Dynamic Combinatorial Chemistry

combinatorial discovery and synthesis under thermodynamic control

Dynamic Combinatorial Chemistry (DCC)

Outline

What dynamic combinatorial chemistry is not

Dynamic Combinatorial Chemistry (let's forget the 'dynamic')

What dynamic combinatorial chemistry is

Dynamic Combinatorial Chemistry (the rationale behind)

Dynamic Combinatorial Chemistry Receptors!

Dynamic Combinatorial Chemistry Unexpected Structures

Dynamic Combinatorial Chemistry

Preparation of a large number of different compounds (ideally) at the same time starting from a series of Building blocks

The 'large number' of different compounds defines a Chemical (Sub)space

Chemical (Sub)space: all the possible molecules that can be obtained from given number of building blocks and a given number of chemical reactions and reaction steps

The 'large number' of different compounds are contained in Libraries

The design of combinatorial chemistry is highly deterministic

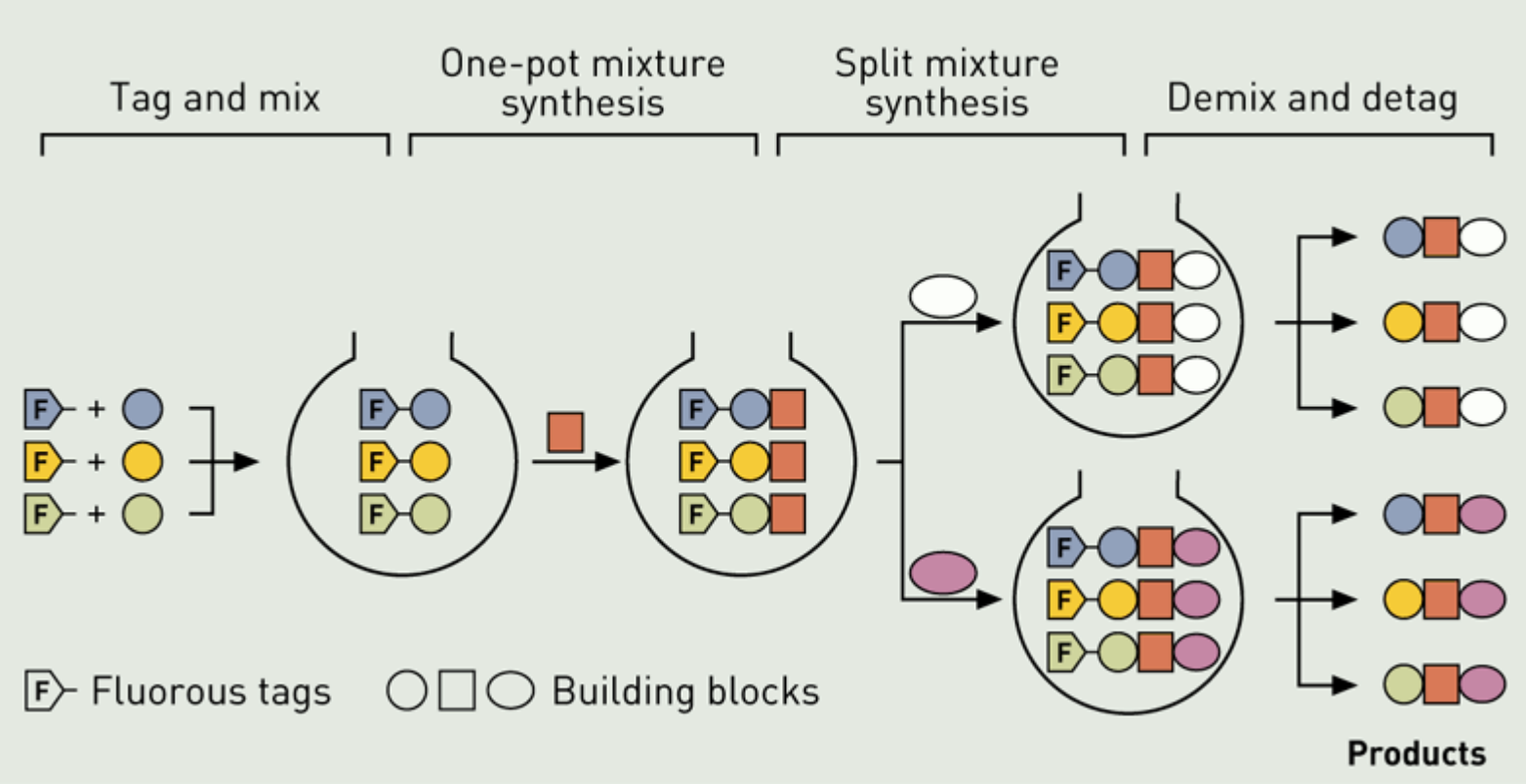
You know exactly where you are going

But it may be nowhere

Dynamic Combinatorial Chemistry

Preparation of a large number of different compounds (ideally) at the same time

Libraries are the products of combinatorial chemistry

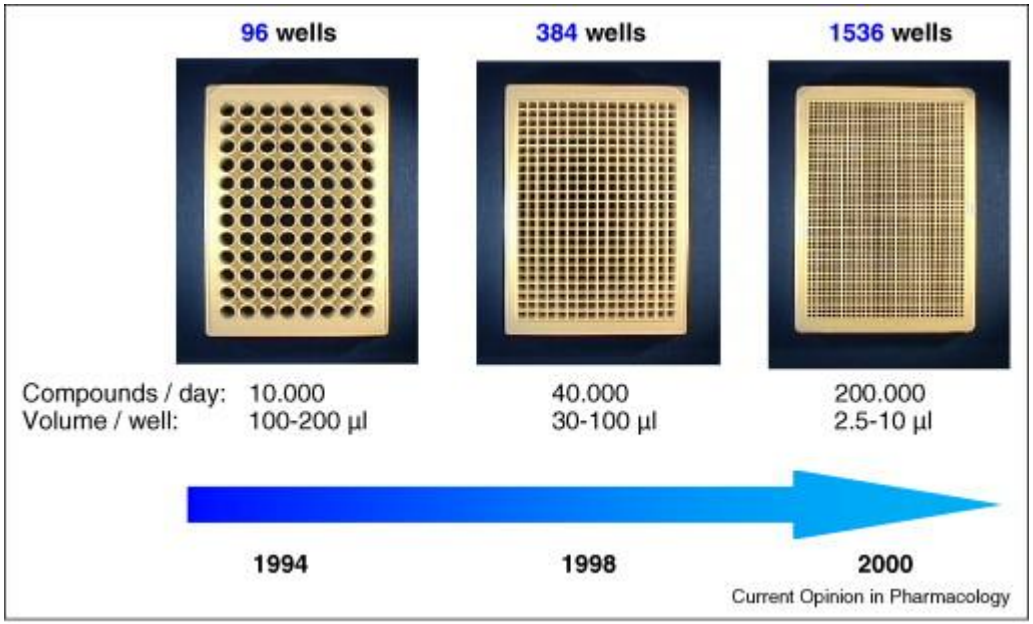


Chem. Eng. News, **2002**, *80*, 43-57

Dynamic Combinatorial Chemistry

How do we know what compound is the good one?

All the compounds have to be tested!
High throughput- screening provides the most promising substances



Enzymatic activity

Host-guest interactions

Curr. Opin. Pharmacol. **2009**, *9*, 580–588

Dynamic Combinatorial Chemistry

Synthesis of a large number of compounds in short time ✓

High structural diversity is easy to achieve ✓

The chemical space explored is large (100-100000 compounds) ✓

Cumbersome screening is needed to identify the “lead compound” X

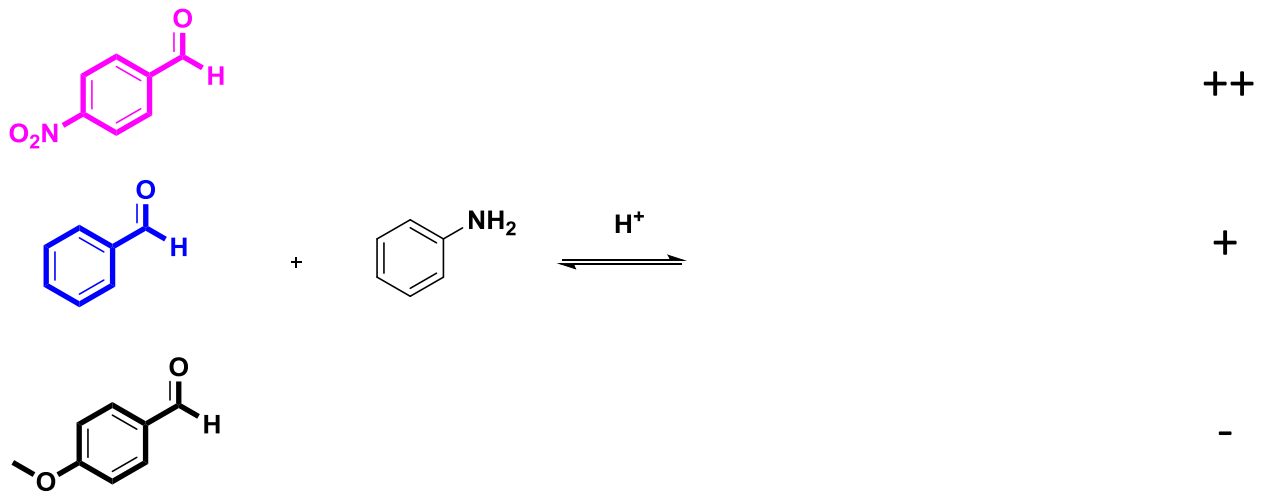
You may even have no “lead compound” at all X

Can we pursue a different approach?

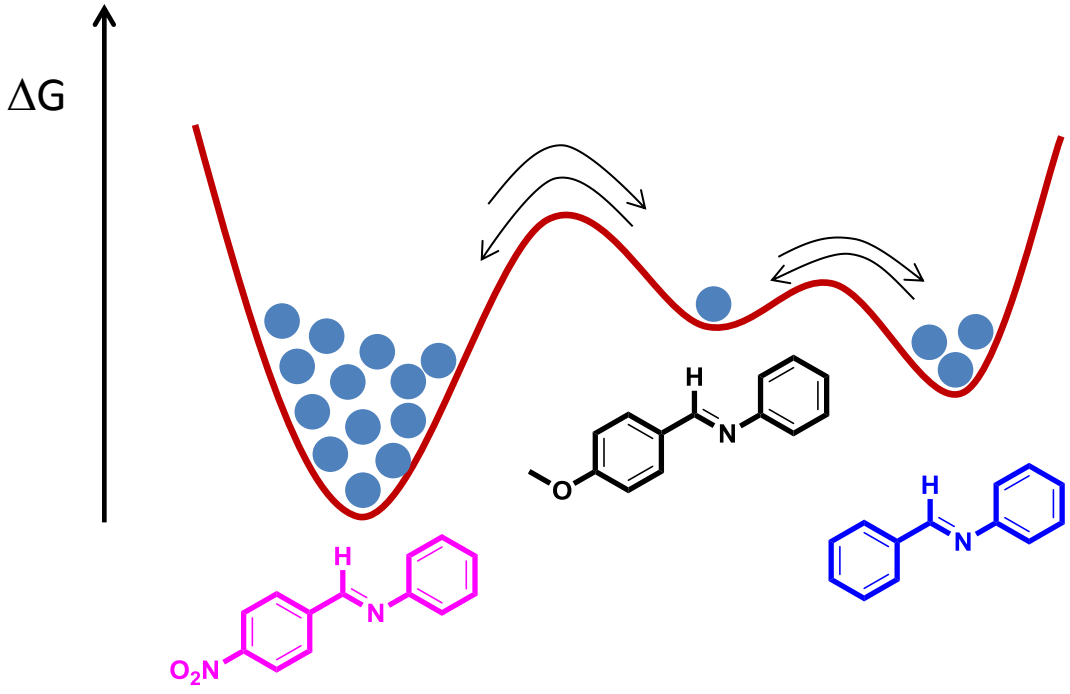
This requires reconceiving the role of libraries

