Allosteric Effects in Organic Chemistry. Site-Specific Binding

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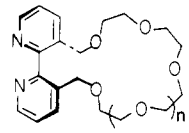
Abstract: The synthesis and binding properties of new macrocyclic polyethers are described. These systems incorporate 2,2′-bipyridyl functions in such a fashion that binding of metal nuclei can occur at either the macrocycle or the bipyridyl function. Evidence is presented that binding of alkali metals occurs at the crown ether cavity while binding of transition metals occurs at the bipyridyl function. Binding of two different metals is interpreted in terms of a simple model for allosteric effects.

The model systems of bioorganic chemistry have helped identify a number of components which contribute to the catalytic efficiency of enzymes. Acid–base and nucleophilic catalysis, approximation, selectivity, and other features have been successfully imitated. The regulation of catalytic activity has not, however, yet been attempted. In enzymology regulation can be accomplished by *allosteric effects:* the binding of an effector at a remote, allosteric site can cause conformational changes at the active site which alter the reactivity of the enzyme to its substrate.[1] This remarkable feature of enzymic catalysis suggests an unusual method for enhancing the selectivity of processes involving small molecules in solution, and we have begun to construct systems capable of allosteric behavior. The minimum requirements appear to be (1) an active site, (2) an allosteric site, and (3) a mechanism (in the engineering sense) which connects them. Here we introduce such a system, demonstrate site-specific binding, and offer evidence for an allosteric effect.

Consider the macrocyclic polyethers **1**. Two binding sites are present: the crown ether for binding to alkali and ammonium ions, and the 2,2′-bipyridyl function for binding to other metal nuclei. These sites, though separated, are not expected to behave independently. Chelation of metals at the bipyridyl function forces the aromatic nuclei toward coplanarity, thereby restricting the conformational freedom of the macrocycle. Since the binding properties of crown ethers are sensitive to changes in conformations[2] or effective "size",[3] chelation at the bipyridyl (allosteric) site alters the reactivity of the crown ether (active) site.[4] Thus structures **1** incorporate the necessary requirements for modeling allosteric behavior.

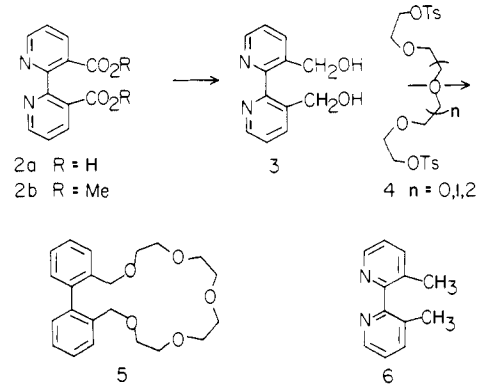


1 a n = 0
b n = 1
c n = 2

Synthesis

The new crown ethers **1** were prepared without difficulty from 1,10-phenanthroline as shown in Scheme I. Permanganate oxidation to 2,2′-binicotinic acid[5] (**2a**), esterification,[6] then reduction gave the diol **3**, mp 144–145 °C. Condensation of **3** with the appropriate glycol ditosylates[7] afforded modest (15–40%) yields of **1a–c**. A parallel sequence starting from biphenic acid gave the control substance **5**, while the model bipicoline **6** was prepared by Ullmann coupling of 2-bromo-β-picoline as described by Case.[8]

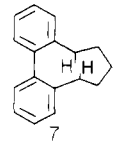
Scheme I



2a R = H
2b R = Me
3
4 n = 0,1,2
5
6

Properties

1. NMR Spectra. The chiral nature of these macrocycles was evident to varying degrees in their NMR spectra. For example, in the 16-membered **1a** and the 19-membered **5** the benzyl protons are diastereotopic and appear as an AB quartet at ambient temperature. Since this pattern persists at even 130



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°C, the racemization process must involve a high activation barrier. For comparison, the bridged biphenyl **7** described by Mislow[9] shows a barrier of 24 kcal/mol caused by the repulsion of the nonbonded benzyl hydrogens as the aromatic nuclei become coplanar. Such repulsions must also exist during racemization of **1**.

