The Kinetic Effects of Water and of Cyclodextrins on Diels–Alder Reactions. Host–Guest Chemistry. Part 18[1]

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The rates of 19 different dienophiles with mostly cyclopentadiene have been measured in a range of solvents. Water, by comparison with methanol, is found to accelerate the cycloadditions by factors ranging from 15–7 680. While there is no simple correlation of the rate enhancement with the hydrophobicity of the substrates, a correlation can be made in the case of acrylates, which show a decreasing rate effect due to water, and with β-cyclodextrin, which is found to lead to inhibition in these and several other cases. Computer analysis of enzyme-like saturation kinetics—observed with some fumarates in the presence of β-cyclodextrin—indicates apparent binding constants for the ternary complex of *ca.* 10^2 dm^3 mol^{-1} and catalytic k_{cat}/k_o ratios of up to 100. Heptakis-6-piperidino-β-cyclodextrin in the form of its ammonium salt leads to rate retardation in most of the cases investigated; sodium dodecylsulphate also decreases the constants. α-Cyclodextrin generates small effects, rate retardation, or in one case complete inhibition.

Diels–Alder cycloadditions between dienes and alkenes have the reputation of being little influenced by their microenvironment,[2] apart from relatively small solvent polarity effects.[3] Although aqueous solutions have been used for a long time[4] it is only recently that Breslow *et al.* have shown that water can provoke dramatic rate increases in these reactions.[5] It has since been shown that rates, yields, and/or product selectivities can be changed significantly in aqueous systems.[6–11] Water is believed to promote the association between the hydrophobic diene and dienophile in much the same way as that which leads to the (moderate) accelerations of Diels–Alder reactions by β-cyclodextrin which have been reported by Breslow *et al.*[5a] In a preliminary communication[12] more significant rate increases and, for the first time, enzyme-analogue saturation kinetics have been demonstrated for the reaction between cyclopentadiene and diethylfumarate with β-cyclodextrin as catalyst, whereas an azoniacyclophane of similar cavity diameter produced only moderate kinetic effects. We could also correlate the rates with the hydrophobicity of a range of different solvents.[12] Similar influences of cyclodextrin and of water on the product diastereoselectivity of the reaction were subsequently found,[13] pointing again to hydrophobic association between the substrate molecules as a common origin of these effects.

Extending the kinetic study to a large number of substrates the present paper aims to study the comparison and predictability of water and macrocyclic cavity effects on Diels–Alder reaction rates. It should also help to distinguish the water effects from the influence of micellization,[6b,11] of surfactants,[10] and of microemulsions.[8] Finally, an effort is made to obtain equilibrium constants and turnover numbers for the ternary complex involved in the cyclodextrin catalysis (or, as will be seen, inhibition) which must be seen in the context of artificial enzyme analogues.[14]

Solvophobicity Effects of Solvents and Substrates.—Substrates were chosen so as to encompass compounds of similar basic structure to ensure comparable reaction mechanisms, but of widely differing hydrophobicity (Scheme 1). This was largely achieved by using derivatives of fumaric or maleic acid as well as of the much more lipophilic acrylic acid with alkyl ester groups of increasing size. In addition some other more hydrophobic dienes as well as styrene were investigated. At the low concentrations chosen for the kinetic measurements there was no indication of turbidity or insoluble material even with solutions containing much (or even neat) water; in addition it was confirmed that under the conditions applied the Beer–Lambert law was obeyed; with most of the dienes the limit for this was found to be *ca.* 3×10^{-4} mol dm^{-3} in water containing $< 0.5\%$ methanol.

