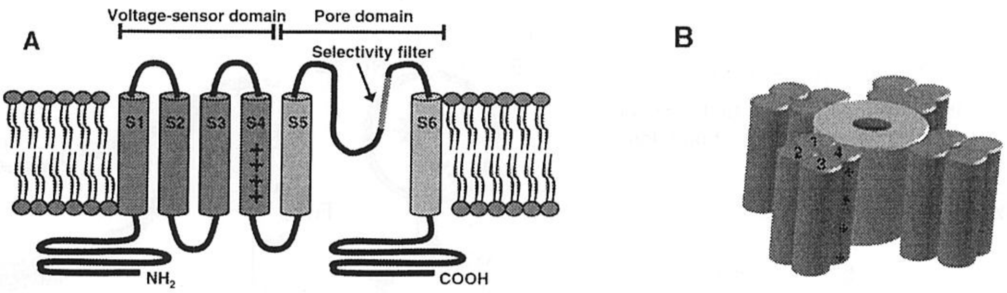
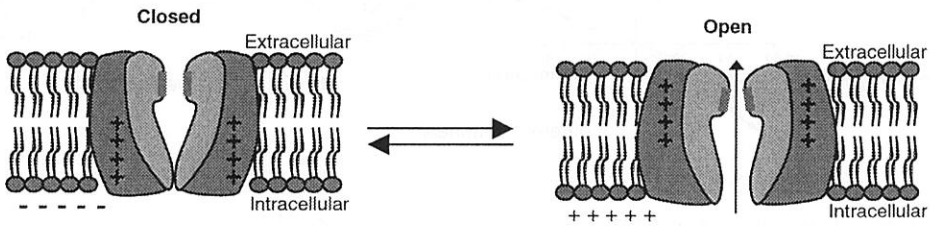
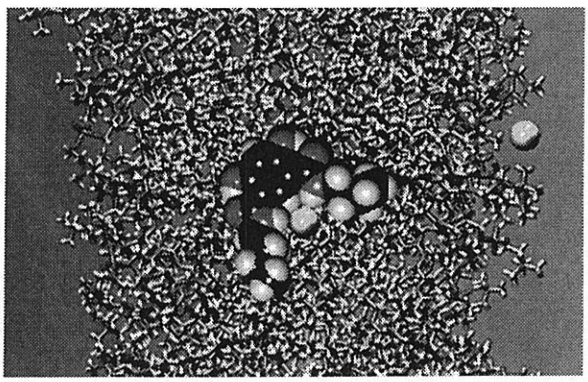
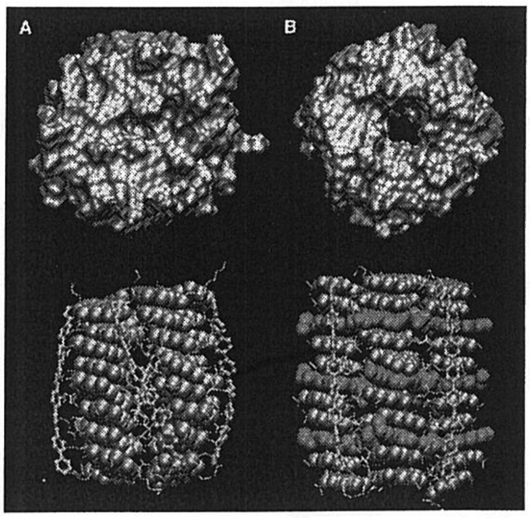
Artificial Ion Channels ~How Can We Regulate Permeability~





" *No painter would ever dream of doing better than Nature,* "
but no painter would stop painting because of this conclusion.





Recent Reviews about arifcial ion channel

Matile, S. et al. *Tetrahedron* **2004**, *60*, 6405.
Matile, S. et al. *Mol. BioSyst.* **2007**, *3*, 658.
Cragg, P. J. et al. *Dalton Trans.* **2007**, 26.
Fyles, T. M. *Chem. Soc. Rev.* **2007**, *36*, 335.
Matile, S. et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 2.
Binder, W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3092.

See also, Tanaka-kun's excellent literature seminar #080604

Contents

1 Introduction

Yang, D. et al. *J. Am. Chem. Soc.* **2007**, *129*, 7264.
Yang, D. et al. *Acc. Chem. Res.* **2008**, *41*, 1428.
Yang, D. ICOS-17 abstract paper.

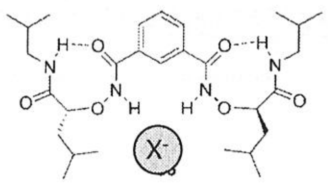


Table 1. Association Constants for the Binding of **1** with Anions[a] in $CDCl_3$ at 25 °C

anions	K (M^{-1})[b]	$\Delta\delta_{max}$ (O-NH)[c]	$\Delta\delta_{max}$ (NH)[c]
Cl^-	>100000	2.17	0.37
Br^-	18000	1.73	0.31
I^-	1500	1.44	0.28
NO_3^-	1100	1.28	0.32
$H_2PO_4^-$	1400[d]	e	0.81

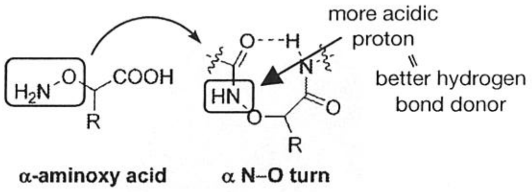
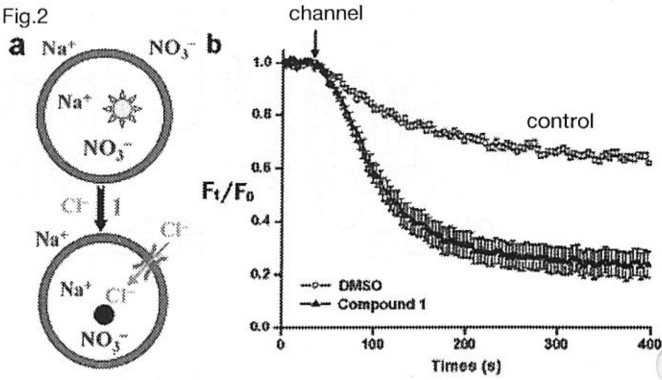
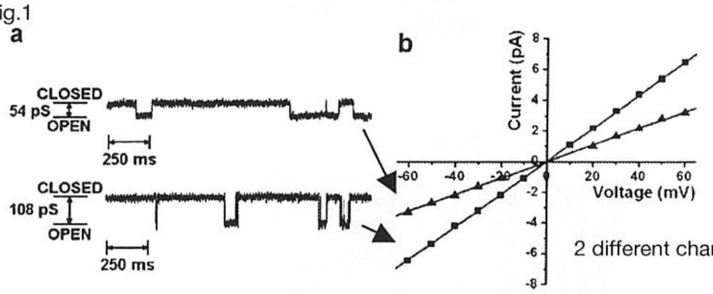


Fig.2



No K^+ or Na^+ permeability

Fig.1



2 different channels

Gale, P. A. and Quesada, R. et al. *J. Am. Chem. Soc.* **2007**, *129*, 1886.

