1228 *Macromolecules* **1997,** *30,* 1228−1230

Dendritic Catalysts: Reactivity and Mechanism of the Dendritic Bis(oxazoline)metal Complex Catalyzed Diels−Alder Reaction[†]

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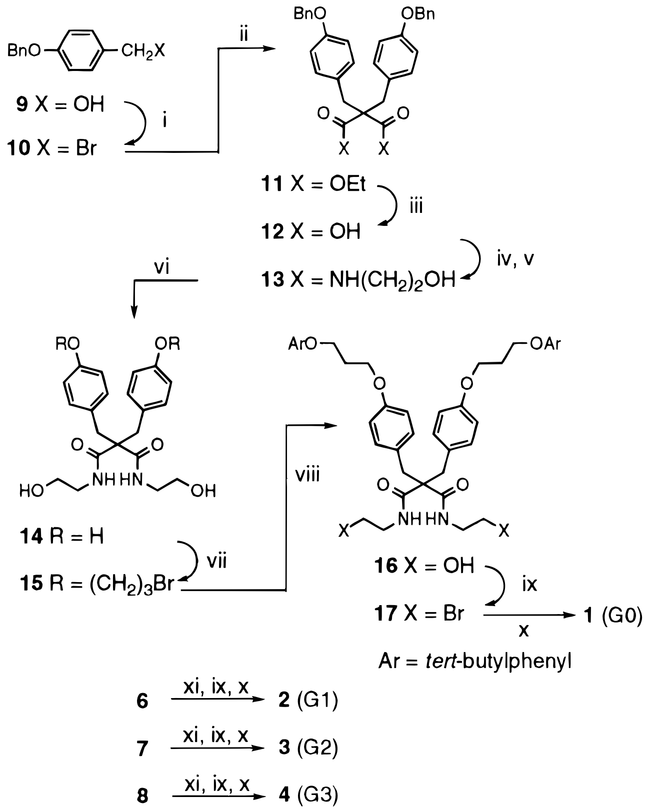
Received August 27, 1996
Revised Manuscript Received November 20, 1996

The idea of incorporating catalytic functionalities into a dendritic structure with the aim to create artificial enzyme mimics (dendrizymes) with improved reactivity and selectivity is one of the active research areas in dendrimer chemistry.[1] Depending on whether the catalytic groups are situated at the central core,[1a,e−g] at the chain end sites,[1b,c] or at both locations[1d] within the dendritic structure, different catalytic properties could be realized. With few exceptions,[1b,f] most reported dendritic catalysts were of lower generations and had a flexible open structure[2] with the catalytic center(s) fully exposed to the surroundings. Hence, the effect of the morphological transformation from a lower generation starfish-like open configuration to a higher generation closed spheroid structure on the catalyst reactivity and selectivity was unknown, although such a morphological transition had been observed by other physical techniques such as photophysical, viscometric, solvatochromic, and host−guest encapsulation studies.[3] Here we reported the kinetic and mechanistic study on the Diels−Alder reaction catalyzed by a series of metallodendritic catalysts prepared from dendritic bis(oxazoline) ligands **1**−**4** of the zeroth to third generations. Our kinetic investigations revealed that the catalyzed reaction followed an enzymatic Michaelis−Menten relationship, demonstrating fast reversible formation of the dendrizyme−dienophile complex, prior to the rate-limiting conversion to the Diels−Alder adduct. Furthermore, the catalytic reactivity and substrate binding profile of the dendrizymes were controlled by the size and generation of the dendritic sector. More interestingly, our kinetic investigations suggested that the catalytic functionality which was exposed to the surroundings in the earlier generations became partially buried inside a dendritic matrix in the third generation.