All reactions measured (Table 1) followed clean second-order kinetics with linear correlation coefficients of $r > 0.998$; this again demonstrates the absence of insoluble material which leads to deviations from the applied linearization. The strong rate increase with increasing solvophobicity can be quantified by equation (1), if we characterize the hydrophobicity of the applied solvents with the 'Sp'[15] values which originate from free energies of transfer ΔG_t for noble gases, hydrocarbons *etc.* from the gas state to a given solvent. We have shown that such ΔG_t or Sp values can describe the variation of host–guest equilibria[16] as well as of rate constants[12] and of product ratios[13] for a large range of solvents.

$$\log k = a \cdot \mathrm{Sp} + \log k_o \qquad (1)$$

The additional effects of medium polarity‡ which of course also change drastically within the solvent systems used could be taken care of by inclusion of an E_T[17] term as a generally accepted measure of solvent polarity:

$$\log k = a \cdot \mathrm{Sp} + mE_T + \log k_o \qquad (2)$$

Multiple least-square correlations, however, for the rates of four different dienophiles with cyclopentadiene in a range of solvents showed no improved descriptions of the observed rate variations as compared with the single-term equation (1), and in fact they demonstrate the absence of significant polarity contributions within this series (Table 2). Similar observations have been made already for the medium dependence of the *exo*/*endo* product ratios.[13] In view of these findings the use of only two rates in two solvents of sufficiently large

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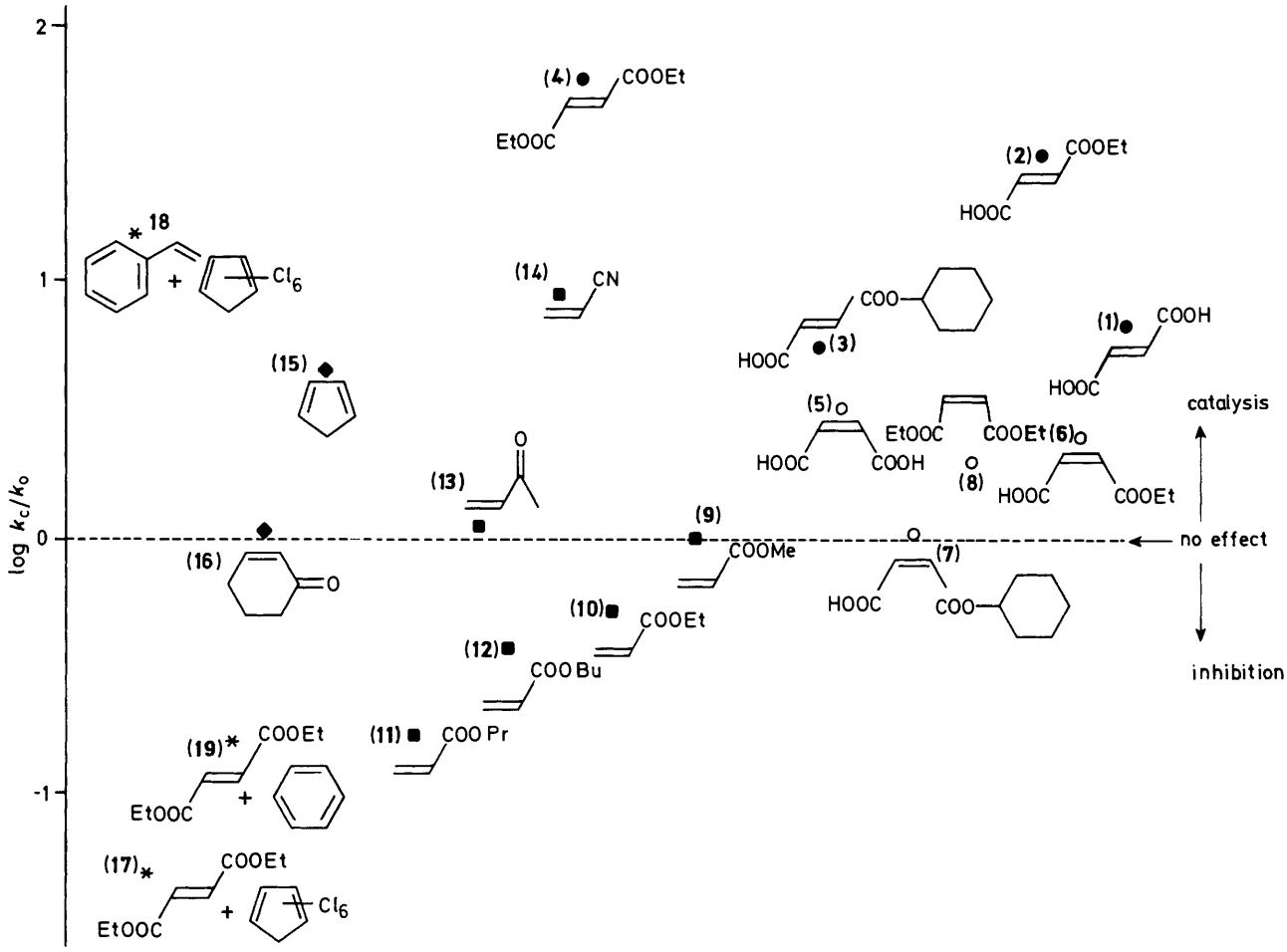
‡ The *exo*/*endo* product ratio (although small) changes with medium polarity variations for Diels–Alder reactions: ref. 3(*a*).



