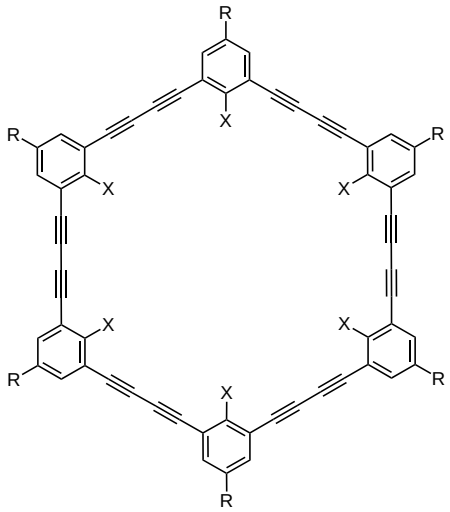
[1] P. van der Meijden, B. W. te Brommelstroet, C. M. Poirot, C. van der Drift, G. D. Vogels, *J. Bacteriol.* **1984**, *1 60*, 629 – 635.
[2] U. Harms, R. K. Thauer, *Eur. J. Biochem.* **1996**, *235*, 629 – 659.
[3] G. M. LeClerc, D. A. Grahame, *J. Biol. Chem.* **1996**, *271*, 18725 – 18731.
[4] E. Stupperich, R. Konle, *Appl. Environ. Microbiol.* **1993**, *59*, 3110 – 3116.
[5] E. Stupperich, 4th European Symposium on Vitamin B_{12} and B_{12} Proteins, Innsbruck, Austria, **1996**.
[6] a) T. M. Zydowsky, L. F. Courtney, V. Frasca, K. Kobayashi, S. J. Benkovic, H. G. Floss, *J. Am. Chem. Soc.* **1986**, *108*, 3152 – 3153; b) L. D. Zydowsky, T. M. Zydowsky, E. S. Haas, J. W. Brown, J. N. Reeve, H. G. Floss, *ibid.* **1987**, *109*, 7922 – 7933.
[7] Only a few reactions are known where OH^- reacts as a leaving group: the base-induced dehydration of aldols[8] and the base-induced epoxidation of Michael systems with H_2O_2 under basic conditions.[9]
[8] A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 1; R. L. Reeves in *Chemistry of the Carbonyl Group* (Ed.: S. Patai), Wiley-Interscience, New York, **1966**, pp. 580 – 593; H. O. House in *Modern Synthetic Reactions*, 2nd ed. (Ed.: W. A. Benjamin), Menlo Park, California, **1972**, pp. 629 – 682.
[9] C. A. Bunton, G. J. Minkoff, *J. Chem. Soc.* **1949**, 665 – 670.
[10] J. T. Jarrett, M. Amaratunga, C. L. Drennan, R. H. Sands, J. D. Scholten, M. L. Ludwig, R. G. Matthews, *Biochemistry*, **1996**, *35*, 2464 – 2475.
[11] R. Thauer, K. Sauer, *Eur. J. Biochem.* **1997**, *249*, 280 – 285.
[12] I. Bertini, *Inorg. Chem.* **1990**, *29*, 1460 – 1463.
[13] J. C. Gonzales, K. Peariso, J. E. Penner-Hahn, R. G. Matthews, *Biochemistry* **1996**, *35*, 12228 – 12234.
[14] J. J. Wilker, S. J. Lippard, *J. Am. Chem. Soc.* **1995**, *117*, 8682 – 8683.
[15] G. N. Schrauzer, J. W. Sibert, R. J. Windgassen, *J. Am. Chem. Soc.* **1968**, *90*, 6681 – 6688.
[16] Monomethylphosphate has been shown to methylate **1a** at 37 °C under the conditions described here. For other substrates such as trimethylphosphate for reaction with vitamin B_{12} derivatives, see a) J. M. Pratt, *Inorganic Chemistry of Vitamin B_{12}*, Academic Press, London, **1972**, chap. 12; b) J. M. Pratt in *Metal ions in Biological Systems*, *Vol. 30* (Eds.: H. Sigel, A. Sigel), Marcel Dekker, New York, **1992**, chap. 8.
[17] L. Tenud, S. Farooq, J. Seibl, A. Eschenmoser, *Helv. Chim. Acta* **1970**, *53*, 2059 – 2069.
[18] Intramolecular cleavage of an ester group separated by seven atoms from the corrin ring has been observed: M. J. Pfammatter, Dissertation, Universität Bern, **1997**.
[19] The heptaethylester **1b** was prepared from vitamin B_{12} and ethanol as described for **1a**.[22] The reference compound heptaethyl-Co-ethylcobyrinate was prepared by reduction of **1b** and alkylation with C_2H_5I, and obtained as a mixture of α/β isomers.
[20] It has not yet been determined whether **2c** or the isomer **3c** is formed under these conditions.
[21] Methylation of **1a** was also observed with anydrous $MgCl_2$ in 7% yield.
[22] S. Müller, A. Wolleb, L. Walder, R. Keese, *Helv. Chim. Acta* **1990**, *73*, 1659 – 1668.
[23] B. Kräutler, C. Caderas, *Helv. Chim. Acta* **1984**, *67*, 1891 – 1896.
[24] B. Grüning, G. Holze, A Gossauer, L. Ernst, *Helv. Chim. Acta* **1985**, *68*, 1771 – 1781.
[25] B. Grüning, A. Gossauer, *Tetrahedron Lett.* **1979**, 3497 – 3498.
[26] Y. Murakami, Y. Hisaeda, A. Kajihara, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3642 – 3646.

