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Dopamine-selective potentiometric responses by new ditopic sensory elements based on a hexahomotrioxacalix[3]arene

Ryosuke Saijo, Saori Tsunekawa, Hiroyuki Murakami, Naohiro Shirai, Shin-ichi Ikeda and Kazunori Odashima*

Graduate School of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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Abstract—New ditopic sensory elements **2** and **3** for catecholamines based on a hexahomotrioxacalix[3]arene, with a boronic acid substituent appended, were designed and synthesized. As an interesting mode of molecular recognition at membrane surfaces, the host, when incorporated into poly(vinyl chloride) (PVC) liquid membranes, displayed excellent potentiometric selectivity for dopamine over other catecholamines (noradrenaline and adrenaline) and inorganic cations (Na^+, K^+, and NH_4^+).

Catecholamines (dopamine, noradrenaline, and adrenaline) are sympathetic neurotransmitters and play important roles in health and disease.[1] The recognition and sensing of dopamine in biological media is a particularly interesting subject. Dopamine is usually detected by HPLC methods.[2] On the other hand, the utilization of synthetic catecholamine receptors in optical detection is a challenging target in molecular recognition.[3] Such motifs have also been employed as ion-selective electrodes mounted on solvent polymeric membranes, which display the potentiometric responses to catecholamines and biogenic amines.[4] We have reported that the hexahomotrioxacalix[3]arene **1a**,[5] when incorporated into a poly(vinyl chloride) (PVC) liquid membrane, displayed a high selectivity in membrane potential changes for dopamine, compared to other catecholamines (noradrenaline and adrenaline) and inorganic cations (Na^+ and K^+).[4a] For further development of sensory elements for catecholamines, new hosts **2** and **3**,[6a,b] based on a hexahomotrioxacalix[3]arene with a boronic acid substituent appended, are described. As a ditopic catecholamine receptor, these hosts have a particular design, in that (1) the formation of tripodal hydrogen bonds between the *ethereal* and *phenolic* oxygens of the host and the NH_3^+ group of dopamine and (2) the boronic acid form a reversible covalent bond to the catechol portion (Fig. 1).[5,7]

The synthesis of host **2** is outlined in Scheme 1. The starting compound, **4**, was prepared according to the literature.[8] The cyclization of **4** with methanesulfonic acid under highly dilute conditions in anhydrous $CHCl_3$ gave **5** in 83% yield. The alkylation of **5** with methyl iodide gave **6** in 86% yield. The diphenyl ether, **7**, was prepared by the method of Buchwald,[9] in which **6** was treated with 3-(4-hydroxyphenyl)propyl acetate, $(CuOTf)_2{\cdot}PhH$, 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD), Cs_2CO_3 in toluene under reflux. The acetyl-protected alcohol was converted into a methylamino group in 4 steps. Finally, reductive amination with *o*-formylphenylboronic acid gave the host **2** in 29% yield from **7**.[10]

The synthesis of host **3** is outlined in Scheme 2. Compound **8**[6c] was prepared by a method similar to that used to prepare **7**, with methyl 3-(4-hydroxyphenyl)propanoate. After the hydrolysis of **8**, condensation with 2-((methylamino)methyl)phenylboronic acid gave the host **3** in 21% yield from **8**.

The complexation ability of hosts **2** and **3**, compared with hosts **1b**[5] and **8** as references, was monitored by the ^1H NMR spectroscopy in $CDCl_3/CD_3OD$ using dopamine hydrochloride (DA) and 2-phenylethylamine hydrochloride (PEA) as guests. The stability constants (K_s) of the host–guest complexes are listed in Table 1. Host **2** displayed strong binding to dopamine, compared

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* Corresponding author. Fax: +81 52 836 3462; e-mail addresses: odashima@phar.nagoya-cu.ac.jp; ikeshin@phar.nagoya-cu.ac.jp

