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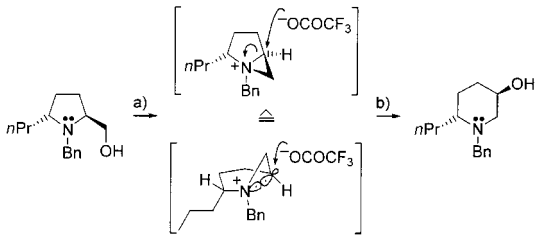
[11] Structure **9** appears in electronic data bases: Beilstein Commander 4.0, search March **1999**.
[12] Cossy and her co-workers have reported the ring enlargement of an L-proline derivative in the synthesis of (−)-pseudoconhydrine (Scheme 6):



Scheme 6. Top: inside-flap attack, bottom: S_N2-type attack; a) $(CF_3CO)_2O$, then Et_3N; b) NaOH.

J. Cossy, C. Dumas, D. G. Pardo, *Synlett* **1997**, 905; further recent examples: J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, J. Martens, *Liebigs Ann.* **1997**, 573 and references therein.
[13] Bicyclic systems with strained bridgehead imine double bonds (*E* and *Z* isomers) have been obtained in a matrix in the dark at low temperature: a) R. S. Sheridan, G. A. Ganzer, *J. Am. Chem. Soc.* **1983**, *105*, 6158; b) J. G. Radziszewski, J. W. Downing, C. Wentrup, P. Kaszynski, M. Jawdosiuk, P. Kovacic, J. Michl, *J. Am. Chem. Soc.* **1985**, *107*, 2799.
[14] J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83.
[15] P. Rabe, *Chem. Ber.* **1908**, *41*, 62.
[16] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data centre as supplementary publication nos. CCDC-115800 (**7**), -115801 (**8**), and 115802 (**2c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Small-Molecule Guanidinium Receptor: The Arginine Cork**

Thomas W. Bell,* Alisher B. Khasanov, Michael G. B. Drew, Anton Filikov, and Thomas L. James

Individual arginine residues are critical to the function of many nucleotide-binding proteins.[1, 2] Small-molecule receptors capable of binding the *N*-alkylguanidinium moiety of arginine could be used in numerous ways, such as antiviral drugs and molecular probes for arginine-rich proteins. Reported herein is a designed, small-molecule receptor that binds *N*-alkylguanidinium cations. Binding selectivity for arginine, relative to lysine, is observed in water and methanol solvents. The solid-state structure of its complex with two *N*-alkylguanidinium cations suggests that it should have a special affinity for the dipeptide ArgArg, and this prediction has been confirmed by microcalorimetric titration in water.

The amino acid arginine is a critical component of many RNA-binding proteins that mediate a wide range of biological processes.[1, 2] While the "basic-domain" class of RNA-binding proteins contain arginine-rich sequences of 10–15 amino acids, highly conserved arginine residues often make specific electrostatic contacts with phosphate groups in the polyribonucleotide backbone. Two examples of such proteins that regulate important steps in the replication of the human immunodeficiency virus type I (HIV-1) are the transcriptional activator Tat[1–4] and the Rev protein.[1, 2, 5] The recently determined structure of the HIV-1 nucleocapsid protein bound to the genomic Ψ-RNA recognition element[6] displays a specific arginine–base interaction (Arg32−A8). RNA recognition processes have become important targets for the development of antiviral and antibiotic drugs.[7, 8] Small molecules tailored to bind specifically to arginine residues could lead to novel pharmaceuticals, as well as molecular probes that could facilitate the characterization of RNA-binding proteins.

