the $v = 2$ state. Hence, the $v = 2$ state has the lowest proton-transfer energy. The energy $E_{T,2}$ of 6500 cm^{-1} (0.82 eV) is less than 20% of the O-H binding energy of 38,750 cm^{-1} (4.8 eV), which shows that the hydrogen bonds in liquid water have a surprisingly strong effect on the properties of the O-H chemical bond.

For pure H_2O, the interactions between the O-H stretch vibrations and the O-H $\cdots$ O hydrogen bonds are quite similar to those in a solution of HDO in D_2O. Therefore, the same qualitative behavior is expected for the vibrational states of hydrogen-bonded H_2O molecules. However, quantitatively there will be small differences, because the O-H stretch vibrations of the H_2O molecule form delocalized symmetric and asymmetric modes.

The strongly delocalized nature of the excited vibrational states of the O-H stretch vibration can have important implications for the mechanism of proton transfer in room-temperature water. Recent Car-Parrinello molecular dynamics simulations showed that the first step of the autodissociation of water

$$H_2O + H_2O \leftrightarrows H_3O^+ + OH^- \quad (1)$$

is formed by the transfer of a proton in the O-H $\cdots$ O system (*24*). In view of this finding, it is interesting to compare the activation energy of the autodissociation of water with the proton-tranfer energies shown in Fig. 4. A water molecule dissociates every 11 hours at 298 K ($k_D = 2.4 \times 10^{-5}$ s^{-1}) (*25*) and every 214 hours at 273 K ($k_D = 1.3 \times 10^{-6}$ s^{-1}) (*26*), from which the activation energy can be estimated to be ~6600 cm^{-1}. This activation energy is much lower than the energy of 12,500 cm^{-1} required for proton transfer in the vibrational ground state and quite similar to the energy of 6500 cm^{-1} of proton transfer through excitation of the $v = 2$ state. Hence, it seems likely that the first step of the autodissociation proceeds through an excited vibrational O-H stretch vibrational state, most probably $v = 2$. Unfortunately, this notion cannot be further experimentally tested by vibrationally exciting water and probing the reaction products, because the energy equilibration of water is too fast to determine the excited degree(s) of freedom through which the products were formed. However, the present findings on the delocalized character of the excited O-H stretch vibrational states should stimulate theoretical work on the reactivity of the O-H groups of water that explicitly includes the quantum-mechanical nature of the proton motion.

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27. We thank D. Frenkel for useful discussions. The research presented in this paper is part of the research program of the Stichting Fundamenteel Onderzoek der Materie (Foundation for Fundamental Research on Matter) and was made possible by financial support from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organization for the Advancement of Research).

25 April 2002; accepted 31 May 2002

Selection and Amplification of Hosts From Dynamic Combinatorial Libraries of Macrocyclic Disulfides

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We have discovered two receptors for two different guests from a single dynamic combinatorial library. Each of the two guests amplifies the formation of a tightly binding host at the expense of unfit library members. Small differences in host-guest binding translate into useful differences in amplification. The selected hosts could be readily synthesized using biased dynamic libraries that contain only the right ratio of those building blocks that were selected by the guests. These results establish dynamic combinatorial chemistry as a practical method not only for the discovery but also for the synthesis of new receptors.

Molecular recognition leading to the binding of a guest to a host involves a complex interplay of subtle noncovalent interactions. The understanding of these interactions is limited, hampering successful design of new host-guest systems. Combinatorial methods in which a guest can choose from a pool of receptors can be useful tools to optimize designs, facilitate access to new hosts, and ultimately aid in the understanding of host-guest interactions. Dynamic combinatorial chemistry (*1–3*) goes a step further: the preferred receptor is not only selected by the guest but also amplified at the expense of the unselected compounds. The key feature of dynamic combinatorial chemistry is the reversible nature of the reaction that links building blocks together (*4*) to form a mixture of compounds [a dynamic combinatorial library (DCL)] that interconvert continuously (Fig. 1). The composition of a DCL is under thermodynamic control, that is, the concentration of each library member is determined by its free energy. Molecular recognition events that lead to the stabilization of a particular member of the library induce a shift of

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the equilibrium favoring the formation of the selected species. Hence, exposing a DCL of potential host molecules to a guest will result in the selection and amplification of the fittest host at the expense of ineffective ones (Fig. 1). Amplification facilitates the identification of the selected hosts. After switching off the exchange of building blocks, amplification should also allow for isolation of this host as a stable species directly from the "frozen" library.