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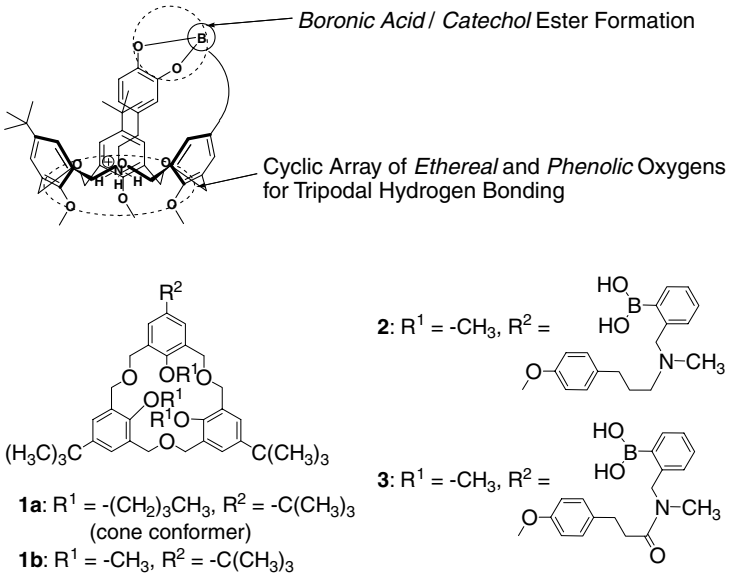
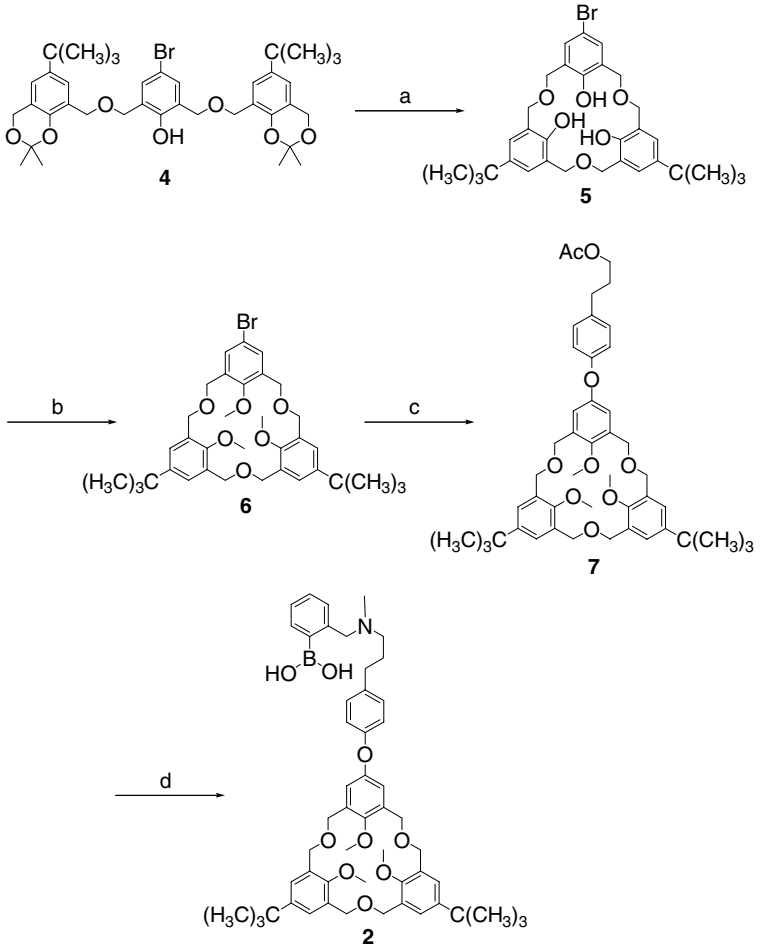
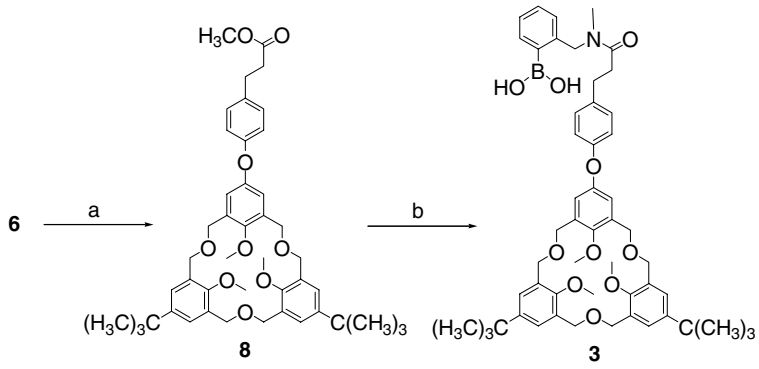