Libraries: from products to reagents, a change in paradigm

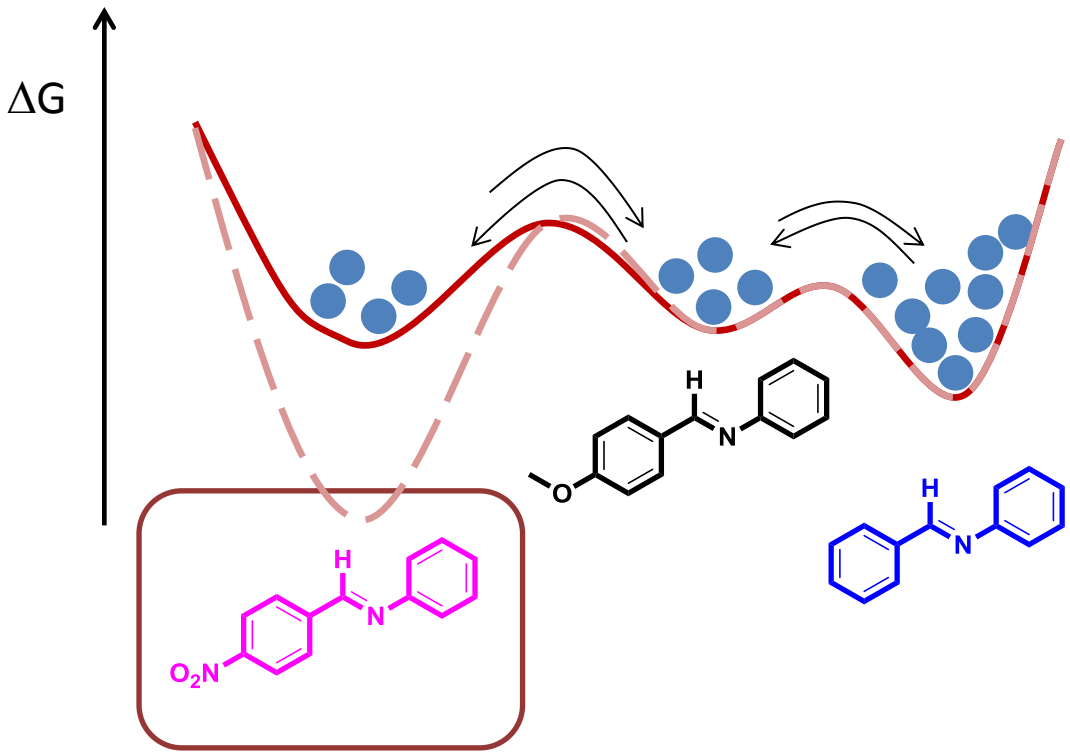
The keys to change are reversibility and ‘acting’ on the thermodynamics of an equilibrium mixture



Reversibility and Thermodynamic control



Reversibility and Thermodynamic control



Dynamic Combinatorial Chemistry

The toolkit

Reversible reactions

Many, a few very successful

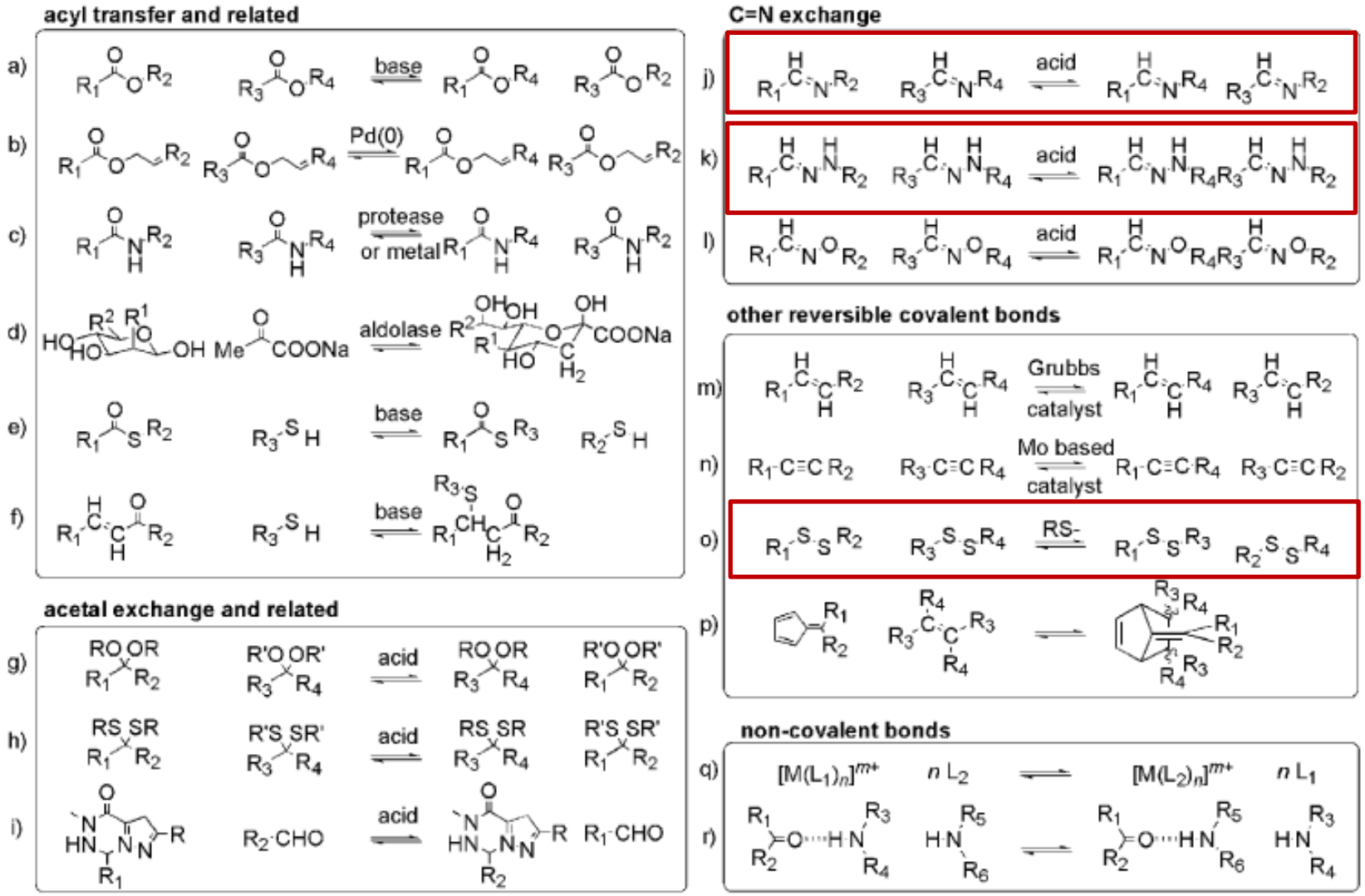
A way to act on the thermodynamic equilibrium of a library

The only limitation is your imagination

Techniques to assess the library composition

Many, a few very successful

Reversible reactions for Dynamic Combinatorial Chemistry



Chem. Rev. **2006,** *106*, 3652–3711

Imine/hydrazone Exchange

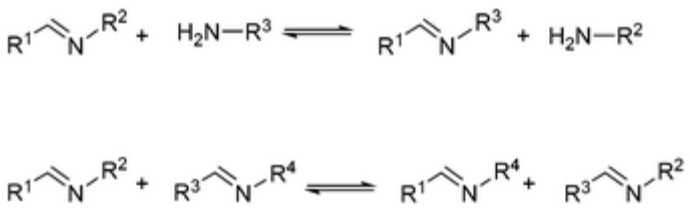
Works nicely in organic solvents (DCM, Chloroform, Tolene)

Requires acid catalysis

Hydrophobic interaction is out of the repertoire of suitable stimuli to direct the library

Imine exchange and imine equilibration may take long time

General Features



Mechanism of Imine (or hydrazone) formation

Aldehydes can be replaced by acetals

Advantages of disulfide exchange

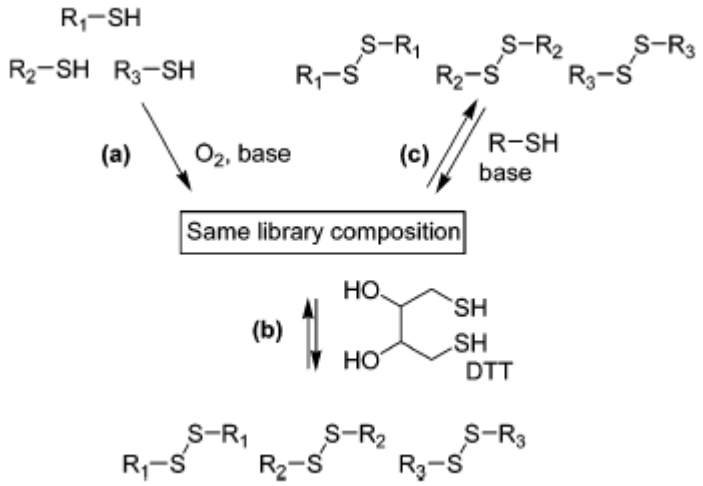
Works nicely in water and under physiological conditions

In water hydrophobic interactions enhance the recognition of a template

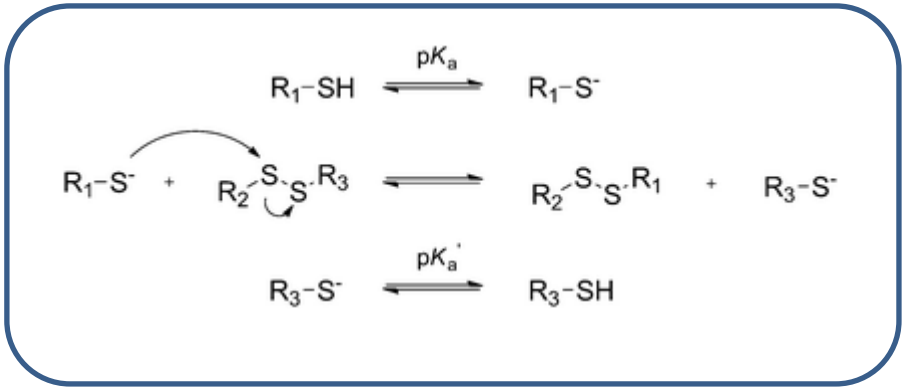
Equilibria of reversible disulfide reactions are very sensitive to weak non-covalent interactions

Because of this sensitivity, several non-covalent interactions acting in concert can be responsible for the structural and constitutional outcomes of disulfide systems (even charge paairing and hydrogen bonding in water!).

