Allosteric binding of anionic guests to a bicyclic host which imitates the action of a 'turnstile'†

Osamu Hirata, Masayuki Takeuchi* and Seiji Shinkai*

A bicyclic host 1, which has a diethynyl tetrafluorophenyl axis and is expected to behave as an anion-binding 'turnstile', has been designed.

The design of artificial allosteric systems is of great significance to regulate the complexation ability or the catalytic activity of artificial receptors in a nonlinear fashion.[1,2] Especially, in a positive homotropic system, the guest binding information in one subunit could be passed to all other subunits in unison.[3] We have recently designed dimeric and oligomeric porphyrins with an axle moiety potentially capable of displaying positive homotropic allosterism, which can be utilized as a new concept to achieve nonlinear amplification of binding events and chemical signals towards high guest selectivity and high guest affinity.[4] In these systems, the porphyrins can rotate (or oscillate) relative to each other like two wheels around a central metal ion,[5] a bridging $C(sp_2)–C(sp_2)$ bond,[6] butadiyne,[7] ethynylene[8] or terphenyl group[9] which act as an axle.

We report herein that a bicyclic host 1 having two bisamide-type anion-binding sites with a diethynyltetrafluorophenyl 'turnstile'[10] displays a cooperative response towards anions.[11,12] Anion recognition events are ubiquitously seen in nature and have frequently been investigated for designing artificial receptors.[13,14] It is often difficult to control selectivity and sensitivity among anions because of their wide range of geometries, low charge to radius ratios and high solvation energies.[13h] Initially, 1 adopts a closed state which prevents the approach of guest anions, but when the first anion is bound to one site, the 'turnstile' is forced to rotate to give an open state which elicits the cooperative binding of a second anion to another site (Fig. 1).
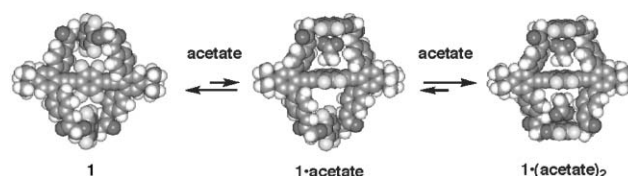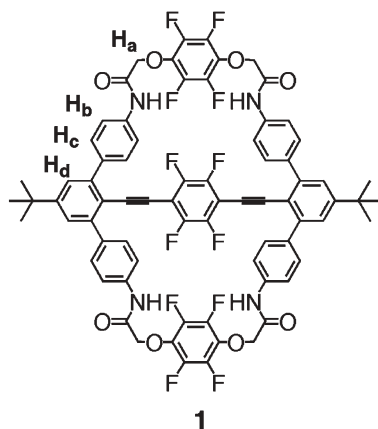

Fig. 1 Cooperative acetate binding to **1** with the energy-minimized structures of free **1**, **1**·acetate 1 : 1 complex and **1**·(acetate)$_2$ 1 : 2 complex.

Taking acetate anion as a guest, the structures of **1**, its 1 : 1 complex and 1 : 2 complex have been energy-minimized (Insight II, Discover 3). It is clearly seen from Fig. 1 that two cavities in **1** can be sterically filled up by a 'turnstile' tetrafluorophenyl group and two 'frame' tetrafluorophenyl groups, but when the first acetate anion is bound, the residual cavity is largely opened and preorganized. The F atoms in the 'turnstile' and 'frame' phenyl groups are introduced to increase the steric crowding for the closed state.

Compound **1** was synthesized according to Scheme 1 and identified by ^{1}H NMR, ^{19}F NMR and HR-FABMS spectroscopic evidence.‡

