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Mini Review

Cyclodextrin Molecular Reactors

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Abstract

The ability of cyclodextrins to form inclusion complexes with hydrophobic species in aqueous solution makes them well-suited to the development of molecular reactors, to be used as miniature reaction vessels in order to control the outcomes of chemical transformations at the molecular level. In this manner, reaction rates can be increased and products may be obtained that are different to those normally accessible from reactions in free solution. Examples used to illustrate these effects include: the application of cyclodextrins to control the regioselectivity of bromination of aromatic substrates with pyridinium dichlorobromate; the use of a metallocyclodextrin to increase the rate of hydrolysis of a phosphate triester by almost five orders of magnitude; the development of modified cyclodextrins to increase the rates and reverse the regioselectivity of nitrile oxide cycloadditions; and the use of a cyclodextrin dimer to change the ratio of formation of indigoid dyes by a factor of more than 3500.

Introduction

Molecular reactors are reaction vessels that affect the assembly of reactants to change the outcomes of chemical transformations at the molecular level. The naturally occurring cyclodextrins (Figure 1) and their derivatives have attracted considerable attention in this regard, since they readily form host–guest complexes with hydrophobic guests in aqueous solution (Scheme 1), and the complexation often alters the pathways of reactions of the included species [1]. These processes occur in water, which is attractive as an environmentally benign solvent. The cyclodextrins also facilitate the use of this medium by increasing the solubility of organic substrates, through their inclusion.

Molecular reactors to alter product distributions

Some of the most straightforward examples of cyclodextrin molecular reactors involve a change in the regioselectivity of reaction of an included substrate as a result of access of a reagent being restricted. Breslow *et al.* [2–4], showed that cyclodextrins alter the regioselectivity of chlorination of anisole (**1**) with hypochlorous acid, in favour of the *para*-substituted product. Similar effects on regioselectivity have been observed with the chlorination of acetanilide (**2**) [5] and in the Reimer–Tiemann reaction of phenol with chloroform [6]. In a related example from our own work [7], cyclodextrins have been shown to act as molecular reactors, to change the ratios of the products of reactions of **1**, **2** and 3-methylanisole (**3**) with pyridinium dichlorobromate (Scheme 2). With **1** and **2**, bromination at the *para* position is favoured over *ortho* substitution, and the effect is greatest with α-cyclodextrin. In the reactions of **3**, more of the monobrominated and less of the dibrominated products are formed, and β-cyclodextrin has the greatest effect. These outcomes indicate that through inclusion of the substrates **1**–**3**, the cyclodextrins restrict access of the reagent adjacent to the methoxy and acetamido groups (Figure 2).

Catalysts and enzyme mimics

Cyclodextrins alter the rates as well as the pathways of chemical transformations and, indeed, among the earliest known examples of cyclodextrin molecular reactors were some that induced increases in the rates of reaction [8–11]. VanEtten and co-workers [8, 9] demonstrated that the naturally occurring cyclodextrins increase the rates of hydrolysis of carboxylate esters through

