H*CH$_2$−), 2.41−2.58 (m, 4H, −C*H*$_2$SCH$_3$), 2.08 (s, 6H, −SC*H*$_3$), 1.75−1.84 (m, 2H, −CHC*H*$_2$−), 1.52−1.68 (m, 2H, −CHC*H*$_2$−), 1.04 (s, 18H, *t*-butyl-C*H*$_3$). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$ = 158 0.6 (guanidinium carbon), 135.4; 131.6; 130.3; 128.1 (aromatic carbons), 69.0 (−*C*H$_2$OSi−), 55.1 (−*C*HCH$_2$), 30.2 (−*C*H$_2$SCH$_3$), 29.1 (−CH*C*H$_2$−), 26.9 (*tert*-butyl-*C*H$_3$), 19.0 (quaternary carbon), 15.1 (−S*C*H$_3$).

**1,3-Bis[(*S*)-1-(*tert*-butyldiphenylsilyl)oxy-4-(dimethylsulfonium)-butan-2-yl]guanidine Trishydroiodide 9.** The guanidinium compound **7** (1.4 g, 1.55 mmol) was dissolved in methyl iodide (5 mL), and the brown mixture was stirred overnight at room temperature under inert atmosphere, resulting in complete conversion of guanidinium compound **7** to the bis-sulfonium compound **9** (as indicated by HPLC analysis). The excess of methyl iodide was evaporated, leaving a brownish residue which was again dissolved in dichloromethane. Finally, the evaporation of dichloromethane left a brown solid residue containing bis-sulfonium salt **9** (1.87 g, 98%), which was directly used in to the next reaction without any further purification.

**9.** $C_{45}H_{68}N_3O_2Si_2SI_3$ (MW 1184.1). HPLC analysis: $R_v$= 10 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer.

**(2*S*,8*S*)-2,8-Di[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydroiodide 2.** To a solution of the bis-sulfonium salt **9** (1.87 g, 1.5 mmol) in dry dichloromethane (50 mL) cooled to less than 5 °C was added diazabicycloundecene(DBU) (1.61 mL, 9 mmol), and then the reaction mixture was stirred and allowed to warm to room temperature. After 4 h of stirring, HPLC analysis showed the completion of reaction yielding a 65:35 mixture of bicyclic guanidinium **2** to its structural isomer **10**. The reaction mixture was quenched by adding acetic acid (1 mL), and then the dichloromethane layer was washed with 1 N acetic acid (40 mL), water (40 mL), and finally by nearly saturated aqueous NaI (2 × 40 mL) solution. The organic layer was dried over magnesium sulfate, and the evaporation of solvent left 940 mg of crude gummy mixture of isomers **2** and **10**. The partial purification of the isomers was achieved by crystallization from acetonitrile at −18 °C where the desired bicyclic guanidinium compound **2** crystallized preferentially to afford 300 mg of slightly brownish colored crystalline solid.

The remaining 1:1 mixture of isomers was separated by reversed-phase MPLC, in 80% methanol/ water containing 30 mmol $NaClO_4$ as elutant to yield bicyclic guanidinium compound **2** (240 mg) and

(58) Ferris, J. P.; Huang, C. H.; Hagan, W. J., Jr. *Nucleosides Nucleotides* **1989**, *8*, 407−414.

isomer **10** (245 mg). Thus, the overall yield of bicyclic guanidinium compound **2** in two steps was 45% along with 20% structural isomer **10**.

**2.** $C_{41}H_{53}N_3O_2Si_2$·HI (MW 804.0). HPLC analysis: $R_v$ = 14 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer. MS-ESI $m/z$ = 676.6 [$(M + H)^+$, 100]. HRMS (micrOTOF-Q) calcd for $C_{41}H_{53}N_3O_2Si_2^+$ 676.3749, found 676.3733. $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 8.07 (s, 2H, guanidinium-*H*), 7.61−7.64 (m, 8H, aromatic), 7.36−7.43 (m, 12H, aromatic), 3.77−3.81 (m, 2H, −C*H*CH$_2$−), 3.58−3.62 (m, 4H, −C*H*$_2$OSi−), 3.11−3.24 (m, 4H, −NC*H*$_2$−), 1.89−1.99 (m, 4H, −CHC*H*$_2$−), 1.06 (s 18H, t-butyl-C*H*$_3$). $^{13}$C NMR (62.9 MHz; $CDCl_3$): $\delta$ = 151.1 (guanidinium carbon), 135.6, 132.4, 130.0, 130.1, 127.9 (aromatic carbons), 65.3 (−CH$_2$OSi−), 49.4 (−*C*HCH$_2$−), 45.0 (N-*C*H$_2$), 26.9 (tert-butyl-*C*H$_3$), 22.7 (−CH*C*H$_2$−), 19.2 (quaternary carbons).