There have been a few reports of artificial receptors that bind arginine or arginine derivatives,[9–11] but what is the best design for the recognition of the arginine side chain in peptides? To be useful for biological applications, such a receptor must be reasonably soluble in water, it must have high affinity for the *N*-alkylguanidinium moiety, and it must display selectivity relative to other cations, particularly versus the *N*-alkylammonium side chain of lysine. We can recognize arginine by means of a hydrogen-bond array that either imitates one of the natural patterns or seeks to improve on nature by de novo design. By following the former biomimetic route Schrader[11] synthesized "molecular tweezers" containing two phosphonate groups capable of binding guanidinium cations by four hydrogen bonds (Figure 1a). The structure of the resulting complex resembles that of the critical arginine residue of Tat (Arg 52) bound to phosphodiesters P22 and P23 of HIV-1 TAR RNA, a feature dubbed the "arginine fork" (Figure 1b) by Frankel et al.[3] Despite the presence of electrostatic interactions between the guanidinium cation and two anionic phosphonate groups of molecular tweezer **2**, only modest binding was observed, even in methanol ($K_d \approx$ 2 mM). This can be attributed to incomplete preorganization of the hydrogen-bond acceptor sites in **2**.

Most receptors designed for the guanidinium cation are flexible crown ether derivatives.[9, 12–16] Our approach to recognition of small, planar molecules is to construct a relatively rigid, planar array of hydrogen-bonding groups by fusing together a series of six-membered rings.[17–23] Nearly perfect host–guest complementarity results from registry between the N−N and N−O hydrogen bond distances and the

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Supporting Information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

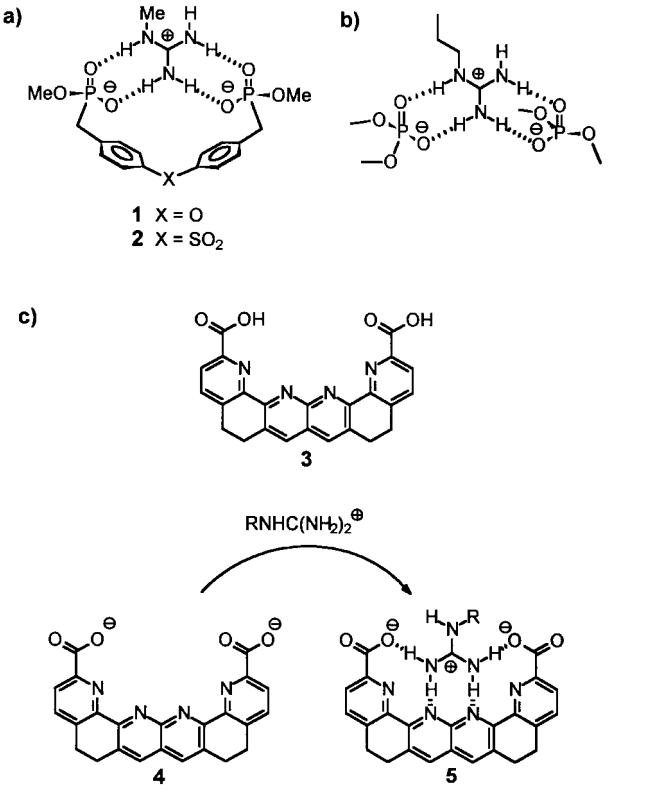
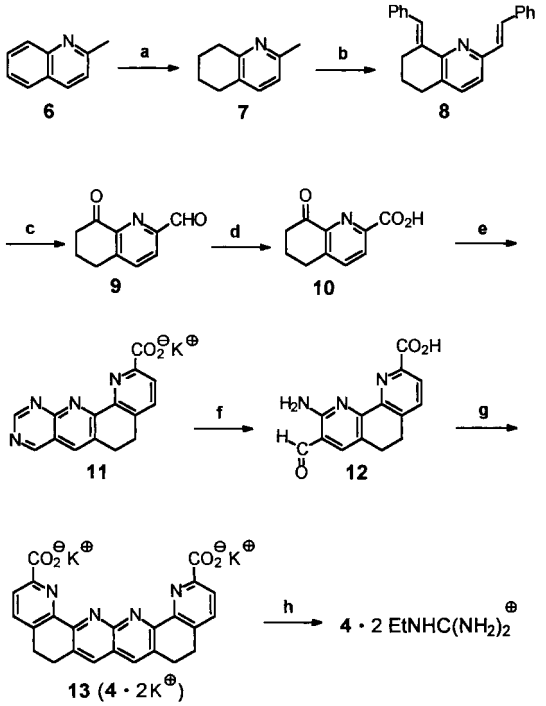


Figure 1. Postulated structures of guanidinium complexes. a) Complexes between *N*-methylguanidinium and "molecular tweezers";[11] b) the "arginine fork" of the complex formed between the HIV-1 Tat and TAR;[3, 4] c) the target arginine receptor in the dicarboxylic acid (**3**) and dianion (**4**) forms, and complex of an *N*-alkylguanidinium guest (**5**).