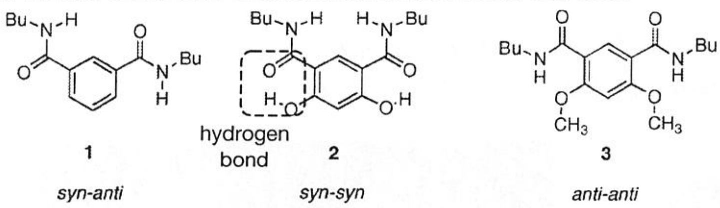


Table 1. Association Constants K_a (M^{-1}) for **1** and **2** Binding Cl^-, Br^-, and I^- (n-Bu_4N^+ Salts) Measured at 298 K in CD_3CN (Errors <10%)

compound	Cl^-	Br^-	I^-
1	195	60	15
2	5230	716	152

Fig.3

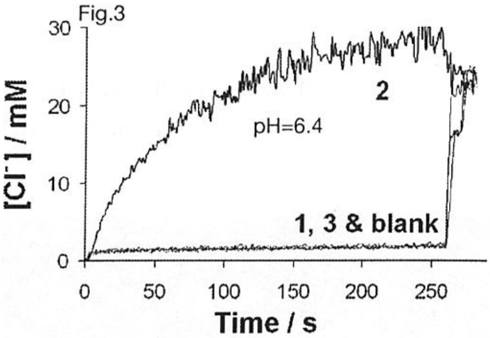
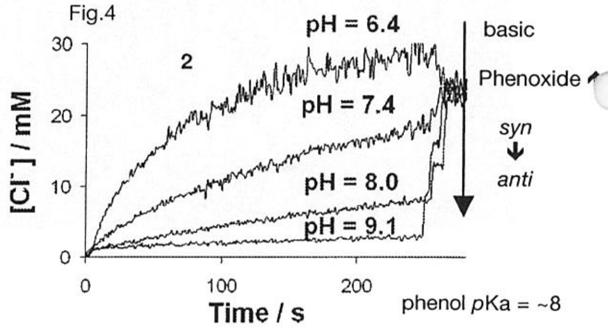


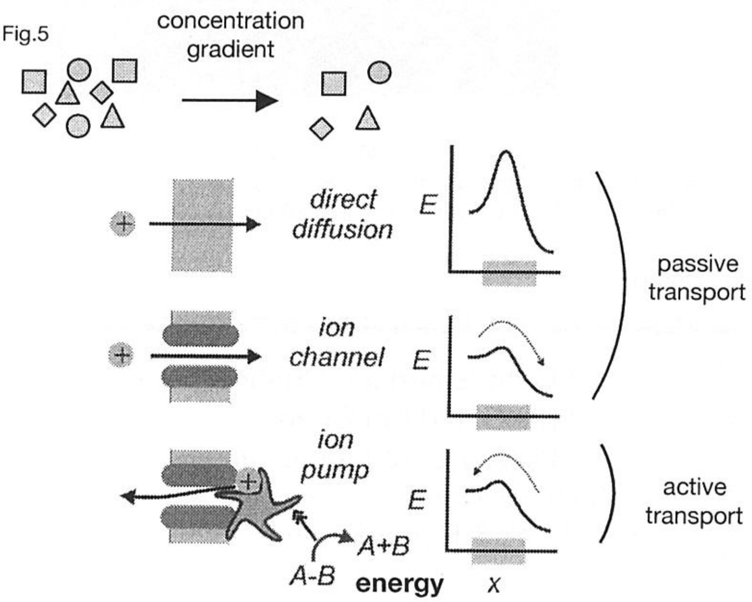
Fig.4



phenol pKa = ~8

2 Review of Ion Channel

Fig.5



Ion channel is the catalyst for ion permeation.

Fig. 6

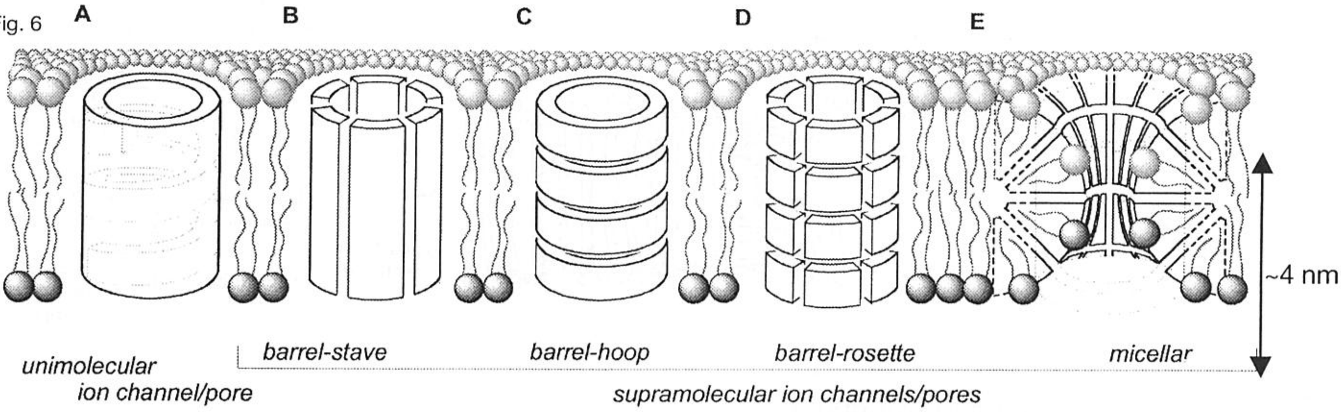
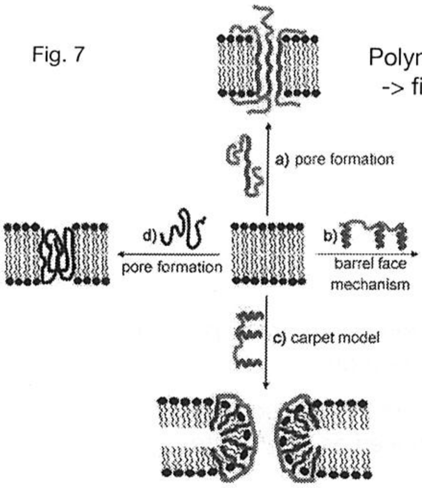


Fig. 7



Polymer induced pore formation
-> final structure is less predictable

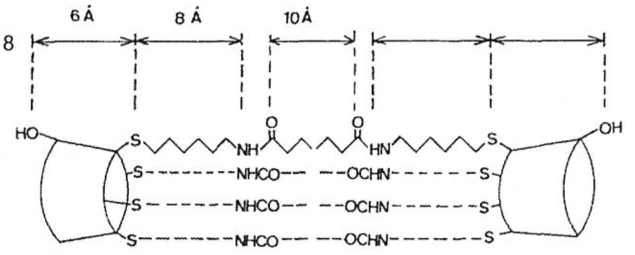
Reauired features

+ membrane-spanning structure(length)
+ significant volume for the passage of the ion
+ the interior of the channel is hydrophilic.
+ enough interaction to embed into a bilayer membrane

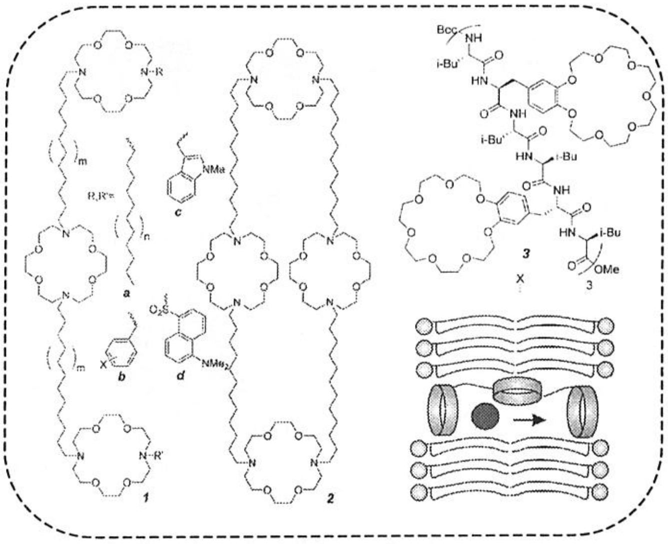
✔ First Artificial Ion Channel

Tabushi, I. et al. *Tetrahedron Lett.* **2007**, *129*, 7264.

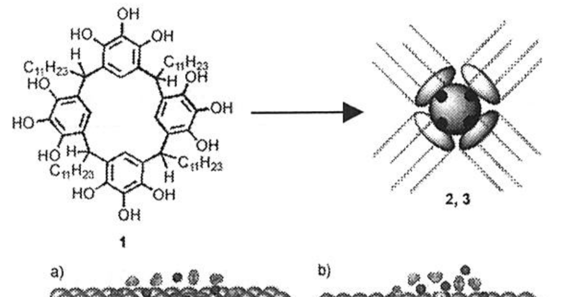
Fig. 8



β-cyclodextrin



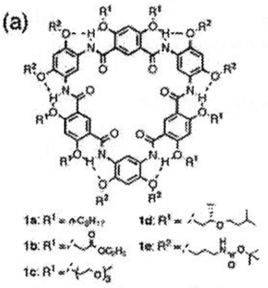
Gokel, G. W. et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 2375



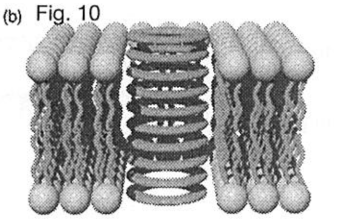
✔ Recent Report

Shao, Z. and Gong, B. et al. *J. Am. Chem. Soc.* **2008**, *130*, 15784.