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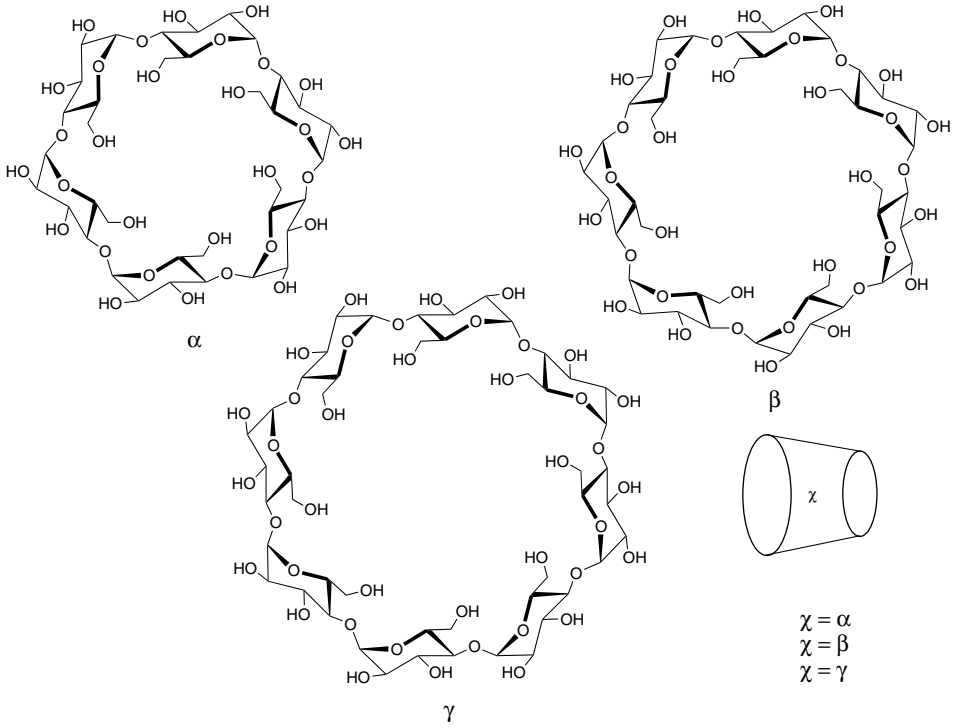
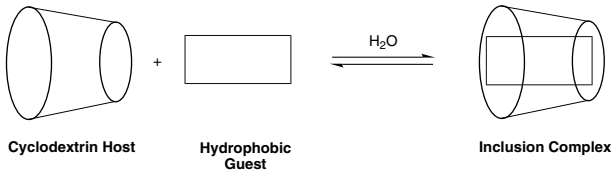


Figure 1. Structures and truncated cone representation of the naturally occurring cyclodextrins.



Scheme 1. Formation of inclusion complexes by cyclodextrins in aqueous solution.

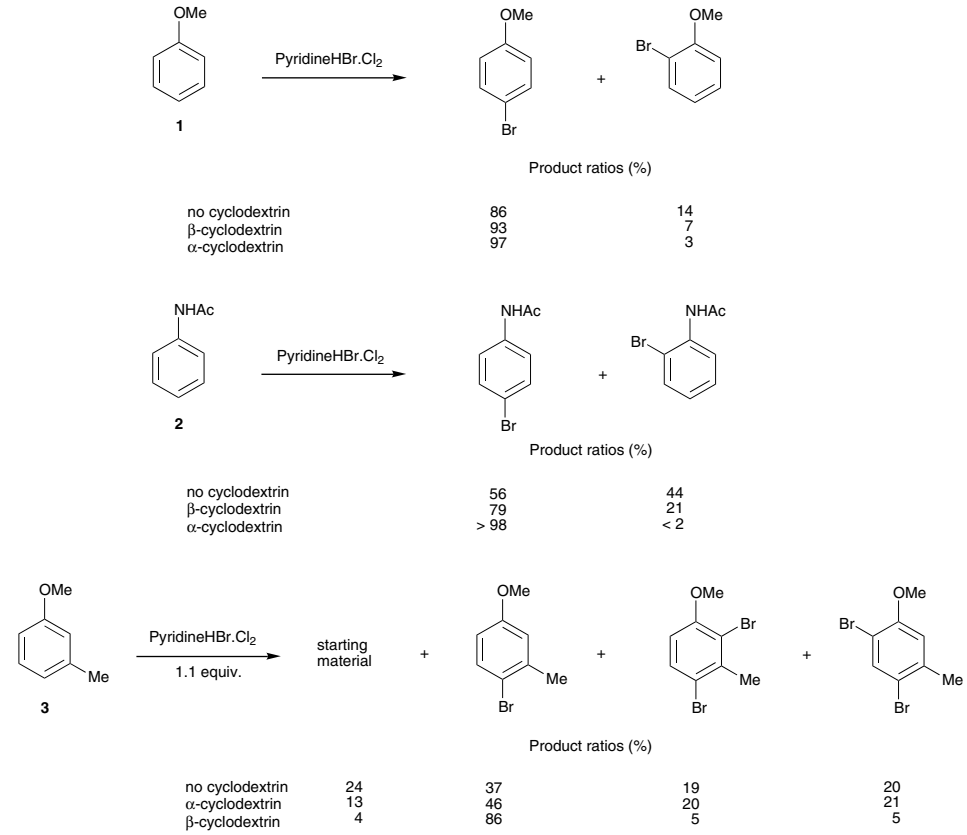
transesterification and subsequent breakdown of the cyclodextrin ester intermediates. With the native cyclodextrins, hydroxy groups are the only functional substituents, but with modified cyclodextrins a much broader range of catalytic groups is available. Simple amino- and carboxy-substituted cyclodextrins provide acid and base catalysis. Another example is shown in Scheme 3, where the metallocyclodextrin **5** catalyses the hydrolysis of the phosphate triester **4**, accelerating the rate of reaction of the cyclodextrin-bound species by almost five orders of magnitude [12]. It appears that the reaction is brought about by metal-bound hydroxide in the ternary complex **6**. The metallocyclodextrin is substrate selective and is a true catalyst, in that there is multiple turn-over of the triester **4**. In this behaviour, cyclodextrins and their derivatives may therefore be regarded as enzyme mimics.