Upon addition of anion [acetate, phosphate, dibenzylphosphinate (Bz_2P), hydrogensulfate and halides as *n*-tetrabutylammonium salts] to a solution of **1** in THF-d_8–DMSO-d_6 5 : 1
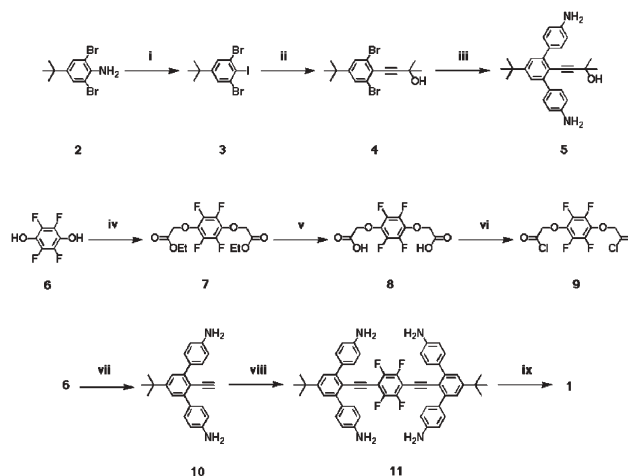
Scheme 1 *Reagents and conditions*: (i) NaNO$_2$, KI, conc. HCl(aq), 0 °C 79%; (ii) 3-methyl-1-butyne-3-ol, Pd(PPh$_3$)$_2$Cl$_2$, CuI, NH(*i*-Pr)$_2$, reflux 39%; (iii) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, Pd(dppf)Cl$_2$, Na$_2$CO$_3$, DME–H$_2$O, reflux 73%; (iv) ethylbromoacetate, K$_2$CO$_3$, THF, reflux 67%; (v) NaOH, THF–EtOH, r.t 93%.; (vi) SOCl$_2$, reflux quant.; (vii) NaOH, toluene, reflux 93%; (viii) 1,4-diiodotetrafluorobenzene, Pd(PPh$_3$)$_2$Cl$_2$, CuI, NH(*i*-Pr)$_2$, reflux 62%; (ix) **9**, 2,6-lutidine, CH$_2$Cl$_2$, r.t. under high dilution conditions, 24%.

1

Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka, 812-8581, Japan. E-mail: taketcm@mbox.nc.kyushu-u.ac.jp; seijitcm@mbox.nc.kyushu-u.ac.jp; Fax: +81-92-642-3611
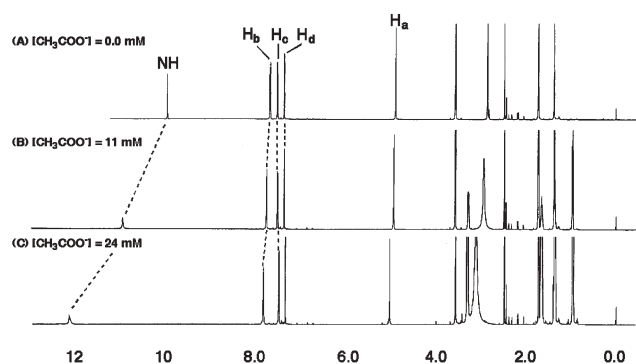† Electronic supplementary information (ESI) available: experimental details. See http://dx.doi.org/10.1039/b506883e

Fig. 2 ^{1}H NMR spectra (600 MHz) of **1** (4.0 mM) in THF-d_8–DMSO-d_6 (5 : 1, v/v) upon addition of acetate anion at 25 °C.

(v/v) mixed solvent, the peak for the NH protons in ^{1}H NMR and those for the F atoms in ^{19}F NMR both shift to lower magnetic fields with an increase in the anion concentration (Figs. 2, S1 and S2†).[15] A typical example for tetra-n-butylammonium acetate is shown in Fig. 2. In Table 1, we summarize the $\Delta\delta$ values for the NH protons and F atoms in the saturated region of the titration experiments. The results in Table 1 show that the shift width correlates to the basicity of each guest anion.

From plots of $\Delta\delta_{NH}$ against guest concentration one can estimate the complexation mode and the association constants (Fig. 3). A plot of $\Delta\delta_{NH}$ *vs.* [**1**]/([**1**] + [acetate]) (Job plot[16]) gave a maximum at 0.33 (Fig. S3), indicating that the complex consists of 1 : 2 **1** : acetate stoichiometry. Although the sigmoidal curvature characteristic of a positive homotropic system is not clearly seen in Fig. 3, the Hill plot for **1** and acetate provides evidence with n (Hill coefficient) = 1.4, showing that the acetate binding to **1** is taking place cooperatively.[17]

Table 1 Anion binding parameter of **1** in THF-d_8–DMSO-d_6 (5 : 1, v/v) at 25 °C

| | Binding constant^b/M^{-1} | | $\Delta\delta$ of **1**·X$^-_2$ complex/ppm^c | |
	n^a	K_1	K_2	N–H	Ar–F
CH$_3$COO$^-$	1.4	144 ± 2	66 ± 3	2.34	0.93, 0.32
Bz$_2$P$^-$	1.4	196 ± 5	71 ± 4	2.02	
Cl$^-$	1.1	110 ± 2	18 ± 2	1.64	0.46, 0.28
Br$^-$	1.5	50 ± 3	18 ± 5	0.73	0.35, 0.22
HSO$_4^-$	1.4	28 ± 1	9 ± 2	0.18	

