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Catalysis by Organic Solids. Stereoselective Intramolecular Ene Reaction of Citronellal Promoted by Microporous Molecular Crystals Having an Extensive Hydrogen-Bonded Network

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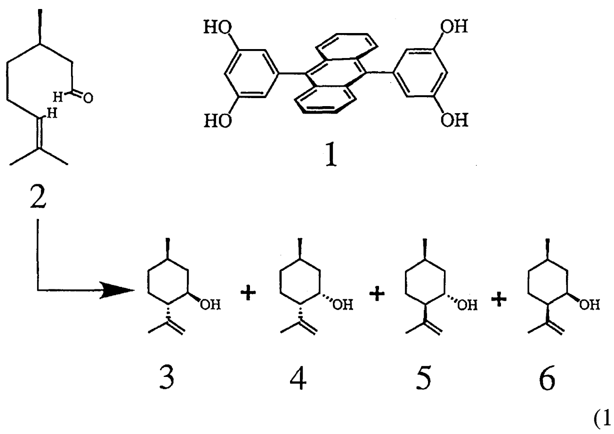
5,5′-(9,10-Anthracenediyl)diresorcinol (**1**) (host) and a terpenoid aldehyde citronellal (**2**, guest) form a 1 : 2 adduct **1**·2(**2**), in which the guest molecules hydrogen-bonded to the host are closely packed in an extended conformation in the microporous crystal structure of the host. When heated in vacuo, the 1 : 2 adduct loses ca. 1 molecule of the guest to give a 1 : 1 adduct **1**·**2**. The guest **2** included in both adducts undergoes a facilitated intra-adduct ene reaction to afford isopulegol as the main product. Such a reaction in the 1 : 1 adduct occurs smoothly and in a highly stereoselective (ca. 98%) manner. The reaction in the 1 : 2 adduct is less stereoselective and exhibits a sigmoidal progression curve having a significant "induction period". The present ene reaction of citronellal (**2**) as either a neat liquid or in a cyclohexane solution is catalyzed by host **1** in the solid state. The allosteric cooperativity observed is discussed in view of a big conformational change associated with the present cyclization reaction.

Solid-state phenomena constitute an important part of organic chemistry. There are numerous examples of lattice inclusion compounds(1) as well as excellent solid-state reactions.(2) So far, however, organic solids have seldom been used as catalysts.(3) This is in marked contrast to an extensive use of various types of inorganic solid catalysts including a class of microporous materials such as zeolites.(4) Microporous organic materials(5) are potential candidates, since network topologies,(6) functional groups involved, and shape and size of the cavities(7) are designable in principle. Their catalytic activities, however, still remain to be explored.

5, 5′- (9, 10- Anthracenediyl)diresorcinol (**1**) (host) (Scheme 1) forms hydrogen-bonded 2D nets.(8) In the resulting large cavities are included a variety of guest molecules.(9) Quite recently, we showed that host **1** simultaneously binds dienophile ($H_2C=CHCOR$; R=H or alkoxy) and diene (1,3-cyclohexadiene) and promotes intermolecular Diels–Alder reactions thereof in either a stoichiometric or a catalytic manner, thereby providing a novel example of catalysis by microporous organic solids.(10) The present work is concerned with an intramolecular ene reaction of citronellal (**2**) (Eq. 1 in Scheme 1). Unimolecular reactions are free from the proximity effects which often play a governing role in preorganized bimolecular processes; the effects of host–guest hydrogen-bonding would become more visible. We report here that host **1** in the solid state indeed catalyzes the present ene reaction in an allosteric manner.



(1)

Scheme 1.

