

Benzene Ring Trimer Interactions Modulate Supramolecular Structures**

Tatsuki Morimoto, Hidemitsu Uno, and Hiroyuki Furuta*

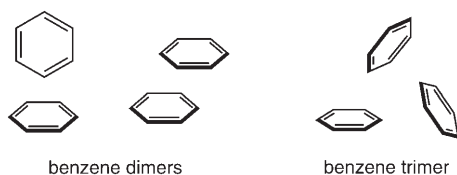
Aromatic–aromatic interactions are ubiquitous and play an important role in a variety of chemical and biological processes.^[1] Interactions within benzene dimers are well documented^[2–4] for a series of aromatic clusters, and their significance in biomolecular structures is widely recognized.^[5] In contrast, because of the difficulty in isolation of artificial model systems, investigations on higher-order aromatic clusters are largely limited to theoretical studies despite the abundance of natural systems, and only a few experimental studies in the gas phase have been reported so far.^[4,6,7] Among such clusters, a cyclic trimer with a C_3 axis was deduced to be the most stable benzene cluster from theoretical calculations as well as measurements of the dissociation energy of the clusters in the gas phase.^[4,7] According to recent high-accuracy quantum mechanical calculations, the stabilization energy of the C_{3h} -symmetric benzene trimer is estimated to be approximately -20 kJ mol^{-1} , that is, roughly -7 kJ per mole of benzene.^[2,6a] Whereas the estimated energy value is

relatively large and seems to be utilized as a modulating interaction in supramolecular architectures, to our knowledge, there is no report of the details of such trimer interactions and structures in solution or even in the solid state. Herein, we report some examples of benzene ring trimers in the solid state and show that the interactions in the trimer can modulate a supramolecular structure in solution.

A cyclic trimeric structure of the benzene derivative chlorobenzene was found in the void space of the crystal packing of a tripyrrolic macrocycle.^[8] In this trimer, three chlorobenzene molecules face one another with dihedral angles of $67.7(3)$, $32.7(3)$, and $59.2(3)^\circ$ and center-to-center distances of the three benzene rings of $4.973(4)$, $4.623(4)$, and $5.004(4) \text{ \AA}$, respectively (see the Supporting Information). Reflecting the packing forces from the surroundings, the ring–ring angles and distances are inequivalent but the latter are comparable to the calculated distance of $4.8 \text{ \AA}$ for the optimized geometry of the C_{3h} -symmetric cyclic benzene trimer.^[6a]

In solution, it is difficult to isolate the pure benzene trimer and evaluate the strength of the interactions owing to the involvement of many interactions from other benzene molecules and the intervention of other clusters. Thus, we developed a dynamic trimerization system involving metal coordination. More specifically, a benzene ring trimer was constructed on a C_3 -symmetric supramolecular platform composed of three mutually metal-coordinated C_1 -symmetric molecules, each of which bears one phenyl (benzene) substituent. In principle, when the three C_1 -symmetric component molecules assemble, two types of trimers with different conformations, namely C_3 - and C_1 -symmetric, are formed (Figure 1). If distinct attractive interactions are present among the three closely located phenyl groups, one of the conformers, the C_3 -symmetric trimer, could be more stabilized. By comparing the two systems with and without phenyl groups, it is possible to extract only the interaction of the benzene ring trimer moiety and evaluate its magnitude.

Previously, we reported the self-assembly of a Zn^{II} complex of an N-confused porphyrin^[9] that bears two phenyl groups around the confused pyrrole ring.^[10] The C_2 -symmetric dimer complex, in which the peripheral nitrogen atom mutually coordinates to the Zn^{II} center of the opposite monomer part, was formed by self-assembly. In a successive study of Zn^{II} coordination of N-confused porphyrins with various substituents, we noticed the facile formation of a trimer by the C_1 -symmetric N-confused porphyrin **1**.^[11] The trimer displays a similar coordination mode to the N-confused porphyrin dimer complex, and so we decided to utilize this trimer as a target supramolecular platform.^[12]



[*] T. Morimoto, Prof. Dr. H. Furuta
Department of Chemistry and Biochemistry
Graduate School of Engineering
Kyushu University
Fukuoka 819-0395 (Japan)
Fax: (+81) 92-802-2865
E-mail: hfuruta@cstf.kyushu-u.ac.jp

Prof. Dr. H. Furuta
PRESTO
Japan Science and Technology Agency (JST)
Kawaguchi, Saitama 332-0012 (Japan)
Prof. Dr. H. Uno
Department of Molecular Science
Integrated Center for Sciences, Ehime University
Bunkyo-cho 2-5, Matsuyama 790-8577 (Japan)