^{a} Hill coefficient. ^{b} Errors < 10%. ^{c} Saturation point of anion titration curve.
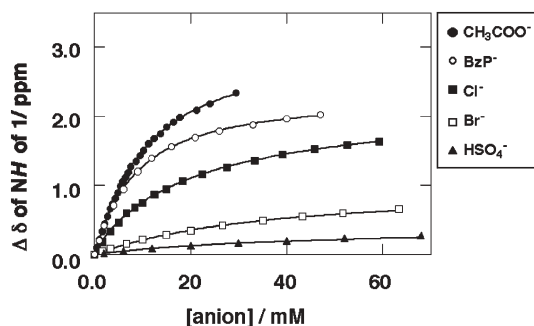
We analyzed the plot for acetate in Fig. 3 with a nonlinear least-squares method assuming the stepwise formation of 1 : 1 and 1 : 2 complexes and the association constants are summarized in Table 1. The association constants thus obtained are K_1 = 144 M^{-1} for the 1 : 1 complex and K_2 = 66 M^{-1} for the 1 : 2 complex (formation from the 1 : 1 complex), which satisfy the prerequisite for positive homotropic allosterism, $K_2 > 0.25K_1$ although the cooperativity is not so high.[17] The Hill coefficients and association constants for four other anions were evaluated by both Hill's equation and a nonlinear least-squares method (Fig. S4†). It is seen from the results summarized in Table 1 that (i) dibenzylphosphinate (Bz$_2$P$^-$), bromide and hydrogensulfate also have n = 1.4–1.5 comparable with that for acetate anion and the K_1 and K_2 values also satisfy the prerequisite for positive homotropic allosterism and (ii) the magnitudes of the K_1 and K_2 values correlate to the basicity of each guest anion.

There are two exceptions, however. Firstly, complexation of **1** with chloride did not satisfy the allosteric binding mode, having n = 1.1 and K_2 (=18 M^{-1}) < 0.25K_1 (=27 M^{-1}), indicating that there is no cooperativity. The K_1 value for chloride is sufficiently high among anions tested herein. Probably, the ion size of the chloride anion is not large enough to regulate the 'turnstile' tetrafluorophenyl group and the first guest binding cannot provide the preorganized open cavity advantageous to the second guest binding.[18] This result means that the slight difference in the ion size between chloride (the radius of chloride anion in an octahedral environment is 1.67 Å[13h]) and bromide (1.82 Å[13h]) has a decisive influence on the cooperativity. Secondly, upon addition of fluoride salt, the colour of the solution of **1** turned from yellow to orange with significant UV-Vis spectrum change, which was not observed for the addition of other anions. Furthermore, the ^{1}H NMR spectrum in the presence of fluoride gave the complicated split patterns. This colour change is rationalized by the acid–base reaction between the NH protons in **1** and fluoride anion rather than the hydrogen-bonding interaction[19] (Fig. S5†).

In conclusion, we have succeeded in the molecular design of a new dynamic host having an allosteric anion-binding function, motivated by the action of a 'turnstile'. Furthermore, the designed host is able to recognize anionic guests, the allosteric binding of which has scarcely been investigated so far in spite of its biological importance. We are now extending this dynamic recognition system to anion-binding in an aqueous system, aiming at the design of an allosteric interface with biologically-important guest anions.

Notes and references

‡ ^{1}H NMR (600 MHz, THF-d_3, δ/ppm, J/Hz) 1.38 (s, 18H), 4.85 (s, 8H), 7.41 (s, 4H) 7.56 (d, J = 8.3, 8H), 7.68 (d, J = 8.3, 8H), 9.29 (s, 4H). ^{19}F NMR(500 MHz, THF-d_8, TFA); −61.1, −81.9 ppm. HR-FABMS (matrix: NBA) calcd. (found) for C$_{74}$H$_{50}$F$_{12}$N$_4$O$_8$ 1350.3437 (1350.3430).

Fig. 3 Plots of $\Delta\delta_{NH}$ of **1** as a function of added anion.

1 For reviews on artificial allosteric systems: (*a*) L. Kovbasyuk and R. Kramer, *Chem. Rev.*, 2004, **104**, 3161; (*b*) M. Takeuchi, A. Sugasaki, M. Ikeda and S. Shinkai, *Acc. Chem. Res.*, 2001, **34**, 865; (*c*) T. Nabeshima, *Coord. Chem. Rev.*, 1996, **148**, 151; (*d*) J. Rebek, Jr., *Acc. Chem. Res.*, 1984, **17**, 258.

