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Substrate Selective Catalysis by Rhodium Metallohosts

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Abstract: A novel supramolecular catalyst functioning according to the principles of enzymatic catalysis is described. It consists of a basket-shaped molecule to which a catalytically active Rh(I) complex is attached. The catalyst selectively hydrogenates and isomerizes allyl-substituted dihydroxyarene substrates that are bound in its cavity. The reactivity of this supramolecular catalyst and its affinity for several substrates is compared with that of the corresponding catalyst without a binding site. Features known from enzymatic catalysis, *e.g.* Michaelis–Menten kinetics and rate enhancement by cooperative binding, are described and discussed.

Introduction

The realization of high efficiency and selectivity in catalytic conversions continues to be a major challenge in chemistry. Impressive progress has been made in the last decades particularly in the area of metal-catalyzed reactions.[1–3]

The rapidly expanding field of supramolecular chemistry has opened intriguing possibilities to design novel types of catalysts that function according to the principles of enzymes. Such catalysts may display selectivity as a result of a process of recognition between a substrate and a receptor.

Several examples of such synthetic catalytic systems—also called *synzymes*—have been reported in the literature. Since the pioneering work of Breslow[4] and Tabushi,[5] many types of host molecules have been provided with catalytic functions, *e.g.* cyclodextrins,[5,6] aza-crown ethers,[7] and cyclophanes.[8] The catalytic functions include basic functionalities such as imidazole[9] and amino[7b,10] groups or acidic functionalities such as thiol[11] and hydroxy[12] groups. In some cases these groups

accelerate reactions in a cooperative manner, in this way mimicking enzymatic processes. Supramolecular catalysis with metal centers has been explored to a much lesser extent. Several transition metal complexes containing receptor sites have been described,[13] but very little catalysis has been achieved with such systems. Cyclodextrines bearing ethylenediamine ligands coordinated to Cu(II) and Zn(II) centers have been reported to display substrate selectivity and to accelerate cleavage reactions of substrates bound in their cavities.[14] Diederich and co-workers have synthesized a porphyrin-bridged cyclophane as a model for cytochrome P-450 enzymes. It is suggested that the conversion of aromatic hydrocarbons by this system is achieved by complexation of the substrates in the cavity of the cyclophane.[15]

In this paper we will describe a supramolecular cavity-containing catalyst that preferentially hydrogenates and isomerizes dihydroxy-substituted allylarenes. The reactivity of this catalyst and its affinity for substrates is compared with that of the corresponding catalyst without a binding site, either HRh(CO)[P(OPh)₃]₃ or HRh[P(OPh)₃]₄. Furthermore, features as known from enzymatic processes, *e.g.* Michaelis–Menten kinetics and cooperative binding, are reported.

Results and Discussion

Supramolecular Catalyst. The catalytic system is based on the clip molecule **1**[16] (see Chart 1), which serves as a frame for the basket-shaped receptor **2a**, previously described by us.[17] Compound **2a** can be easily functionalized with triaryl phosphite ligands to give the receptor ligand **2b**. Addition of (acac)Rh-

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Chart 1

2 a: R = -H

b: R = -CH₂- ⬡ -O - P- (OPh)₂

c: R = -CH₂- ⬡

P = P(OPh)₃

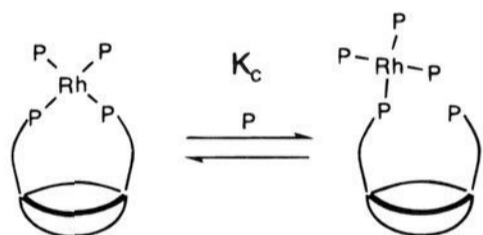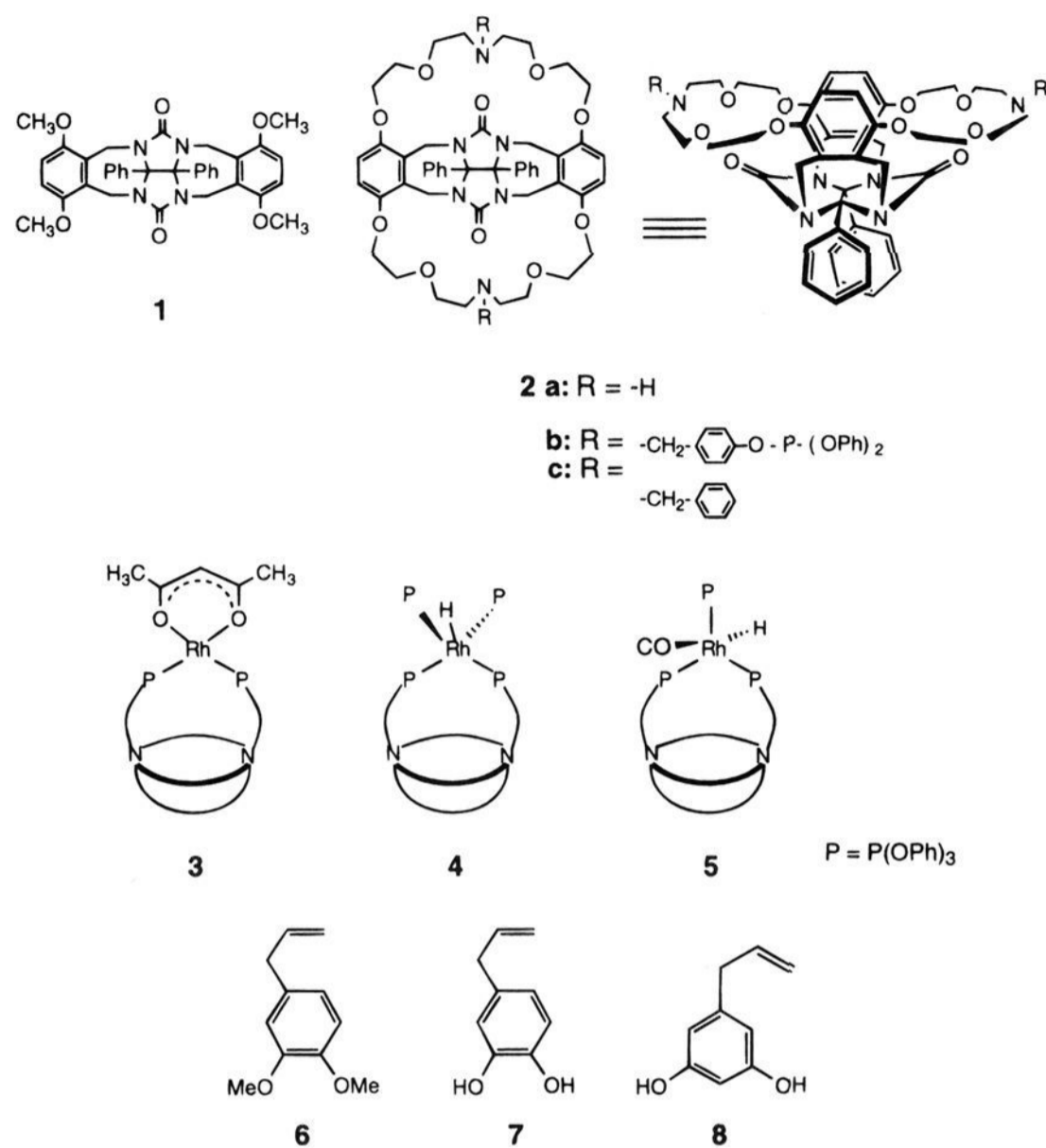**3**　　**4**　　**5**

