Biomimetic Asymmetric Synthesis. Enantioselective Weitz-Scheffer Epoxidation of Vitamin K_3 and Analogues in the Presence of Cyclodextrins

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The asymmetric epoxidation of vitamin K_3 and analogues in aqueous alkaline buffer solution or in DMF/solid Na_2CO_3, in the presence of α- and β-cyclodextrin has been investigated. The enantiomeric excesses in the products were up to 48%. The various factors that control the enantioselectivity of the process have been examined. Different mechanisms are involved in aqueous medium and dipolar aprotic solvent.

Introduction

Cyclodextrins (Cds), together with micellar aggregates, are among the most extensively investigated biomimetic models of enzymes. Indeed, these cyclic oligomers consisting of 1,4-linked D-glucopyranose units are synthetic molecular catalysts for a variety of reactions, providing both a receptor site for substrate binding and a reactive site for its subsequent transformation.[1] Cyclodextrins can influence the enantioselectivity and the reaction rate, in particular in the cleavage of carboxylic acid esters.[2] The functionalization of their hydroxyl groups and the selection of the appropriate substrate geometry may afford over a millionfold rate enhancement. The largest enantioselectivity factor reported in the literature is greater than 60,[3a] the average value being much lower.[3b] Cyclodextrins, in particular β-Cd, are also powerful resolving agents for racemic mixtures;[4a] their recognition ability has been recently exploited in the case of fenoprofen[4b] and of unfunctionalized cycloalkanes.[4c]

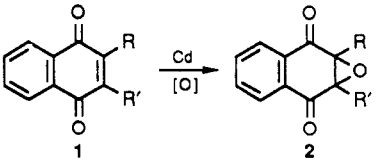
Although a considerable amount of success has been obtained with chemically modified Cds,[5] less satisfactory has been the utilization of simple Cds as a tool for asymmetric synthesis. The observed stereoselectivities are generally poor, the enantiomeric excess (ee) being $\leq$10%. Better results have been obtained in the borohydride reduction of ketones ($\leq$32% ee),[6] in the oxidation of sulfides to sulfoxides ($\leq$33.7% ee),[7a,b] and in the Diels-Alder reaction of cyclopentadiene with maleic acid derivatives (21% ee).[7c] The only remarkable exceptions to this trend, observed for reactions performed in aqueous solutions, are represented by the asymmetric reduction of ketones with crystalline cyclodextrin complexes of amine-boranes, recently found by Sakuraba and co-workers ($\leq$91% ee),[8a] and with sodium borohydride in the presence of alkaline salts ($\leq$84% ee).[8b] Complete enantioselectivity has been achieved in the asymmetric halogenation of olefins using cyclodextrin complexes in the solid state, but when the reaction was repeated under homogeneous conditions in DMSO solution the ee dropped to 6%.[9]

In this paper we examine the factors that control the enantioselectivity of the Weitz-Scheffer asymmetric epoxidation of alkyl-substituted 1,4-naphthoquinones (vitamin K and analogues) promoted by Cds. A range of substrates and the effect of variation of the reaction medium, the base, and oxidizing agent are investigated. The quinones used were 2-methyl (**1a**, vitamin K_3), 2-*n*-butyl (**1b**), 2-*n*-octyl (**1c**), 2-*n*-octadecyl (**1d**), 2-phenyl (**1e**), 2-methyl-3-ethyl (**1f**), and 2-methyl-3-phytyl (**1g**) 1,4-naphthoquinone.

Table I. Oxidation of 1a in Aqueous Buffer, pH 9, Containing β-Cd at 25 °C for 4 Days[a]

oxidant	yield (%)	CD (360 nm)	ee (±2%)[b]
t-BuOOH	33	(+)	22
H_2O_2	100	(+)	2
NaOCl	98	(+)	1
$PhC(CH_3)_2OOH$	47		0
MCPBA	100	(+)	2

[a] Quinone/oxidant/β-Cd molar ratio 1:2:5. [b] Determined from the specific rotation of the product and/or by ^1H NMR spectroscopy using $Eu(dcm)_3$ as chiral shift reagent and by CD spectroscopy.