Synthesis and Association Behavior of [4.4.4.4.4.4]Metacyclophanedodecayne Derivatives with Interior Binding Groups

Yoshito Tobe,* Naoto Utsumi, Atsushi Nagano, and Koichiro Naemura

Recently Moore et al. disclosed the intriguing properties of phenylacetylene macrocycles (PAMs), which are based on self-organization properties owing to $\pi-\pi$ stacking interactions.[1] Moreover, Höger et al. reported the guest binding ability of a large macrocyclic metaparacyclophane to a large amine guest.[2] These properties based on weak intermolecular interactions can be fine-tuned by modifying the ring size, shape of the macrocycles, and the substituents on the periphery or interior of the macrocyclic framework. As an extension of our work on diethynylbenzene macrocycles (DBMs),[3] we disclose here the synthesis and novel association behavior of the hexameric DBM **1**, which has cyano groups in the interior of the macrocyclic framework. DBM **1** can be regarded as an extended derivative of the cyanospherand, which was shown to bind metal cations.[4] In contrast to the cyanospherand, we anticipated that **1** would be capable of binding relatively large molecules by ion-dipole or hydrogen-bonding interaction, because **1** possesses a well-defined cavity of about 7 Å diameter into which the geometrically ordered cyano groups are pointing. In addition, it is interesting to study the effect of cyano groups on the self-association behavior, since it has been well demonstrated that the $\pi-\pi$ interaction is sensitive to the substituent on aromatic rings.[5] It turned out that **1** exhibited novel association behavior; it



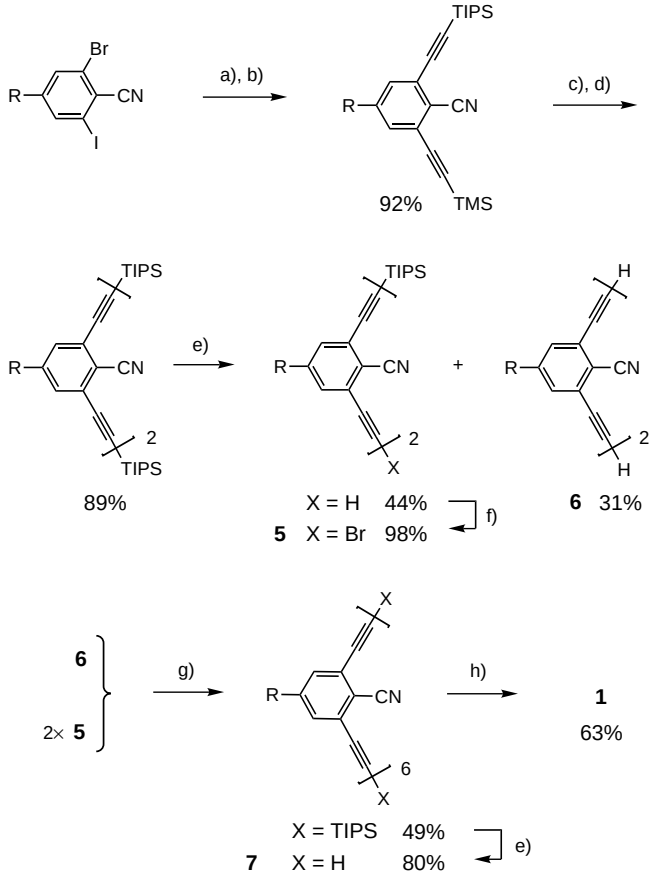
1	R=$CO_2C_8H_{17}$	X=CN
2	R=$CO_2C_8H_{17}$	X=H
3	R=H	X=CN
4	R=H	X=H

