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Dynamic combinatorial library for fullerene receptors based on metal-assisted self-assembly

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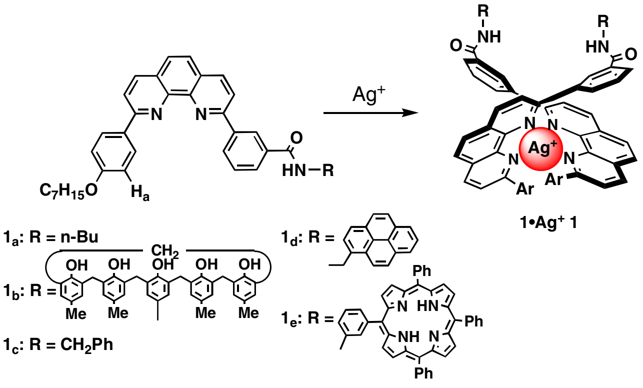
Abstract—A dynamic combinatorial library was prepared by the metal-induced self-assembly of phenanthroline derivatives having a guest binding unit. The binding assay using ESI mass spectrometry found out the effective combination of guest binding units for fullerene binding.

The demand for the discovery of new drugs as well as new materials is the driving force for the development of new combinatorial libraries.[1] Parallel and split-pool methods on a solid support are the effective techniques to find target compounds with combinatorial chemistry.[2] These methods require the optimization of reaction conditions and the development of new synthetic ways for library construction on solid supports. In contrast, permutation–combination-based combinatorial synthesis could greatly simplify the generation of diverse library;[3] however, the resulting library faces serious problems, which involve unequal amounts of products and difficulties for their identification and characterization.

Permutation–combination-based dynamic combinatorial chemistry has recently emerged.[4] The dynamic equilibrium among library members, formed via permutation and combination of subunits, has many advantages for supramolecular chemistry. The amplification of a desired member by the templation of a guest is a characteristic feature in the dynamic library.[5] The guest recognizes and stabilizes a desired member of the library. This selective molecular recognition event induces a shift of the equilibrium toward the formation of the desired member, and away from others not to be involved in the recognition event. Thus, the desired member is amplified, and easier to identify it in the diverse library.



We have reported that calix[5]arene derivatives and double-calix[5]arenes are good hosts for C_{60} and C_{70}.[6,7] In our recent study, calix[5]arenes possessing a bipyridine unit assemble via silver coordination to form a dimeric complex, which equilibrates with its monomer in chloroform solution.[8] We envisioned to utilize the metal-assisted self-assembly for the construction of the dynamic library for fullerene receptors.[9] In this letter, we report the preparation and screening of a permutation–combination-based dynamic combinatorial library of fullerene receptors via self-assembly of phenanthrolines $\mathbf{1}_{a\text{–}e}$ possessing fullerene binding units through metal-coordination.

The synthesis of phenanthrolines is outlined in Scheme 1. The treatment of phenanthroline with 4-heptyloxyphenyllithium, prepared from 4-heptyloxybromobenzene, followed by oxidation with manganese dioxide

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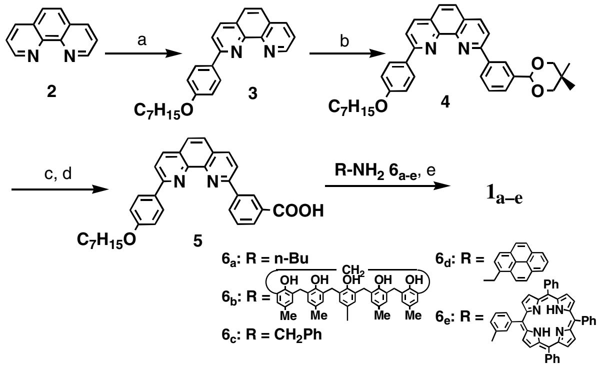

Scheme 1. Reagents and conditions: (a) 4-heptyloxybromobenzene, *t*-BuLi, THF, −78 °C, and then MnO_2 48%; (b) 2-(3-bromophenyl)-5,5-dimethyl-1,3-dioxane, *t*-BuLi, THF, −78 °C, and then MnO_2 76%; (c) aqueous 10% HCl, THF, 40 °C 99%; (d) $TBAMnO_4$, pyridine, THF, 91%; (e) EDCI, HOAt, DMF ($\mathbf{1}_a$: 65%, $\mathbf{1}_b$: 45%, $\mathbf{1}_c$: 61%, $\mathbf{1}_d$: 15%, $\mathbf{1}_e$: 55%).

provided **3**. The aryllithium, prepared from 2-(3-bromophenyl)-5,5-dimethyl-1,3-dioxane,[10] reacted with **3** and the subsequent oxidation afforded **4**. The deprotection of **4**, followed by the oxidation of the resultant aldehyde group gave carboxylic acid **5**. The condensation reactions between **5** and amino derivatives $\mathbf{6}_{a\text{–}e}$ furnished $\mathbf{1}_{a\text{–}e}$.

