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Lattice Inclusion Complexation in Water. Hydrogen Bonding in Selective Guest Binding and Catalysis

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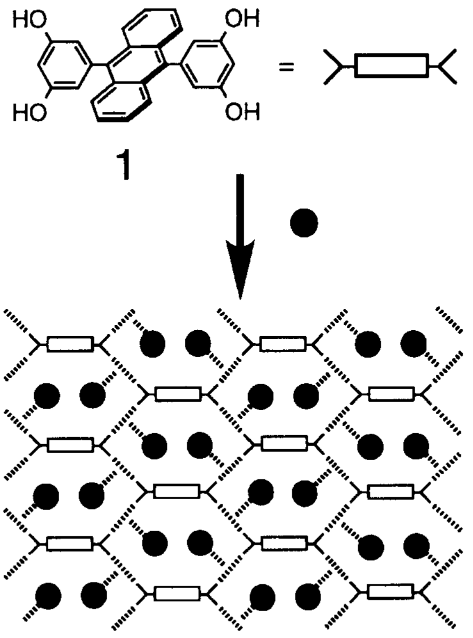
When immersed in an aqueous solution of alcohol or alkyl acetate as a guest, 9,10-bis(3,5-dihydroxyphenyl)anthracene **1** as a hydrogen-bonded solid host incorporates two mols of the guest together with 5—8 mols of water. The binding isotherm shows a sharp threshold guest concentration characteristic of guest-induced phase-transition. The threshold concentrations as a measure of affinities are highly dependent on the hydrophobicities of the guests. Host **1** also catalyzes the Diels–Alder reaction of acrylaldehyde and 1,3-cyclohexadiene in an aqueous environment. The preserved 1 : 2 (host-to-guest) stoichiometry, spectroscopic evidence ($\Delta\nu_{C=O}$), guest-desorption behaviors, and X-ray powder-diffraction studies indicate that host–guest hydrogen-bonding in collaboration with apolar interactions is responsible for the selective guest-binding and catalysis under the present aqueous conditions.

Hydrogen bonding plays essential roles in maintaining biological structures and functions.[2] The last two decades have seen a significant development in the use of hydrogen bonds in various self-assembling systems, ranging from bimolecular host–guest complexes in solution to 3-dimensionally networked organic solids.[3] Most workers in these areas have been forced to employ apolar organic media under anhydrous conditions, since polar solvents, water in particular, severely interfere with intermolecular hydrogen-bond formations.[4] Water in fact has long been the last solvent of choice for many organic chemists, since polar species are extensively solvated (hydrated) in this medium and hence rendered interaction- and reaction-inactive. *Nature* does seem to overcome this problem by using multiple interactions, as illustrated by the multiple hydrogen-bonding to maintain double helical structures of DNA's and characteristic secondary structures (α-helices and β-sheets) of proteins. Concurrent polar and apolar interactions often found in protein-substrate complexes may be taken as another example. It should also be noted that the hydrogen-bonded biopolymers are extensively hydrated. Formation of stable hydrogen-bonded complexes in water remains a challenge.[5] Effective polar interactions in water may also provide a clue for designing "green" or ecological molecular transformation systems free from organic solvents.[6]



1

2

Chart 1.

9,10-Bis(3,5-dihydroxyphenyl)anthracene **1**, an X-shaped phenolic tetrol with an orthogonal anthracene spacer, forms crystalline 1 : 2 adducts **2** with various polar guests such as esters, where the two guest molecules (●) are included in each cavity of a hydrogen-bonded (O–H···O–H) molecular sheet formed by host **1** via host–guest hydrogen-bonding (O–H···O–H···O=C), as schematically shown in Chart 1.[7] The included volatile guests such as ethyl acetate can be removed to give what we call the guest-free apohost[8] with collapsed cavities.[9] Upon subsequent treatment with a guest as solid, liquid, or gas, the apohost regenerates a 1 : 2 adduct with restored X-ray powder diffractions of the adduct.[8] The present work is concerned with guest binding from an aqueous solution,[10] where the main issue is how essential hydrogen-bonding interactions are compatible with water. We report here that the characteristic guest-binding and catalytic properties observed under anhydrous conditions are retained also under the present aqueous conditions.