Fig. 9 (a)



(b) Fig. 10



Davis, J. T. et al. *J. Am. Chem. Soc.* **2009**, *131*, 2458.

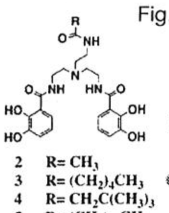
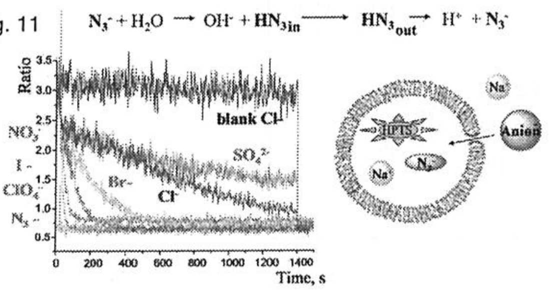


Fig. 11



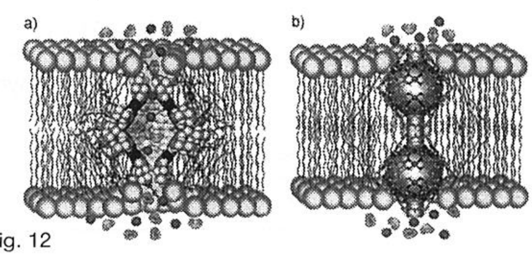


Fig. 12

Gramicidin
toxic peptide produced by *Bacillus brevis*

Amphotericin B
antifungal agent

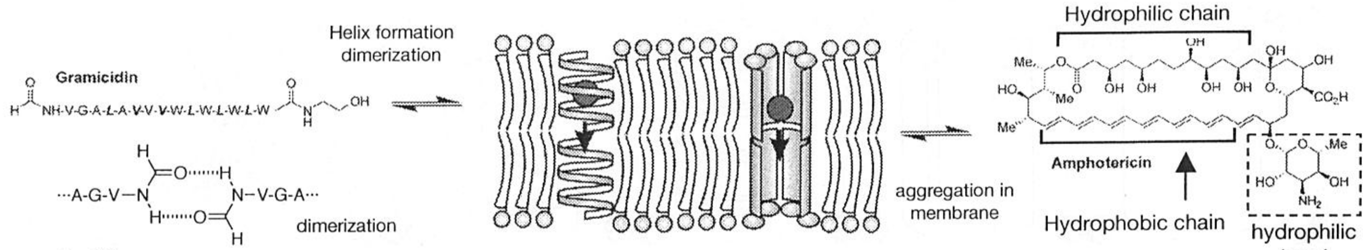


Fig.13

3 Regulation of a natural Ion Channel

Fig.14

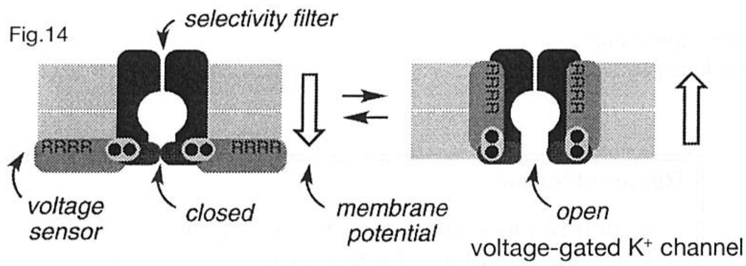
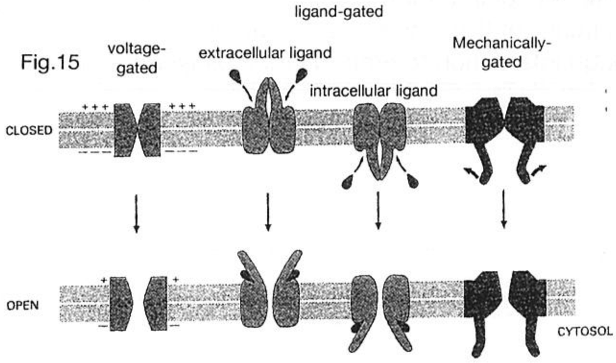


Fig.15



A complete “off” response is more important than a complete “on” response.

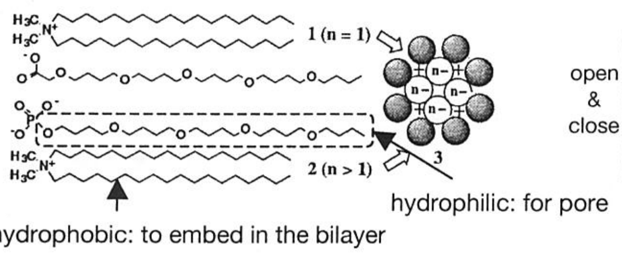
→ The lowest energy isomer is often chosen as “off” state.

4 Gated Ion Channel

4.1 Voltage Gated Ion Channel

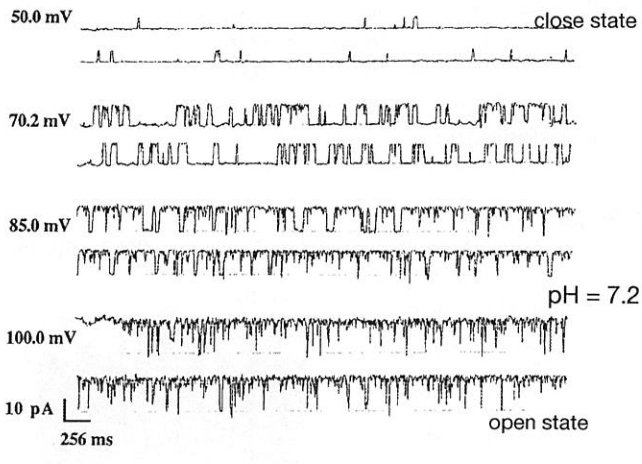
First example: Kobuke, Y. et al. *Chem. Lett.* **1995**, 435.

Fig.16

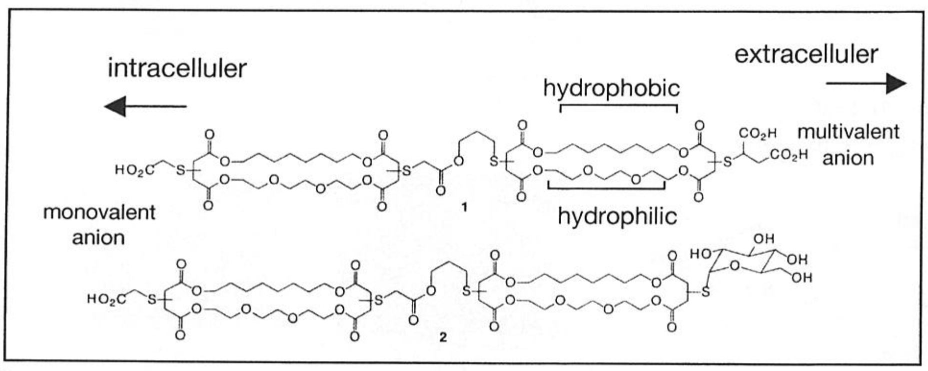


different valency is important

Fig.17



Fyles, T. M. et al. *J. Am. Chem. Soc.* **1998**, *120*, 2997.



Different valency at both hydrophilic head made transmembrane orientation.