Self-assembled dimers $[\mathbf{1}\cdot Ag^+\cdot\mathbf{1}]TfO^-$ quickly formed when a half amount of silver triflate was added to a solution of **1** in dichloromethane at room temperature. The aromatic proton Ha of the heptyloxyphenyl group of complex $[\mathbf{1}_a\cdot Ag^+\cdot\mathbf{1}_a]TfO^-$ appeared at 6.3 ppm, and the amide N–H resonance showed up at 6.6 ppm as a triplet (Fig. 1a). Proton Ha of complex $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ resonated at 5.9 ppm (Fig. 1b). When these complexes were mixed in a 1:1 ratio, the triplet and doublet signals split to give rise to the new signals, pointed by the arrows (Fig. 1c). Saturation transfer experiments revealed that the new signals exchange with their parents, a fact which suggests the formation of heterodimer $[\mathbf{1}_a\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$. These results indicate that a sizable energetic barrier exists in the equilibrium among the heterodimer and the homodimers (Fig. 1c). The ESI mass spectrum of the mixture and the peak intensities of ^1H NMR confirmed the formation of the heterodimer and the homodimers in a ratio of 1:2:1 (Fig. 2).

Upon the addition of diethyl 1,2-methano[60]fullerene-61,61-dicarboxylate **7** (Fig. 3) to a solution of the mixture, the aromatic signal of $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ quickly disappeared, and a new signal emerged at 6.2 ppm (Fig. 1d), which is consistent with the formation of $\mathbf{7} \subset [\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ (Fig. 1e) with the consumption of $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ (Fig. 1d). Interestingly, the intensities of the aromatic protons of the heterodimer decreased upon the addition of **7**, indicating that the equilibrium was shifted toward homodimer $\mathbf{7} \subset [\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ by the addition of **7**. This clearly suggested that the complex having the effective guest binding units was amplified via dynamic equilibrium.

The study of noncovalently bound complexes by electrospray ionization mass spectrometry[11] has rapidly gained momentum. A large number of reports have dealt with the mass spectrometric characterization of noncovalent complexes, such as supramolecular metal complexes.[12] ESI-MS spectrometry has proven to be an indispensable tool in supramolecular chemistry. The silver cation labeling of the self-assembling complexes $[\mathbf{1}\cdot Ag^+\cdot\mathbf{1}]TfO^-$

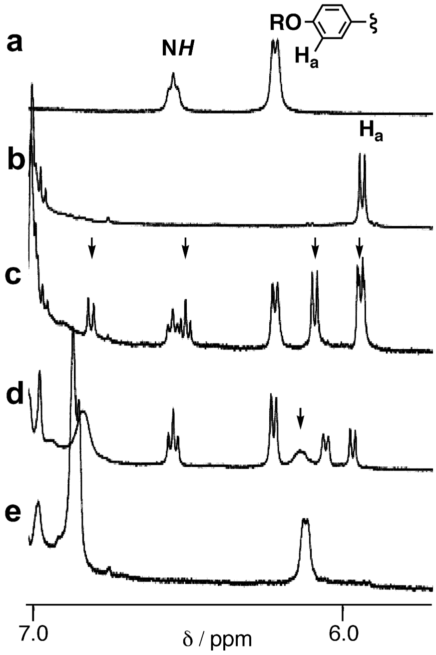

Figure 1. ^1H NMR spectra (500 MHz) of: (a) $[\mathbf{1}_a\cdot Ag^+\cdot\mathbf{1}_a]TfO^-$ (5.0 mmol/L), (b) $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ (5.0 mmol/L), (c) a 1:1 mixture of $[\mathbf{1}_a\cdot Ag^+\cdot\mathbf{1}_a]TfO^-$ and $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$, (d) after addition of 1.6 equiv **7**, (e) **7** $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ in chloroform-*d* at 298 K.

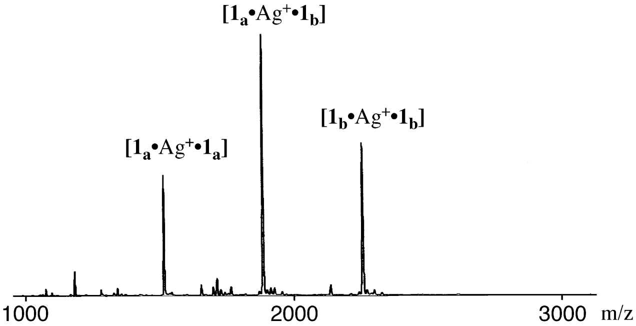

Figure 2. ESI mass spectrum of a 1:1 mixture of $[\mathbf{1}_a\cdot Ag^+\cdot\mathbf{1}_a]TfO^-$ and $[\mathbf{1}_b\cdot Ag^+\cdot\mathbf{1}_b]TfO^-$ in chloroform.