Since the introduction of these concepts in 1996 (*5*), several reactions have been shown to be reversible under one set of conditions and inactive under others, allowing large and diverse DCLs to be generated (*1*). The key question is whether molecular recognition is powerful enough to induce amplification of target molecules in DCLs. Although promising template-induced shifts in mixture composition have been observed in small model libraries (*6–16*), it is as yet unclear whether useful shifts will occur in libraries of more realistic size and diversity. The only theoretical study on this topic predicts that template effects are insufficient for dynamic combinatorial chemistry to be of much practical value (*17*).

We demonstrate here that molecular recognition-induced shifts in the composition of libraries of realistic size and diversity can be impressive. Moreover, we show that exposure of a single DCL of macrocyclic disulfides to two different guests amplifies the formation of two hosts. Amplification was even more pronounced in second-generation biased libraries that contained only the building blocks selected by the templates, providing a high-yielding synthetic route to the selected hosts. These results demonstrate the practicality of dynamic combinatorial chemistry.

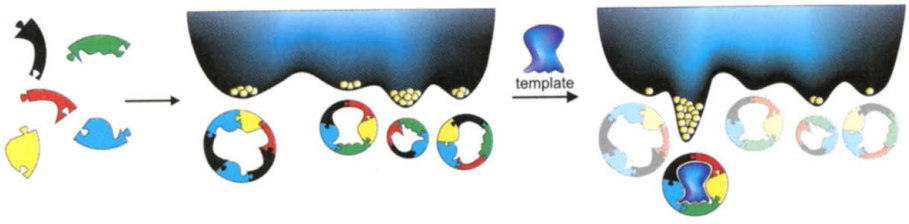

Fig. 1. A small dynamic combinatorial library and its free energy landscape, showing the effect of adding a template that strongly and selectively binds to one of the equilibrating species.