[*] Prof. Dr. Y. Tobe, N. Utsumi, A. Nagano, Prof. Dr. K. Naemura
Department of Chemistry
Faculty of Engineering Science, Osaka University
Toyonaka, Osaka 560 (Japan)
Fax: (+81) 6-850-6229
E-mail: tobe@chem.es.osaka-u.ac.jp

  1433-7851/98/3709-1285 $ 17.50+.50/0

formed heteroaggregates with its analogue **2** and 2:1 (host: guest) complexes with organic cations.

Compound **1** was synthesized by intramolecular coupling of open-chain precursor **7,** which was prepared by heterocoupling of dimer units **5** and **6** (Scheme 1).[6] The hexamer **2,** which has no cyano groups, was synthesized in a similar fashion.[7]



Scheme 1. Synthesis of **1** ($R = CO_2C_8H_{17}$). a) triisopropylsilylacetylene, $[Pd_2(dba)_3]\cdot CHCl_3$, CuI, PPh_3, NEt_3, 70 °C; b) trimethylsilylacetylene, $[Pd_2(dba)_3]\cdot CHCl_3$, CuI, PPh_3, NEt_3, 70 °C; c) LiOH, THF/H_2O, room temperature, 5 min; d) CuCl, *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA), O_2, acetone, room temperature; e) Bu_4NF, THF/H_2O, room temperature; f) *N*-bromosuccinimide (NBS), $AgNO_3$, acetone, room temperature; g) $[Pd_2(dba)_3]\cdot CHCl_3$, CuI, iPr_2NH, benzene, room temperature; h) $Cu(OAc)_2$, pyridine/benzene (3:2,[**7**] = 5.0×10^{-4} mol L^{-1}), room temperature. dba = dibenzylideneacetone, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

We found that **2** self-associated to form a dimer in solution ($CDCl_3$) with $\Delta G = -3.4$ kcal mol^{-1} at 293 K.[7] In contrast, the chemical shift of the aromatic protons of **1** did not show any concentration dependence in $CDCl_3$ even in the wide concentration range of 8.9×10^{-5} to 9.9×10^{-3} mol L^{-1}, indicating that **1** did not self-associate. We attribute this to the electrostatic repulsion between the nitrogen atoms, and the nonplanarity of the macrocyclic framework of **1**.[8] On the other hand, when **1** and **2** were mixed in $CDCl_3$, the chemical shift of the aromatic protons of **1** moved upfield depending on the concentrations of the both components (Figure 1). Since the plots of the chemical shift change did not fit the theoretical curve obtained by assuming the competitive formation of heterodimer **1**·**2** and homodimer (**2**)$_2$, we