Scheme 1. Catalysis and inhibition effects of β-cyclodextrin on Diels–Alder reactions. Unless noted otherwise all dienophile reactions are with cyclopentadiene as the diene. The rate constants k_c and k_o are in 0.009 mol dm^{-3} β-cyclodextrin and pure water, respectively.

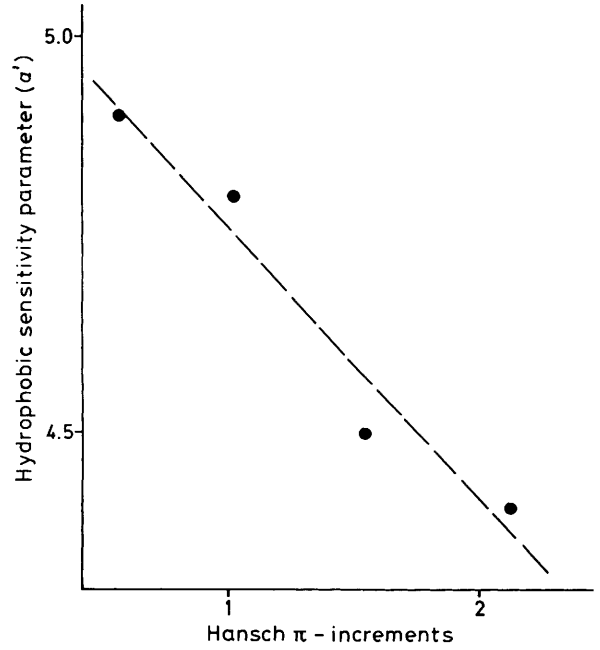


Figure 1. Sensitivity parameter with solvophobicity changes (a') *vs.* Hansch hydrophobicity increments π for acrylic esters H_2C=CHCOR with R = Me, Et, Pr, and Bu.

solvophobicity difference, such as water and neat methanol, in order to define a sensitivity parameter a' of a given reaction against Sp changes seems justified. In fact, a' differs from the slope a in equation (1) only by $< 10\%$ in the reactions in which a larger number of solvents was studied (Table 1).