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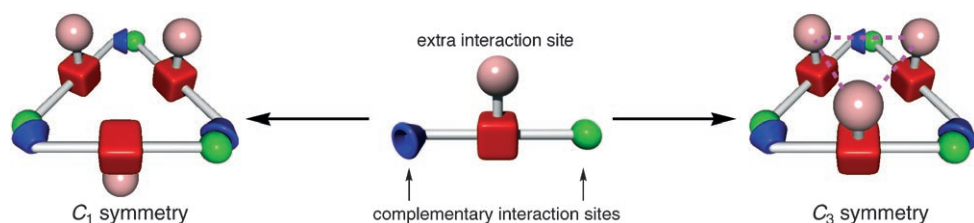


Figure 1. Supramolecular trimer formation: from a C_1 -symmetric monomer to C_1 -symmetric and C_3 -symmetric trimers.

When a mixture of **1** and zinc acetate in CH_2Cl_2 was stirred for 2 h at room temperature, metal coordination to the inner and outer nitrogen atoms of **1** and subsequent trimerization took place to afford trimers of the Zn complex (**1-Zn**). The formation of C_3 -symmetric (**2a**) and C_1 -symmetric (**2b**) trimer complexes (Figure 2 A) was confirmed by ^1H NMR spectroscopic analyses. In particular, the signals for the inner-core CH protons, which are sensitive to the symmetry of the trimers, were well-enough resolved to utilize as reporter signals for the respective trimers (Figure 2 B).

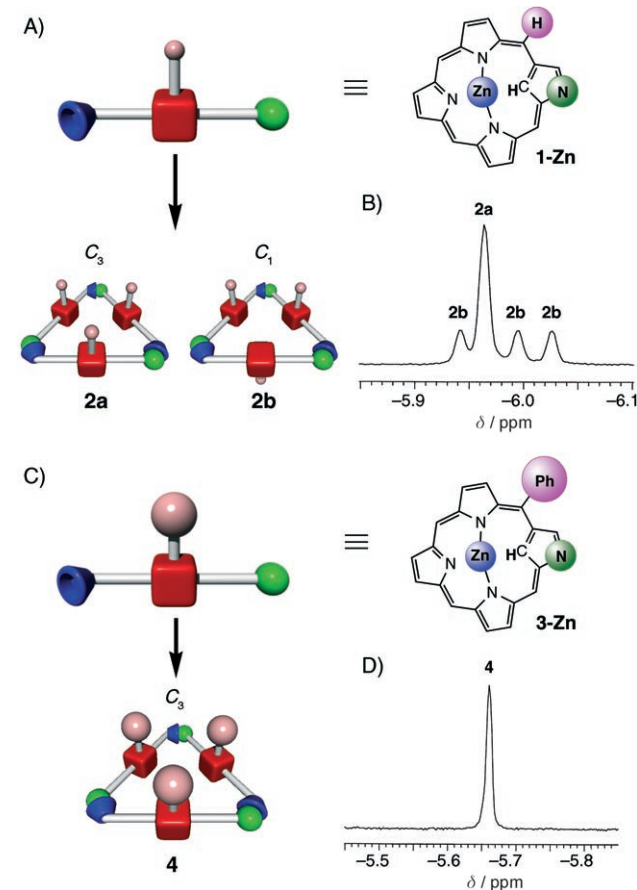


Figure 2. A) Formation of C_3 -symmetric trimer **2a** and C_1 -symmetric trimer **2b** from **1-Zn**. B) Partial ^1H NMR spectra showing the ^1H NMR signals of the inner CH proton in **2**. C) Formation of the C_3 -symmetric trimer **4** from **3-Zn**. D) Partial ^1H NMR spectra showing the signal of the inner CH proton in **4**. (Green ball: peripheral N atom; blue cone: Zn metal; small pink ball: H atom; large pink ball: Ph; red cube: porphyrin framework. See the Supporting Information for the schematic trimer structures.)

That is, only one singlet signal was observed for the inner CH protons in **2a**, whereas three different singlet signals could be detected with **2b** owing to the three inequivalent monomer parts. ESI mass spectrometry revealed intense fragmented monomer peaks along with small peaks corresponding to oligomers

up to the tetramer, which is probably a result of the lability of the trimer complexes under the measuring conditions (in which methanol was required to observe the spectra). The C_3 -symmetric trimer **2a** was more stable than the C_1 -symmetric trimer **2b**, and the molecular distribution was approximately 6:4 at 25°C in $[\text{D}_8]\text{toluene}$ (i.e. $\Delta G = +0.5 \text{ kJ mol}^{-1}$). The enthalpy and entropy changes on going from **2a** to **2b** were estimated as $\Delta H = (+3.9 \pm 0.2) \text{ kJ mol}^{-1}$ and $\Delta S = (+11.5 \pm 0.7) \text{ JK}^{-1} \text{ mol}^{-1}$, respectively. The entropy value is almost similar to the statistical value of $9.1 \text{ JK}^{-1} \text{ mol}^{-1}$ ($= R \ln 3$), which in general is related to the change from a C_3 -symmetric to a C_1 -symmetric species.

