described for the synthesis of 8-methoxybenzo[a]pyrene, 50 mg (0.145 mmol) of ethyl 9-methoxy-4-chryseneacetate-*1*-^{13}C (**15a**-*carboxy*-^{13}C) was converted to 9-methoxybenzo[a]pyrene-*5*-^{13}C by initial treatment with diisobutylaluminum hydride followed by diluted methanesulfonic acid. Workup and chromatography as described provided 9-methoxybenzo[a]pyrene-*5*-^{13}C (26 mg, 64% yield from **15a**-*carboxy*-^{13}C) as bright greenish yellow flakes: mp 144.5–147 °C, lit.[18] mp 150 °C; TLC R_f 0.71 (toluene); ^{13}C NMR ($CDCl_3$) δ 128.06 (*C_5).

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Synthesis, Rapid Resolution, and Determination of Absolute Configuration of Racemic 2,2′-Binaphthyldiyl Crown Ethers and Analogues via β-Cyclodextrin Complexation

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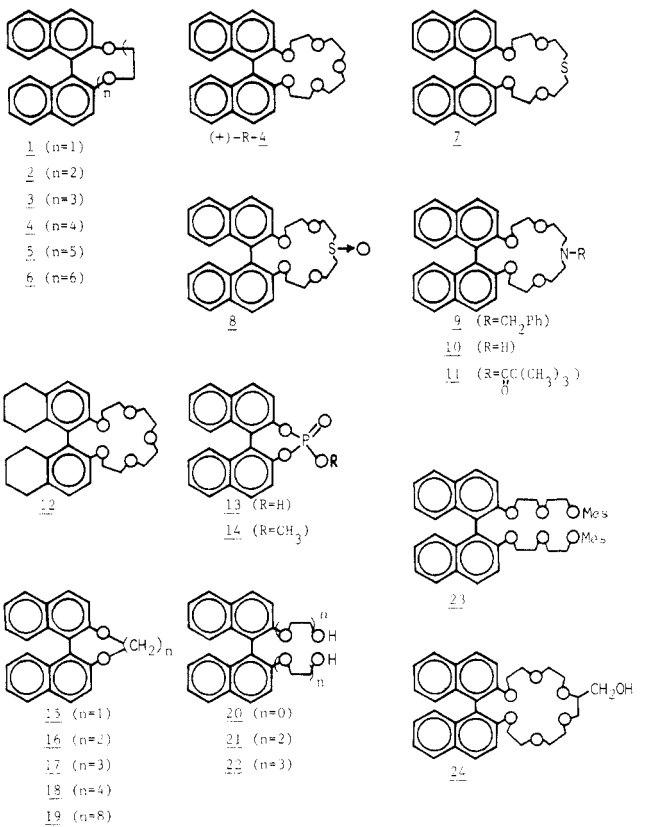
Twenty racemic and four diastereomeric 2,2′-binaphthyldiyl crown ethers and analogues were synthesized. Chiral interactions between these compounds and immobilized β-cyclodextrin were examined. Thirteen of the enantiomeric pairs and two of the diastereomers were successfully resolved. It was found that relatively small changes in the structure of these compounds could have large effects on chiral recognition. In general, the (−)-*S* enantiomers formed stronger inclusion complexes with β-cyclodextrin than did the (+)-*R* enantiomers.

It is well-known that cyclodextrins can catalyze certain hydrolyses and transacylation reactions of racemic substrates with some degree of stereospecificity.[1-11] More recently, properly immobilized cyclodextrins have been shown to produce highly efficient separations of some enantiomers.[12-18] Previously, in somewhat analogous studies, Cram and co-workers studied the chiral interaction and separation of organoamines with chiral crown ethers.[19-22] Despite extensive bodies of work on both cyclodextrins and crown ethers, little has been done to study the interactions and complexes between these compounds. In one of the few studies in this area, Vögtle and Müller have reported that small symmetrical crown ethers and cryptands will crystallize with γ-cyclodextrin as 1:1 and 2:1 complexes.[23]

In the present work several racemic and diastereomeric 2,2′-binaphthyldiyl crown ethers and analogues have been synthesized. Chiral interaction and separation of these species via complexation by immobilized β-cyclodextrin were studied. As a result of the high degree of chiral recognition in this system, β-cyclodextrin bonded phases offer a convenient means to separate optical isomers of many 2,2′-binaphthyldiyl derivatives, in addition to evaluating the optical purity of syntheses involving such compounds and determining the absolute configuration of structurally related compounds.

