Synthesis and Complexing Properties of a Semirigid System Containing Two Convergent Macrocyclic Polyethers

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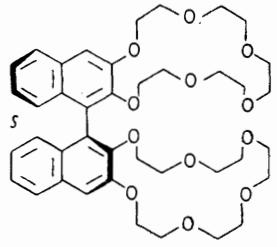
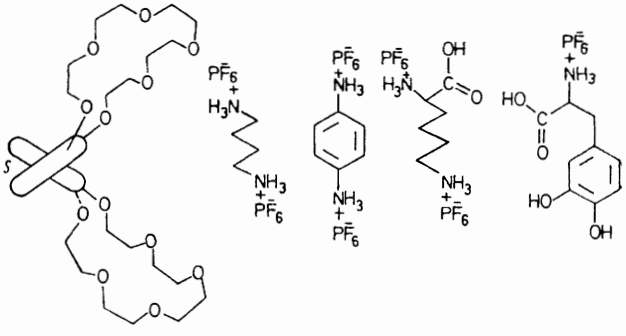
Summary Racemic bis-1,1′(2,3-naphtho-18-crown-6) has been synthesized and found to complex and lipophilize by complementary arrangement of the binding sites, the hexafluorophosphate salts of tetramethylenediamine, pentamethylenediamine, *p*-phenylenediamine, and racemic salts of DOPA, lysine, cystine, and glutamic acid.

SUBSTRATE–ENZYME binding site relationships are multiple, and complementary in location, electronic character, and shape. In the design of synthetic hosts to bind simple organic guest compounds containing multiple functional groups, the problem of reconciling the convergence of potential binding sites with a low molecular weight can be solved in several ways. One solution involves incorporating the binding sites into polycyclic macro-ring cages which are rigid enough not to collapse on one another, and yet have large enough holes for entry and departure of guests.[1] A second solution is to incorporate a rigid unit into the macro-ring assemblies of the binding sites which holds the assemblies in a convergent relationship. We report here the synthesis and complexing properties of the host (*RS*)-(**1**), each of whose enantiomers contains a C_2 axis. The binaphthyl unit of either enantiomer of (**1**) in Corey–Pauling–Koltun (CPK) molecular models holds two convergent 18-crown-6 units at the correct distance from one another to complex simultaneously the hydrogen bonding parts of a variety of biologically important polyfunctional guest compounds. Throughout this investigation, only racemic materials were used.

Treatment of 2,2′,3,3′-tetrahydroxy-1,1′-binaphthyl (*RS*)-(**2**) (60% from 2,3-dihydroxynaphthalene)[2] with pentaethyleneglycol ditosylate in a mixture of H_2O, KOH, and tetrahydrofuran (THF) (refluxed and stirred under nitrogen for 1·5 days) gave (*RS*)-(**1**) (30%, after gel permeation chromatography), m.p. 159·5—161 °C (crystallized from wet CH_2Cl_2–Et_2O), which required three days at 142 °C *in vacuo* to dry for characterization.†‡ Since CPK models indicated



(*S*)-(1)



(*S*)-(1) as host guests

that three structures isomeric to (*RS*)-(**1**) (one is threaded) could be assembled given (*RS*)-(**2**) and two pentaethylene

† Carbon and hydrogen analyses were within 0·30% of theory; ^{1}H n.m.r. spectra in $CDCl_3$ were as expected.

‡ 70 eV mass spectrum gave the molecular ion.

glycol units, (*RS*)-(**1**) was also prepared by coupling two 2,3-naphtho-18-crown-6 units (**3**).[3] Cycle (**3**) was brominated (1·3 equiv.) at 0 °C in CH_2Cl_2 to give 1,4-bromo-2,3-naphtho-18-crown-6†‡ (**4**; 6%, m.p. 109—110 °C) and 1-bromo-2,3-naphtho-18-crown-6†‡ (**5**; 65%, oil) which were separated by chromatography. A filtered Grignard solution made from (**5**) in dry THF under nitrogen was added to a mixture of powdered anhydrous $CoCl_2$, THF, and EtBr,[4] and the resulting solution after 1 h was warmed (precipitate). The desired product, m.p. 164—165 °C [undepressed by admixture with (*RS*)-(**1**)] was isolated by chromatography and crystallization (2·3%), and possessed the t.l.c. and spectroscopic properties of (*RS*)-(**1**).