Next, the supramolecular trimer **4** with phenyl substituents was prepared from the phenyl-substituted porphyrin Zn^{II} complex **3-Zn** by the same procedure as used for preparing platform **2** (Figure 2 C). The trimeric structure of **4** was explicitly confirmed by X-ray single-crystal analysis (Figure 3).^[13] The platform is constructed by the mutual coordination of the peripheral nitrogen atom and the Zn^{II} center of the adjacent monomer, and the three phenyl groups are arranged on the same side of the platform. Focusing on the benzene trimer moiety, the benzene rings (a, b, and c in Figure 3) are closely located with center-to-center distances (r_{ab} , r_{bc} , r_{ca}) of 5.04(1), 4.93(1), and 5.33(1) Å, respectively. The dihedral angles between the three phenyl groups (a-b, b-c, c-a) are 82.0(7), 75.3(7), and 55.8(7) $^\circ$, respectively. Similar to the case of the chlorobenzene trimer, these values are inequivalent and the ring-to-ring distances are close to the calculated distance for the cyclic benzene trimer. The close contact of the three phenyl groups in **4** thus strongly suggests interactions in the benzene ring trimer moiety.

The introduction of phenyl substituent groups dramatically changed the distribution of the trimer in solution. In contrast to the presence of two species in trimer **2** from **1-Zn**, the phenyl-substituted species **3-Zn** afforded only one type of trimer **4** at 25°C in chloroform (Figure 2 D). The simplified ^1H NMR spectra of **4** are consistent with the observation of a C_3 -symmetric trimer in the solid state. Even at 100°C in toluene, the ^1H NMR signals of a trimer with C_1 symmetry were not detected. The preferential formation of the C_3 -symmetric trimer could be attributed to the stabilization by an additional interaction between the three phenyl groups in **4**. In fact, the close contact of the three phenyl groups in solution was clearly shown in the chemical shifts of the phenyl protons, whereby the five proton signals split and were highly shifted upfield ($\delta = 6.28, 6.63, 7.54, 7.82$, and 7.91 ppm), compared to the two overlap signals of the monomer **3** ($\delta = 8.31$ and 7.87 ppm). At 50°C in CDCl_3 , the two sets of split signals for

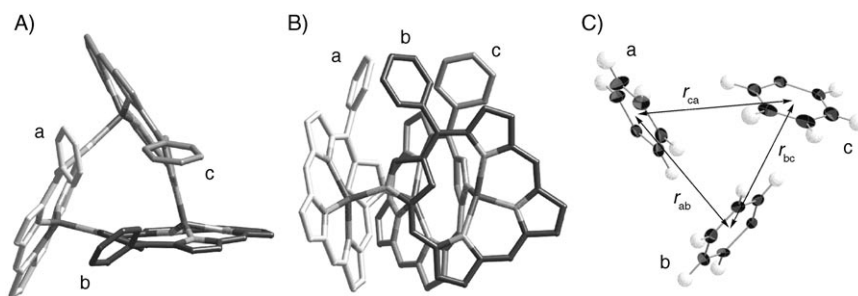


Figure 3. X-ray crystal structure of trimer **4**: A) top view and B) side view. Hydrogen atoms are omitted for clarity. C) ORTEP drawings of the benzene trimer part (50% probability level of thermal ellipsoids).

the *ortho* and *meta* protons coalesced to afford broad singlet signals at $\delta = 6.52$ and 7.68 ppm, respectively, which infers the rotation of the phenyl substituents in the trimer structure.^[14]

To evaluate the stabilization energy of a cyclic benzene ring trimer interaction, we planned to compare the relative amounts of the C_3 - and C_1 -symmetric trimers from **3-Zn** in solution. However, as described above, the large difference in stability energy prevented such an estimation. Consequently, we examined the dissociation reactions of **2a** and **4** instead (Figure 4). In principle, the difference in the dissociation