2 For recent artificial allosteric recognition systems: (*a*) H. Kawai, R. Katoono, K. Nishimura, S. Matsuda, T. Fujiwara, T. Tsuji and T. Suzuki, *J. Am. Chem. Soc.*, 2004, **126**, 5034; (*b*) N. C. Giannneschi, S.-H. Cho, S. T. Nguyen and C. A. Mirkin, *Angew. Chem., Int. Ed.*, 2004, **43**, 5503; (*c*) S.-Y. Chang, H.-Y. Jang and K.-S. Jeong, *Chem. Eur. J.*, 2004, **10**, 4358; (*d*) J. Raker and T. E. Glass, *J. Org. Chem.*, 2002, **67**, 6113; (*e*) T. Nabeshima, T. Saiki, J. Iwabuchi and S. Akine, *J. Am. Chem. Soc.*, 2005, **127**, 5507; (*f*) P. Thordarson, E. J. A. Bijsterveld, J. A. A. W. Elemans, P. Kasák, R. J. M. Nolte and A. E. Rowan, *J. Am. Chem. Soc.*, 2003, **125**, 1186; (*g*) G. Ercolani, *Org. Lett.*, 2005, **7**, 803; (*h*) P. D. Jones and T. E. Glass, *Tetrahedron*, 2004, **60**, 11057.

3 (*a*) J.-P. Changeux and S. J. Edelstein, *Neuron*, 1998, **21**, 959; (*b*) J. Wyman and S. J. Gill, *Binding and Linkage*, University Science Books, Mill Valley, CA, 1990.

4 S. Shinkai, A. Sugasaki, M. Ikeda and M. Takeuchi, *Acc. Chem. Res.*, 2001, **34**, 494.

5 (*a*) M. Takeuchi, T. Imada and S. Shinkai, *Angew. Chem., Int. Ed.*, 1998, **37**, 2096; (*b*) M. Ikeda, M. Takeuchi, A. Sugasaki, A. Robertson, T. Imada and S. Shinkai, *Supramol. Chem.*, 2000, **12**, 321; (*c*) M. Ikeda, T. Tanida, M. Takeuchi and S. Shinkai, *Org. Lett.*, 2000, **2**, 1803; (*d*) A. Sugasaki, M. Ikeda, M. Takeuchi, K. Koumoto and S. Shinkai, *Tetrahedron*, 2000, **56**, 4717; (*e*) A. Sugasaki, M. Ikeda, M. Takeuchi and S. Shinkai, *Angew. Chem., Int. Ed.*, 2000, **39**, 3839; (*f*) A. Sugasaki, K. Sugiyasu, M. Ikeda, M. Takeuchi and S. Shinkai, *J. Am. Chem. Soc.*, 2001, **123**, 10239; (*g*) A. Robertson, M. Ikeda, M. Takeuchi and S. Shinkai, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 739.

6 M. Ikeda, S. Shinkai and A. Osuka, *Chem. Commun.*, 2000, 1047.

7 Y. Kubo, M. Ikeda, A. Sugasaki, M. Takeuchi and S. Shinkai, *Tetrahedron. Lett.*, 2001, **42**, 7435.

8 (*a*) M. Ayabe, M. Ikeda, Y. Kubo, M. Takeuchi and S. Shinkai, *Angew. Chem., Int. Ed.*, 2002, **41**, 2790; (*b*) O. Hirata, M. Yamamoto, K. Sugiyasu, Y. Kubo, M. Ikeda, M. Takeuchi and S. Shinkai, *J. Supramol. Chem.*, 2002, **2**, 133.

9 Y. Kubo, A. Sugasaki, K. Sugiyasu, M. Ikeda, K. Sonoda, A. Ikeda, M. Takeuchi and S. Shinkai, *Org. Lett.*, 2002, **4**, 925.

10 Bedard and Moore reported a pioneering work for a molecular turnstile: (*a*) T. C. Bedard and J. S. Moore, *J. Am. Chem. Soc.*, 1995, **117**, 10662; Recently, Garcia-Garibay *et al.* and Gladysz *et al.* independently reported a molecular gyroscope: (*b*) Z. Dominguez, H. Dang, M. J. Strouse and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2002, **124**, 2398; (*c*) T. Shima, F. Hampel and J. A. Gladysz, *Angew. Chem., Int. Ed.*, 2004, **43**, 5537.

11 Rebek *et al.* have already reported artificial allosteric cation recognition by bicyclic crown ether derivatives: J. Rebek, Jr., T. Costello, L. Marshall, R. Wattley, R. C. Gadwood and K. Onan, *J. Am. Chem.*, 1985, **107**, 7481.

