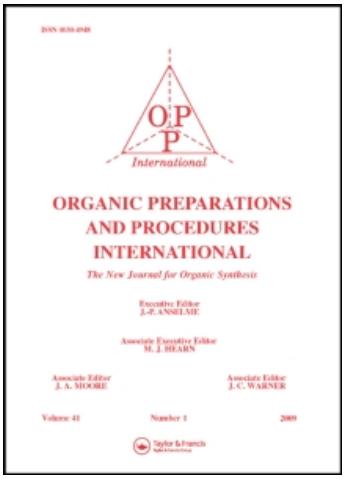

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BIOMIMETIC MODELING OF ASYMMETRIC SYNTHESIS OF ARYLALKYL SULFOXIDES USING β-CYCLODEXTRIN COMPLEXES

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2. Dimethyl 1,3-acetonedicarboxylate (3b) is substantially less expensive than di-t-butyl 3-oxoglutarate (3a).

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7. Compounds 1 and 2 were isolated as a mixture of regioisomers (see ref. 1a for details).

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BIOMIMETIC MODELING OF ASYMMETRIC SYNTHESIS OF ARYLALKYL SULFOXIDES USING β -CYCLODEXTRIN COMPLEXES†

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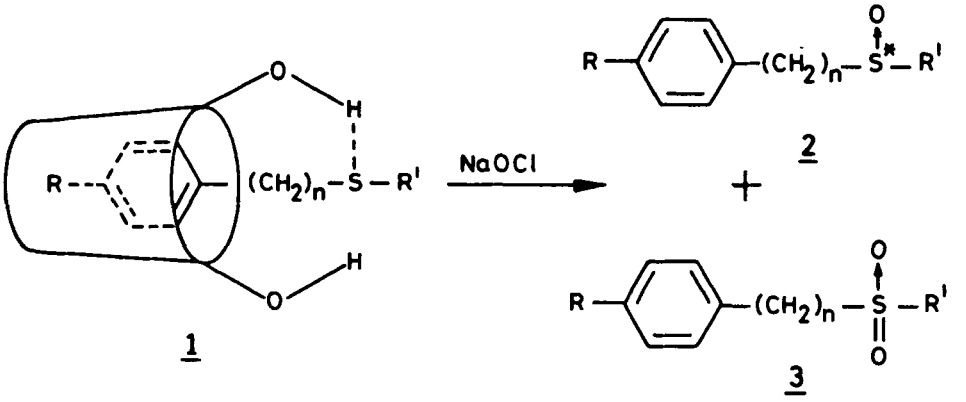
Chiral sulfoxides are becoming increasingly important as chiral auxiliaries in asymmetric synthesis for the transfer of chirality from sulfur to carbon.[1] So far chiral sulfoxides have been obtained mainly through menthyl sulfinate esters.[2] To date, no general and easily accessible method has been reported for the asymmetric oxidation of prochiral sulfides.[3] A more sophisticated and practical approach for asymmetric induction would be through "host-guest" complexation involving water as the reaction medium as observed in physiological processes. In continuation of our studies on biomimetric asymmetric synthesis,[4] we now report a simple method for the asymmetric oxidation of prochiral sulfides (1) in water employing β-cyclodextrin (β-CD) as a chiral template and sodium hypochlorite as an oxidizing agent.

The inclusion complexes were prepared by adding the pure sulfide in ethanol to an aqueous solution of β-cyclodextrin in equimolar ratio at 60° to yield crystalline complexes, as shown by the upfield shift of H-3 and H-5 protons of cyclodextrin.[5] All the sulfides (1) formed inclusioncompounds on an equimolar basis with cyclodextrin as determined from the amount of

sulfide extracted from a known amount of the complex. The unique asymmetric oxidation of these sulfide:β-cyclodextrin complexes by sodium hypochlorite (and not reagents such as hydrogen peroxide and m-chloroperbenzoic acid) may be explained through the initial formation of β-cyclodextrin hypochlorite as found by Breslow in the chlorination of anisole.[6]



a) R = H, $R^1 = CH_3$, n = 0; b) R = H, $R^1 = CH_2CH_2CH_3$, n = 0; c) R = H, $R^1 = CHMe_2$, n = 0; d) R = 4-CH_3, $R^1 = CH_3$, n = 0; e) R = 4-CH_3, $R^1 = CH_2CH_3$, n = 0; f) R = 4-CH_3, $R^1 = CH_2CH_2CH_3$, n = 0; g) R = 4-CH_3, $R^1 = CHMe_2$, n = 0; h) R = 4-Cl, $R^1 = CH_3$, n = 0; i) R = 4-Cl, $R^1 = CH_2CH_3$, n = 0; j) R = 4-Cl, $R^1 = CH_2CH_2CH_3$, n = 0; k) R = 4-Cl, $R^1 = CHMe_2$, n = 0; l) R = H, $R^1 = CH_3$, n = 1; m) R = H, $R^1 = CHMe_2$, n = 1.

Hence, it was considered of interest to first generate β-cyclodextrin hypochlorite,[6] and then attempt oxidation of various sulfides as functionalized cyclodextrins are known to show better selectivity in some enzyme models.[7] However, the results (Table) show that there was moderate increase in the enantioselectivity of only isopropyl substituted sulfides (1c, 1g, 1k and 1m); no change in stereoselectivity was observed with other sulfides. Sulfides with isopropyl group as a substituent showed enhanced enantioselectivity whereas no appreciable stereoselectivity was observed with sulfides with straight chain and lower alkyl groups. Among the sulfides studied, isopropyl p-chlorophenylsulfide (1k) appeared to be the "best fit" in the cyclodextrin cavity for favorable control of geometry in the approach of the substrate to the active site showing an ee up to 52%.