General Features



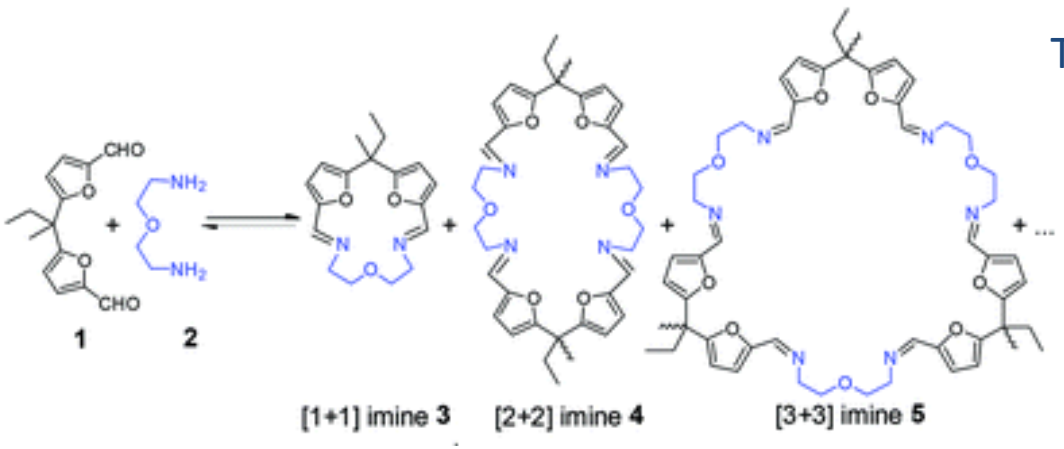
Mechanism



Chem. Soc. Rev., **2014**, *43*, 1861

What do we mean by reversibility and thermodynamic control?

Let's make an example



Two Building blocks aldehyde + amine

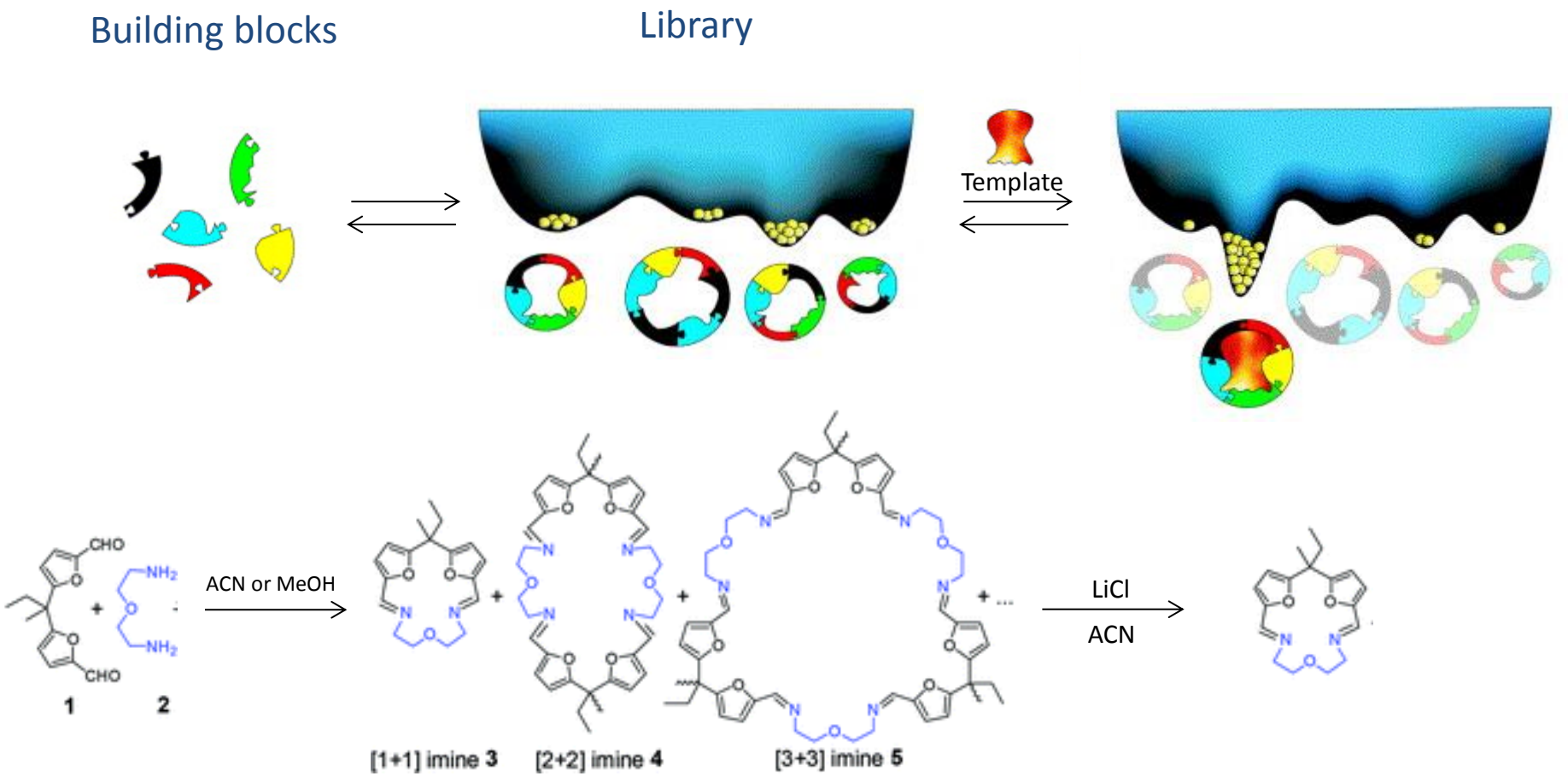
Equilibrium library of imines

A single component re-establishes the library composition

Org. Biomol. Chem. , **2014**, *12* , 3827

Reversibility and Thermodynamic control

Molecular recognition come into play



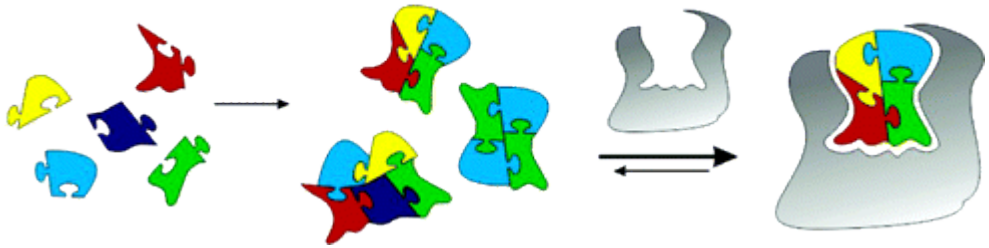
Curr Opin Chem Biol **2002**, *6*, 321-327 *Org. Biomol. Chem.* **2014**, *12* , 3827--3830

Types of dynamic combinatorial libraries

Selection of a host by a separately introduced guest

Discovery and synthesis of new host moleculels

Selection of a guest by a separately introduced host



Discovery and synthesis of new ligands for natural receptors

Chem. Rev. **2006,** *106*, 3652–3711

Is a template always necessary to direct a library?

DCC – combinatorial chemistry under thermodynamic control – is a tool for the efficient synthesis of libraries of complex structures whose individual properties may be explored through the library 's response to the stabilizing influences of (usually) external stimuli.

A template is just an example of external stimulus

Selection through Molecular Recognition of an External Template

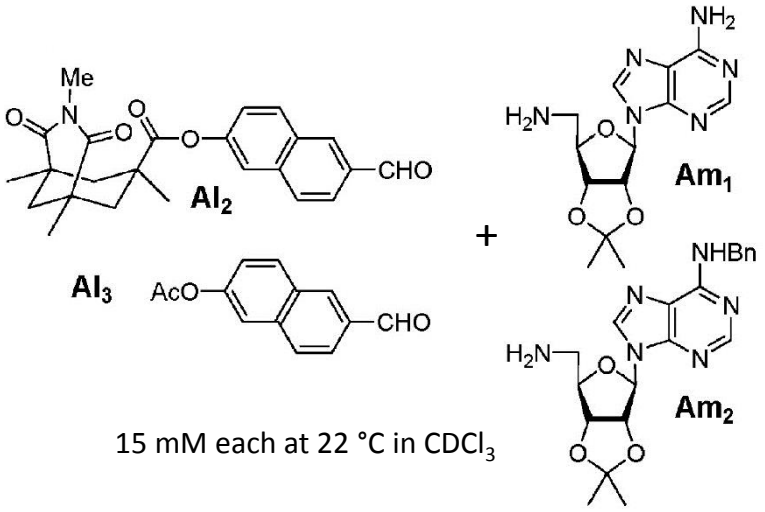
Selection through Self - Templating

Selection Directed by External Physical Stimuli

Selection Through a Stabilizing Phase Change

Dynamic Combinatorial Chemistry, Reek and Otto Ed. 2010 WILEY-VCH Verlag

Self-templating as an internal stimulus



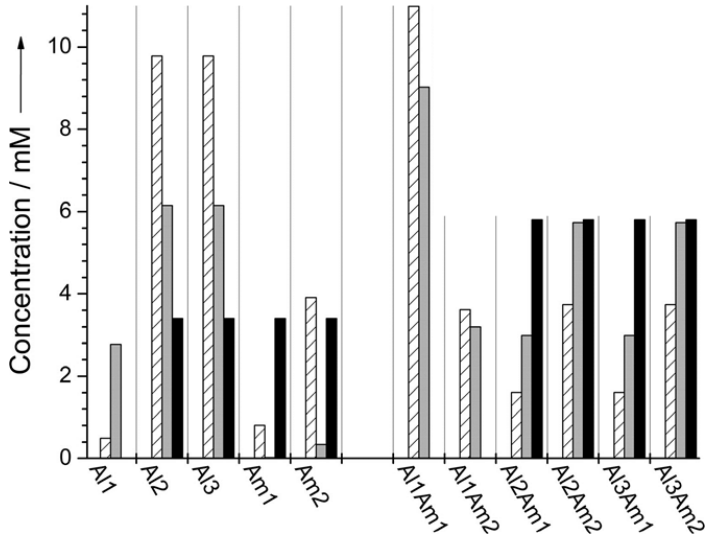
15 mM each at 22 °C in $CDCl_3$

22 °C $CDCl_3$

Al_2Am_1 Al_2Am_2

Al_3Am_1 Al_3Am_2

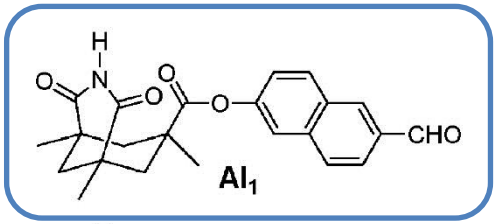
Thermodynamic equilibrium after 113 hours

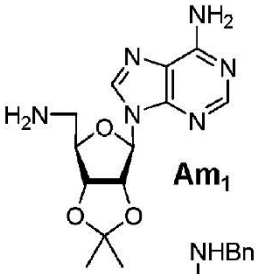


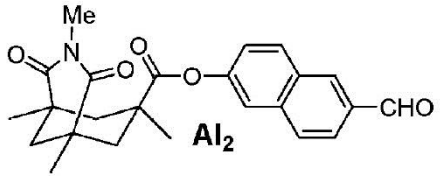
No preference for a s specific imine

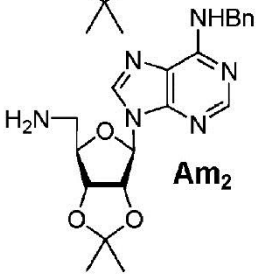
J. Am. Chem. Soc. **2008**, *130*, 1826-1827