In contrast, the 19-membered **1b** (Figure 1) and the 22-membered **1c** showed sharp singlets for the benzyl protons even at 250 MHz. The most likely reason is that these macrocycles can adopt conformations in which these protons appear equivalent. The alternative explanation requires a rapid racemization process in which one of the aromatic rings passes through the macrocycle. Space-filling models (CPK) show this process to be unlikely in 19-membered **1b** or **5**, but possible in the 22-membered **1c**. No attempts have been made at resolution of these compounds.

2. Binding to Group 2 and Transition Metals. Combination of the waxy solid **1b** or the oily **1c** with $ZnCl_2$, $HgCl_2$, $PdCl_2$, or $W(CO)_6$ afforded crystalline complexes **8**. These substances gave microanalysis values in excellent agreement with that calculated for 1:1 complexes except in the case of **8b**, which gave values more consistent with a 2:1 (Hg to ligand) compo-

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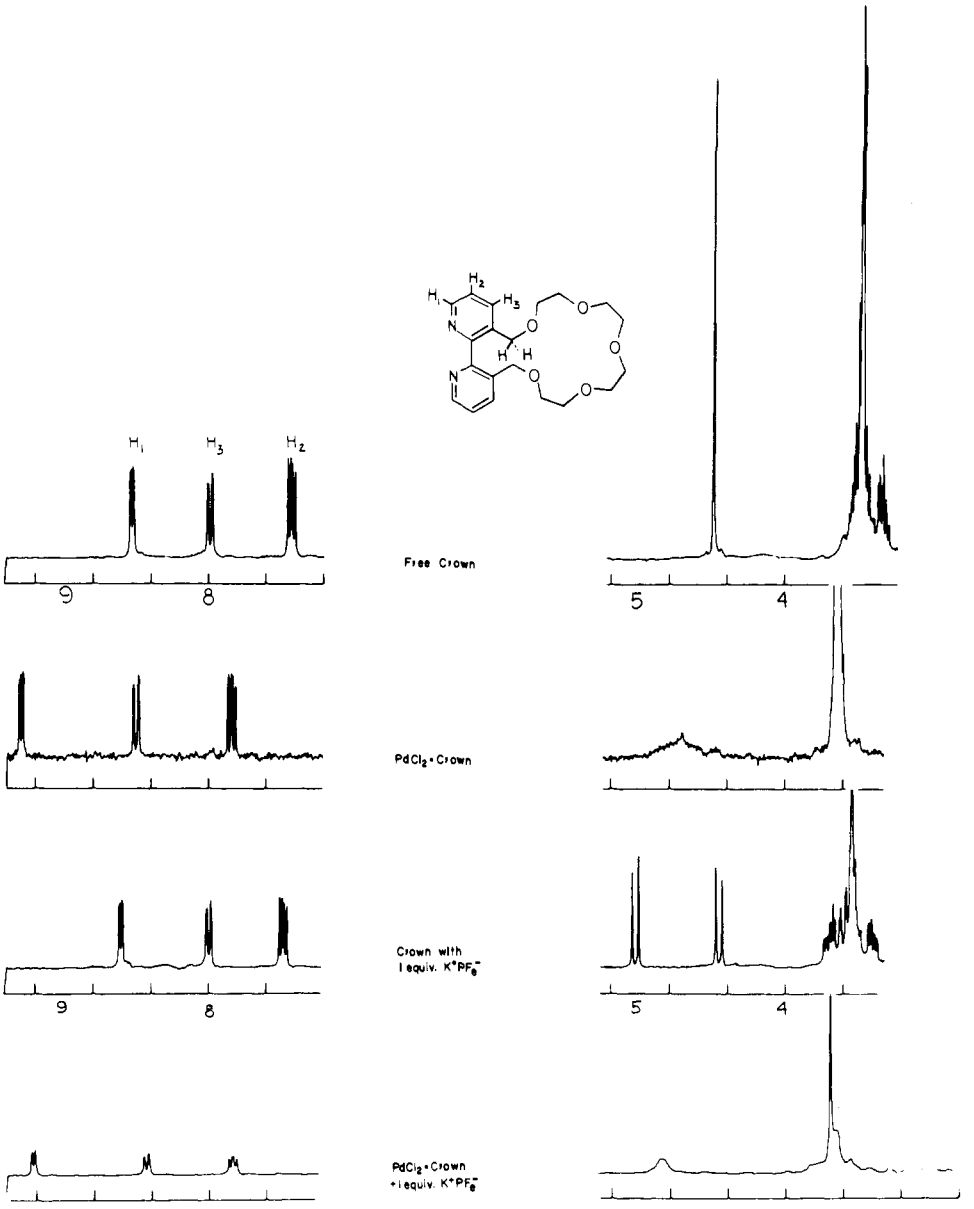
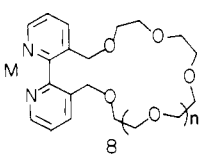


Figure 1.