Results and Discussion

Synthesis. Racemic 2,2′-binaphthyldiyl-11-crown-3 **2**, 2,2′-binaphthyldiyl-14-crown-4 **3**, and 2,2′-binaphthyldiyl-20-crown-6 **5** were prepared by condensation of racemic 1,1′-bi-2-naphthol (**20**) with the appropriate ditosylates in a CsF–CH_3CN reaction mixture.[24,25] Isolated yields of **2**, **3**, and **5** were 73%, 18%, and 55%, respectively. Optically active (+)-(*R*)-2,2′-binaphthyldiyl-17-crown-5 **4**



was also obtained by the cesium-assisted cyclization of (+)-(*R*)-1,1′-bi-2-naphthol with tetraethylene glycol dito-

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Table I. Separation Data for Several Racemic and Diastereomeric 2,2′-Binaphthol Derivatives on β-CD Bonded Phases

compd	k' of (+)-*R* enantiomer[a]	α[b]	*Rs*[c]	column	mobile phase[d]	flow rate, mL/min
1	4.88	1.10	1.00	*e*	40/60	1.0
2	2.46	1.17	1.51	*f*	40/60	1.0
3	1.83	1.28	1.78	*f*	40/60	1.0
4	2.44	1.11	1.12	*e*	40/60	0.75
5	2.31	1.10	0.83	*e*	40/60	0.75
6	1.85	1.08	0.70	*e*	40/60	0.75
7	29.00	1.10	0.63	*g*	30/70	1.50
8	2.12	1.11	1.00	*e*	40/60	1.0
11	8.30	1.05	0.82	*e*	40/60	1.0
12	12.18	1.19	0.95	*g*	30/60	1.50
15	7.20	1.10	1.21	*e*	40/60	1.0
16	4.88	1.10	1.04	*e*	40/60	1.0
17	3.17	1.09	1.00	*e*	45/55	1.0
18	3.76	1.02	0.30	*e*	45/55	1.0
24	9.15	1.15	1.05	*e*	40/60	1.0

[a] The (+)-*R* enantiomer was the first peak eluted in each case (based on the negative Cotton effect at 230 nm). The k' is the capacity factor and is equal to $(t-t_0)/t_0$, where t is the retention time of the solute of interest and t_0 is the retention time of an unretained solute. [b] α is the separation factor and is equal to the ratio of the (−)-*S* enentiomer's k' over the (+)-*R* enantiomer's k'. [c] Rs is the resolution and is equal to 2 $(t_2-t_1/w_1 + w_2)$ where t and w are the peak retention times and peak widths, respectively. [d] Numbers represent the volume ratio of methanol/water. [e] A 25 cm + 10 cm β-CD column in series. [f] A 25-cm β-CD column. [g] A 10-cm β-CD column.

sylate in 20% yield. Crown ether sulfoxide **8** was prepared from thiacrown **7** by oxidation with *m*-chloroperbenzoic acid in dichloromethane at 0 °C. Dimesylate **23** was obtained in 99% yield after treatment of **21** with methanesulfonyl chloride and triethylamine. Following a previously reported method,[26] dimesylate **23** was reacted with benzylamine and solid sodium carbonate in acetonitrile to form the benzyl-protected monoazacrown **9** in 54% yield. Hydrogenolysis of **9** using 10% palladium on carbon in dioxane afforded a 62% yield of monoazacrown **10**. Acylation of **10** with trimethylacetyl chloride in the presence of triethylamine in benzene gave amide **11** in 78% yield. Reaction of 1,1′-bi-2-naphthol with 1,8-dibromooctane and anhydrous potassium carbonate in DMF produced compound **19** in 6% yield. The structures of all new compounds were verified by infrared (IR) and proton magnetic resonance (^{1}H NMR) spectroscopy and by elemental analysis.