Results and Discussion

Binding Isotherms. Apohost **1** is polycrystalline. It is completely insoluble in water but is hydrated with ca. 12 mols (by ^{1}H NMR and TG) of H_2O to give an aqua complex **1**·(ca. $12H_2O$).[10] When dipped in an aqueous solution of alcohol or alkyl acetate as a guest, apohost **1** binds the guest with a smooth progression curve followed by a plateau region after ca. 0.5 h. In Figs. 1A, 1B, and 1C are shown the binding isotherms at 25 °C for ROH (R = Me (methyl), Et (ethyl), ^{i}Pr (isopropyl), and Pr (propyl)), CH_3CO_2R (R = Et, Pr, and Bu (butyl)), and *cis-* and *trans-*1,2-cyclohexanediol, respectively, where the plateau or equilibrium guest/host ratios are plotted against concentrations (C) of the guest in the aqueous phase. There are three characteristic aspects in the binding isotherms. (1) All the guests investigated show a saturation guest/host ratio of ca. 2. (2) The uptake of two guest molecules occurs in an either monophasic or biphasic (stepwise) manner almost *vertically* at sharp threshold concentration(s) (C_{th}). (3) The C_{th}'s are highly guest-dependent and decrease (the affinities increase) with increasing sizes of the alkyl moieties (R) in the alcohol or ester guests.

Items 1—3 are also what are characteristic of the guest-binding to apohost **1** (Eq. 1, G = guest) under anhydrous conditions.[7—9] The guest/host ratio of 2 comes from the number of hydrogen-bonding sites (O–H···O–H) in the networked host.[7,8] The vertical isotherm observed for a gaseous guest is a result of phase transition for a two-component/three-phase system (host and guest as components and two solid phases for apohost and adduct and one gas phase for the guest).[9] The threshold guest pressure actually represents the equilibrium pressure for Eq. 1, which is automatically set when the temperature as the sole degree of freedom ($f = c-p+2 = 2-3+2 = 1$) is fixed.[9] Combined evidence from the preserved 1 : 2 (host-to-guest) stoichiometry (item 1), guest-induced phase-transition (item 2), and selectivity in guest binding (item 3) indicates that the essential host–host hydrogen-bonding in the host network as well as the host–guest hydrogen-bonding in guest-binding *survive* under the present aqueous conditions.

$$\mathbf{1} + 2\text{G} \rightleftharpoons \mathbf{1}\cdot(2\text{G}). \qquad (1)$$

$$\mathbf{1}\cdot(\text{ca. }12H_2O) + 2\text{G} \rightleftharpoons \mathbf{1}\cdot(2\text{G})\cdot[(5\text{—}8)H_2O] + (4\text{—}7)H_2O. \qquad (2)$$

Host–Guest Hydrogen-Bonding. The 1 : 2 adducts are actually obtained as hydrates containing several (5—8) water molecules, as confirmed by ^{1}H NMR and thermogravimetry (TG). Thus, the present guest-binding might be better represented as a guest/water exchange between aqua complex **1**·(ca. $12H_2O$) and hydrated host–guest adduct **1**·(2G)·[(5—8)H_2O] (Eq. 2). This is a reversible process. When, for example, the ethanol adduct **1**·(2EtOH)·(ca. $8H_2O$) is dipped in pure water, desorption of the ethanol guests occurs with a half-life of ca. 15 min to give the aqua complex.

The above-suggested host–guest hydrogen-bonding is further supported by a significant body of evidence. (1) The ester guests in hydrated host–guest adducts show a characteristic hydrogen-bond shift to lower wavenumber in $\nu_{\text{C=O}}$. The observed $\Delta\nu_{\text{C=O}}$ values of 40 cm^{-1} for ethyl acetate in **1**·($2CH_3CO_2Et$)·(ca. $5H_2O$), 42 cm^{-1} for propyl acetate in **1**·($2CH_3CO_2Pr$)·(ca. $5H_2O$), and 42 cm^{-1} for butyl acetate in **1**·($2CH_3CO_2Bu$)·(ca. $5H_2O$) are comparable to those for the corresponding anhydrous 1 : 2 adducts ($\Delta\nu_{\text{C=O}}$ = 52, 42, and 42 cm^{-1}, respectively). (2) When two guest molecules are adsorbed essentially in a single step, as in the case of methanol, ethanol, 1-propanol, and butyl acetate (Figs. 1A and 1B), the resultant hydrated adduct exhibits essentially the same X-ray powder diffractions as those for the corresponding anhydrous adduct, as shown in Figs. 2A and 2B for the ethanol adducts.[11] Since the X-ray powder diffractions are sensitive to the included, i.e., hydrogen-bonded,