Scheme 1. Synthesis of the target arginine receptor as the dipotassium salt (**13**). Conditions: a) H_2 (1 atm), 10% Pd/C, CF_3CO_2H, 20 °C; b) benzaldehyde, Ac_2O, 150–160 °C; c) 1) O_3/O_2, CH_2Cl_2/CH_3OH, −77 °C; 2) Me_2S, CH_2Cl_2/CH_3OH, −77 → 20 °C; d) CrO_3/H_2SO_4, $(CH_3)_2CO$, 20 °C; e) 4-amino-5-pyrimidinecarbaldehyde,[26] KOH, CH_3OH, reflux; f) HCl, H_2O, reflux; g) **10**, KOH, EtOH, reflux; h) ethylguanidinium sulfate, H_2O, reflux. See Supporting Information for microanalytical and spectroscopic details on **13**.

host hexagonal lattice distance (determined by C–N and C–C covalent bonds), which bear an approximate 2:1 relationship. Previously reported hexagonal lattice receptors, including a guanidinium-binding torand,[19] are neutral molecules with hydrophobic *n*-alkyl side chains. Such compounds are useful as extractants and membrane transport agents,[17, 18] but their poor water solubilities limit homogeneous binding studies to organic solvents. The dicarboxylic acid **3**, which lacks alkyl side chains, was expected to be soluble in water, particularly in the dianionic form **4** (Figure 1c). The nitrogen and oxygen hydrogen-bond acceptor sites in **4** are preorganized for binding *N*-alkylguanidinium cations to form complex **5**. Electronic interactions (conjugation) between the carboxylate groups and the neighboring pyridine rings should stabilize the coplanar conformation. Rotation about the pyridine–carboxylate bond is expected, but identical structures are produced as a result of the symmetry of the carboxylate group. The combination of receptor preorganization and attractive electrostatic interactions between the dianionic host and cationic guest led to our hypothesis that complexes of type **5** would be stable, even in aqueous media.

The target arginine receptor was synthesized in seven steps as the dipotassium salt **13** (Scheme 1). The benzene ring of quinaldine (**6**) was selectively reduced by catalytic hydrogenation with palladium-on-carbon in trifluoroacetic acid, by using a modification of the procedure of Vierhapper and Eliel.[24] Condensation of **7** with benzaldehyde in acetic anhydride gave dibenzylidene derivative **8**, which was conveniently purified by vacuum distillation. Ozonolysis[25] of **8** gave ketoaldehyde **9**, which underwent Jones oxidation to ketoacid **10**. Friedländer condensation of **10** with 4-aminopyrimidine-5-carbaldehyde[26] gave **11**, which was hydrolyzed to the aminoaldehyde **12**. A second condensation of **10** with **12** gave receptor **13**, which was purified by recrystallization and obtained in 18% overall yield from quinaldine. The molecular symmetry of **13** results from the use of the same ketone (**10**) in both Friedländer condensations (steps e and g), but two different ketones could be used to make unsymmetrical molecules of type **13** bearing functional groups other than carboxylate. This route could also be used for the preparation of arginine receptors that are substituted to allow immobilization, attachment of other recognition sites, or conjugation to biomolecules.

As anticipated, dipotassium salt **13** has a relatively high solubility in water (about 0.3 M). It is slightly soluble in methanol and insoluble in dimethyl sulfoxide (DMSO), dichloromethane, and chloroform. The corresponding carboxylic acid (**3**) has very low water solubility (about 4 μM), but it is moderately soluble in DMSO. The ability of **13** to bind *N*-alkylguanidines was tested by mixing an aqueous solution with a dilute solution of ethylguanidinium sulfate in water, which resulted in the formation of a yellow precipitate. Crystals of this complex formed when a hot aqueous solution was cooled to room temperature but crumbled upon drying under vacuum or in air. According to results of combustion microanalysis and ^1H NMR spectroscopy dried samples of the

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complex consisted of the receptor dianion (**4**) and *N*-ethylguanidinium cation in exactly a 1:2 ratio. This stoichiometry is expected for a simple salt of a dicarboxylic acid with a base, but the predicted binding motif (**5**, Figure 1c) was proven by X-ray crystallographic analysis[27] of a single crystal of hydrated complex [**4**·2 EtNHC$(NH_2)_2^+$].