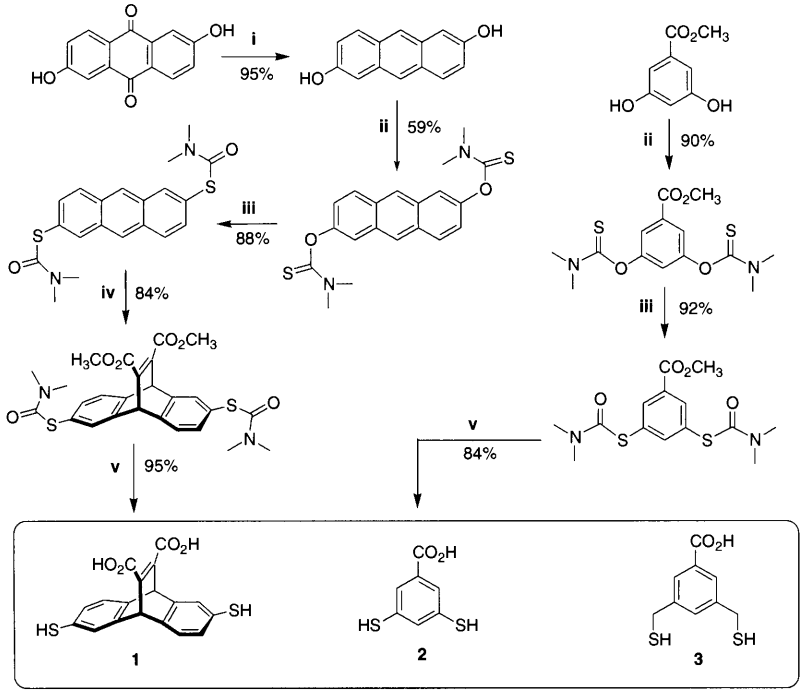

Fig. 2. Synthetic routes to building blocks **1** and **2**. Reduction **i** was carried out using $NaBH_4$ following a literature procedure (*28*). Reaction with *N,N*-dimethylthiocarbamoyl chloride (**ii**) was performed analogously to a procedure in (*29*). Rearrangement **iii** required heating a solution of the thiocarbamate (1 g) in diphenyl ether (10 ml) to 240°C for 3 hours. Diels-Alder reaction **iv** was performed by stirring a 0.45-M solution of the diene with 2.5 equivalents dimethyl acetylene dicarboxylate in diphenyl ether for 1.25 hours at 190°C. The adduct was chromatographed over silica gel (a gradient of 5 to 10% acetonitrile in chloroform). Basic deprotection **v** was carried out similar to a procedure in (*29*). The synthesis of **3** has been described previously (*30*).

We (*18*) and others (*19*) have recently adapted disulfide chemistry for the generation of DCLs in water. Dynamic libraries of macrocyclic disulfides form spontaneously upon stirring a mixture of dithiols at pH 7 to 9 in an open vial. Oxygen from the air is sufficient to oxidize the thiols to disulfides. Subsequent disulfide exchange is mediated by residual amounts of thiolate anion. Exchange ceases upon protonation or removal of the thiolate, allowing isolation and handling of individual library members.

We have previously demonstrated that highly diverse DLCs can be obtained by mixing dithiol building blocks of very different chemical nature (*18*). We have since prepared a new, more focused set of building blocks (dithiols **1** to **3**) specifically aiming at molecular recognition. The design of these building blocks (Fig. 2) was inspired by the family of cyclophane receptors developed by Dougherty and co-workers (*20–23*). Dithiols **1** to **3** feature hydrophobic aromatic surfaces that are well separated from the carboxylate groups required for water solubility.

A DCL was prepared by mixing equimolar amounts of building blocks **1** to **3** in water at pH 8 to 9 in an open vial (*24*). After oxidation, analysis of the resulting DCL by electrospray ionization mass spectrometry (ESI-MS) revealed the presence of 45 different macrocyclic disulfides of unique mass. The actual number of different macrocycles in the library will be much larger due to the occurrence of stereoisomers and sequence isomers. More quantitative information on the library distribution was derived from high-performance liquid chromatography (HPLC) analysis (Fig. 3A). In the absence of any guest molecules, two major constituents are present. Isolation of these compounds

Table 1. Equilibrium constants K and Gibbs energies ΔG, enthalpies ΔH, and entropies ΔS of binding of guests **4** and **5** to hosts **6** (major diastereomer) and **7** (mixture of stereoisomers) at 298 K, determined with isothermal titration microcalorimetry. Guest solutions (0.85 mM) were titrated into host solutions (0.075 mM), all prepared in 10 mM borate buffer (pH 9.0).

Guest	Parameter	Host	
		6	**7**
4	K (M^{-1})	2.5×10^5	4.5×10^4
4	ΔG (kJ/mol)	−30.8	−26.6
4	ΔH (kJ/mol)	−41.6	−26.8
4	$T\Delta S$ (kJ/mol)	−10.8	−0.2
5	K (M^{-1})	2.8×10^4	7.1×10^5
5	ΔG (kJ/mol)	−25.4	−33.4
5	ΔH (kJ/mol)	−41.3	−47.8
5	$T\Delta S$ (kJ/mol)	−15.9	−14.4

using preparative HPLC and subsequent ESI-MS analysis showed these to be the mixed dimer of **2** and **3** and a mixed trimer containing all three building blocks. Apart from the two major components, the HPLC trace of the DCL contained at least 36 smaller peaks corresponding to other library members.