The sensitivity parameters a' in Table 1 demonstrate that the acceleration effects owing to solvent hydrophobicity vary by up to three powers of magnitude. Thus, the rate constant increases from an unpolar hydrocarbon-like solvent (Sp = 0.00) and water (Sp = 1.0), is only $10^{1.6}$ (*ca.* 40) for the reaction of cyclopentadiene and fumaric acid, but $10^{4.7}$ (*ca.* 50 000) for the reaction of perchlorocyclopentadiene and diethyl fumarate. The corresponding sensitivity parameter a' could in principle be a function of the hydrophobicities of the different substrates used; these can be quantified by hydrophobic Hansch parameters P which are based on the corresponding partition coefficients between octan-1-ol and water.[18] Inspection of the effect of different substrates (Table 1) already indicates that the replacement of an ethyl by a cyclohexyl group in different esters does not necessarily lead to higher a' values. In fact, the only rough correlation which exists for the four acrylic esters investigated (Figure 1) shows a declining sensitivity a' value with increasing substrate hydrophobicity (since P values for these esters were not available we have used in Figure 1 hydrophobic increments π[19] instead for the varying alkyl group in the esters). These results make it clear that hydrophobic association can be in fact counter-productive if the water-driven combination leads to association at the 'wrong' location in the substrate or to dienophile–dienophile association.

Table 1. Rate constants for Diels–Alder reactions.[a]

Compound	Diene[b]		Dienophile[c] R	Dienophile[c] R′	Dioxane 82.2%[d]	MeOH 100%	MeOH 50%	H_2O 100%	a'[e]	β-CYD[f] 9×10^{-3} mol dm^{-3}	Pip-β-CYD[g] 10^{-3} mol dm^{-3}
(1)	Cp	*E*	COOH	COOH	1.05	1.24	11.7	24.1	1.6	172	—
(2)	Cp	*E*	COOH	COOEt	1.28	1.51	18.4	47.2	1.9	1 490[l]	—
(3)	Cp	*E*	COOH	$COOC_6H_{11}$	—	1.03	—	31.8	1.9	177	—
(4)	Cp	*E*	COOEt	COOEt	1.83	1.37	—	148	2.5	9 270	94.6[m]
(5)	Cp	*Z*	COOH	COOH	1.20	1.00	3.40	20.8	1.6	68.3	—
(6)	Cp	*Z*	COOH	COOEt	0.16	0.17	—	8.0	2.1	20.9[n]	—
(7)	Cp	*Z*	COOH	$COOC_6H_{11}$	—	0.22	—	30.8	2.7	32.3	—
(8)	Cp	*Z*	COOEt	COOEt	0.019	0.020	—	6.55	3.1	12.0	—
(9)	Cp	—	H	COOMe	—	(0.031)[h]	—	238	4.9	235	36.3[o]
(10)	Cp	—	H	COOEt	—	0.031[i]	—	225	4.8	121	60.8[p]
(11)	Cp	—	H	COOPr	—	0.031[h]	—	135	4.5	23.9	135
(12)	Cp	—	H	COOBu	—	0.031	—	100.3	4.4	38	86.7
(13)	Cp[j]	—	H	COMe	—	0.76	—	44.0	2.2	109	—
(14)	Cp	—	H	C≡N	—	0.040	—	0.59	1.5	5.37	—
(15)	Cp	—	Cyclopentadiene		—	(0.0019)[k]	10.4	16.6	4.6[k]	74.9	15.8
(16)	Cp	—	Cyclohexen-2-one		—	0.0013	—	4.15	4.4	4.60	—
(17)	$CpCl_6$	*E*	COOEt	COOEt	—	0.088	—	555	4.7	28.9	—
(18)	$CpCl_6$	—	H	Ph	—	0.28	—	459	4.0	6 963	—
(19)	1,3-Cyclo-hexadiene	*E*	COOEt	COOEt	—	0.029	—	35.3	3.9	5.8	—

