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Harnessing the Energy of Molecular Recognition in a Nanomachine Having a Photochemical On/Off Switch

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The literal definition of a machine is an apparatus consisting of interrelated parts with separate functions and used in the performance of some kind of work. With molecular machines, the work involves regulating molecular motions and occurs in response to external stimuli which may be either chemical, thermal, or photochemical.[1−4] A stimulus initially produces a system that is out of equilibrium and, as equilibration occurs, work is done.[3] This is illustrated by molecular shuttles,[4] where a stimulus changes the balance of the molecular recognition events to destabilize the original conformation and cause the components to move. Here we report a molecular machine where the work output resulting from molecular recognition is harnessed to constrain the geometry of an amide bond, and the apparent work performed in this process is quantified. Further, a more advanced form of the device exists as two isomers that are interconverted photochemically. Only one of the isomers exhibits the molecular recognition and performs the work, so the photoisomerization turns the machine on and off.

The molecular machine is illustrated in Figure 1 and its operation is shown in Schemes 1 and 2. The basic form **1** (Scheme 1) comprises an aryl substituent attached to β-cyclodextrin. These behave as the piston and cylinder, respectively, of a molecular pump. The pump is fueled by 1-adamantanol. The compression stroke of the piston involves intramolecular complexation of the aryl substituent within the cyclodextrin annulus in water, in response to using hexane to extract the competitive guest, 1-adamantanol, from the aqueous solution and therefore from the cyclodextrin cavity. This molecular recognition process provides strain energy to alter the ratio of the (*E*)- and (*Z*)-isomers of the amide group linking the cyclodextrin to the phenyl substituent, which therefore serves as a torsion bar. The decompression piston stroke simply involves the addition of 1-adamantanol with the reverse consequences.

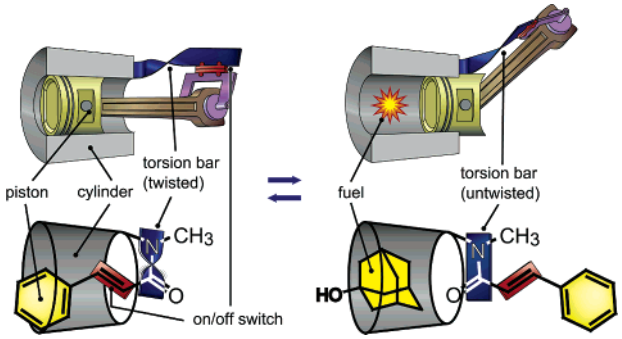
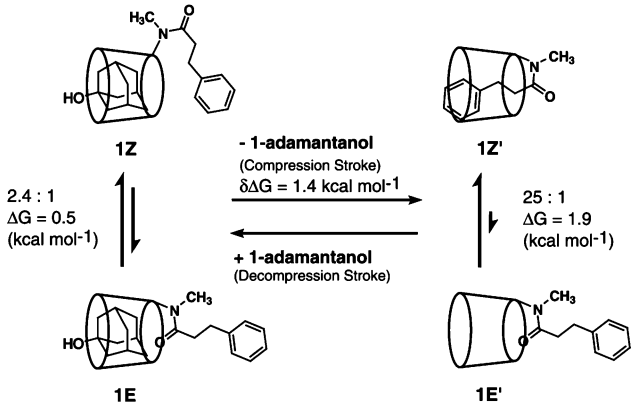


Figure 1. Schematic representation of a mechanical machine and its molecular counterpart.

Scheme 1. Operation of 6^A-Deoxy-6^A-(*N*-methyl-3-phenylpropionamido)-β-cyclodextrin **1** as a Molecular Machine



The conformations of the machine **1** were determined in D_2O at 25 °C, primarily using 2D ^{1}H NMR spectroscopy. This included distinguishing between the amide (*Z*)- and (*E*)-isomers **1Z** and **1E**, and **1Z′** and **1E′**, and the phenyl substituent when free and included in the cyclodextrin, as well as precluding the formation of dimeric Janus complexes.[5] The methyl group was incorporated into the machine as a convenient handle for analysis, and the isomer ratios were calculated by integrating the corresponding signals for those protons in 1D ^{1}H NMR spectra. In the presence of 1-adamantanol, when the phenyl substituent is not complexed, the (*Z*)-isomer **1Z** is in excess only by a ratio of 2.4:1. Complexation of the aryl group by the cyclodextrin through removal of the 1-adamantanol causes a more than 10-fold increase in the proportion of the (*Z*)-isomer **1Z′**, to a ratio of 25:1.

Under any particular set of conditions, the ratio of amide isomers reflects the difference in their ground state free energies (ΔG),[6] and the alteration in the ratio resulting from a change in conditions reflects the work performed on the amide bond ($\delta\Delta G$).[7] The difference between the ratios of the isomers **1Z** and **1E**, and **1Z′** and **1E′**, in water containing 1-adamantanol, and in water alone, is directly attributable to the cyclodextrin−phenyl group host−guest interaction. These ratios correspond to ΔG values of 0.5 and 1.9 kcal mol^{-1}, respectively, on which basis the energy apparently harnessed by the amide torsion bar as a result of the extraction of 1-adamantanol and the consequent inclusion complex formation is $\delta\Delta G = 1.4$ kcal mol^{-1}.