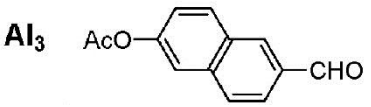
Self-templating as an internal stimulus







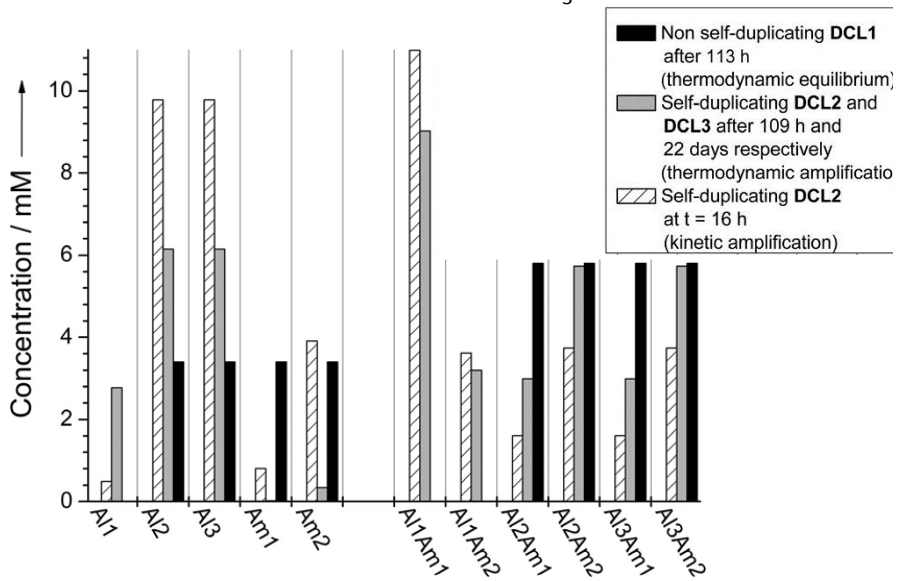


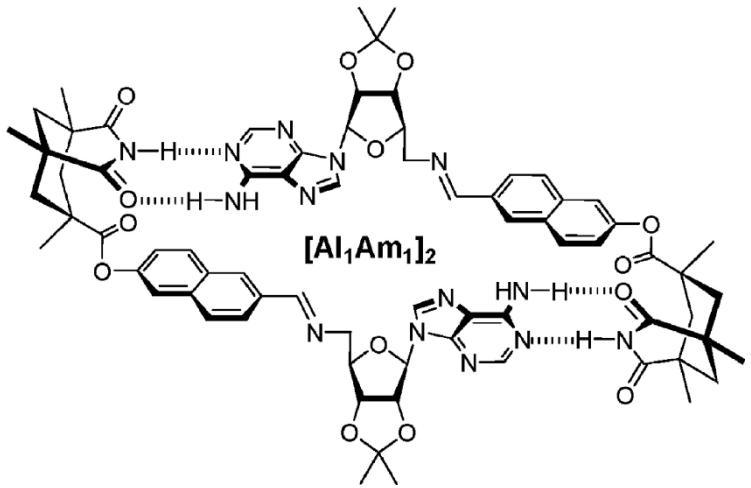


22 °C $CDCl_3$

Al_1Am_1 Al_1Am_2
Al_2Am_1 Al_2Am_2
Al_3Am_1 Al_3Am_2

15 mM each at 22 °C in $CDCl_3$





J. Am. Chem. Soc. **2008**, *130*, 1826-1827

Advantages of disulfide exchange

What weak non-covalent interactions can we exploit to direct a disulfide-based library under thermodynamic control?

Hydrogen bonding interactions (even in water!)

Cation – π interactions

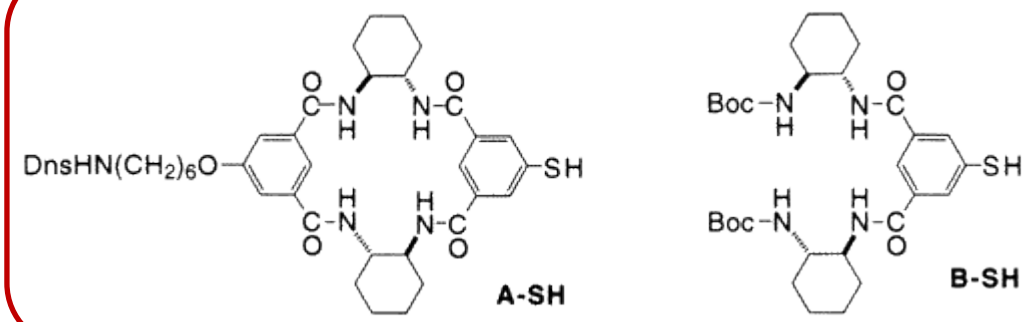
Hydrophobic effect

Aromatic donor-acceptor interactions

Selection (Re-equilibration of disulfide libraries) through hydrogen bonding

An early example (a proof of principle indeed)

Library components (solvent: $CHCl_3$)



Templates

Ac(D)Pro(L)Val(D)Val-PS

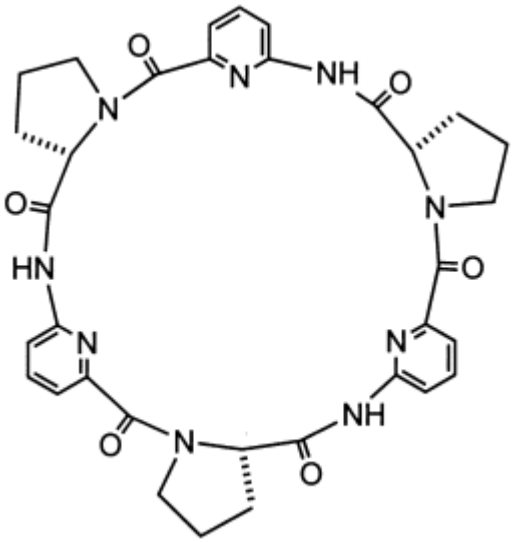
Ac(L)Asn(L)Pro(D)Xxx-PS

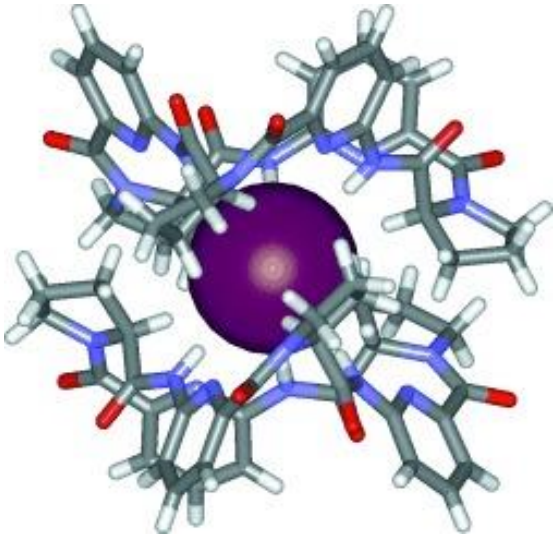
Ac(L)Pro(L)Pro(D)Xxx-PS

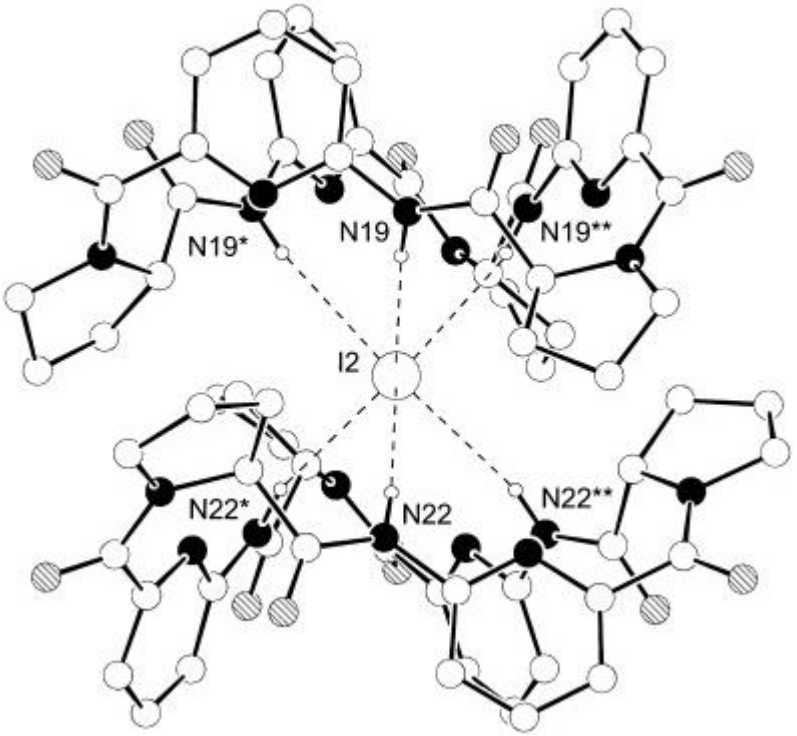
	(2)**A-SS-B**	↔	**B-SS-B** + **A-SS-A**	K_{eq}
Absence of tripeptide-PS:	43%		57%	1.8

J. Org. Chem. **1998**, *63*, 904-905

An early example (a proof of principle indeed) An anion binder







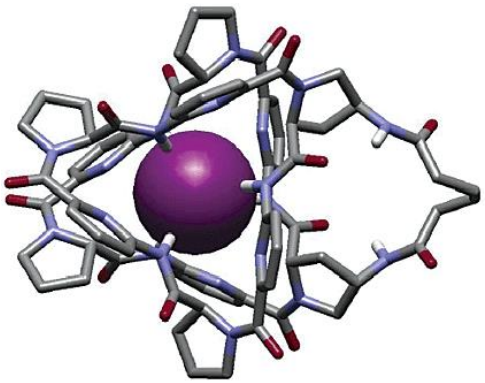
stability of the halide complexes (80 %D_2O/CD_3OD)

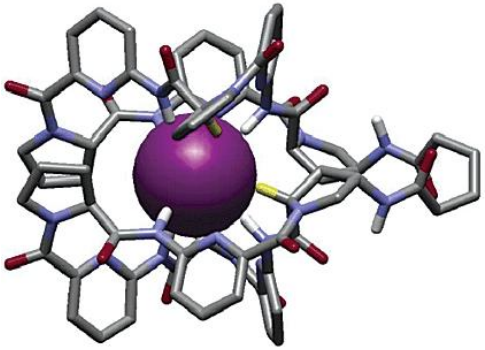
$Cl^- < Br^- < I^-$

Angew. Chem. Int. Ed. **2001**, *40*, 2648-2651

Selection (Re-equilibration of disulfide libraries) through hydrogen bonding

Modelling of a
'oyster' receptor





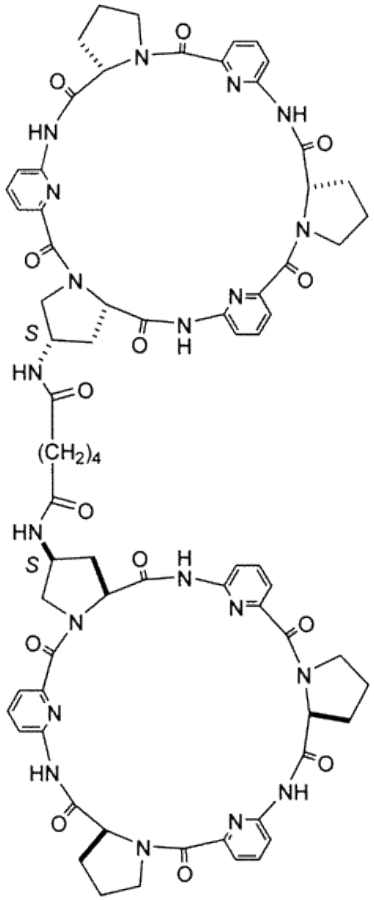


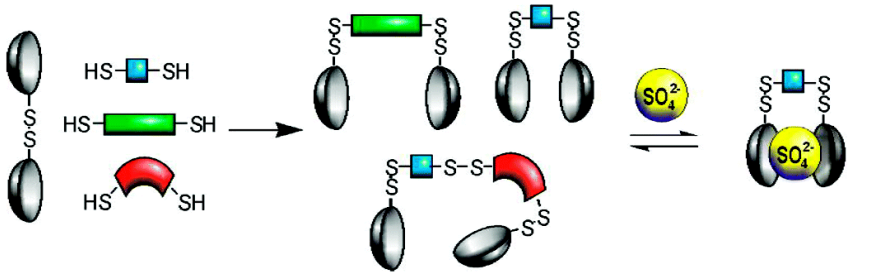
Table 1. Stability of Various Anion Complexes of **2** in 50% D_2O/CD_3OD Determined by NMR Titrations at $T = 298$ K[a]