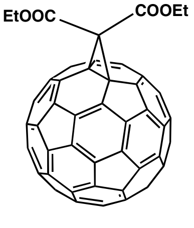

Figure 3. The structure of diethyl 1,2-methano[60]fullerene-61,61-dicarboxylate **7**.

was the advantage for ESI-MS measurements in non-polar aprotic solvents.

A permutation–combination-based dynamic library was prepared via self-assembly of $\mathbf{1}_{\mathbf{b-e}}$ upon the addition of silver triflate. The dynamic equilibrium gives rise to the 10 discrete library members. As expected, ESI mass measurement of the library gave the 10 peaks, assignable to the discrete library members (Fig. 4a). Upon the addition of C_{60} into a solution of the library, four new peaks appeared, and they were assigned to four newly formed complexes $C_{60} \subset [\mathbf{1}_\mathbf{b}{\cdot}Ag^{+}{\cdot}\mathbf{1}_{\mathbf{b-e}}]$ (Fig. 4b). As a result, the calix[5]arene moiety is crucial to take up a C_{60} molecule. As we noted in our previous reports, the cavity of a calix[5]arene is complementary to the exterior of a C_{60} molecule, and shows the strong binding ability to it.[7] Thus, the result is quite convincing. Competition experiment between C_{60} and C_{70} should give information of their relative binding affinities toward the library members. C_{70} bound only to the two discrete hosts: one is made up of a calix[5]arene and a porphyrin ring, the other has two porphyrin rings, which gave the complexes $C_{70} \subset [\mathbf{1}_\mathbf{b}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{e}]$ and $C_{70} \subset [\mathbf{1}_\mathbf{e}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{e}]$. Their peak intensities are close to those of $C_{60} \subset [\mathbf{1}_\mathbf{b}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{b}]$ and $C_{60} \subset [\mathbf{1}_\mathbf{b}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{e}]$ (Fig. 4c). Since C_{70} is known as a better electron acceptor than C_{60}, C_{70} perhaps showed the preferential binding to the porphyrin-based hosts through charge transfer interaction.[13]

To verify the binding abilities of the given hosts for C_{60} and C_{70}, self-assembled hosts $[\mathbf{1}_\mathbf{b}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{b}]PF_6^{-}$ and $[\mathbf{1}_\mathbf{e}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{e}]PF_6^{-}$ were prepared as a stable tetrahedral complex in solution. Their binding constants for C_{60} and C_{70} were determined by standard UV–vis titration (Table 1).[14] These hosts showed much greater binding abilities than **8** (Fig. 5).[7] The binding trends are slightly different from those given by ESI mass spectrometry. The mass peaks attributable to $C_{60} \subset [\mathbf{1}_\mathbf{e}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{e}]$ and $C_{70} \subset [\mathbf{1}_\mathbf{b}{\cdot}Ag^{+}{\cdot}\mathbf{1}_\mathbf{b}]$ were not observed; however, the corresponding Cu complexes $[\mathbf{1}_\mathbf{b}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{b}]PF_6^{-}$ and $[\mathbf{1}_\mathbf{e}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{e}]PF_6^{-}$ showed a strong binding to C_{60} and C_{70}. This may come from the difference between the structural flexibilities of the complexes $\mathbf{1}{\cdot}Cu^{+}{\cdot}\mathbf{1}$ and $\mathbf{1}{\cdot}Ag^{+}{\cdot}\mathbf{1}$.