Results and Discussion

Crystal Structures. Recrystallization of host **1** from citronellal (**2**) affords a 1 : 2 adduct **1**·2(**2**). The crystal structure(11) of this adduct shares the characteristic aspects with those of adducts **1**·2(guest) (guest=achiral ester or ketone) so far investigated.(8,9) (1) The host forms a hydrogen-bonded (O–H···O–H, l_{O-O}=2.80 Å) network to give a 2D sheet composed of anthracene columns and large cavities, each of which incorporates two guest molecules via host–guest hydrogen-bonding (Fig. 1a, where and hereafter different moieties are shown in different colors, i.e., anthracene rings in red, resorcinol rings in black, and guest

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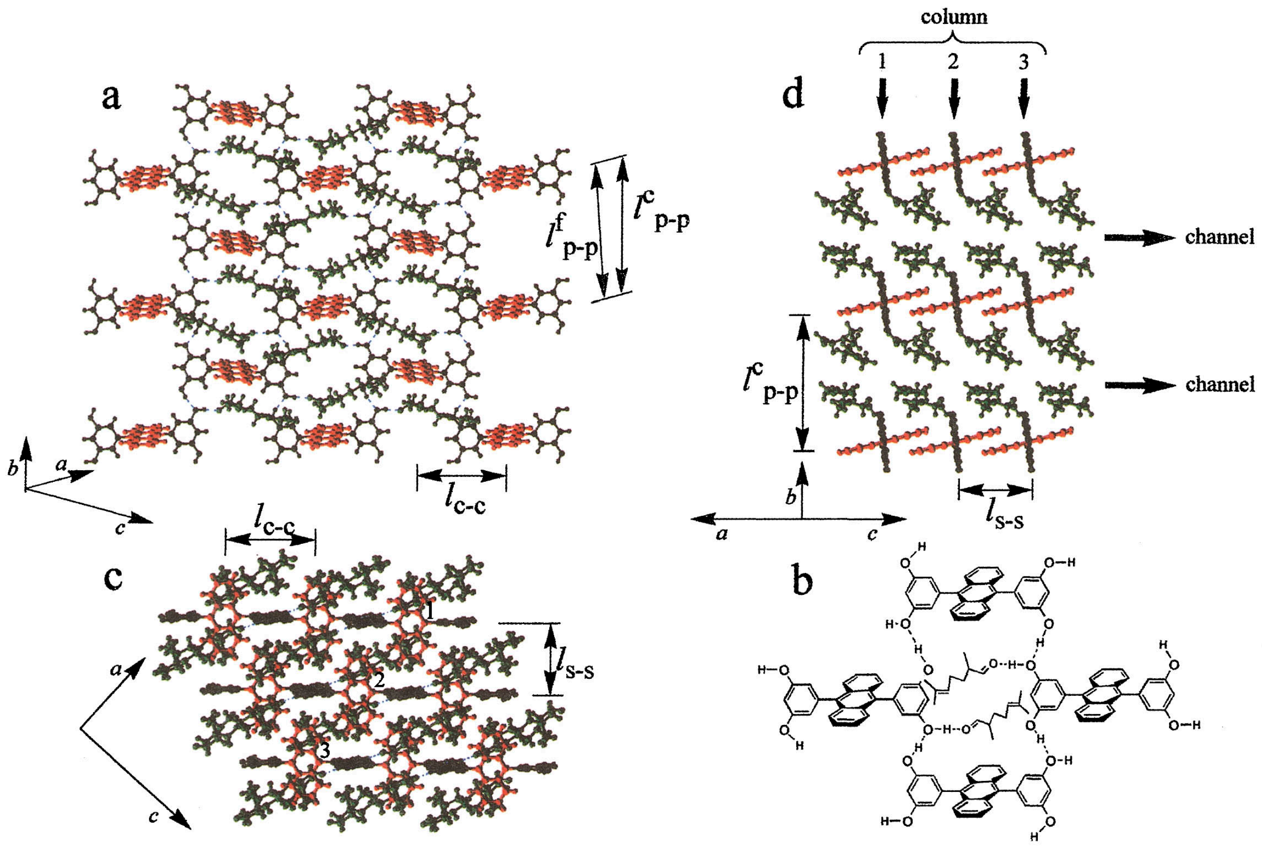

Fig. 1. Structure of the crystal of adduct **1**·2(**2**): front view of a molecular sheet (a), schematic representation of the guest-binding mode in a cavity (b), top view of three neighboring sheets (c), and side view of three adjacent columns (designated as 1, 2, and 3 in (c)) in neighboring sheets (d). The anthracene rings, resorcinol rings, and guest molecules are shown in red, black, and green, respectively, and hydrogen bonds are represented in light blue.