	M =	n =
a	$HgCl_2$	1
b	"	2
c	$ZnCl_2$	1
d	"	2
e	$PdCl_2$	1
f	"	2
g	$W(CO)_4$	1

sition. The NMR spectra of these compounds in solution revealed that the metals are bound to the bipyridyl nitrogens. The simplicity of the spectra indicate complexes of high symmetry and the downfield shifts observed for the aromatic protons are quite similar to those observed in the corresponding complexes of the model bipicoline **6**. In addition, the broadening of the signal for the benzylic hydrogens (Figure 1) indicates that racemization is occurring in these complexes. In **8e**, for example, these signals appear as an AB quartet at low temperatures and a singlet at high temperatures with coalescence at 10 °C (90 MHz).[10]

3. Binding to Alkali Metals. The ability of the new macrocycles to bind alkali metals was established in a qualitative sense by NMR spectroscopy. For example, the spectrum of **1b** in the presence of 1 equiv of $K^+PF_6^-$ is shown in Figure 1. The aromatic region remains undisturbed while the signals in the macrocycle suffer considerable changes, indicating that the latter is the site of binding. Again the most dramatic change is in the signal for the benzyl protons which separate to an AB quartet upon complexation. In Figure 2 the degree of this separation is shown to be a function of ion ($NaBPh_4$) to **1b** ratio.

While estimation of association constants, K_a, can be made from the spectra of Figure 2,[11] we found it more convenient to determine these values by the technique involving extractions of alkali salts, e.g., picrates, from aqueous solution into organic phases by crown ethers.[12] The appropriate expression,[13] assuming that only 1:1 complexes are formed, is given in eq 1. The distribution constant of the metal picrate in the absence of the complexing agents is K_d, F is the fraction of crown complexed, and $[M^+]_i$ and $[C]_i$ are the initial concentrations of salts in the aqueous volumes (V_{H_2O}) and the complexing agents in the $CHCl_3$ volumes (V_{CHCl_3}), respectively. The results given in Table I are based on this expression using published[13] values of K_d for alkali and ammonium picrates.

$$K_a = \frac{F}{K_d(1-F)\{[M^+]_i - F[C]_i(V_{CHCl_3}/V_{H_2O})\}^2} \quad (1)$$

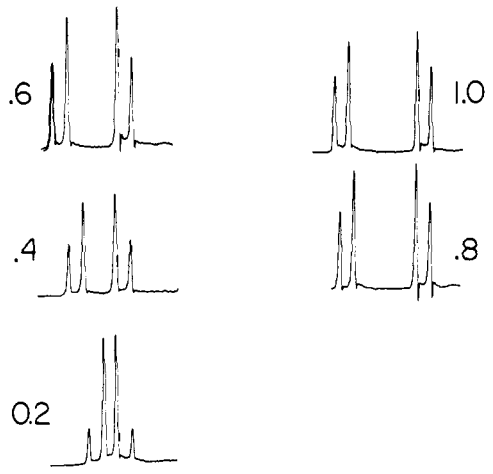


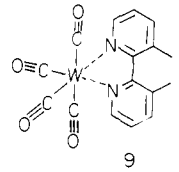
Figure 2. The NMR spectrum of the benzyl protons of **1b** as $NaBPh_4$ is added up to 1 equiv.

Table I. Log K_a for Picrate Extractions

	Li^+	Na^+	K^+	NH_4^+	Rb^+	Cs^+
1a	4.3	3.6	3.8	4.0	3.7	4.2
1b	5.0	4.6	5.1	4.8	4.2	5.1
1c	6.0	6.0	5.5	6.0	6.2	6.6
5	4.2	4.6	4.5	4.2	4.0	3.9
6			1.8	1.5		

4. Binding to Two Different Metals. Addition of alkali ions to the solutions of bipyridyl complexes **8** had little effect on their NMR spectra (Figure 1). This indicated that binding to the ether cavity may be much diminished when the nitrogens of the bipyridyl are involved in chelation. Determining the degree of diminution has posed a number of experimental problems. Both Zn and Hg were removed from their respective complexes **8** during extractions. The Pd complexes bound irreversibly to picrates and reacted with tetraphenylborates,[14] whereas the complex **9** bound reversibly to picrates with high ($>10^3$) association constants. We are currently exploring the determination of *K*a's by conductance using alkali chlorides in MeOH as described by Frensdorff;[3b] these measurements should circumvent the difficulties involving incompatible counterions.