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1a,2a: R = CH_3, R' = H
1b,2b: R = C_4H_9, R' = H
1c,2c: R = *n*-C_8H_{17}, R' = H
1d,2d: R = *n*-$C_{18}H_{37}$, R' = H
1e,2e: R = C_6H_5, R' = H
1f,2f: R = CH_3, R' = C_2H_5
1g,2g: R = CH_3, R' = phytyl

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Table II. Effect of Base in Epoxidation of 1a with *t*-BuOOH in Dipolar Aprotic Solvents in the Presence of β-Cd at 25 °C[a]

base	solvent	time (h)	yield (%)	CD (360 nm)	ee (±2%)
Na_2CO_3	DMF	2	96	(-)	24
$NaHCO_3$	DMF	3	0		
NaOH	DMF	0.2	53	(-)	14
Na_2CO_3	DMSO	3.5	65	(-)	14
$NaHCO_3$	DMSO	20	80	(-)	7
NaOH	DMSO	0.3	66	(-)	9

[a] Quinone/oxidant/β-Cd molar ratio 1:2:5.

Table III. Effect of β-Cd/Substrate Molar Ratio in Epoxidation of 1a and 1c with *t*-BuOOH at 25 °C[a]

S	β-Cd/S	conditions	time (h)	yield (%)	CD (360 nm)	ee (±2%)
1a	5	buffer pH 9	96	33	(+)	22
1a	1	buffer pH 9	32	91	(+)	8
1a	0.5	buffer pH 9	32	100		0
1a	5	DMF/Na_2CO_3	2	96	(-)	24
1a	1	DMF/Na_2CO_3	16	69	(-)	20
1a	0.5	DMF/Na_2CO_3	16	42	(-)	13
1c	5	DMF/Na_2CO_3	4	90	(-)	41
1c	1	DMF/Na_2CO_3	6.5	50	(-)	24
1c	0.5	DMF/Na_2CO_3	24	50	(-)	15

[a] S = substrate.

Results

The reactions were carried out by stirring at room temperature a heterogeneous mixture of substrate and oxidant in aqueous borate buffer (pH 9) in the presence of α-Cd or β-Cd. They were also repeated in organic solvents in the presence of solid bases. The crude products were isolated by preparative layer chromatography and the ee were determined by optical rotation and/or by ^1H NMR spectroscopy using europium chiral shift reagents or circular dichroism (CD) spectroscopy.

2-Methyl-1,4-naphthoquinone was used as the standard substrate for optimizing the reactions conditions. Table I contains the results obtained in the oxidtion of **1a** with various oxidizing agents in aqueous buffer solution at pH 9 in the presence of excess β-Cd. *tert*-Butyl hydroperoxide gave the best results, while hydrogen peroxide, cumene hydroperoxide, sodium hypochlorite, and *m*-chloroperbenzoic acid afforded racemic or almost racemic epoxide **2a**. Usually higher chemical yield corresponds to lower ee. The prevailing enantiomer of **2a**, when present, always has the 2*S*,3*R* absolute configuration, independent of the oxidant used. The configuration was attributed on the basis of the positive Cotton effect at 360 nm.[10] By analogy, the same absolute configuration can be attributed to the 2-alkyl-substituted 1,4-naphthoquinones **2b–d,f,g**, since all display positive CD activity at 360 nm.[11]

The effect of the nature of the solid base on the enantioselectivity was examined next for the epoxidation of **1a** performed in dipolar aprotic solvents (DMF, DMSO) in the presence of β-Cd (Table II). Sodium carbonate gave the highest ee in both solvents; an intermediate behavior was found with sodium hydroxide, whereas no formation of epoxide **2a** was observed with sodium bicarbonate when DMF was used as solvent. It is interesting to note that in both aprotic dipolar solvents, independent of the base used, the epoxidation of **1a** has the opposite stereochemical course with respect to the reaction carried out in aqueous buffer. The prevailing epoxide **2a** has in fact the 2*R*,3*S* absolute configuration in the nonaqueous medium.