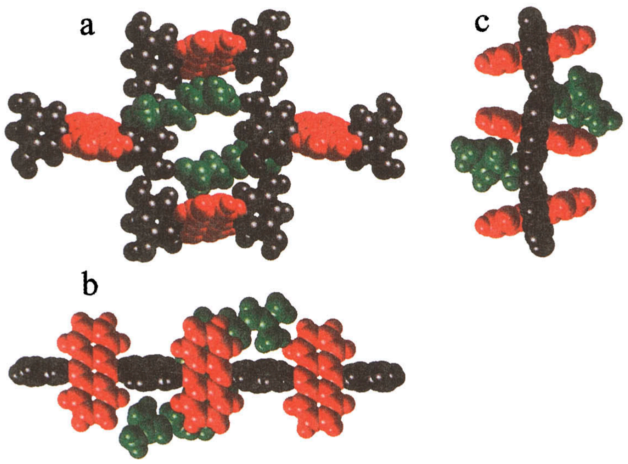

Fig. 2. Space-filling models of a cavity with two guest molecules bound in the crystal of adduct **1**·2(**2**): front view (a), top view (b), and side view (c). The colors have the same meanings as in Fig. 1.

molecules in green and hydrogen bonds are represented in light blue).[12] The guest-binding mode in a cavity is explained in Fig. 1b. (2) The sheets are layered in a staggered manner, as shown in a top view (Fig. 1c) of three neighboring sheets. (3) The cavities in different sheets are linked to form intersheet channels, as shown in a side view (Fig. 1d) of three neighboring columns designated as 1, 2, and 3 in Fig. 1c. The inter-ring, intercolumn, and intersheet distances are l^{f}_{a-a}=13.89 Å and l^{c}_{a-a}=13.95 Å, l_{c-c}=9.80 Å, and l_{s-s}=7.49 Å, respectively.

The two guest molecules in each cavity are oppositely directed in an extended conformation with their C=O groups hydrogen-bonded to the host (O–H···O–H···O=C, l_{O-OC}= 2.70 Å) in one cavity and the alkenyl moieties extending into the adjacent cavities in neighboring sheets (Fig. 1c and 1d). Figure 2 shows the space-filling models of the front (a), top (b), and side (c) views of a cavity with two guest molecules bound.

Intra-adduct Reactions. The ene reaction of citronellal (**2**) (Eq. 1 in Scheme 1) is very slow in the absence of any Lewis acid promoter. The estimated half-life of the reaction at 70 °C is $\tau \cong 7000$ h, corresponding to the first-order rate constant of $k_1 \cong 1\times10^{-4}$ h^{-1} (cf. Figs. 4 and 5). Single crystals of adduct **1**·2(**2**) at this temperature are initially stable but later undergo an ene reaction of included guest **2**. The intra-adduct reaction is accompanied by loss of single crystallinity and affords cyclized products as a mixture of stereoisomers, i.e., isopulegol (**3**), *neo*-isopulegol (**4**), *iso*-isopulegol (**5**), and *neoiso*-isopulegol (**6**) in a ratio of 87 : 8 : 7 : 0. The time-course of the reaction is shown in Fig. 3 (solid line), where the products/**1** ratios are the molar ratios of total products formed to host **1** used, i.e., (**3**+**4**+**5**+**6**)/**1**. The sigmoidal progres-

