

Two-Component Supramolecular Gels Derived from Amphiphilic Shape-Persistent Cyclo[6]aramides for Specific Recognition of Native Arginine**

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Abstract: A unique supramolecular two-component gelation system was constructed from amphiphilic shape-persistent cyclo[6]aramides and diethylammonium chloride (or triethylammonium chloride). This system has the ability to discriminate native arginine from 19 other amino acids in a specific fashion. Cyclo[6]aramides show preferential binding for the guanidinium residue over ammonium groups. This specificity was confirmed by both experimental results and theoretical simulations. These results demonstrated a new modular displacement strategy, exploring the use of species-binding hydrogen-bonded macrocyclic foldamers for the construction of two-component gelation systems for selective recognition of native amino acids by competitive host–guest interactions. This strategy may be amenable to developing a variety of functional two-component gelators for specific recognition of various targeted organic molecular species.

Supramolecular gels represent one of the most important soft materials using noncovalent interactions (hydrogen bonding, π – π interactions, metal–ligand coordination, van der Waals forces, and hydrophobic effects) for forming nanofibrillar structures able to “freeze” solvents in the rigid gel framework.^[1] Their many functional applications of interest include recognition,^[2] drug delivery,^[3] tissue engineering,^[4] catalysis,^[5] and crystal growth,^[6] as a result of their built-in specific responsiveness toward external stimuli and their

ability to adapt to their surroundings. Particularly, multi-component gelation systems where two or more constructing species interact through noncovalent or covalent forces to form a gel have shown significant advantages, such as the ready adjustment of gel performance and in exquisite microstructural tunability,^[7] while providing an additional level of control in the hierarchical assembly process. Two-component gel systems have been widely investigated with diverse scaffolds,^[8,9] among which comparatively fewer are fabricated with macrocyclic compounds, such as crown ether,^[10] calixarene,^[11] porphyrin,^[12] cyclodextrin,^[13] cucurbituril,^[14] pillararene,^[15] and other cyclic species.^[16] Some recently reported macrocycle-based two-component gelation systems did exhibit stimuli-responsive sol–gel transitions that however were induced by the competitive binding of guests of different types in an indiscriminate fashion.^[13a,15b]

Shape-persistent aromatic oligoamide macrocycles^[17] have emerged as a new class of host molecules concomitant with the development of their acyclic analogues.^[18] These macrocycles feature full amide linkages with backbones enforced by intramolecular hydrogen bonds. Among these systems, those developed by Gong and co-workers are particularly intriguing in view of the simplicity of synthesis and the high-yield production of the circular products.^[19] We recently demonstrated that these highly efficient kinetic macrocyclization reactions arise from both the hydrogen-bonded backbones and the remote steric effect.^[20] With their shape-persistent aromatic surfaces, the macrocycles carrying extra-annular alkyl side chains are prone to self-aggregation in both polar and nonpolar solvents as a consequence of the cooperative action of dipole–dipole and π – π stacking interactions.^[21] With their correctly arranged amide oxygen atoms pointing inwards, the near-planar six-residue macrocycles,^[22] dubbed cyclo[6]aramides, have shown highly selective recognition of guanidinium ions,^[23] efficient separation of metal ions,^[24] and a high affinity for dialkylammonium salts.^[25] Remarkably, a cyclo[16]aramide with a larger nanosized cavity could accommodate even a depsipeptide antibiotic valinomycin.^[26] However, these macrocycles have never been employed as gelators to construct two-component gelation systems for selective recognition of molecular species.

Protein α -amino acids are considered as fundamental constituents of a wide variety of biomolecules. In this family, arginine is essential to the functioning of polypeptides such as enzymes and antibodies.^[27] It also plays an important role as the precursor for nitric oxide in arginine metabolism.^[28] Despite much progress made in the recognition of amino

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acids and their derivatives by small neutral molecules and macrocycles,^[27,29] the use of macrocycle-based gels for distinguishing native or modified amino acids is rather rare.^[11b] There are few examples of 2D planar (or near-planar) shape-persistent macrocyclic compounds, such as arylene ethynylene macrocycles and macrocyclic fluoropentamers, that are able to act as gelators,^[30] none of which have demonstrated any recognition ability for amino acids. Herein, we present a modularly tunable strategy for constructing supramolecular two-component gelation systems based on amphiphilic shape-persistent cyclo[6]aramide **1** and diethylammonium chloride (DEA-HCl) or triethylammonium chloride (TEA-HCl) (Figure 1; for synthesis see the Supporting Information),

Table 1: Minimum gelation concentrations for **1**, **1**·DEA-HCl, and **1**·TEA-HCl in various organic solvents at 25 °C.^[a]

Entry	solvent	1	1 ·DEA-HCl	1 ·TEA-HCl
1	methanol	I	0.78	1.29
2	THF	I	1.08	3.06
3	ethanol	I	0.89	1.00
4	acetonitrile	P	1.16	1.27
5	<i>i</i> -propanol	I	1.30	2.19
6	<i>n</i> -propanol	I	0.79	0.91
7	<i>n</i> -butanol	I	0.78	0.90

[a] [Guest]/[Host] given in (wt%), where the guest molecule is DEA-HCl or TEA-HCl. P = precipitation, I = insoluble.