1 vs **2**

First bilayer was prepared and then amphiphile was added

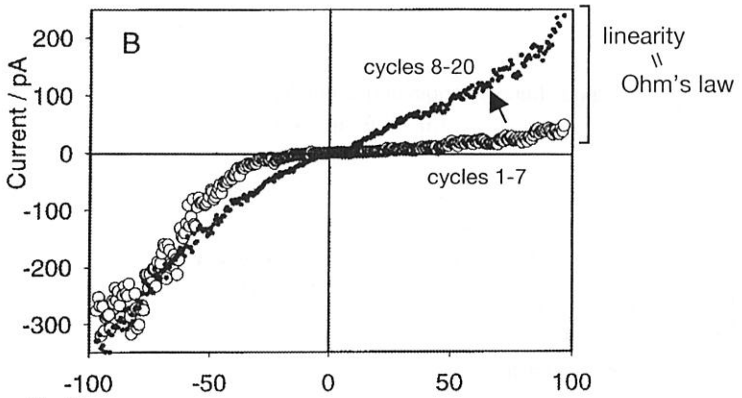
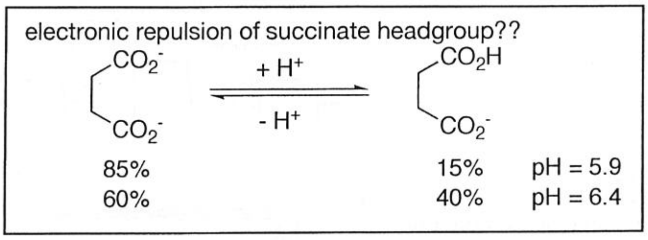
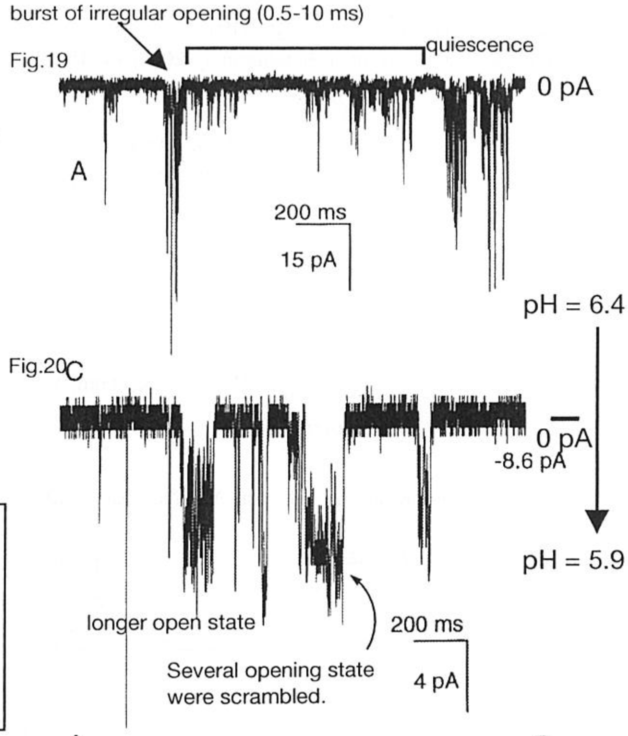


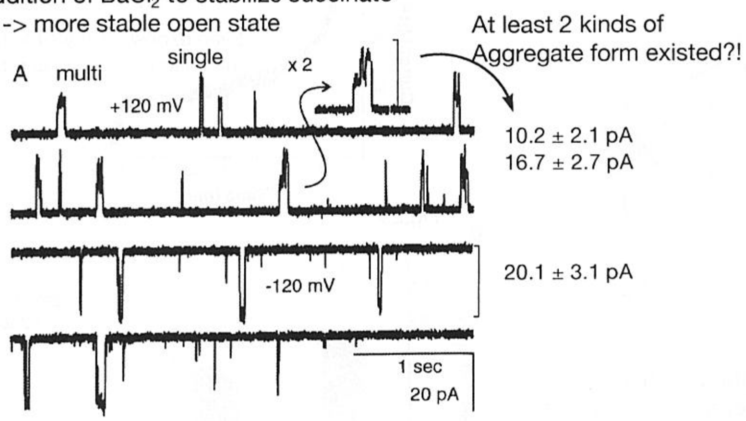
Fig.18





Addition of $BaCl_2$ to stabilize succinate
-> more stable open state

Fig.21



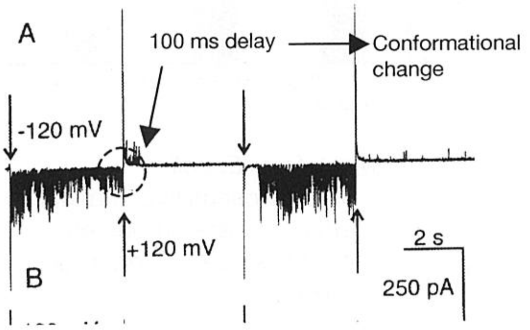
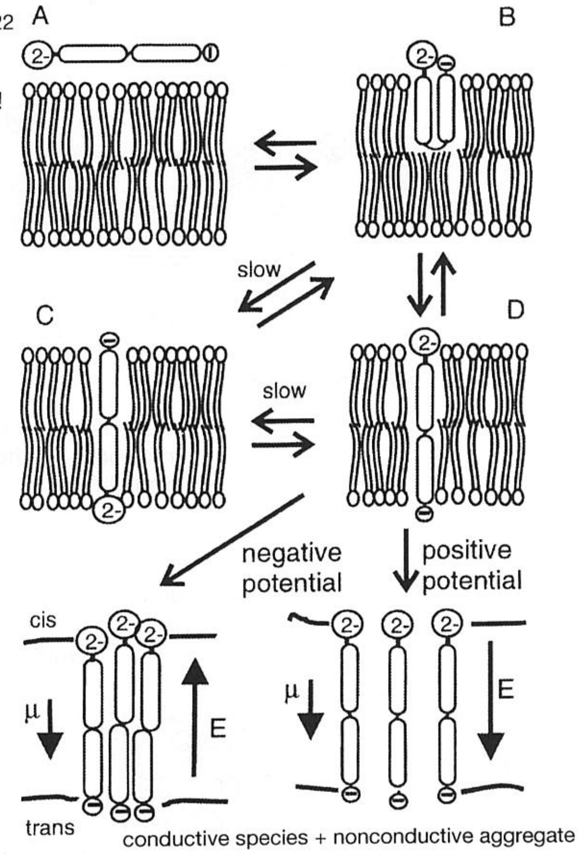


Fig.22



Gokel, G. W. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1848.

Cl⁻ channel

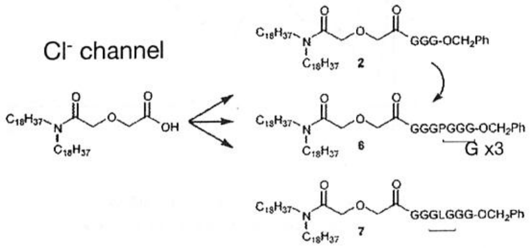


Fig.23

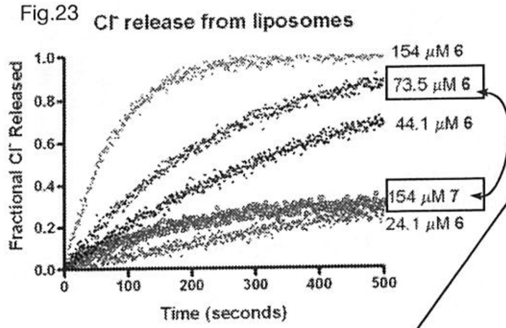
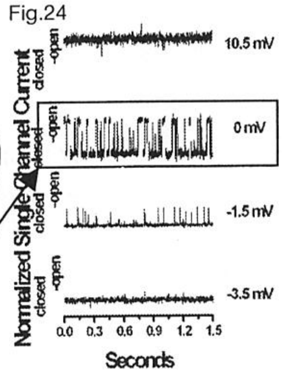


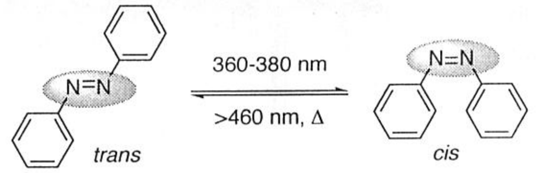
Fig.24



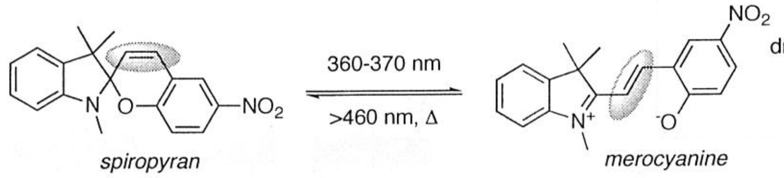
-2~2 mV was the best area

4.2 Light Gated Ion Channel

Review: Trauner, D. et al. *Biochemistry* **2006**, *45*, 15129.



large chane in length and geometry
(ΔL ~7 Å, $\Delta\mu$ ~3 D)



dramatic increase in polarity
($\Delta\mu$ ~15 D)