Table IV. Oxidation of 1c in DMF Containing β-Cd and Solid Na_2CO_3 at 25 °C[a]

oxidant	time (days)	yield (%)	CD (360 nm)	ee (±2%)
t-BuOOH	0.2	90	(-)	41
$PhC(CH_3)_2OOH$	0.25	87	(-)	19
MCPBA	7	0[b]		0

[a] Quinone/oxidant/β-Cd molar ratio 1:2:5. [b] The starting material was quantitatively recovered.

Table V. Effect of Substituent in Positions 2 and 3 in the Epoxidation of 1a–g with *t*-BuOOH in DMF/Solid Na_2CO_3 with β-Cd at 25 °C[a]

R	R′	time (h)	yield (%)	CD (360 nm)	ee (±2%)
CH_3	H	2	96	(-)	24
n-C_4H_9	H	5	76	(-)	30
n-C_8H_{17}	H	4	90	(-)	41
n-$C_{18}H_{37}$	H	264	47	(-)	27
C_6H_5	H	4	88	(-)	5
CH_3	C_2H_5	2	35		0
CH_3	phytyl[b]	24	28		0

[a] Quinone/oxidant/β-Cd molar ratio 1:2:5. [b] With solid NaOH as base.

Another important parameter influencing the stereoselectivity of the epoxidation of **1a** with *tert*-butyl hydroperoxide is the amount of β-Cd employed. In aqueous buffer solution the highest optical yield in the formation of epoxide **2a** was obtained with a β-Cd/substrate ratio of 5:1 (Table III). A stoichiometric amount of β-Cd decreased the ee and catalytic β-Cd led to racemic epoxide **2a** in quantitative chemical yield. Increasing the concentration of β-Cd has an apparent retarding effect on the reaction rate.

In the dipolar aprotic solvent β-Cd acts as a catalyst, since the chemical conversion of **1a** into **2a** increases with larger amounts of β-Cd, the best ee being observed with a β-Cd/substrate ratio of 5:1 (Table III). Similar results were obtained starting from the 2-*n*-octyl derivative **1c**.

The epoxidation behavior of **1c** could be investigated only in DMF/solid Na_2CO_3, since in aqueous buffer the quinone is completely unreactive even after a long reaction time (8 days), probably as a consequence of its insolubility in the reaction medium. As with **1a**, the best ee is observed with a β-Cd/substrate ratio of 5:1. *tert*-Butyl hydroperoxide is also the oxidant of choice in the oxidation of **1c** in anhydrous DMF and sodium carbonate (Table IV). Under these conditions the prevailing enantiomeric epoxide **2c** has the 2*R*,3*S* absolute configuration.

The behavior of the quinone **1b** parallels that observed for **1a** both in aqueous buffer solution and in DMF/solid Na_2CO_3 with *t*-BuOOH and β-Cd. In the former case, 2*S*,3*R* epoxide **2b** was obtained in 30% chemical yield and 1% ee after 5 days at 25 °C, whereas in the latter case the reaction was much faster, leading to the epoxide **2b** with the opposite absolute configuration in 80% yield and 30% ee after 5 h at 25 °C. Quinone **1e** did not react with *t*-BuOOH in aqueous buffer solution, pH 9, in the presence of β-Cd in the usual conditions and was recovered unchanged after a very long reaction time (11 days).

The DMF/solid Na_2CO_3 reaction medium was suitable for studying the effect of lengthening the alkyl chain in position 2 on the degree of asymmetric induction in the presence of β-Cd. The results collected in Table V show that the ee increases substantially on passing from the 2-methyl (**1a**) to the 2-octyl (**1c**) through the 2-butyl derivative (**1b**) and diminishes for the **1d** derivative with the longer 2-octadecyl alkyl chain. In all cases, the prevailing

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Table VI. Effect of Nature of Cd in Epoxidation of 1a-c with *t*-BuOOH at 25 °C[a]

		α-Cd				β-Cd			
R	conditions	time (h)	yield (%)	CD (360 nm)	ee (%)	time (h)	yield (%)	CD (360 nm)	ee (%)
CH_3	buffer pH 9	48	100		0	96	33	(+)	22
CH_3	DMF/Na_2CO_3	24	99		0	2	96	(-)	24
n-C_4H_9	DMF/Na_2CO_3	24	79	(-)	39	5	76	(-)	30
n-C_8H_{17}	DMF/Na_2CO_3	3.5	61	(-)	48	4	90	(-)	41

[a] Quinone/oxidant/Cd molar ratio 1:2:5.