	K_a	$\Delta\delta_{max}$	radius[23]
Na_2SO_4	3.5×10^5	0.20	230
NaI	8900	0.94	220
KI	11000	0.93	220
$(CH_3)_4NI$	11300	0.93	220
NaBr	5300	0.48	196
NaCl	710	0.19	181
$NaNO_3$	130	0.61	179

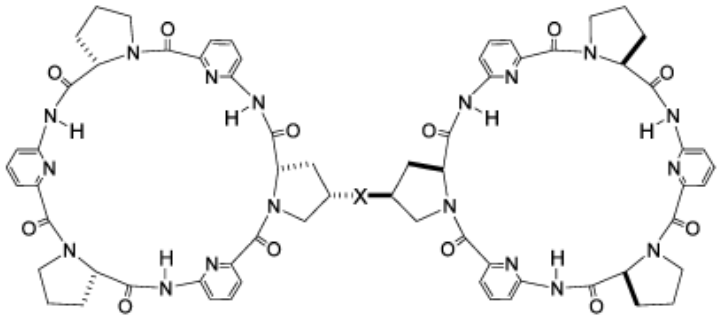
[a] K_a stability constants in M^{-1}. Errors in K_a <15%. $\Delta\delta_{max}$ = maximum chemical shifts of the receptor signal followed during the titration in ppm: In the case of the sulfate complex, the signal of protons in the 3 position of an aromatic subunit were used, in all other cases, the signal of the protons in α position of the substituted proline rings. Ionic radii of the anions are in pm.

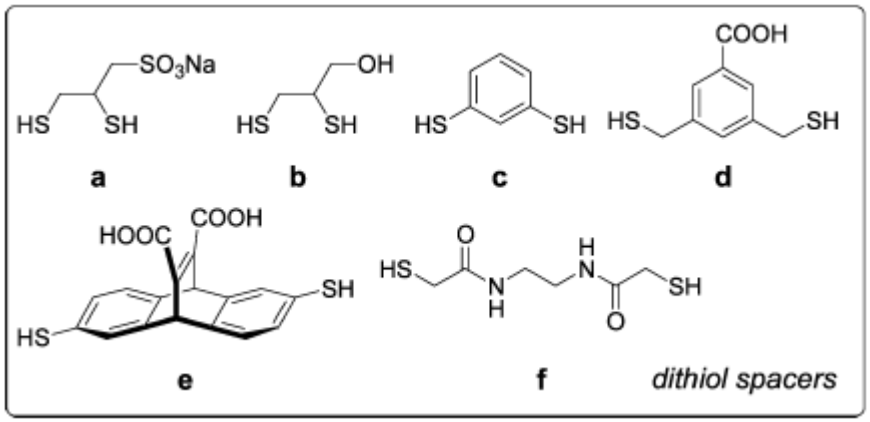
J. Am. Chem. Soc. **2002**, *124*, 12752-12760

Selection (Re-equilibration of disulfide libraries) through hydrogen bonding



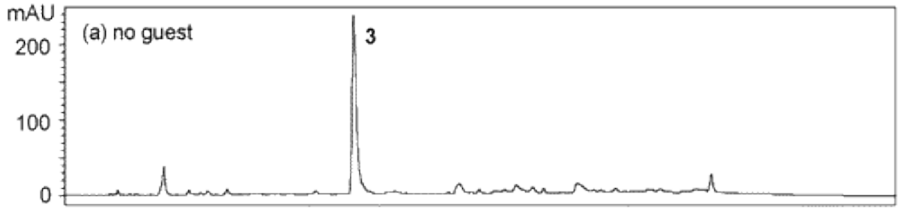
Building blocks Library Best Binder



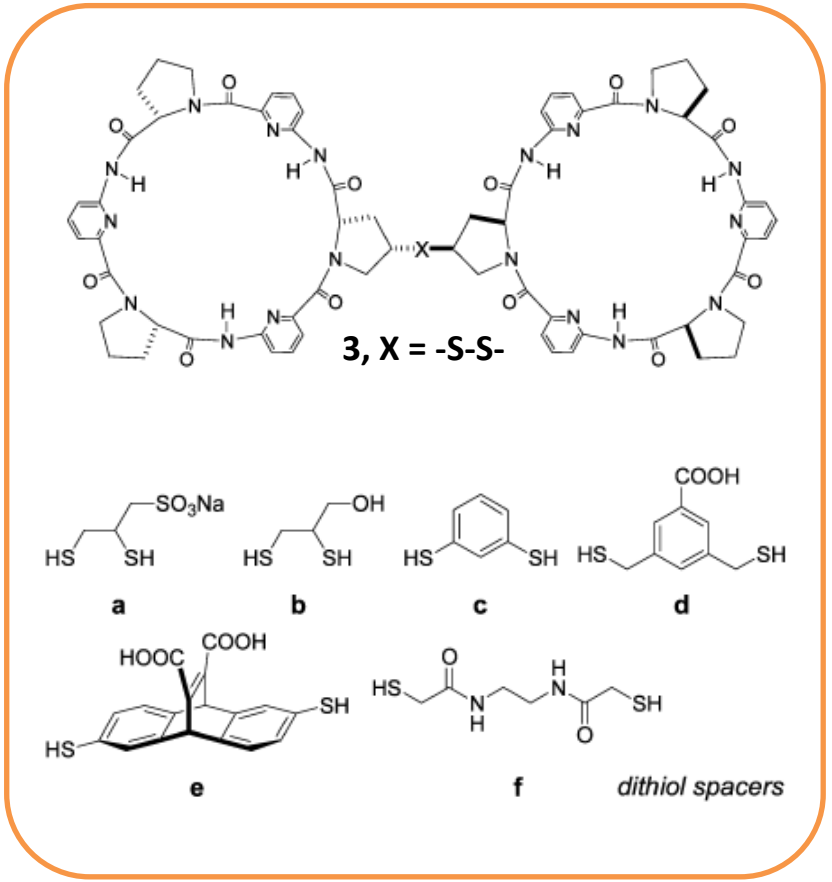


J. Am. Chem. Soc. **2002**, *125*, 7804-7805

Selection (Re-equilibration of disulfide libraries) through hydrogen bonding



Building blocks



J. Am. Chem. Soc. **2002**, *125*, 7804-7805

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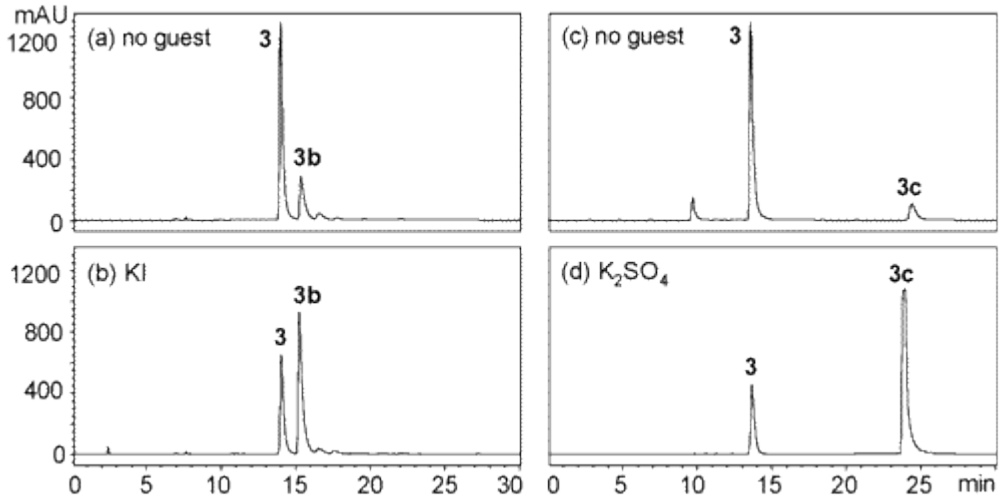
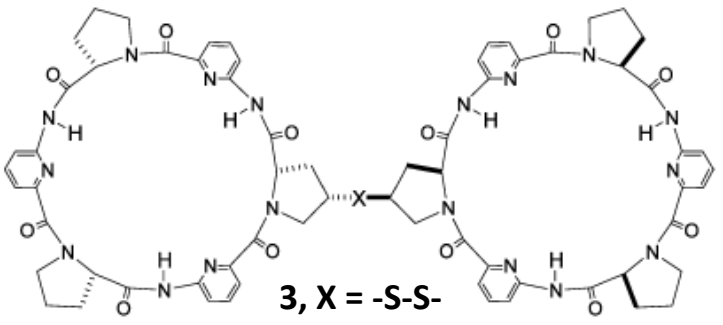


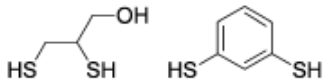
Table 1. Association Constants, Gibbs Energies, Enthalpies, and Entropies of Binding of KI and K_2SO_4 to Receptors **2**, **3b**, and **3c**[a]

		K_a	ΔG°	ΔH°	$T\Delta S^\circ$
KI	**2**	3.3×10^3	−20.0	−4.3	15.7
	3b	2.9×10^4	−25.5	−20.7	4.8
	3c	5.6×10^4	−27.1	−13.4	13.7
K_2SO_4	**2**	2.0×10^5	−30.2	10.7	41.0
	3b	5.4×10^6	−38.4	1.8	40.1
	3c	6.7×10^6	−39.0	3.7	42.7

[a] Recorded in 2:1 (v/v) acetonitrile/water at 298 K; binding constants in M^{-1} and energies in kJ mol^{-1}.