6　　**7**　　**8**

Figure 1. Interconversion equilibrium between the chelated form of compound **4** and a form in which one of the ligands of the receptor molecule is replaced by a P(OPh)₃ ligand.

(CO)₂ (Hacac = acetylacetone) to the latter compound results in the displacement of the two CO ligands from the rhodium complex and the formation of the Rh(I) diketone complex **3**. Subsequent reaction with H₂ in the presence of a small excess of additional triphenyl phosphite yields the rhodium(I) hydride complex **4**. A similar reaction with H₂ and CO leads to the rhodium(I) carbonyl hydride complex **5**. When an excess of P(OPh)₃ is present in solution, an equilibrium is established between the chelated forms of these complexes and forms in which one of the ligands of the receptor molecule is replaced by a free phosphite ligand. For complex **4** the equilibrium constant for the chelation (Figure 1) was determined; it amounted to $K_c = 0.034$ M⁻¹. This value implies that in the presence of 1 equiv of additional P(OPh)₃ still 97% of the rhodium is in the chelated form. The synthesis and conformational properties of these metallocages will be described in detail elsewhere.[18] In Figure 2 a drawing and a computer generated structure of compound **4** are presented.

The receptor part of complexes **3**–**5** can bind catechol (1,2-benzenediol) and resorcinol (1,3-benzenediol) by π–π stacking

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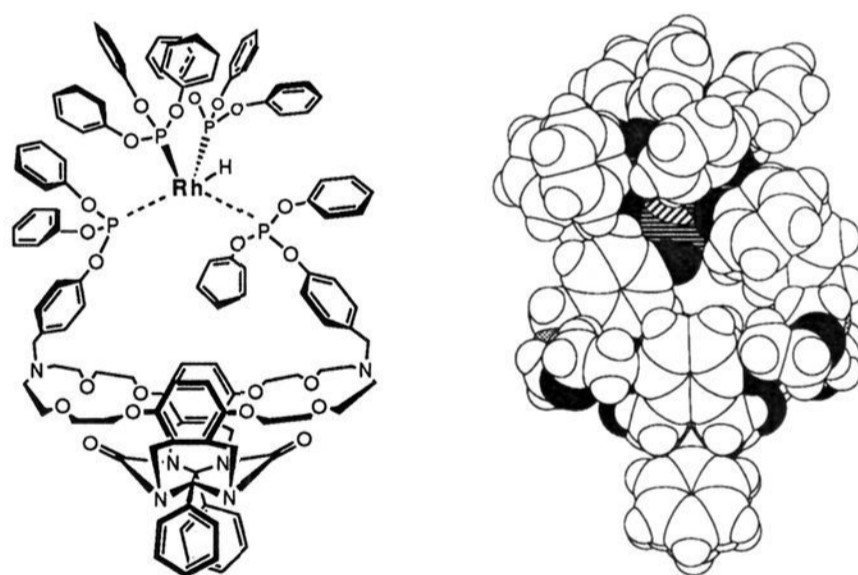
Figure 2. Drawing and computer-generated structure of compound **4**.

interactions with the xylylene side walls and by hydrogen bonds with the carbonyl urea functions (see also below).[19] In the case of resorcinol, two simultaneous hydrogen bonds are formed between the OH groups and the π-*electrons* of the carbonyl groups of the receptor. Most likely, the intramolecular hydrogen bond in catechol is maintained, leaving only one OH group available for binding in the cleft.[20] When compound **1** is enlarged to give the basket-shaped molecules of type **2**, the binding of catechol and resorcinol is slightly improved.

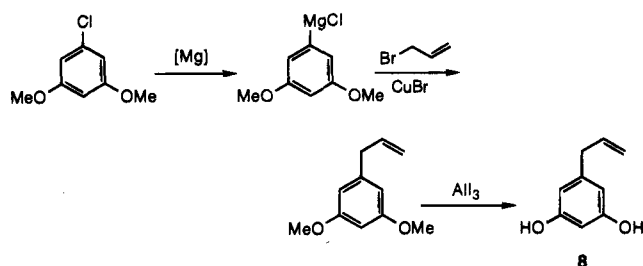**Substrates.** In order to study the relation between reactivity and binding, substrates **6**–**8** were synthesized. The catechol

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(20) The binding constants of catechol and phenol in compound **2c** have similar values, *viz.* 70 and 60 M⁻¹, respectively.