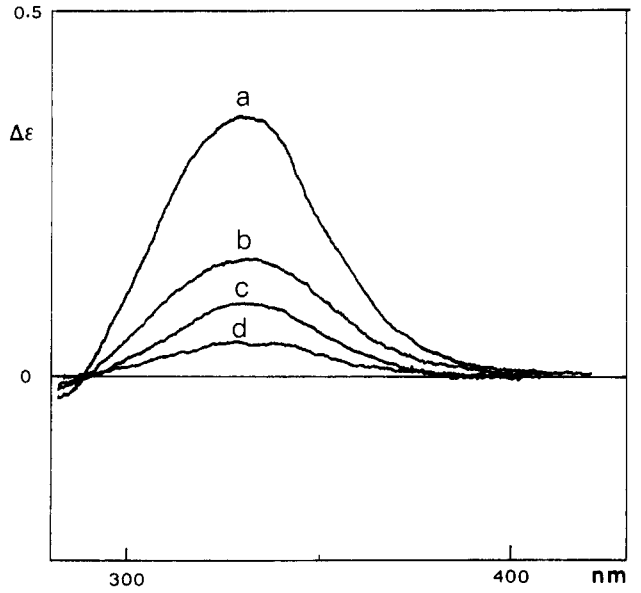

Figure 1. Circular dichroism spectra of solutions containing 2.8×10^{-4} M **1a** and 5.6×10^{-3} M β-Cd: (a) aqueous buffer pH 9; (b) the same buffer containing 5% DMF (v/v); (c) the same buffer containing 10% DMF (v/v); (d) the same buffer containing 20% DMF (v/v).

epoxide had the 2*R*,3*S* absolute configuration. Phenyl substitution at position 2 of the quinone led to the epoxide **2e** in good chemical yield but low optical purity (product with negative CD activity at 360 nm). The importance of steric factors in this reaction is confirmed by the low reactivity of the 2-methyl-3-ethyl (**1f**) and 2-methyl-3-phytyl (**1g**) derivatives.

We have also examined the effect on stereoselectivity of the size of the cavity of cyclodextrins. To this end we compared the epoxidation of substituted 1,4-naphthoquinones with *t*-BuOOH in the presence of β-Cd or α-Cd, having a cavity of diameter 6–7 Å and 5 Å, respectively,[1b,c] (Table VI). With α-Cd the quinone **1a** gave the racemic epoxide **2a** both in aqueous buffer and DMF/Na_2CO_3 in very high chemical yield. A different situation was met with in the epoxidation of quinones **1b** and **1c** in DMF/Na_2CO_3, since in both cases α-Cd afforded the corresponding epoxides **2b,c** having the 2*R*,3*S* absolute configuration with slightly higher stereoselectivity than β-Cd.

In order to obtain some information on the mechanism responsible for the asymmetric induction in the epoxidation, we recorded CD spectra of several systems in aqueous buffer and in DMF/Na_2CO_3 media. The formation of inclusion complexes between 2-substituted 1,4-naphthoquinones and β-CD can be followed by CD spectroscopy through the appearance of optical activity within the low-energy absorption bands of the naphthoquinone chromophore.[12a] While we obtained CD evidence for the formation of inclusion complexes between the naphthoquinones and β-Cd in the aqueous buffer, we found rather surprisingly that no system gives rise to optical activity in DMF solutions. We could also show the formation of an inclusion complex between cumyl hydroperoxide and β-Cd in aqueous buffer through the positive CD activity developed in the aromatic chromophore.