**(2*S*,6*R*)-2,6-Di[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydroperchlorate 10.** $C_{41}H_{53}N_3O_2Si_2$·$HClO_4$ (MW 776.51). HPLC analysis: $R_v$ = 16 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, UV254 nm, flow = 1 mL/min, gradient from 80% $CH_3OH$ to 90% $CH_3OH$ in 5 min and then 90% $CH_3OH$ for 10 min more, 0.1% TFA as a buffer. MS-ESI: $m/z$ = 676.6 [$(M + H)^+$, 100]. $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 7.59−7.62 (m, 8H, aromatic), 7.34−7.48 (m, 12H, aromatic), 6.98 (d, 1H, guanidinium), 6.72 (bs, 1H, guanidinium), 3.49−3.69 (m, 5H, −C*H*$_2$OSi− + −C*H*CH$_2$−), 3.42 (m, 1H, −C*H*CH$_2$−), 3.07−3.30 (m, 4H, −NC*H*$_2$−), 1.70−1.97 (m, 4H, −CHC*H*$_2$−), 1.05 (2s, 18H, tert-butyl-C*H*$_3$). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$ = 150.7 (guanidinium carbon), 135.5, 135.4, 132.6, 132.3, 130.2, 130.2, 128.0, 127.8 (aromatic carbons), 65.2, 63.0 (−CH$_2$OSi−), 57.0, 50.0 (−CHCH$_2$−), 44.3, 35.1 (−NCH$_2$−), 26.7, 26.7 (tert-butyl-*C*H$_3$), 22.7, 21.5 (−CH*C*H$_2$−), 19.0, 19.0 (quaternary carbons).

**(2*S*,8*S*)-2,8-Dihydroxymethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydrochloride 13.** To a solution of the bicyclic guanidinium iodide **6** (1.0 g, 1.24 mmol) in dry THF (25 mL) were added triethylamine hydrochloride (513 mg, 3.73 mmol) and fluoride (1.25 g, 3.73 mmol) supported on polymer. The suspension was stirred at room temperature. In the initial 2 h of stirring, the reaction mixture became a clear solution with polymer bits in it. After continued stirring overnight, a precipitation occurred in the reaction mixture. The precipitate was filtered off, and the residue was taken up in methanol (15 mL) and stirred vigorously for 15 min. Filtration separated the product solution from the polymer, which was repeatedly washed with methanol. The combined filtrates and washings were evaporated in vacuo to afford a white solid compound **13** (400 mg) (containing triethylamine hydrochloride salt). A small sample was purified for analysis using SPE, and the remainder was used as is in the further reaction without any purification.

**13.** $C_9H_{17}N_3O_2$·HCl (MW 235.7). HPLC analysis: $R_v$ = 7 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3OH$ to 50% $CH_3OH$ in 10 min and then to 90% $CH_3OH$ in next 10 min, 0.1% TFA as a buffer. MS-ESI: $m/z$ = 200.4 [$(M + H)^+$, 100]. $^1$H NMR (360 MHz; $CD_3OD$): $\delta$ = 3.6−3.7 (m, 2H, −C*H*CH$_2$−), 3.4−3.5 (m, 4H, −CH$_2$OH), 3.43−3.41 (m, 4H, −NC*H*$_2$−), 2.0−2.1 (m, 2H, −CHC*H*$_2$−), 1.85−1.80 (m, 2H, −CHC*H*$_2$−). $^{13}$C NMR (90.56 MHz; $CD_3OD$): $\delta$ = 152.4 (guanidinium carbon), 64.9 (−CH$_2$-OH), 51.6 (−CHCH$_2$), 46.4 (N-*C*H$_2$−), 23.9 (−CH*C*H$_2$−).

**(2*S*,8*S*(-2,8-Dimethylsulfonyloxymethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydrochloride 14.** The above reaction residue containing dihydroxymethylguanidinium chloride **13** (400 mg, 1.24 mmol) was suspended in dry dichloromethane (20 mL) under nitrogen atmosphere. The mixture was cooled to 0 °C in an ice bath, and triethylamine (0.520 mL, 3.72 mmol) was added. Then the solution of methanesulfonyl chloride (0.560 mL, 7.44 mmol) in dichloromethane (4 mL) was added dropwise. The initial suspension disappeared to give a clear solution, and then product started precipitating out from the reaction mixture. After being stirred for 30 min, the reaction mixture was evaporated to dryness by a jet of nitrogen and the colorless residue was used in further reaction without any purification.