Trauner, D. and Kramer, R. H. et al. *Nat. Neurosci.* **2004**, *7*, 1381.

a Fig.25

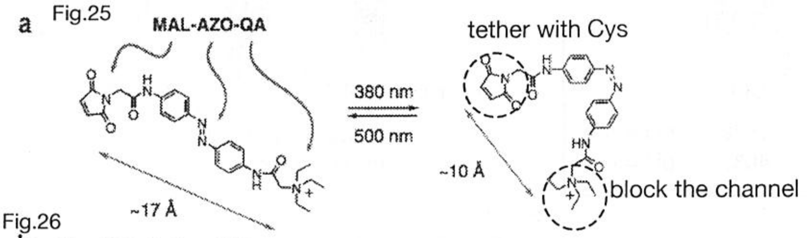
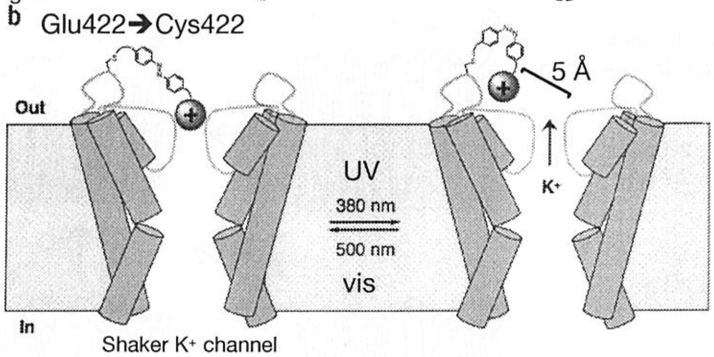
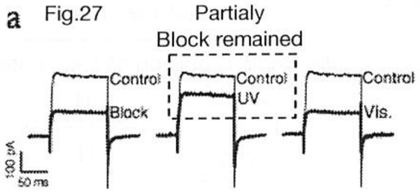


Fig.26
b Glu422→Cys422



By the mutation of the channel, channel opened after the irradiation of visible light.

a Fig.27



d Fig.28

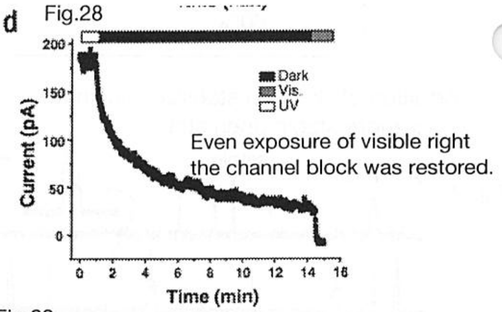
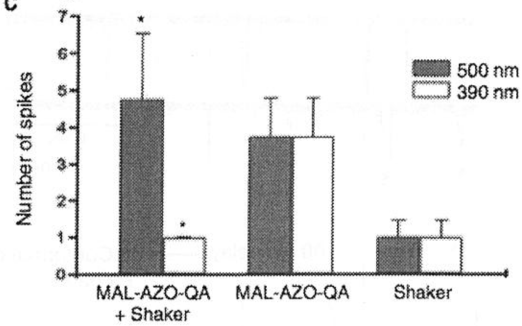
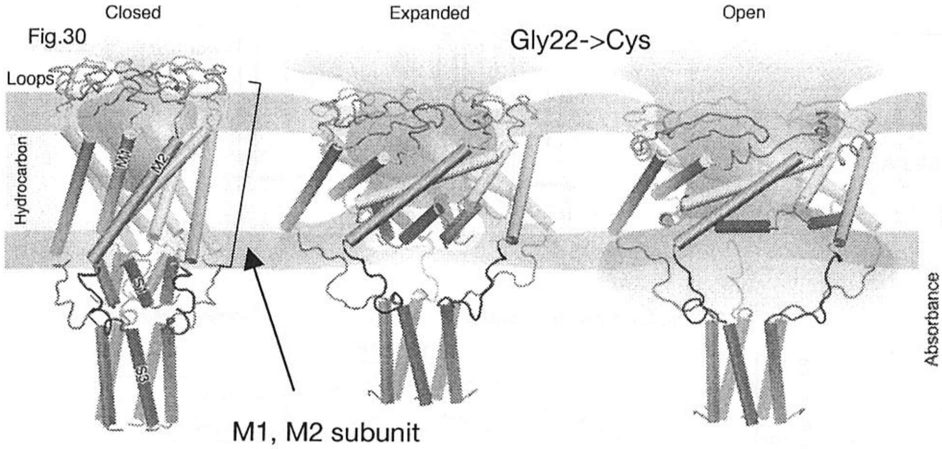


Fig.29
c



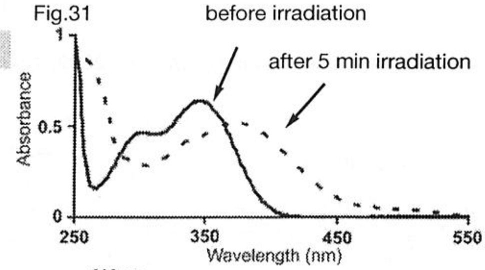
Sukharev, S. et al. *Trends Neurosci.* **2004**, *27*, 345.

Fig.30



MscL from *E. coli*
mechanosensitive channel
efflux of water to prevent cell lysis due to high turgor pressure

Fig.31



Feringa, B. L. et al. *Science* **2005**, *309*, 755.

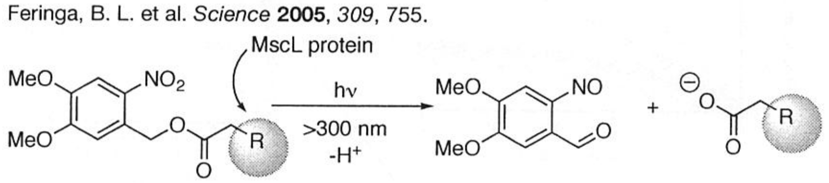
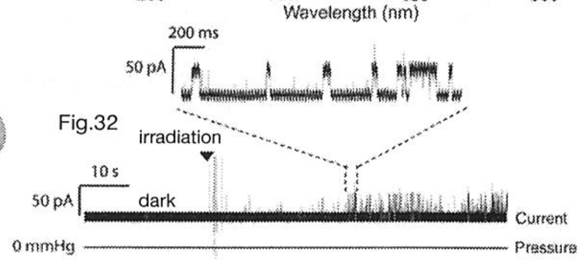
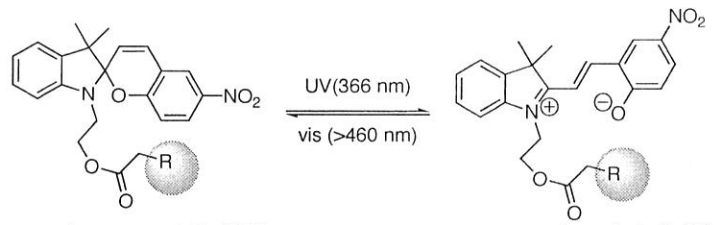
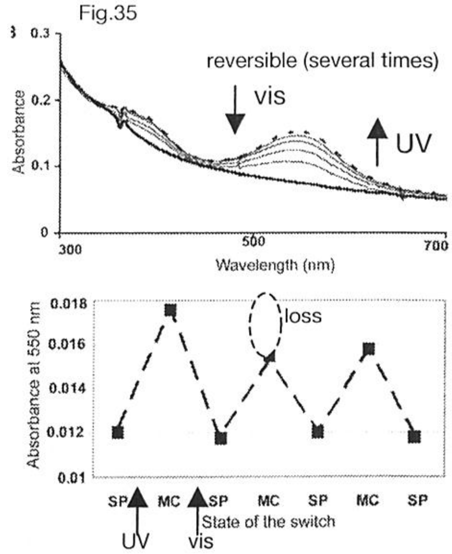
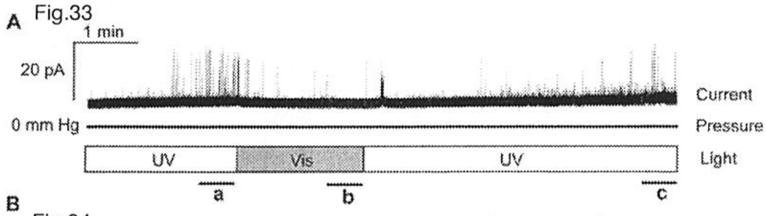