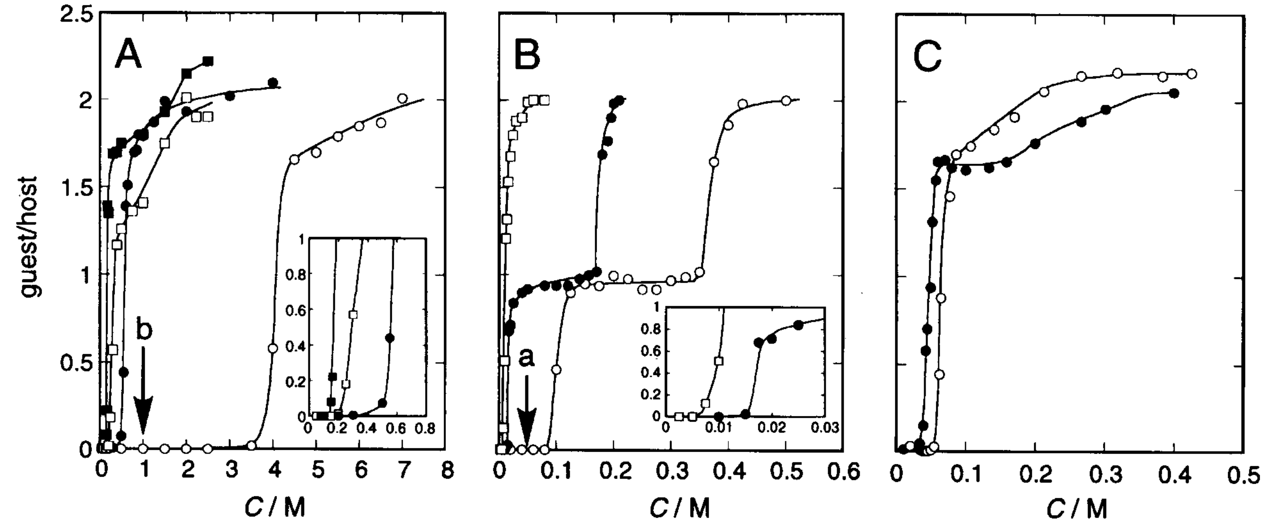


Fig. 1. Binding isotherms for various guests with apohost **1** under aqueous conditions at 25 °C: A, methanol (○), ethanol (●), 2-propanol (□), and 1-propanol (■); B, ethyl acetate (○), propyl acetate (●), and butyl acetate (□); C, *cis-* (○) and *trans-*cyclohexane-1,2-diols (●). Arrows a and b represent the equimolar concentrations under competitive conditions for CH_3CO_2Et/CH_3CO_2Bu and MeOH/EtOH, respectively. Insets in A and B: expansion of the C_{th} region.

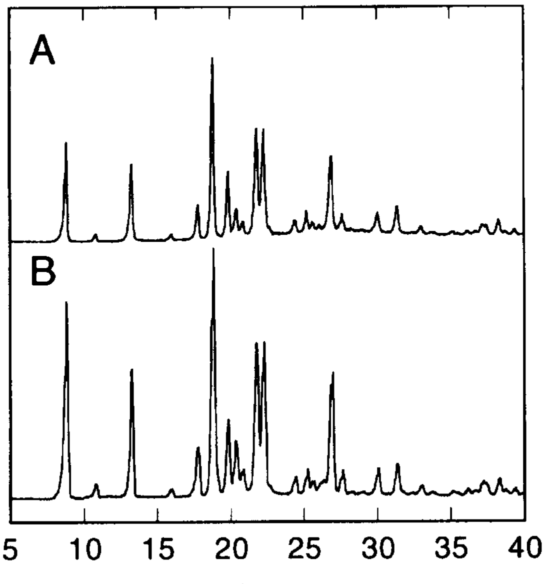


Fig. 2. X-ray powder diffraction patterns for the hydrated and anhydrous ethanol adducts **1**·(2EtOH)·(ca. $8H_2O$) (A) and **1**·(2EtOH) (B). The latter sample was prepared by solid-gas complexation of apohost **1** with gaseous EtOH at 25 °C.

