Host-Guest Complexation. 25. Effects of Substituents on the Complexing Properties of Chorands[1]

Thomas W. Bell,*[2] George M. Lein, Hideo Nakamura, and Donald J. Cram*[3]

Departments of Chemistry, University of California at Los Angeles, Los Angeles, California 90024, and State University of New York at Stony Brook, Stony Brook, New York 11794

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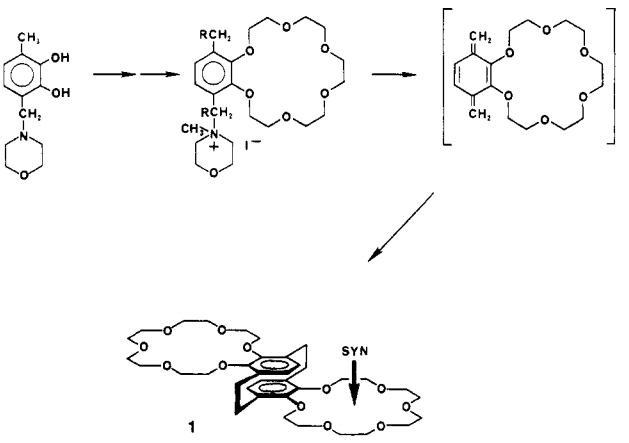
The syntheses of three benzannelated 18-crown-6 chorands (**3**, **6**, and **7**) and three dibenzo-20-crown-6 chorands (**10b–d**) are reported, along with their free energies of association toward Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates in $CDCl_3$ at 25 °C. For the 18-membered chorands, as well as previously reported paracyclophane-18-crown-6 and naphtho-18-crown-6 hosts, the average negative free energies of association ($-\Delta G°_{av}$) for Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates were qualitatively correlated with the degree of coplanarity of β-aryl substituents and the aromatic rings. The results are interpreted in terms of conformational organization of ligating sites in comparison with organization observed in crystalline complexes. Substituents were found to enhance complexation in the dibenzo-20-crown-6 series. This is interpreted as an effect of ligating-site preorganization and free-host destabilization. Substituent effects in chiral bicyclohexyl (**13**) and *meso*-bicyclohexyl hosts (**14**) are explained in similar terms.

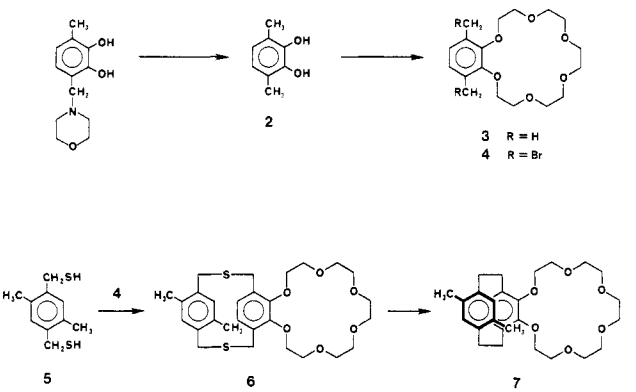
The polyethylene glycols, or glycands, may be considered the conceptual starting point for the evolution of the field of biomimetic complexation by synthetic organic hosts.[4] The introduction of macrocyclic rings in the chorands,[5] or crown ethers, restricts the number of available nonbinding conformations,[6] leading to better organization of ligating sites than for the glycands. This trend continued with the cryptands, in which the formation of additional bridges further reduced nonbinding conformations.[7] Finally, in the spherands nonbinding host conformations are eliminated altogether.[8] In the entire sequence beginning with the glycands and currently ending with the spherands, the burden of organizing the ligating sites in orientations required for binding is gradually transferred from the complexation process to the synthesis of the host.

The numerous recent reviews of chorand chemistry attest to the wide attention this compound class has enjoyed in host-guest complexation studies.[9-21] The crystal structures of 18-crown-6 itself and of several of its analogues[22] indicate that the cavity that is occupied by a guest metal ion in complexes is filled in the free host by inward-turning methylene groups. Replacement of the conformationally mobile CH_2CH_2, CH_2OCH_2, or $CH_2CH_2OCH_2CH_2$ units of 18-crown-6 by a variety of rigidifying groups have substantially improved binding free energies and specificities toward guests.[22] If substituents are attached to rigidifying units incorporated into chorands, then

Scheme I



Scheme II



(1) For support of this work we thank the Division of Basic Sciences of the Department of Energy, Contract AT(04-3)34, P.A.218.
(2) State University of New York at Stony Brook, Stony Brook, NY 11794.
(3) University of California at Los Angeles, Los Angeles, CA 90024.
(4) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571.
(5) We prefer the terms "glycand" and "chorand" for these host classes because they emphasize the roles they play as ligands for metal and ammonium cations in host-guest chemistry.
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(12) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85–142.
(13) (a) Izatt, R. M.; Christensen, J. J., Eds. "Progress in Macrocyclic Chemistry"; Wiley: New York, 1979; Vol. 1. (b) *Ibid.*, 1981; Vol. 2.
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chorand conformations may be further restricted through steric interactions. Reported here are the syntheses of several new chorands and correlations of their structures with their binding properties toward alkali-metal and ammonium ions. Of particular concern are the substituent effects of groups attached to rigidifying subunits of our hosts.

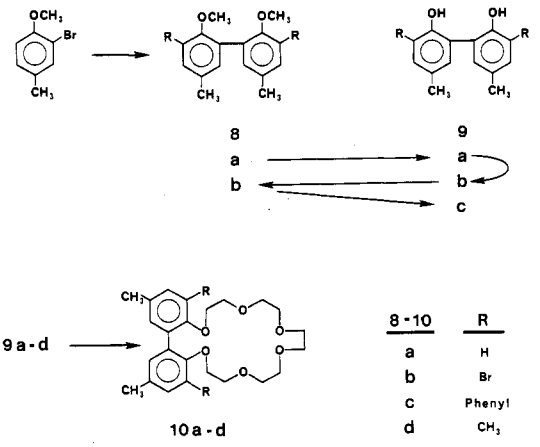
Results

We have reported[23] the synthesis of 4,5,15,16-bis(18-crown-6)[2.2]paracyclophane (1)[24] from 3-(morpholinomethyl)-6-methylcatechol (Scheme I). This host, which contains two 18-crown-6 rings annelated to two different benzene rings of [2.2]paracyclophane, was prepared by dimerization of *p*-phenylene-18-crown-6, which was produced by a Hoffman elimination reaction, as shown. Nuclear magnetic resonance spectral studies revealed that alkylammonium ions form complexes with this host in which the alkyl group is deshielded and therefore syn to the opposite benzene ring.[23]