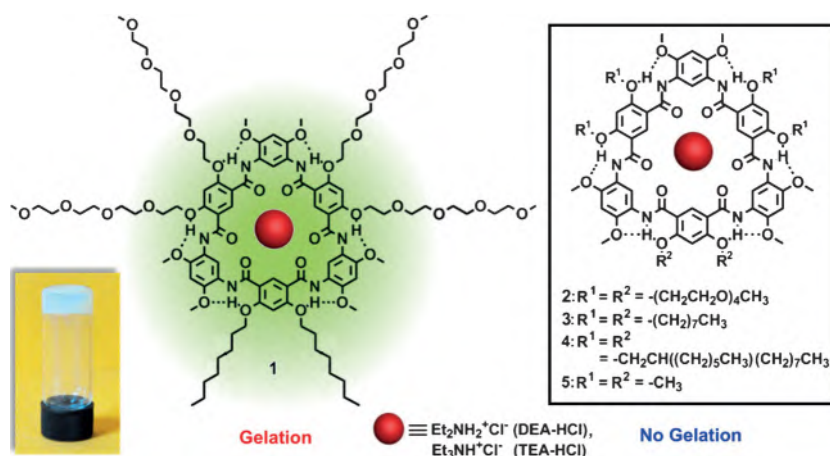


Figure 1. Two-component gelation systems consisting of amphiphilic cyclo[6]aramide **1** and DEA-HCl (or TEA-HCl) salts. Alternative cyclo[6]aramides **2–4** failed to undergo gelation in methanol in the presence of ammonium salts.

and their ability to specifically recognize arginine through a competitive displacement process. To our knowledge, this work represents the first example employing two-component gelation systems based on macrocycles for visual specific discrimination of organic guests, specifically native amino acids in this work.

Cyclo[6]aramide **1** was insoluble in methanol, and unable to form a gel. Simply by mixing DEA-HCl in methanol with **1**, a clear solution formed after heating at circa 65 °C, and it turned into a thermoreversible gel within several minutes upon cooling. Use of TEA-HCl led to a similar gelation result. In stark contrast to **1**, compound **2** with six tetraethylene glycol (TEG) side chains and **3** (or **4**) bearing six alkyl groups (Figure 1) did not undergo gelation in methanol in the presence of DEA-HCl or TEA-HCl under identical conditions. This difference in gelation behavior suggests the important role played by the peripherally located amphiphilic side chains of **1** (i.e., TEG and alkyl groups) in inducing gel formation. The results of gelation tests for the ability of **1** to form gel-phase materials in the presence of the second component, alkylammonium chloride, are summarized in Table 1. In general, **1** entraps polar solvents more efficiently with DEA-HCl as the second component than TEA-HCl. For example, the minimum gelation concentration (MGC) in

methanol was found to be 0.78% in the presence of DEA-HCl and increases to 1.29% using TEA-HCl (Entry 1, Table 1). The higher gelation ability of **1** with DEA-HCl may result from an enhanced binding of the less sterically crowded cation $Et_2NH_2^+$ of DEA-HCl compared to the larger Et_3NH^+ of TEA-HCl through charge-assisted hydrogen bonds that facilitate intermolecular aromatic stacking. The likely species responsible for gel formation was revealed by mass spectrometry to be a 1:1 ratio of the host–guest complex [**1**·DEA + H]⁺ (Figure S16a in the Supporting Information). The two-dimensional NOESY spectrum of a solution of an equimolar mixture of **1** and DEA-HCl in a solvent mixture of CD_3OD and $CDCl_3$ (4:1, v/v) disclosed correlations between the signals attributable to the interior aromatic

protons of **1** and alkyl protons *l* or *m* from DEA-HCl (Figure S19). No NOE correlations between signals attributable to the exterior aromatic protons and peripheral side chain protons of **1** and the protons denoted *l* or *m* were detected. In the case of TEA-HCl, similar results were obtained (see Figures S16b and S18). These results suggest that alkylammonium ions are bound inside the cavity of **1** instead of locating about the periphery of **1**. Note, molecule **1** is unable to gelate in nonpolar solvents such as dichloromethane, chloroform, and 1,2-dichloroethane with or without DEA-HCl or TEA-HCl.