**14.** $C_{11}H_{21}N_3O_6S_2$·HCl (MW 391.9). HPLC analysis: $R_v$ = 10 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3OH$ to 50% $CH_3OH$ in 10 min and then to 90% $CH_3OH$ in next 10 min, 0.1% TFA as a buffer. $^1$H NMR (360 MHz; $CD_3CN$): $\delta$ = 9.03 (bs, 2H, guanidinium), 4.27 (dd, 2H, −C*H*$_2$O−), 4.12 (dd, 2H, −C*H*$_2$O−), 3.74−3.80 (m, 2H, −C*H*CH$_2$−), 3.26−3.37 (m, 4H, −NC*H*$_2$−), 3.21 (s, 6H, −SC*H*$_3$), 2.01−2.08 (m, 2H, −CHC*H*$_2$−), 1.78−1.86 (m, 2H, −CHC*H*$_2$−); $^{13}$C NMR (90.56 MHz; $CD_3CN$): $\delta$ = 152.7 (guanidinium carbon), 71.5 (−CH$_2$O−), 48.3 (−*C*HCH$_2$−), 45.5 (−NCH$_2$−), 37.9 (−S*C*H$_3$), 22.6 (−CH*C*H$_2$−).

**(2*S*,8*S*)-2,8-Diazidomethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidine Hydroperchlorate 15.** The reaction residue obtained above containing the bicyclic guanidinium compound **14** (1.24 mmol) was dissolved in absolute DMF (20 mL), and finely powdered sodium azide (1.5 g, 23 mmol) was added. The mixture was stirred in an oil bath at 90 °C. After being stirred overnight, the reaction mixture was cooled to room temperature and then DMF was removed under reduced pressure. The solid residue obtained was taken up in dichloromethane (20 mL), and the insoluble part was filtered and washed with dichloromethane (2 × 10 mL). The combined dichloromethane layers were washed with nearly saturated aqueous $NaClO_4$ solution (2 × 30 mL), dried over magnesium sulfate, and evaporated in vacuo to leave a gummy substance which was recrystallized from methanol/water to furnish bisazide **15** (260 mg, 60% over three steps) as a colorless crystalline compound.

**15.** $C_9H_{15}N_9$·$HClO_4$ (MW 349.7). HPLC analysis: $R_v$ = 12 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3OH$ to 50% $CH_3OH$ in 10 min and then to 90% $CH_3OH$ in next 10 min, 0.1% TFA as a buffer. IR (methanol) $\nu$: 2109 $cm^{-1}$ ($N_3$).

**(2*S*,8*S*)-2,8-Diaminomethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidine Hydroperchlorate 11.** To a solution of bisazide **15** (260 mg, 0.74 mmol) dissolved in methanol (25 mL) was added 10% Pd−C (50 mg).The suspension was stirred at room temperature under an atmosphere of $H_2$. After being stirred for 3 h, the reaction mixture was filtered through a pad of Celite, and the evaporation of filtrate gave bisaminoguanidinium compound **11** (211 mg, 95%) as a gummy substance which solidified on standing.

**11.** $C_9H_{19}N_5$·$HClO_4$ (MW 297.7). HPLC analysis: $R_v$ = 4 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3OH$ to 50% $CH_3OH$ in 10 min and then to 90% $CH_3OH$ in next 10 min, 0.1% TFA as a buffer. MS-ESI $m/z$ = 198.3 [$(M + H)^+$, 100]. HRMS (micrOTOF-Q) calcd for $C_9H_{20}N_5^+$ 198.1713, found 198.171. $^1$H NMR (360 MHz; $CD_3OD$): $\delta$ = 3.33−3.42 (m, 6H, −C*H*CH$_2$−, −C*H*$_2$NH$_2$), 2.68−2.83 (m, 4H, −NC*H*$_2$−), 2.05−2.10 (m, 2H, −CHC*H*$_2$−), 1.80−1.89 (m, 2H, −CHC*H*$_2$−). $^{13}$C NMR (90.56 MHz; $CD_3OD$): $\delta$ = 152.3 (guanidinium carbon), 51.8 (−CHCH$_2$−), 46.3 (−CH$_2$NH$_2$), 46.1 (−NCH$_2$), 24.7 (−CH*C*H$_2$−).