This biomimetic modelling of asymmetric oxidation of prochiral sulfides in water through "host-guest" complexation using the easily available β-cyclodextrin as chiral template holds promise for obtaining functionalized chiral sulfoxides (0.4 ~ 52% ee) and also for preparing new chiral synthons.

TABLE. Oxidation of Sulfides to Sulfoxides

	Yield of 2 (%)	mp.°C (lit)	E. e. (%) (Configuration)	Yield of 3 (%)	mp. °C (lit)
a	65	Oil[h],[9]	2.4[a](S)	12	85-86 (88)[9]
b	68	Oil[h],[10]	1.1[b](R)	15	44-45 (43.5-44.5)[11]
c	62	Oil[h],[12]	25.6[b,g](S)	10	Oil[h],[13]
d	68	74-75 (73-74.5)[14]	1.8[c](R)	17	85-86 (86-87)[15]
e	66	Oil[h,14]	1.5[c](R)	14	59-60 (56-57)[16]
f	64	Oil[h]	0.4[d,f]	12	51-52 (50)[17]
g	69	Oil[h,14]	21.8[c,g](R)	15	78-79 (77-79)[18]
h	72	Oil[h,19]	1.2[e](R)	16	97-98 (96.5-97.5)[20]
i	68	Oil[h]	-	20	Oil[h,21]
j	65	Oil[h]	-	18	73-75
k	74	64-65	52.0[d,f,g]	12	86-87 (88-89)[22]
l	70	58-59 (57-58)	2.0[e](S)	16	124-125 (127)[23]
m	67	Oil[h,10]	16.8[d,f,g]	15	66-67 (65)[23]

a) Measured by the specific rotation of the isolated sulfoxide with use of the maximum specific rotation given in U. Folli, D. Iarossi, F. Montanari and G. Torre, J. Chem. Soc. (C), 1317 (1968). b) Based on the maximum specific rotation given in M. Mikoajczyk and J. Drabowicz, J. Am. Chem. Soc., 100, 2510 (1978). c) Based on the maximum specific rotation given in K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, J. Am. Chem. Soc., 87, 1958 (1965). d) Measured by ^{1}H nmr with [Eu(hfc)$_3$] as chiral shift reagent. e) Based on the maximum specific rotation given in P. Pitchen, E. Dunach, M. N. Deshmukh and H. B. Kagan, J. Am. Chem. Soc., 106, 8188 (1984). f) Absolute configuration unknown. g) ee observed for the sulfoxides obtained by the reaction of sulfides with β-cyclodextrin hypochlorite. Low ee was observed for these compounds when the reaction was carried out by using sulfides: β-CD complex and NaOCl: (ee) c: (5.8); g: (2.6); k: (40); m: (3.6). However, for a, b, d, e, f, h, i, j and l the same stereoselectivities were observed with β-cyclodextrin hypochlorite as well as with sulfides:β-CD complex and NaOCl. h) Product was clean (tlc, ^{1}H nmr and mass) and distillation was not necessary.

EXPERIMENTAL SECTION

^{1}H nmr spectra were recorded on JEOL FT FX-90Q spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Enantiomeric excesses were determined by ^{1}H nmr with

the aid of [Eu(hfc)$_3$] as chiral shift reagent. β-Cyclodextrin was obtained from Aldrich Chemical Company, USA. The starting sulfides were synthesized as reported inliterature.[8]

Inclusion Complexes. General Procedure.- These were prepared by addition of a solution of the sulfide (2 mmol) in ethanol (2 ml) to β-cyclodextrin (2 mmol) in water (50 ml) at 60°. The crystalline complexes obtained after cooling were collected and dried.

Reaction of Sulfide: β-CD Complexes with Sodium Hypochlorite. General Procedure.- To a solution of sulfide:β-CD complex (1) in water (20 ml of distilled water was used per gram of the complex), cooled to 5-10° was added sodium hypochlorite (2 ml of 5% NaOCl was added for each mmol of the sulfide present in the complex). After the mixture was stirred at that temperature for 6 hrs, it was extracted with chloroform (3 x 50 ml). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was flash chromatographed on silica gel using chloroform:n-hexane (1:1) as eluent; the sulfones were eluted first followed by the sulfoxides. The yields are shown in Table 1. The physical properties of the sulfoxides and of the sulfones isolated were in agreement with those reported.

Reaction of Sulfides with β-Cyclodextrin Hypochlorite.[6] General Procedure.- To β-cyclodextrin (3 mmol) in 80 ml of distilled water, cooled to 5-10° was added 5% NaOCl (10 ml) and the mixture was stirred until it became clear (15 min). Then the sulfide (3 mmol) in ethanol (3 ml) was added dropwise and stirred at that temperature for 6 hrs, and the products were isolated as described above.

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DIMETHYL 4-NITROPHENYLMALONATE

Submitted by (01/16/90)

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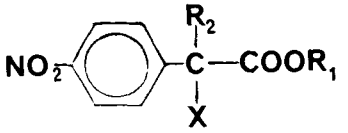
A simple high-yielding preparation of the title compound 1a and its facile C-methylation to the



a) R_1 = Me; R_2 = H; X = CO_2Me
b) R_1 = R_2 = Me; X = CO_2Me
c) R_1 = X = H; R_2 = Me