[a] Rate constants *k* in 10^3 dm^3 mol^{-1} s^{-1}, at (20.0 ± 0.05) °C, except with **(17)**, **(18)** ($CPCl_6$ reactions): at 60.0 ± 0.05 °C. [b] Cp: Cyclopentadiene; $CpCl_6$: Hexachlorocyclopentadiene. [c] Dienophiles R–CH=CH–R′ with configuration *E* or *Z*, if applicable; Et: ethyl; Pr: propyl; Bu: butyl; C_6H_{11}: cyclohexyl. [d] In vol/vol (%) mixtures. [e] *a′*: sensitivity parameter against hydrophobicity variation, see text. [f] With β-cyclodextrin in water. [g] With heptapiperidino-β-cyclodextrin · 7HCl in water. [h] Value *k* of **(10)** or **(12)**. [i] Value in 30% MeOH: 19.6. [j] From ref. 5(*a*). [k] In ethanol; *a′* value by comparison with EtOH instead of MeOH. [l] Other rate constants measured: for **(2)**: 768 (0.002 mol dm^{-3} β-CYD), 1 160 (0.005 mol dm^{-3} β-CYD), 1 570 (0.015 mol dm^{-3} β-CYD), 1 307 (0.007 mol dm^{-3} β-CYD). [m] Other constants for **(4)**: 0.72 (dioxane); 0.80 (MeCN); 1.25 (DMF); 137.4, 49.0, 15.8, 8.9, 4.2, 0.84 (10, 30, 50, 60, 70, 90% dioxane); 82.4, 58.1, 23.6 (10, 30, 60% MeOH); 24.3 (0.07 mol dm^{-3} CP66 in 50% dioxane); 420 (0.01 mol dm^{-3} CP66 in 10% dioxane); 1 891, 6 709, 10 367 (0.001, 0.005, 0.015 mol dm^{-3} β-CYD; 31.6 (0.01 mol dm^{-3} α-CYD). [n] For **(6)** 14.6 (0.005 mol dm^{-3} β-CYD), 27.9 (0.015 mol dm^{-3} β-CYD). [o] For **(9)**: 172.4 (with 0.02 mol dm^{-3} sodium dodecyl sulphate). [p] For **(10)**: 175 (0.005 mol dm^{-3} β-CYD); <2 (0.01 mol dm^{-3} α-CYD).

Table 2. Multiple correlations of rate constants (log k[a]) with solvophobicity parameters Sp[b] and polarity constants $E_{T(30)}$[c] for the reaction of cyclopentadiene and selected dienophiles; [log k_2 = $(a \pm \Delta a)\mathrm{Sp} + (m \pm \Delta m)E_T + (c \pm \Delta c)$].

Dienophile	a	± Δa	m	± Δm	c	± Δc	r[d]
Diethyl fumarate	2.2	0.4	0.02	0.02	−4.0	1.0	0.9761
Ethyl fumarate	2.1	0.8	0.0	0.05	−2.5	2.7	0.9865
Fumaric acid	1.8	0.8	0.5	0.0	−2.7	2.7	0.9817
Maleic acid	1.9	0.7	0.0	0.0	−1.6	2.2	0.9836

[a] From Table 1, with values in 13 solvents for DEF, and four solvents for the other dienophiles. [b] Ref. 15. [c] Ref. 18. [d] Multiple correlation coefficient *r*.

It is therefore to be expected that formation of micelles or of microemulsions will lead to rate constant increases only under very special circumstances. In this context we also studied the influence of an often used surfactant (SDS, sodium dodecyl sulphate), and in fact found substantial rate decreases (Table 1), in accordance with earlier conclusions by Breslow *et al.*[5] The catalytic effect of micelle formation in Diels–Alder reactions claimed by several earlier workers[6,11] is likely to be due not to an increase of true rate constants but of overall reaction velocities inasmuch as the low solubilities of the substrates in water limit the attainable rates.