Controlled assembly of substrates and reagents

A wide variety of other processes are also affected by cyclodextrins, including Diels–Alder reactions [13] and [2 + 2]-photochemical cycloadditions [14]. Whereas these have often involved the fortuitous self-assembly of reagents, our interest has turned towards the controlled assembly of reactive species, in order to manipulate the outcomes of chemical reactions by design [1, 15–17]. This has also been a focus of the Breslow group, who have developed efficient systems for the functionalisation and particularly hydroxylation of substrates [18, 19]. Our work has primarily been concerned with carbon–carbon bond-forming reactions.

Reversal of regioselectivity of nitrile oxide cycloadditions

In one prototype, *β*-cyclodextrin has been used to reverse the regioselectivity of nitrile oxide cycloadditions [15]. Nitrile oxides (dipoles) undergo [3 + 2]-cycloadditions with alkenes and alkynes (dipolarophiles) to give isoxazolines and isoxazoles, respectively. With unsymmetrical dipolarophiles there exists the possibility of formation of regioisomeric mixtures of products, but in practice it is generally found that in these systems the regioselectivity is determined by steric effects and the more encumbered end of the dipolarophile becomes attached to the oxygen of the nitrile oxide [20]. Accordingly, monosubstituted alkenes and alkynes usually afford predominantly the corresponding 5-substituted isoxazolines and isoxazoles. However, by using *β*-cyclodextrin as a molecular scaffold, it has been possible to change the outcome. Tethering the dipolarophiles to the cyclodextrin and then allowing the preassociation of the modified cyclodextrins with aromatic nitrile oxides, as host–guest complexes, controls



Scheme 2. Bromination of **1**, **2** and **3** with pyridinium dichlorobromate in water at 298 K.