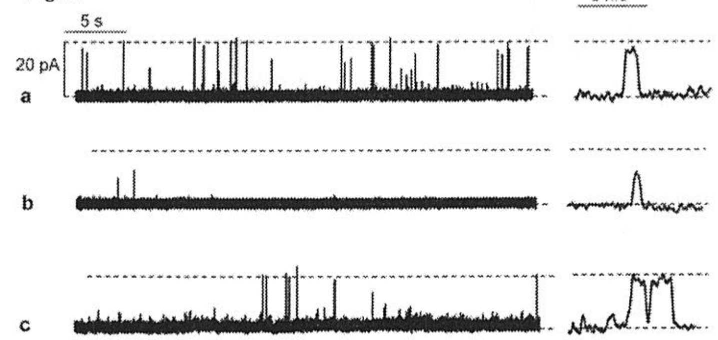
Fig.32

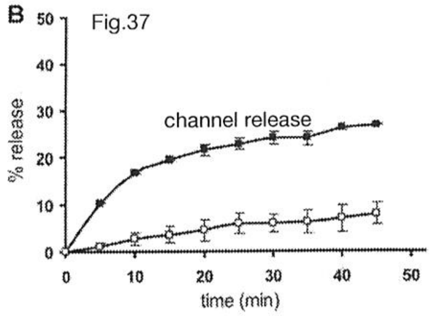






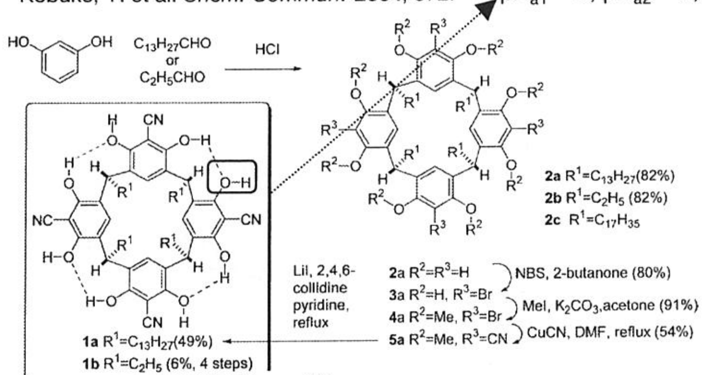


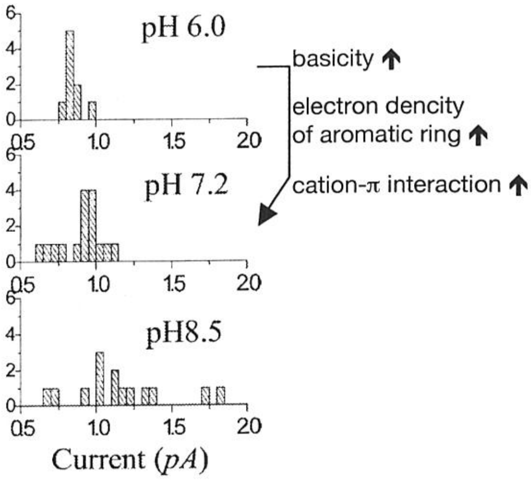


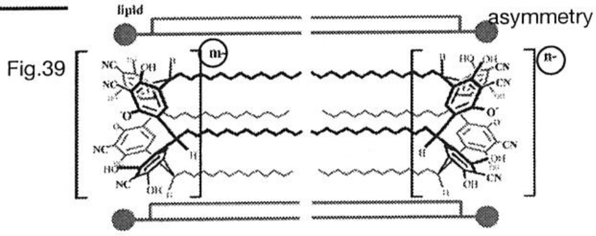


4.3 pH Gated Ion Channel

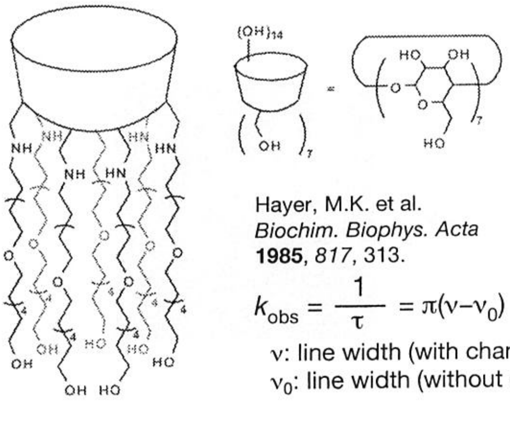
Kobuke, Y. et al. *Chem. Commun.* **2004**, 872. $pK_{a1} = 5$, $pK_{a2} = 6$, $pK_{a3} = 11$, $pK_{a4} = 11.7$





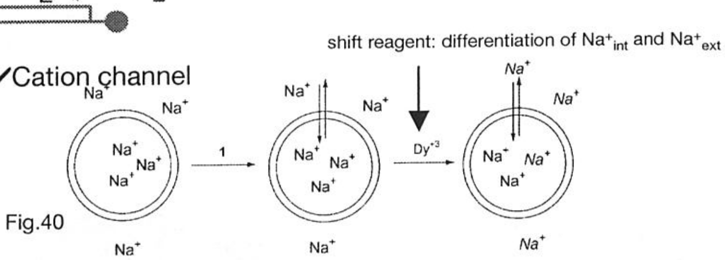


Gin, M. S. et al. *ChemBioChem* **2007**, *8*, 1834.



✔Cation channel

shift reagent: differentiation of Na^+_{int} and Na^+_{ext}



Hayer, M.K. et al. *Biochim. Biophys. Acta* **1985**, *817*, 313.

$$k_{obs} = \frac{1}{\tau} = \pi(\nu - \nu_0)$$

ν: line width (with channel)
ν_0: line width (without channel)

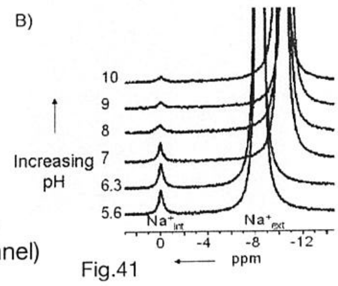
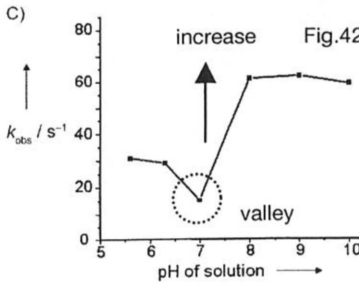
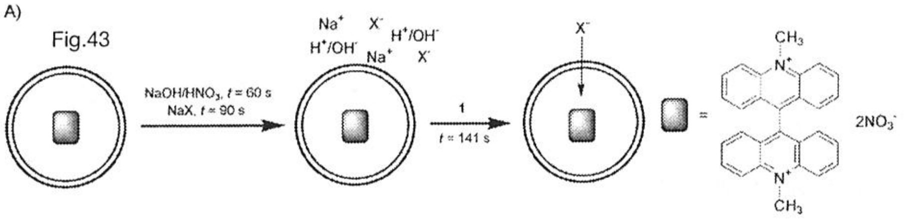