The dendritic ligands **1**−**4** are made up of two components: the catalytic core group and the dendritic sector. The catalytic group consists of a bis(oxazoline) moiety, metal complexes of which are known to catalyze reactions[4] such as cyclopropanation of olefins and the Diels−Alder reaction. The dendritic sectors chosen are the known polyether dendrimers **5**−**8**.[5]

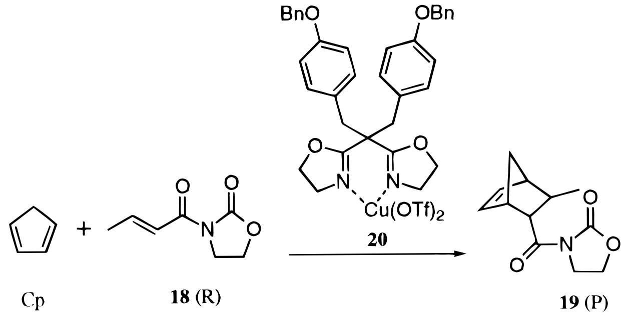
The construction of the catalytic core began with the readily available 4-(benzyloxy)benzyl alcohol (**9**) (Scheme 1). Treatment of **9** with concentrated hydrobromic acid in glacial acetic acid afforded the corresponding benzyl bromide **10** as a solid in 70% yield. Di-*C*-alkylation of diethyl malonate with the bromide **10** gave the diester **11** as an oil in quantitative yield. Alkaline hydrolysis of **11** resulted in the formation of a separable mixture of the decarboxylated monoacid (27%) and the diacid **12** (65%). Conversion of **12** into the diacyl chloride followed by *in situ* trapping with excess 2-ethanolamine gave the diamide **13** as a solid in 69% yield. The benzyl groups were then dismantled to give the diphenol **14** in 88% yield, which was subsequently converted to the dibromide **15** in 78% yield by reacting with excess 1,3-dibromopropane.

Scheme 1. Synthesis of Dendritic Ligands 1−4[a]



[a] Reagents: (i) 47% HBr, HOAc; (ii) NaH (2 equiv), diethyl malonate, THF; (iii) KOH, H_2O/EtOH; (iv) DMF, $(COCl)_2$, CH_2Cl_2; (v) ethanolamine (5 equiv), CH_3CN; (vi) H_2, Pd on C, EtOH; (vii) 1,3-dibromopropane (10 equiv), K_2CO_3, acetone; (viii) **5**, K_2CO_3, acetone; (ix) CBr_4, PPh_3, THF; (x) NaOH, EtOH/THF; (xi) **15**, K_2CO_3, acetone.

Scheme 2. Diels−Alder Reaction between Cyclopentadiene and Dienophile (R) Catalyzed by Bis(oxazoline)copper(II) Complex 20



The assembly of dendritic sectors of different generations **5**−**8**[5] onto the catalytic core **15** could be achieved by a general coupling procedure (K_2CO_3, acetone). Thus, reaction of 4-*tert*-butylphenol (**5**) with the core **15** gave aryl ether **16** in 60% yield. Conversion of the two primary hydroxyl groups in **16** into the dibromide **17** proceeded smoothly (PPh_3, CBr_4). Cyclization of **17** with sodium hydroxide in ethanol/THF afforded the zeroth generation bis(oxazoline) dendrimer **1** as an oil in 43% overall yield from **16**. Similarly, coupling of the phenols of higher generations **6**−**8** onto **15** followed by bromination/cyclization afforded dendritic ligands **2**−**4** in 36,

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[†] Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

S0024-9297(96)01281-8 CCC: $14.00

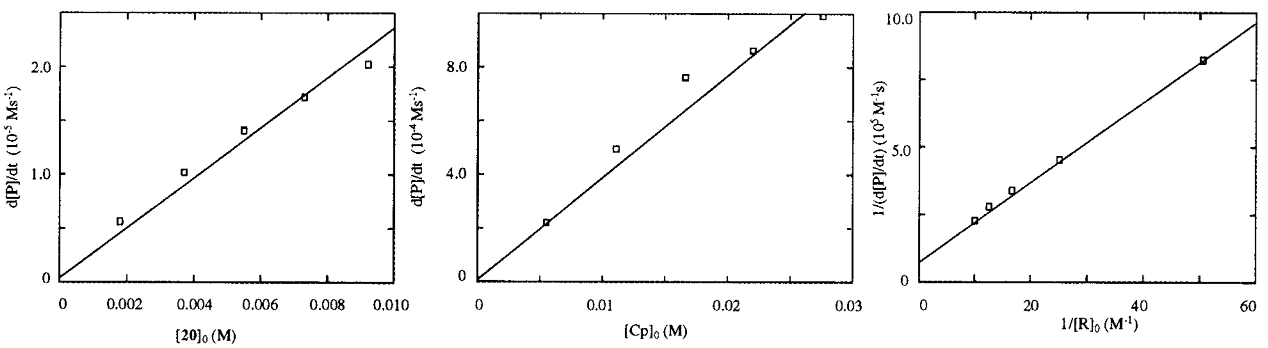
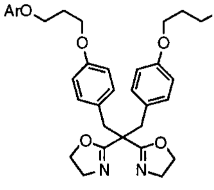