In a qualitative survey, potential guests were selected to evaluate the use of CPK molecular models of complexes in order to predict the complementary arrangement of binding sites between host and guest. One unit of the bifunctional host (*RS*)-(**1**) was compared to two units of the monofunctional host (**3**) in both lipophilizing and binding abilities. Solutions of (*RS*)-(**1**) (0·05M) or of (**3**) (0·1M) in $CDCl_3$ containing 0—10% CD_3CN were shaken at 25 °C with D_2O containing guest (0·05—1·5M) (pH 0—1 with HPF_6). The ^1H n.m.r. spectrum of the organic layer was used to estimate the ratios of guest to host ([G]:[H]) present at equilibrium. When complexed, the two hosts showed broadening of their methylene ^1H n.m.r. spectral bands. With (**3**), broadening was relatively slight, but with (*RS*)-(**1**) it was extensive and accompanied by gross changes in the fine structure and peak positions. In no runs could the host be detected in the D_2O layer, and in the absence of a host, no guest could be detected in the organic layer. The results are in the Table.

When the tetramethylenediamine and *p*-phenylenediamine salts were extracted with (*RS*)-(**1**) in $CDCl_3$, 1:1 complexes crystallized from the oily third layer that formed, and were characterized.† The detailed *X*-ray crystal structure of tetramethylenediamine salt complex with (*RS*)-(**1**) was determined.[5] As expected from examination of the CPK model, the two inside faces of the macrocycles complexed the two ammonium groups, and the four methylene groups were between the two macrocycles in two *gauche* and one (central) *anti* conformations. The complex possessed a C_2 axis, and the dihedral angle for the two naphthalene rings was 78°.

In $CDCl_3$, 1 equiv. of (*RS*)-(**1**) extracted 1 equiv. of racemic DOPA salt from D_2O (run 5) whereas (**3**) in complexing this salt formed a third insoluble layer (run 6). In $CDCl_3$–CH_3CN(6%), 1 equiv. of (*RS*)-(**1**) extracted 0·50 equiv. of racemic lysine salt from D_2O (run 3), whereas (**3**) in complexing this salt formed a third layer (run 4). In runs 14 and 15 in $CDCl_3$–CD_3CN(7%), both (*RS*)-(**1**) and (**3**) gave 2 layers with the lysine salt, (*RS*)-(**1**) gave [G]:[H] = 0·50, whereas (**3**) gave a normalized (corrected to 2 mol of host per mol of guest) [G]:[H] of 0·90. In CDCl$_3$–6%CD$_3$CN, both (*RS*)-(**1**) and (**3**) extracted from D_2O the salts of racemic DOPA, or pentamethylenediamine (runs 7–10). With the DOPA salt, (*RS*)-(**1**) gave [G]:[H] = 0·25 (run 7), and (**3**) gave a normalized [G]:[H] of 0·28 (run 8) in the organic layer. With pentamethylenediamine salts, (*RS*)-(**1**) gave [G]:[H] = 0·72 (run 9) and (**3**) gave a normalized [G]:[H] of 0·92. In $CDCl_3$–CD_3CN(10%) with (*RS*)-(**1**), a higher concentration of the salt gave [G]:[H] *ca.* 1 for racemic lysine and cystine salts, but <0·05 for the racemic glutamic acid salt (runs 11, 12, and 13, respectively).

All these comparisons indicate that one molecule of host (*RS*)-(**1**) containing two attached and convergent sets of binding sites is much better at extracting the diamine salts into chloroform than are two molecules of nonattached (**3**) each containing one set of binding sites. Thus the bifunctional host with two co-operatively acting binding sites appears to cover more completely with a lipophilic skin the diamine salts than do two monofunctional hosts. However, when enough of the more polar acetonitrile is present in the chloroform to dissolve both types of complexes, one molecule of the bifuctional host is roughly comparable in binding ability to two molecules of the monofunctional host. Probably the advantages of the collection and orientation of binding sites prior to complexation in (*RS*)-(**1**) are counterbalanced by the loss of several conformational degrees of freedom of the guests when complexed by this relatively rigid host as compared to complexation by two

TABLE. Abilities of bifunctional host (*RS*)-(**1**) and monofunctional host (**3**) to complex and lipophilize polyfunctional guests at 25 °C