Meanwhile, a compatible system for extractions has been found in the tungsten complex **8g** with BPh_4^- ions. In parallel experiments with **1b** and its complex **8g** a modest allosteric effect was found. Table II gives relative *K*a's for these and



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controls **5** and **9** normalized to that of **1a** since K_d is not known.

Discussion

Two trends can be identified from the picrate extraction experiments. Firstly, the extent of binding appears to be largely a function of the number of oxygen atoms in the macrocycle. Secondly, there is little, if any, ion selectivity shown by a given macrocycle. However, some binding does not involve the ethereal region (**1b** vs. **5** and spot checks with **6**), and it is possible that the inherent selectivity of the ethers could be masked by some selectivity in binding to the bipyridyl regions.[16] The selectivity issue is further clouded by the uncertainty in whether only 1:1 complexes are formed in all cases.

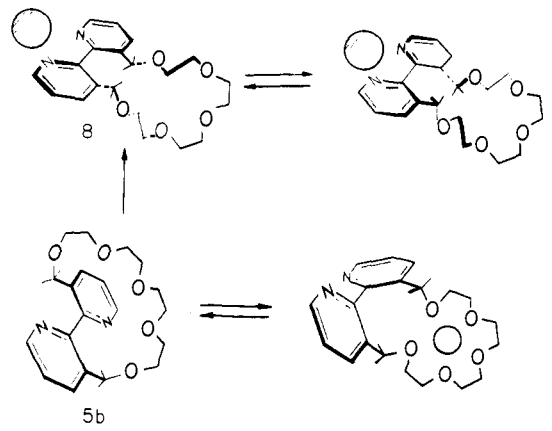
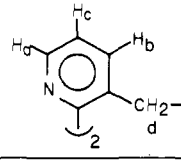


Figure 3.

Table II. Relative K_a for $Na^+BPh_4^-$

1a	1.0				
1b	7.5	**5**	7.6	**8g**	1.4
1c	42				
9	0.6				

Table III. NMR Features of Bipyridine Derivatives in $CDCl_3$



$J_{ab} = 2$, $J_{ac} = 5$, $J_{bc} = 8$

	3 (R = OH)	**6** (R = H) (in acetone-d_6)	**1a**	**1b**[a]	**1c**
δH_a	8.5	8.44	8.5	8.54	8.57
δH_c	7.34	7.28	7.29	7.34	7.35
δH_b	7.85	7.73	7.88	7.94	7.95
δ d	4.40 (s)	2.11 (s)	4.41, 4.54 AB q J = 13 Hz	4.51 (s)	4.52 (s)

[a] 250-MHz spectrum in Figure 1.

A reasonable interpretation of these systems—subject to the ambiguities noted above—can be made by reference to Figure 3. The free crown may adopt a variety of conformations in solution, wherein the size of the crown cavity is related to the dihedral angle defined by the two aromatic rings. In the figure this angle is shown at its maximum value (slightly less than 180°). Binding to an alkali metal gathers the oxygen atoms and in particular brings the benzylic oxygens close to each other. This fixes the position of the benzyl hydrogens and the size of the dihedral angle (ca. 90° for the case shown). This facile adjustability of the ethereal cavity size can be the cause of the nonselectivity shown by these systems for various ions.

Chelation at the bipyridyl site forces the sets of benzylic hydrogens toward each other and lowers the dihedral angle to near 0°. The consequence is that the benzylic oxygens are directed away from one another in such a manner that they cannot both be a part of the ether cavity. Space-filling molecular models indicate that, at best, four of the five oxygens in **8** can direct lone pairs toward the center of a cavity. Accordingly, the affinity toward sodium decreases to about that observed in the case of **1a**. Whether this explanation can be used to develop selectivity in these systems is the focus of our present research. In addition, we are currently constructing related systems which incorporate subunits and cooperative binding.