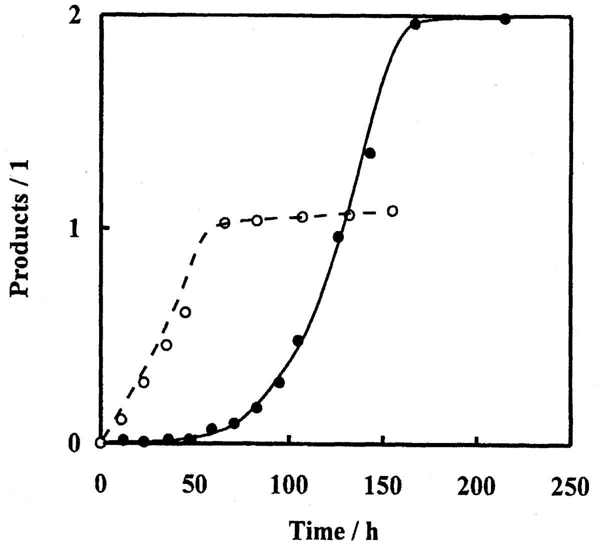

Fig. 3. Time-courses of the ene reactions of cictronellal (**2**) in isolated adducts **1**·2(**2**) (solid line) and **1**·**2** (dashed line) at 70 °C: products/**1** are molar ratios of total products formed (**3**+**4**+**5**+**6**) to host **1** used.

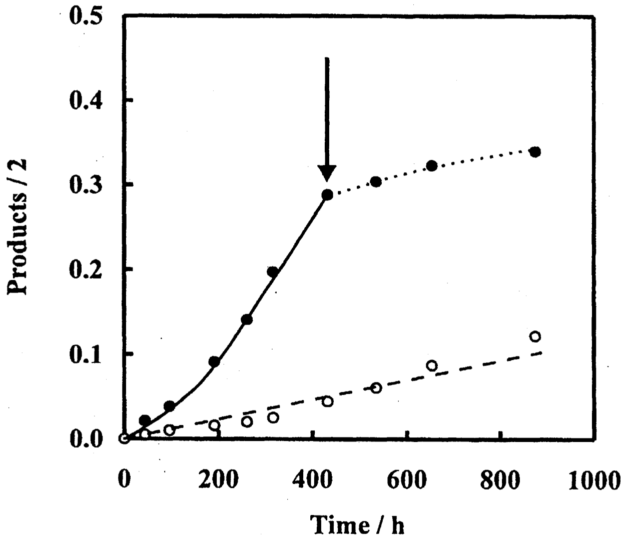

Fig. 4. Time-courses of the ene reactions of citronellal (**2**) at 70 °C in the absence (dashed line) and presence (solid line) of host **1** (**1**/**2**=0.1 mol/mol) as an insoluble catalyst: products/**2** are molar ratios of total products formed (**3**+**4**+**5**+**6**) to substrate **2** used. The arrow indicates that the insoluble host **1** was filtered at this point; the time-course thereafter for the supernatant liquid phase is shown by the dotted line.

sion curve is completely reproducible for repeated runs and is indicative of an allosteric acceleration of the reaction.

When treated in vacuo at room temperature, adduct **1**·2(**2**) loses ca. 1 molecule of the guest. The resulting 1 : 1 adduct **1**·**2** is no longer single-crystalline but most likely has a structure similar to that of the 1 : 2 adduct. This is because the powder X-ray diffractions of adduct **1**·**2** are very similar to those of adduct **1**·2(**2**). Citronellal (**2**) in the *half-filled* 1 : 1 adduct reacts smoothly at 70 °C without showing any notable *induction period* (Fig. 3, dashed line). The half-life of this