12 For positive homotropic allosteric anion sensing systems: (*a*) M. Yamamoto, A. Sugasaki, M. Ikeda, M. Takeuchi, K. Frimat, T. D. James and S. Shinkai, *Chem. Lett.*, 2001, 520; (*b*) M. Takeuchi, T. Shioya and T. M. Swager, *Angew. Chem., Int. Ed.*, 2001, **41**, 13474; (*c*) J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch and H. Furuta, *J. Am. Chem. Soc.*, 2004, **126**, 16507.

13 For reviews and books on artificial anion sensing systems: (*a*) M. D. Best, S. L. Tobey and E. V. Anslyn, *Coord. Chem. Rew.*, 2003, **240**, 3; (*b*) J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17; (*c*) J. M. Llinares, D. Powell and K. Bowman-James, *Coord. Chem. Rev.*, 2003, **240**, 57; (*d*) C. R. Bondy and S. J. Loeb, *Coord. Chem. Rev.*, 2003, **240**, 77; (*e*) K. Choi and A. D. Hamilton, *Coord. Chem. Rev.*, 2003, **240**, 101; (*f*) R. Martínez-Máñez and F. Sancenón, *Chem. Rev.*, 2003, **103**, 4419; (*g*) P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486; (*h*) F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609; (*i*) T. S. Snowden and E. V. Anslyn, *Curr. Opin. Chem. Biol.*, 1999, **3**, 740; (*j*) J. L. Sessler and J. M. Davis, *Acc. Chem. Res.*, 2001, **34**, 989; (*k*) A. Bianchi, K. Bowman-James and E. Garcia-Espana, *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, 1997; (*l*) P. Singh and B. A. Moyer, *Fundamentals and Applications of Anion Separations*, Kluwer Academic Publishers, New York, 2003.

14 For recent anion sensing systems: (*a*) J. L. Sessler, D. An, W.-S. Cho, V. Lynch and M. Marquez, *Chem. Commun.*, 2005, 540; (*b*) V. Amendola, M. Boiccchi, L. Fabbrizzi and A. Palchetti, *Chem. Eur. J.*, 2005, **11**, 120; (*c*) N. Matsumi, M. Miyake and H. Ohno, *Chem. Commun.*, 2004, 2852; (*d*) M. J. Chmielewski, M. Charon and J. Jurczak, *Org. Lett.*, 2004, **6**, 3501; (*e*) R. K. Mahajan, I. Kaur, R. Kaur, S. Uchida, A. Onimaru, S Shinoda and H. Tsukube, *Chem. Commun.*, 2003, 2238; (*f*) A. L. Sisson, J. P. Clare, L. H. Taylor, J. P. H. Charmant and A. P. Davis, *Chem. Commun.*, 2003, 2246; (*g*) K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 10241; (*h*) S. O. Kang, J. M. Lliares, D. Powell, D. VanderVelde and K. Bowman-James, *J. Am. Chem. Soc.*, 2003, **125**, 10152; (*i*) S. Kubik, R. Kirchner, D. Nolting and J. Seidel, *J. Am. Chem. Soc.*, 2002, **124**, 12752; (*j*) Y. Kubo, M. Yamamoto, M. Ikeda, M. Takeuchi, S. Shinkai, S. Yamaguchi and K. Tamao, *Angew. Chem., Int. Ed.*, 2003, **42**, 2036; (*k*) S. Yamaguchi, T. Shirasaka, S. Akiyama and K. Tamao, *J. Am. Chem. Soc.*, 2002, **124**, 8816; (*l*) C. R. Bondy, P. A. Gale and S. J. Loeb, *J. Am. Chem. Soc.*, 2004, **126**, 5030.

15 The UV-Vis spectrum of **1** was scarcely affected by anion addition, whereas the emission form **1** was quenched by anions (Fig. S6).

16 A. Job, *Ann. Chim. (10th series)*, 1928, **9**, 113.

17 (*a*) B. Perlmutter-Hayman, *Acc. Chem. Res.*, 1986, **19**, 90; (*b*) K. A. Connors, *Binding Constants*, John Wiley & Sons, New York, 1987.

18 Unfavorable electrostatics for the second chloride cannot be ruled out due to the higher charge density of the chloride anion.

19 (*a*) M. Boiocchi, L. D. Boca, D. E. Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *J. Am. Chem. Soc.*, 2004, **126**, 16507; (*b*) M. Boiocchi, L. D. Boca, D. E. Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Chem. Eur. J.*, 2005, **11**, 3097.