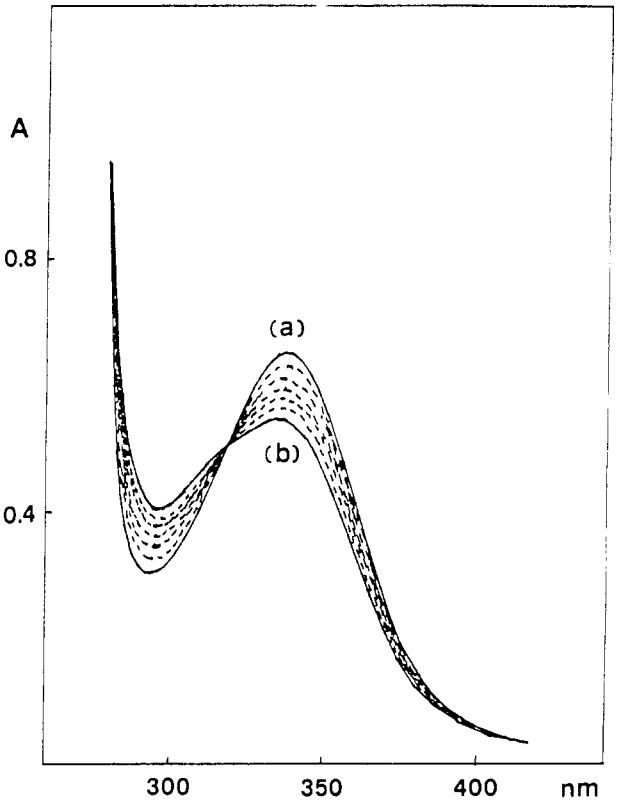

Figure 2. Absorption spectral changes observed during the oxidation of **1a** (6×10^{-4} M) by *t*-BuOOH (1.2×10^{-3} M) in aqueous buffer, pH 9, in the presence of β-Cd (3×10^{-3} M); optical path length 0.5 cm. Curve a is the spectrum taken immediately after the addition of the oxidant, and curve b the spectrum obtained after 1 h reaction time. The dashed curves are intermediate spectra recorded at regular time intervals of 10 min.

The inclusion equilibrium between **1a** and β-Cd could be investigated quantitatively to obtain the association constant (K) for the reasonable solubility of the guest in the aqueous buffer at pH 9. From a double reciprocal plot of the CD intensity change with the change in β-Cd concentration, the value of $K = 60$ M^{-1} for the inclusion equilibrium was obtained. This value is in the range found for the binding of other aromatic compounds to β-Cd[12b,c] and indicates a moderate affinity of **1a** for β-Cd. It is interesting to note that the addition of increasing amounts of DMF to aqueous buffer solutions of **1a** and β-Cd progressively decreases the induced optical activity (Figure 1), as if DMF competed against **1a** in the binding to β-Cd. This conclusion seems confirmed by ^{1}NMR experiments carried out on **1a** in deuterated DMF or DMSO in the presence of excess β-Cd, where only the signals due to

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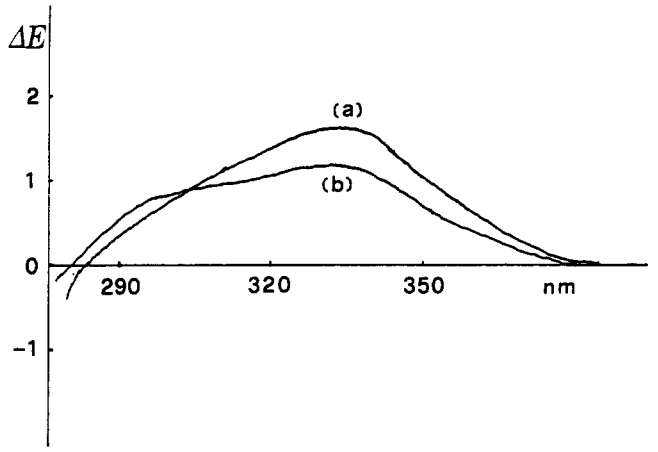

Figure 3. Circular dichroism spectra of **1a** (6×10^{-4} M) in aqueous buffer, pH 9, in the presence of β-Cd (3×10^{-3} M) and *t*-BuOOH (1.2×10^{-3} M); spectrum a was recorded immediately after the addition of the oxidant, and spectrum b was obtained after 1 h.

unbound **1a** can be detected.

