Pure Appl. Chem., Vol. 77, No. 11, pp. 1865–1871, 2005.
DOI: 10.1351/pac200577111865

Cyclodextrin-based catalysts and molecular reactors*

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Abstract: The naturally occurring cyclodextrins and their derivatives have been developed as miniature reaction vessels, to manipulate the outcomes of chemical transformations at the molecular level. In this manner, the rate of hydrolysis of a phosphate triester has been enhanced by almost five orders of magnitude, and the ratios of products obtained from electrophilic aromatic substitution reactions, from competing reactions to give indigoid dyes, and from nitrile oxide cycloadditions have all been changed, by factors of up to 3500 times.

Keywords: Cyclodextrins; molecular reactors; catalysts; templates; reaction control.

Molecular reactors are miniature reaction vessels that control the assembly of reagents to affect the outcomes of chemical transformations at the molecular level [1]. In many ways, they are analogous to the reaction vats used in chemical industry, the flasks used in chemical laboratories, and even the cooking pots used in kitchens. In each case, containers are used to bring together the required ingredients. After the chemical reactions have taken place, sometimes as a result of stirring or heating, the products are removed and the containers may be reused. The unique aspect of molecular reactors is that they act at the molecular level, and it is implicit that this changes the outcomes of the reactions, to make them different from those that would result when using bulk reaction media, such as common solvents. Where molecular reactors act in this manner, without themselves being altered, by definition they are operating as catalysts.

The starting materials we use to develop molecular reactors are the naturally occurring cyclodextrins **1–3** (Fig. 1). These cyclic oligosaccharides have been known for more than a century [2], and they are now also used extensively in the pharmaceutical industry [3], in household and personal care products [4], and as food additives [5]. All these applications are related to the shape and consequent properties of the cyclodextrins **1–3**. Their shape resembles a truncated cone (Fig. 1) or may be visualized as being similar to a donut. Their exterior surfaces are hydrophilic due to the presence of the hydroxyl groups, while the annulus of the cone or hole in the middle of the donut is hydrophobic, being surrounded by carbon–hydrogen bonds and ether linkages. As a result, in aqueous solution, cyclodextrins form inclusion complexes with hydrophobic guests (Scheme 1).

*Paper based on a presentation at the 17th International Conference on Physical Organic Chemistry (ICPOC-17), Shanghai, China, 15–20 August 2004. Other presentations are published in this issue, pp. 1807–1921.

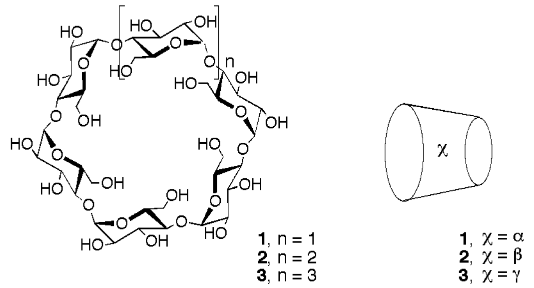
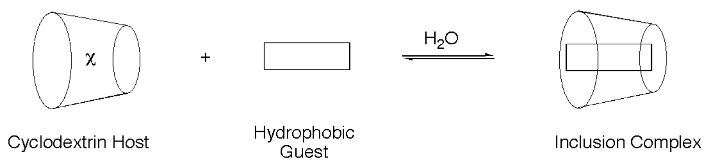


Fig. 1 The structures and truncated cone representation of the naturally occurring cyclodextrins **1–3**. A substituent drawn at the narrow end of the cone indicates that it replaces one of the primary hydroxyl groups.