Since the oxygen atoms from both the four TEG ether side chains and internal amide carbonyl groups in **1** may interact with ammonium ions, it is possible for one macrocyclic molecule to bind more than one alkylammonium ion. Thus, we first examined the dependence of the gel–sol transition temperature (T_{gel}) on different ratios of **1** to DEA-HCl to determine the stoichiometry of the complex responsible for gelation in methanol. As shown in Figure 2, the T_{gel} values increases rapidly with increasing additions of DEA-HCl, and reaches a plateau value with after the addition of 1 equivalent of the ammonium salt. Further additions of ammonium ions did not lead to a further increase in thermal stability. In the case of TEA-HCl, a similar trend was

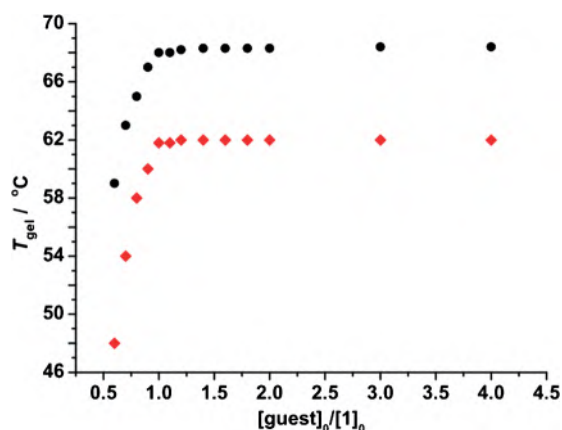


Figure 2. Dependence of the gel–sol transition temperature T_{gel} on the molar ratio of ammonium salt/cyclo[6]aramide **1** showing saturation at 1:1 stoichiometry in methanol. For the DEA-HCl experiment (red diamonds), $[1]_0$ was held constant at 7 mM. For the TEA-HCl experiment (black circles), $[1]_0$ was held constant at 12 mM.

obtained, strongly suggesting the formation of a 1:1 host–guest complex that is responsible for gelation.

Scanning electron microscopy (SEM) images of the the xerogel superstructures of the two-component gels (1:1 complex) showed the presence of network fibrillar structures containing dense cross-links with a width of approximately 365 nm (see Figures S8 and S9). Transmission electron microscopy (TEM) images of the xerogels revealed bundles of the individual filaments, pointing to a higher level of order (see Figure S10 and S11). These images indicated that the two-component gelators formed highly interpenetrated networks. To gain further insight into the assembly process involving the amphiphilic cyclo[6]aramide and alkylammonium ions, the xerogel was prepared from a solution of **1** and DEA-HCl in methanol, deposited on glass, and was studied by wide-angle X-ray diffraction (Figure S12). The diffractogram revealed a single sharp peak dominating over the low angle region at an angle of $2\theta = 3.3^\circ$, indicative of columnar assemblies.^[30a,d] A d -spacing of 2.64 nm was calculated from the angle of this primary diffraction peak. The presence of three other prominent peaks at 1.53 nm, 1.31 nm, and 1.03 nm, with ratios of d -spacings of about $1:1/\sqrt{3}:1/2:1/\sqrt{7}$, indicated that these columns are packed in a hexagonal lattice in the 1:1 complex **1**·DEA-HCl. The reflection around 0.37 nm was attributed to resulting from the corresponding π – π stacking interactions between the coplanar aromatic backbones (2θ , 20–30°).^[21,31] Similar results were obtained for **1**·TEA-HCl (Figure S13). Thus, the information retrieved from the wide-angle X-ray diffraction analysis supports the stacking of the macrocyclic molecules into nanotubular structures, which is consistent with the observation of very long fibers from SEM and TEM images. Therefore, it is clear that a two-component gelation system based on the amphiphilic cyclo[6]aramide **1** and alkylammonium ions was constructed. To our knowledge, there are no other two-component gelation systems fabricated from shape-persistent H-bonded 2D macrocycles through host–guest interactions.

As formation of the gel relies on macrocyclic host–guest interactions, introduction of another competitive guest to the two-component gelation system is expected to induce a change in the supramolecular structure and eventually may lead to the collapse of the macroscopic gel, possibly enabling the visual discrimination of guest molecules. It has been established that cyclo[6]aramides can specifically recognize guanidinium ions.^[23] Thus, the possibility for the stimuli-specific responses of the two-component gels toward arginine (specifically the L-form, denoted L-Arg) was first explored by adding L-Arg (1 equivalent) to a gel formed from **1**·DEA-HCl (20 mM) in methanol. When the mixture was heated to approximately 65°C and cooled to room temperature, the gel containing L-Arg collapsed to form an opaque solution (Figure S23). Interestingly, under the same conditions the gel remains unchanged with the use of 19 other amino acids (1 equivalent). Thus, specific discrimination of L-Arg from the other 19 amino acids could be achieved by direct visual observation of the breakdown of the two-component gel. It should be further noted that a complete gel collapse occurred only when L-Lys (2 equivalents) was used. Even under these conditions, we still observed a striking difference in gel transformation between L-Arg and L-Lys. The gel turned into a clear solution upon addition of L-Arg, but addition of L-Lys produced only an opaque solution (Figure S24). These results confirm the selective nature of the gel response toward L-Arg using the amphiphilic cyclo[6]aramide, implying that native amino acids bearing a guanidyl group may be appropriate candidates to compete with secondary ammonium ions, and give rise to gel collapse.