Scheme 1

derivative **7** was easily obtained by demethylation of 4-allyl-2-methoxyphenol (eugenol) with lithium diphenylphosphide.[21] Methylation of eugenol yielded the substrate 1-allyl-3,4-dimethoxybenzene (**6**) which is comparable to **7** with regard to the electron-donating properties of the substituents. 5-Allyl-resorcinol (**8**) was synthesized from 5-chloro-1,3-dimethoxy-benzene by the following sequence of reactions (see Scheme 1): (i) a Grignard reaction with magnesium activated according to Rieke (~50%),[22] (ii) a Cu(I)-assisted coupling of the Grignard reagent with allyl bromide (44%), and (iii) demethylation with AlI_3 in CS_2 (80%).[23]

Binding Experiments. The association constants, K_{assoc} = [host—guest complex]/[host][guest], for the complexation of **7** and **8** in the model compound **2c** were measured by ^1H NMR titrations, monitoring the shift of various cage and guest signals. They amounted to K_{assoc} = 90 ± 20 M^{-1} and K_{assoc} = 2200 ± 200 M^{-1} for **7** and **8**, respectively. Substrate **6** is not bound in the cavity of **2c**.

The binding properties of metallocage **3** were also evaluated with the help of ^1H NMR titrations. We were not able to measure the binding affinities of **7** and **8** because these substrates were found to react with the Rh center. Therefore, titrations were carried out with the model compounds resorcinol and catechol. A titration with resorcinol gave an association constant of K_{assoc} = 3100 ± 300 M^{-1}, in good agreement with the values measured for the reference compounds **1** (K_{assoc} = 2600 ± 400 M^{-1})[19a] and **2c** (K_{assoc} = 2900 ± 300 M^{-1}).[19b] It was not possible to determine the binding constant of catechol, as no suitable probe signal was available because of serious overlap of signals. We assume that the binding constant of catechol in **3** is on the same order of magnitude as those of catechol in **1** (K_{assoc} = 60 ± 10 M^{-1})[19a] and in **2c** (K_{assoc} = 70 ± 30 M^{-1}).[19b]

Catalytic Reactions with Rh(I) Carbonyl Hydride Host 5. Initial experiments were carried out with complex **5**. Under 1 atm of argon and in the presence of a small excess of $P(OPh)_3$, a solution of **5** in $CHCl_3$ was able to isomerize an equimolar amount of substrate **7** to the corresponding (*E*)- and (*Z*)-methylstyrenes. The ratio between the *E*- and *Z*-isomers was found to be approximately 3:1. In a separate experiment, the reference substrate allylbenzene showed a much lower reactivity and only the *E*-isomer was obtained. The progress of the reactions was monitored by ^1H NMR. The results are depicted in Figure 3 and summarized in Table 1. In 2 h, 66% of allylcatechol is converted, whereas in the same period, only 12% of allylbenzene has reacted. The conversion of 4-allylcatechol starts immediately, whereas for allylbenzene a lag phase of about 10 min is observed. In accordance with the literature,[24] we believe that the actual catalyst for the isomerization reaction is the hydride complex **4**. The CO displacement which converts **5** into **4** is probably facilitated by the fact that the substrate is
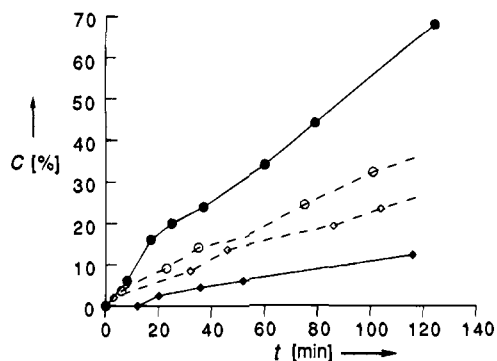
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Figure 3. Isomerization of 4-allylcatechol (○) and allylbenzene (◇) by compound **5** (solid lines and filled marks) and by HRh(CO)-[P(OPh)$_3$]$_3$ (dotted lines and open marks). Conditions: [Rh] = [substrate] ≈ 17 mM, *T* = 25 °C, solvent chloroform.

Table 1. Product Composition of the Experiments with Complex **5**[a]

				product[c]		
entry	catalyst[b]	substrate	condition	isomerization	hydroformylation	hydrogenation
1	**5**	**7**	Ar	66		
2	**5**	allylbenzene	Ar	12		
3	HRh(CO)P$_3$	**7**	Ar	36	8	
4	HRh(CO)P$_3$	allylbenzene	Ar	27	12	9
5	**5**	**7**	H$_2$	54	24	17

[a] Conditions: [Rh] = [substrate] ≈ 17 mM, *T* = 25 °C, solvent chloroform. [b] P = P(OPh)$_3$. [c] After 2 h in percent.
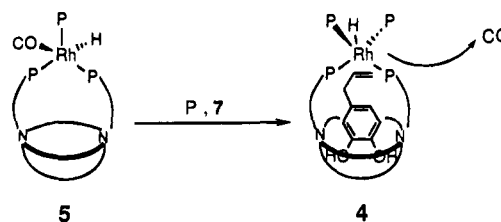
Figure 4. Substrate-induced formation of complex **4** from complex **5**.

bound in the cavity (Figure 4). This could explain the observed induction time in the case of allylbenzene. Support for this explanation comes from the ^{31}P NMR spectra, which indicate that after 2 h 23% of the initial carbonyl hydride complex **5** had been converted into the hydride complex **4** when **7** is the substrate and only 7% when allylbenzene is the substrate.

Isomerization experiments under the same conditions with the reference complex HRh(CO)[P(OPh)$_3$]$_3$ revealed no substantial difference in reactivity between the two substrates (Table 1 (entries 3 and 4), Figure 3). After 2 h the reaction mixture of **7** contained 36% of the (*E*)-methylstyrene derivative and 8% of the *n*-aldehyde [4-(3,4-dihydroxyphenyl)butanal], the latter as a result of a hydroformylation of the substrate. In the case of allylbenzene 9% of the hydrogenated product propylbenzene was observed in addition to 27% of (*E*)-methylstryrene and 12% of *n*-aldehyde. The proton that is required to complete the hydroformylation and hydrogenation processes under these conditions most likely comes from a second carbonyl hydride complex. During the reaction a decrease of the ratio between the hydride signal and the internal standard in the ^1H NMR spectrum was observed. This decrease was proportional to the increase of the intensity of the signals arising from the hydrogenated and hydroformylated products. The complex which is formed from this process possibly is a bimetallic rhodium complex or a μ-CO-bridged rhodium dimer.[25] We cannot exclude that in the case of HRh(CO)[P(OPh)$_3$]$_3$ the latter

dimer is actually responsible for the isomerization reaction, although such a complex could not be detected by ^{31}P NMR. Apparently, as no hydroformylation and hydrogenation occur, hydride transfer is not possible in the reaction with the supramolecular catalyst. This may be the result of the shielding of the complex by the bulky ligand system.