We next exposed the DCL to different guest molecules and monitored the response. A dramatic change in library composition was observed upon addition of 2-methylisoquinolinium iodide guest **4** [see Supporting Online Material (SOM)]: one of the minor components in the initial library was amplified at the expense of most of the other library members (Fig. 3B). The selected host (**6**) proved to be a mixed trimer containing two units of **1** and one unit of **2**. Because we used building block **1** as a racemic mixture, **6** was obtained as a mixture of stereoisomers. The meso form of **6** could be separated from the racemic mixture of *ll*-**6** and *dd*-**6** using HPLC. However, amplification was not stereoselective: the ratio of *meso*-**6** to *dd*/*ll*-**6** in the presence of guest **4** was comparable to that obtained in the absence of guest.

Exposure of the same dynamic library to *N*-methylated morphine **5** (SOM) led to the amplification of homotrimeric host **7** as a mixture of diastereomers (Fig. 3C). Again, the selected host was only a minor species in the library in the absence of its guest.

The structures of the two selected hosts are fundamentally different from the receptor developed by Dougherty and co-workers (*20*–*23*) that inspired our building block design. The disulfide analog of this receptor would be a **1**-**2**-**1**-**2** cyclic tetramer. ESI-MS results suggest that this species is present in the mixed libraries, but it was not amplified upon exposure to a number of different guests that have high affinities for the Dougherty host.

A set of control experiments indicates that the observed library distributions reflect equilibrium compositions. First, library composition in the absence of template is independent of the way in which this library was generated. Mixing a preformed library of **1** and **3** with a preformed library of **2** gives essentially the same product distribution as that obtained by oxidizing a mixture of the three dithiols **1** to **3** (*25*). Second, the composition of the dynamic mixture obtained after adding guests is the same, irrespective of whether the guest is present from the start of the experiment or added later to the preformed library (*25*).

Our templating results demonstrate that molecular recognition can be efficient enough to lead to marked changes in composition of libraries of realistic size and diversity, greatly facilitating the identification of the selected hosts. However, we wanted to see whether we could optimize amplification such that the selected receptors could be isolated directly from the library. Thus far, the library composition was chosen to cover a broad variety of potential hosts. Having identified the selected hosts, we could adjust the library compositions to favor their formation. We prepared a second generation of biased libraries that contained only those building blocks that were selected by the guest in the appropriate ratio. To produce host **6**, we mixed building blocks **1** and **2** in a 2:1 ratio. In the absence of any guest, a diverse library was obtained in which the desired host was only a minor constituent (5 to 10%, Fig. 4A). In the presence of guest **4**, host **6** was efficiently amplified and at equilibrium consti-