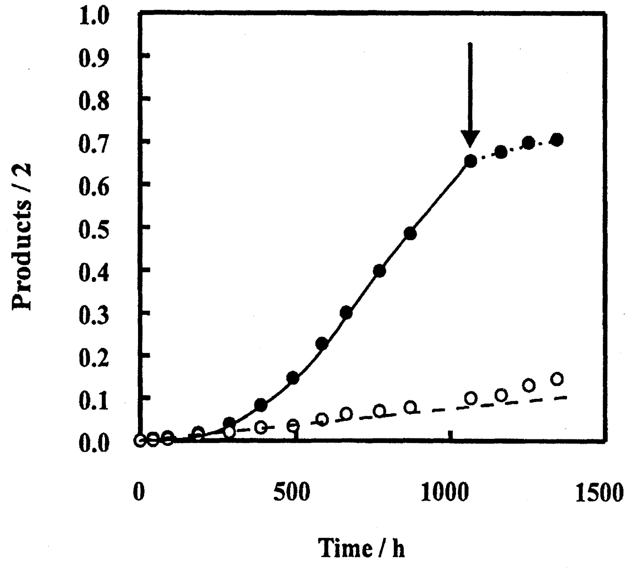

Fig. 5. Time-courses of the ene reactions of citronellal (**2**) in cyclohexane (**2** : cyclohexane=1 : 20) at 70 °C in the absence (dashed line) and presence (solid line) of host **1** (**1**/**2**=0.1 mol/mol) as an insoluble catalyst: products/**2** are molar ratios of total products formed (**3**+**4**+**5**+**6**) to substrate **2** used. The arrow indicates that insoluble host **1** was filtered at this point; the time-course thereafter for the supernatant liquid phase is shown by the dotted line.

reaction is $\tau \cong 40$ h ($k_1 \cong 1.7\times10^{-2}$ h^{-1}). Thus, the reaction in adduct **1**·**2** is ca. 200-times faster than the spontaneous reaction ($\tau \cong 7000$ h and $k_1 \cong 1\times10^{-4}$ h^{-1} as noted above). The acceleration of the present *unimolecular* reaction in the adducts can be primarily ascribed to host–guest hydrogen-bonding (Fig. 1). There is no doubt that substrate **2** in adduct **1**·**2** is hydrogen-bonded to the host, as evidenced by a large (20 cm^{-1}) shift to lower wavenumber in $\nu_{\mathrm{C=O}}$ upon adduct formation in a similar manner as in single crystalline adduct **1**·2(**2**) ($\Delta\nu_{\mathrm{C=O}}$=24 cm^{-1}). Ene reactions, like Diels–Alder reactions, are well known to be promoted by acids, Lewis acids in particular.

Stereoselectivity is another important aspect of the reaction in adduct **1**·**2**. It gives a remarkable preference for isopulegol (**3**). The observed selectivity of **3**:**4**:**5**:**6**= 98 : 2 : 0 : 0 may be compared with that for the reaction in the 1 : 2 adduct **1**·2(**2**) (87 : 8 : 7 : 0), for the uncatalyzed reaction (61 : 18 : 13 : 8 at 70 °C or 60 : 20 : 15 : 5 at 180 °C[13]), or for the Zn(II)-promoted reaction at 5—10 °C (**3** : (**4**+**5**+**6**)= 96 : 4).[14]

The sigmoidal progression curve for the 1 : 2 adduct (Fig. 3, solid line) suggests that (1) the reactivity of guest **2** in the initial single crystals is kept low and (2) it is rendered much more reactive as the reaction proceeds. Item 1 is understandable on the basis of the crystal structure (Figs. 1 and 2). Guest **2** is closely packed in an *extended* conformation. There must be little room for it to undergo a conformational change into the folded form required for the cyclization. On the same line is explainable why the potentially porous half-packed 1 : 1 adduct **1**·**2** allows a smooth intra-adduct reaction