Cyclodextrin Effects.—Enzyme-like saturation kinetics were observed in the two cases where the β-cyclodextrin

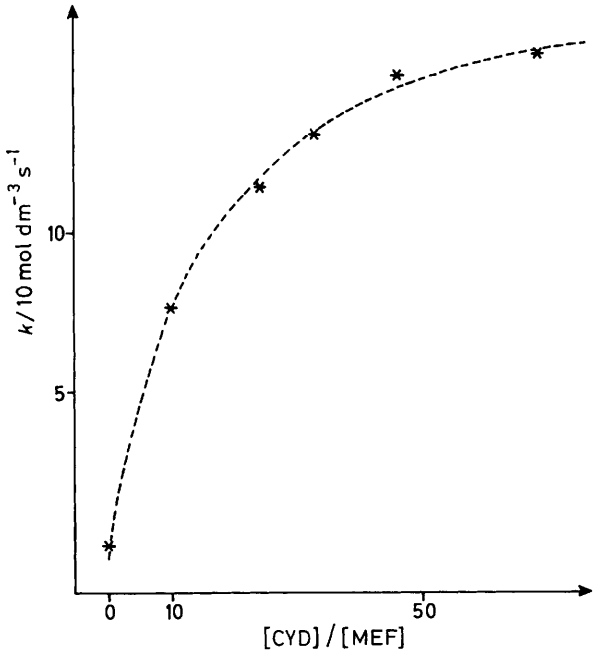


Figure 2. Diels–Alder rate constants *k vs.* molar ratios of β-cyclodextrin: monoethyl fumarate [β-CYD]:[MEF]; experimental points (* * *); theoretical curve from computer simulated points, (– – –). (Calculated values k_{cat} = 1.90 mol dm^{-3} s^{-1}; k_c/k_o = 40; K = 320 mol^{-1}).

concentration was varied up to the solubility limit (Figure 2). The experimental points can be satisfactorily computer simulated on the basis of a program used for the analysis of host–guest equilibria [16b] if several simplifications are made: the observed rate constants are taken as the sum of the uncatalysed reaction (k_o) and the apparent rate of a ternary complex (k_c) with an apparent formation constant K_{app}, neglecting any contributions from binary or ternary complexes which contain only diene or dienophile with cyclodextrin. The constants obtained by the non-linear computer fit [16b] (Figure 2) for monoethyl fumarate and cyclopentadiene are k_c = 1.9 mol dm^{-3} s^{-1} (k_c/k_o = 48) with K_{app} = 320 dm^3 mol^{-1}; for diethyl fumarate and cyclopentadiene (Figure not shown) k_c = 14.9 mol dm^{-3} s^{-1} (k_c/k_o = 100) with K_{app} = 158 dm^3 mol^{-1}. These values correspond satisfactorily to the constants derived from a preliminary analysis; [12] the apparent formation constants K are also in the order of binary equilibrium constants reported for cyclodextrins in the literature. [19] α-Cyclodextrin, which is too small to accommodate substrate and co-substrate within the cavity shows retardation instead of catalysis (Table 1, footnote *m*); with ethylacrylate complete inhibition is observed.

All other diene–dienophile combinations were measured at only one or two β-cyclodextrin concentrations (Table 1), which are close to the solubility limit. Scheme 1 illustrates that 11 combinations show rate increases by β-cyclodextrin, four remain essentially unaffected, and five show distinct rate decreases. In a similar manner to the observations on association effects by water, a larger hydrophobic alkoxy group in the ester dienophile [*cf.* (**1**)–(**4**)] leads rather to smaller catalytic activities of cyclodextrin. In the acrylic ester series (**9**)–(**12**) the inhibition again seems to increase with increasing hydrophobicity of the dienophile. This would be in accord with an increasing complexation of two dienophiles instead of diene and dienophile within the cavity. Other substrates such as styrene (**18**) or the *trans*-diesters (**1**)–(**4**) are likely to be too large for a preferred formation of an unproductive complex with two dienophiles. The fact, however, that even cyclopentadiene (**15**) itself reacts faster in the presence of β-cyclodextrin suggests that a total insertion of both diene and dienophile within the cavity might not be necessary for an effective catalysis. The large variations illustrated in Scheme 1 demonstrate that much needs to be done before one can hope to predict catalytic and inhibitory effects in such ternary inclusion complexes.