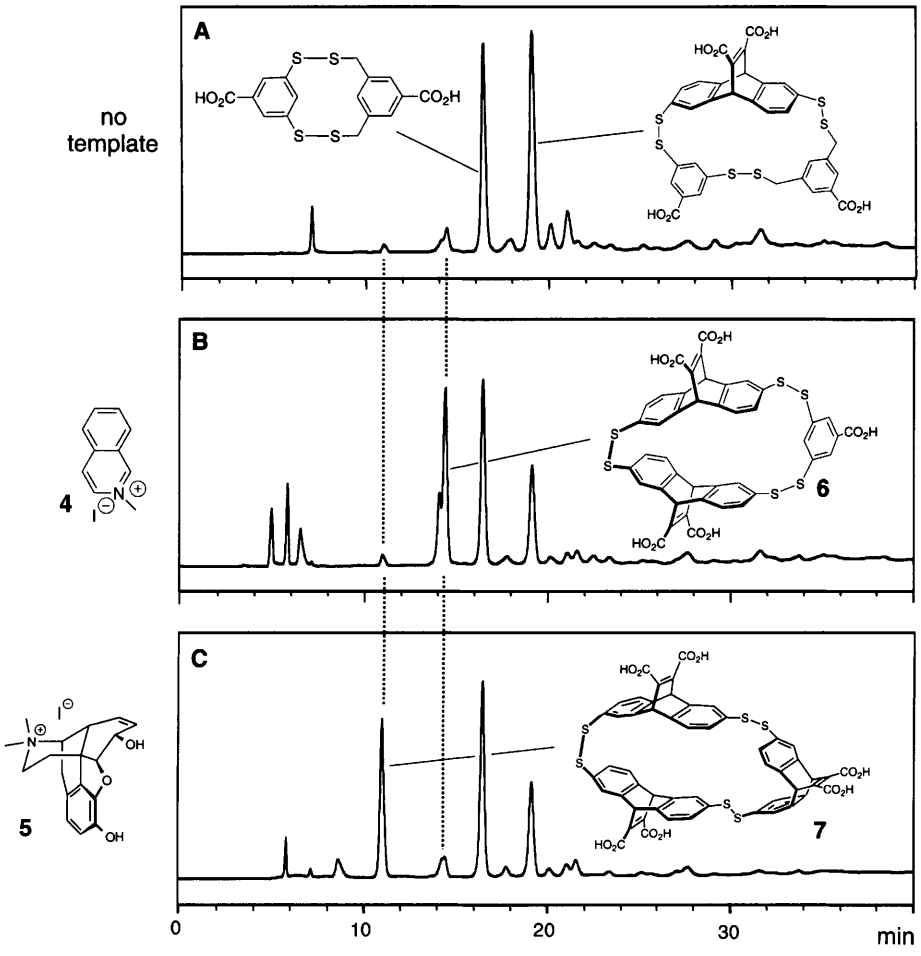

Fig. 3. HPLC analyses of the DCL made from dithiols **1**, **2**, and **3** (3.3 mM each) (**A**) in the absence of any template; (**B**) in the presence of **4** inducing the amplification of host **6**; and (**C**) in the presence of morphine derivative **5** leading to the amplification of host **7**. Hosts **6** and **7** are obtained as mixtures of stereoisomers (see text). HPLC analyses were performed with a 250-mm by 4.6-mm, 5-μm particle size Hypersil SAX anion exchange column and a gradient of 0.025 to 0.5 M ammonium formate in a 55:35:10 mixture of 2-propanol, acetonitrile, and water.

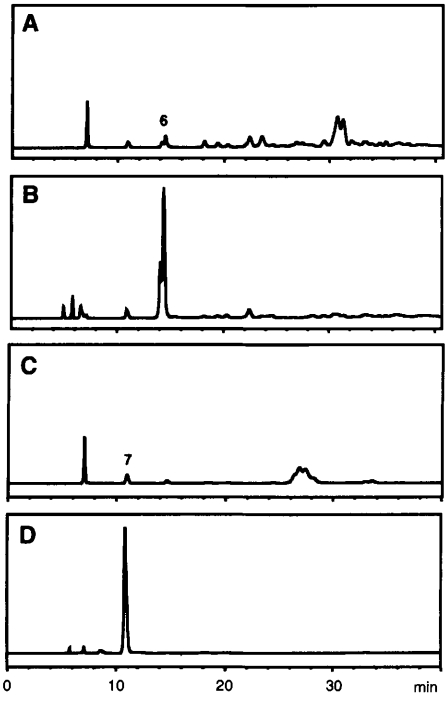

Fig. 4. HPLC analysis of a DCL made from (**A**) dithiols **1** (6.7 mM) and **2** (3.3 mM) in the absence and (**B**) presence of guest **4**; (**C**) dithiol **1** (10 mM) in the absence and (**D**) presence of guest **5**. HPLC conditions are the same as those described in Fig. 3.

tuted 60 to 65% of the total material in the library (Fig. 4B). Similarly, host **7** can be produced in >95% yield from a small library prepared by oxidizing dithiol **1** in the presence of guest **5** (Fig. 4D). In the absence of the guest, this trimeric host is produced in only 6% yield (Fig. 4C).