Although a specific response to L-Arg is now possible, it is unclear if the selectivity would be retained in the presence of all the other 19 amino acids, especially when lysine, a competitive binding species, is also present. Therefore, a mixture consisting of 20 amino acids (1 equivalent of each) was added to the **1**·DEA-HCl gel (20 mM) in methanol and tested with a heating–cooling procedure. The gel was found to collapse. In a control experiment, a mixture containing 19 amino acids (1 equivalent of each) excluding L-Arg failed to cause the gel to sol transformation, indicating that the specific response towards L-Arg indicated by collapse of the gel was maintained in competitive environments. More importantly, the MALDI-TOF mass spectral experiment with a sample composed of 20 amino acids and **1**·DEA-HCl provided strong evidence for the specific recognition of L-Arg. An intense peak attributable to the complex $[\text{1}\cdot\text{Arg} + \text{H}]^+$ was observed at m/z 2151.2 (Figure 3a). This strongly suggests the preference of cyclo[6]aramide gel **1** to bind the amino acid L-Arg over the other amino acids.

The binding of L-Arg was further validated by the 2D NOESY spectra of a solution containing an equimolar mixture of **1**, DEA-HCl, and L-Arg (each 5 mM) in CD₃OD (see Figure S20). Correlations between the signals attributable to the interior aromatic protons of **1** (denoted i and/or k) and protons of L-Arg (denoted n or o) were observed. In contrast, no cross-peaks associated with the interaction of DEA-HCl and the macrocycle appeared, strongly suggesting that competitive complexation by arginine occurred within the cavity of the macrocycle. In other words, arginine can

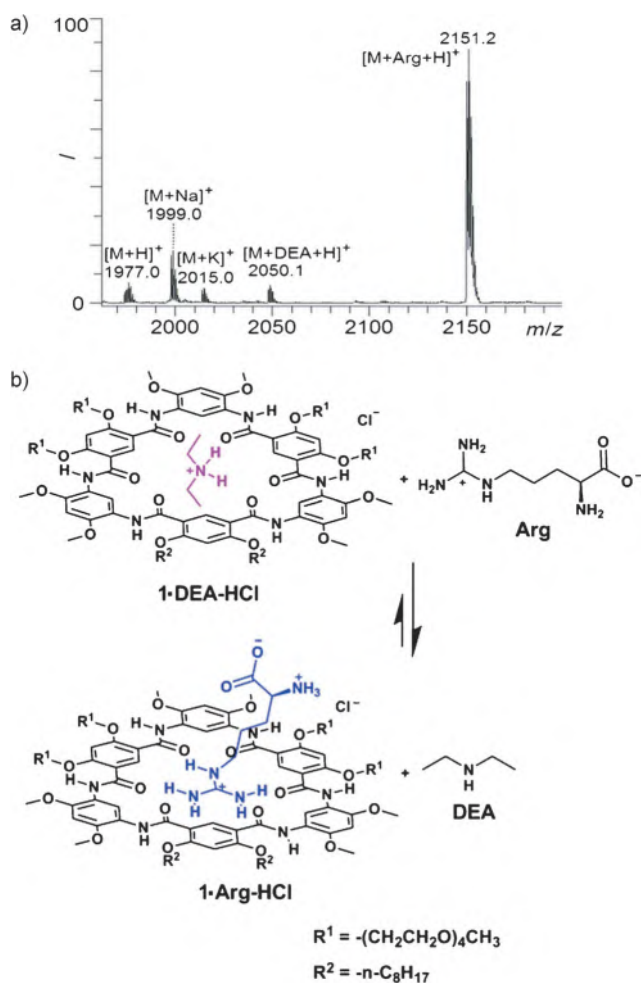


Figure 3. a) MALDI-TOF spectrum of **1** in the presence of DEA-HCl, and 1 equivalent of each of 20 amino acids (L-Arg, L-Lys, L-His, L-Ala, L-Asn, L-Ile, L-Leu, L-Gln, L-Met, L-Thr, L-Gly, L-Ser, L-Phe, L-Val, L-Pro, L-Tyr, L-Trp, L-Asp, L-Cys, and L-Glu), in methanol; b) Competitive displacement of diethylammonium chloride (DEA-HCl) by L-Arg that leads to the collapse of the gel.

replace diethylammonium in the cavity of the macrocycle, a likely determining factor that causes the collapse of the gel (Figure 3b). These results from ^1H NMR spectroscopic experiments indicated that the amino residue of L-Arg is protonated through a proton-transfer process from DEA-HCl, either in the presence or absence of the cyclo[6]aramide (Figure S17).

To pinpoint the binding site that dominates the recognition process, two model compounds, dodecylguanidinium chloride (DDGC) and alanine methyl ester hydrochloride (AME-HCl), were employed to mimic the function of the guanidinium and the ammonium moieties in the molecule of L-Arg. The first indication that **1** binds DDGC more tightly than AME-HCl came from the MALDI-TOF spectra (see Figure S16). When using an equimolar mixture of DDGC and the amphiphilic cyclo[6]aramide **1**, the highest intensity peak in the mass spectrum was detected at m/z 2204.2, corresponding to the complex $[\mathbf{1}\cdot\text{DDGC}-\text{Cl}]^+$. However, when AME-HCl was used, formation of the complex $[\mathbf{1}\cdot\text{AME}+\text{H}]^+$ was