In order to prepare new hosts with potential for enantiomer recognition and to study the complexation properties of a single 18-crown-6 ring attached to [2.2]paracyclophane, we selected the dithia[3.3]cyclophane synthetic strategy outlined in Scheme II. The starting material was again 3-(morpholinomethyl)-6-methylcatechol, which was catalytically hydrogenolyzed to afford 3,6-dimethylcatechol (**2**)[25] in 75% yield. Reaction of **2** with KOH and pentaethylene glycol ditosylate[4,26] led to a 53% yield of 3,6-dimethylbenzo-18-crown-6 (**3**),[27] which serves as a useful model for a bis-β-branched benzo-18-crown-6 (cf. **9**) free from out-of-plane distortion due to paracyclophane ring strain.[28] Bromination of **3** with *N*-bromosuccinimide gave a mixture of mono- and dibromides, from which pure 3,6-bis(bromomethyl)benzo-18-crown-6 (**4**)[29] was obtained (35%) by conversion to the corresponding diacetate, purification, and regeneration of **4** with HBr in chloroform.

The dithia[3.3]cyclophane **6**[30] was prepared (26%) from dibromide **4** and the known dithiol **5**[31] by using Mitchell's single-step method.[32] For ring contraction of **6** to paracyclophane **7**, Givens' photochemical SO_2 extrusion procedure[33] was chosen, since it was suspected that strong bases or potent methylating agents involved in other methods[34] might attack the crown ether ring. Accordingly, oxidation of **6** with *m*-chloroperoxybenzoic acid gave a 95% yield of the crude bissulfone, which upon photolysis afforded the desired 13,16-dimethyl-4,5-(18-crown-6)[2.2]-paracyclophane (**7**).[35]

Scheme III



We also examined the effects of simple β-substituents on the complexation properties of dibenzo-20-crown-6 hosts. The syntheses of a series of chorands based on the 3,3′-disubstituted 1,1′-biphenyl subunit are outlined in Scheme III. The preparation of key intermediate **8a** by reaction of 2-bromo-4-methylanisole with *tert*-butyllithium, followed by oxidative coupling of the resulting anion with cobalt(II) chloride, has been already reported.[36] We have more recently found that the yield of **8a** may be nearly doubled if the coupling is carried out in THF with 1.1 molar equiv of iron(III) tris(acetylacetonate). Treatment of dimethyl ether **8a** with boron tribromide gave diol **9a** in 96–99%, as described earlier.[36] Bromination of **9a** afforded **9b** (95%), which was methylated with methyl iodide to furnish **8b** (80%). Treatment of **8b** with phenylmagnesium bromide in tetrahydrofuran in the presence of a catalytic amount of bis(triphenylphosphine)nickel(II) chloride,[37] followed by demethylation with boron tribromide, gave biphenyldiol **9c** directly in 24% yield.

An additional diol (**9d**), bearing methyl groups in the 3 and 3′ positions, was prepared by oxidative phenol coupling as described in the literature.[38] Each of the four [1,1′-biphenyl]-2,2′-diols (**9a–d**) was converted to the corresponding dibenzo-20-crown-6 derivative (**10a–d**)[39] by reaction with sodium hydroxide and pentaethylene glycol ditosylate[4,26] in 2% water/tetrahydrofuran. Yields of the chromatographically purified chorands varied from 41% to 67%, comparing favorably with that previously reported for the synthesis of host **10a**.[40]

The complexing abilities of each of the new 18-crown-6 and 20-crown-6 hosts were evaluated by extraction of lithium, sodium, potassium, rubidium, cesium, ammonium, methylammonium, and *tert*-butylammonium picrates from D_2O into $CDCl_3$, according to a published method.[41,43] The

(23) Helgeson, R. C.; Tarnowski, T. L.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6411–6418.
(24) Systematic name for **1**: 2,3,5,6,8,9,11,12,14,15,18,19,22,23,25,2-6,28,29,31,32,34,35,38,39-tetracosahydro-17,40:20,37-diethenocyclododeca[1,2-*b*:7,8-*b*']bis[1,4,7,10,13,16]hexaoxacyclooctadecin.
(25) Systematic name for **2**: 3,6-dimethyl-1,2-benzenediol.
(26) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405–6410.
(27) Systematic name for **3**: 2,3,5,6,8,9,11,12,14,15-decahydro-17,20-dimethyl-1,4,7,10,13,16-benzohexaoxacyclooctadecin.
(28) In the crystal structure of [2.2]paracyclophane, the bridge carbons (i.e., β-branches) are bent about 23° out of the plane of the four unsubstituted carbon atoms of the attached benzene ring: Hope, H.; Bernstein, J.; Trueblood, K. N. *Acta Crystallogr., Sect. B.* **1972**, *28*, 1733–1743.
(29) Systematic name for **4**: 2,3,5,6,8,9,11,12,14,15-decahydro-17,20-bis(bromomethyl)-1,4,7,10,13,16-hexaoxacyclooctadecin.
(30) Systematic name for **6**: 2,3,5,6,8,9,11,12,14,15,18,20,25,27-tetradecahydro-22,31-dimethyl-17,28:21,24-diethenocyclotetradeca[3,4-*b*]-1,4,7,10,13,16,19,26-hexaoxadithiacyclooctadecin.
(31) (a) von Braun, J.; Nelles, J. *Chem. Ber.* **1934**, *67*, 1094–1099. (b) Nakashima, C.; Oda, R. *Nippon Kagaku Zasshi* **1965**, *86*, 645–646 (*Chem. Abstr.* **1966**, *65*, 633g).
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(35) Systematic name for **7**: 2,3,5,6,8,9,11,12,14,15,18,19,24,25-tetradecahydro-21,29-dimethyl-17,26:20,23-diethenocyclododeca[1,2-*b*]-1,4,7,10,13,16-hexaoxacyclooctadecin.
(36) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T., Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566.
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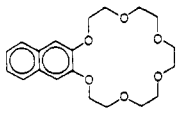
(38) Haynes, C. G.; Turner, A. H.; Waters, W. A. *J. Chem. Soc.* **1956**, 2823–2831.
(39) Systematic name for **10a**: 6,7,9,10,12,13,15,16,18,19-decahydro-2,23-dimethyldibenzo[*q*,*s*][1,4,7,10,13,16]hexaoxacycloeicosin. To obtain the names of hosts **10b**, **10c**, and **10d**, replace "2,23-dimethyl" in the name of **10a** with "4,21-dibromo-2,23-dimethyl", "4,21-diphenyl-2,23-dimethyl", and "2,4,21,23-tetramethyl", respectively.
(40) Reinhoudt, D. N.; de Jong, F.; van de Vondervoort, E. M. *Tetrahedron* **1981**, *37*, 1753–1762.