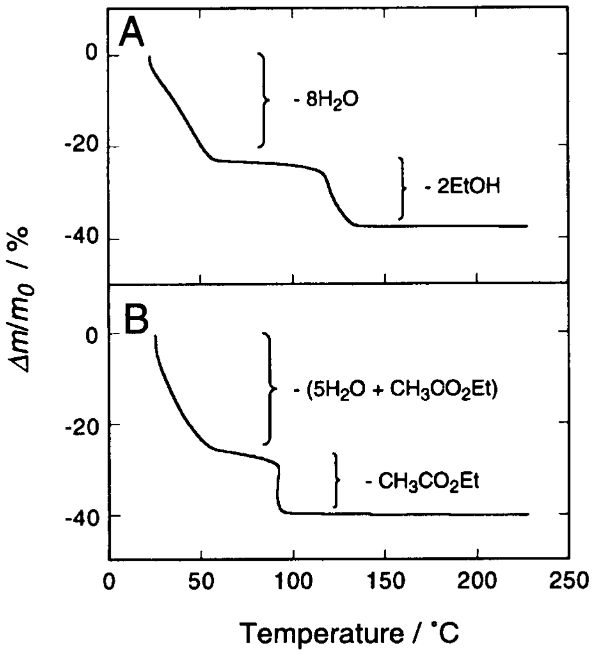


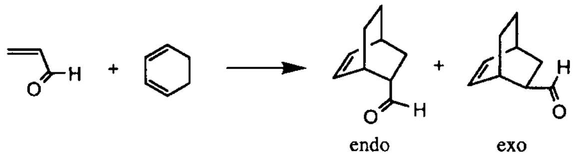
Fig. 3. TG thermograms for the hydrated ethanol and ethyl acetrate adducts **1**·(2EtOH)·(ca. $8H_2O$) (A) and **1**·($2CH_3CO_2Et$)·(ca. $5H_2O$) (B) at a heating rate of 20 °C min^{-1}

guests,[8] the above results indicate that the hydrogen-bonded arrays of host and guest in the hydrated adducts remain the same as that in anhydrous adducts. (3) Guests in hydrated adducts are more firmly bound to the host than water. Figure 3A shows the TG thermogram for the ethanol adduct **1**·(2EtOH)·(ca. $8H_2O$). The coincluded water molecules are in fact volatile. They escape from the host even at room temperature and are completely removed with a correct weight loss corresponding to $8H_2O$ (determined by ^{1}H NMR) when the adduct is heated at > 60 °C. The resulting anhydrous ethanol adduct **1**·(2EtOH), unambiguously identified by means of spectroscopy and diffractometry, can get rid of the ethanol guests only at elevated (> 100 °C) temperature. It must be ethanol molecules that are hydrogen-bonded to the host and water seems to be only weakly adsorbed. Unfortunately, numerous trials to obtain hydrated adducts as single crystals have so far been unsuccessful. Desorption of ethyl acetate from adduct **1**·($2CH_3CO_2Et$)·(ca. $5H_2O$) occurs in a stepwise manner (Fig. 3B), in accord with a stepwise adsorption isotherm for this guest (Fig. 1B). The loss of water and one guest molecule at ≤ 75 °C is followed by the loss of the second at ca. 90 °C.

Hydrophobic Contribution. Hydrogen bonding may be effective in noncompeting apolar organic media or in (liquid) crystals, but is almost useless for the binding of common organic molecules in water.[4] With this in mind, it is surprising that such simple molecules as ethanol (C_{th} = 0.5 M) and ethyl acetate (C_{th} = 0.1 M) are hydrogen-bonded to the present solid host in preference to water as a medium (ca. 55 M) (1 M = 1 mol dm^{-3}). A survey of selectivity explains why. The affinities in terms of the (first) threshold concentrations increase with respect to the alkyl moieties in the order of R = Me (C_{th} = 4 M) < Et (0.5 M) < ^{i}Pr (0.3 M) < Pr (0.2 M) for the alcohol guests ROH (Fig. 1A) and R = Et (0.1 M) < Pr (0.015 M) < Bu (0.01 M) for the acetate guests CH_3CO_2R (Fig. 1B). Cyclohexanol (not shown in the Figure for clarity) also has a much higher affinity (C_{th} = 0.005 M) than *cis*-(0.06 M) or *trans*-1,2-cyclohexanediols (0.04 M) (Fig. 1C). The desorption temperatures for included ROH's, as another measure of their affinities, increase with decreasing C_{th}'s in the order of R = Me (103 °C) < Et (122 °C) < Pr (130 °C). There is evidently a hydrophobic contribution. The present guest-binding under aqueous conditions is actually driven by a cooperation of polar (hydrogen bonding) and apolar (hydrophobic) binding forces, occurring in the cyclophane-like guest-binding cavities roofed and floored by the anthracene moieties which are linked together by polar pillars.[7,8] It is interesting to note that the host–guest stoichiometry is governed by hydrogen-bonding, while the affinity is controlled by hydrophobicity.