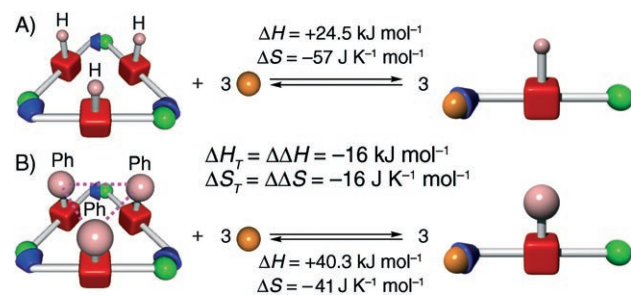


Figure 4. Schematic drawings of the dissociation reactions of the trimer complexes **2a** (A) and **4** (B) in the presence of $[D_5]$ pyridine (orange ball).

energies of **2a** and **4** should correspond to the stabilization energy of the benzene-ring trimer moiety. For the dissociation study, we used a mixed solvent of $[D_8]$ toluene and $[D_5]$ pyridine and estimated the corresponding energies from the molecular ratios of the trimer and the dissociated monomer, which could be determined from the signals in the ^1H NMR spectra at variable temperatures. Accordingly, the changes in enthalpy and entropy for the dissociation of **2a** and **4** were estimated as $\Delta H = (+24.5 \pm 0.8) \text{ kJ mol}^{-1}$ and $\Delta S = (-57 \pm 3) \text{ J K}^{-1} \text{ mol}^{-1}$, and $\Delta H = (+40.3 \pm 0.9) \text{ kJ mol}^{-1}$ and $\Delta S = (-41 \pm 3) \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. The stabilization enthalpy and the Gibbs free energy of our benzene ring trimer were thus calculated as $\Delta H_T = -16 \text{ kJ mol}^{-1}$ and $\Delta G_T = -11 \text{ kJ mol}^{-1}$ at 25°C . The large energy terms could explain the exclusive formation of the C_3 -symmetric trimer **4**. Moreover, the smaller entropy change of **4** compared to that of **2**, with the difference being $16 \text{ J K}^{-1} \text{ mol}^{-1}$, might reflect the ordered structure of **4** owing to the formation of the benzene ring trimer.

Interestingly, the enthalpy per interaction site of the trimer (ca. -5.3 kJ mol^{-1}) is almost the same magnitude as those of benzene ring dimers estimated in artificial model systems (-5.0 to -6.3 kJ mol^{-1}).^[1c] This observation is compatible with the recent claim from theoretical studies that the interaction energies in larger benzene clusters can be estimated by the simple sum of the interaction energies of the isolated benzene dimers,^[6a] though model systems usually afford lower values than those obtained by calculation probably as a result of a modification of the benzene rings in the former.

The Gibbs free energy of trimerization, $\Delta G_T = -11 \text{ kJ mol}^{-1}$ at 25°C , that is, approximately -4 kJ mol^{-1} per benzene–benzene interaction, is much higher than those for artificial aromatic ring dimer systems reported previously (-1.4 kJ mol^{-1} at 22°C for a phenyl–phenyl pair by Hunter and co-workers,^[3a] -1.0 kJ mol^{-1} at 22°C for a phenyl–tolyl pair by Wilcox and co-workers,^[3d] and -2.0 kJ mol^{-1} at 25°C for a phenyl–naphthyl pair by Jennings et al.^[1c]). This result simply shows that the large entropy loss associated with trimer formation is well overcome by the enthalpy gain in the cyclic trimer with three interaction sites.

In conclusion, from evaluation of the stabilization energy of a C_3 -symmetric supramolecule bearing three phenyl groups, it was shown that there is an attractive interaction between the three benzene moieties in solution and that its magnitude is of a similar order to that obtained from ab initio calculations.^[2,6a] The negative free energy change associated with benzene ring trimerization is large enough to stabilize certain supramolecular systems as shown here. Thus, the presence of such multiple-site interactions in higher-order aromatic clusters in biopolymers may contribute to stabilization of their tertiary structures to some extent, as one of several noncovalent hydrophobic interaction.^[5c,15] Although the benzene core in our system has a large substituent, the role of the porphyrin group is merely to provide a platform and the unique triangular interaction in the cyclic trimer should be ubiquitous. Thus, we believe that the benzene ring trimer interaction could serve as a kind of modulator for elaborated supramolecular systems, such as catalysts,^[16] C_3 -symmetric (supra)molecules,^[17] and foldamers.^[18]

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- [1] a) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244–1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250; b) C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urry, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651–659; c) W. B. Jennings, B. M. Farrell, J. F. Malone, *Acc. Chem. Res.* **2001**, *34*, 885–894;

