Handbook of Green Chemistry

Edited by Paul T. Anastas

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Green Solvents

Volume 5: Reactions in Water

Volume Editor:
Chao-Jun Li

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The Editor

Prof. Dr. Paul T. Anastas
Yale University
Center for Green Chemistry & Green Engineering
225 Prospect Street
New Haven, CT 06520
USA

Volume Editor

Prof. Dr. Chao-Jun Li
McGill University
Department of Chemistry
801 Sherbrooke Street West
Montreal, QC H3A 2K6
Canada

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About the editors

Series Editor

Paul T. Anastas joined Yale University as Professor and serves as the Director of the Center for Green Chemistry and Green Engineering there. From 2004–2006, Paul was the Director of the Green Chemistry Institute in Washington, D.C. Until June 2004 he served as Assistant Director for Environment at the White House Office of Science and Technology Policy where his responsibilities included a wide range of environmental science issues including furthering international public-private cooperation in areas of Science for Sustainability such as Green Chemistry. In 1991, he established the industry-government-university partnership Green Chemistry Program, which was expanded to include basic research, and the Presidential Green Chemistry Challenge Awards. He has published and edited several books in the field of Green Chemistry and developed the 12 Principles of Green Chemistry.

Volume Editor

Chao-Jun Li (FRSC, UK) received his PhD at McGill University (1992) and was an NSERC Postdoctoral fellow at Stanford University (1992–1994). He was an Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000–2003) at Tulane University, where he received a NSF CAREER Award (1998) in organic synthesis and the 2001 US Presidential Green Chemistry Challenge Award (Academic). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. He serves as the Co-Chair of the Canadian Green Chemistry and Engineering Network, the Director of CFI Infrastructure for Green Chemistry and Green Chemicals, and Co-Director the FQRNT Center for Green Chemistry and

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Catalysis (Quebec). He is the current Associate Editor for Americas for the journal of *Green Chemistry* (published by the Royal Society of Chemistry). He has been widely recognized as the leader in Green Chemistry for Organic Synthesis in developing innovative and fundamentally new organic reactions that defy conventional reactivities and have high synthetic efficiency.

List of Contributors

Ronald Breslow
Columbia University
Department of Chemistry
3000 Broadway
New York, NY 10027
USA

Peter Dunn
Pfizer UK
Pfizer Green Chemistry Lead
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

Jan B.F.N. Engberts
University of Groningen
Stratingh Institute
Nijenborgh 4
9747 AG Groningen
The Netherlands

José M. Fraile
Universidad de Zaragoza-CSIC
Instituto de Ciencia de Materiales de Aragón
Facultad de Ciencias
Departamento de Química Orgánica
50009 Zaragoza
Spain

Jean-Pierre Genêt
ENSCP
UMR 7573
Laboratoire de Synthèse Sélective Organique et Produits Naturels
11 rue P. et M. Curie
72231 Paris Cedex 05
France

Clara I. Herrerías
Universidad de Zaragoza-CSIC
Instituto de Ciencia de Materiales de Aragón
Facultad de Ciencias
Departamento de Química Orgánica
50009 Zaragoza
Spain

Ferenc Joó
Hungarian Academy of Sciences
Research Group of Homogeneous Catalysis
and
University of Debrecen
Institute of Physical Chemistry
1 Egyetem tér
4010 Debrecen
Hungary

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Ágnes Kathó
University of Debrecen
Institute of Physical Chemistry
1 Egyetem tér
4010 Debrecen
Hungary

Jaap E. Klijn
University of Groningen
Stratingh Institute
Nijenborgh 4
9747 AG Groningen
The Netherlands

Shū Kobayashi
The University of Tokyo
School of Science and Graduate School of Pharmaceutical Sciences
Department of Chemistry
Hongo
Bunkyo-ku
Tokyo 113-0033
Japan

Lucie Leseurre
ENSCP
UMR 7573
Laboratoire de Synthèse Sélective Organique et Produits Naturels
11 rue P. et M. Curie
72231 Paris Cedex 05
France

Li Liu
Chinese Academy of Sciences
Institute of Chemistry
Center for Chemical Biology
Beijing National Laboratory for Molecular Science (BNLMS)
Beijing 100080
China

André Lubineau
Université Paris-Sud 11
Institut de Chimie Moléculaire et des Matériaux d'Orsay
CNRS UMR 8182
Laboratoire de Chimie Organique Multifonctionnelle, Bâtiment 420
15 rue Georges Clémenceau
91405 Orsay
France