The above results clearly indicate that the conversion of the bound substrate is accelerated by compound **5**, whereas that of the nonbound is delayed as compared to the conversion with HRh(CO)[P(OPh)₃]₃. The fact that in the case of **7** the Z-isomer is also formed may be ascribed to steric congestion of groups within the cavity of the bulky ligand system, as is indicated by CPK models. This observation supports the idea that the isomerization of 4-allylcatechol at least partly takes place *inside* the cavity of **5**.

When complex **5** is stirred with substrate **7** in chloroform under an hydrogen atmosphere (1 atm), after 2 h, almost all the substrate is converted. The reaction products are (*E*)- and (*Z*)-3,4-dihydroxy-β-methylstyrene (54%, *E/Z* ratio = 3), 4-(3,4-dihydroxyphenyl)butanal (24%), and 3,4-dihydroxy-1-propyl-benzene (17%) (Table 1, entry 5).

Catalytic Reactions with Rh(I) Hydride Host 4. Comparison of Substrates and Catalysts. The catalytic hydroformylation reaction of substrate **7** with complex **5** under an H₂/CO atmosphere gave a complicated mixture of reaction products. Therefore, we changed our program to hydrogenation reactions with the hydride complex **4**.

Catalytic conversions of substrates **6**−**8** were studied in chloroform under an hydrogen atmosphere with **4** and compared with the corresponding catalyst without a receptor unit (HRh-[P(OPh)₃]₄).[26] Under these conditions the substrates were converted to the corresponding propyl derivatives (hydrogenation) and β-methylstyrenes (isomerization). The conversion of substrate and product formation were followed by GLC. The conditions were taken such ([Rh] = 5.4 mM, substrate/catalyst = 10:1, 0.4 atm of partial H₂ pressure, 1 equiv excess of P(OPh)₃) that the conversion was slow and the product could be analyzed easily.

First the reactivity of the substrates **6**−**8** toward HRh-[P(OPh)₃]₄ was examined. The formation of the hydrogenated products *versus* time is depicted in Figure 5, and the kinetic data are summarized in Table 2 (entries 1−3). It is clear that the phenolic hydroxyl groups of the highly soluble substrates **7** and **8** deactivate the catalyst for hydrogenation and stimulate the isomerization reaction. The ratio of hydrogenated and isomerized product decreases in the series **6** > **7** > **8**. The same conclusion can be drawn from the ratios of the initial rates, $(v_{init})_{hydrogenation}/(v_{init})_{isomerization}$, although it should be noted that the comparison between the product ratios and the rate ratios can only be qualitative because of the kinetic complexity of the reaction. The origin of the observed effect is not completely clear. It is known that catechols in solution have one of their OH groups intramolecularly hydrogen bonded to the other OH group.[27] Hence less than two H-bonds may be available for deactivation. In line with this, 5-allylresorcinol (**8**), which is not able to form such intramolecular hydrogen bonds, gives a much higher amount of isomerized product. Eugenol (entry 4) has only one OH group, and the ratio of hydrogenated to isomerized product lies in between those of substrates **6** and **7** (Table 2 (entry 4) and Figure 5 (top)).
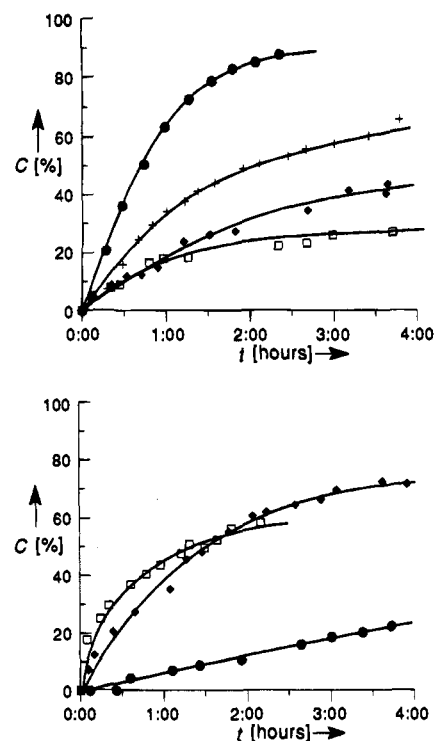

Figure 5. Hydrogenation of **6** (●), eugenol (+), **7** (◇), and **8** (□) by HRh[P(OPh)₃]₄ (top) and compound **4** (bottom). Conditions: [Rh] = 5.4 mM, *T* = 25.0 ± 0.1 °C, 1 additional equiv of P(OPh)₃, solvent chloroform.

Hydrogenation experiments carried out under the same conditions with the supramolecular catalyst **4** demonstrate that the receptor has a profound effect on the catalytic reaction (Figure 5 (bottom) and Table 2 (entries 5−7)). Similar to the stoichiometric isomerization reaction with **5**, the catalytic conversion of the bound substrates **7** and **8** and **4** was accelerated, whereas that of the nonbound substrate **6** was delayed. For the supramolecular catalyst and the model compound, the ratio of the initial rates {v_{init}(**4**)/v_{init}(HRh-[P(OPh)₃]₄)} for the conversion of substrates **6**, **7**, and **8** amounted to 0.1, 2.0, and 4.7, respectively.

Recently, we found that the rate determining step in the hydrogenation of allylbenzene with HRh[P(OPh)₃]₄ is the oxidative addition of hydrogen to the rhodium center.[26] Increasing the partial hydrogen pressure in the reaction of **4** with substrate **7** from 0.4 to 1 atm led to a nearly proportional increase in rate (Table 2, entry 11 *vs* entry 6).[28] This suggests that also for the supramolecular catalyst the addition of H₂ to the rhodium phosphite complex is the limiting step of the catalytic process. We found that under 1 atm of H₂ the catalyst is even able to slowly hydrogenate the formed β-methylstryrene derivatives.