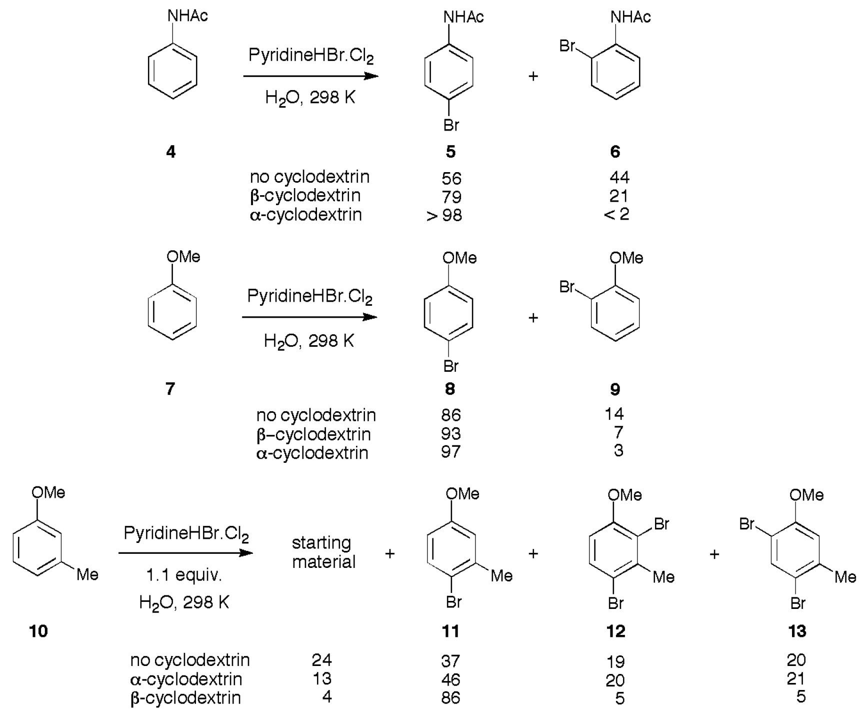
Scheme 1

In a simple example of the use of cyclodextrins as molecular reactors taken from our own work, but which is derivative of earlier studies by Breslow et al. [6–8], and other groups [9–11], of the effect of cyclodextrins on electrophilic aromatic substitution reactions, each of the native cyclodextrins **1** and **2** affects the regioselectivity of bromination of acetanilide **4** and anisole **7** with pyridinium dichlorobromate (Scheme 2) [12]. In the absence of a cyclodextrin, acetanilide **4** reacts to give a 56:44 mixture of the *para*- and *ortho*-brominated compounds **5** and **6**. The ratio of these products is changed to 79:21 when the reaction is carried out in the presence of β-cyclodextrin **2**, whereas the use of α-cyclodextrin **1** results in the formation of 4-bromoacetanilide **5** as the only detectable product. Similar results are observed with the bromination of anisole **7**. These effects may be attributed to the cyclodextrins **1** and **2** acting as molecular reactors, by including acetanilide **4** and anisole **7** in the orientation shown in Fig. 2, whereby their *ortho* positions are shielded from reaction, while their *para* positions remain accessible to the brominating agent.

The bromination of 3-methylanisole **10** is unusual in that the monobromide **11** is more reactive than the starting material (i.e., the bromo group *activates* the system toward electrophilic aromatic substitution), so subsequent reactions occur to produce the dibromides **12** and **13** (Scheme 2) [12]. In this case, the cyclodextrins **1** and **2** restrict the extent of formation of the dibromides **12** and **13**, with β-cyclodextrin **2** having the greatest effect.

In terms of providing a method for the synthesis of the *para*-brominated products **5** and **8**, and the monobromide **11**, an obvious advantage of using the cyclodextrins **1** and **2** is to increase the yields. Just as importantly, the quantities of the corresponding reaction by-products are reduced and product isolation becomes more straightforward, particularly through the use of α-cyclodextrin **1** with acetanilide **4** where there is no need to separate product isomers. An added bonus from using the cyclodextrins **1** and **2** is that they increase the solubility of the substrates **4**, **7**, and **10** in water, making it practical to use this as a cheap and environmentally benign alternative to the organic solvents commonly used for such transformations. The aqueous cyclodextrin solutions can also be used repeatedly, in batch-style processes, by adding the reactants, allowing the reactions to proceed before extracting the products with organic solvents, and then repeating these steps.

While the methods described above represent very efficient procedures for selectively producing the bromides **5**, **8**, and **11**, these effects of the cyclodextrins **1** and **2** are due to a somewhat fortuitous self-assembly of the reagents. However, by modifying the cyclodextrins **1–3**, it is also possible to con-



Scheme 2

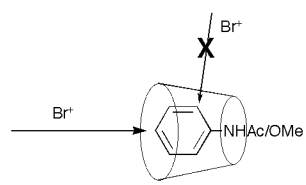
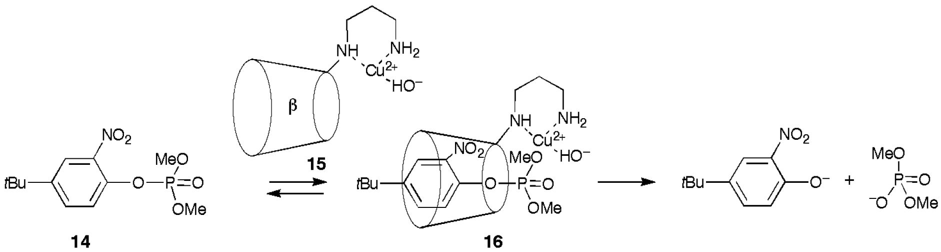


Fig. 2 Effect of the cyclodextrins **1** and **2** in blocking access of a brominating agent to the *ortho* positions of acetanilide **4** and anisole **7**.

trol the assembly of reagents, in order to manipulate the outcomes of chemical reactions by design. In this regard, the cyclodextrins **1–3** are being used as scaffolds and templates for the construction of molecular reactors [13].