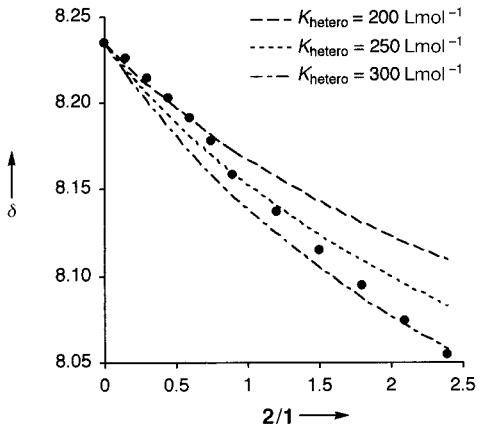


Figure 1. Chemical shift of the signal of the aromatic proton of **1** ($CDCl_3$; 303 K). The plot shows the observed values (●) from the titration of **1** with **2**, and the calculated values (dashed lines) based on the assumption of the formation of a heterodimer **1**·**2** and a homodimer (**2**)$_2$ with the given association constants K_{hetero} and the association constant K_{homo} = 174 L mol^{-1}, respectively. The ideal chemical shift of heterodimer **1**·**2** was assumed to be constant ($\delta_{hetero} = 7.0$).

deduce that **1** associates with **2** to form not only dimer **1**·**2** but also higher aggregates, that is, oligomers. Thus, the cyano groups of **1**, which hinder this self-association, serve to enhance an attractive $\pi-\pi$ stacking interaction toward **2** owing to their electron-withdrawing effect.

While hexamer **1** did not bind neutral molecules in $CDCl_3$,[9] distinct changes in the ^{1}H NMR chemical shifts were observed with cationic species such as tropylium tetrafluoroborate ($Tr^+BF_4^-$) and guanidinium tetraphenylborate ($Gu^+BPh_4^-$) in $CDCl_3/CD_3CN$ (8/2) (Figure 2). Although we expected the formation of 1:1 complexes,[10] the Job plots showed maxima at $x = 0.6-0.65$ of the mole fraction of **1**, indicating the competitive formation of 1:1 and 2:1 (host: guest) complexes. Moreover, from the nonlinear least-squares regression analysis of the titration curve (Figure 2), we estimated the association constants K_{11} and K_{21} for 1:1 and 2:1 complexations, respectively, with $Tr^+BF_4^-$ to be 4.0×10^1 and 6.3×10^4 L mol^{-1}, respectively, and with $Gu^+BPh_4^-$ to be

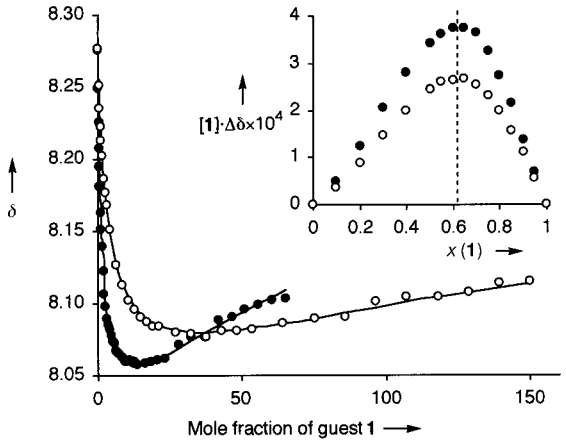


Figure 2. Chemical shift of the signal of the aromatic proton of **1** ($CDCl_3$/CD_3CN: 8/2; 303 K) in the titration with $Tr^+BF_4^-$ (●) and $Gu^+BPh_4^-$ (○). The lines were generated by computer-assisted curve fitting. Insert: Job plots for titration of **1** with $Tr^+BF_4^-$ (●) and $Gu^+BPh_4^-$ (○). Total concentration of host plus guest was maintained at 2.3×10^{-3} mol L^{-1}.

  1433-7851/98/3709-1286 $ 17.50+.50/0

4.0×10^1 and 2.5×10^4 L mol^{-1}, respectively. In contrast, the linear hexamer **11** did not show any binding ability to $Tr^+BF_4^-$.