Building blocks





b **c**

Simplified dithiol repertoire a, biased library

J. Am. Chem. Soc. **2002**, *125*, 7804-7805

Selection through hydrogen bonding, educated guesses and rational design of a polyamine binder

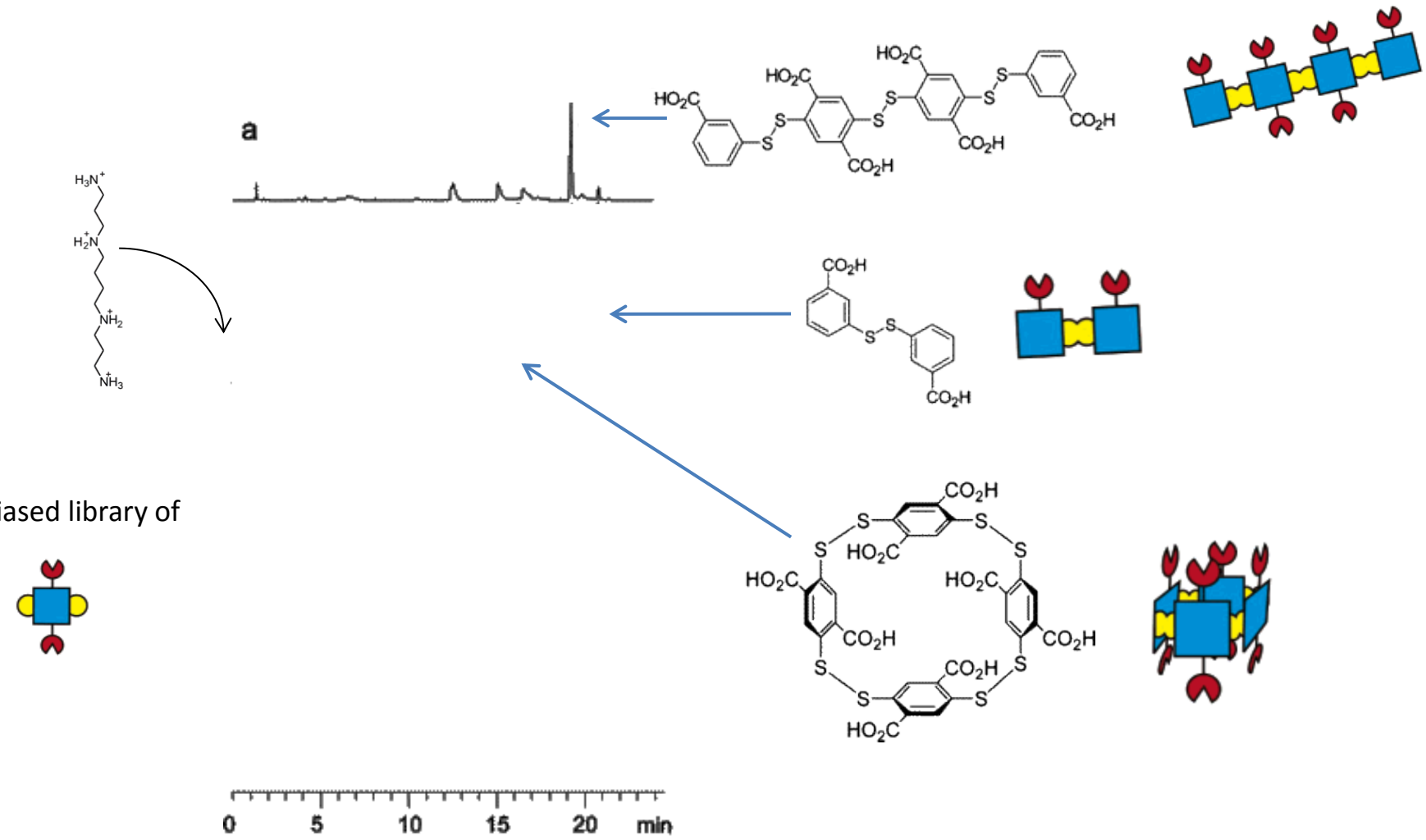
Spermine

Building blocks

Templated library

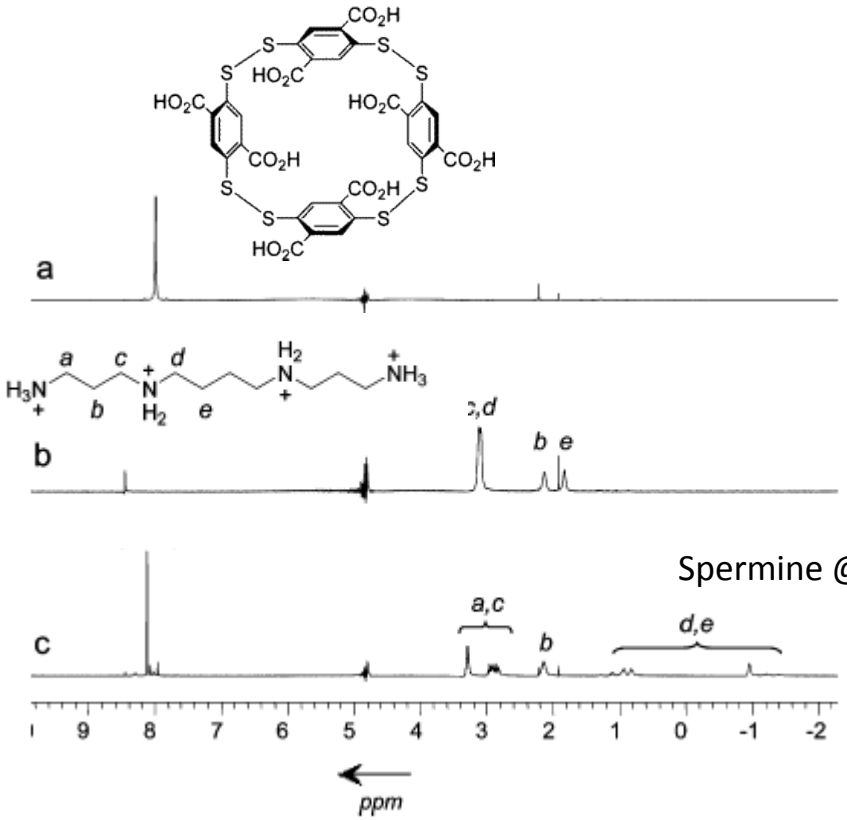
J. Am. Chem. Soc. **2006**, *128* , 10253 – 10257

Selection through hydrogen bonding, educated guesses and rational design of a polyamine binder

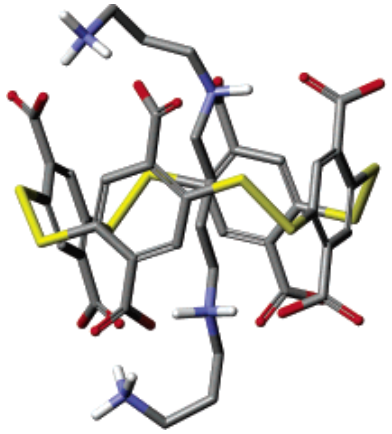


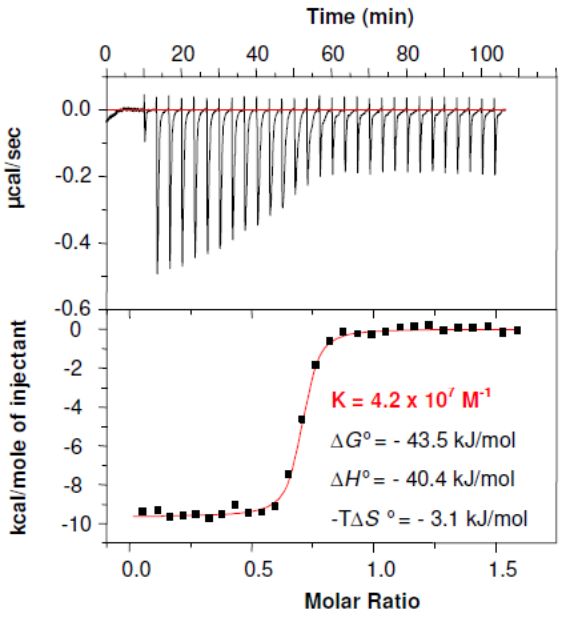
J. Am. Chem. Soc. **2006**, *128* , 10253 – 10257

Selection through hydrogen bonding, educated guesses and rational design of a polyamine binder



Spermine @

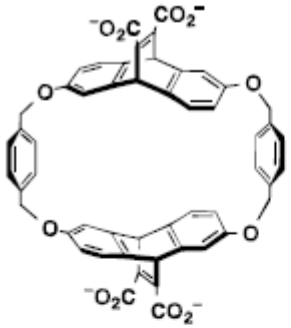




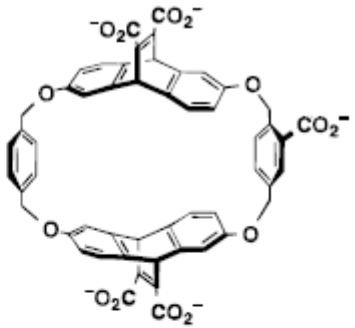
K_D 22 nM !, (water pH 7.4)

J. Am. Chem. Soc. **2006**, *128* , 10253 – 10257

Cation – π interactions
Adapting cyclophane chemistry to disulfide based DCC



1



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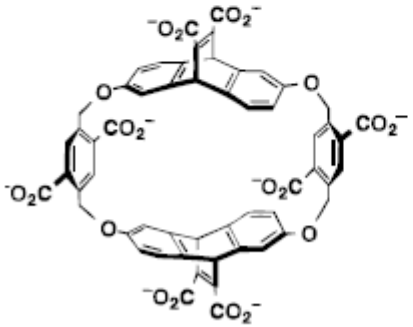
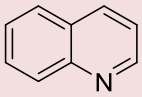
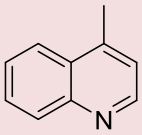
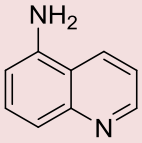
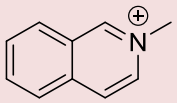
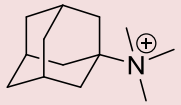


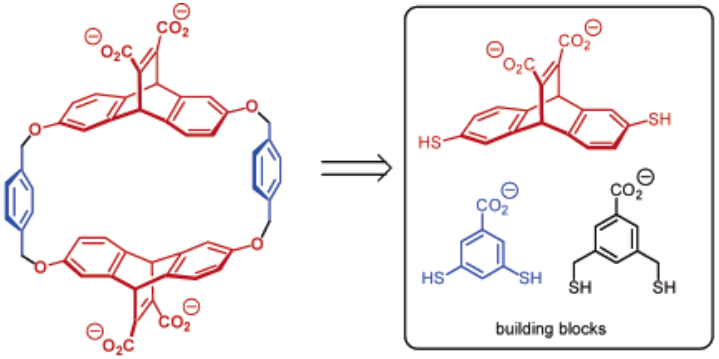
3

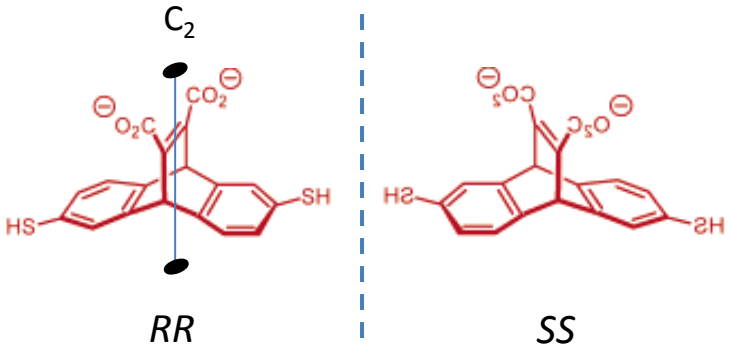
Guests	Host [$-\Delta G^0$ (Kcal/mol)]		
	1	**2**	**3**
	5.3	5.1	-
	5.9	5.8	5.5
	5.7	5.6	5
	7.2	7.8	9.0
	6.7	6.6	6.1