The fact that the nonbound substrate **6** is converted by compound **4** shows that the rhodium center is not completely shielded from the solution and is accessible from the outside. Consequently, we cannot exclude that also substrates **7** and **8** are partly converted outside the cavity of **4**. It is known that isomerization reactions generally are much faster than hydrogenation reactions.[29] Going from HRh[P(OPh)₃]₄ to **4**, the hydrogenation/isomerization selectivity ratio (Table 2, last

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Table 2. Kinetic Data for the Hydrogenation and Isomerization of Alkenes by Complex **4** and HRh[P(OPh)₃]₄[a]

| | | | | | hydrogenation | | isomerization | | |
entry	catalyst[b]	substrate	p(H₂) (atm)	substrate/catalyst ratio	%	$v_{init} \times 10^6/$ $M \cdot s^{-1}$	%	$v_{init} \times 10^6/$ $M \cdot s^{-1}$	H/I ratio[c]
1	HRhP₄	6	0.4	10	91	15.8	9	2.8	10.1
2	HRhP₄	7	0.4	10	55	3.9	45	3.9	1.2
3	HRhP₄	8	0.4	10	46	3.0	54	8.5	0.9
4	HRhP₄	eugenol	0.4	10	78	6.8	22	3.1	3.5
5	4	6	0.4	10	85	1.3	15	1.1	5.7
6	4	7	0.4	10	83	8.6	17	5.7	4.8
7	4	8	0.4	10	56	14.0	44	11.9	1.3
8	4	7	0.4	5	84	3.6	16	5.1	5.3
9	4	7	0.4	15	60	8.2	40	6.3	1.5
10	4	7	1.0	5	98	17.5	2	10.1	49.0
11	4	7	1.0	10	97	29.2	3	11.3	32.3
12	4	7	1.0	15	92	41.4	8	15.2	11.5
13	4	7	1.0	20	91	50.9	9	21.6	10.1
14	4	7	0.4	10[d]	85	3.4 29.8[e]	15	9	5.7
15	HRhP₄	7	0.4	10[d]	57	3.8	43	4.3	1.3
16	4	6	0.4	10[d]	75	2.6	25	4.7	3.0

[a] Conditions: [Rh] = 5.4 mM, T = 25.0 ± 0.1 °C, 1 additional equiv of P(OPh)₃, solvent chloroform. [b] P = P(OPh)₃. [c] Ratio of hydrogenated and isomerized product. [d] Resorcinol was added. [e] After an induction period of *ca.* 30 min.

Scheme 2
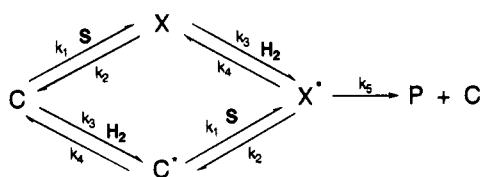
C = catalyst
C* = catalyst with oxidatively added H₂
S = substrate
X = complex between catalyst and substrate
X* = complex with oxidatively added H₂
P = hydrogenation product

column) for substrates **7** and **8** increases, whereas that for **6** decreases. The same trend is visible in the ratios of the initial rates, $(v_{init})_{hydrogenation}/(v_{init})_{isomerization}$. When the performance of the catalytic center is improved by increasing the hydrogen pressure, this selectivity ratio is enhanced further (Table 2, entries 6 and 11). These observations might indicate that the hydrogenation reaction *preferentially* takes place inside the cavity, whereas the faster isomerization reaction occurs on the outside. This suggestion is supported by observations from other experiments (vide infra).

Kinetics. In order to obtain more detailed information about the kinetics of the reactions with the supramolecular catalyst we monitored the conversion of **7** at different substrate concentrations. To prevent any possible complication due to product inhibition we only used initial rates. The data for the hydrogenations at 0.4 atm of hydrogen pressure (Table 2, entries 6, 8, and 9) revealed that already at low concentrations of substrate saturation kinetics occurred, probably because of the poor reactivity of the rhodium center under these conditions. Therefore, we also carried out reactions at 1 atm of H₂. These data are collected in Table 2, entries 10–13. A double-reciprocal plot of the initial substrate concentration *vs* the initial rate gave a straight line, indicative of Michaelis–Menten-like kinetics.

The kinetic scheme for the catalytic hydrogenation of a substrate that is bound in the cavity of the supramolecular catalyst is shown in Scheme 2. The complex between the

substrate (S) and the catalyst (C) is denoted by X, while an asterisk is used to indicate that the rhodium center has reacted with hydrogen. We assume that the oxidative addition of hydrogen to complex X proceeds at the same rate as that to C and that the association constant K_{assoc} for the binding of the substrate in the activated catalyst C* is the same as that for the binding in C. Molecular dynamics calculations which we carried out suggest that the rhodium centers of **4** with and without a bound substrate are equally well accessible.[18]

The kinetic equations are the following (concentrations are in italic, c_0 is the initial concentration of **4**):

$$\frac{dp}{dt} = k_5 x^* \tag{1}$$

$$\frac{dx}{dt} = k_1 sc + k_4 x^* - (k_2 + k_3(pH_2))x^* \tag{2}$$

$$\frac{dx^*}{dt} = k_1 sc^* + k_3(pH_2)x - (k_2 + k_4 + k_5)x^* \tag{3}$$

and the conservation equation is

$$c_0 = c + c^* + x + x^* \tag{4}$$

We define $K_{assoc} = k_1/k_2$ and $K_p = k_3(pH_2)/k_4$. Applying the steady state approximation for x and with $c = x/(sK_{assoc})$ gives eqs 5 and 6:

$$c = \frac{x^*}{sK_{assoc}K_p} \tag{5}$$

$$x = \frac{(k_1 + k_4 K_{assoc}K_p)x^*}{K_{assoc}K_p(k_2 + k_3(pH_2))} \tag{6}$$