Table I. Comparison of Association Data for Alkali Metal or Ammonium Picrates toward Paracyclophane Hosts and 2,3-Naphtho-18-crown-6 (11)

host no.	M⁺ of M⁺ picrate⁻	$10^{-3}K_a$,[a] M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G°_{av}$,[b] kcal/mol
11[c]	Li	22.5	5.9	
	Na	1220	8.3	
	K	85900	10.8	
	Rb	11300	9.6	
	Cs	1250	8.3	8.7
	NH_4	9850	9.5	
	$MeNH_3$	334	7.5	
	t-$BuNH_3$	105	6.9	
1[d]	Li	15	5.7	
	Na	150	7.0	
	K	17300	9.8	
	Rb	2650	8.7	
	Cs	390	7.6	8.0
	NH_4	6710[e]	9.2	
	$MeNH_3$	107	6.8	
	t-$BuNH_3$	0.9[e]	4.0	
7	Li	15.9	5.7	
	Na	63	6.5	
	K	7660	9.4	
	Rb	1230	8.3	7.5
	Cs	134	7.0	
	NH_4	880	8.1	
	$MeNH_3$	18.2	5.8	
	t-$BuNH_3$	0.4	3.5	
3	Li	6.5	5.2	
	Na	22	5.9	
	K	173	7.1	
	Rb	60	6.5	6.1
	Cs	15	5.7	
	NH_4	24	5.9	
	$MeNH_3$	4.6	5.0	
	t-$BuNH_3$	1.4	4.3	
6	Li	3.9	4.9	
	Na	13	5.6	
	K	251	7.3	
	Rb	79	6.7	6.1
	Cs	12	5.5	
	NH_4	43	6.3	
	$MeNH_3$	2.6	4.6	
	t-$BuNH_3$	0.2	3.1	

[a] The method for determining K_a values has been described in refs 41 and 43. All values are at 25 °C. [b] Average of the $-\Delta G°$ values for association of each host with Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrate. [c] Reference 43. [d] Reference 23. [e] Correction of the original value given in ref 23.

UV absorbances of the organic layers at 380 nm yielded association constants and free energies of association, which are listed in Table I for the 18-crown-6 series, including the previously reported values[23,43] for hosts 1 and 2,3-naptho-18-crown-6 (11).[42]



11

The complexation data for 20-crown-6 systems **10b–d** are listed in Table II, in comparison with the reported values for **10a**.[36] Also included in the tables are the $-\Delta G°_{av}$ values for each host. This parameter can be used as a measure of the overall binding ability toward spherical (M^+) or near-spherical (NH_4^+) cations.[43,44]

Table II. Association Data for Alkali Metal or Ammonium Picrates toward Dibenzo-20-crown-6 Derivatives

host no.	M⁺ of M⁺ picrate⁻	$10^{-3}K_a$,[a] M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G°_{av}$,[b] kcal/mol
10a[c] (R = H)	Li	14	5.6	
	Na	120	6.9	
	K	1300	8.3	
	Rb	390	7.6	7.2
	Cs	150	7.0	
	NH_4	310	7.5	
	$MeNH_3$	20	5.8	
	t-$BuNH_3$	1.6	4.3	
10b (R = Br)	Li	32	6.1	
	Na	990	8.1	
	K	13000	9.7	7.9
	Rb	1300	8.3	
	Cs	320	7.5	
	NH_4	700	7.9	
	$MeNH_3$	61	6.5	
	t-$BuNH_3$	41	6.3	
10c (R = C_6H_5)	Li	19	5.8	
	Na	650	7.9	
	K	14000	9.7	
	Rb	1400	8.4	7.9
	Cs	265	7.4	
	NH_4	1300	8.3	
	$MeNH_3$	100	6.8	
	t-$BuNH_3$	8.7	5.3	
10d (R = CH_3)	Li	57	6.5	
	Na	5900	9.2	
	K	85000	10.8	8.8
	Rb	6700	9.3	
	Cs	940	8.1	
	NH_4	5100	9.1	
	$MeNH_3$	800	8.0	
	t-$BuNH_3$	69	6.6	

[a] All values were determined at 25 °C as described in refs 41 and 43. [b] Average of the $-\Delta G°$ values for association of each host with Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrate. [c] Reference 36.

Discussion

18-Crown-6 Hosts. It may be seen from Table I that the overall binding abilities ($-\Delta G°_{av}$) for the five hosts descend in the following order: **11 > 1 > 7 > 3 = 6**. This effect cannot be correlated entirely with general steric bulk, since the cyclophane chorands (1, 6, and 7) occupy greater space than planar hosts 3 and 11. Instead, any large deviations of the $-\Delta G°$ value for *tert*-butylammonium from $-\Delta G°_{av}$ can be attributed to host–guest repulsive steric interactions, since this deviation is greatest (4 kcal/mol) for the two [2.2]paracyclophanes (1 and 7); increasing guest size is expected to diminish the stabilities of the syn alkylammonium complexes[23] of these systems. The slight superiority of host 1 to 7 may be due in part to steric repulsion caused by the methyl group located over the macrocyclic ring of 7 but may also reflect the potential for 2:1 (guest–host) complexation by 1.

The relative binding abilities of 1, 3, 6, 7, and 11 are explained as consequences of the effects of substituents on ligating-site organization (Figure 1). An X-ray crystal structure of the complex of 11 with *tert*-butylammonium perchlorate has shown that the mean plane of the macrocycle is nearly coplanar with the naphthalene ring.[22,45] The two sp^2-hybridized aryl ether oxygen atoms are or-

(41) Timko, J. M.; Moore, S. S.; Walba, D. M.; Hiberty, P. C.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 4207–4219.
(42) Systematic name for 11: 2,3,5,6,8,9,11,12,14,15-decahydronaphtho[2,3-*b*]-1,4,7,10,13,16-hexaoxacyclooctadecin.
(43) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.
(44) Bell, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 1163–1171.
(45) Knobler, C. B.; Trueblood, K. N.; Weiss, R. M., unpublished results.