Figure 1. Schematic representation of the complexation geometry of the host–guest complex between host **2** and dopamine hydrochloride.



Scheme 1. Synthesis of host **2**. Reagents and conditions: (a) methanesulfonic acid, dry $CHCl_3$, rt, 1 h, 83%; (b) MeI, NaH, DMF, rt, 5 h, 86%; (c) 3-(4-hydroxyphenyl)propyl acetate, $(CuOTf)_2{\cdot}PhH$, TMHD, Cs_2CO_3, toluene, reflux, 43 h, 44%; (d) i—KOH, $EtOH/H_2O$, rt, 1.5 h; ii—MsCl, Et_3N, $CHCl_3$, rt, 5.5 h; iii—LiBr, acetone, rt, 13 h; iv—$MeNH_2$, K_2CO_3, THF/H_2O, reflux, 4 h; v—*o*-formylphenylboronic acid, $CHCl_3$/MeOH, then $NaBH_4$, rt, 7 h, 29% from **7**.



Scheme 2. Synthesis of host **3**. Reagents and conditions: (a) methyl 3-(4-hydroxyphenyl)propanoate, $(CuOTf)_2{\cdot}PhH$, TMHD, Cs_2CO_3, toluene, reflux, 40 h, 69%; (b) i—KOH, $EtOH/H_2O$, rt, 1.5 h; ii—2-((methylamino)methyl)phenylboronic acid, BOP, Et_3N, THF, rt, 4 h, 21% from **8**.

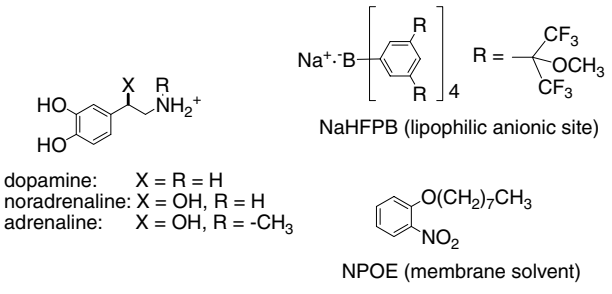
Table 1. Stability constants (K_s) for the host–guest complexes in $CDCl_3/CD_3OD$ = 80/20 at an ambient temperature (ca. 25 °C) with TMS as the external standard

Guests	K_s [M^{-1}]			
	Host **1b**	Host **2**	Host **3**	Host **8**
DA	400	3200	480	60
PEA	1700	<10	350	480

DA, dopamine hydrochloride; PEA, 2-phenylethylamine hydrochloride.

with hosts **1b** and **8**. Such a large improvement was not observed with host **3**. This indicates that N–B bond formation between the boron atom and the neighboring nitrogen atom of host **2** accelerates the association of boronic acid with catechol portion of dopamine.[11] On the other hand, the selectivity of host **3** for dopamine over 2-phenylethylamine was improved, compared with hosts **1b** and **8**, because of the steric hindrance effect of the linker (**1b** vs **8**) and the strong binding between the boronic acid and catechol (**3** vs **8**).