As shown in Figure 2 the UV spectrum of the **1a**–β-Cd complex in aqueous buffer at pH 9 changes with time in the presence of *t*-BuOOH. The absorption maximum at 337 nm decreases in intensity and a species absorbing at approximately 310 nm is formed. The spectra recorded within 1–2 h after the addition of the oxidant show an isosbestic point at 318 nm, which reflects the occurrence of a simple equilibrium between two absorbing species in solution. On longer reaction times some nonnegligible amounts of the epoxide begin to form and the absorption spectrum becomes correspondingly more complicated. The CD spectra of the same mixture show parallel changes (Figure 3). The positive CD band at 335 nm of the **1a**–β-CD complex shifts to higher energy with some decrease in intensity after the addition of *t*-BuOOH, but clearly the oxidant does not displace the quinone from β-Cd.

Discussion

In previous investigations we examined the Weitz–Scheffer epoxidation of *trans*-chalcone and related systems in the presence of catalytic amounts of cyclodextrins, eventually modified at their hydroxyl groups, both in aqueous solution and in organic solvents.[13] The optical yields were very low (≤11%) or nil. No better results were obtained by Takahashi and co-workers in the epoxidation of *trans*-cinnamaldehyde and chalcone (ee up to 8%).[14] We thought that the low enantioselectivity of these reactions was due to the large conformational mobility of the starting material and thus anticipated that conformationally more rigid substrates, like the substituted 1,4-naphthoquinones investigated here, could give better results. These compounds are particularly important in view of the involvement of vitamins K and their epoxides in metabolic processes; among others, vitamin K_1 (**1g**) is indispensible for blood coagulation and its epoxide is the major metabolite in the liver.[15] Recently vitamin K_3 epoxide and analogues have been prepared in high optical purity by Wynberg and Pluim,[11] under phase-transfer conditions, and by some of us,[16] in the presence of bovine serum albumin.

The results of the present study clearly show that the mechanism of the asymmetric Weitz–Scheffer epoxidation of vitamins K and analogues is drastically different in aqueous buffer solution and dipolar aprotic solvents. In the former case, the substrate is confined into the cyclodextrin cavity, as shown by the CD spectra and the slower reaction rate with respect to the epoxidation carried out in the absence of Cd. In aqueous buffer solution, *t*-BuOOH can also give an inclusion complex with Cd,[17] and this can further contribute to a reduction in the reaction rate. Since the epoxidation of **1a** is aqueous buffer is a slow process, it is possible to observe spectroscopically the formation of an intermediate just after the addition of the oxidant. Such observation is in agreement with the mechanism proposed for the epoxidation of substituted 1,4-naphthoquinones, which proceeds through an anionic intermediate.[11] The existence of inclusion complexes between 2-substituted 1,4-naphthoquinones and Cds also explains the increase of the ee in the products with higher Cd/quinone ratios. Interestingly, the specific inclusion catalysis by β-Cd has been used for the one-step preparation of vitamin K_1 or K_2 analogues.[18]