A steady state approximation for x* combined with eq 6 yields

$$c^* = \frac{(k_2 + k_5)x^*}{k_1 s} = \frac{K_M x^*}{s} \tag{7}$$

Substituting eqs 5, 6, and 7 into eq 4 and solving for x* gives

$$x^* = \frac{c_0 s K_{assoc}K_p}{(1 + K_M K_{assoc}K_p) + K_{assoc}(K_p + 1)s} \tag{8}$$

(29) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987.
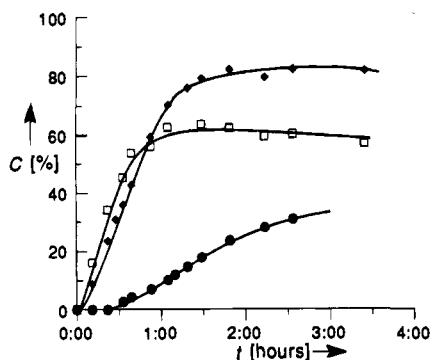
Figure 6. Competitive hydrogenation of **6** (●), **7** (◆), and **8** (□) by compound **4**. Conditions: [Rh] = 5.4 mM, [substrate]/[Rh] = 3, T = 25.0 ± 0.1 °C, 1 additional equiv of P(OPh)$_3$, solvent chloroform.

Table 3. Zero-Order Rate Constants for the Hydrogenation of Substrates **6–8** under Competitive Conditions[a]

substrate	hydrogenation %	$k_o \times 10^6$/M·s^{-1}	isomerization (%)	H/I ratio[b]
6	40[c]	0.8[d]	20[c]	2
7	80	3.2[e]	20	4
8	60	3.7	40	1.5

[a] Conditions: [Rh] = 5.4 mM, [substrate]/[Rh] = 3, T = 25.0 ± 0.1 °C, 1 additional equiv of P(OPh)$_3$, solvent chloroform. [b] Ratio of hydrogenated and isomerized product. [c] After 4 hrs. [d] After an induction period of 22 min. [e] After an induction period of *ca.* 3 min.

and finally into eq 1 gives

$$v = k_5 x^* = \frac{AVs}{B + s} \qquad (9)$$

in which $V = k_5 c_0$, $K_M = (k_2 + k_5)/k_1$, $A = K_p/(K_p + 1)$, and $B = (1 + K_M K_{assoc} K_p)/(K_{assoc}(K_p + 1))$. Equation 9 is a modified Michaelis–Menten equation[30] and explains the observed linearity of the double-reciprocal plot (see above). From this plot the constant B in eq 9 can be derived; it amounts to $B = 0.17 \pm 0.02$ M^{-1}. Assuming that the association constant for the binding of **7** in **4** is the same as for the binding of this substrate in **2c** ($K_{assoc} \approx 100$ M^{-1}), we may conclude from the value of B that K_p must be small compared to K_M and K_{assoc}, which is in line with the observation that the oxidative addition of hydrogen is the decisive step in the catalytic cycle.

The isomerization reaction did not follow eq 9. Both the rate and the order in substrate concentration increase with increasing s_0, indicating that this reaction is mechanistically different from the hydrogenation reaction.

Competition Experiment. The hydrogenation reactions were also studied under competitive conditions (3 equiv each of the substrates **6–8**, 0.4 atm of H$_2$). The results are shown in Figure 6. The hydrogenation of the resorcinol derivative **8** started immediately, followed by the hydrogenation of the catechol derivative **7** after an induction period of approximately 3 min. The reactions were zero-order in substrate. The rate constants are summarized in Table 3. During the first 22 min the nonbound substrate **6** did not react. After that time, when 50% of **7** and 75% of **8** had reacted, **6** was slowly converted. This experiment clearly demonstrated that the supramolecular system is a substrate selective catalyst.

Remarkably, Table 3 shows that the rate of conversion of **7** is not significantly slowed down by **8**. This indicates that this substrate and its reaction products do not block the catalyst as one would expect on the basis of their binding constants. We
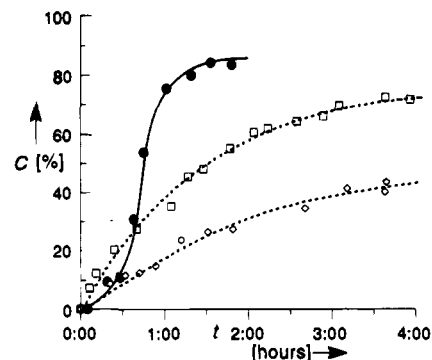
(30) Mahler, H. R.; Cordes, E. H. *Biological Chemistry*; Harper & Row: New York and John Weatherhill: Tokyo, 1966.

Figure 7. Effect of resorcinol (●) on the hydrogenation of **7** by compound **4**. For comparison also the blank reactions without any additives are shown: **7** and HRh[P(OPh)$_3$]$_4$ (◇); **7** and **4** (□). Conditions: [Rh] = 5.4 mM, T = 25.0 ± 0.1 °C, 1 additional equiv of P(OPh)$_3$, solvent chloroform.
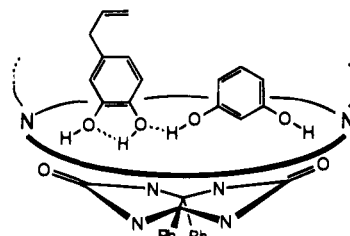

Figure 8. Possible geometry for the cooperative binding of substrate **7** with resorcinol in the cavity of **4**.

tentatively ascribe this to a cooperative effect in the binding of **7** and **8** in the cavity of **4** (see next paragraph).