Chiral Interaction with β-Cyclodextrin. Differential interactions of enantiomers with β-cyclodextrin can be evaluated in a number of ways including measuring binding constants using spectroscopic changes (e.g., the Benesi–Hildebrand approach[27]) or by using differences in chromatographic retention. Chromatographic techniques can use cyclodextrin as a mobile phase modifier[28-32] or as a bonded stationary phase.[12-18] It was found that ultraviolet and fluorescence spectroscopic methods were not sufficiently sensitive to detect differences in the binding of enantiomers to β-CD in this case. Differential binding and separation of enantiomeric 2,2′-binaphthyldiyl derivatives were easily detected by LC, however. The β-cyclodextrin (β-CD) bonded phases produced separations with greater resolution and efficiency than β-CD mobile phases. Consequently, most of the relevant data was produced with β-cyclodextrin bonded phases.

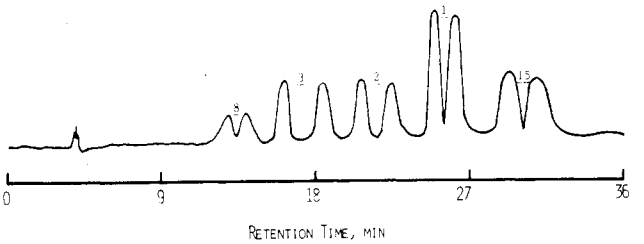

Figure 1. Liquid chromatographic separation of enantiomers of compounds **8**, **3**, **2**, **1**, and **15**. A gradient from 40% methanol (aqueous) to 45% methanol (aqueous) over 15 min was used. The flow rate was 1.0 mL/min, and the wavelength of detection was 254 nm.

Table I summarizes the separation data for 13 racemic 2,2′-binaphthyldiyl derivatives. A typical enantiomeric separation of several of these compounds is shown in Figure 1. Compounds not listed in Table I showed no enantiomeric resolution (Rs = 0). One can make a number of interesting observations from this data. No enantiomeric separation was observed for compounds **20–23**. It seems that chiral recognition by β-CD requires the cyclization of the 2- and 2′-hydroxyl groups of the binaphthyl moiety. For cyclized derivatives, both the size and com-

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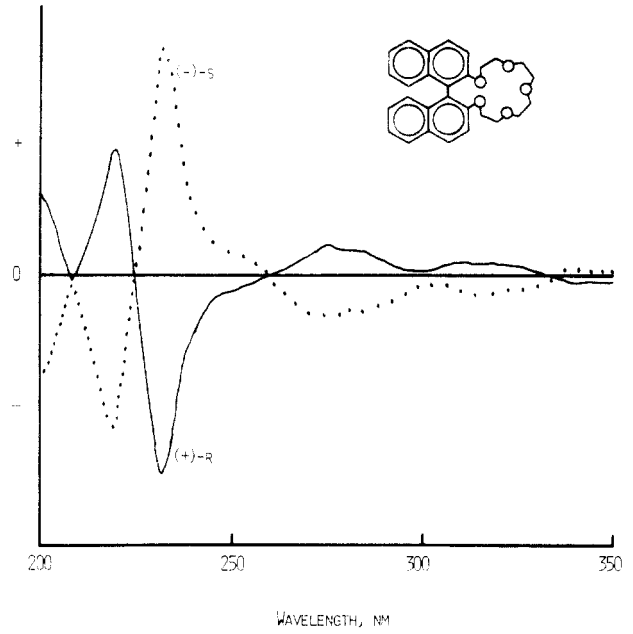

Figure 2. CD spectra of (−)-(*S*)-**4** and (+)-(*R*)-**4**.

position of the ring affected chiral recognition by β-CD. For the chiral crown ethers (compounds **1–6**), enantiomeric resolution increases with the size of crown moiety up to crown-4 (compound **3**) and then decreases. In the case of the hydrocarbon analogues of the crown ethers (compounds **15–19**), chiral recognition decreases with ring size. In fact no enantiomeric resolution is observed for **19** while the analogous crown ether (compound **5**) is resolved.