In the more advanced version of the machine, shown in Scheme 2, the alkene moiety between the phenyl substituent and the amide group serves as a photochemical on/off switch. Irradiation at 300 nm converts the trans cinnamide **2** to the cis isomer **3**, while the reverse process occurs at 254 nm.[8] The ratios of the amide isomers of **2** and **3** were determined under the conditions and in the manner described above for **1**. The ratio of the isomers **3Z** and **3E** of

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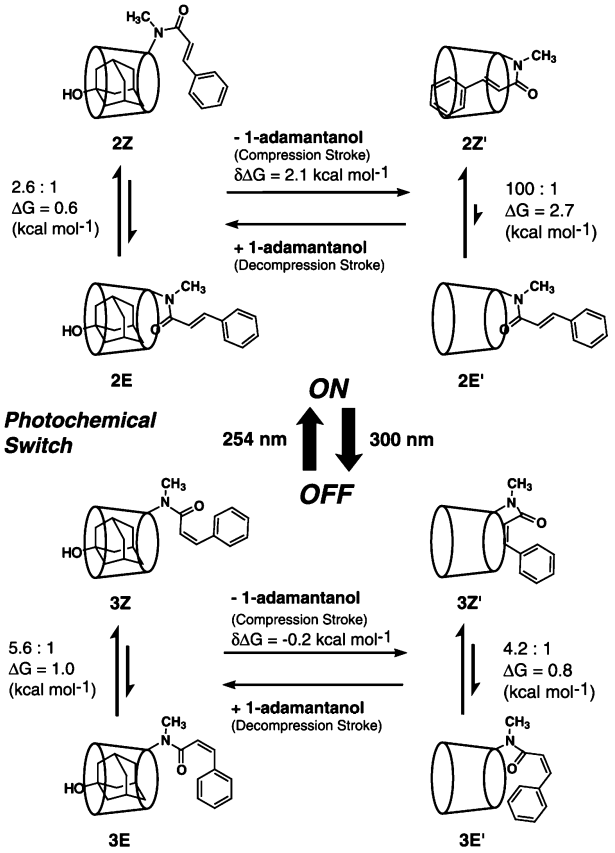
Scheme 2. Operation of *trans*-6^A-Deoxy-6^A-(*N*-methylcinnamido)-β-cyclodextrin **2** and the Cis Isomer **3** as a Molecular Machine Having a Photochemical On/Off Switch



5.6:1, found when 1-adamantanol is present in the mixture, is very similar to that of **3Z′** and **3E′** of 4.2:1, measured in the absence of the competitive guest. This is consistent with the NMR spectra recorded for this system, which show little interaction of the phenyl group with the cyclodextrin cavity, irrespective of the presence of 1-adamantanol. The small difference between the ΔG values for the isomers **3Z** and **3E** (1.0 kcal mol^{-1}), and **3Z′** and **3E′** (0.8 kcal mol^{-1}), shows a corresponding lack of work on the amide bond ($\delta\Delta G = -0.2$ kcal mol^{-1}). Thus the cis double bond prevents the host−guest interaction and in that mode the machine is turned off. By contrast, the ratio of the trans cinnamide amide isomers **2Z′** and **2E′** in water alone (100:1) is much greater than that of **2Z** and **2E** in water containing 1-adamantanol (2.6:1). The increase is attributable to removal of 1-adamantanol causing complexation of the aryl substituent by the cyclodextrin, as observed in NMR spectra. In this case the energy harnessed by the amide bond, as calculated from the difference between the ΔG values for the isomers in the presence of 1-adamantanol (0.6 kcal mol^{-1}) and in its absence (2.7 kcal mol^{-1}), is $\delta\Delta G = 2.1$ kcal mol^{-1}. It follows that the trans alkene moiety allows complexation, and in this mode the machine is turned on.

The conformations of the cyclodextrin derivatives **1**−**3** were also examined in d_6-DMSO. The NMR spectra show that in this solvent there is little interaction of the aryl substituent with the cyclodextrin cavity, consistent with there being no driving force for the inclusion.[9] As expected on this basis, the ratios of the (*Z*)- and (*E*)-amide isomers in DMSO were found to be remarkably similar to those in water containing 1-adamantanol. It follows from the different conformations and ratios of the amide isomers in DMSO and water without 1-adamantol, that changing the solvent in this way, and vice versa, drives these molecular machines in a similar manner to the addition and removal of 1-adamantanol to aqueous solutions.

In summary, the apparatus illustrated in Figure 1 and exemplified by the cyclodextrin derivatives **1**−**3** constitutes a molecular machine where the output energy of molecular recognition is harnessed to do work and constrain the geometry of an amide bond. In the case of the cinnamides **2** and **3**, their photoisomerization provides the machine's on/off switch. The apparent work performed on the amide bond is 1.4, 2.1, and −0.2 kcal mol^{-1}, with the propionamide **1**, and the cinnamides **2** and **3**, respectively. This demonstration that work output can be harnessed and quantified in such molecular devices takes us one step closer to their practical application.

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Supporting Information Available: Details for the synthesis of **1**−**3** and their operation as molecular machines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The work performed to stabilize the amide (*Z*)-isomer is the inverse of the apparent stability and increase in proportion of that isomer. Therefore the ΔG and $\delta\Delta G$ values are calculated from the inverse of the amide (*Z*)-/(*E*)-isomer ratios.

(8) Irradiation of the trans alkene **2** at 300 nm affords a 1:9 mixture of **2** and **3** in the photostationary state, from which the cis isomer **3** was isolated using HPLC. Irradiation of the cis isomer at 254 nm affords a 1:1 mixture of **2** and **3**. The efficiency of the photoreversion is limited by the overlapping absorptions of **2** and **3** at this wavelength. Sources of lower wavelength light that might be more effective are not readily available.

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