Rate Enhancement by Resorcinol. Addition of resorcinol to substrate **7** and compound **4** in chloroform under 0.4 atm of hydrogen was found to result in a considerable enhancement of the rate of the hydrogenation reaction (Figure 7). After an induction period of approximately 25 min the rate suddenly increased from 3.4 to 29.8 μM·s^{-1} (Table 2, entry 14). Resorcinol had no effect on the activity of the rhodium center as we checked separately: the rate of conversion of **7** by HRh-[P(OPh)$_3$]$_4$ in the presence of resorcinol was the same as that without resorcinol (Table 2, entries 2 and 15). The conversion of the nonbound substrate **6** by **4** was also faster in the presence of resorcinol, but the rate increase was much smaller (factor of 2, Table 2 (entries 5 and 16)). This feature may be ascribed to the fact that on binding a resorcinol molecule in the cavity of **4** the metal center is slightly lifted, making it more accessible from the outside for a substrate molecule.[18] These results suggest that resorcinol and **7** are involved in a process of cooperative binding, as is shown in Figure 8. In this way the catechol moiety of **7** can preserve its intramolecular H-bond and more favorably bridge the distance between the carbonyl groups of the receptor molecule. For the future this offers the interesting possibility of carrying out bimolecular bond-forming reactions in the cavities of molecules of type **2**.

The rate of the isomerization reaction of **7** by **4** also slightly increased on addition of resorcinol but showed no induction period. Moreover, resorcinol caused the H/I ratio to be improved (Table 2, entries 6 and 14). These observations support the idea that the isomerization reaction preferentially takes place on the outside of the metallohost.

Concluding Remarks

We have shown that it is possible to design and synthesize a supramolecular rhodium catalyst which can discriminate between different added substrates by the process of molecular

recognition. The catalyst mimics properties displayed by enzymes, such as Michaelis—Menten kinetics and rate enhancement by a cosubstrate or a cofactor. The rate-limiting component of our rhodium catalysts **4** and **5** is the metal center and the sequence of the processes at this center. We are currently working on improved supramolecular catalytic systems which do not have these drawbacks.

Experimental Section

Reagents and Solvents. Unless otherwise indicated, commercial materials were used as received. Chloroform, chloroform-d_1, and CS_2 were distilled from phosphorus pentoxide. All solvents were stored on molecular sieves under an inert atmosphere. Triphenyl phosphite was distilled prior to use. 5-Chloro-1,3-dimethoxybenzene was purified by flash chromatography over a short column with basic alumina (eluent: hexane).

Apparatus. ^{1}H NMR spectra were recorded on Bruker WH-90, Bruker WM-200, Varian Gemini 300, and Varian XL-200 instruments. Chemical shifts (δ) are reported in parts per million downfield from internal $(CH_3)_4Si$. Abbreviations used are s = singlet, d = doublet, m = multiplet, and br = broad. ^{31}P NMR spectra were recorded on Bruker WM-200 and Bruker AM-400 instruments. Chemical shifts (δ) are reported in parts per million downfield from external $OP(OMe)_3$. Elemental analyses were determined with a Carlo Erba Ea 1108 instrument. For thin layer chromatography Merck Silica Gel 60 F_{254} plates were used. The hydrogenation and isomerization reactions were monitored on a Varian 3700 gas chromatograph with a flame ionization detector. The substrates and their reaction products were separated on a CP-SIL 5CB capillary column (25 m × 0.25 mm i.d., df (film thickness) = 0.25 μm, temperature program). The detector signal was integrated by a HP 3390A integrator.

2a,8,9,12,13,14,15,17,18,25,26,29,30,31,32,34,35,38b-Octadecahydro-2a,38b-diphenyl-13,30-bis[[4-(diphenylphosphito)phenyl]methyl]-1H,4H-6,37:20,23-dietheno-2,22:3,21-dimethano-5H,11H,28H,38H-7,10,16,19,24,27,33,36-octaoxa-2,3,4a,13,300,38a-hexaazacyclopenta[cd]cyclotetratriacont[g]azulene-1,4-dione (2b). This compound was synthesized as described elsewhere.[18]

Compounds 3, 4, and 5. These complexes were prepared as described elsewhere.[18]

1-Allyl-3,4-dimethoxybenzene (6). A mixture of 100 g (61 mmol) of eugenol, 16.8 g (122 mmol) of K_2CO_3, and 10.4 g (73 mmol) of methyl iodide in 150 mL of aceton was refluxed overnight. The solvent was removed under reduced pressure, and the product was extracted in a CH_2Cl_2/water mixture. The combined organic layers were washed with 1 N aqueous NaOH (3×), dried ($MgSO_4$), and evaporated to dryness. The resulting oil was purified by flash chromatography over a short column with basic alumina (eluent: pentane). After removal of the solvent under reduced pressure 8.4 g (77%) of **6** was obtained as a light yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.87−6.70 (m, 3H, ArH) 6.06−5.89 (m, 1H, CH$_2$C*H*=CH$_2$), 5.17−5.01 (m, 2H, CH$_2$CH=C*H*$_2$), 3.87 (s, 3H, OMe), 3.34 (d, 2H, CH$_2$C*H*=CH$_2$, J = 8 Hz). Anal. Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 74.25; H, 7.94%.

4-Allylcatechol (7). To a solution of 11.5 g (0.07 mol) of eugenol in 30 mL of dry THF was added stepwise 2.1 g (0.07 mol) of a dispersion of NaH in oil (80%). After the evolution of gas had stopped a solution of 13.4 g (0.07 mol) of LiPPh$_2$ in 60 mL of THF was added.[21] After stirring for 3 h, 2 mL of water was added and the mixture was poured into 200 mL of degassed 0.2 N aqueous NaOH. The yellow solution was washed with ether (4×), and the combined organic layers were extracted with 100 mL of 0.2 N aqueous NaOH. The combined water layers were acidified with concentrated HCl to pH = 6. The resulting emulsion was extracted with ether, and the organic layers were washed with water (5×), dried ($MgSO_4$), and evaporated to dryness. Purification by column chromatography (eluent: 2% MeOH in CHCl$_3$) gave 5.97 g (57%) of a brownish oil which could be further purified by sublimation. A yield of 3.9 g (37%) of 4-allylcatechol was obtained

as a bright white solid: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.84−6.60 (m, 3H, ArH), 6.02−5.85 (m, 1H, CH$_2$C*H*=CH$_2$), 5.12−5.03 (m, 2H, CH$_2$CH=C*H*$_2$), 4.96 (br, 2H, OH), 3.29 (d, 2H, CH$_2$C*H*=CH$_2$, J = 8 Hz). Anal. Calcd for C$_9$H$_{10}$O$_2$: C, 71.98; H, 6.71. Found: C, 72.22; H, 6.32%.