A number of synthetic variations of the 2,2′-binaphthyldiyl–crown-5 **4** were made so as to observe their effect on chiral recognition by β-CD. It was found that replacing one of the crown oxygens with sulfur or sulfoxide affected the chromatographic retention to a greater extent than the resolution (Rs) or separation factor (α). Surprisingly, however, the azacrown **10** showed no enantiomeric resolution while the related amide **11** was easily separated. Changes in the binaphthyl ring system affected enantiomeric resolution as well as retention. For example, enantiomers of compound **12** are retained five times as long and are more poorly resolved than those of its unsaturated analogue, **4**. It is apparent that chiral recognition by β-CD is dependent on both the nature and size of the "crown" substituent and the binaphthyl ring system.

Chiral stationary phases are potentially useful in organic synthesis for a number of reasons including the evaluation of enantiomer excess, preparative separation of enantiomers, and the determination of absolute configuration. The (+)-*R* enantiomer of compound **4** was synthesized in order to evaluate the potential of β-CD bonded phases in the latter of these. Circular dichroism spectra were taken of all separated enantiomers (Table I) and of (+)-(*R*)-**4**, which was synthesized from (+)-(*R*)-1,1′-bi-2-naphthol. CD spectra of (+)-(*R*)-**4** and (−)-(*S*)-**4** are shown in Figure 2. It was found that the first eluting peak of any enantiomeric pair (Table I) had a negative Cotton effect at 230 nm which was analogous to that of the (+)-(*R*)-**4** standard (Figure 2). This indicates that chromatographic retention might be used to evaluate specific configuration for related compounds with this system.

Previous work has shown that inclusion complex formation is usually necessary for chiral recognition by β-CD.[16] However, it is apparent from the data in Table I that longer retention of a compound does not automatically produce better enantiomeric resolution. Thus, in addition to inclusion complex formation, there may also be more traditional reversed-phase retention mechanisms at work. This can be demonstrated by independent measurement of the binding constants of 2,2′-binaphthyldiyl derivatives with free cyclodextrin. Typical results are shown in Table II. If chromatographic retention is strictly a function of inclusion complexation, then the order of the capacity factors (Table I) will mimic that of the binding constants (Table II). It is clear from the data that this is not always the case. Thus, while inclusion complexation may be necessary for chiral recognition, it is not the only factor involved in retention.

Table II. Binding Constants (K_b) of Four 2,2′-Binaphthol Derivatives with β-CD[a]

compd	ex, nm	em, nm	K_b
1	284	375	206
2	284	375	407
3	284	365	195
15	284	365	100

[a] The K_b values were determined with free β-CD in 10% methanol (aqueous) using fluorescence changes and Benesi–Hildebrand[27] plots.

Experimental Section

Methods. Melting points were taken with a Mel-Temp melting point apparatus and are uncorrected. IR spectra were obtained with a Nicolet MX-S spectrometer and are recorded in reciprocal centimeters. ^{1}H NMR spectra were recorded with a Varian EM360 spectrometer in deuteriochloroform, and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Mass spectra were taken on a 5995B Hewlett-Packard spectrometer. Optical rotation was recorded with a Perkin-Elmer 141 polarimeter. Elemental analysis was performed by Galbraith Laboratories, Inc. of Knoxville, TN. All separations were done at room temperature (21 °C) by use of a Shimadzu Model LC-4A liquid chromatograph with a variable wavelength detector. Additional information for specific compounds is given in Table I. Circular dichroism spectra were measured in a 1-cm cell with a Jasco 500A spectropolarimeter. CD spectra were taken of all optical isomers after LC separation (Table I) and collection. In order to obtain a sufficient amount of sample for the CD analyses, at least two successive chromatographic injections were required and the appropriate fractions added together. Fluorescence measurements were performed with a Perkin-Elmer LS-5 fluorescence spectrophotometer. Additional parameters are given in Table II.