We next investigated the potentiometric selectivities of hosts **1b**, **2**, **3**, and **8** incorporated into PVC matrix liquid membranes (membranes I, II, III, and IV, respectively). The membrane components were as follows: *o*-nitrophenyl octyl ether (NPOE) as a membrane solvent, PVC as a polymer matrix,[12] and sodium tetrakis[3,5-bis(1,1,1,3,3,3-hexafluoro-2-methoxy-2-propyl)phenyl]borate (NaHFPB) as a lipophilic anionic site [host:NaHFPB = 1:0.30 (molar ratio)]. This mixture resulted in stable and reproducible membrane potentials. The electrode cell for the potential measurements was as follows: Ag | AgCl | satd aq KCl | 1 M CH_3COOLi | sample solution | membrane | 10^{-2} M NaCl | AgCl | Ag.



The potentiometric response curves for membrane III and a blank membrane are shown in Figures 2a–b, respectively. Cationic responses were observed in all cases due to complexation between the monocationic guests and the neutral hosts in the membrane boundary region. The relative magnitudes of membrane potential

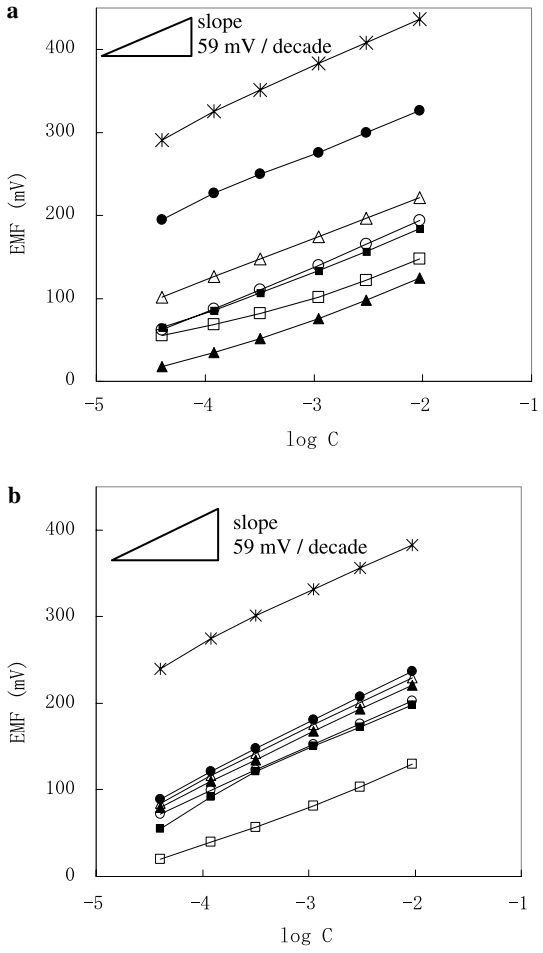


Figure 2. Membrane potential (electromotive forces; EMF) vs concentration curves for dopamine (●, DA), noradrenaline (■, NA), adrenaline (▲, AD), 2-phenylethylamine (∗, PEA), and inorganic cations (□, Na^+; △, K^+; ○, NH_4^+), measured at room temperature with (a) membrane III incorporated with host **3** and (b) blank membrane without a host.

Table 2. Potentiometric selectivity coefficients ($K^{pot}_{A,B}$) for PVC matrix liquid membranes (I, III and IV) incorporated with hosts (**1b**, **3**, and **8**) and blank membrane without a host[a]

Guests	Membrane[b]			
	I	III	IV	Blank
PEA	190	100	260	380
DA	1	1	1	1
NA	0.043	0.0040	0.070	0.28
AD	—[c]	0.00033	—[c]	0.55
NH_4^+	0.016	0.0073	0.029	0.18
K^+	0.052	0.012	0.099	0.66
Na^+	0.0038	0.00072	0.0031	0.0091

DA, dopamine; NA, noradrenaline; AD, adrenaline; PEA, 2-phenylethylamine.