**5-Nitroisophthalic Acid Dichloride 17.** To a suspension of 5-nitroisophthalic acid **16** (20 g, 95 mmol) in dry dichloromethane (120 mL) under nitrogen was added dropwise oxalyl chloride (75 mL, 393 mmol). Then DMF (0.5 mL) was added cautiously to the reaction mixture. After the reaction mixture was stirred for 22 h at room temperature, a clear solution was obtained. The evaporation of excess oxalyl chloride and solvent left a solid residue, which was recrystallized, from carbon tetrachloride to afford **17** (12 g, 51%) as colorless crystalline substance.

**17.** $C_8H_3Cl_2NO_4$ (MW 248.0). Mp: 60 °C ($CCl_4$) (lit.[59] mp 59−61 °C). $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 9.20 (d, $J$ = 1.52 Hz,

(59) Baek, J.-B.; Tan, L.-S. (United States Air Force, U.S.A.). Pat. Appl. US US 2003, 6 pp.

2H), 9.10 (t, $J$ = 1.52 Hz, 1H). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$ = 165.8 (*C*O), 149.0, 137.6, 136.2, 131.0 (aromatic carbons).

**5-Nitroisophthalic Acid Azide 18.**[60] To a solution of acid chloride **17** (5 g, 20 mmol) dissolved in dichloromethane (100 mL) under nitrogen was added trimethylsilyl azide (12 mL, 80 mmol). After being stirred for 16 h at room temperature, the excess trimethylsilyl azide and solvent were removed under reduced pressure to obtain the acid bisazide **18** (4.8 g, 92%) as colorless residue which was pure enough to be used in the next step without any purification.

**18.** $C_8H_3N_7O_4$ (MW 261.1). $^1$H NMR (360 MHz; $CDCl_3$): $\delta$ = 9.05 (d, $J$ = 1.1 Hz, 2H), 8.94 (t, $J$ = 1.1 Hz, 1H). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$ = 169.6 (*C*O), 148.7, 135.0, 133.2, 128.7 (aromatic carbons).

**1,3-Diisocyanato-5-nitrobenzene 12.**[42,60] The solution of bisazido compound **18** (4.8 g, 18.4 mmol) in dry toluene (100 mL) was slowly added to an empty round-bottom flask preheated in an oil bath at 110 °C. The evolution of nitrogen was observed which seized after 1 h of addition. The reaction mixture was then cooled to room temperature and solvent was removed under reduced pressure to yield a yellowish solid residue. The residue was recrystallized from petroleum ether at −20 °C to afford white crystals of **12** (2.6 g, 70%), which turn slightly yellowish on standing. This solid can be sublimed at 80 °C/ 0.1 Torr to get white crystalline compound.

**12.** $C_8H_3N_3O_4$ (MW 205.13). Mp = 80−81 °C (petroleum ether). IR ($CCl_4$) $\nu$: 2255 cm$^{-1}$ (NCO). $^1$H NMR (360 MHz; $CDCl_3$): $\delta$= 7.79 (d, $J$ = 1.97 Hz, 2H), 7.14 (t, $J$ = 1.97 Hz, 1H). $^{13}$C NMR (90.56 MHz; $CDCl_3$): $\delta$= 149.4 (*C*O), 136.0, 126.5, 125.8, 117.2 (aromatic carbons).

**Macrocycle 4.** To the mixture of bisaminoguanidinium compound **11** (105 mg, 0.35 mmol) and EDIPA (0.25 mL, 1.5 mmol) in DMF (25 mL) under nitrogen atmosphere cooled in an ice salt bath was added the solution of freshly sublimed bisisocyanato reagent **12** (75 mg, 0.36 mmol) dissolved in dry dichloromethane (7 mL) over a period of 1.5 h using a syringe pump. After complete addition of reagent, the reaction mixture was allowed to warm slowly to room temperature and then quenched by addition of TFA (0.25 mL). The removal of solvent under reduced pressure left a yellowish residue. The residue was taken up in $CH_3CN$ (10 mL) and filtered to remove most of the polymeric impurities. The filtrate was concentrated to half of its volume, and then dilution with water resulted in precipitation of the product. The precipitate was filtered, washed with water (5 mL), and dried to get yellow powder (90 mg), which was then subjected to reversed phase MPLC using 30% acetonitrile/water along with 0.5% TFA. The fractions containing the product were pooled and concentrated to get a yellow solid (34 mg, 10%). This solid was dissolved in 70% acetonitrile/water mixture and passed through an anion exchange resin (AG 4-x4) containing iodide as a counterion. The evaporation of solvent gave **4** as a yellow solid.