José A. Mayoral
Universidad de Zaragoza-CSIC
Instituto de Ciencia de Materiales de Aragón
Facultad de Ciencias
Departamento de Química Orgánica
50009 Zaragoza
Spain

Véronique Michelet
ENSCP
UMR 7573
Laboratoire de Synthèse Sélective Organique et Produits Naturels
11 rue P. et M. Curie
72231 Paris Cedex 05
France

Chikako Ogawa
The University of Tokyo
School of Science and Graduate School of Pharmaceutical Sciences
Department of Chemistry
Hongo
Bunkyo-ku
Tokyo 113-0033
Japan
Present address:
Eisai Research Institute
Lead Identification
4 Corporate Drive
Andover, MA 01810
USA

Vivek Polshettiwar
US Environmental Protection Agency
National Risk Management Research Laboratory
Sustainable Technology Division
26 W. Martin Luther King Drive
Cincinnati, OH 45268
USA

Yves Queneau
INSA-Lyon
Laboratoire de Chimie Organique
Bâtiment J. Verne
20 avenue A. Einstein
69621 Villeurbanne
France
and
Université Lyon 1
Institut de Chimie et Biochimie Moléculaires et Supramoléculaires
INSA-Lyon
CNRS, UMR 5246
CPE-Lyon
Bâtiment CPE
43 boulevard du 11 novembre 1918
69622 Villeurbanne
France

Natalie A. Rebacz
University of Michigan
Chemical Engineering Department
2300 Hayward
Ann Arbor, MI 48109
USA

Phillip E. Savage
University of Michigan
Chemical Engineering Department
2300 Hayward
Ann Arbor, MI 48109
USA

Marie-Christine Scherrmann
Université Paris-Sud 11
Institut de Chimie Moléculaire et des Matériaux d'Orsay
CNRS UMR 8182
Laboratoire de Procédés et Substances Naturelles
Bâtiment 410
15 rue Georges Clémenceau
91405 Orsay
France

Roger A. Sheldon
Delft University of Technology
Department of Biotechnology
Julianalaan 136
2628 BL Delft
The Netherlands

Rajender S. Varma
US Environmental Protection Agency
National Risk Management Research Laboratory
Sustainable Technology Division
26 W. Martin Luther King Drive
Cincinnati, OH 45268
USA

Dong Wang
Chinese Academy of Sciences
Institute of Chemistry
Center for Chemical Biology
Beijing National Laboratory for Molecular Science (BNLMS)
Beijing 100080
China

Xiaofeng Wu
University of Liverpool
Liverpool Centre for Materials and Catalysis
Department of Chemistry
Liverpool L69 7ZD
UK

Jianliang Xiao
University of Liverpool
Liverpool Centre for Materials and
Catalysis
Department of Chemistry
Liverpool L69 7ZD
UK

1
The Principles of and Reasons for Using Water as a Solvent for Green Chemistry

Ronald Breslow

1.1
Introduction

Chemical reactions used to manufacture important compounds such as medicinals are essentially always carried out in solution, and this is also true of the research work that is used to invent the new compounds and to develop appropriate ways to manufacture them. In the past, continuing into the present, the solvents used are normally volatile organic compounds (VOCs), and these pose an environmental problem. Their vapors can contribute to the greenhouse effect that causes global warming, and in some cases the solvent vapors can catalyze the destruction of the ozone layer that protects the Earth and its living inhabitants from short-wavelength ultraviolet solar radiation. The vapors may also be toxic to humans, plants, or animals, or they may cause diseases.

The liquids themselves can be a problem. If they are released into the earth, rivers or the ocean, they can cause direct environmental damage, while also slowly releasing their vapors. In principle, the solvents can be completely captured and purified for reuse during manufacturing, but it is difficult to prevent some loss to the environment. Hence there is interest in using environmentally benign liquids as the solvents in chemical reactions.

One possibility is supercritical carbon dioxide, which is a liquid under pressure and which has attractive solvent properties. However, unless it is completely contained and reused, it will release gaseous carbon dioxide, a greenhouse gas. Thus interest has increasingly turned to water as the solvent for chemical reactions.