The driving force for the formation of the 1:1 complex between **1** and the organic cations is the electrostatic ion–dipole interaction between the cation and the cyano groups preorganized to point inside the cavity of **1**. Regarding the driving force for the extremely facile formation of 2:1 complexes, we assume that the electrostatic interaction between the guest molecule in the 1:1 complex and the cyano groups of free **1** is most important.[11] Figure 3 shows that the electrostatic potential surface derived based on the AM1 calculations for a planar conformer of the model compound **3** changes dramatically when it binds a guest cation (Tr^+) to form a complex **3**·Tr^+.[12] As a result of the development of positive charge, the 1:1 complex **1**·Tr^+ could bind another molecule of **1** by electrostatic interaction. In addition, a $\pi-\pi$ stacking interaction between the aromatic rings of **1** may also be operative, because the calculated electron densities on the aromatic rings of **3**·Tr^+ are substantially reduced compared to that of **3**. In this respect, it should be pointed out that in the optimized geometry of complex **3**·Tr^+ the host molecule **3** adopts a planar conformation, which is favorable for $\pi-\pi$ stacking. Accordingly, it is deduced that complexation of **1** with a guest cation induces aggregation to another molecule of **1** to form 2:1 complexes.

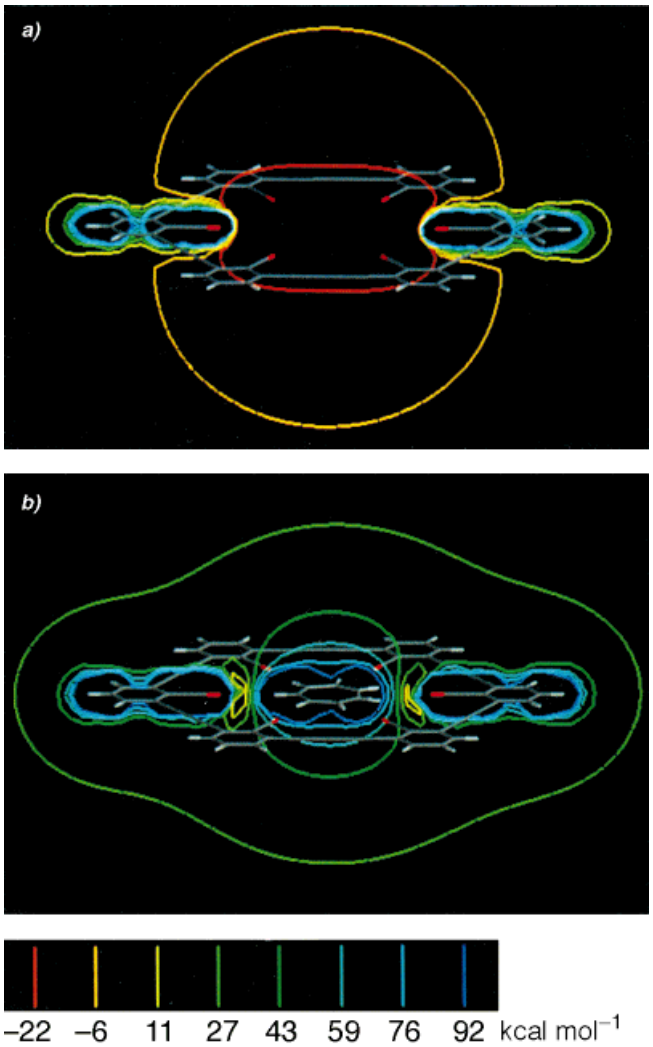


Figure 3. Contour plots for the calculated electrostatic potential surface (scales in kcal mol^{-1}) of **3** (a) and **3**·Tr^+ complex (b), sliced through the mirror plane that bisects the benzene rings. Calculations were done using the AM1 Hamiltonian implemented in SPARTAN 5.0.

In summary, we have synthesized the diethynylbenzene macrocycle **1,** which has intraannular cyano groups, and demonstrated its novel association behavior by which it forms heteroaggregates with **2** and 2:1 (host:guest) complexes with tropylium and guanidinium cations.

Received: November 25, 1997
Revised version: January 19, 1998 [Z11196IE]
German version: *Angew. Chem.* **1998**, *110*, 1347–1349

Keywords: carbocations · cyclophanes · host–guest chemistry · macrocycles · molecular recognition

[1] Self-association in solution: a) J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1992**, *114*, 9701; b) A. S. Shetty, J. Zhang, J. S. Moore, *ibid*. **1996**, *118*, 1019; discotic nematic liquid crystalline phase: c) J. Zhang, J. S. Moore, *ibid*. **1994**, *116,* 2655; highly ordered crystalline structure: d) D. Venkataraman, S. Lee, J. Zhang, J. S. Moore, *Nature* **1994**, *371*, 591.