[a] Potentiometric selectivities are given by selectivity coefficients ($K^{pot}_{A,B}$), determined at unbuffered solution with DA as a standard.[13]

[b] For the compositions of the membranes, see References and Notes.[12]

[c] Could not be estimated because of the large deviation from the Nernstian slope due to weak complexation.

changes are listed in Table 2 as potentiometric selectivity coefficients ($K^{pot}_{A,B}$).[13] Unfortunately, it was not possible to estimate the potentiometric selectivity coefficients of membrane II because of severe interference by protons. Thus, the amine linkage of host **2** appears to undergo protonation at the membrane boundary region. Except for 2-phenylethylamine (PEA), membrane I, in which host **1b** was incorporated, displayed potentiometric selectivity for dopamine (DA) over other catecholamines and inorganic cations. On the other hand, membrane III, in which host **3** was incorporated, displayed higher selectivities for DA than membrane I, with host **1b** incorporated and membrane IV, with host **8** incorporated. The host-induced changes in membrane potential [EMF (Fig. 2a) − EMF (Fig. 2b)] were ca. +90 mV for DA and <+20 mV for the other catecholamines and inorganic guests. The potentiometric selectivity coefficient for DA over noradrenaline (NA) was particularly remarkable ($K^{pot}_{DA,NA} = 0.0040$).

The potentiometric selectivity coefficient for DA over adrenaline (AD) in the membranes I and IV could not be estimated. On the other hand, it could be estimated in the membrane III ($K^{pot}_{DA,AD} = 0.00033$). This result would be due to the increase of the potentiometric response of AD caused by the effect of the interaction between the boronic acid group of host **3** and the catechol unit. Compared with host **1b** and **8**, host **3** also displayed an improved potentiometric selectivity for DA over PEA. This demonstrates the effect of the ditopic binding sites, that is, the *ethereal* and *phenolic* oxygens of the host for the NH_3^+ group of dopamine and the boronic acid substituent of the host for the catechol portion. However, much stronger binding to DA is necessary, to potentiometric discriminate between DA and PEA, because the PEA response of blank membrane is about 400-fold stronger than DA. It should be noted that selectivity reflects the difference in lipophilicity for each guest.

In conclusion, host **3** having ditopic binding sites displayed particularly high potentiometric selectivities for dopamine in comparison with host **1b**, having only a monotopic binding site. Efforts to improve dopamine selectivity even further are now in progress.