not observed. Therefore, it is most likely that the terminal guanidinium residue of arginine is the binding moiety that interacts with **1**. The 2D NOESY experiment of a solution containing an equimolar mixture of **1** and DDGC (each 5 mM) in CDCl_3 provided further evidence for the interaction of the guanidinium moiety with **1** and the presence of the guanidinium ion in the cavity of **1** (Figure S21). The amino acid lysine (Lys) could be considered as a combination of dodecylammonium chloride (DDAC) and AME-HCl. From ^1H NMR spectroscopy titrations in $\text{CD}_3\text{OD}/\text{CDCl}_3$ (11:9, v/v), binding constants between a nonaggregational cyclo[6]aramide **4** and DDGC, DDAC, DEA-HCl, or AME-HCl were calculated to be 1.2×10^5 , 6.5×10^4 , 1.8×10^4 , and $5.0 \times 10^3 \text{ M}^{-1}$, respectively (Table S1). Thus, the binding affinities of the macrocycle towards different guest molecules decrease in the order of DDGC (guanidinium part of L-Arg) > DDAC (alkylammonium part of L-Lys) > DEA-HCl > AME-HCl. Given the fact that the guanidinium moiety is the strongest binder among all the guests tested and the nonaggregational macrocycle **4** shares the same number of interior carbonyl oxygen atoms as **1**, the binding constants strongly suggest that **1** should follow a similar binding trend as **4** toward various guests, that is, L-Arg > L-Lys > DEA-HCl.

To comprehend the recognition event from a microscopic view, extensive molecular dynamics (MD) simulations were carried out for three complex systems, specifically **5**-arginine, **5**-lysine, and **5**-diethyl ammonium (DEAH^+). In each case, the guest molecules were found to remain stably around the cavity (Figure S33). On the basis of the calculated binding energies, our computational results revealed that the binding affinity of cyclo[6]aramide for different guests decreases in the order of L-Arg > L-Lys > DEAH^+ (Table S2). Thus, the results of the calculations provide a partial explanation for the competitive binding observed between L-Arg and DEAH^+ in the cyclo[6]aramide system.

The two-component gel assembly and recognition event may involve a two-stage process: a) gel assembly through host-guest interactions between the alkylammonium guest and the macrocyclic host **1**, and b) collapse of the gel by the competitive binding of the arginine guest molecule through proton transfer from alkylammonium to arginine, resulting in the displacement of the alkylammonium ion from **1** (Figure 4). For the gel hierarchical assembly process, a mixture containing the amphiphilic cyclo[6]aramide and DEA-HCl was heated in methanol to afford a clear solution where the ammonium cation was introduced into the cavity of the macrocycle by host-guest interactions. Upon cooling, intermolecular aggregation led to assembled bundles, whose formation were caused by π - π stacking and van der Waals forces among side chains. Eventually, a three-dimensional fibril network was produced with the ability to gelate solvent molecules. Collapse of the gel occurred when L-Arg was added, as evidenced by a significant decrease in the average size of aggregates from 1040.0 nm for a mixture of **1** (5.0 mM) and DEA-HCl (5.0 mM) in $\text{CH}_3\text{OH}/\text{CHCl}_3$ (7:3, v/v) to 8.0 nm upon addition of 1 equivalent of L-Arg (Figures S14 and S15). This could be rationalized by the stronger binding capability and higher basicity of the guest (Arg) molecule that favorably facilitates proton transfer from the alkylammonium salt. It is

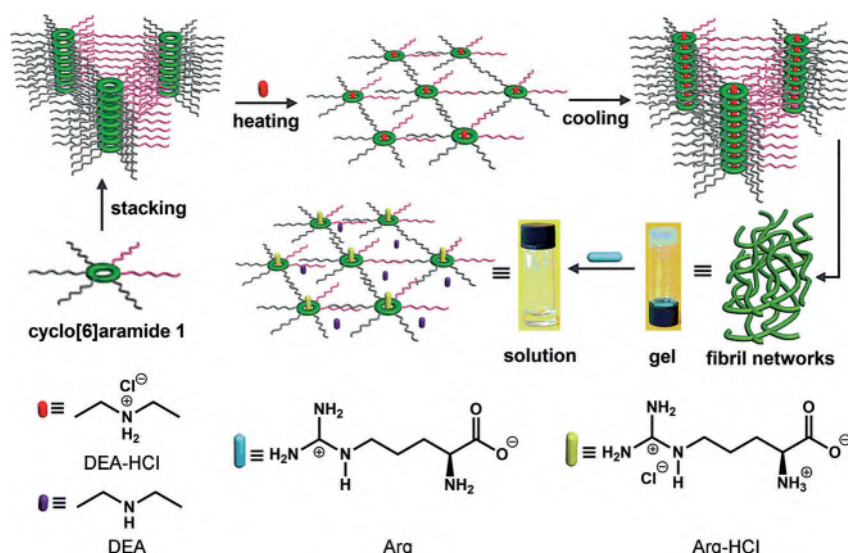


Figure 4. Representation of a two-component gel assembly involving **1** and DEA-HCl. Competitive binding of L-Arg to **1** induces the collapse of the gel, which is caused by proton transfer from DEA-HCl to L-Arg, allowing the specific recognition of L-Arg.

likely that the bulky arginine bound inside the cavity prevents the occurrence of efficient π - π stacking among macrocyclic planar backbones, thus leading to significantly less aggregation.