5-Allyl-1,3-dimethoxybenzene. To a suspension of 0.88 g (36 mmol) of freshly prepared activated Mg[22] in 100 mL of dry THF was added 5.18 g (30 mmol) of 5-chloro-1,3-dimethoxybenzene, and the mixture was refluxed for 4 h. The progress of the reaction was followed by quenching an aliquot of the reaction mixture in acidic water, subsequently extracting the products with CH$_2$Cl$_2$, and recording an ^{1}H NMR spectrum. After the mixture was cooled to room temperature, a catalytic amount of CuBr, codissolved with LiBr in 1 mL of THF, and 5.44 g (45 mmol) of allyl bromide were added to the reaction mixture. The mixture was stirred overnight and quenched with 3 mL of saturated aqueous NH$_4$Cl. The solvent was removed under reduced pressure, water was added, and the mixture was neutralized to pH $\approx$ 7. The product was extracted with ether (3×), and the combined organic layers were washed with 0.5 N aqueous Na$_2$S$_2$O$_4$ and with water. The solution was dried ($MgSO_4$) and evaporated to dryness. The resulting oil was purified by column chromatography (silica, eluent: hexane/benzene = 3:2) to give 1.18 g (44%) of 5-allyl-1,3-dimethoxybenzene as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.84−6.60 (m, 3H, ArH), 6.02−5.85 (m, 1H, CH$_2$C*H*=CH$_2$), 5.12−5.03 (m, 2H, CH$_2$CH=C*H*$_2$), 4.96 (br, 2H, OH)), 3.29 (d, 2H, CH$_2$CH=CH$_2$, J = 8 Hz).

5-Allylresorcinol (8). A mixture of 0.38 g (14 mmol) of Al cuttings and 2.7 g (21 mmol) of I$_2$ in 30 mL of CS$_2$ was refluxed for 2 h under inert atmosphere. To the resulting solution was added 0.5 g (2.8 mmol) of 5-allyl-1,3-dimethoxybenzene and the mixture was refluxed overnight. After cooling to room temperature the mixture was quenced with saturated aqueous NH$_4$Cl. The solvent was removed under reduced pressure, water was added, and the mixture was neutralized to pH $\approx$ 7. The product was extracted with ether (3×), and the combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The resulting oil was purified by column chromatography (silica; eluent: hexane/EtAc = 2:1, v/v) to yield 340 mg (80%) of **8** as a yellowish sticky syrup: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.28 (d, 2H, ArH, J = 3 Hz), 6.21 (tr, 1H, ArH, J = 3 Hz), 6.000−5.84 (m, 1H, CH$_2$C*H*=CH$_2$), 5.16−5.03 (m, 2H, CH$_2$CH=C*H*$_2$), 4.80 (br, 2H, OH), 3.29 (d, 2H, CH$_2$CH=CH$_2$, J = 8 Hz); Anal. Calcd for C$_9$H$_{10}$O$_2$: C, 71.98; H, 6.71. Found: C, 71.54; H, 6.96%.

Isomerization Experiments with 5 and HRh(CO)[P(OPh)$_3$]$_3$. A stream of CO was bubbled through a solution of 20 mg (10.2 μmol) of **5** or 11.2 mg (10.2 μmol) of HRh(CO)[P(OPh)$_3$]$_3$[31] in CDCl$_3$, and the volume was subsequently adjusted to 0.6 mL ([Rh] $\approx$ 17 mM). After addition of 1.5 mg (10.2 μmol) of **7** the mixture was transferred to an NMR tube and sealed under argon. Periodically a NMR spectrum was recorded. In the case of the reactions with allylbenzene (10.2 μmol, 1.2 mg) the substrate was added from a stock solution. The product compositions were determined by integration of the peaks in the ^{1}H NMR spectra.

Hydrogenation Experiments with HRh[P(OPh)$_3$]$_4$. To 21.3 mg (15.8 μmol) of HRh[P(OPh)$_3$]$_4$ in a 50 mL glass vessel was added 4.9 mg (15.8 μmol) of P(OPh)$_3$ dissolved in 1.5 mL of chloroform. The vessel was placed in an autoclave, filled with Ar, and substrate (number of equivalents × 15.8 μmol) solved in 1.6 mL of chloroform was added. The autoclave was evacuated quickly and refilled twice with argon. Finally, an overpressure of 0.4 or 1.0 atm of hydrogen gas was applied. Control experiments confirmed that after this procedure the concentration of the catalyst was 5.4 ± 0.3 mM. Samples were taken by opening a valve under a stream of argon. The reaction was stopped by rapidly freezing the samples in liquid nitrogen. Control experiments indicated that by this procedure no change in the product composition took place.

Hydrogenation Experiments with 4. The catalyst was prepared in situ by adding 4 mg of (acac)Rh(CO)$_2$ to a chloroform solution containing 24 mg (15.8 μmol) of **2b** and 14.7 mg (47 μmol) of P(OPh)$_3$. Subsequently Ar was bubbled through the solution to remove the CO.

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(31) Keblys, K. A. U.S. Patent 3,907,847, 1975.

The solution was stirred overnight under 10 atm of hydrogen pressure. ^{31}P NMR spectroscopy revealed that the purity of the thus obtained catalyst was >95%. The volume was adjusted to 1.5 mL, and the same procedure as described for HRh[P(OPh)$_3$]$_4$ was followed.

Data Processing. For all the components involved in the reaction, calibrations were made using 1,4-di-*tert*-butylbenzene as the internal standard. The hydrogenation products were synthesized separately by stirring the substrate overnight in acetic acid with a catalytic amount of palladium on carbon under 10 atm of hydrogen pressure. The isomerized products were prepared by stirring the corresponding substrates overnight in methanol under an argon atmosphere with a catalytic amount of palladium on carbon and a drop of concentrated hydrochloric acid. The integrated areas obtained from the GC tracks were multiplied by the slopes of the corresponding calibration curves and afterward renormalized to 100%. The initial rates were determined following standard procedures.

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