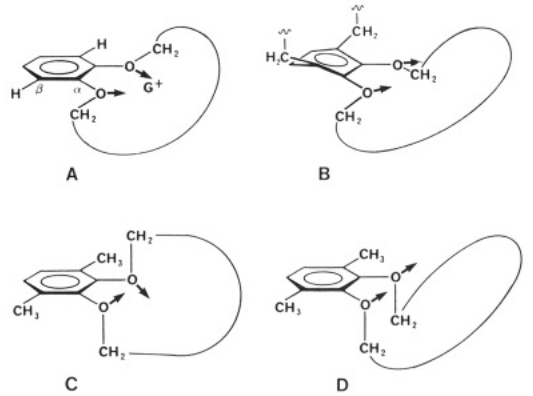


Figure 1. Effect of β-substituents on oxygen dipole orientations in benzo-18-crown-6 derivatives.

ienced with their electric dipoles focused on the cationic center. The guest is in this way maximally stabilized and the host experiences π-conjugative stabilization, as well. A consequence of this presumed "ideal" ligand organization is that two chorand methylene groups lie in close proximity to the β-hydrogen atoms of the aromatic ring. These features are summarized in formula A of Figure 1.

Formula B (Figure 1) depicts the structural situation for the [2.2]paracyclophane hosts **1** and **7**. The β-positions are attached to bridging carbon atoms that are drawn out of the mean plane of the aromatic ring. Space filling (CPK) molecular models suggest that these bridge methylene groups should sterically exclude the nearest ether methylene groups from coplanar positions. As a result, the aryl ether oxygen dipoles must be less well-organized for complexation than in A and be oriented slightly toward the opposite (upper) aromatic ring. This analysis very nicely explains *both* the depressed association constants of **1** and **7**, relative to **11**, and the preference for syn complexation of alkylammonium ions by **1**.[23]

It is remarkable that the $-\Delta G°_{av}$ values for the dimethyldibenzo-18-crown-6 **3** and the dithia[3.3]paracyclophane-18-crown-6 **6** are identical (6.1 kcal/mol) and 2.6 kcal/mol lower than the value for napththo host **11**. Molecular models show that uncomplexed **6** should be relatively unstrained and that the bridge methylene groups should occupy the same positions as the β-methyl substituents of **3**. In both hosts, then, organization of aryl oxygen dipoles is disrupted by β-substituents, leading to alternative conformations of the macrocyclic ring, such as C and D shown in Figure 1. We would expect conformation D, in which the oxygen dipoles are roughly parallel, to form stronger complexes than C, in which they are divergent, but both should be much poorer than B or A, as observed.

The trend visible in these results is that the introduction of copolanar β-substituents to benzannelated 18-crown-6 hosts reduces binding ability by disorganizing binding sites, the [2.2]paracyclophane hosts providing an interesting intermediate case. We suspect that this trend is general for 18-membered chorands that are fused to six-membered rings. Steric effects of this type have been indicated by Stoddart in some carbohydrate hosts.[15] Additional examplex in which alkyl substituents destabilize alkali-metal complexes are *n*-octyl-18-crown-6[46] and methylated di-

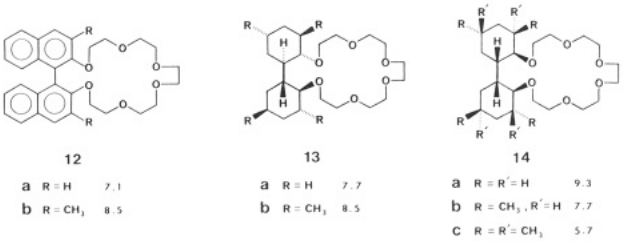


Figure 2. Average negative free energies of association (Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates, $CDCl_3$, 25 °C, except Rb^+ value excluded for **12a**) for 20-crown-6 hosts.[43,44]

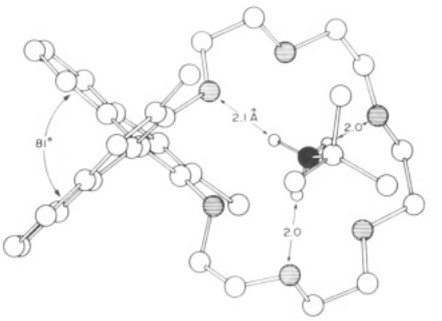


Figure 3. Solid-state geometry of the complex of *tert*-butylammonium perchlorate with host **12b**.[50,51]

benzo-18-crown-6 hosts.[47] Although these cases involve α-substituents (directly attached to the macrocyclic ring), we believe that these phenomena may also be rationalized by considering the effect of substitution on ligand organization, which is indicated by crystal structures of 18-crown-6[16,17,22,48] and dibenzo-18-crown-6[49] complexes.

20-Crown-6 Hosts. According to the $-\Delta G°_{av}$ values for dibenzo-20-crown-6 hosts **10a–d**[39] listed in Table II, β-substitution of the aromatic rings improves, rather than reduces, overall binding ability. This value increases by 0.7 kcal/mol (10%) for bromo or phenyl substitution of **10a**, and methyl groups enhance binding by a further 0.9 kcal/mol. Interestingly, the magnitude and direction of the methyl substituent effect (1.6 kcal/mol) is very similar to that observed for the dinaphtho-20-crown-6 system (**12**),[43,50] as shown in Figure 2. We attribute these effects to conformational restrictions of the macrocyclic rings, leading to better organization of some of the ligating sites prior to complexation.

The crystal-structure conformation of the 3,3′-dimethyldinaphtho-20-crown-6 host **12b**[50] is depicted in Figure 3.[51] An important feature of this structure is that the Ar–O–CH_2 planes are rougly perpendicular to the naphthalene rings. As a result, the aryl oxygen dipoles converge directly on the bound cationic center. Molecular models demonstrate that in the cases of **10** and **12** macrocycle conformations in which one or both Ar–O–CH_2 planes are coplanar with the aromatic rings lead to poorer convergence of the oxygen dipoles. The results imply that β-aryl substituents in **10** and **12** *destabilize free hosts* relative to their complexes by blocking lower energy conformations of the free host *in favor of ideal ligating site organization* in complexes.[52] The fact that both bromo

(46) Ideda, I.; Yuamamura, S.; Nakatsuji, Y.; Okahara, M. *J. Org. Chem.* **1980**, *45*, 5355–5358. The authors' assertion that these effects are insignificant may be true for applications of these hosts as phase-transfer catalysts, but deviations of 0.6–1.2 kcal/mol (10–15% of the observed values) would appear to be quite significant on the energy scale of conformational effects.

(47) Parsons, D. G.; Truter, M. R.; Wingfield, J. N. *Inorg. Chim. Acta* **1981**, *47*, 81–86.

(48) Hilgenfeld, R.; Saenger, W., in ref 20b, pp 1–82.