Water is the solvent in which biochemical reactions are performed in Nature, and it is environmentally benign. However, it is a good solvent only for organic chemicals that have polar groups, such as alcohols and carboxylic acids. This may not be an insuperable problem. Over 20 years ago we reported that the special selectivities seen in water solution (see below) were also seen in some water suspensions, where one soluble component reacted with one that was poorly soluble [1, 2]. We pointed out that such suspensions in water could well be generally more practical ways to use water in

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manufacturing [2]. Recently, Sharpless and co-workers described a remarkable acceleration of a reaction in such a suspension, which they called reactions ON water [3, 4]. The large reported rate effect was seen in only one particular case, but even without a large acceleration the selectivities that we describe below could perhaps make suspensions in water a practical way for the environmentally benign properties of water to be generally useful even with insoluble reaction components.

One industry that has switched from VOCs to water is the paint industry. We are all familiar with the water-based paints that no longer emit strong solvent odors, and these have been widely adopted for painting automobiles, for instance. It is essentially impossible to capture all the solvent vapors that are released when a vehicle is spray painted, but when the solvent is water there is no problem.

Water is not simply an environmentally benign solvent; it has special properties that are essentially unique, related to what is called the "hydrophobic effect." This is the tendency for hydrocarbons or molecules with hydrocarbon components to avoid contact with water, and to associate instead with other hydrocarbon species in water. This is what makes aqueous soap solutions dissolve grease, and it is the driving force in biology for the associations that produce cell membranes, and that cause nucleic acids to form the famous double helix. It drives the folding of proteins into their shapes in enzymes and antibodies, and it also promotes the binding of biological substrates into enzymes and antibodies [5].

As described below, the hydrophobic effect has now been used to mimic biological chemistry and to provide remarkable selectivities in the field called biomimetic chemistry. It has even been used to permit the discovery of the geometries of the transition states for some interesting reactions, information that is otherwise inaccessible. The remainder of this chapter describes examples of the use of the unique property of water to achieve not just solubility but also selectivity, but the examples will be mainly chosen from our own work. Hence it is important to refer to a number of sources in which other authors have also described their use of water and the hydrophobic effect in chemical studies.

Some of the work of our group has been presented as chapters in the books *Structure and Reactivity in Aqueous Solution* [6], *Green Chemistry* [7], and most recently *Organic Reactions in Water* [8]. In addition, in various review articles our work has been placed in context with that of other groups [2, 5, 9–20]. The remainder of this chapter describes the various contexts in which we have seen the special properties of water as a solvent.

1.2
Binding of Two Species Together Driven by the Hydrophobic Effect in Water

Cyclodextrins are molecules composed of glucose units linked in rings, the most common being α-cyclodextrin (six glucose units), β-cyclodextrin (seven glucose units) and γ-cyclodextrin (eight glucose units) (Scheme 1.1). The three exposed hydroxyl groups on each glucose unit make then water soluble, but they have an internal cavity that is less polar, and that will bind hydrocarbons such as aromatic rings using the hydrophobic effect in water. In later sections it is described how such

cyclodextrin–substrate complexes can catalyze reactions, imitating enzymes. Here the cases where binding alone was studied are described.

alpha-cyclodextrin n = 6
beta-cyclodextrin n = 7
gamma-cyclodextrin n = 8

Scheme 1.1 The three cyclodextrins used – α, β, and γ-cyclodextrin – and two ways in which they are symbolized.

In one example, we saw that some dipeptides would selectively bind into simple β-cyclodextrin in water [21], and that the large steroid lithocholic acid bound strongly [22], as did cocaine [23]. When we linked two β-cyclodextrins together, we achieved even better binding of cholesterol [24], and such cyclodextrin dimers also showed strong and selective hydrophobic binding of compounds with two phenyl groups [25], of peptides with two hydrophobic amino acid components [26], and of oligopeptides whose binding promoted the formation of a helix [27].

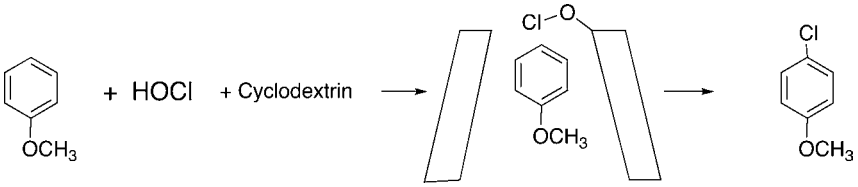
We also tied two β-cyclodextrins with *two* links, which made a hinge that could let the two cyclodextrins close around a substrate, and also another geometry in which they were prevented from cooperating [28]. As hoped, the dimer with the correct geometry was a very strong binder of hydrophobic substrates, since the double link had frozen out the incorrect geometries. Interestingly, in one study we saw that such strong double binding was reflected in a better enthalpy, rather than entropy [29]. Our early work with cyclodextrin dimers has been reviewed [30]. We also examined a dimer of a cyclophane, another species with an internal cavity that binds hydrophobic groups [31]. The findings were similar to those with the cyclodextrin dimers. In addition, we examined some trimers of cyclodextrins, but did not see as much cooperativity as one might expect [32].