In the solid-state structure of the complex (Figure 2) one of the two *N*-ethylguanidinium cations resides in the receptor cleft, as expected. The second cation binds externally to one of

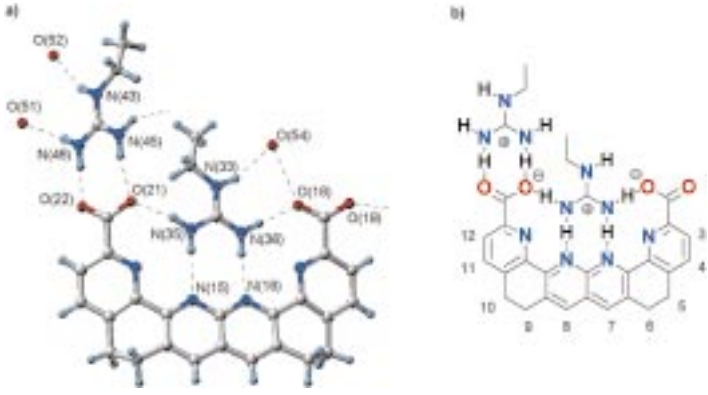

Figure 2. The crystal structure of [**4**·2 EtNHC$(NH_2)_2^+$] showing the receptor molecule and the two *N*-ethylguanidinium cations. Also shown are three water molecules that act as hydrogen bond acceptors for three N–H donors of the cations. The fourth water molecule (not shown) is hydrogen bonded only to other water molecules. Hydrogen bonds are shown as dotted lines. a) Conformation of the complex in the crystal; b) diagram representing the idealized structure of the complex.

the two carboxylate groups. The receptor is not completely planar, but is folded to form a structure with approximate mirror symmetry (Figure 2a). Figure 2b is an idealized version of the structure showing the positions of the two *N*-ethylguanidinium cations and the pattern of hydrogen bonds. The hydrogen-bonded N–O distances (2.83, 2.87 Å), and N–N distances (3.00 – 3.06 Å) are relatively small, as expected for strong hydrogen bonds. The six heteroatoms of the receptor (O(18), N(1), N(16), N(15), N(14), and O(21)) deviate only slightly from a plane (rms 0.14 Å), which intersects the plane of the cleft-bound *N*-ethylguanidinium ion (atoms N(33), C(34), N(35), and N(36)) at an angle of 6.7°. This good fit is aided by a twisting of the carboxylate groups; thus the N(14)-C-C-O(21) and N(1)-C-C-O(18) torsion angles are 26.5 and 11.8°, respectively. It is particularly important to note that the ethyl fragments of the two guests are in close proximity, which suggests that receptor **13** might form strong complexes with the dipeptide diarginine and might recognize ArgArg sequences in proteins.

The ability of receptor **13** to bind guanidinium guests in water was examined by several methods, including ^{1}H NMR and UV/Vis spectroscopy, as well as microcalorimetry. The signals of **13** in D_2O solutions are significantly shifted in the ^{1}H NMR spectrum upon addition of guanidinium or *N*-ethylguanidinium sulfate. In the absence of guanidinium guests the ^{1}H NMR chemical shifts of **13** are also concentration-dependent in the range of 0.1 mM to 0.1M, which complicates the calculation of the dissociation constants. Receptor **13** and its complexes apparently aggregate in water through hydrophobic interactions between nonpolar regions of the molecule that are remote from the charged carboxylate groups. The UV/Vis absorption spectra of aqueous solutions of **13** follow Beer's Law over the concentration range of 1 – 100 μM, which suggests the absence of aggregation at low concentration. In order to understand the ionization states of **13** in water we performed a series of pH titrations and followed changes in the UV/Vis spectrum (Figure 3). Addition of HCl to aqueous solutions of **13** caused a bathochromic shift of the π-π* band ($\lambda_{max} = 384$ nm) and a loss of fine structure (Figure 3b). As previously observed for pyridine-2-carboxylic acid,[28] initial protonation apparently occurs mainly on the nitrogen atom to form a monoanion with a half-zwitterionic structure (see Figure 3a). The second protonation gives a neutral molecule, probably consisting of three forms that are in rapid equilibrium. A plot of the absorbance at 414 nm versus pH gave a titration curve that was modeled graphically (see Supporting Information) to give the equilibrium values $pK_{a1} = 4.7$ and $pK_{a2} = 6.0$. These first and second ionization constants are lower and higher, respectively, than that of pyridine-2-carboxylic acid ($pK_a = 5.2$),[28] which indicates that the two protonation sites interact significantly.