(49) Bright, D.; Truter, M. R. *J. Chem. Soc. B* **1970**, 1544–1550. Bush, M. A.; Truter, M. R. *Ibid.* **1971**, 1440–1446.

(50) Systematic name for **12b**: 4,5,7,8,10,11,13,14,16,17-decahydro-2,19-dimethyldinaphtho[2,1-*q*:1′,2′-*s*][1,4,7,10,13,16]hexaoxacycloeicosin.

(51) Goldberg, I. *J. Am. Chem. Soc.* **1980**, *102*, 4106–4113.

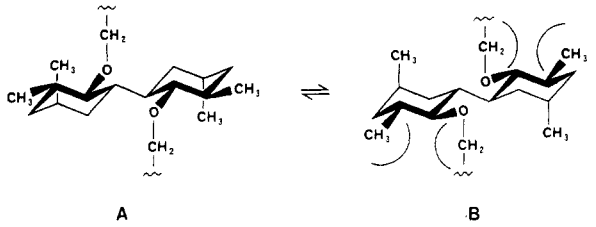


Figure 4. Proposed major conformations of host **13b**.[54]

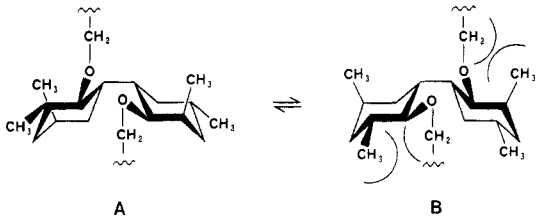


Figure 5. Proposed major conformations of host **14b**.

and methyl substituents in **10** enhance complexation is consistent with our steric explanation, since they should occupy similar volumes.[53] The lower $-\Delta G°_{av}$ for **10b** (7.9 kcal/mol) than for **10d** (8.8 kcal/mol) may be attributed to the electronegativity of the bromine atom.

As may be seen from Figure 2, a similar, though smaller (0.8 kcal/mol), enhancement of binding ability is observed when methyl groups are placed in the corresponding 3,3′ equatorial positions of the chiral trans-transoid-trans bicyclohexyl host **13a**.[54] This is not surprising, since the gross geometry of the equatorially fused bicyclohexyl subunit is similar to those of the biaryl units of **10** and **12**, but conformational analysis of **13** is complicated by the possibility of the two nonequivalent major conformations about the bicyclohexyl bond, as shown in Figure 4. Molecular models indicate that conformation A (Figure 4) enables a tightly packed circular organization of six oxygen ligands and should form stronger complexes than B, in which complete convergence of the oxygen dipoles is precluded. The effect of the equatorial methyl groups in **13b**, then, may be both to orient the cyclohexyl ether oxygen dipoles in A (as in **10d** and **12b**) and to destabilize B through slight steric interactions shown in Figure 4.

In contrast to the results for **10**, **12**, and **13**, the effect of β-branching on trans-cisoid-trans host **14** is to markedly reduce binding ability (cf. Figure 2). The $-\Delta G°_{av}$ value for the tetramethyl derivative **14b** is 1.5 kcal/mol lower than that for parent system **14a**, and octamethyl host **14c** is worse yet by 2.0 kcal/mol. Rotation about the bicyclohexyl bond of **14a** gives two equivalent major conformations in which the ligating sites are well-organized for complexation, according to models. These become nonequivalent for the tetramethyl host (**14b**), as shown in Figure 5. In conformation B one axial and one equatorial methyl substituent disturb the orientations of the nearest oxygen dipoles through the steric interactions shown, thus reducing overall binding ability. In addition, complexes of conformation A may be somewhat destabilized by repulsive steric interactions between the guest and the closely situated axial methyl group. Models indicate that both A and B conformations of octamethyl host 14c would be quite strained relative to conformations with inward-turning methyl groups. The poorer binding abilities of **14b** and **14c** relative to **14a** may be primarily attributed, then, to disruption of ligating-site organization due to the steric bulk of nearby (β) axial substituents.

It is striking that β-substituents in annelated 20-crown-6 hosts **10**, **12**, and **13** enhance complex stabilities, whereas methylation of **14** has the opposite effect. Therefore, these phenomena cannot be simply explained by inductive changes in ligand basicity or by steric repulsion between host and guest. They may be explained by considering whether substitution should favor or disfavor chorand conformations in which the ligating sites are optimally organized *prior to complexation*. A generalization that emerges from this analysis for bis-annelated 20-crown-6 hosts is that coplanar substituents (β-aryl or β-equatorial) should improve binding, whereas perpendicular substituents (β-axial) should diminish complexing ability.

Conclusions

The complexing abilities of several 18-crown-6 and 20-crown-6 chorands toward alkali-metal and ammonium cations may be qualitatively correlated with the degree of preorganization of ligating sites. Crystal structures of chorand complexes may be used to approximate ideal ligating-site organization. In 18-crown-6 chorands that are rigidified by annelation to a six-membered ring, coplanar β-substituents destabilize complexes. In bis-annelated 20-crown-6 hosts, chorand preorganization is enhanced by coplanar β-substituents, where perpendicular alkyl groups destabilize host–guest complexes.

Experimental Section

General Procedure. All reagents and solvents were reagent grade, unless otherwise specified. Anhydrous tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, whereas anhydrous diethyl ether was distilled either from sodium benzophenone ketyl or from lithium aluminum hydride. Gravity column chromatography was conducted either with use of E. Merck silica gel 60 (0.063–0.200 mm) or MCB neutral activated alumina (80–325 mesh). Medium-pressure chromatography was performed by using a 250 mm × 25 mm Altex column packed with E. Merck silica gel 60 (0.040–0.063 mm) with elution at 4.0 mL min^{-1}. Gel permeation chromatography was conducted with a $^3/_8$ in. (o.d.) by 20 ft column packed with 200 g of either 60-Å or 100-Å Styragel beads (Waters Associates Inc., 37–75-μm particle size) with elution by CH_2Cl_2 at a flow rate of 4.0 mL min^{-1} and a pressure of 250–600 psi. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were recorded on an AEI MS-9 mass spectrometer at 70 eV. ^1H NMR spectra were obtained on a Varian T-60 (60 MHz) or a Bruker WP-200 (200 MHz) spectrometer and chemical shifts are reported in ppm relative to internal $(CH_3)_4Si$. The procedures and instrumentation for measurement of K_a values were exactly as described elsewhere.[41,43]

3,6-Dimethylcatechol (2).[25] A mixture of 90 g (0.4 mol) of 3-(morpholinomethyl)-6-methylcatechol,[23] 12 g of 10% palladium-on-carbon, and 400 mL of ethanol was hydrogenated at about 100 psi until hydrogen uptake ceased. The catalyst was removed by filtration through Celite and the filtrate was diluted with 500 mL of CH_2Cl_2 and extracted with 300-mL portions of 1 N aqueous HCl and saturated aqueous NaCl. Solvent evaporation in vacuo gave 42.5 g of crude product, which was sublimed at 90–130 °C (0.1mm) to afford 41.8 g (75%) of pure **2**: mp 99–100 °C (lit.[55] mp 101 °C).