We synthesized some cyclodextrin dimers with photocleavable links as potential carriers of anticancer photodynamic sensitizers [33, 34]. We also saw that some cyclodextrin dimers could bind to proteins and prevent their aggregation [35]. Furthermore, we saw that some of our cyclodextrin dimers and trimers could bind to amyloid protein and prevent the aggregation that causes Alzheimer's disease [36]. Some other studies with cyclodextrin dimers will be presented in Section 1.5 on mimics of metalloenzymes.

1.3 Aromatic Chlorination

In our earliest work using cyclodextrins to bind substrates, we examined the chlorination of anisole by hypochlorous acid in water with and without added α-cyclodextrin [37, 38]. We saw that the anisole in solution was chlorinated in both

the *ortho* and *para* positions, but in the complex with α-cyclodextrin only the *p*-chloroanisole was formed. The kinetic studies showed that the chlorination involved the prior attachment of chlorine to a hydroxyl group of the cyclodextrin, and then its transfer to the bound anisole (Scheme 1.2).



Scheme 1.2 α-Cyclodextrin catalyzed the selective chlorination of anisole in water by an intra-complex transfer of a chlorine atom.

We also examined other substrates, whose behavior reflected this same mechanism [38]. In this case, the cyclodextrin is acting as a mimic of the enzyme chlorinase, except that interestingly the enzyme mimic was more selective than was the enzyme itself. In a later study, we established which hydroxyl group was the chlorine transfer agent, and showed that a cyclodextrin polymer could perform the selective chlorination in a flow reactor [39].

1.4 Acylation of Cyclodextrins by a Bound Ester

Komiyama and Bender examined the reaction of *m*-nitrophenyl acetate with cyclodextrins, and saw that they transferred the acetyl group to a hydroxyl of the cyclodextrin, with a modest 250-fold rate enhancement over the hydrolysis rate in water under the same conditions [40]. Our modeling of this process indicated that the starting material could occupy the cyclodextrin cavity, but that the tetrahedral intermediate for acetyl transfer would have its nitrophenyl group largely pulled from the cavity. This picture was confirmed by a study of the effect of high pressure on the reaction rate, which indicated that the volume of the transition state was larger than that of the starting complex, as such a geometric change would cause [41]. Such a loss of binding would be energetically unfavorable for the reaction, accounting for the very modest rate of the acetyl transfer process. We therefore created a series of substrates that could avoid this problem.

Molecular models indicated that compound **1**, based on a ferrocene core, would be able to acylate a cyclodextrin hydroxyl while still retaining most of the binding of the ferrocene unit in the cyclodextrin cavity. We synthesized **1**, and saw that indeed it acylated β-cyclodextrin with a 51 000-fold rate acceleration [42]. However, high-pressure studies [41] indicated that although indeed the transition state for the reaction retained most of the binding into the cyclodextrin cavity, it was not yet the ideal substrate. By modifying the cyclodextrin itself – adding a floor to the cavity – and adjusting the substrate further, we achieved a rate acceleration of ca 10^6-fold [43].

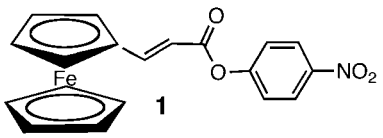
With an even better substrate geometry, we achieved a rate acceleration of 10^8-fold, and the reaction was also enantioselective (cyclodextrin is composed of chiral glucose units), with a 20 : 1 preference for one substrate enantiomer over the other [44]. The optimizations and their explanations were described in a full paper [45], and theoretical calculations on the geometric factors involved were described in another publication [46].

The very high rates of the best substrates reflected a rigid geometry that favored the first step of acylation – addition of the cyclodextrin hydroxyl to the ester carbonyl to form a intermediate – but in the next step, departure of the *p*-nitrophenoxide ion to form the product acylated cyclodextrin, this rigidity was undesirable. Some flexibility was needed in the substrate to permit the rotation involved in this second step. When we incorporated such flexibility, both steps were well catalyzed even with an ordinary ester, where the second step could be rate limiting [47]. Thus, these studies on cyclodextrin acylation by bound substrates indicated the enormous rate accelerations that can be achieved using the hydrophobic effect to promote catalyst–substrate binding in a well-designed geometry.