Figure 1. Initial rate of Diels–Alder adduct (P) formation *vs* [**20**]$_0$ ([R]$_0$ = 0.0843 M and [Cp]$_0$ = 1.52 M) (left). Initial rate of Diels–Alder adduct (P) formation *vs* [Cp]$_0$ ([R]$_0$ = 0.32 M and [**20**]$_0$ = 0.0050 M) (middle). Plot of 1/{d[P]/d*t*} *vs* 1/[R]$_0$ ([Cp]$_0$ = 2.39 M and [**20**]$_0$ = 0.001 22 M) (right). Temperature all at 25.0 ± 0.1 °C.



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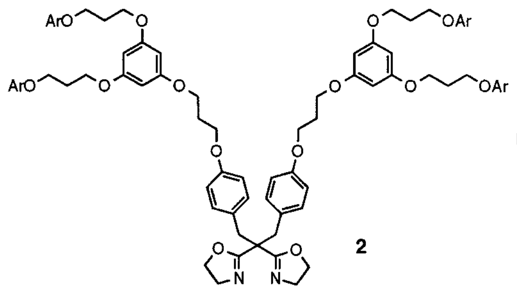

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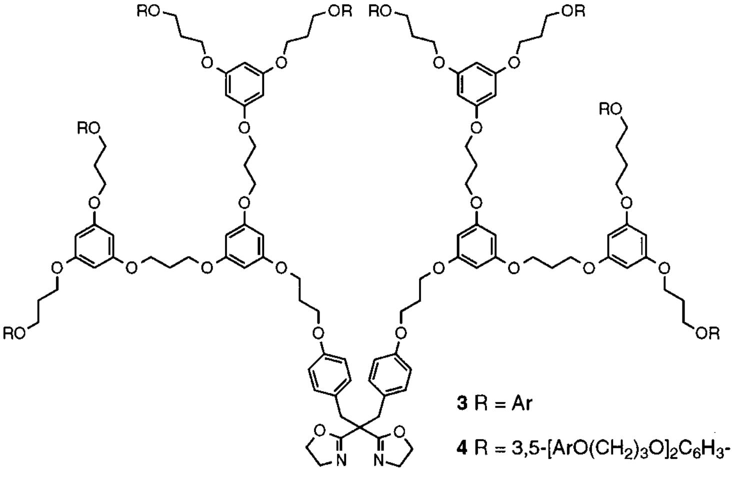
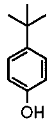


3 R = Ar

4 R = 3,5-[ArO(CH$_2$)$_3$O]$_2$C$_6$H$_3$-



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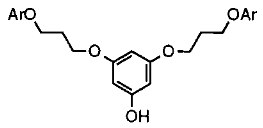

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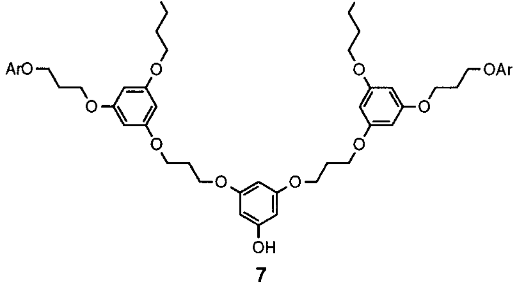