Fig.41

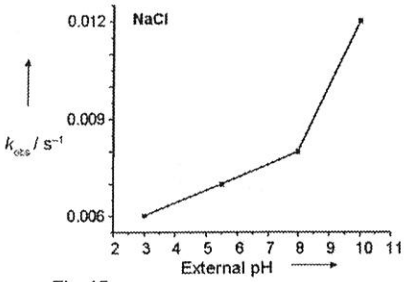


✔Anion channel

A) Fig.43



D) Fig.44



E) Fig.45

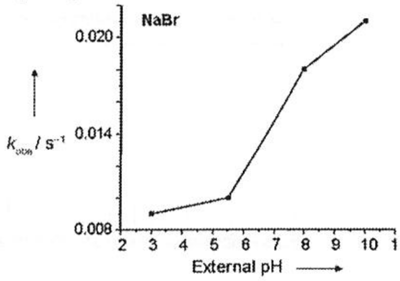
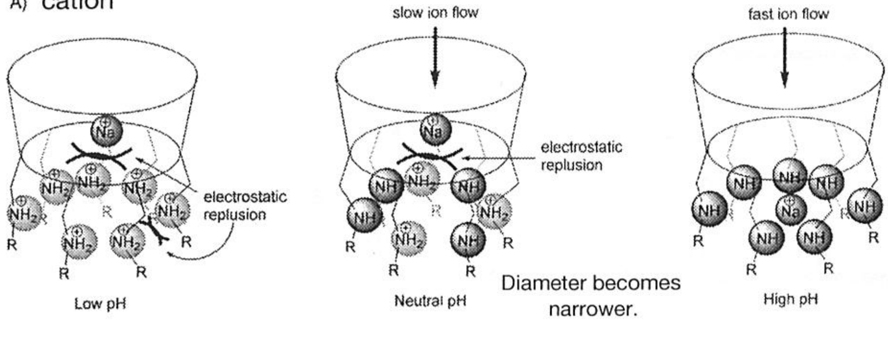
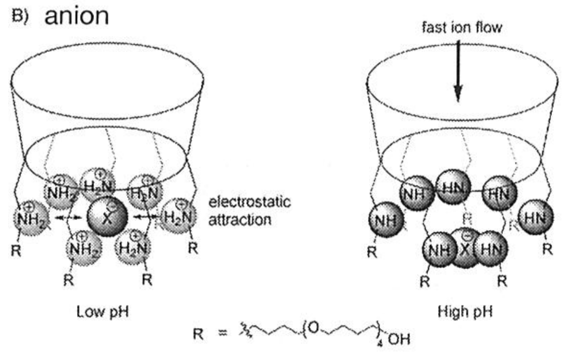


Fig.46

A) cation



B) anion



Chiu, H.-C. et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 1875.

Fig.47

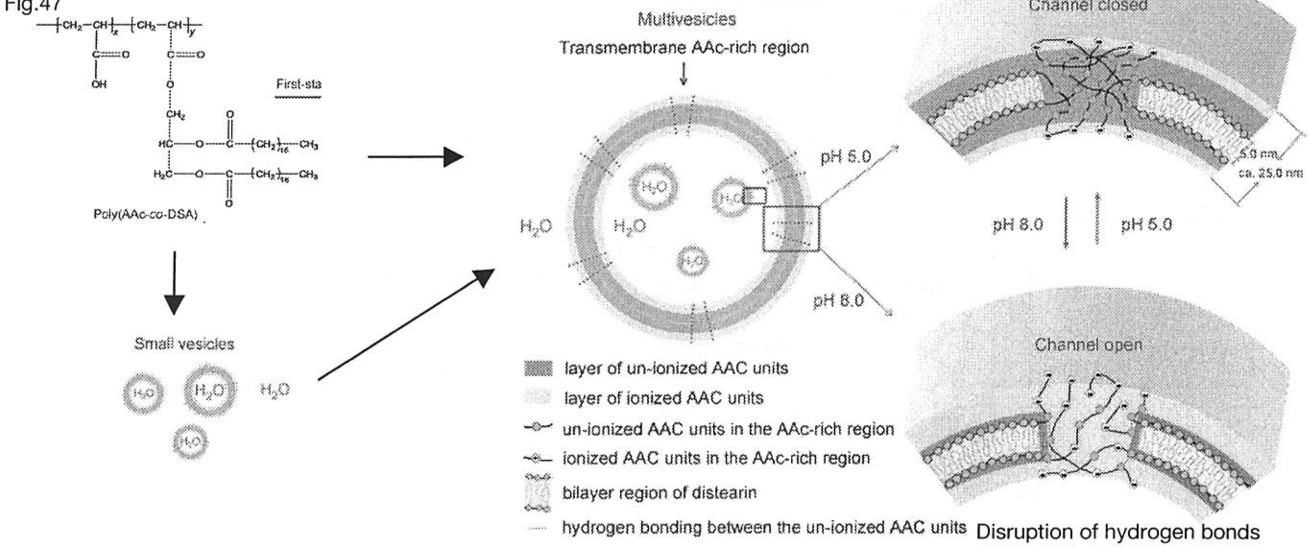
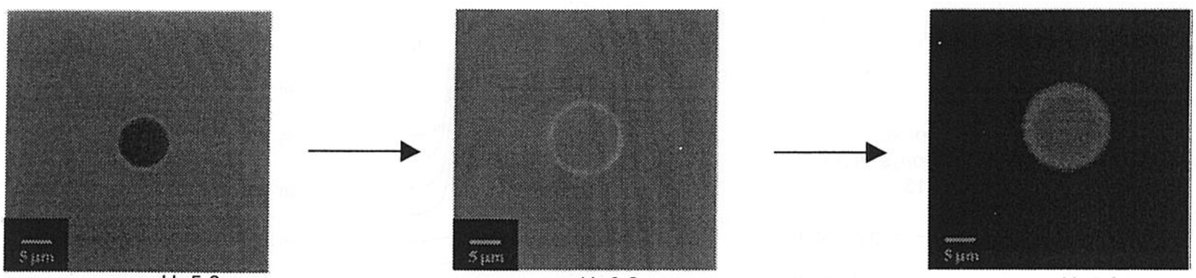


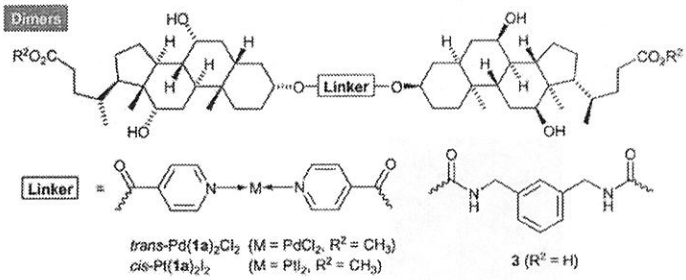
Fig.48

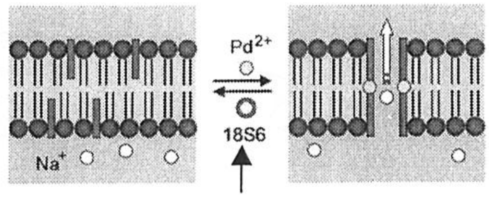


pH=5.0 pH=8.0 pH=5.0

4.4 Ligand Gated Ion Channel

Webb, S. J. et al. *Chem. Commun.* **2008**, 4007.





Hexathia-18-crown-6

Fig.49

Table 1 Rate constants for ion transport[a]

	k for $Na^+/\times10^{-4}\ s^{-1}$	k for $K^+/\times10^{-4}\ s^{-1}$
1a	3.0 ± 1.5	0.4 ± 0.1
$PdCl_2$	1.5 ± 0.5	1.5 ± 1.0
1a + $PdCl_2$	27.0 ± 1.0	13.0 ± 2.0
3	0.3 ± 0.1	2.3 ± 1.3

[a] Background rate subtracted.

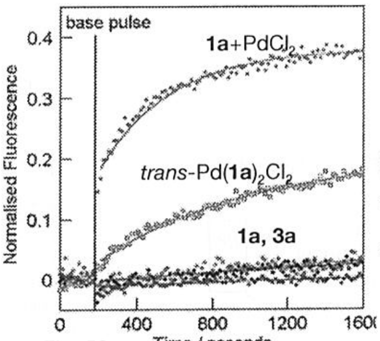


Fig. 50

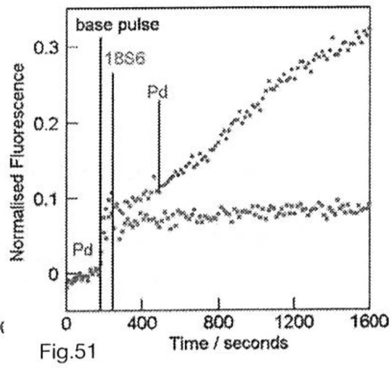


Fig.51

Kim, K. et al. *J. Am. Chem. Soc.* **2004**, *126*, 15944.