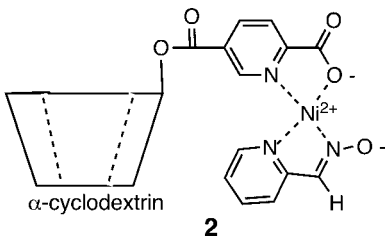
Such work accomplishes two goals. It indicates that incorporating the factors we believe play a role in enzymatic catalysis does indeed lead to very good catalysis, approaching the rates of the best enzymes. This helps confirm our ideas about how enzymes are able to function so effectively. At the same time, these studies strengthen ordinary chemistry. They show how to make effective catalysts with good rates and selectivities, adopting the principles but not the details of enzymatic reactions.

1.5
Mimics of Metalloenzymes Using the Hydrophobic Effect in Water

For hydrolytic enzymes, the formation of an acyl-enzyme intermediate is only a first step; for catalysis, the intermediate must hydrolyze to regenerate the catalyst and liberate the product carboxylate ion. In many hydrolytic enzymes, including the most effective ones, substrate binding involves both the hydrophobic effect induced by water and some binding to the metal ion itself, which is held in the enzyme by typical coordinating groups. In our first study of mimics for such enzymes, we constructed an artificial enzyme **2** comprised of an α-cyclodextrin ring for hydrophobic binding and an attached pyridinecarboxylate to bind a Ni(II) ion [48]. The nickel also bound a nucleophilic oxime group.



1



2

We found that *p*-nitrophenyl acetate was hydrolyzed in a two-step process, after it was hydrophobically bound into the cyclodextrin. First the nucleophilic oxime removed the acetyl group, in a nickel-catalyzed reaction, and then the nickel ion catalyzed the hydrolysis of this intermediate, regenerating the catalyst. The geometry permitted this process, not the direct acylation of cyclodextrin as in the systems in the previous section. However, the rate acceleration was modest, reflecting the many degrees of flexible freedom in the catalyst.

We constructed some metal ligands mirroring those in metalloenzymes such as carbonic anhydrase, and studied their ability to bind zinc(II), the metal ion in carbonic anhydrase and in carboxypeptidase, and other metal ions [49]. In a study of the hydrolysis of a phosphate triester, we saw evidence that a bound Zn(II) acted as a bifunctional catalyst, delivering a hydroxide ion to the phosphorus while coordinating to the phosphate oxygen atom to stabilize the phosphorane intermediate in hydrolysis [50]. We have seen such a process in many enzyme mimics that also use hydrophobic binding of substrates, as discussed below.

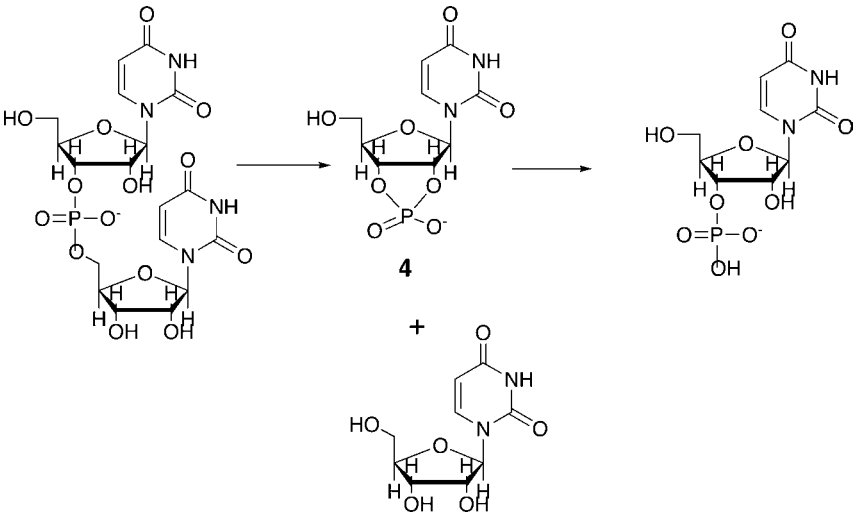
Carboxypeptidase uses metal ion catalysis in the hydrolysis of an amide group, a peptide bond. In a relevant study we used Co(III) to lock the amide oxygen to a metal ion [cobalt(III) is substitution inert], and saw hydrolysis of the amide with the assistance of phenol groups of the catalyst [51]. Apparently the phenol group and some others that we examined play a role in the second step of amide hydrolysis, fragmentation of the tetrahedral intermediate. We also attached α-cyclodextrin to a macrocyclic zinc ligand that held the metal so strongly that it could exist as the zinc hydroxide without losing the zinc [52]. The compound bound phosphate esters into the cyclodextrin using the hydrophobic effect in water, and then used the bifunctional zinc hydroxide mechanism to hydrolyze the substrate. In related work, we catalyzed the cyclization/cleavage of a model for conversion of RNA to its cyclic phosphate using the well-bound zinc macrocycle with an attached thiol or imidazole second catalytic group [53].