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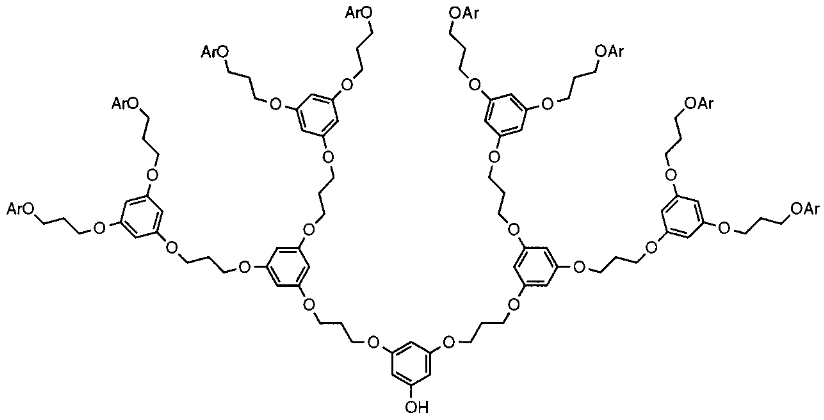

8

Ar = 4-*tert*-butylphenyl-

23, and 27% overall yields, respectively, from **15**. The structural identities of these compounds were confirmed by their ^{1}H and ^{13}C NMR, mass spectral, and elemental analysis.

Although the bis(oxazoline)copper(II) complex catalyzed Diels–Alder reaction had been known for some time, little was known about the reaction mechanism.[6] The dendritic copper(II) catalysts of the different generations (G*n*) were prepared by stirring a 1:1 mixture of the dendritic ligand and copper(II) triflate under N$_2$ in a dichloromethane solution at 25.0 ± 0.1 °C until complete dissolution of the solid copper(II) triflate. The reaction was also monitored by UV spectroscopy to ensure complete complexation.[7] The Diels–Alder reaction between cyclopentadiene (Cp) and the crotonyl imide **18** (R) was conducted (Scheme 2) according to the literature[6] and the reaction kinetics monitored by gas chromatography[8] for the appearance of the Diels–Alder adduct **19** (P). Employing the pseudo-order kinetics technique[9] on a simple bis(oxazoline)copper complex **20**, it was discovered that the initial rate of the reaction d[P]/d*t* was directly proportional to [**20**] and to [Cp], while a plot of 1/[R] *vs* 1/(d[P]/d*t*) gave a straight line not passing through the origin (Figure 1). Hence the rate equation of the Diels–Alder reaction had the form

$$\frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{k_1 k_2 [20][\mathrm{R}][\mathrm{Cp}]}{k_{-1} + k_1[\mathrm{R}]} \qquad (1)$$

This equation could be rationalized by the following mechanism:

Table 1. K_c and k_2 Values of the Diels−Alder Reactions

catalyst	K_c (M^{-1})	$10^3 k_2$ (M^{-1} s^{-1})
G0	10.4 ± 0.2	3.3 ± 0.1
G1	9.8 ± 1.1	3.3 ± 0.3
G2	7.8 ± 1.1	3.2 ± 0.4
G3	5.7 ± 0.5	1.9 ± 0.2

$$\mathbf{20} + \mathrm{R} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{20}\text{−}\mathrm{R} \xrightarrow[\mathrm{Cp}]{k_2} \mathbf{20} + \mathrm{P}$$

Applying steady state approximation on the catalyst−dienophile complex **20**−R, eq 2 could be obtained,[10] where 0 denoted the initial concentration of the reactants.

$$\frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{k_1 k_2 [20]_0 [\mathrm{R}][\mathrm{Cp}]}{k_{-1} + k_1[\mathrm{R}] + k_2[\mathrm{Cp}]} \qquad (2)$$

If the rate of the Diels−Alder reaction between **20**−R and Cp was slow compared to both the rates of formation and the decomplexation of the **20**−R complex, *i.e.*, $k_{-1} \gg k_2[\mathrm{Cp}]$ and $k_1[\mathrm{R}] \gg k_2[\mathrm{Cp}]$, we had

$$\frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{k_1 k_2 [20]_0 [\mathrm{R}][\mathrm{Cp}]}{k_{-1} + k_1[\mathrm{R}] + k_2[\mathrm{Cp}]} \cong \frac{k_1 k_2 [20]_0 [\mathrm{R}][\mathrm{Cp}]}{k_{-1} + k_1[\mathrm{R}]} \qquad (3)$$