**4.** $C_{34}H_{44}N_{16}O_8$·2HI (MW 1060.6). HPLC analysis: $R_v$ = 13 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3CN$ to 50% $CH_3CN$ in 10 min and then to 90% $CH_3CN$ in next 10 min, 0.1% TFA as a buffer. MS-ESI: $m/z$ = 919.1 [(M + TFA)$^+$, 100], 805.3 (M$^+$, 75), 403.3 (M$^{2+}$, 50). HRMS (micrOTOF-Q) calcd for $C_{34}H_{46}N_{16}O_8^{2+}$ 403.1842, found 403.1839. $^1$H NMR (250 MHz; DMSO-$d_6$): $\delta$ = 9.35(bs, 4H, amide protons), 8.06 (bs, 4H, aromatic protons), 7.7(m, 2H, aromatic protons), 7.3(m, 4H, amide protons), 6.05(bs, 4H, guanidinium protons), 3.5−3.1(m, 20H, -aliphatic), 2.14−1.91 (m, 4H, aliphatic), 1.83−1.61 (m, 4H, aliphatic). $^{13}$C NMR (90.55 MHz; DMSO-$d_6$): $\delta$ = 155.3 (−CO−), 150.5 (guanidinium carbons), 148.4, 141.6, 111.7, 104.9 (aromatic carbons), 48.1 (−$CHCH_2$−), 45.0 (−$NCH_2$), 43.2 (−$CHCH_2NH$−), 23.6 (−$CHCH_2$−).

**(2*S*,8*S*)-2,8-Bis[[3-(3-nitrophenyl)ureido]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydroiodide 3.** To the bisaminoguanidinium compound **11** (105 mg, 0.35 mmol) in the mixture of dry DMF (5 mL) and 10 mL of dry toluene under nitrogen atmosphere was added the solution of freshly distilled reagent **36** (150 mg, 0.9 mmol) dissolved in dry toluene (7 mL). After complete addition of reagent, the reaction mixture was at first heated at 100 °C for 15 min and then stirred at rt for 2 h. The removal of solvent under reduced pressure left a yellowish residue. The residue was taken up in $CH_3CN$ (10 mL) and kept at −20 °C where unwanted urea impurity crystallizes out leaving behind desired compound **3** in the solution. Further purification was obtained by SPE (50% acetonitrile/water as an eluent). The fractions containing the product were pooled and concentrated to get a yellow solid. This solid was dissolved in 70% acetonitrile/water mixture and passed through an anion exchange resin (AG 4-x4) containing iodide as a counterion. The evaporation of solvent gave **3** as a yellow solid (160 mg, 85% yield).

**3**. $C_{23}H_{28}N_9O_6$·HI (MW 653.1). HPLC analysis: $R_v$ = 18 mL, RP Aqua $C_{18}$, 250 × 4.60 mm, 5 $\mu$m column, $UV_{254}$, flow = 1 mL/min, gradient from 10% $CH_3CN$ to 50% $CH_3CN$ in 10 min and then to 90% $CH_3CN$ in next 10 min, 0.1% TFA as a buffer. MS-ESI: $m/z$ = 526.4 [M$^+$, 100]. HRMS (micrOTOF-Q) calcd for $C_{23}H_{28}N_9O_6^+$ 526.2163, found 526.2167. $^1$H NMR (360 MHz; $CD_3CN$): $\delta$ = 8.40(t, 2H, $J$ = 2.15 Hz, aromatic protons), 8.32 (s, 2H, amide H), 7.72−7.69 (m, 2H, aromatic protons), 7.60−7.57-(m, 2H, aromatic protons), 7.36 (t, 2H, $J$ = 8.17 Hz, aromatic protons), 6.95(bs, 2H, guanidinium protons), 6.13 (t, 2H, $J$ = 5.8 Hz, amide H), 3.56−3.51 (m, 2H, −$CHCH_2$−), 3.40−3.21 (m, 8H, −aliphatic), 2.04−1.98 (m, 2H, aliphatic), 1.81−1.71 (m, 2H, aliphatic). $^{13}$C NMR (90.56 MHz; $CD_3CN$): $\delta$ = 156.7 (−*C*O−), 152.0 (guanidinium carbon), 149.5, 142.1, 130.6, 124.8, 117.3, 113.3 (aromatic carbons), 50.2 (−*C*$HCH_2$−), 46.2 (−$NCH_2$), 44.1 (−$CHCH_2NH$−), 24.5 (−$CHCH_2$−).

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**Supporting Information Available:** General experimental methods and materials, copies of $^1$H and $^{13}$C NMR and mass spectra for all of the compounds described in the Experimental Section and isothermal calorimetric titration experimental graphs corresponding to the entries depicted in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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