We constructed cyclodextrin dimers with a catalytic metal ion bound to the linking group. In the first example, esters that could hydrophobically bind into both cyclodextrins, stretching along the linking, were hydrolyzed by bound copper(II) hydroxide using the bifunctional nucleophilic bound hydroxide plus electrophilic metal ion mechanism, in one case achieving a 220 000-fold rate acceleration over uncatalyzed hydrolysis in water [54]. We also saw that such a cyclodextrin dimer could bind a bis-*p*-nitrophosphate anion to an La(III) ion coordinated to the linking group and then achieve catalytic cleavage of the phosphate ester with added hydrogen peroxide [55]. In a full paper describing such cyclodextrin dimer catalysts for ester hydrolysis, we saw as much as a 10^7-fold rate acceleration [56]. Using cyclodextrin dimers with bound metal ions, we saw a 10^3-fold acceleration of the hydrolysis of a bound benzyl ester, less reactive than some of the *p*-nitrophenyl esters used in earlier studies [57].

In another approach, we constructed a β-cyclodextrin that had both a metal ion binder and an imidazole general base catalyst attached to the cyclodextrin, and examined the hydrolysis of a *tert*-butylcatechol cyclic phosphate **3** that hydrophobically bound to the cyclodextrin [58]. The hydrolysis was accelerated ca 10^3-fold. We describe other studies of such a hydrolysis in the next section.

1.6
Mimics of the Enzyme Ribonuclease

Ribonucleic acid (RNA) is cleaved by the enzyme ribonuclease in an overall two-step process (Scheme 1.3). In the first step there is a cyclization/fragmentation in which the hydroxyl group on C-2 of the ribose attacks the phosphate group of the RNA chain and produces a cyclic phosphate **4** while breaking the chain at that point. In the second step, this cyclic phosphate is hydrolyzed to release the C-2 hydroxyl again while opening the cyclic phosphate ring. The enzyme can catalyze both of these rather different steps.

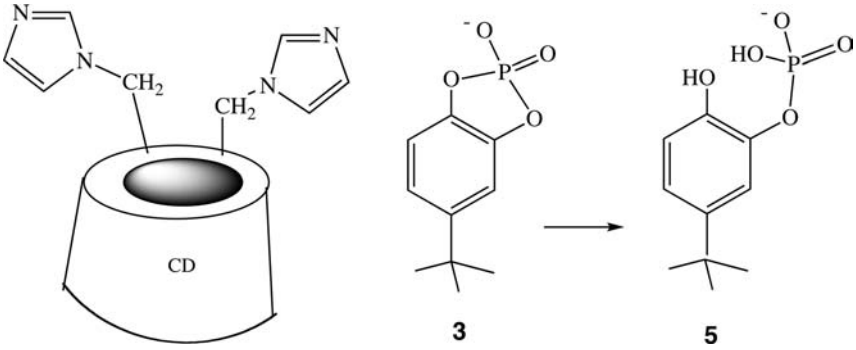


Scheme 1.3 The enzyme ribonuclease cleaves RNA by a cyclization, then a hydrolysis of the cyclic phosphate. It is shown for uridyluridine, a dinucleotide component of RNA.

The major catalytic groups in bovine ribonuclease A are two imidazole rings of the amino acid histidine, although an ammonium ion of lysine also plays a role. At the optimum pH for the enzyme, one imidazole is protonated and serves as a general acid catalyst, whereas the other imidazole is unprotonated and acts as a general base. We decided to produce a mimic of this enzyme by using hydrophobic binding of a substrate into the cyclodextrin cavity in water, in which the cyclodextrin also had two imidazole rings replacing two hydroxyls of the cyclodextrin.