Thus, the initial rate of the reaction became

$$\frac{\mathrm{d[P]}}{\mathrm{d}t} = \nu_{\mathrm{init}} = \frac{k_1 k_2 [20]_0 [\mathrm{R}][\mathrm{Cp}]}{k_{-1} + k_1[\mathrm{R}]} \rightarrow \frac{k_1 k_2 [20]_0 [\mathrm{R}]_0 [\mathrm{Cp}]_0}{k_{-1} + k_1[\mathrm{R}]_0} \qquad (4)$$

Equation 4 is the modified Michaelis−Menten equation for enzyme kinetics. Hence, the binding constants of **20** as well as those of the other dendritic ligand complexes G_nR ($K_c = k_1/k_{-1}$) and the rate constants k_2 of the different dendrimer-catalyzed reactions (Table 1) could be obtained from a Lineweaver−Burk plot.[11] Two important findings were noted. Firstly, the binding constant decreased with increasing dendrizyme generation. This destablization was probably due to the increased distortion of the GR complex from its optimal geometry, as a result of the increasing steric repulsion between the two larger dendritic sectors at the higher generations. Secondly, the rate constant k_2 for the Diels−Alder reaction remained essentially the same from G0 to G2 but dropped suddenly at G3. This rate-determining process involved the Diels−Alder reaction between the catalyst−dienophile complex and Cp, and the reaction rate should be determined by the steric accessibility of the catalytic cavity. The sudden drop of k_2 at the G3 catalyst suggested that the catalytic core which was essentially open to the surroundings at G0−G2 became partially buried in the interior of the dendritic matrix at G3. For G0−G2, due to the smaller size of their dendritic sectors, the catalytic core remained exposed to the surroundings and thus k_2 was insensitive to the dendrimer generation, whereas for the third generation catalyst, the steric repulsion between the two large dendritic sectors might be so severe that one or both of them had to move toward the catalytic core in order to relieve the steric strain, resulting in a decrease of steric accessibility around the catalytic core. This folding back of the dendritic sector had been used to explain the unusual solubility behavior of some metallodendrizymes[1e] and was in line with similar observations on a sudden change in physical properties across different dendrimer generations by other techniques.[3]

Acknowledgment. This work was supported by the Research Grants Council, HK (CUHK 466/95P).

Supporting Information Available: Spectroscopic and analytical data for dendritic ligands **1**−**4** and Lineweaver−Burk plots for the various copper(II)−dendritic ligand catalyzed Diels−Alder reactions (3 pages). Ordering information is given on any current masthead page.

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(7) All copper(II)−dendritic ligands gave similar UV spectra with $\lambda_{\max}$ at approximately 720 nm. However, dendritic ligands of higher generations required a longer time (3 h) for complete complexation than ligands of lower generations (1 h). The dendrizyme complexes did not lose their catalytic activities in 1 week on standing at 20 °C.

(8) GC conditions: GC analyses were performed on a Helwett Packard 5890 Series II gas chromatograph on a capillary column (DB-1) equipped with an FID detector. Temperatures: injector temperature, 220 °C; oven temperature, 180 °C; detector temperature, 250 °C with a head pressure of 7 psi and a nitrogen flow of 80 mL/min. R_t (dienophile R) = 4.3 min, R_t (adduct P) = 11.4 min.

(9) In this kinetic experiment involving three reacting partners, pseudo-order kinetic conditions were satisfied by keeping the concentrations of two of the components constant. This condition was automatically fulfilled by the catalyst component because it was continuously regenerated and therefore remained constant during the reaction. The concentration of the other component was maintained essentially constant by using a large excess of this reagent. Only the initial kinetic data of the reaction with less than 15% product conversion were taken into account. Separate pseudo-first-order measurements were conducted with each reactant (apart from the catalyst **20**) in excess.

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