The UV/Vis absorption spectrum of receptor **13** in water or methanol is not significantly affected by complexation of guanidinium cations, so the binding of various guests was evaluated by ^{1}H NMR spectroscopy and microcalorimetry. As mentioned previously, receptor **13** aggregates in water at concentrations needed for NMR spectroscopy, so methanol was chosen as the solvent for NMR titrations. The ^{1}H NMR signals of the hydrogen atoms at positions 7 and 8 (see Figure 2b) shift downfield upon complexation of cationic guests in CD_3OD. A sample binding isotherm is shown in Figure 3c for the complexation of the amino acid (+)-L-lysine, which bears a primary ammonium group on its side chain. The experimental data points best fit the theoretical curve calculated from a dissociation constant (K_d) of 34 μM (see Supporting Information). Similar titrations with methylguanidinium chloride or arginine gave K_d values for the 1:1 complexes that were too large to be measured accurately by this experimental method. As shown in Table 1 lower limits of 10 μM were estimated for the K_d values of these guests. Thus, receptor **13** binds guanidinium cations in methanol at least three times more strongly than a primary ammonium guest, and **13** binds the methylguanidinium cation at least 200 times more strongly than does molecular tweezer **2**.[11] Also shown in Table 1 are the corresponding K_d values in water as measured by microcalorimetry (see Supporting Information). Again, the two molecules bearing guanidinium groups (methylguanidinium and Arg) are bound by **13** more strongly than lysine, which has a primary ammonium group. Dipeptides bearing two positive charges ($ArgArgNH_2$, ArgArgOH, and LysLysOH), are all bound more strongly than the monocations (methylguanidinium, Arg, and Lys). Thus, the primary interaction between cationic guests and the dianionic receptor is electrostatic, but molecular recognition based on hydrogen-bond complementarity distinguishes between guests of the same charge. As expected from the solid-state