(Fig. 3, dashed line). If these interpretations are correct, item 2 above further suggests that the reaction sites with substrate **2** become less closely packed in an allosteric manner as the reaction occurs somewhere else in the crystal. The mechanism of this cooperativity is totally unknown at present. This may simply be due to microscopic cracking, which occurs in the adduct upon loss of single crystallinity. Whatever the mechanistic details may be, such an allosteric control of the reactivity is in principle not unexpected. This is because the cavities in a network material are more or less connected with each other and hence a conformational change occurring in one cavity may be transmitted to the neighboring cavities.$^{15)}$

Catalytic Reactions. When dipped in citronellal (**2**), guest-free apohost **1** readily binds two molecules of the former to give the reactant adduct **1**·2(**2**). When, on the other hand, the product adduct **1**·2(**3**) is dipped in **2**, a facile guest-exchange takes place to regenerate the reactant adduct **1**·2(**2**). These elementary processes, coupled with the intra-adduct reactions shown above, suggest that the host should catalyze the present ene reaction of citronellal (**2**) to isopulegol (**3**). In Fig. 4 are shown the time-courses of the reactions using **2** as a neat liquid at 70 °C in the absence (dashed line) and presence (solid line) of a catalytic amount of host **1** (**1**/**2**=0.1 mol/mol) which remains mostly insoluble. Figure 5 shows a similar set of time-courses for reactions using a cyclohexane solution of **2**, in which the host is completely insoluble.

Clearly, the reactions in the presence of the host are faster than those in its absence. In addition, the facilitated reactions go beyond the amount of host **1** used. Furthermore, when the insoluble host is removed by filtration at ca. 30% (Fig. 4) or ca. 70% (Fig. 5) conversion, as marked by an arrow in the Figures, the resulting supernatant solution exhibits almost the same rate thereafter (dotted line) as the uncatalyzed reference run. These results indicate that host **1** *in the solid state* in fact catalyzes the reaction. The catalytic reactions show no essential dependence on whether the host or its adduct is pulverized or not. The effect of pulverization on the catalytic activities of the host is only by a factor of ca. 1.3, as in the case of Diels–Alder reactions.$^{10)}$ Thus, the size effect is quite modest at best. This strongly suggests that the present catalysis is not a simple surface phenomenon. In other words, product **3** and its stereoisomers formed inside the solid host are replaceable by reactant **2** at least at an early stage of the reaction, although intrinsic affinities are **3**≫**2**.$^{16)}$ Otherwise, the catalytic reactions are similar to the stoichiometric single-turnover reaction of the fully-packed adduct **1**·2(**2**). Thus, the timecourses are more or less sigmoidal and the stereoselectivities are not high; **3** : **4** : **5** : **6**=64 : 24 : 12 : 0 or 69 : 18 : 13 : 0 for the run with or without cyclohexane as a diluter, respectively.$^{17)}$

Concluding Remarks

The present work may be summarized as follows. (1) The intramolecular ene reaction of citronellal is catalyzed by host **1** in the solid state, where the catalysis is primarily ascribed to host-guest hydrogen-bonding. (2) The *tense* host–guest adduct initially formed is not responsible for the catalysis. As the reaction proceeds, the crystal structure changes so as to be more suited for the reaction. We have noted a similar effect before for the intracavity Diels–Alder reactions.$^{10)}$ Such a cooperative or allosteric effect may be a potential general aspect of organic network materials. (3) The stereoselectivity of the intracavity reaction may be reflected on the remarkable preference (up to 98%) for isopulegol in the reaction of half-packed adduct **1**·**2**. Unfortunately, however, this stereoselective reaction can not be made catalytic since half-packing of the cavities is not readily achieved under the catalytic conditions.$^{17)}$