[2] a) S. Höger, V. Enkelmann, *Angew. Chem.* **1995**, *107*, 2917; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2713; b) D. L. Morrison, S. Höger, *Chem. Commun*. **1996**, 2313.

[3] Y. Tobe, N. Utsumi, K. Kawabata, K. Naemura, *Tetrahedron Lett*. **1996**, *37*, 9325.

[4] K. Peak, C. B. Knobler, E. F. Maverick, D. J. Cram, *J. Am. Chem. Soc.* **1989**, *111,* 8662.

[5] a) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112,* 5525; b) F. Cozzi, M. Cinquini, R. Annuziata, T. Dwyer, J. S. Siegel, *J. Am. Chem. Soc*. **1992**, *114*, 5729.

[6] **1**: pale orange solid; m.p. >220 °C (decomp); ^{1}H NMR (270 MHz, $CDCl_3$, 30 °C): $\delta = 8.24$ (s, 12H; CH), 4.38 (t, $J = 6.8$ Hz, 12H; CH_2), 1.80 (quintet, $J = 6.8$ Hz, 12H; CH_2), 1.30 (m, 60H; CH_2), 0.9 (t, $J = 6.8$ Hz, 18H; CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, 30 °C): $\delta = 163.4$, 134.1, 133.9, 126.4, 123.9, 114.2, 80.3, 79.1, 66.7, 31.8, 29.2, 29.1, 28.5, 25.9, 22.6, 14.1; UV ($CHCl_3$): λ_{max} (logε) = 375 (4.93), 328 (4.98), 304 (4.97), 296 (4.98), 280 (5.18), 253 nm (5.23); MALDI-TOF MS: *m/z* 1854 [M − H+Na$^+$].

[7] The details for the synthesis and self-association properties of **2** will be reported elsewhere. **2**: pale yellow solid; m.p. >225 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, 14.9 mmol L^{-1}): $\delta = 7.23$ (s, 12H; CH), 7.07 (s, 6H; CH), 4.02 (s, 12H; CH_2), 1.69 (m, 12H; CH_2), 1.40 (m, 60H; CH_2), 0.97 (t, $J = 6.7$ Hz, 18H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$, 30 °C, 14.9 mmol L^{-1}): $\delta = 163.2$, 138.3, 132.4, 130.29, 130.3, 122.0, 79.8, 75.7, 65.5, 32.0, 29.5, 29.3, 28.5, 26.1, 22.8, 14.3; UV ($CHCl_3$): λ_{max}(logε) = 338 (5.21), 315 (5.30), 296 (5.08), 278 nm (4.93); MALDI-TOF MS: *m/z* 1683 [M^++H].

[8] The most stable geometry of the model compound **3** estimated by AM1 calculations is a chair conformation with a bent angle of about 35°. The planar conformation of **3** is less favored by 0.7 kcal mol^{-1}. Because the model compound **4** adopts a planar conformation, the dipole–dipole repulsion between the neighboring cyano groups must be responsible for the preference of nonplanar geometry of **3**.

[9] The neutral molecules examined include benzene, halobenzene derivatives, phenol, and aniline.

[10] AM1 calculations indicate large enthalpy gains for the complexation in the gas phase between the model compound **3** and Tr^+ (37 kcal mol^{-1}) and Gu^+ (38 kcal mol^{-1}), though the former cation has the wrong symmetry and the latter cation is too small to fit the cavity of **3**.

[11] Because of the instability of the complexes, we were not able to obtain crystals suitable for X-ray structure determination. We do not have, therefore, any structural information on the 2:1 complexes.

[12] A similar electrostatic potential surface was obtained for the 1:1 complex **3**·Gu^+.

  1433-7851/98/3709-1287 $ 17.50+.50/0