Again, to use an example from our own work, which is illustrated in Scheme 3, the complex of 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin with Cu^{II} **15** catalyzes the hydrolysis of the organophosphate triester **14** [14]. In aqueous 0.05 mol dm^{-3} HEPES buffer at pH 7.0 and 298 K, the interaction of the triester **14** with the metallocyclodextrin **15** is characterized by an association constant for the formation of the ternary complex **16** of 235 mol^{-1} dm^3, and a pseudo-first-order rate constant for reaction of the included species (k_{inc}) of 3.1×10^{-2} s^{-1}. By comparison, under the same conditions, the pseudo-first-order rate constant for the uncatalyzed hydrolysis of the triester **14** (k_{un}) is 3.2×10^{-7} s^{-1}. On this basis, the metallocyclodextrin **15** accelerates the rate of hydrolysis of the triester **14** (k_{inc}/k_{un}) by 97 000 times. The metallocyclodextrin **15** is a true catalyst, in that multiple turnover of the substrate **14** is observed. Water bound to copper in the metallocyclodextrin **15** has a pK_a of 7.84 [15], and the hydrolysis at pH 7.0 is most probably brought about by the corresponding hydroxide.

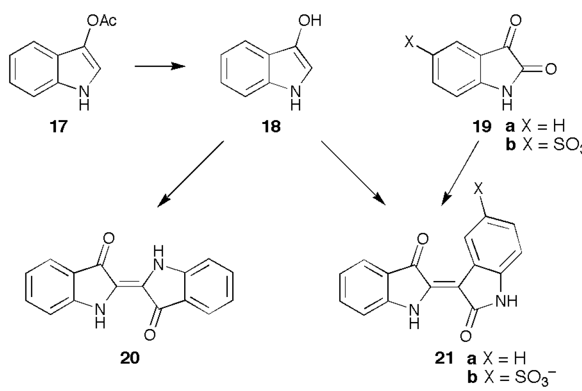
The reaction of the triester **14** catalyzed by the metallocyclodextrin **15** is a hydrolytic process. Cyclodextrin-based molecular reactors have also been developed to control the outcomes of



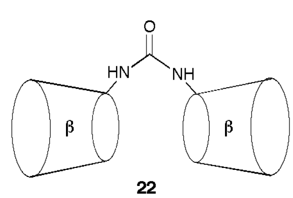
Scheme 3

carbon–carbon bond-forming reactions and to affect the regioselectivity of incorporation of functional groups. Breslow's group has been especially active in these areas [16,17], and, in particular, they have reported some quite advanced systems for the controlled hydroxylation of steroids [16].

We have exploited cyclodextrin dimers to bias competing reactions of indoxyl **18** and isatin **19a** to give indigoid dyes (Scheme 4) [18]. In aqueous solution at pH 10.0, indoxyl acetate **17** hydrolyzes to indoxyl **18**, which can either oxidize to isatin **19a** or undergo oxidative dimerization to give indigo **20**. Indoxyl **18** also reacts with isatin **19a** to give indirubin **21a**. From studies of the cooperative binding of dyes by cyclodextrin dimers [19], it was apparent that the urea derivative **22** more readily adopted the conformation of indirubin **21a** than that of indigo **20**, and it was therefore anticipated that it would favor the reaction of indoxyl **18** with isatin **19a**. Accordingly, under conditions where in the absence of a cyclodextrin indoxyl **18** and isatin **19a** reacted to give a mixture of indigo **20** and indirubin **21a** in yields of 16 and 13 %, respectively, in the presence of the cyclodextrin dimer **22**, the yields of indigo **20** and indirubin **21a** were 0.03 and 1.0 %. Thus, the cyclodextrin **22** changed the ratio of formation of the dyes **20** and **21a** by a factor of approximately 40.