	Host			Guest (racemic when chiral)			
Run No.	Structure	Solvent	Conc. /M	Structure	Conc. /M	No. layers	[G]:[H] $CDCl_3$ layers
1	(**1**)	$CDCl_3$[a]	0·05	$PF_6NH_3[CH_2]_4NH_3PF_6$	0·05[b]	3	1
2	(**1**)	$CDCl_3$[a]	0·05	*p*-$PF_6NH_3C_6H_4NH_3PF_6$	0·10[b]	3	0·4
3	(**1**)	$CDCl_3$–CD_3CN[c,d]	0·05	$PF_6NH_3[CH_2]_4CHCO_2H(NH_3PF_6)$	0·50[c]	2	0·5
4	(**3**)	$CDCl_3$–CD_3CN[c,d]	0·10	$PF_6NH_3[CH_2]_4CHCO_2H(NH_3PF_6)$	0·50[c]	3	—
5	(**1**)	$CDCl_3$[a]	0·05	3,4-$(HO)_2C_6H_3CH_2CHCO_2H(NH_3PF_6)$	1·5[c]	2	1
6	(**3**)	$CDCl_3$[a]	0·10	3,4-$(HO)_2C_6H_3CH_2CHCO_2H(NH_3PF_6)$	1·5[c]	3	No host
7	(**1**)	$CDCl_3$–CD_3CN[c,d]	0·05	3,4-$(HO)_2C_6H_3CH_2CHCO_2H(NH_3PF_6)$	0·50[e]	2	0·25
8	(**3**)	$CDCl_3$–CD_3CN[c,d]	0·10	3,4-$(HO)_2C_6H_3CH_2CHCO_2H(NH_3PF_6)$	0·50[e]	2	0·14
9	(**1**)	$CDCl_3$–CD_3CN[c,d]	0·05	$PF_6NH_3[CH_2]_5NH_3PF_6$	0·050[e]	2	0·72
10	(**3**)	$CDCl_3$–CD_3CN[c,d]	0·10	$PF_6NH_3[CH_2]_5NH_3PF_6$	0·050[e]	2	0·46
11	(**1**)	$CDCl_3$–CD_3CN[c,f]	0·05	$PF_6NH_3[CH_2]_4CHCO_2H(NH_3PF_6)$	1·2[c]	2	1
12	(**1**)	$CDCl_3$–CD_3CN[c,f]	0·05	$[SCH_2CHCO_2H(NH_3PF_6)]_2$	1·2[c]	2	0·9
13	(**1**)	$CDCl_3$–CD_3CN[c,f]	0·05	$HO_2C[CH_2]_3CHCO_2H(NH_3PF_6)$	1·2[c]	2	<0·05[g]
14	(**1**)	$CDCl_3$–CD_3CN[c,h]	0·05	$PF_6NH_3[CH_2]_4CHCO_2H(NH_3PF_6)$	0·50[c]	2	0·50
15	(**3**)	$CDCl_3$–CD_3CN[c,h]	0·10	$PF_6NH_3[CH_2]_4CHCO_2H(NH_3PF_6)$	0·50[c]	2	0·45

[a] 1·0 ml. [b] 2·5 ml. [c] 0·45 ml. [d] CD_3CN, 6% v/v. [e] 0·90 ml. [f] CD_3CN, 10% v/v. [g] Positive ninhydrin test. [h] CD_3CN, 7% v/v.

molecules of (**3**). Furthermore, two molecules of (**3**) have four potentially complexable faces than can lead to **2**:**1** complexes of the guests, whereas one molecule of (*RS*)-(**1**) has only two 'inside' faces available for the formation of **1**:**1** complexes with guests. This difference in the statistics of the faces favours (**3**) as the host. Complexation of (*RS*)-(**1**) on its 'outside' faces would lead to polymeric complexes which are not likely to be extractable.

These experiments demonstrate that host compounds containing two assemblies of binding sites can be designed (based on examination of the CPK molecular model) that will bind and orient, in a semi-predictable way, guest compounds that contain two bindable functional groups which are located in a complementary manner. A plane projection of the host (*S*)-(**1**) is drawn in the form of 'jaws' which can 'close' on each of the four oriented guest compounds. In CPK molecular models of each of the four resulting complexes, the hydrophilic sites of the guests are completely covered with a 'skin' of lipophilic C–H bonds. For simplicity, only (*S*)-(**1**) is formulated, although (*RS*)-(**1**) was used. Molecular models suggest little chiral recognition would be found in complexation between these hosts and guests. Uses of the (*R*)- and (*S*)-2,2′,3,3′-binaphthyl unit as a cornering, chiral, and shaping unit in host design are being examined further.

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