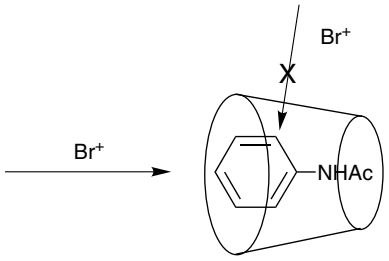
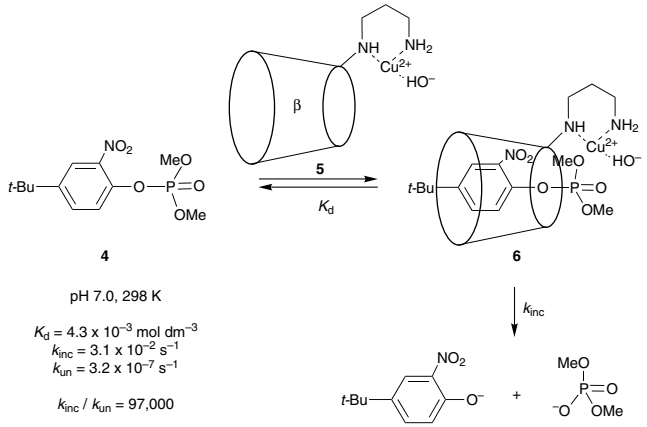


Figure 2. Effect of a cyclodextrin restricting access of a brominating agent to the *ortho* position of **2**.



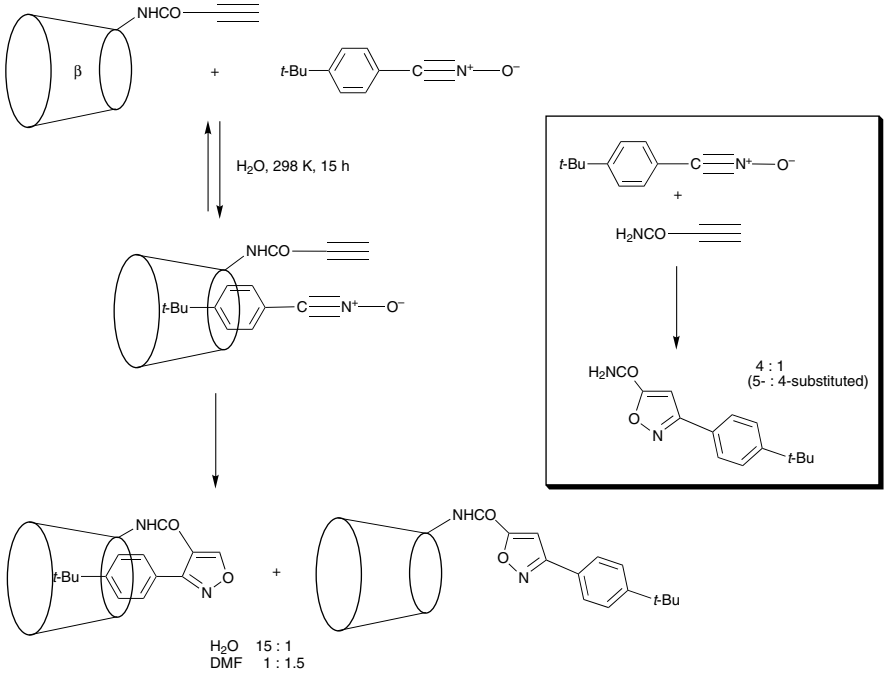
Scheme 3. Hydrolysis of the triester **4** catalysed by the metallocyclodextrin **5**.

the relative orientations of the dipoles and dipolarophiles, to afford primarily 4-substituted isoxazolines and isoxazoles (Scheme 4).