On the contrary, in dipolar aprotic solvents there is no spectroscopic evidence for the formation of inclusion complexes. The reasons why naphthoquinones are not included or immobilized by Cds in DMF are unclear, since the binding of small molecules by Cds in this solvent has been described in the literature.[19] It is possible that in this solvent the naphthoquinones or the cyclodextrin adopt a conformation unfavourable for the formation of the inclusion adduct or that the solvent can favorably compete with the substrate in the inclusion. A strong evidence in favor of the latter explanation is the disappearance of optical activity in the CD spectrum of the menadione (**1a**)–β-Cd complex when DMF is added. This result tallies with those reported by Kobayashi and co-workers who found that complexation of ferrocenes with Cds does not occur in DMF or DMSO.[20a] In agreement with our finding, it has already been reported that the equilibrium

$$\text{acetophenone} + \beta\text{-Cd} \rightleftharpoons [\text{acetophenone} \subset \beta\text{-Cd}]$$

is much more shifted to the left in DMF than in water.[20b] The occurrence of a different mechanism in dipolar aprotic solvents is confirmed by the favorable effect of Cds on the reaction rate, in contrast with the results in aqueous buffer medium. Also, the prevailing epoxide products have opposite configuration in aqueous medium (2*R*,3*S*) and in DMF (2*S*,3*R*).

For alkyl chains in position 2 longer than methyl the degree of asymmetric induction in DMF/Na_2CO_3 is independent of the nature of the Cd used as chiral auxiliary. The 2-methyl derivative **1a** occupies a critical position in the enantioselective epoxidation as shown by the data obtained with α-Cd and β-Cd. While use of the former leads to racemic epoxide **2a**, either in aqueous or in DMF solutions, that of the latter leads to asymmetric synthesis in both cases.

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While the mechanisms of epoxidation are clearly different in the two solvents, it is difficult to give account for the higher enantioselectivities observed in DMF with respect to the aqueous medium. Actually, the weaker binding of substrates to Cds in dipolar aprotic solvents like DMF, with respect to water,[19] agrees with the lower stereoselectivities observed, for instance, for the borohydride reduction of ketones with β-Cd in DMF or DMSO than in water.[6] Low optical purities have also been observed in the bromination of α,β-unsaturated acids with β-Cd in DMSO, in contrast with the results obtained with β-Cd in the solid state.[9] In spite of all this, the epoxidation of 2-octyl-1,4-naphthoquinone with *t*-BuOOH in the presence of Cds occurs with the highest enantioselectivities reported so far in dipolar aprotic solvents. It is possible that the oxidant can still give an inclusion complex or be immobilized by interaction with the polar groups of the dextrin in DMF, so that the stereoselectivity of the reaction can be originated by the asymmetric environment provided by the oxidant. Though, it is impossible to probe by CD spectroscopy the formation of inclusion complexes between the peroxides and β-Cd in DMF because of its low-energy cutoff.

In conclusion, the results reported here, as a whole, seem to indicate the necessity of several factors for obtaining a substantial enantiofacial selectivity in the Weitz–Scheffer epoxidation: among them the presence of a hydrophobic chain of suitable length in the substrate and a decrease of the degrees of freedom in the substrate–cyclodextrin and possibly also in the oxidant–cyclodextrin interactions seem to play an important role. These favorable effects are optimal for 2-octyl-1,4-naphthoquinone, a further increase of the alkyl chain destroys the delicate balance and leads to lower enantioselection.

Experimental Section

Proton NMR spectra were recorded in $CDCl_3$ on a Varian 390 instrument. Enantiomeric excesses were determined by ^1H NMR with the aid of $Eu(dcm)_3$ or $Eu(hfc)_3$ as chiral shift reagents using a Varian XL 200 instrument. Electronic spectra were recorded on a Perkin-Elmer Lambda 5 spectrophotometer and CD spectra on a Jasco J-500 C dichrograph. The aqueous buffer solutions and *t*-BuOOH (70% in water) were obtained from Fluka. α-Cd and β-Cd were commercial products and used without further purification. The quinone **1a** is commercially available, while compounds **1b**,**c**,**e**,**f** were obtained according to Wynberg's procedure.[11] 2-*n*-Octadecyl-1,4-naphthoquinone was synthesized in 19% yield by the same method from nonadecanoic acid,[11] mp 70 °C (lit.[21] 84–85 °C). 2-Methyl-3-phytyl-1,4-naphthoquinone (vitamin K_1) was a gift from Hoffmann-La Roche consisting of a ~9:1 *E*/*Z* mixture.