3,6-Dimethylbenzo-18-crown-6 (3).[27] A mixture of 1.0 g (7.2 mmol) of 3,6-dimethylcatechol (**2**), 0.97 g (14.5 mmol) of powdered 85% KOH, and 40 mL of THF was stirred under N_2 for 1 h at ambient temperature and then 3.9 g (7.2 mmol) of pentaethylene glycol ditosylate[4,26] was added in one portion. The resulting

(52) We have previously suggested this explanation for substituent effects in **12**[43] and Reinhoudt has advanced essentially the same interpretation for similar substituent effects on the complexation of *tert*-butylammonium hexafluorophosphate by dibenzo-20-crown-6.[40]

(53) The van der Waals radii of bromo and methyl groups are 1.95 and 2.0 Å, respectively.

(54) Systematic name for **13b**: [2*R*-(2*R**,4*R**,4a*S**,20a*S**,21*R**,23*R**,24a*R**,24b*R**)]-docosahydrodibenzo[*q*,*s*][1,4,7,10,13,16]hexaoxacycloeicosin.

(55) Baker, W.; Bondy, H. F.; Gumb, J.; Miles, D. *J. Chem. Soc.* **1953**, *1615*–1619.

mixture was heated under reflux for 18 h and then half of the THF was evaporated in vacuo. The residue was distributed between saturated aqueous NaCl and CH_2Cl_2 and the organic phase was extracted with H_2O and dried ($NaSO_4$). Solvent removal in vacuo gave a residue, which was gravity chromatographed on 100 g of alumina with ether, followed by 1:1 (v/v) ether/CH_2Cl_2, affording 1.3 g (53%) of host **3** as a pale yellow oil. Analytically pure material was obtained by recrystallization from heptane: mp 47–48 °C; MS, *m/e* 340 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.22 (s, CH_3, 6 H), 3.60–4.25 (M, CH_2, 20 H), 6.80 (s, Ar H, 2 H). Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.66; H, 8.20.

3,6-Bis(bromomethyl)benzo-18-crown-6 (4).[29] A mixture of 20.1 g (59 mmol) of host **3**, 31.6 g (0.18 mol) of *N*-bromosuccinimide, 2.2 g of benzoyl peroxide, and 550 mL of CCl_4 was heated under reflux for 1 h. The cooled mixture was filtered and the filtrate was extracted with aqueous $NaHSO_3$ and then dried (Na_2SO_4). Evaporation of the solvent in vacuo left 31.4 g of a viscous oil, which was heated under reflux for 1.5 h with 20.3 g (0.2 mol) of potassium acetate in 160 mL of acetic acid. The reaction mixture was distributed between 450 mL of CH_2Cl_2 and 200 mL of saturated aqueous NaCl. The organic phase was thoroughly washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. From the residual oil (26 g), 9.9 g of diacetate corresponding to dibromide **4** was isolated by gravity chromatography on 350 g of silica gel with ethyl acetate: ^1H NMR (60 MHz, $CDCl_3$) δ 2.08 (s, CH_3CO_2, 6 H), 3.65–4.30 (m, CCH_2O, 20 H), 5.10 (s, Ar CH_2, 4 H), 7.05 (s, Ar H, 2 H). The diacetate was dissolved in 50 mL of $CHCl_3$ and added over a period of 5 min to a saturated solution of HBr in 350 mL of $CHCl_3$. The mixture was stirred at ambient temperature for 5 h and then extracted with several volumes of aqueous $NaHCO_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and then evaporated in vacuo, furnishing 10.3 g (35%) of dibromide **4**. Recrystallization from ether gave an analytically pure sample: mp 102.5–103.5 °C; MS, *m/e* 406 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 3.70–4.55 (m, CCH_2O, 20 H), 4.60 (s, Ar CH_2Br, 4 H), 7.15 (s, Ar H, 2 H). Anal. Calcd for $C_{18}H_{26}O_6Br_2$: C, 43.40; H, 5.26. Found: C, 43.48; H, 5.35.

Dithia[3.3]paracyclophane Host 6.[30] A solution of 10.4 g (20.9 mmol) of dibromide **4** and 4.1 g (20.0 mmol) of dithiol **5**[31] in 500 mL of benzene was added dropwise under N_2 over 72 h to a well-stirred solution of 2.8 g (49mmol) of 85% KOH in 750 mL of 95% ethanol. Solvent evaporation left a residue, which was distributed between 200 mL of CH_2Cl_2 and 150 mL of saturated aqueous NaCl. The organic phase was dried (Na_2SO_4) and evaporated in vacuo to afford about 10 g of a viscous oil. Chromatography on 150 g of silica gel with chloroform/ethyl acetate gave 3.0 g (26.9%) of crystalline product. Recrystallization from methanol produced analytically pure **6**: mp 96.0–97.0 °C; MS, *m/e* 534 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.16 (s, CH_3, 3 H), 2.31 (s, CH_3, 3 H), 3.46–4.80 (m, CCH_2O, Ar CH_2S, 28 H), 6.63 (s, Ar H, 1 H), 6.67 (s, Ar H, 2 H), 6.68 (s, Ar H, 1 H). Anal. Calcd for $C_{28}H_{38}O_6S_2$: C, 62.89; H, 7.16. Found: C, 62.77; H, 7.18.

13,16-Dimethyl-4,5-(18-crown-6)[2.2]paracyclophane (7).[35] A solution of 1.2 g (2.2 mmol) of dithia[3.3]paracyclophane host **6** in 30 mL of $CHCl_3$ was stirred at about 0 °C as a solution of 2.3 g (11 mmol) of 85% *m*-chloroperoxybenzoic acid in 20 mL of $CHCl_3$ was added dropwise over 20 min. The reaction mixture was allowed to warm to ambient temperature, stirred for 4 h, then recooled to 0 °C, and quenched by addition of saturated aqueous Na_2SO_3. The resulting mixture was stirred for 15 min and then extracted with aqueous K_2CO_3 to remove benzoic acid. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 1.4 g (95%) of crystalline bissulfone, which was sufficiently pure to proceed with the next step but could be recrystallized from benzene: mp 224–226 °C.