Materials. Unless specified otherwise reagent grade reactants and solvents were obtained from commercial suppliers and used as received. Acetonitrile was kept over molecular sieves (5 Å). DMF was distilled over calcium hydride prior to use. Dioxane was purified by distillation from sodium metal. Compounds **1** and **7** were obtained according to the literature methods.[33] Racemic 2,2′-binaphthyldiyl–17-crown-5 **4** and 2,2′-binaphthyldiyl–23-crown-7 **6** were prepared by the Okahara closure from diols **20** and **21**, respectively.[34] Partial saturation of crown **4** produced **12**.[35] Acid phosphate **13** was prepared via its chloride by Cram's procedure.[36] Treatment of **13** with diazomethane produced methyl ester **14**.[37] Compound **15–17** were obtained from 1,1′-bi-2-naphthol and the appropriate dibromides according to the literature.[38] Diols **21**, **22**,[34] and hydroxycrown **24**[25] were available from a previous study. Ditosylates of the appropriate

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glycols were prepared by standard procedure.[39] β-Cyclodextrin bonded phase columns and bulk β-CD were obtained from Advanced Separation Technologies Inc., Whippany, NJ.

General Procedure for the Preparation of 2, 3, (+)-(*R*)-4, and 5. A 250-mL flask was evacuated, filled with nitrogen, and charged with 1,1'-bi-2-naphthol (0.86 g, 3.0 mmol) followed by 50 mL of dry acetonitrile. To this solution was added anhydrous cesium fluoride (2.28 g, 15.0 mmol), and the mixture was stirred at room temperature for 1 h. A solution of the appropriate ditosylate (3.0 mmol) in acetonitrile (20 mL) was added, and the mixture was stirred at 65 °C for 48 h. After filtration the solvent was removed in vacuo, and the residue was column chromatographed to afford a pure product. Specific details concerning purification of each of the products are given below.

Compound 2.[33] Column chromatography on alumina with benzene–ether (9:1) as eluent gave a 74% yield of pure **2**: *m/e* 356 (M^+; base peak).

Compound 3.[36] Chromatography on alumina with 30/60 petroleum ether–ethyl acetate (2:1) afforded an 18% yield of **3**.

Compound (+)-(*R*)-4.[40] Chromatography [alumina, petroleum ether–ethyl acetate (2:1)] gave a 20% yield of (+)-(*R*)-**4**: $[\alpha]^{20}_D$ +63.2° (*c* 2.5, $CHCl_3$). See the Results and Discussion section for further details.

Compound 5.[36] Chromatography [alumina, petroleum ether–ethyl acetate (1:1)] gave a 55% yield of pure **5**.

Preparation of Compound 8. A solution of *m*-chloroperbenzoic acid (0.20 g, 1.2 mmol) in 20 mL of dichloromethane was added dropwise to a stirred solution of thiacrown **7** (0.60 g, 1.3 mmol) in dichloromethane (13 mL) at 0 °C. The mixture was washed with an aqueous saturated solution of sodium bicarbonate (3 × 30 mL), dried over $MgSO_4$, and evaporated to give the crude reaction product. Purification by column chromatography (alumina, ethyl acetate and then ethyl acetate–methanol, 20:1) afforded 0.45 g (73%) of a glassy solid: IR (deposit on NaCl) 1126, 1091 (C–O), 1041 (S–O); ^1H NMR 2.3–4.45 (m, 16), 6.95–7.6 (m, 8), 7.65–8.1 (m, 4). Anal. Calcd for $C_{28}H_{28}O_5S$: C, 70.57; H, 5.92. Found: C, 70.34; H, 6.07.

Preparation of Dimesylate 23. A solution of diol **21** (6.48 g, 14.0 mmol) and triethylamine (6.2 mL, 45.0 mmol) in 60 mL of dichloromethane was cooled to −10 °C, and a solution of mesyl chloride (3.89 g, 34.0 mmol) in dichloromethane (60 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, diluted with cold dichloromethane (50 mL), and washed with 5% HCl, water, 5% $NaHCO_3$, and water again. After drying ($MgSO_4$) and filtration the solvent was evaporated to give 8.5 g (99%) of pure **23** as a heavy viscous pale yellow oil: IR (neat) 1352, 1175 [S(=O)$_2$], 1136 (C–O); ^1H NMR 2.80 (s, 6), 2.9–3.15 (m, 4), 3.3–3.55 (m, 4), 3.7–3.85 (m, 4), 4.0–4.25 (m, 4), 7.0–7.5 (m, 8), 7.65–8.1 (m, 4). Anal. Calcd for $C_{30}H_{34}O_{10}S_2$: C, 58.24; H, 5.54. Found: C 57.90; H, 5.68.