In summary, this work demonstrated a unique approach to construct a supramolecular two-component gelation system based on amphiphilic shape-persistent cyclo[6]aramides and diethylammonium chloride (or triethylammonium chloride). Driven by host-guest interactions, these two-component gels exhibited stimuli-responsive gel collapse, enabling highly specific discrimination of L-arginine from 19 other amino acids. The specificity observed was largely attributed to the higher binding affinity of the macrocycle for L-Arg than for the other amino acids. The binding of L-Arg was achieved through supramolecular displacement of the second component (for example, alkylammonium) as revealed by both binding affinity experiments and theoretical simulations. A gel assembly and collapse process with emphasis on competitive host-guest interactions was proposed to rationalize the recognition event. With their ready synthetic availability and the possibility to specifically tailor the system, these macrocycles should provide a useful supramolecular amphiphilic synthon. Based on this system, it should be possible to create diverse novel organic gelation systems with selective recognition abilities or other functions by modifying either component of the two-component gelation system in a specific controllable manner.

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- [1] a) D. K. Smith, *Chem. Soc. Rev.* **2009**, *38*, 684; b) J. A. Foster, J. W. Steed, *Angew. Chem. Int. Ed.* **2010**, *49*, 6718; *Angew. Chem.* **2010**, *122*, 6868; c) G. Yu, X. Yan, C. Han, F. Huang, *Chem. Soc. Rev.* **2013**, *42*, 6697; d) C. Tomasini, N. Castellucci, *Chem. Soc. Rev.* **2013**, *42*, 156; e) M. D. Segarra-Maset, V. J. Nebot, J. F. Miravet, B. Escuder, *Chem. Soc. Rev.* **2013**, *42*, 7086; f) S. S. Babu, V. K. Praveen, A. Ajayaghosh, *Chem. Rev.* **2014**, *114*, 1973; g) R. G. Weiss, *J. Am. Chem. Soc.* **2014**, *136*, 7519.
- [2] a) P. Mukhopadhyay, Y. Iwashita, M. Shirakawa, S. Kawano, N. Fujita, S. Shinkai, *Angew. Chem. Int. Ed.* **2006**, *45*, 1592; *Angew. Chem.* **2006**, *118*, 1622; b) X. Chen, Z. Huang, S.-Y. Chen, K. Li, X.-Q. Yu, L. Pu, *J. Am. Chem. Soc.* **2010**, *132*, 7297; c) T. Tu, W. Fang, X. Bao, X. Li, K. H. Dötz, *Angew. Chem. Int. Ed.* **2011**, *50*, 6601; *Angew. Chem.* **2011**, *123*, 6731; d) Y. Zheng, A. Hashidzume, Y. Takashima, H. Yamaguchi, A. Harada, *Nat. Chem.* **2012**, *3*, 831; e) T. Tu, W. W. Fang, Z. M. Sun, *Adv. Mater.* **2013**, *25*, 5304; f) X. Yan, D. Xu, X. Chi, J. Chen, S. Dong, X. Ding, Y. Yu, F. Huang, *Adv. Mater.* **2012**, *24*, 362; g) S. Dong, B. Zheng, D. Xu, X. Yan, M. Zhang, F. Huang, *Adv. Mater.* **2012**, *24*, 3191; h) S. Dong, Y. Luo, X. Yan, B. Zheng, X. Ding, Y. Yu, Z. Ma, Q. Zhao, F. Huang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1905; *Angew. Chem.* **2011**, *123*, 1945.
- [3] F. Zhao, M. L. Ma, B. Xu, *Chem. Soc. Rev.* **2009**, *38*, 883.
- [4] A. R. Hirst, B. Escuder, J. F. Miravet, D. K. Smith, *Angew. Chem. Int. Ed.* **2008**, *47*, 8002; *Angew. Chem.* **2008**, *120*, 8122.
- [5] D. Díaz Díaz, D. Kühbeck, R. J. Koopmans, *Chem. Soc. Rev.* **2011**, *40*, 427.
- [6] D. K. Kumar, J. W. Steed, *Chem. Soc. Rev.* **2014**, *43*, 2080.
- [7] a) L. E. Buerkle, S. J. Rowan, *Chem. Soc. Rev.* **2012**, *41*, 6089; b) W. Edwards, D. K. Smith, *J. Am. Chem. Soc.* **2014**, *136*, 1116.
- [8] a) A. R. Hirst, D. K. Smith, *Chem. Eur. J.* **2005**, *11*, 5496; b) Z. Qi, C. A. Schalley, *Acc. Chem. Res.* **2014**, *47*, 2222.
- [9] a) M. de Loos, J. van Esch, R. M. Kellogg, B. L. Feringa, *Angew. Chem. Int. Ed.* **2001**, *40*, 613; *Angew. Chem.* **2001**, *113*, 633; b) A. R. Hirst, D. K. Smith, M. C. Feiters, H. P. M. Geurts, A. C. Wright, *J. Am. Chem. Soc.* **2003**, *125*, 9010; c) W. Cai, G.-T. Wang, P. Du, R.-X. Wang, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2008**, *130*, 13450; d) R. Amemiya, M. Mizutani, M. Yamaguchi, *Angew. Chem. Int. Ed.* **2010**, *49*, 1995; *Angew. Chem.* **2010**, *122*, 2039; e) L. Meazza, J. A. Foster, K. Fucke, P. Metrangolo, G. Resnati, J. W. Steed, *Nat. Chem.* **2013**, *5*, 42; f) W. Edwards, D. K. Smith, *J. Am. Chem. Soc.* **2013**, *135*, 5911; g) W. Ichinose, J. Ito, M. Yamaguchi, *Angew. Chem. Int. Ed.* **2013**, *52*, 5290; *Angew. Chem.* **2013**, *125*, 5398.
- [10] a) Z. S. Ge, J. M. Hu, F. H. Huang, S. Y. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 1798; *Angew. Chem.* **2009**, *121*, 1830; b) M. Zhang, D. Xu, X. Yan, J. Chen, S. Dong, B. Zheng, F. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7011; *Angew. Chem.* **2012**, *124*, 7117; c) X. Yan, T. R. Cook, J. B. Pollock, P. Wei, Y. Zhang, Y. Yu, F. Huang, P. J. Stang, *J. Am. Chem. Soc.* **2014**, *136*, 4460.
- [11] a) Y.-S. Zheng, S.-Y. Ran, Y.-J. Hu, X.-X. Liu, *Chem. Commun.* **2009**, 1121; b) J. Zhang, D.-S. Guo, L.-H. Wang, Z. Wang, Y. Liu, *Soft Matter* **2011**, *7*, 1756.
- [12] Y. G. Li, T. Y. Wang, M. H. Liu, *Soft Matter* **2007**, *3*, 1312.