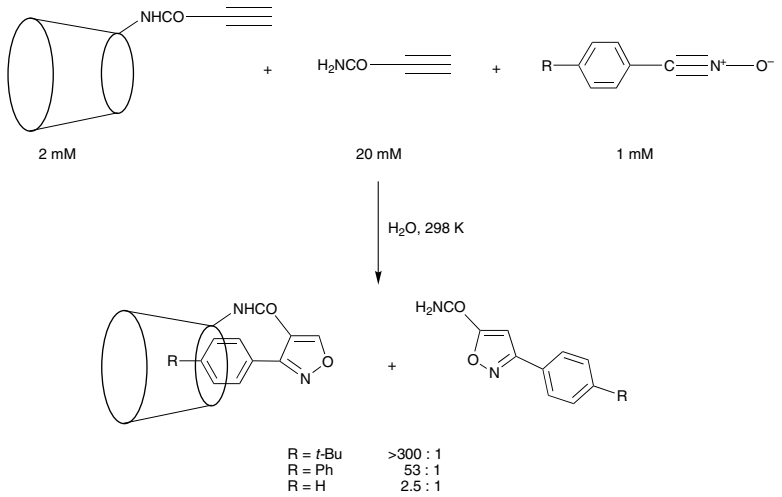
The reactions occur efficiently in water at room temperature, and there is strong evidence that they proceed through the formation of host–guest complexes. When *N*,*N*-dimethylformamide is used in place of water as the solvent, under which conditions complex formation is expected to be less favoured, the effect of the cyclodextrin is reduced, as it is in cases with less hydrophobic nitrile oxides which are less prone to inclusion complex formation. The rate of reaction of nitrile oxides with dipolarophiles is significantly enhanced through the complexation, as indicated by the competitive reactions shown in Scheme 5. Nitrile oxides react selectively with cyclodextrin-substituted dipolarophiles, even in the presence of a 10-fold excess of the corresponding dipolarophiles lacking the cyclodextrin substituent, and rate accelerations of more than three orders of magnitude have been observed. Thus the cyclodextrins alter both the rate and regioselectivity of the cycloadditions in a manner that is predetermined by the control of the alignment of the nitrile oxides and dipolarophiles in the host–guest complexes.

Biasing the ratio of formation of indigoid dyes

In another prototype, a urea linked β-cyclodextrin dimer has been used as a molecular reactor, to bias reactions of



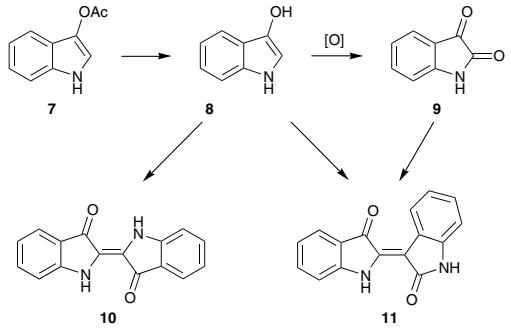
Scheme 4. Effect of a cyclodextrin to reverse the regioselectivity of nitrile oxide cycloaddition.



Scheme 5. Effect of a cyclodextrin substituent on competitive reactions of an alkyne with nitrile oxides.

indoxyl (**8**) and isatin (**9**) in water, to give indigo (**10**) and indirubin (**11**) (Scheme 6) [16]. Under basic conditions, indoxyl acetate (**7**) undergoes hydrolysis to give **8**, which then reacts by oxidation to give **9** or through oxidative dimerisation to give **10**. **8** also reacts with **9** to give **11**. The urea derivative is known [21] to preferentially adopt a conformation matching the geometry required for the reaction of **8** with **9** (Figure 3). Therefore, by carrying out the reaction of **8** with **9** in the presence of the urea derivative, the ratio of formation of **10** to **11** is changed, in favour of the latter by a factor of approximately 30 (Table 1). Neither β-cyclodextrin nor other cyclodextrin dimers show this effect.

An adverse side effect of this templating is that the cyclodextrins substantially reduce the yields of both **10** and **11**. Although the ratio of **11** to **10** increases, the yield of **11** actually decreases by more than a factor of 10. This is a consequence of complexation of **8** and **9** in the cyclodextrins reducing the frequency of their productive interactions. It highlights one of the common limitations associated with the use of molecular reactors but it is one that can be overcome by developing systems where the reactivity of reagents is increased by the



Scheme 6. Competing reactions to give **10** and **11**.