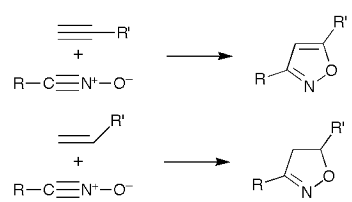
Scheme 4



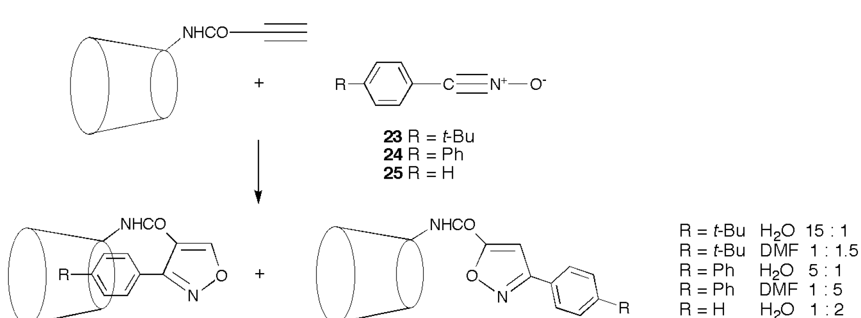
Presenting this material in lectures provides an opportunity to assess how much the audience are paying attention. If there is no sniggering or interruption at this point, they are either asleep or too polite to point out that the ratio of the dyes **20** and **21a** has only been changed by reducing their combined yield by a factor of almost 30 and the yield of indirubin **21a** by 13 times. It is difficult to argue that the use of the cyclodextrin dimer **22** in this system constitutes a real practical advantage!

This effect of the cyclodextrin **22** to reduce the yields of the dyes **20** and **21a** is a consequence of the complexation of indoxyl **18** and isatin **19a** increasing their effective steric bulk and reducing the frequency of their productive collisions. This is likely to be a common effect associated with the use of molecular reactors, but it can be addressed by developing systems where the reactivity of the reagents is actually increased as a result of their inclusion. In this particular example, this was achieved through the use of the isatinsulfonate **19b** instead of isatin **19a**. In aqueous solution, the sulfonate **19b** is in equilibrium with the corresponding hydrate, which deprotonates with a pK_a of 9.55. The cyclodextrin complexes the sulfonate **19b** in preference to both the hydrate and the anion, to increase the pK_a of the hydrate and decrease the extent of hydration of the complexed isatinsulfonate **19b**. More of the material is therefore present as the sulfonate **19b** when it is complexed, and since this is the form that reacts with indoxyl **18**, this reactivity is increased. As a result, under conditions where in the absence of a cyclodextrin indoxyl **18** and the isatinsulfonate **19b** reacted to give a mixture of indigo **20** and the indirubinsulfonate **21b** in yields of 25 and 1.4 %, respectively, in the presence of the cyclodextrin dimer **22** the yields of indigo **20** and the indirubinsulfonate **21b** were <0.1 and 22 %. In this case, the cyclodextrin **22** changed the ratio of formation of the dyes **20** and **21b** by a factor of at least 3500, without any decrease in yield.

We have also developed cyclodextrin-based molecular reactors to reverse the regioselectivity of nitrile oxide cycloadditions [20–22]. Nitrile oxides (dipoles) react with alkynes and alkenes (dipolarophiles) to give isoxazoles and isoxazolines, respectively. With mono-substituted dipolarophiles, there exists the possibility of formation of regioisomeric mixtures of products, but in practice it is almost invariably found that, in these systems, the 5-substituted cycloadducts predominate (Scheme 5) [23]. However, by using β-cyclodextrin **2** as a molecular scaffold, it has been possible to change the outcome. Tethering the dipolarophiles to the cyclodextrin and then allowing preassociation of the modified cyclodextrins with aromatic nitrile oxides, as host–guest complexes, controls the relative orientation of the dipoles and dipolarophiles, to afford primarily 4-substituted isoxazoles and isoxazolines (Scheme 6).



Scheme 5



Scheme 6

The magnitude of the reversal of the regioselectivity depends on the extent of complexation of the nitrile oxide by the cyclodextrin. As a result, the effect is greater with the *tert*-butylphenyl- and biphenyl-nitrile oxides **23** and **24**, than with phenylnitrile oxide **25**, and less when the reactions are carried out in *N,N*-dimethylformamide rather than water, because complexation is disfavored by the former.

Thus, cyclodextrins can be used as scaffolds and templates, to design and build molecular reaction vessels, in order to manipulate the outcomes of chemical transformations at the molecular level. Product ratios may be substantially changed, and reaction rates may be significantly increased. In addition, the molecular reactors work most efficiently in water, often at room temperature and near neutral pH, so this makes them attractive for use both in the laboratory and in chemical industry.

ACKNOWLEDGMENTS

The author gratefully acknowledges the support of the Australian Research Council and the contributions of an enthusiastic group of coworkers. Individual contributions are noted in the references.

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