- d) M. C. T. Fyee, J. F. Stoddart, *Acc. Chem. Res.* **1997**, *30*, 393–401.
- [2] M. O. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2006**, *110*, 10656–10668.
- [3] a) F. J. Carver, C. A. Hunter, D. J. Livingstone, J. F. McCabe, E. M. Seward, *Chem. Eur. J.* **2002**, *8*, 2847–2859; b) E. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193; c) R. Laatikainen, J. Ratilainen, R. Sebastien, H. Santa, *J. Am. Chem. Soc.* **1995**, *117*, 11006–11010; d) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498; e) E. Arunan, H. S. Gutowsky, *J. Chem. Phys.* **1993**, *98*, 4294–4296; f) J. R. Grover, E. A. Walters, E. T. Hui, *J. Phys. Chem.* **1987**, *91*, 3233–3237.
- [4] a) H. Krause, B. Ernstberger, H. J. Neusser, *Chem. Phys. Lett.* **1991**, *184*, 411–417; b) A. de Meijere, F. Huisken, *J. Chem. Phys.* **1990**, *92*, 5826–5834.
- [5] a) R. Bhattacharyya, U. Samanta, P. Chakrabarti, *Protein Eng.* **2002**, *15*, 91–100; b) N. Kannan, S. Vishveshwara, *Protein Eng.* **2000**, *13*, 753–761; c) G. B. McGaughey, M. Gagné, A. K. Rappé, *J. Biol. Chem.* **1998**, *273*, 15458–15463; d) S. K. Burley, G. A. Petsko, *Science* **1985**, *229*, 23–28.
- [6] a) T. P. Tauer, C. D. Sherrill, *J. Phys. Chem. A* **2005**, *109*, 10475–10478; b) C. Gonzalez, E. C. Lim, *J. Phys. Chem. A* **2001**, *105*, 1904–1908; c) O. Engkvist, P. Hobza, H. L. Selzle, E. W. Schlag, *J. Chem. Phys.* **1999**, *110*, 5758–5762.
- [7] T. Iimori, Y. Aoki, Y. Ohshima, *J. Chem. Phys.* **2002**, *117*, 3675–3686.
- [8] H. Uno, Y. Fumoto, K. Inoue, N. Ono, *Tetrahedron* **2003**, *59*, 601–605.
- [9] a) H. Furuta, T. Asano, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 767–768; b) P. J. Chmielewski, L. Latos-Grażyński, K. Rachlewicz, T. Głowiak, *Angew. Chem.* **1994**, *106*, 808–810; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 779–781.
- [10] a) H. Furuta, T. Morimoto, A. Osuka, *Inorg. Chem.* **2004**, *43*, 1618–1624; b) H. Furuta, T. Ishizuka, A. Osuka, *J. Am. Chem. Soc.* **2002**, *124*, 5622–5623.
- [11] T. Morimoto, S. Taniguchi, A. Osuka, H. Furuta, *Eur. J. Org. Chem.* **2005**, 3887–3890.
- [12] a) J. Wojaczyński, L. Latos-Grażyński, M. M. Olmstead, A. L. Blach, *Inorg. Chem.* **1997**, *36*, 4548–4554; b) M. Toganoh, N. Harada, T. Morimoto, H. Furuta, *Chem. Eur. J.*, DOI:10.1002/chem200600776.
- [13] Crystallographic data for **4**-CHCl₃: C₇₉H₄₉Cl₃N₁₂Zn₃, *M_r* = 1468.84, monoclinic, space group *P*1̄, *a* = 15.225(3), *b* = 15.442(3), *c* = 16.500(2) Å, *α* = 91.865(7)°, *β* = 109.600(7)°, *γ* = 115.960(8)°, *V* = 3211(1) Å³, *Z* = 2, *ρ*_{calcd} = 1.519 g cm^{−3}, *T* = −140 °C, 107414 measured reflections, 14666 unique reflections (*R*_{int} = 0.066), 8269 with *I* ≥ 3σ(*I*) used in refinement, *R* = 0.065, *R*_w = 0.095, GOF = 1.062. CCDC 622718 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge @Crystallographic Data Centre via @www.ccdc.cam.ac.uk/data_request/cif.
- [14] See the Supporting Information.
- [15] J. Liu, W. Yong, Y. Deng, N. R. Kallenbach, M. Lu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 16156–16161.
- [16] M. Nishio, Y. Umezawa, M. Hirota, Y. Takeuchi, *Tetrahedron* **1995**, *51*, 8665–8701.
- [17] S. E. Gibson, M. P. Castaldi, *Angew. Chem.* **2006**, *118*, 4834–4837; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718–4720.
- [18] M. T. Stone, J. M. Heemstra, J. S. Moore, *Acc. Chem. Res.* **2006**, *39*, 11–20.