Table IV. Physical Data for Metal Complexes 8

complex	components	mp, °C	anal., % C	H	N	M	Cl	NMR features benzyl δ	aromatic δ
8a	**1b**·$HgCl_2$	138	36.97	4.08	4.21	31.27 (Hg)	10.79	4.43, 4.62	7.46
			calcd 37.19	4.06	4.34	31.05	10.98	AB q, J = 12 Hz	8.1, 8.53
8b	**1c**·$2HgCl_2$	145	27.48	3.14	2.91	41.72 (Hg)	14.75	4.41, 4.69	7.4
			calcd 28.94	3.21	3.07	39.61	14.23	AB q, J = 14 Hz	8.04, 8.3
8c	**1b**·$ZnCl_2$	240	46.87	5.35	5.47		14.10	4.4, 4.6	7.3
			calcd 47.03	5.13	5.48		13.88	AB q, J = 14 Hz	8.41, 8.53
8d	**1c**·$ZnCl_2$	182	47.51	5.59	4.98	11.60 (Zn)	13.00	4.4, 4.63	
			calcd 47.63	5.45	5.05	11.78	12.78	AB q, J = 13 Hz	
8e	**1b**·$PdCl_2$	151	43.70	5.00	5.01	19.11 (Pd)	13.02	4.52	7.48
			calcd 43.54	4.75	5.08	19.28	12.85	broad s	8.30, 9.30
8f	**1c**·$PdCl_2$	190	44.58	5.18	4.75	18.03 (Pd)	12.04	4.62	7.57
			calcd 44.35	5.08	4.70	17.86	11.90	broad s	8.38, 9.38
8g	**1b**·$W(CO)_4$	143 dec	43.26	4.13	4.07	27.17 (W)		4.60	7.44
			calcd 43.01	3.91	4.18	27.42		broad d J = 11 Hz	8.20, 9.14

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., high-resolution mass spectra were obtained on a Varian CH-5 instrument, and NMR spectra were obtained at 60 MHz unless otherwise specified.

3,3'-Dicarbomethoxy-2,2'-bipyridine (2b). A solution of 2,2'-binicotinic acid,[5] 3.22 g (13.2 mmol), and *N*-methylmorpholine, 2.93 mL (26.4 mmol), in 100 mL of MeOH at 0 °C was treated with methyl chloroformate, 2.04 mL (26.4 mmol), over a 10-min period. After the solution was stirred for 30 min at ambient temperature the solvent was evaporated and the solid residue was partitioned between $CHCl_3$ (100 mL) and 25 mL of saturated $NaHCO_3$. The organic phase was washed with two additional portions of bicarbonate solution, then evaporated to give crystalline **2b**, 3.07 g (86%), mp 151 °C (lit.[6] mp 152 °C).

3,3'-Dimethylol-2,2'-bipyridine (3). A commercial solution of Vitride (sodium bis[2-methoxyethoxy]aluminum hydride) containing 24 mmol of reagent in 20 mL of ether was added dropwise over a 30-min period to a solution of diester **2b**, 1.5 g (5.5 mmol), in 150 mL of THF at 0 °C under N_2. After 1 h at 0 °C the excess reagent was decomposed by the addition of saturated NH_4Cl solution. $CHCl_3$ (100 mL) was added, the solution was decanted, and the residue was washed with 3 × 100 mL of $CHCl_3$. Evaporation of the combined organic layers gave a tan solid which was recrystallized from benzene to yield 1.0 g (84%) of the diol **3**, mp 144–145 °C. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.44; H, 5.79; N, 12.97. Table III gives NMR data for this substance and the bipyridyl crown ethers derived from it.

Bipyridyl Crown Ethers 1a–c. The following general procedure, given for **1b**, was employed. The diol **3**, 2.57 g (11.9 mmol), in 400 mL of THF was treated, under N_2, with KH oil dispersion (88.5 mmol) followed by refluxing for 1 day. A solution of tetraethylene glycol ditosylate[7c] in 50 mL of THF was added and refluxing was continued for another day. The cooled solution was quenched by the addition of 10 mL of H_2O followed by evaporation of the volatiles. The residue was dissolved in 300 mL of $CHCl_3$, then extracted into 1 N HCl (3 × 100 mL). The combined aqueous phases were neutralized with 2.5 N KOH, then extracted with 3 × 100 mL of $CHCl_3$. Evaporation of the combined organic phases gave the crude product which was purified by column chromatography on alumina using acetone–CH_2Cl_2 (3:7) as eluent. The appropriate fraction was freed of volatiles by Kugelrohr evaporation to give 1 g (25%) of **1b** as a waxy semisolid. Exact mass: calcd for $C_{20}H_{26}N_2O_5$, 374.184; found, 374.182.