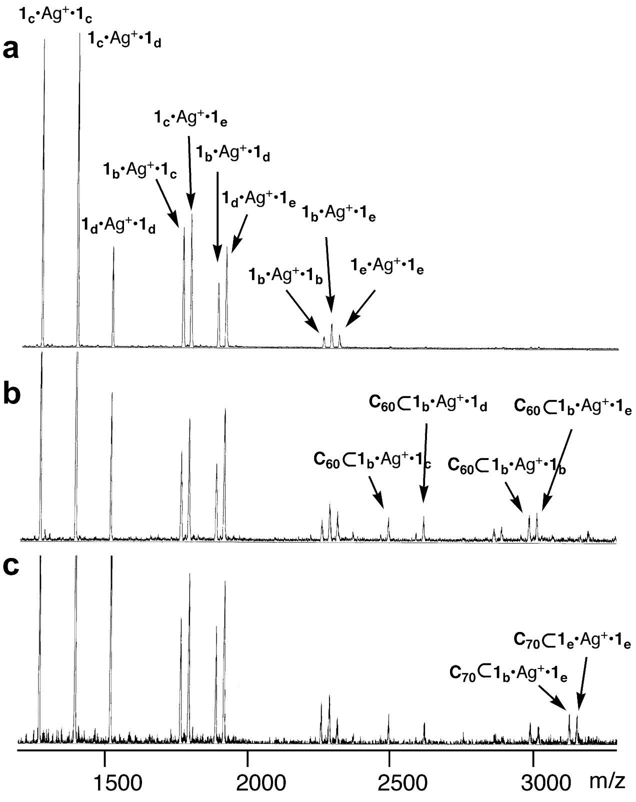

Figure 4. ESI mass spectra of the combinatorial library: (a) without a guest, (b) with C_{60}, (c) with a 1:1 mixture of C_{60} and C_{70} in 1,1,2,2-tetrachloroethane.

Table 1. Binding constants (K_a/M^{-1}) of $[\mathbf{1}_\mathbf{b}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{b}]PF_6^{-}$, $[\mathbf{1}_\mathbf{e}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{e}]PF_6^{-}$, and **7** for C_{60} and C_{70} in 1,1,2,2-tetrachloroethane at 298 K

	K_a	
	C_{60}	C_{70}
$[\mathbf{1}_\mathbf{b}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{b}]PF_6^{-}$	13,000 ± 700	15,000 ± 600
$[\mathbf{1}_\mathbf{e}{\cdot}Cu^{+}{\cdot}\mathbf{1}_\mathbf{e}]PF_6^{-}$	9600 ± 800	4900 ± 300
8	4900 ± 200	5000 ± 200

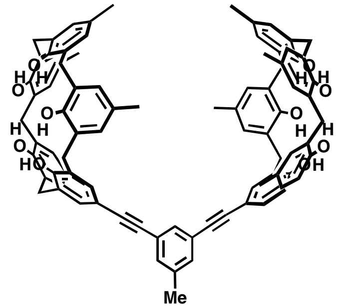

Figure 5. The structure of host **8**.

In summary, we found the new hosts showing strong binding to fullerene via a permutation–combination-based combinatorial library, which was prepared by metal-coordination driven self-assembly. This method permits a quick generation of diverse combinatorial library from a mixture of discrete subunits.

Acknowledgements

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References and notes

1. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600.
2. Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry: Synthesis and Application*; John Wiley & Sons: New York, 1997.
3. Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2289–2337; Carell, T.; Winter, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059–2061;

Carell, T.; Winter, E. A.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2061–2064.

4. Ziegler, M.; Miranda, J. J.; Andersen, U. N.; Johnson, D. W.; Leary, J. A.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 733–736; Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1270–1273.
5. Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463; Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Drug Discov. Today* **2002**, *7*, 117–125; Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2106–2110.
6. Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 997–998; Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 259–260; Haino, T.; Yanase, M.; Fukazawa, Y. *Tetrahedron Lett.* **1997**, *38*, 3739–3742.
7. Haino, T.; Yanase, M.; Fukunaga, C.; Fukazawa, Y. *Tetrahedron* **2006**, *62*, 2025–2035.
8. Haino, T.; Araki, H.; Yamanaka, Y.; Fukazawa, Y. *Tetrahedron Lett.* **2001**, *42*, 3203–3206.
9. Goodman, M. S.; Jubian, V.; Linton, B.; Hamilton, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 11610–11611.
10. Neef, G.; Wiechert, R.; Ottow, E.; Rohde, R.; Beier, S.; Elger, W.; Henderson, D. *Eur. Pat. Appl.* **1986**, *55*.
11. Przybylski, M.; Glocker, M. O. *Angew. Chem., Int. Ed.* **1996**, *35*, 806.
12. Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed.* **1997**, *36*, 613; Stang, P. J.; Cao, D. H.; Chen, K.; Gray, G. M.; Muddiman, D. C.; Smith, R. D. *J. Am. Chem. Soc.* **1997**, *119*, 5163; Piguet, C.; Hopfgartner, G.; Bocquet, B.; Schaad, O.; Williams, A. F. *J. Am. Chem. Soc.* **1994**, *116*, 9092; Bitsch, F.; Dietrich-Buchecker, C. O.; Khémiss, A.-K.; Sauvage, J.-P.; Dorsselaer, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 4023; Vincenti, M.; Dalcanale, E.; Soncini, P.; Guglielmetti, G. *J. Am. Chem. Soc.* **1990**, *112*, 445; Schalley, C. A.; Martín, T.; Obst, U.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1999**, *121*, 2133; Schalley, C.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568.
13. Zheng, J.-Y.; Tashiro, K.; Hirabayashi, Y.; Kinbara, K.; Saigo, K.; Aida, T.; Sakamoto, S.; Yamaguchi, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1858–1861; Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838–842.
14. Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987.