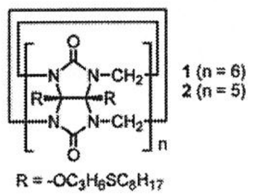
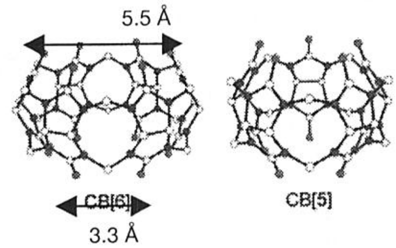


Fig.52



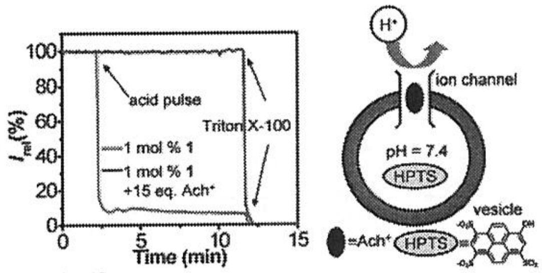


Fig.53

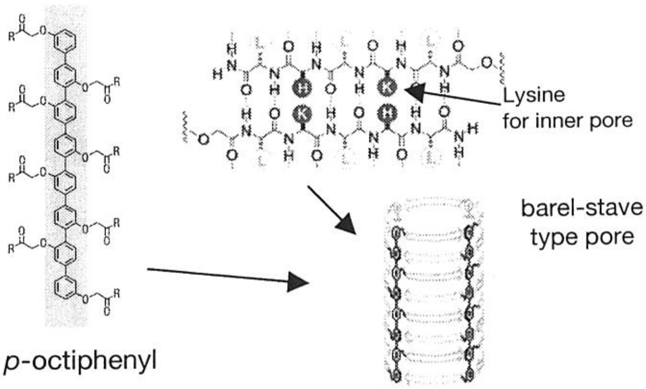
Ach block the channel

5 Artificial Tongue

Matile, S. et al. *Science* **2002**, *298*, 1600.
Matile, S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 13592.

Matile, S. et al. *J. Am. Chem. Soc.* **2005**, *127*, 9316.
Matile, S. et al. *Nat. Mater.* **2007**, 6,576.

Fig.54



p-octiphenyl

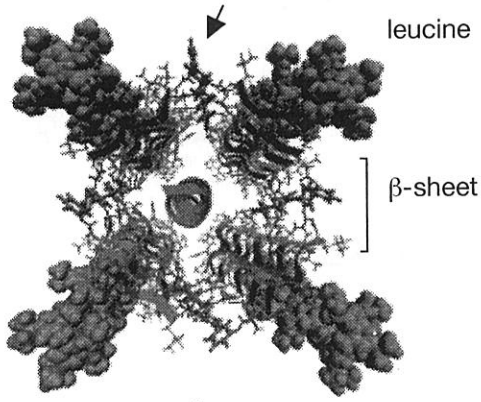


Fig.55 **4**

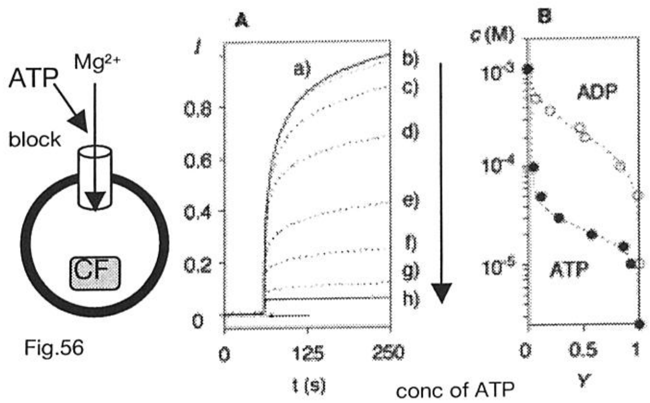


Fig.56

$IC_{50}^{ADP}/IC_{50}^{ATP}=10$

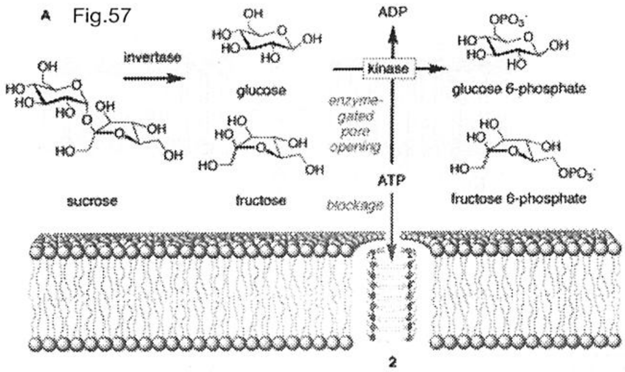


Table 1. Sucrose Content of Soft Drinks Determined with Pore **2**[a]

	beverage	expected (gL⁻¹)	found (gL⁻¹)
1	Coca-Cola	106	111 ± 7
2	Coca-Cola Light	0	0
3	Red Bull	113	118 ± 13
4	Fanta Orange	101	98 ± 9
5	Nestea Lemon	76	78 ± 7

D

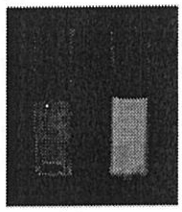


Fig.58 *Coca-Cola Light* *Coca-Cola*

✔ How can we detect another substrate ?

Fig.59

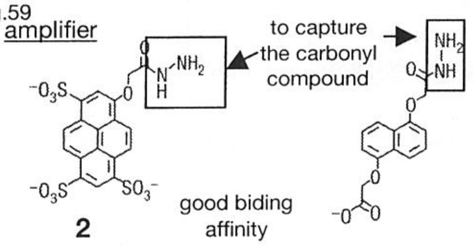


Fig.60

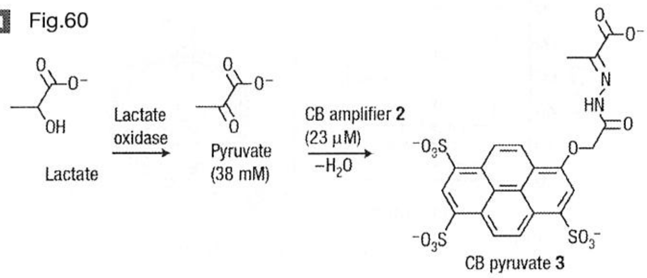


Fig.62

Analyte	Sucrose	Lactose	Acetate	Lactate	Citrate	Glutamate
Sample	Coca-Cola	Milk	Rice vinegar	Sour milk	Orange juice	Soy sauce
c (mM)	325 ± 20[a]	122 ± 6	757 ± 80	54 ± 4	46 ± 5	nd[b]
Cosubstrate	ATP	ATP	ATP	--	–	Pyruvate
Amplifier	–	–	–	**2**	**2**	**5**
Pore	**1**	**1**	**1**	**1**	**1**	**4**
Enzyme	Invertase hexokinase	β-galactosidase hexokinase	Acetate kinase	Lactate oxidase	Citrate lyase	Trans-aminase

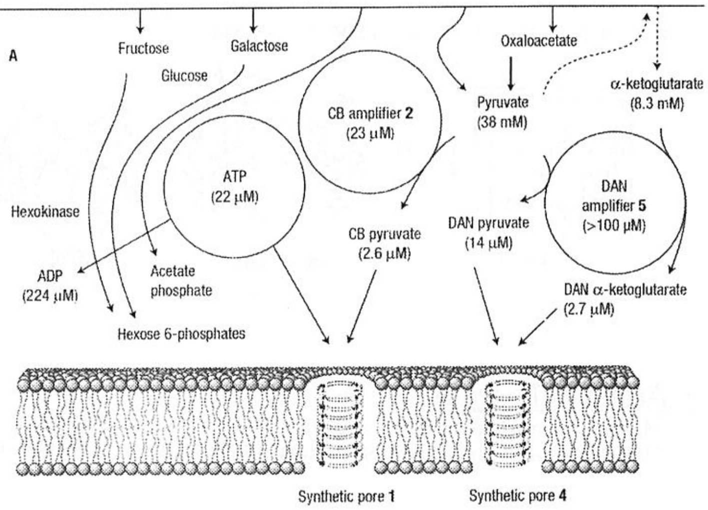
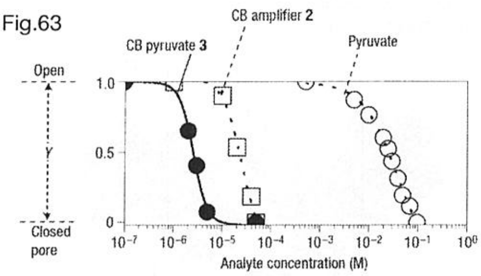


Fig.63



6 Outlook & Remark