These yields are impressive for macrocyclization reactions, which are notorious for producing only small quantities of the desired ring size. Note also that the high-dilution conditions normally required for macrocyclizations are not necessary in these thermodynamically controlled templated syntheses.

We have isolated hosts **6** (major diastereomer) and **7** (mixture of stereoisomers) using preparative HPLC (SOM) and studied the interaction with guests **4** and **5** using ESI-MS and microcalorimetry. The 1:1 host-guest complexes could be detected as main peaks in the mass spectrum together with the free hosts (fig. S1). Binding constants, enthalpies, and entropies obtained by microcalorimetry (fig. S2) are shown in Table 1. The binding constants for the optimal host-guest pairs (**4·6** and **5·7**) are 6 to 25 times higher than those for the mismatched pairs (**4·7** and **5·6**). Apparently, the guests can select a tightly binding host from a number of closely related structures. Most importantly, relatively small differences in binding energies are sufficient to lead to large differences in extent of amplification.

Thermodynamic analysis shows that binding is invariably enthalpy-driven and counteracted by entropy, suggesting that binding is dominated by electrostatic interactions including cation-π interactions (*26, 27*) and possibly also salt-bridge formation. To substantiate this hypothesis, we are currently studying the binding thermodynamics of a wider range of guests. The results of these studies will be reported in due course.

Our results establish dynamic combinatorial chemistry as a powerful and practical tool for the discovery of artificial receptors. Subtle differences in affinity lead to useful differences in amplification. Moreover, the underlying dynamic chemistry can be used directly for large-scale preparations. Reversibility ensures that side products are recyclable, allowing, at least in theory, complete conversion into the desired product even in systems where the templating efficiencies are much smaller than those described herein.

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31. We thank A. R. Fersht and C. M. Johnson for the use of their isothermal titration microcalorimeter and technical assistance. We acknowledge support from the European Union (Marie Curie Fellowship HPMF-CT-1999-00069) and the Royal Society (University Research Fellowship) to S.O., from the Fundación Antorchas and the Consejo Nacional de Investigaciones Cientificas y Tecnicas (Argentina) to R.L.E.F. and from EPSRC to J.K.M.S.

Supporting Online Material

www.sciencemag.org/cgi/content/full/297/5581/590/DC1
Materials and Methods
Figs. S1 and S2

29 March 2002; accepted 3 June 2002

Band Gap Fluorescence from Individual Single-Walled Carbon Nanotubes

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Fluorescence has been observed directly across the band gap of semiconducting carbon nanotubes. We obtained individual nanotubes, each encased in a cylindrical micelle, by ultrasonically agitating an aqueous dispersion of raw single-walled carbon nanotubes in sodium dodecyl sulfate and then centrifuging to remove tube bundles, ropes, and residual catalyst. Aggregation of nanotubes into bundles otherwise quenches the fluorescence through interactions with metallic tubes and substantially broadens the absorption spectra. At pH less than 5, the absorption and emission spectra of individual nanotubes show evidence of band gap–selective protonation of the side walls of the tube. This protonation is readily reversed by treatment with base or ultraviolet light.

Single-walled carbon nanotubes are elongated members of the fullerene family (*1*) that are currently the focus of intense multidisciplinary study because of their unique physical and chemical properties and their prospects for practical applications (*2*). A major obstacle to such efforts has been the diversity of tube diameters, chiral angles, and aggregation states in nanotube samples obtained from the various preparation methods. Aggregation is particularly problematic because the highly polarizable, smooth-sided fullerene tubes readily form parallel bundles or ropes with a van der Waals binding energy of ~500 eV per micrometer of tube-tube contact (*3*, *4*). This bundling perturbs the electronic structure of the tubes, and it confounds all attempts to separate the tubes by size or type or to use them as individual macromolecular species. Although efforts from this laboratory (*5*, *6*) and others (*7–12*) have reported some progress in producing suspensions enriched