In our first study (Scheme 1.4), we attached the imidazoles on opposite sides of the cyclodextrin cavity and examined the ability of this catalyst to hydrolyze compound **3**, a cyclic phosphate as a rough mimic of the cyclic phosphate that is hydrolytically cleaved in the second step of the enzymatic process [59]. We saw that there was a pH optimum for this hydrolysis that was essentially identical with that of the enzyme itself, indicating that both the general base and the general acid versions of the imidazoles were cooperating in the hydrolysis process. The substrate was selectively cleaved to **5**, leaving the phosphate group *meta* to the *tert*-butyl group. By moving the

imidazoles out slightly, we could reverse the selectivity, now leaving the phosphate group *para* to the *tert*-butyl group [60].



Scheme 1.4 β-Cyclodextrin with two attached imidazole rings catalyzes the hydrolysis of a bound cyclic phosphate ester in water with specificity, and with geometric and isotopic evidence that indicates a process involving a phosphorane intermediate.

A method called proton inventory had been applied to ribonuclease [61]. By observing the rate with different ratios of H_2O and D_2O, it is possible to deduce whether one or two protons are moving in the rate-determining step, and it was concluded that two protons were moving. This means that as the general base imidazole is removing the proton from the C-2 hydroxyl group the general acid imidazolium ion is transferring its proton to the substrate in a simultaneous bifunctional process. We applied this test to our bisimidazolecyclodextrin enzyme mimic, and saw the same result, and with almost the same data as had been seen with the enzyme [62].

We also varied the structure of the bisimidazolecyclodextrin catalyst. We were able to synthesize isomers with the two imidazoles on neighboring glucose units, which we called the A,B isomer, and also an isomer with imidazoles on the A,C units and on the A,D units [63]. If the cleavage mechanism had involved direct attack on the phosphate group while a proton was being placed on the leaving oxygen, the A,D isomer should have been the best. However, we saw that the most active isomer was A,B, with the acid and base groups on neighboring glucose units. This absolutely requires a mechanism in which the hydrolysis proceeds through an intermediate with five oxygens on phosphorus, a phosphorane, which later fragments to the final product. As we shall describe, we saw evidence for the same mechanism with a different model system.

We examined the hydrolysis of a simple dinucleotide, uridyluridine, in water solution with imidazole buffer. Since this process does not involve the hydrophobic special effects of water, it will not be described in detail and rather the relevant references are listed [64–73]. The evidence points to a phosphorane intermediate for this simple buffer-catalyzed process, and we suggested that the enzyme may well be using the same mechanism, rather than a direct cleavage. There is not general agreement on this idea for the enzyme. We have published an account of both the

cyclodextrin studies and the buffer studies in ribonuclease mimics [74], and an account of the result of variation in the geometries of the bisimidazolecyclodextrins and the substrate, which made it clear how important it is to have a relatively tight fit of the substrate in the hydrophobic cavity of the cyclodextrin [75].

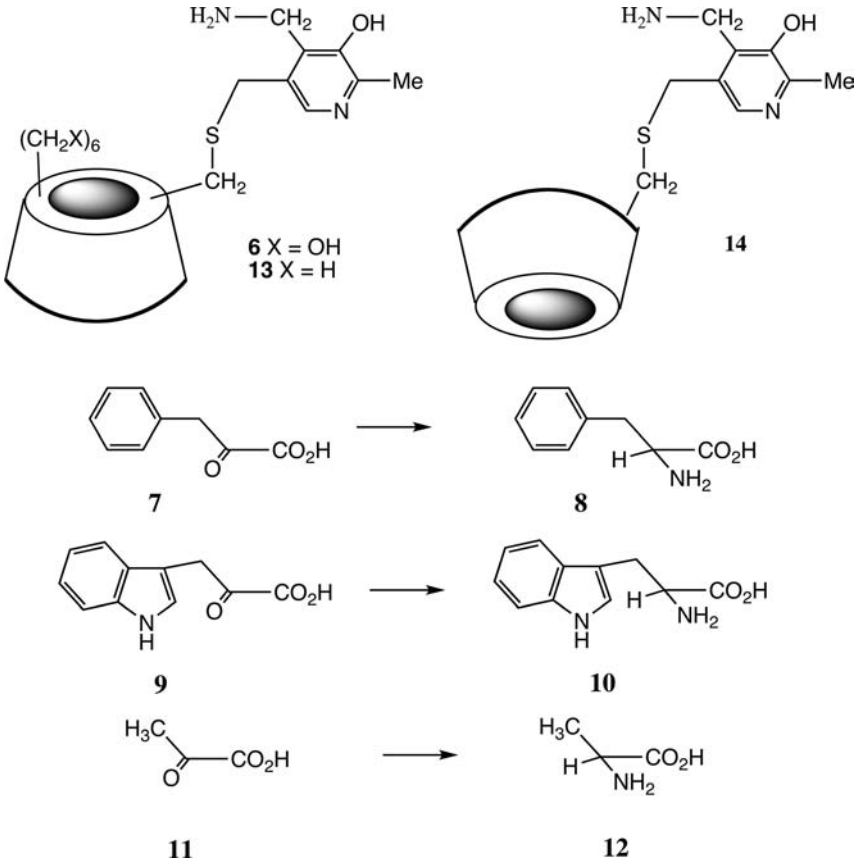
1.7 Mimics of Enzymes that Use Pyridoxamine Phosphate and Pyridoxal Phosphate as Coenzymes