With pentaethylene glycol ditosylate the procedure afforded **1c** (15%). Calcd for $C_{22}H_{30}N_2O_6$, 418.210; found, 418.212. With triethylene glycol ditosylate **1a**, mp 103 °C, was obtained in 50% yield. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.29; H, 6.88; N, 8.50.

Biphenyl crown ether 5 was obtained as an oil in 30% yield by the general procedure, using 2,2'-dimethylolbiphenyl[15] and tetraethylene glycol ditosylate. Calcd for $C_{22}H_{28}O_5$, 371.194; found, 371.194. NMR ($CDCl_3$): δ 3.5 (m, 16) 4.29, 4.41 (AB q, J = 7, 4 Hz) 7.3 (m, 8).

3,3'-Dimethyl-2,2'-bipyridine (6) was prepared as described by Case.[8] Its NMR ($CDCl_3$) is given in Table III. Metal complexes were prepared by the procedures described for the complexes **8** (vide infra). $ZnCl_2$: mp 280–282 °C; NMR (acetone-d_6) δ 2.16, 7.60, 8.06, 8.35. $PdCl_2$: mp >300 °C dec; NMR ($CDCl_3$) δ 2.43, 7.53, 7.85, 9.35. $W(CO)_4$: mp 188–190 °C dec; NMR ($CDCl_3$) δ 2.35, 7.36, 8.16, 9.03.

Metal Complexes 8. The $ZnCl_2$ and $HgCl_2$ complexes **8a–d** were prepared by combining equimolar amounts of **1** and the appropriate halides in ethanol for 15 min. Evaporation of the solvent and recrystallization from acetone gave nearly quantitative yields of the complexes (physical data in Table IV). $PdCl_2$ complexes **8e** and **8f** were prepared by combining **1** in MeOH with aqueous solutions of $NaPdCl_4$ and recrystallizing the resulting orange precipitates from water. The complexes with tungsten were prepared by refluxing an equimolar solution of **6** or **1b** and $W(CO)_6$ in xylene under N_2 for 3 h. Cooling and dilution with petroleum ether gave dark red precipitates which were triturated with hexane and dried in vacuo to give **8g** as dark red crystals.

Picrate Extractions with 1 and 5. The general procedure of Cram[13] was used. Typically a solution (0.5 mL) of picrate in H_2O (0.008 M) and **1** (0.2 mL) in $CHCl_3$ (0.075 M) were combined in a centrifuge tube and stirred vigorously for 3 min. A blank tube was also prepared from **1** in $CHCl_3$ and H_2O without picrate. The layers were separated and 0.05 mL of the organic phases was removed and diluted to 5 mL with MeCN. The UV spectrum of the picrate-containing sample was taken against the blank. The absorbance at the appropriate wavelength[13] was used to calculate the date in Table I. None of the crowns were found in the aqueous phases.

Extractions with NaB(Ph)$_4$. Solutions of $NaB(Ph)_4$ in D_2O (8 mL, 0.01 M) and crowns **1a, b, 5**, and **8a** in $CDCl_3$ (4 mL, 0.0194 M) were combined and stirred vigorously for 10 min. The layers were separated and the organic phases were concentrated to obtain NMR spectra. Integration gave the concentration of $NaB(Ph)_4$ to crown, from which the data of Table II were calculated.

Acknowledgment. We are indebted to the National Institutes of Health for financial support and Mr. T. Costello for technical assistance.

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(16) Large ($>10^3$) association constants as measured by the extraction technique were observed between any picrate and the complex **9**, suggesting that the picrate ion itself is involved in bonding.