A further increase in catalytic activity could in principle be expected if (*i*) the binding constant K were enlarged and (*ii*) the cycloaddition in the ternary complex were accelerated *e.g.* by the presence of electron-withdrawing substituents at the host compound; this could exert similar effects to Lewis acids on the applied dienophile. Towards these aims, a 6-heptapiperidino-β-cyclodextrin was synthesized starting from the known reaction product [20] from β-cyclodextrin with tosyl chloride. The amino derivative obtained after subsequent treatment with excess piperidine* was identified by the expected ^{13}C n.m.r. signals and was used in aqueous solutions in the form of its hydrochloride. The results (Table 1, last column) showed no effect for two diene–dienophile combinations, but for three combinations distinct inhibition by the cyclodextrin derivative, which again can be the result of either unproductive orientations in the ternary complex or of preferred complexation with either diene or dienophile.

* The heptapiperidino compound has so far been only mentioned without spectroscopic identification in the patent: H. Kurita, M. Kawazn, and K. Takashima, Jap. Kokai 7485, 015 (1974); (*Chem. Abstr.*, 1975, **82**, 4533s).

Experimental

N.m.r. spectra (^{13}C and ^{1}H) were measured at 100.3 MHz or 400 MHz, respectively, with a Bruker AM 400 system. Kinetic measurements were performed under the conditions noted in Table 1; the solvent compositions refer to vol/vol mixtures. Absorbance changes were measured at the appropriate wavelength (nm) as follows: for cyclopentadiene 239; 1,3-cyclohexadiene 257; hexachlorocyclopentadiene 322; and styrene 246. Reactions in water and water–methanol mixtures were followed by continuous automatic data collection with subsequent second-order processing of usually 50 points. Slower reactions in neat methanol or in dioxane–water mixtures were analysed by measuring 5–8 samples at appropriate intervals after dilution of each sample with 50% methanol–water.

Heptakis(6-O-*tosyl*)-β-*cyclodextrin*.[20]—A solution of β-cyclodextrin (11.35 g, 10 mmol)—which was dried before use at 100 °C *in vacuo* for 1 h—and purified tosyl chloride (14.30 g, 75 mmol) in absolute pyridine (50 cm^3) was stirred at room temperature for 48 h. After being poured onto ice–water the mixture was filtered and the resulting precipitate was washed thoroughly to remove the pyridine and recrystallized from methanol (400 cm^3) to give the product (7.95 g, 36%); δ_C(ppm, [$^2H_6$]DMSO; internal TMS as reference) 144.60, 129.74, 127.37, 132.61 (aromatic signals *p*, *m*, *o*, *i* from –SO_2), 101.75, 71.22, 71.58, 81.00, 69.25, 68.53 (C-1 to C-6 sugar signals), and 20.98 (CH_3).

Heptakis[6-*deoxy*-6-(1-*piperidino*)]-β-*cyclodextrin*.—A solution of the heptatoluene-4-sulphonate (0.55 g, 0.25 mmol) and piperidine (0.85 g, 10 mmol) in methanol (5 cm^3) was refluxed with stirring for 48 h. The residue obtained after cooling and addition of water was washed with water and diethyl ether, dried, and converted into the hydrochloride by dissolution in hydrochloric acid. The product was precipitated by diluting the acidic solution with acetone, and was then washed and dried to yield a colourless hydrochloride (0.34 g, 73%); δ_C(ppm, in D_2O with CH_3OH as internal reference at 49.0 ppm) 57.38, 22.69, 20.95 (piperidine signals α, β, γ to N), 100.30, 71.82, 71.54, 81.12, 67.07, and 55.40 (sugar signals C-1 to C-6).

Other Products.—These were commercially available and purified prior to use if necessary (cyclopentadiene, styrene), or were obtained by standard procedures from maleic anhydride [(**6**) and (**7**)] and from fumaryl dichloride [(**3**)], respectively.

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