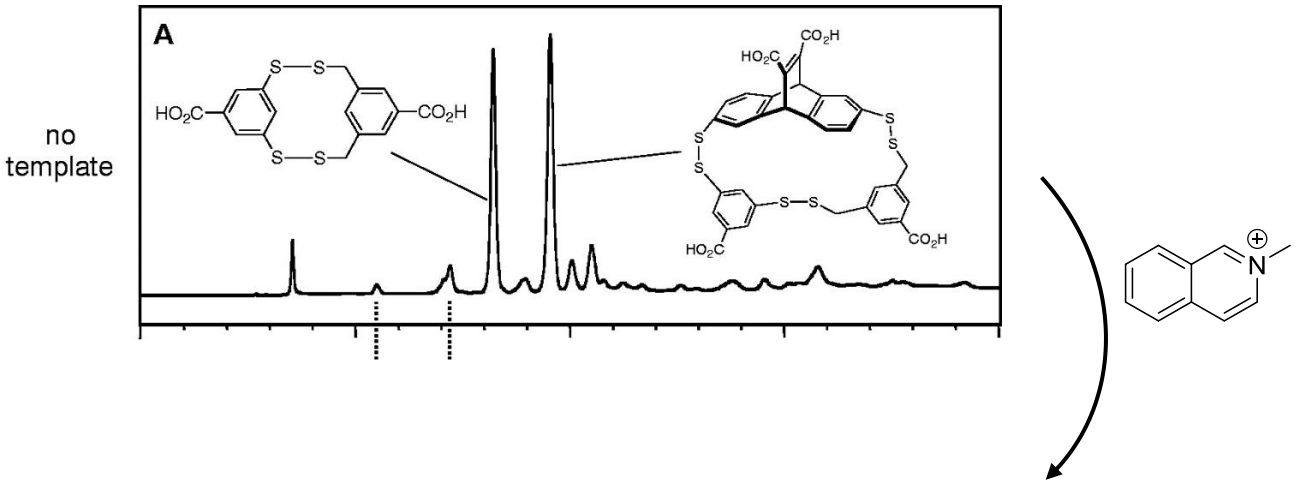
Determined in Borate buffer

J. Am. Chem. Soc. **1999,** *121,* 1192-1201

Adapting cyclophane chemistry to disulfide based DCC

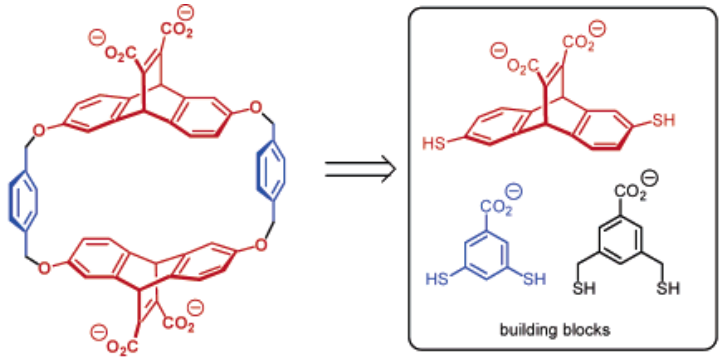


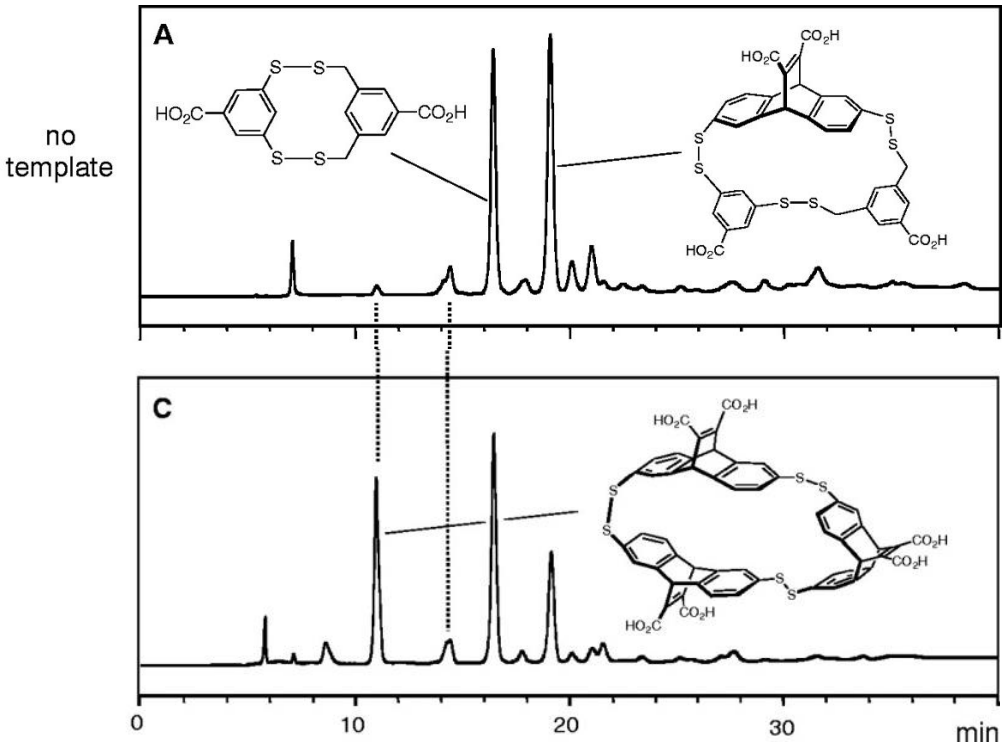


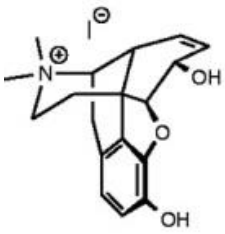


Science **2002**, *297*, 590-593

Adapting cyclophane chemistry to disulfide based DCC

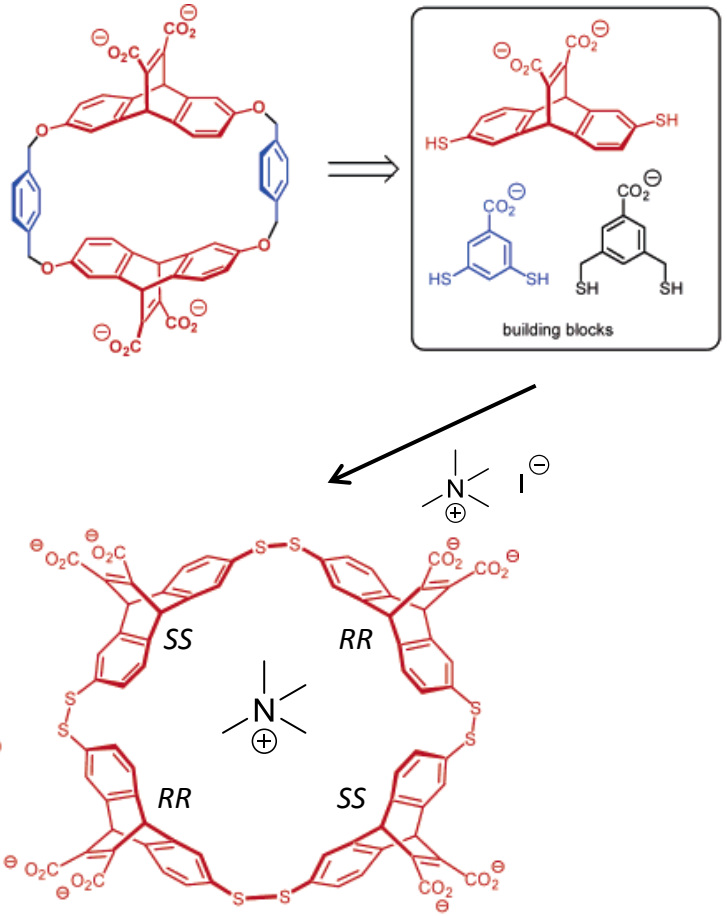


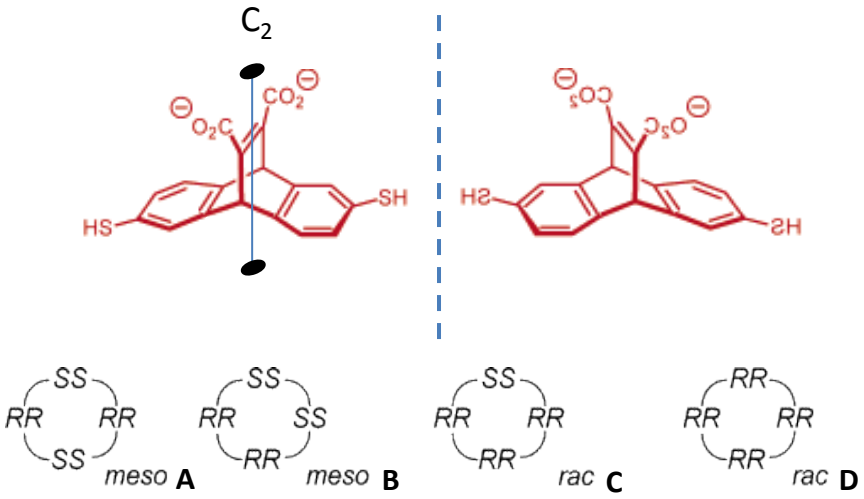




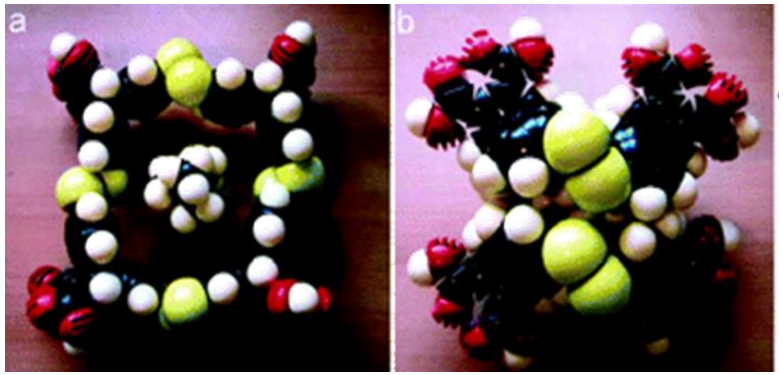
Science **2002**, *297*, 590-593

Adapting cyclophane chemistry to disulfide based DCC





Only *meso* A can fold to encapsulate the cation

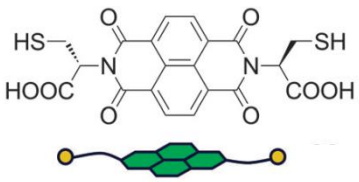


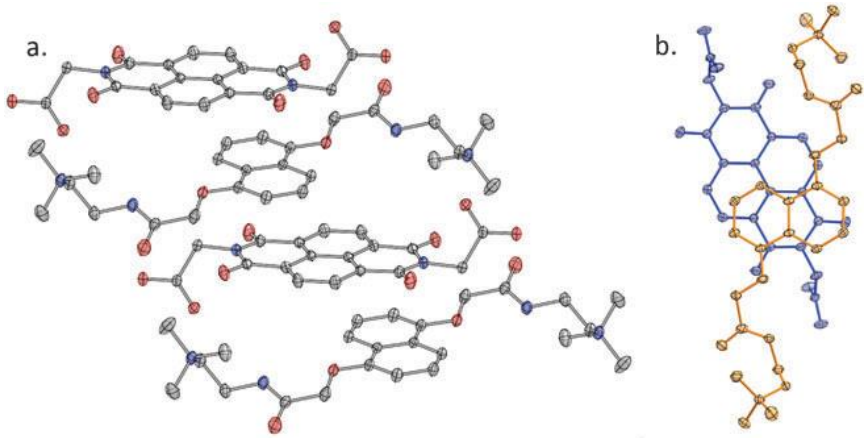
$K_b = 4 \cdot 10^6\ M^{-1}$ (in 10 Mm borate buffer pH 9.0)