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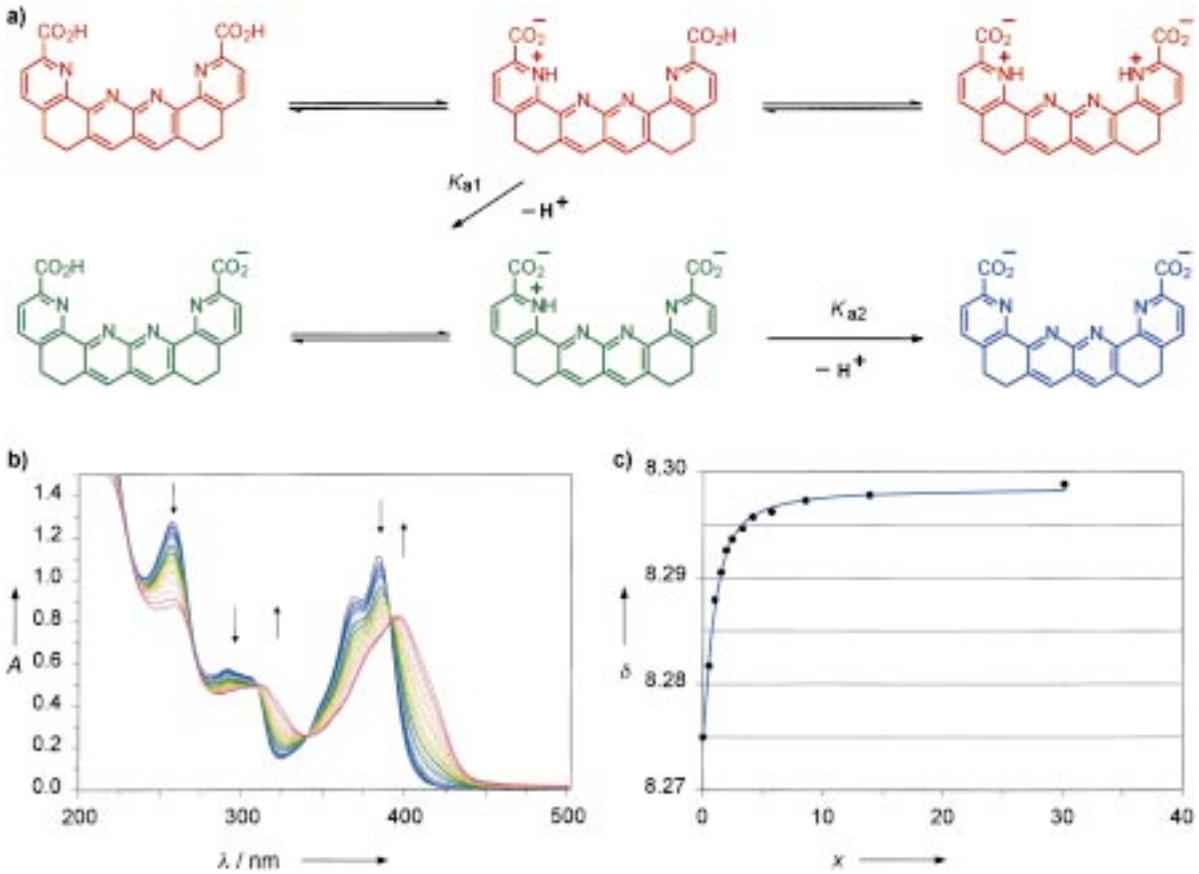

Figure 3. Acid–base and host–guest titrations of the arginine receptor. a) Ionization states and tautomeric forms, color-coded to pH titration (Figure 3b): magenta: neutral forms of dicarboxylic acid **3**, including zwitterionic tautomers; green: monoanionic forms, including half-zwitterionic tautomer; blue: dianionic form; b) UV/Vis absorption spectra of an aqueous solution of **13** (38.8 μM) during titration with aqueous HCl, color-coded to Figure 3a; c) plot of ^{1}H NMR chemical shifts of hydrogen atoms 7 and 8 of the bis(tetramethylammonium) salt of receptor **13** (see Figure 2b) as a function of lysine concentration in CD_3OD (receptor concentration: 80 μM). The solid line is the best-fit curve calculated from $K_d = 34$ μM. See Supporting Information for experimental details.

Table 1. Thermodynamic data for 1:1 complexes of receptor **13** as determined by ^{1}H NMR spectroscopic and microcalorimetric titration methods.[a]

Guest	K_d [μM] (CD_3OD)	K_d [μM] (H_2O)	ΔH° [kcal mol^{-1}] (H_2O)
methylguanidinium	≤ 10	4300 ± 400	+ 1.3 ± 0.3
arginine (Arg)	≤ 10	1100 ± 100	+ 0.49 ± 0.05
lysine (Lys)	34 ± 3	7000 ± 2000	− 0.14 ± 0.02
$ArgArgNH_2$		60 ± 6	− 5.6 ± 0.6
ArgArgOH		50 ± 20	− 2.1 ± 0.2
LysLysOH		250 ± 30	− 1.5 ± 0.2

[a] K_d = dissociation constant; ΔH° = enthalpy. Values were determined by ^{1}H NMR titration (CD_3OD) and microcalorimetry (H_2O). See Supporting Information for experimental details.

structure of the 2:1 complex of *N*-ethylguanidinium with **13** (see Figure 2), the best dipeptide guest is diarginine, which is bound with remarkably high affinity in water.