We have constructed a number of such mimics. In general, they use the hydrophobic effect in water to bind the substrates for the reactions, with the pyridoxal or pyridoxamine unit coenzyme mimics covalently attached to a cyclodextrin or a hydrophobic polymer. In a few cases we have also used the hydrophobic effect to bind reversibly a coenzyme mimic itself. Some of the resulting rate effects are truly enormous.

In our first study, we covalently linked a pyridoxamine unit to β-cyclodextrin in compound **6** and examined its ability to convert α-keto acids to amino acids in water (Scheme 1.5) [76]. This directly mimics the process used by enzymes to synthesize most amino acids. We compared the conversion of phenylpyruvic acid **7** to phenylalanine **8** and of indolepyruvic acid **9** to tryptophan **10**, both of which can exhibit hydrophobic binding into the cyclodextrin cavity, with the conversion of pyruvic acid **11** to alanine **12**, in which there was no hydrophobic binding of the small methyl group.

The two aromatic compounds had essentially the same rate as did simple pyruvic acid when pyridoxamine was used without the attached cyclodextrin, but hydrophobic binding of keto acids **7** and **9** led to about a 100-fold preference over alanine with the enzyme mimic **6**. With **6**, the tryptophan was formed with a 33% enantiomeric excess (*ee*) of the L-isomer, induced by the chirality of the cyclodextrin unit, and phenylalanine was formed with a 67% *ee* [77]. We saw similar results with compound **13**, in which the pyridoxamine was attached on one of the primary carbons of β-cyclodextrin and the other primary carbons were converted to methyl groups, forming a deeper hydrophobic pocket [78]. Even higher selectivities were seen in some of our later work using the hydrophobic effect in amino acid synthesis.

In **6**, the pyridoxamine is attached on the primary side of the cyclodextrin, but we also examined a compound **14** in which it was attached to the secondary side [77]. All the acylations of cyclodextrin described earlier were directed to the secondary side. We found that with **14** there was also a preference for the formation of phenylalanine and tryptophan, rather than alanine, reflecting the hydrophobic binding of the two aromatic ring substrates in water. However, the preference was less than with the original primary-side linked compound **6**, and the chiral inductions were also smaller. Apparently in this class of compounds, the primary side of the cyclodextrin is the better place for attachment of the pyridoxamine unit. A full paper summarized these results [79]. We also prepared a couple of transaminase mimics with *two* links between the pyridoxamine and the cyclodextrin [80]. The much better geometric control that this afforded led to very high selectivities among substrates with different geometries themselves.



Scheme 1.5 Three different versions of a pyridoxamine attached to a cyclodextrin convert keto acids to amino acids in water with a preference for those hydrophobic substrates that can bind into the cyclodextrin cavity, imitating in part a biological process by which the amino acids are formed.

Although the cyclodextrins are conveniently available compounds for incorporating hydrophobic binding in water into enzyme mimics, they are not unique. We also used some novel synthetic macrocycles that could carry a pyridoxamine unit and bind hydrophobic substrates into their cavity in water solution [81]. We saw that compound **15** converted phenylpyruvic acid to phenylalanine 15 times more rapidly than did simple pyridoxamine, again reflecting acceleration by hydrophobic binding of the substrate. However, the effect was not as large as with **6**, carrying a pyridoxamine attached to the primary side of β-cyclodextrin. Also, there was of course no chiral induction with the achiral synthetic macrocycle.

In a successful attempt at chiral induction, we synthesized compound **16**, which has no hydrophobic binding group but has a chain carrying a basic unit that can deliver the new proton of the amino acid with geometric control [82]. We saw that as much as a 94 : 6 ratio of D- to L-tryptophan was seen with the enantiomer of **16** that