The phase transition represents an extreme case of coherent bulk phenomena having an infinite positive cooperativity. Different guests form different adducts having different crystal structures and hence powder diffractions. A question relevant to the selectivity under competitive conditions is whether the phases with different guests are independent from each other. The threshold concentrations (C_{th}) for ethyl acetate (0.1 M) and butyl acetate (0.01 M) differ greatly. Competition between these at an equimolar concentration (0.05 M) in between (arrow a in Fig. 1B) results in almost exclusive incorporation of the higher-affinity butyl guest; (CH_3CO_2Bu)/**1** = 1.96 and (CH_3CO_2Et)/**1** = 0.03; (CH_3CO_2Bu)/(CH_3CO_2Et) ≅ 60. In a similar manner, a selectivity factor of EtOH/MeOH ≅ 40 is obtained in the competition of ethanol (C_{th} = 0.5 M) and methanol (4 M) at 1.0 M (arrow b in Fig. 1A). Thus, these is little mismatch incorporation of a lower-affinity guest in the networked adduct phase for the higher-affinity guest. This type of solid-state complexation accompanied by a phase transition may find an interesting application to selective extraction of high-affinity guests even in low quantities.

Catalysis. Host **1** catalyzes the Diels–Alder reaction of acrylaldehyde ($H_2C=CHCHO$) and 1,3-cyclohexadiene (Eq. 3).[12] This is also the case under the present aqueous conditions. In Fig. 4 are shown the time courses of the reaction in the absence (●) and presence (○; 3—17 mol % with respect to the limiting substrate acrylaldehyde) of host **1** as insoluble powders in a water/cyclohexadiene two-phase mixture which is 0.25 M in acrylaldehyde (acrylaldehyde/diene = 1/20). The smooth progression curves and the increasing rates with increasing amounts of **1** leave no doubt that the latter is acting as a catalyst. Furthermore, the catalysis is exerted by the solid state of **1**, since the supernatant liquid separated from the solid material by centrifugation in the course of reaction shows no catalysis at all. Figure 4 also includes the previous data (squares with dashed lines) to show that the catalytic efficiency under the present aqueous conditions is comparable to that under the anhydrous conditions (time courses d vs. d′).



(3)

Control experiments reveal the following elementary processes, where benzene (C_6H_6) is used as a nonreactive analog of cyclohexadiene (C_6H_8). (1) When dipped in an aqueous solution of acrylaldehyde (1 M), host **1** adsorbs ca. 1 mol of the aldehyde, together with several mols of water as above, with a shift of $\Delta\nu_{C=O}$ = 17 cm^{-1}.[13] (2) From a water/benzene two-phase mixture 1.3 M in acrylaldehyde are coextracted acrylaldehyde and benzene to give a ternary adduct **1**·(0.4acrylaldehyde)·($2C_6H_6$). (3) When treated with a water/cyclohexadiene two-phase mixture, the ternary adduct undergoes an intra-adduct Diels–Alder reaction to give a product adduct **1**·(0.4product)·($2C_6H_8$), where the product is the Diels–Alder product in Eq. 3 (*endo*/*exo* = 95/5). (4) Upon treatment with a water/benzene two-phase mixture containing acrylaldehyde, the product adduct is converted to the reactant adduct **1**·(0.4acrylaldehyde)·($2C_6H_6$) with liberation of the product into the bulk organic phase. These observations suggest that the catalytic mechanism proposed for the anhydrous reaction[12] also applies to the present aqueous reaction. The mechanism would involve coadsorption of dienophile and diene, an intra-adduct reaction which is facilitated by the activation of the dienophile via hydrogen-bonding to the host, and product/reactant exchange to drive a catalytic cycle or turnover.