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6. (a) Host **2**; a white solid: mp 94–96 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.29 (s, 18H, *t*-Bu), 2.03 (quin, J = 7.9 Hz, 2H, $ArCH_2CH_2$), 2.56 (s, 3H, NCH_3), 2.64 (t, J = 7.3 Hz, 2H, NCH_2CH_2), 2.96 (t, J = 7.3 Hz, 2H, $ArCH_2CH_2$), 3.11 (s, 3H, OCH_3), 3.27 (s, 6H, OCH_3), 4.07 (s, 2H, $ArCH_2N$), 4.42 (s, 4H, $ArCH_2O$), 4.49 (s, 4H, $ArCH_2O$), 4.50 (s, 4H, $ArCH_2O$), 6.83 (d, J = 8.5 Hz, 2H, Ar*H*), 6.87 (s, 2H, Ar*H*), 7.09 (d, J = 7.6 Hz, 1H, Ar*H*), 7.14–7.17 (m, 1H, Ar*H*), 7.16 (d, J = 8.5 Hz, 2H, Ar*H*), 7.23 (t, J = 7.6 Hz, 1H, Ar*H*), 7.32 (dd, J = 7.6, 2.7 Hz, 4H, Ar*H*), 7.57 (d, J = 7.6 Hz, 2H, Ar*H*). IR (KBr disk) ν_{max} 3425 (νOH), 2950, 1470, 1380, 1215, 1080 cm^{-1}. HRMS for $C_{52}H_{67}BNO_9$ $[M+H]^+$: Calcd, 860.4903. Found, 860.4863.; (b) Host **3**; a white solid: mp 109–111 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.29 (s, 18H, *t*-Bu), 2.66–2.75 (m, 2H, $COCH_2$), 2.83 (s, 3H, NCH_3), 2.86–2.96 (m, 2H, $ArCH_2CH_2$), 3.11 (s, 3H, OCH_3), 3.27 (s, 6H, OCH_3), 4.42 (s, 4H, $ArCH_2O$), 4.48 (s, 4H, $ArCH_2O$), 4.50 (s, 4H, $ArCH_2O$), 4.60 (s, 2H, $ArCH_2N$), 6.84 (d, J = 8.5 Hz, 2H, Ar*H*), 6.87 (s, 2H, Ar*H*), 7.05 (d, J = 8.2 Hz, 1H, Ar*H*), 7.12 (d, J = 8.2 Hz, 2H, Ar*H*), 7.21 (d, J = 8.2 Hz, 1H, Ar*H*), 7.25–7.26 (m, 1H, Ar*H*), 7.32 (d, J = 8.5 Hz, 4H, Ar*H*), 7.35–7.29 (m, 1H, Ar*H*). IR (KBr disk) ν_{max} 3425 (νOH), 2950, 1620 (νC=O), 1490, 1360, 1215, 1070 cm^{-1}. HRMS for $C_{54}H_{68}BNO_{10}Na$ $[M+2MeOH–2H_2O+Na]^+$: Calcd, 924.4828. Found, 924.4868.; (c) Host **8**; colorless hard gum: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 18H, *t*-Bu), 2.63 (t, J = 7.6 Hz, 2H, $COCH_2$), 2.92 (t, J = 7.6 Hz, 2H, $ArCH_2CH_2$), 3.08 (s, 3H, OCH_3), 3.24 (s, 6H, OCH_3), 3.68 (s, 3H, $COOCH_3$), 4.44 (s, 4H, $ArCH_2O$), 4.49 (s, 4H, $ArCH_2O$), 4.50 (s, 4H, $ArCH_2O$), 6.86 (d, J = 8.5 Hz, 2H, Ar*H*), 6.94 (s, 2H, Ar*H*), 7.12 (d, J = 8.8 Hz, 2H, Ar*H*), 7.29 (d, J = 2.1 Hz, 4H, Ar*H*). IR (KBr disk) ν_{max} 2950, 1740 (νC=O), 1480, 1215, 1070 cm^{-1}. HRMS for

$C_{45}H_{56}O_9Na$ $[M+Na]^+$: Calcd, 763.3817. Found, 763.3801. Anal. Calcd for $C_{45}H_{56}O_9 \cdot 0.55CHCl_3$: C, 67.83; H, 7.07. Found: C, 67.82; H, 7.01.

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13. Potentiometric selectivity coefficients ($K^{pot}_{A,B}$) were determined at room temperature (ca. 25 °C) by the separate solution method (Srinivasan, K.; Rechnitz, G. A. *Anal. Chem.* **1969**, *41*, 1203). For potentiometric selectivity coefficients, see: (a) *CRC Handbook of Ion-Selective Electrodes: Selectivity Coefficients*; Umezawa, Y., Ed.; CRC Press: Boca Raton: USA, 1990; (b) Umezawa, Y.; Bühlmann, P.; Umezawa, K.; Tohda, K.; Amemiya, S. *Pure Appl. Chem.* **2000**, *72*, 1852; (c) Umezawa, Y.; Umezawa, K.; Bühlmann, P.; Hamada, N.; Nakanishi, J.; Aoki, H.; Sato, M.; Nishimura, Y.; Xiao, K. P. *Pure Apple. Chem.* **2002**, *74*, 923; (d) Umezawa, Y.; Bühlmann, P.; Umezawa, K.; Hamada, N. *Pure Appl. Chem.* **2002**, *74*, 995; (e) Umezawa, Y. In *Encyclopedia of Supramol. Chem*; Atwood, J., Steed, J., Eds.; Marcel Dekker: USA, 2004; p 747.