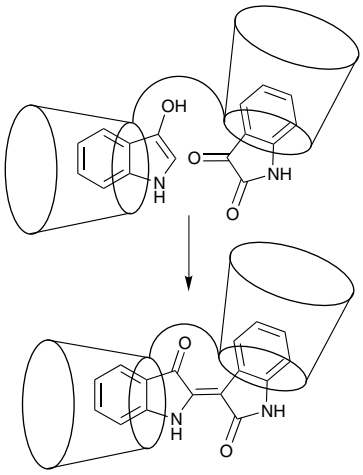


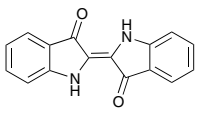
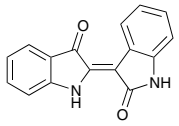
Figure 3. Effect of a urea linked β-cyclodextrin dimer to template formation of **11**.

complexation. This is illustrated by the results obtained when **8** was treated with **12**, instead of **9**. Under the reaction conditions, in aqueous solution at room temperature and pH 10.0, **12** is in equilibrium with the hydrate (pK_a 9.55) and the anion of the hydrate (Scheme 7). Cyclodextrins selectively complex the non-hydrated, non-ionised form, which is also the species that reacts with **8**. This effectively increases the reactivity of **12** that is complexed over that present in free solution. The result is that β-cyclodextrin and its dimeric derivatives increase the ratio of formation of the indirubinsulfonate **13** to **10**, without substantially decreasing the combined product yield. With the urea linked cyclodextrin dimer, which aligns **12** and **8**, as well as selectively complexing the reactive form of **12**, the net result is to increase the ratio of formation of **13** to **10** by a factor of at least 3500 (Table 2).

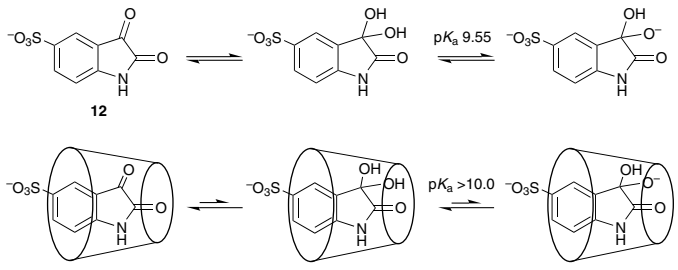
Conclusion

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. Products may be obtained that would otherwise not be formed in free solution, and reaction rates may be significantly increased. The reactions occur efficiently in water, often at room temperature and near neutral pH, so there is every reason to expect that the methods will be taken up by industry in the near future.

Table 1. Yields of indigo (**10**) and indirubin (**11**) formed in reactions of indoxyl (**8**) and isatin (**9**) in water at 298 K and pH 10.0

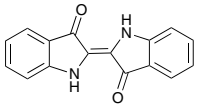
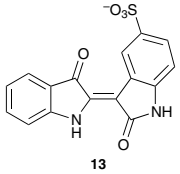
	Yield (%)	
	 **10**	 **11**
No cyclodextrin (CD)	16	13
β-CD	2.5	2.5
β-CDNHCO$(CH_2)_2$CONH-β-CD[a]	0.5	0.7
β-CDNHCOCONH-β-CD[a]	0.2	0.6
β-CDNHCONH-β-CD[a]	0.03	1.0

[a] Here β-CD is a C^6-substituted β-cyclodextrin.



Scheme 7. Hydration of **12** and deprotonation of the hydrate in water at pH 10.0.

Table 2. Yields of **10** and **13** formed in reactions of **8** and **12** in water at 298 K and pH 10.0

	Yield (%)	
	 **10**	 **13**
No cyclodextrin (CD)	25	1.4
β-CD	1.6	11
β-CDNHCO$(CH_2)_2$CONH-β-CD[a]	6.0	16
β-CDNHCOCONH-β-CD[a]	1.8	36
β-CDNHCONH-β-CD[a]	<0.1	22

[a] Here β-CD is a C^6-substituted β-cyclodextrin.

Acknowledgements

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