Experimental

General Procedures. Guest-free apohost **1** was prepared as reported.$^{1)}$ Single crystals (approximate size, $2\times1\times1$ mm^3) of adduct **1**·2(**2**) were obtained by allowing a hot solution of host **1** in guest **2** to cool gradually to room temperature. Adduct **1**·2(**2**) was treated in vacuo for 10 h at room temperature to give half-filled adduct **1**·**2**. Intra-adduct reactions were monitored in the following way. Several pieces of adduct **1**·2(**2**) or **1**·**2** contained in a sealed ampule under nitrogen were heated at 70 °C. The ampule was opened at an appropriate time interval. The content was dissolved in DMSO-d_6 and analyzed by ^{1}H NMR for the composition of host **1**, reactant **2**, and products **3**—**6**; characteristic olefinic-proton resonances were δ=4.67 (**3**), 4.70 (**4**), 4.62 (**5**), and 4.57 (**6**). Catalytic reactions were carried out at 70 °C in the following way. In a vessel was sealed under nitrogen a mixture of cytronellal (**2**) and host **1** (either as nonpulverized pieces or pulverized powders) with or without cyclohexane in a molar ratio of **1** : **2** : cyclohexane=0.1 : 1 : 0 or 0.1 : 1 : 20. The reactions were monitored by taking an aliquot of the liquid phase at an appropriate time interval and analyzing it by ^{1}H NMR. It was found that host **1** is only very slightly soluble in neat citronellal at 70 °C. The solubility of the host in the cyclohexane solution of **2** was unmeasureably small.

X-Ray Crystal Structure Determinations.$^{18)}$ Diffraction data were obtained at 20 °C on a Rigaku AFC7R four-circle automated diffractometer with graphite-monochromated Cu $K\alpha$ radiation. A selected crystal ($0.2\times0.2\times0.2$ mm^3) was mounted on a glass fiber. The linear absorption correction was applied in each case. The intensity data were collected using the ω–2θ scan technique and were corrected for both Lorentz and polarization effects.

The structures were solved by the direct methods and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. Some hydrogen atoms were located from difference Fourier maps and the rest were introduced at calculated positions; their parameters were refined isotropically. The weighting scheme was $w^{-1}=\sigma^2(F_o)$. Atomic scattering factors and anomalous dispersion terms were taken from International Tables for X-ray Crystallography. All calculations were performed by using the teXsan crystallographic software package of Molecular Structure Corporation. The crystal structures were visualized by using the Serius 2 set of computer programs of Molecular Simulations Incorporated.

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11) $C_{46}H_{54}O_6$, $M=702.93$, monoclinic, $P2_1$, $a=9.166(2)$, $b=13.9499(9)$, $c=16.164(1)$ Å, $\beta=97.55(1)^\circ$, $V=2048.9(5)$ Å^3, $Z=2$, $d_{\mathrm{calcd}}=1.139\ \mathrm{g\,cm^{-3}}$, Cu$K\alpha$ ($\lambda=1.54178$ Å), 6834 reflections measured, 3193 unique reflections, 1687 reflections used ($I>3\sigma(I)$), 488 parameters to $R=0.069$ and $R_w=0.099$, GOF=1.48.

12) The anthracene and resorcinol rings in compound **1** are roughly orthogonal with a dihedral angle of 85°. The two resorcinol rings directly linked via a hydrogen bond are nearly coplanar with a tilt angle of 5°.

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15) Guest binding to host **1** in the solid state shows remarkably sigmoidal binding isotherms (unpublished results).

16) Competitive cocrystallization of host **1** from an equimolar mixture of cyctronellal (**2**) and isopulegol (**3**) results in an almost exclusive formation of adduct **1**·2(**3**).

17) We thought that the formation of fully-packed adduct **1**·2(**2**) could be suppressed when a dilute solution of guest **2** in cyclohexane as an inert solvent was used. Under these conditions, the guest/host ratio could in fact be kept low (**2**/**1** < 1). Actually, however, a lot of cyclohexane molecules were also coincluded to fill the cavities.

18) Full crystal data are deposited as Document No. 70044 at the Office of the Editor of Bull. Chem. Soc. Jpn.