The epoxynaphthoquinones **2a**–**c**,**e** are known to be in the optically active form and the physical properties of our specimens were in agreement with those reported in the literature.[11] 2-*n*-Octadecyl-1,4-naphthoquinone 2,3-epoxide was obtained in the optically active form as an inseparable mixture with the starting quinone (lit.[22] mp 91.8–92.3 °C for the racemic epoxide). ^1H NMR ($CDCl_3$): δ 0.87 (3 H, t), 1.25–1.38 (32 H, m), 1.80–1.93 (1 H, m), 2.23–2.36 (1 H, m), 3.87 (1 H, s), 7.73–7.80 (2 H, m), 7.93–7.97 (1 H, m), 8.00–8.04 (1 H, m).

Epoxidation of Substituted 1,4-Naphthoquinones. Typical Procedure. (A) Aqueous Medium. To a magnetically stirred, clear solution of α-Cd or β-Cd (0.8 mmol) in 50 mL of aqueous buffer solution, pH 9, was added the quinone (0.16 mmol). The mixture was stirred for 15–20 min to complete the dissolution of the enone and then the oxidant (0.32 mmol) was added. The reaction was kept stirring at room temperature for the appropriate time; then it was thoroughly extracted with diethyl ether (5 × 80 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The crude residue was then purified by preparative layer chromatography (light petroleum ether–diethyl ether 8:2, v:v, as eluant).

(B) Organic Solvent. To a clear solution of α-Cd or β-Cd (0.8 mmol) in 2.5 mL of anhydrous DMF or DMSO was added the naphthoquinone (0.16 mmol). When the substrate was completely dissolved, the oxidant (0.32 mmol) and a small amount of solid base were added. The reaction mixture was stirred at room temperature for the time needed; then it was extracted with diethyl ether (3 × 80 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum; the residue was purified as above.

Determination of the Association Constant of 1a to β-Cd in Aqueous Buffer pH 9. To 2-mL samples of **1a** (7×10^{-4} M) in aqueous buffer solution, pH 9, were added various amounts of a 10^{-2} M β-Cd solution in the same buffer in order to have quinone:β-Cd molar ratios varying from 1:10 to 1:25. Each sample was then diluted to a final volume of 10 mL with buffer, thermostated at 23 °C for a few hours, and then analyzed by CD spectroscopy. The binding constant (*K*) was calculated by using the following expression

$$\frac{1}{\Delta\theta} = \frac{1}{K\Delta\theta_\infty}\frac{1}{[\beta\text{-Cd}]} + \frac{1}{\Delta\theta_\infty}$$

where $\Delta\theta$ is the CD intensity produced by a given β-Cd concentration, $\Delta\theta_\infty$ the CD intensity for complete formation of the adduct, and [β-Cd] the concentration of β-Cd in the aqueous buffer. *K* and $\Delta\theta_\infty$ can be evaluated from the slope and intercept of the plot of $1/\Delta\theta$ vs $1/[\beta\text{-Cd}]$. The determination of *K* was carried out by using a least-square regression program on a minicomputer.

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Registry No. **1a**, 58-27-5; **1b**, 34491-88-8; **1c**, 41245-46-9; **1d**, 2197-60-6; **1e**, 2348-77-8; **1f**, 2589-56-2; **1g**, 84-80-0; (2*R*,3*S*)-**2a**, 61840-91-3; (2*S*,3*R*)-**2a**, 105016-62-4; (2*R*,3*S*)-**2b**, 73377-73-8; (2*S*,3*R*)-**2b**, 113774-89-3; (2*R*,3*S*)-**2c**, 129029-48-7; (2*S*,3*R*)-**2c**, 120294-78-2; (2*R*,3*S*)-**2d**, 129029-49-8; (2*S*,3*R*)-**2d**, 128924-93-6; (2*R*,3*S*)-**2e**, 73377-82-9; (2*S*,3*R*)-**2f**, 113774-90-6; (2*S*,3*R*)-**2g**, 85955-78-8; α-Cd, 10016-20-3; β-Cd, 7585-39-9.

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