Nitroxides. 87. ESR Determination of the Thermodynamic Data for the Association of Two Paramagnetic Enantiomers with β-Cyclodextrin

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Abstract: Starting from (*R*)-(+)-3-methylcyclohexanone (and from racemic 3-methylcyclohexanone) (1″*R*,3″*R*)- (and racemic) dispiro[2,2,6,6-tetramethylpiperidine-1-oxyl]-4,4′-(oxazolidine-3′-oxyl)-2′,1″(3″-methylcyclohexane) have been prepared. Their complexation with β-cyclodextrin has been studied by electron spin resonance and the association constants of the two enantiomers have been determined, thus providing direct spectroscopic evidence for the enantiomeric selectivity in the complexation by cyclodextrin. The ratio of association constants measured by ESR is similar to the ratio of association constants of related diamagnetic enantiomers of the 3-methylcyclohexanone.

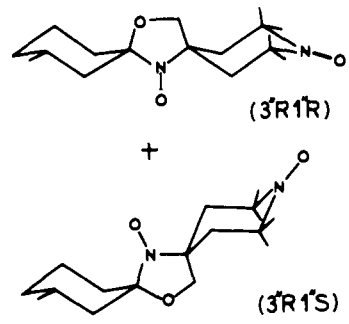
In solution, cyclodextrins form inclusion complexes without covalent binding with many molecules.[1-5] They selectively complex one of the two enantiomers of an optically active molecule; the precipitating inclusion complex is enriched in one of the enantiomers.[6a,b]

Cooper and Mac Nicol have shown by microcalorimetry a distinct discrimination in the binding of optical isomers.[7] Recently, we have used an ESR displacement method to show this selective association in solution with diamagnetic enantiomers.[8]

In this article, we want to determine by ESR the association constants K^+ and K^- of β-cyclodextrin with the two enantiomers of an optically active *paramagnetic* molecule. Since biradicals with large dipolar splitting allow an easy determination of the inclusion equilibrium thermodynamic data,[5] we have chosen to study the inclusion of an optically active nitroxide biradical in β-cyclodextrin.

This biradical (B) has been prepared from 3-methylcyclohexanone and a biradical spin label.[8-10] Two forms have been obtained: an optically active form (B*d*) from (*R*)-(+)-3-methylcyclohexanone and a racemic form (B*dl*) from racemic (±)-3-methylcyclohexanone. In principle two epimers can be obtained (Scheme I) in which the nitrogen is cis or trans to the methyl substituent in the cyclohexane ring [starting from (*R*)-(+)-3-methylcyclohexanone, these two epimers are 1″*R*,3″*R* and 1″*S*,3″*R*]. In each case, a single product has been obtained and shown to be unique by chromatography and recrystallization. The two forms have the same nuclear magnetic resonance spectra.[8] By comparison with the NMR spectra of oxazolidinic monoradicals,[11-13] it can be deduced that the cyclohexane ring is in a chair conformation and that the nitrogen and the methyl group are both in equatorial position. This shows that the single product obtained is the 3″*R*,1″*R* biradical from the 3*R* ketone and the racemic mixture of 3″*R*,1″*R* and 3″*S*,1″*S* biradicals from the racemic ketone.

Scheme I



Electron Spin Resonance Study

The ESR spectra have been recorded on a Varian E 12 spectrometer equipped with a variable-temperature accessory. Samples have been prepared by adding 10 μL of a solution of biradical B*d* (or B*dl*) in dimethyl sulfoxide (Me_2SO) to 1 mL of a Me_2SO/water (1/1 by volume) mixture or to 1 mL of a β-cyclodextrin solution in the same solvent. The following concentrations have been used: (I) β-cyclodextrin 5×10^{-2} M, B*d* (or B*dl*) 10^{-3} M; (II) β-cyclodextrin 10^{-2} M, B*d* (or B*dl*) 0.25×10^{-3} M.

In the absence of cyclodextrin, biradical B*d* (or B*dl*) (10^{-3} M in the Me_2SO/water solvent) shows a single broad line of ca. 40 G width (from which a rotational correlation time can be estimated, $\tau_c \simeq 10^{-10}$ s).[14] In the presence of cyclodextrin (5×10^{-2} M) at 20 °C, biradical B*d* (10^{-3} M) shows the spectrum presented in Figure 1. At the center of the spectrum, three narrow lines (c, d, e) superimposed on a broad line can be observed: we assign these three narrow lines to monoradical traces (less than 3% of biradical) and the broad line to uncomplexed biradical. On each side of the central lines, four lines (a, b, f, g) are observed, the symmetrical lines being separated

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