- [13] a) T. Taira, Y. Suzuki, K. Osakada, *Chem. Eur. J.* **2010**, *16*, 6518; b) Z.-X. Zhang, K. L. Liu, J. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 6180; *Angew. Chem.* **2013**, *125*, 6300.
- [14] Y. Liu, Y. Yu, J. Gao, Z. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 6576; *Angew. Chem.* **2010**, *122*, 6726.
- [15] a) S. Y. Dong, J. Y. Yuan, F. H. Huang, *Chem. Sci.* **2014**, *5*, 247; b) Z.-Y. Li, Y. Zhang, C.-W. Zhang, L.-J. Chen, C. Wang, H. Tan, Y. Yu, X. Li, H.-B. Yang, *J. Am. Chem. Soc.* **2014**, *136*, 8577.
- [16] a) Y.-L. Zhao, I. Arahamian, A. Trabolsi, N. Erina, J. F. Stoddart, *J. Am. Chem. Soc.* **2008**, *130*, 6348; b) S.-Y. Hsueh, C.-T. Kuo, T.-W. Lu, C.-C. Lai, Y.-H. Liu, H.-F. Hsu, S.-M. Peng, C.-h. Chen, S.-H. Chiu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9170; *Angew. Chem.* **2010**, *122*, 9356; c) S. Ito, H. Takata, K. Ono, N. Iwasawa, *Angew. Chem. Int. Ed.* **2013**, *52*, 11045; *Angew. Chem.* **2013**, *125*, 11251.
- [17] For reviews on shape-persistent aromatic oligoamide macrocycles, see: a) B. Gong, *Acc. Chem. Res.* **2008**, *41*, 1376; b) Z.-T. Li, J.-L. Hou, C. Li, *Acc. Chem. Res.* **2008**, *41*, 1343; c) D.-W. Zhang, X. Zhao, J.-L. Hou, Z.-T. Li, *Chem. Rev.* **2012**, *112*, 5271; d) K. Yamato, M. Kline, B. Gong, *Chem. Commun.* **2012**, *48*, 12142; e) H. L. Fu, Y. Liu, H. Q. Zeng, *Chem. Commun.* **2013**, *49*, 4127; f) B. Gong, Z. F. Shao, *Acc. Chem. Res.* **2013**, *46*, 2856.
- [18] a) Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1997**, *119*, 10587; b) L. H. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. S. Atreya, D. K. Sukumaran, T. Szyperki, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 16528; c) W. Cai, G.-T. Wang, Y.-X. Xu, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6936; d) Y. Yan, B. Qin, C. L. Ren, X. Y. Chen, Y. K. Yip, R. J. Ye, D. W. Zhang, H. B. Su, H. Q. Zeng, *J. Am. Chem. Soc.* **2010**, *132*, 5869; e) Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Grélard, H. Jiang, I. Huc, *Science* **2011**, *331*, 1172; f) D.-W. Zhang, X. Zhao, Z.-T. Li, *Acc. Chem. Res.* **2014**, *47*, 1961.
- [19] a) L. H. Yuan, W. Feng, K. Yamato, A. R. Sanford, D. G. Xu, H. Guo, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 11120; b) S. L. Zou, Y. Z. He, Y. A. Yang, Y. Zhao, L. H. Yuan, W. Feng, K. Yamato, B. Gong, *Synlett* **2009**, 1437.
- [20] W. Feng, K. Yamato, L. Q. Yang, J. S. Ferguson, L. J. Zhong, S. L. Zou, L. H. Yuan, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 2629.
- [21] Y. A. Yang, W. Feng, J. C. Hu, S. L. Zou, R. Z. Gao, K. Yamato, M. Kline, Z. H. Cai, Y. Gao, Y. B. Wang, Y. B. Li, Y. L. Yang, L. H. Yuan, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 18590.