$-\Delta G^0$ 38 KJ/mol ca 9 Kcal/mol

J. Am. Chem. Soc. 2005, 127, 8902-8903

Selection driven by aromatic donor-acceptor interactions





Binding studies

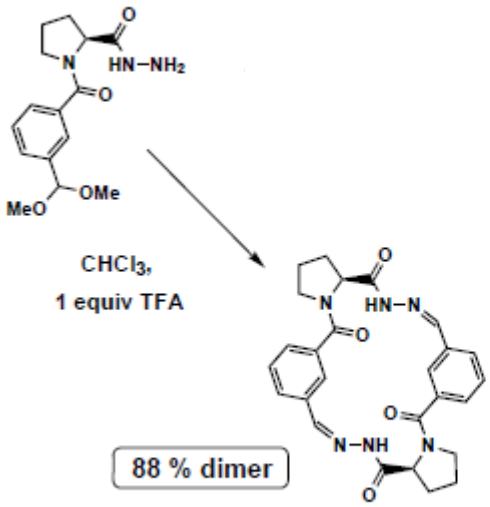
The first association constant to the tetramer is 10^6 M^{-1}

The second association constant to the tetramer is 10^4 M^{-1}

Binding (outside) the dimer 7700±110 M^{-1}

Chem. Commun., **2009**, 419–421

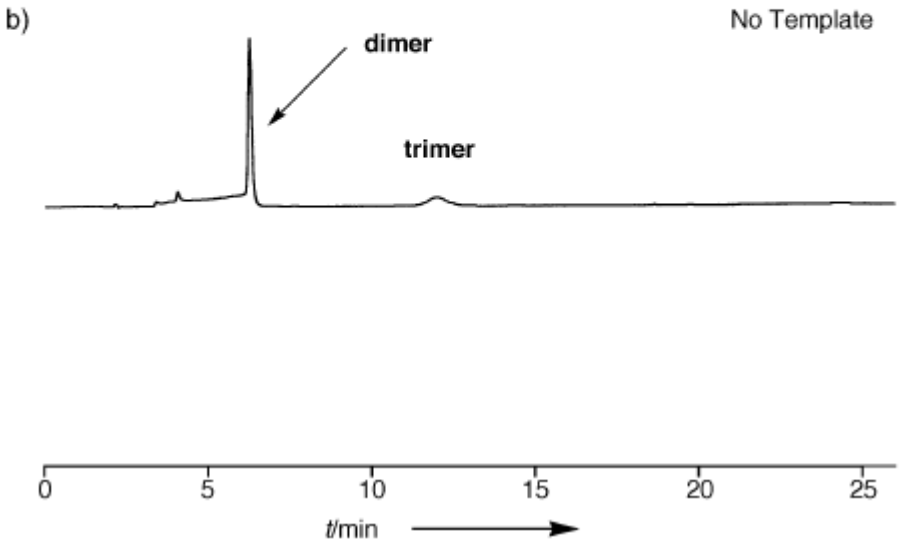
Hydrazone exchange, an acetylcholine receptor



Binding analyses
(NMR $CDCl_3/CD_3OD$ (95:5)

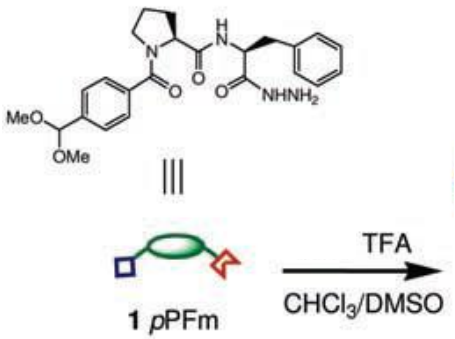
ACh Kb 230 M^{-1}

NMQ Kb 150 M^{-1}



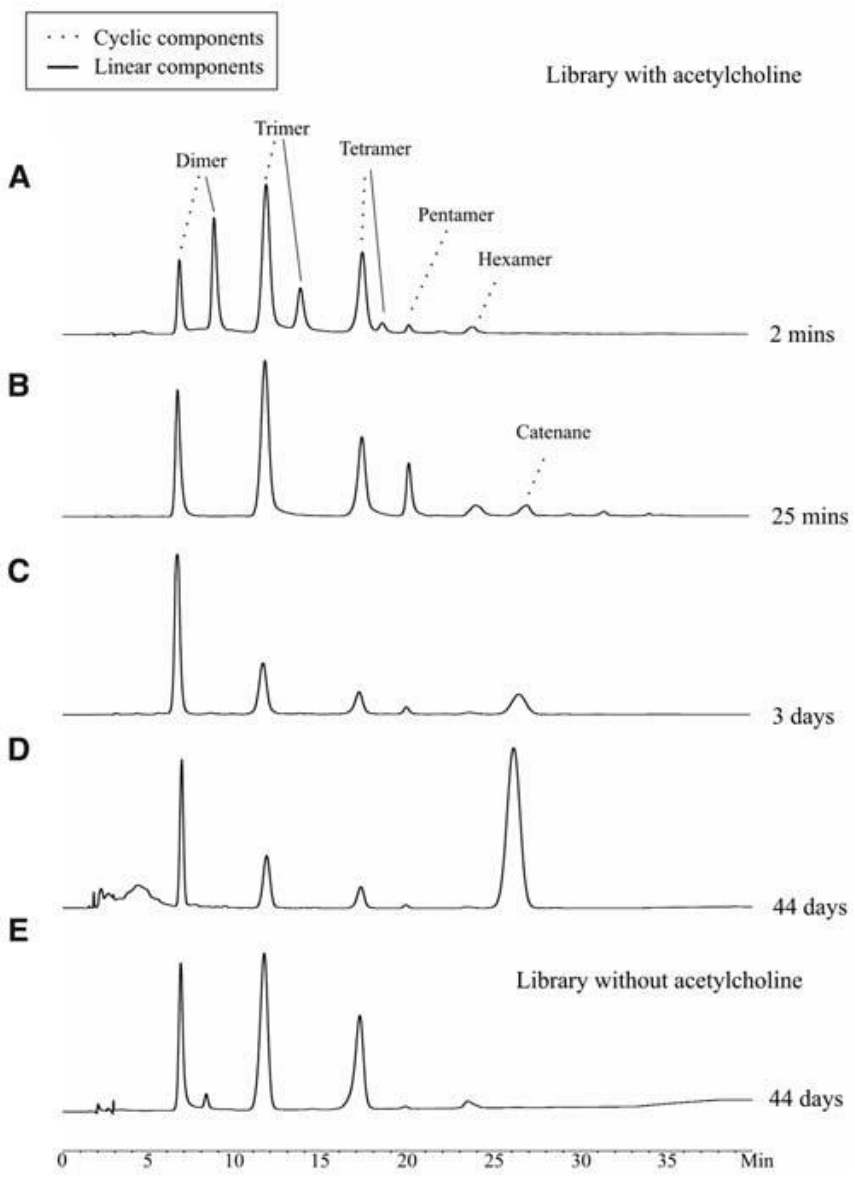
Angew. Chem. Int. Ed. **2001**, *40*, 424-428

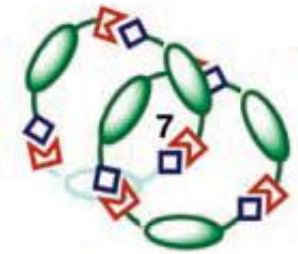
Surprising structures from a hydrazone library



Science **2005**, *308*, 667-669

Surprising structures from a hydrazone library





67% isolated yield

Binding Studies
in 95:5 $CHCl_3$/DMSO

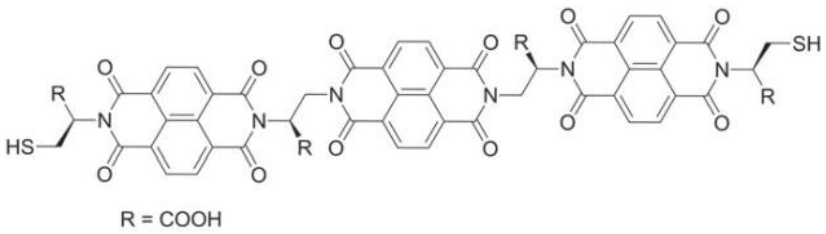
Catenane Kb $1.4 \cdot 10^7\ M^{-1}$

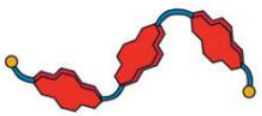
Tetramer Kb $5.7 \cdot 10^3\ M^{-1}$

Trimer Kb $1.5 \cdot 10^3\ M^{-1}$

Science **2005**, *308*, 667-669

Hydrophobic collapse into compact surprising structures

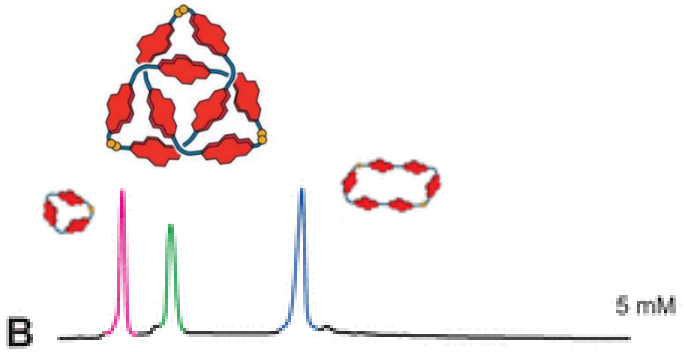


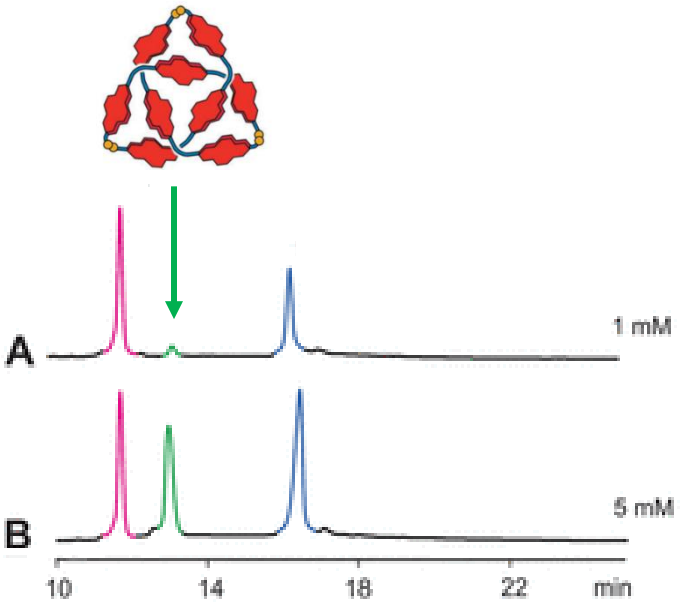


H_2O /O_2

pH 8.0

Library





Science, **2012**, *338*, 783-785

Essential Literature

Dynamic Combinatorial Chemistry, Reek and Otto Ed. 2010 WILEY-VCH Verlag

Black, S. P.; Sanders, J. K. M.; Stefankiewicz, A. R. *Chem. Soc. Rev.* **2014**, *43*, 1861-1872

Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M., Otto , S. *Chem. Rev.* **2006**, *106*, 3652-3711.