A suspension of 0.3 g (0.5 mmol) of the bissulfone of **6** in 650 mL of degassed benzene (spectroscopic grade) was irradiated in a photolysis well (Hanovia 450-W high-pressure Hg lamp, Vycor filter), with continuous N_2 ebullition. After 1.5 h benzene was removed by evaporation in vacuo, leaving 230 mg of residue, which was purified by gel permeation chromatography on 60-Å Styragel. Thus obtained was 199.5 mg (83%) of the [2.2]paracyclophane host **7**, which could be further purified by recrystallization from *n*-hexane: mp 60.5–61.5 °C; MS, *m/e* 470 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.01 (s, CH_3, 3 H), 2.20 (s, CH_3, 3 H), 2.50–3.50 (m, Ar CH_2, 8 H), 3.65–4.20 (m, CCH_2O, 20 H), 6.08 (s, Ar H, 1 H), 6.11, 6.49 (AB q, J_{AB} = 8.0 Hz, Ar H, 2 H), 6.50 (s, Ar H, 1 H). Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.55; H, 8.16.

2,2′-Dimethoxy-5,5′-dimethyl[1,1′-biphenyl] (8a). A solution of 50 g (0.25 mol) of 2-bromo-4-methylanisole in 400 mL of anhydrous THF was stirred under N_2 at about −78 °C as 114 mL of a 2.3 M solution of *n*-butyllithium in hexane was added. The resulting solution was stirred for 10 min longer at −78 °C and then transferred by cannula into a solution of 100 g (0.28 mol) of anhydrous iron(III) acetylacetonate in 200 mL of anhydrous THF. The resulting red suspension was stirred at ambient temperature for 15 h and then concentrated in vacuo. The residue was distributed between 500 mL of ethyl acetate and 1 L of 2 N aqueous HCl. The organic layer was washed with four 400-mL portions of 2 N aqueous HCl, two 300-mL portions of water, and 300 mL of saturated aqueous NaCl, then dried ($MgSO_4$), and evaporated under reduced pressure. The residue was distilled by using a short-path apparatus at 120–150 °C (0.4 mm) to yield 23.4 g of crude **8a** as a viscous yellow oil, which was recrystallized from 50 mL of petroleum ether (bp 30–60 °C). Thus obtained was 22.4 g (75%) of pure **8a**, which was identical with material obtained by the previously reported method.[36]

3,3′-Dibromo-5,5′-dimethyl[1,1′-biphenyl]-2,2′-diol (9b). A solution of 3.6 g (17 mmol) of 5,5′-dimethyl[1,1-biphenyl]-2,2′-diol (**9a**)[36] in 200 mL of chloroform was stirred under N_2 as a solution of 5.4 g (34 mmol) of bromine in 20 mL of chloroform was added dropwise. The resulting mixture was stirred at ambient temperature for 20 min and then decolorized by addition of aqueous Na_2SO_3. The organic phase was washed with water, dried (Na_2SO_4), and concentrated in vacuo to afford 5.9 g (95%) of diol **9b**, which was pure according to its ^1H NMR spectrum and TLC behavior on silica gel (1,2-dichloroethane). Recrystallization from ether gave an analytical sample: mp 141–143 °C; MS, *m/e* 370 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, Ar CH_3, 6 H), 5.80 (s, Ar OH, 2 H), 7.23 (m, Ar H, 4 H). Anal. Calcd for $C_{14}H_{12}O_2Br_2$: C, 45.20; H, 3.25. Found: C, 45.20; H, 3.31.

3,3′-Dibromo-2,2′-dimethoxy-5,5′-dimethyl[1,1′-biphenyl] (8b). A mixture of 5.8 g (16 mmol) of diol **9b**, 300 mL of acetone, 10 g of K_2CO_3, and 8.5 g (60 mmol) of methyl iodide was stirred under N_2 and heated under reflux for 1.5 h. Solvent and excess methyl iodide were removed by distillation, and the residue was dissolved in aqueous NaOH. The resulting solution was stirred for 6 h at 25 °C and then extracted with 300 mL of chloroform. The organic phase was dried (Na_2SO_4) and evaporated in vacuo, giving a viscous oil, which was dissolved in pentane. Storage of the solution at −20 °C afforded 4.95 g (80%) of product **8b**: mp 84–85 °C; MS, *m/e* 398 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, Ar CH_3, 6 H), 3.55 (s, OCH_3, 6 H), 7.20 (m, Ar H, 4 H). Anal. Calcd for $C_{16}H_{16}O_2Br_2$: C, 48.03; H, 4.03. Found: C, 48.15; H, 4.03.

5′,5″-Dimethyl[1,1′:3′,1″:3″,1‴-quaterphenyl]-2′,2″-diol (9c). A mixture of 1.13 g (2.88 mmol) of dibromide **8b**, 0.1 g of bis(triphenylphosphine)nickel(II) chloride, 5 mL of anhydrous ether, and 3.5 mL of a 3.2 M solution of phenylmagnesium bromide in ether was stirred under N_2 and heated under reflux for 18 h. The cooled reaction mixture was distributed between 150 mL of chloroform and 150 mL of 1 M aqueous HCl. The organic layer was dried ($MgSO_4$), solvents were removed under reduced pressure, and the residue was dissolved in a minimum volume of CH_2Cl_2. The resulting solution was filtered through 50 g of silica gel, using CH_2Cl_2 to completely elute the product. The combined filtrates were concentrated to 100 mL in vacuo and then stirred under N_2 at 5 °C as 0.27 mL of boron tribromide was added. The resulting mixture was stirred for 12 h at ambient temperature and then poured into 100 mL of water. The organic phase was dried ($MgSO_4$) and evaporated to dryness in vacuo. Medium-pressure chromatography of the residue on silica gel with 3:7 (v/v) CH_2Cl_2/cyclohexane gave 0.33 g (32%) of crude **9c** as a brown oil. In order to destroy a bromoterphenyl sideproduct that has the same R_f value as the desired **9c**, the crude material was dissolved in 50 mL of anhydrous THF and stirred with 0.5 g of magnesium turnings for 24 h. Evaporation of the THF and medium-pressure chromatography of the residue as above yielded 0.25 g (24%) of purified **9c** as a yellow oil after drying at 80 °C in vacuo: MS, *m/e* 366 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 2.374 (s, Ar CH_3, 6 H), 5.658 (s, Ar OH, 2 H), 7.36 (m, Ar H, 14 H). Anal.

Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 84.96; H, 6.26.

Dibenzo-20-crown-6 Hosts (10a-d).[39] The following procedure for host **10a** is representative. A solution of 1.53 g (2.8 mmol) of pentaethylene glycol ditosylate[4,26] in 60 mL of THF was added to a solution of 0.6 g (2.8 mmol) of diol **9a**[36] and 0.47 g (11 mmol) of NaOH in 130 mL of THF and 8 mL of water. The resulting solution was stirred under N_2 and heated under reflux for 72 h and then cooled and acidified (pH 4) with 2 N aqueous HCl. Evaporation of the solvent in vacuo gave a residue, which was distributed between 200 mL of water and 200 mL of ethyl acetate. The organic layer was washed with 200-mL portions of water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to dryness under reduced pressure. Gel permeation chromatography of the residue on 100-Å Styragel, followed by gravity chromatography on 75 g of silica gel with ether, gave 0.56 g of host **10a** as a white solid. Recrystallization from 95% ethanol at -20 °C yielded 0.47 g (41%) of **10a** as white crystals: mp 96.5-97.5 °C; MS, m/e 416 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 2.299 (s, Ar CH_3, 6 H), 3.48-4.17 (m, CH_2, 20 H), 6.846 (d, J = 8.3 Hz, Ar H, 2 H), 6.996 (d, J = 2.0 Hz, Ar H, 2 H), 7.065 (dd, J = 2.0, 8.3 Hz, Ar H, 2 H). Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.20; H, 7.78.

Host **10b** was prepared according to the method described above for **10a** by heating a solution of 3 g (8.1 mmol) of diol **9b**, 1 g (25 mmol) of NaOH, 4.4 g (8.1 mmol) of pentaethylene glycol ditosylate, 600 mL of THF, and 20 mL of water for 120 h. The product was purified by gel permeation chromatography on 100 Å Styragel, followed by flash chromatography[56] on 100 g of silica gel with ether. The resulting light yellow oil was dried at 100 °C in vacuo, yielding 2.6 g (56%) of host **10b**: MS, m/e 574 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 2.292 (s, Ar CH_3, 6 H), 3.53-3.90 (m, CH_2, OH), 7.118 (d, J = 2.2 Hz, Ar H, 2 H), 7.363 (d, J = 2.2 Hz, Ar H, 2 H). Anal. Calcd for $C_{24}H_{30}O_6Br_2$: C, 50.19; H, 5.27. Found: C, 50.13; H, 5.18.

Host **10c** was similarly prepared from 0.23 g (0.63 mmol) of diol **9c**, 0.08 g (2 mmol) of NaOH, and 0.38 g (0.69 mmol) of pentaethylene glycol ditosylate in 40 mL of THF and 1.6 mL of water (reflux time, 48 h). Gel permeation chromatography on 100-Å Styragel, followed by medium-pressure chromatography on silica gel with ether, afforded a yellowish oil, which was dried at 80 °C in vacuo, yielding 0.142 g (40%) of host **10c**: MS, m/e 568 (M^+); ^1H NMR (60 MHz, $CDCl_3$) δ 2.36 (s, Ar CH_3, 6 H), 3.15-3.75 (m, CH_2, 20 H), 7.05-7.70 (m, Ar H, 14 H). Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 76.17; H, 7.08.

Host **10d** was similarly prepared from 1.0 g (4.1 mmol) of diol **9d**,[38] 0.5 g (13 mmol) of NaOH, and 2.5 g (4.5 mmol) of pentaethylene glycol ditosylate in 300 mL of THF and 10 mL of water (reflux time 56 h). Gel permeation chromatography on 100-Å Styragel, followed by gravity chromatography on 50 g of silica gel with ether, gave a yellowish oil, which was dried at 100 °C in vacuo. Thus obtained was 1.23 g (67%) of host **10d**: MS, m/e 444 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 2.267 (s, Ar CH_3, 6 H), 2.317 (s, Ar CH_3, 6 H), 3.45-3.78 (m, CH_2, 20 H), 6.945 (d, J = 2.2 Hz, Ar H, 2 H). Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.16.

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Fluorinated Carbohydrates. 2. Selective Fluorination of Gluco- and Mannopyranosides. Use of 2-D NMR for Structural Assignments†

Peter J. Card* and Gade S. Reddy

Central Research & Development Department, E. I. du Pont de Nemours & Co., Experimental Station, Wilmington, Delaware 19898

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Methyl and phenyl α-glucosides, or suitably protected derivatives, may be selectively fluorinated with (diethylamino)sulfur trifluoride (DAST) at the 4- or 6-position to afford the corresponding fluorinated galacto- or glucopyranoside. In contrast to the α-glucosides, the β-glucosides underwent ring fluorination at C-3 to give the 3-deoxy-3-fluoro-β-allo derivatives. High yields of primary fluorinated (C-6) products were obtained from both α- and β-glucosides by use of appropriate reaction times. Use of 6-*O*-trityl derivatives of methyl α- and β-glucosides gave methyl 4-deoxy-4-fluoro-α-galactopyranoside (**22**) and methyl 3-deoxy-3-fluoro-β-allopyranoside (**19**), respectively. Use of 2-D NMR (COSY) for structural assignments is also described. Fluorinated *p*-nitrophenyl α- and β-gluco- and -galactopyranosides (such as **15**) have also been prepared by the above DAST reactions. 6-*O*-Pivaloate esters of methyl α-gluco- and α- and β-galactopyranosides have been prepared as an acid and DAST-stable 6-O protecting group. Proof of an intramolecular fluoride-ion delivery mechanism for the S_N2 displacement reaction at C-4 in methyl α-D-mannopyranoside is described. Methyl 4-amino-4,6-dideoxy-6-fluoro-α-D-glucopyranoside, methyl 6-amino-3,6-dideoxy-3-fluoro-β-D-allopyranoside, and methyl 6-amino-4,6-dideoxy-4-fluoro-α-D-talopyranoside were also prepared via the above methodology.

The altered hydrogen-bonding properties present in carbohydrates bearing a fluorine atom in place of an hydroxyl group have been exploited in biochemical investigations (enzyme-carbohydrate interactions, lectin-carbohydrate affinities, antibody-carbohydrate binding, etc.).[1-5] The syntheses of fluorinated sugars, however, are both tedious and time consuming because of (1) the protection and deprotection steps required to set up the desired hydroxyl group for the introduction of fluoride, (2) the low nucleophilicity of fluoride ion, and (3) fluoride ion catalyzed elimination reactions.[6,7] As part of a program concerned with the synthesis of modified carbohydrates, we

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