- [22] Y. B. Wang, Y. B. Li, Y. Luo, M. Xu, X. M. Zhang, Y. Y. Guo, G. H. Wei, L. H. Yuan, B. Gong, Y. L. Yang, C. Wang, *ChemPhysChem* **2012**, *13*, 3598.
- [23] A. R. Sanford, L. H. Yuan, W. Feng, K. Yamato, R. A. Flowers, B. Gong, *Chem. Commun.* **2005**, 4720.
- [24] L. J. Zhong, L. Chen, W. Feng, S. L. Zou, Y. Y. Yang, N. Liu, L. H. Yuan, *J. Inclusion Phenom. Macrocyclic Chem.* **2012**, *72*, 367.
- [25] a) J. C. Hu, L. Chen, Y. Ren, P. C. Deng, X. W. Li, Y. J. Wang, Y. M. Jia, J. Luo, X. S. Yang, W. Feng, L. H. Yuan, *Org. Lett.* **2013**, *15*, 4670; b) J. C. Hu, L. Chen, J. Shen, J. Luo, P. C. Deng, Y. Ren, H. Q. Zeng, W. Feng, L. H. Yuan, *Chem. Commun.* **2014**, *50*, 8024.
- [26] Y. B. Li, C. H. Liu, Y. Z. Xie, X. Li, X. L. Fan, L. H. Yuan, Q. D. Zeng, *Chem. Commun.* **2013**, *49*, 9021.
- [27] L. Mutihac, J. H. Lee, J. S. Kim, J. Vicens, *Chem. Soc. Rev.* **2011**, *40*, 2777.
- [28] S. M. Morris, Jr., *Am. J. Clin. Nutr.* **2006**, *83*, 508.
- [29] Y. Zhou, J. Yoon, *Chem. Soc. Rev.* **2012**, *41*, 52.
- [30] a) K. Balakrishnan, A. Datar, W. Zhang, X. Yang, T. Naddo, J. Huang, J. Zuo, M. Yen, J. S. Moore, L. Zang, *J. Am. Chem. Soc.* **2006**, *128*, 6576; b) M. Shirakawa, N. Fujita, H. Shimakoshi, Y. Hisaeda, S. Shinkai, *Tetrahedron* **2006**, *62*, 2016; c) D. Díaz Díaz, T. Torres, R. Zentel, R. Davis, M. Brehmer, *Chem. Commun.* **2007**, 2369; d) C. L. Ren, S. Y. Xu, J. Xu, H. Y. Chen, H. Q. Zeng, *Org. Lett.* **2011**, *13*, 3040; e) J. Vollmeyer, S.-S. Jester, F. Eberhagen, T. Prangenberg, W. Mader, S. Höger, *Chem. Commun.* **2012**, *48*, 6547.
- [31] X. B. Zhou, G. D. Liu, K. Yamato, Y. Shen, R. X. Cheng, X. X. Wei, W. L. Bai, Y. Gao, H. Li, Y. Liu, F. T. Liu, D. M. Czajkowsky, J. F. Wang, M. J. Dabney, Z. H. Cai, J. Hu, F. V. Bright, L. He, X. C. Zeng, Z. F. Shao, B. Gong, *Nat. Commun.* **2012**, *3*, 949.

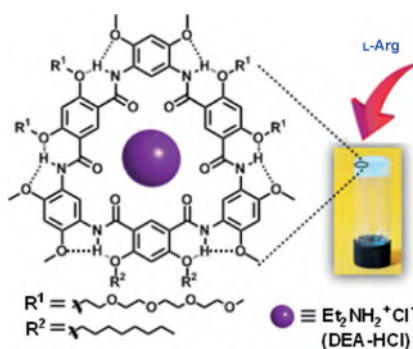
Communications



Supramolecular Gels

Y. He, M. Xu, R. Gao, X. Li, F. Li, X. Wu,
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L. Yuan*     

Two-Component Supramolecular Gels
Derived from Amphiphilic Shape-
Persistent Cyclo[6]aramides for Specific
Recognition of Native Arginine



Picking and choosing: A supramolecular two-component gelation system based on the amphiphilic cyclo[6]aramidema-crocycle and diethylammonium chloride is reported. This system provides a modularly tunable approach for creating functional two-component gel systems for highly specific recognition of L-arginine (L-Arg) from 19 other amino acids by competitive host-guest interactions.