Preparation of Compound 9. A mixture of dimesylate **23** (7.50 g, 12.1 mmol), benzylamine (1.43 g, 13.4 mmol), and anhydrous sodium carbonate (6.2 g) in dry acetonitrile (180 mL) was stirred and refluxed for 3 days. The reaction mixture was filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography on alumina with petroleum ether–ethyl acetate (3:1) as eluent to give 3.51 g (54%) of **9** as white crystals: mp 122–124 °C; IR (deposit on NaCl) 1140, 1100 (C–O); ^1H NMR 2.3–2.7 (m, 4), 3.15–4.50 (m, 14), 6.9–8.1 (m, 17). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61. Found: C, 78.65; H, 6.72.

Preparation of Compound 10. A solution of **9** (2.90 g, 5.4 mmol) in dioxane (150 mL) containing 10% Pd/C (0.30 g) was hydrogenated at 55 °C and under 50 psi of hydrogen for 4 days. The catalyst was filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography on alumina with ethyl acetate–methanol (10:1) as eluent to afford 1.5 g (62%) of pure **10** as a glassy solid: IR (deposit) 3312 (N–H), 1134, 1091 (C–O); ^1H NMR 2.5–2.9 (m, 4), 3.05–4.6 (m, 13), 7.0–8.15 (m, 12); MS, *m/e* 443 (M^+; base peak). Anal. Calcd for $C_{28}H_{29}NO_4 \cdot H_2O$: C, 73.28; H, 6.72. Found: C, 72.96; H, 6.77.

Preparation of Compound 11. A solution of **10** (0.50 g, 1.1 mmol) and triethylamine (0.2 g, 1.1 mmol) in benzene (10 mL) was cooled with an ice bath, and trimethylacetyl chloride (0.14 g, 1.1 mmol) in benzene (10 mL) was added dropwise with stirring. The reaction mixture was stirred overnight at room temperature and then poured into water. The organic layer was separated and washed with 5% HCl, 10% $NaHCO_3$, and water. After drying ($MgSO_4$) and evaporation of the solvent the crude product was obtained, which was further purified by column chromatography on alumina with petroleum ether–ethyl acetate (2:1) as eluent to give 0.46 g (78%) of pure **11** as a glassy solid: IR (deposit) 1622 (C=O), 1130–1120 (C–O); ^1H NMR 1.23 (s, 9), 3.45 (s, 12), 3.6–4.4 (m, 4), 6.9–8.05 (m, 12). Anal. Calcd for $C_{33}H_{37}NO_5$: C, 75.12; H, 7.07. Found: C, 75.38; H, 7.27.

Preparation of Compound 18. A solution of 2.99 g (11.0 mmol) of 1,8-dibromooctane in DMF (35 mL) was added dropwise under nitrogen over 5 h to a stirred mixture of 1,1'-bi-2-naphthol (2.86 g, 10.0 mmol) and anhydrous potassium carbonate (3.04 g, 22.0 mmol) in DMF (50 mL) at 85 °C. After the reaction mixture was heated for an additional 18 h it was poured into water and extracted with benzene. After the mixture was dried ($MgSO_4$) the solvent was removed in vacuo. The residue was purified by column chromatography on alumina with petroleum ether–benzene (2:1) as eluent to afford 0.23 g (6%) of white crystals: mp 165–166 °C; IR (deposit) 1145, 1091 (C–O); ^1H NMR 0.7–1.8 (m, 12), 3.65–4.35 (m, 4), 6.9–8.05 (m, 12); MS, *m/e* 396 (M^+; base peak). Anal. Calcd for $C_{28}H_{28}O_2$: C, 84.81; H, 7.12. Found: C, 84.56; H, 7.17.

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