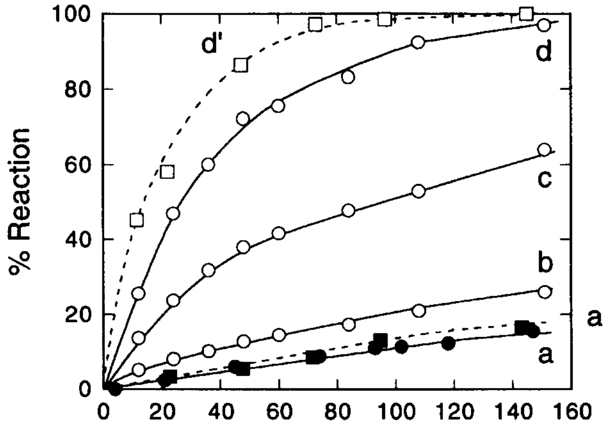


Fig. 4. Time courses of the acrylaldehyde–1, 3-cyclohexadiene Diels–Alder reaction at 25 °C in the absence (a) and presence of insoluble apohost **1** (b, 3 mol%; c, 8 mol%; d, 17 mol% in reference to the limiting reactant acrylaldehyde) as a catalyst under aqueous conditions of water/diene/acrylaldehyde = 111/20/1 (mol/mol/mol). Runs a′ and d′ with dashed lines refer to the reaction under anhydrous condition in the absence (a′) and presence (d′) of 17 mol% apohost **1**, respectively.

Conclusions

This is probably the first systematic study on lattice inclusion complexation under aqueous conditions; a major question is if the hydrogen bonds survive in water, which is believed to be a hydrogen-bond breaker. A short conclusion is that hydrogen bonding in collaboration with hydrophobic effects is a remarkable interaction in water. Host **1** is hydrophobic and water-insoluble; the multiple hydrogen-bonded network therein is maintained in the aqueous environment. Guest molecules are bound to host **1** in preference to water via hydrogen bonding because hydrophobic forces as a collaborator come into play. The water molecules are neither hydrogen-bond breakers nor good competitors; they more likely stabilize the host–host and host–guest hydrogen-bonds via hydration. In addition, the host–guest hydrogen-bonding provides a source of acid catalysis. These characteristic features seem to be also essential for the maintenance of biological structures and enzymatic catalysis.

Experimental

Apohost **1** was prepared by removing the guest molecules from single crystalline adduct **1**·($2CH_3CO_2Et$)·($2C_6H_6$) at 180 °C in vacuo.[9] Guest binding under aqueous conditions was performed by dipping finely ground apohost **1** (ca. 5 mg) in a solution of a guest in water (50 mL) at 25 °C. The mixture was shaken for 2 days to allow equilibrium to be reached. The host material recovered was taken on a filter paper to get rid of excess guest and water adsorbed on the surface. It was then subjected to ^{1}H NMR analysis as a DMSO-d_6 solution, as well as to thermal analysis as such for the amounts of the guest and water incorporated.

Thermal analysis was performed by using a Seiko Denshi TG/DTA 220U thermal analysis system. Each sample (ca. 5 mg) was loaded on an Al open-sample pan under the stream of nitrogen (300 mL min^{-1}). TG thermograms were recorded at a heating rate of 20 °C min^{-1}. X-ray powder diffractions were obtained with a Rigaku RINT2000V L-type diffractometer with Cu $K\alpha$ at a scan rate of 4 deg min^{-1}. IR spectra were obtained for KBr disks (host–guest adducts) or neat liquids (free guests) with a JASCO FT/IR-350 spectrophotometer.

Catalytic Diels–Alder reactions of acrylaldehyde and 1,3-cyclohexadiene were carried out in the following manner. Into a two-phase mixture of water (3 mL) and cyclohexadiene (2.9 mL, 30 mmol) containing finely ground apohost **1** (100 mg, 0.25 mmol) was injected acrylaldehyde (102 µL, 1.5 mmol) under vigorous stirring at 25 °C. The progress of the reaction was monitored by ^{1}H NMR for aliquots taken from the organic layer. The extent of the reaction was evaluated by referring to cyclohexadiene in the equation: (percent reaction) = [product]/([product]+[acrylaldehyde]) × 100 = [product]/{([product]+[cyclohexadiene])/20} × 100.

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