Receptor **13** binds arginine in water at least four times more strongly than does a previously reported water-soluble crown ether.[9] The aqueous binding energy of **13**·Arg (4.0 kcal mol^{-1}) is about 1 kcal mol^{-1} less than that of the Arg–NH_2 complex of a recently reported cyclophane host that binds guanidinium guests in water by a combination of salt bridge and cation–π interactions.[29] The most stable complex of this latter host with an arginine-containing dipeptide has a comparable binding energy (5.8 kcal mol^{-1}) to that of the ArgArg complex of **13**, which exhibits high selectivity for ArgArg relative to LysLys. This "arginine cork" may eventually lead to novel chemotherapeutic approaches, as mentioned previously, and it may also prove useful as a molecular probe for arginine residues. Its magnetically anisotropic aromatic rings could make it useful as an NMR probe, and by binding to arginine side chains **13** might be used to aid crystallization of "basic region" proteins. Both effects could assist the structural characterization of numerous, biologically important peptides and proteins.

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[27] Crystal data for $[\mathbf{4}\cdot 2\,EtNHC(NH_2)_2^+]$: $C_{30}H_{42}N_{10}O_8$, $M_r = 670.74$, triclinic, space group $P\bar{1}$, $a = 10.974(11)$, $b = 11.412(10)$, $c = 14.128(15)$ Å, $\alpha = 70.56(1)$, $\beta = 79.36(1)$, $\gamma = 88.51(1)^\circ$, $U = 1639$ Å^3, $Z = 2$, $\rho = 1.359$ Mg m^{-3}, $F(000) = 712$. A total of 5828 independent reflections was measured on a Marresearch Image Plate by using $Mo_{K\alpha}$ radiation. Distances are O(18)–N(36) 2.829(6), O(18)–O(54) 2.710(7), O(21)–N(35) 2.871(5), O(21)–N(45) 2.912(5), O(22)–N(46) 2.848(6), N(33)–O(54) 3.037(7), N(43)–O(52) 2.886(7), N(46)–O(51) 2.890(7), O(51)–O(52) 3.167(10), N(35)–N(15) 3.060(5), N(36)–N(16) 2.999(4) Å. Individual host and guest moieties are connected by intermolecular hydrogen bonds between O(19) and N(45) (symmetry element $1-x, -y, 2-z$), distance 2.936(6) Å, to form a helix. Other hydrogen bonds involving water molecules are also present in the unit cell (O(18)···O(52) $(2-x, -y, 2-z)$ 2.882(8), O(19)···O(53) $(x,y,1+z)$ 2.753(6), O(19)···O(51) $(x-1, y+1, z)$ 2.936(7), O(21)···O(53) $(1-x, -y, 1-z)$ 2.817(6) Å), as are water–water hydrogen bonds. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103868. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Controlled Arrangement of Supramolecular Metal Coordination Arrays on Surfaces**

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The arrangement of special functional units with nanometer dimensions into defined molecular architectures on surfaces is one of the major goals in supramolecular, polymer, and material science in view of the potential applications of these systems in nanotechnology with regards to molecular information storage devices or functional surfaces.[1] This requires a precise control of the structures at very different length scales ranging from molecular size to micrometers. One promising approach for the construction of nanometric size objects comes from supramolecular chemistry.[1] It has been demonstrated in the last few years that information stored in molecular components can be read out by noncovalent interactions, for example, hydrogen-bonding[2] or metal-ligand[3] interactions, to assemble the final well-ordered architectures. Recently a new class of coordination arrays presenting a two-dimensional $[2 \times 2]$ grid-type architecture based on transition metal ions with octahedral coordination geometry was described (Figure 1a).[4, 5] These complexes were found to present interesting electronic, magnetic, and structural properties, such as electronic interactions between the metal centers and an antiferromagnetic transition at low temperatures[5, 6] (Figure 1b). They are formed by the spontaneous self-assembly of 4,6-bis(2′,2″-bipyridyl-6-yl)pyrimidine ligands[4] (or its functionalized derivatives[7]) and suitable metal ions such as Co^{II} (Figure 1a).[5]

Besides the design and synthesis of "isolated" grid units, the ordered and stable arrangement of such metallo-supramolecular architectures on surfaces or in thin films is of special

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