Glycophanes, Cyclodextrin–Cyclophane Hybrid Receptors for Apolar Binding in Aqueous Solutions. A Stereoselective Carbohydrate–Carbohydrate Interaction in Water†

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Abstract: The synthesis and complexing properties of a new type of neutral chiral receptors, glycophanes **4–6** and **9–14**, are reported. They may be considered as cyclodextrin–cyclophane hybrids because carbohydrate molecules, lipophilic cavities, and aromatic interactions are involved. They are built from α,α'-trehalose and 2,7-dihydroxynaphthalene or 4,4′-isopropylidenediphenol. The water soluble glycophane **12** displays a general affinity for electron-deficient aromatic guests (nitro derivatives of phenol and benzenesulfonic and benzenecarboxylic acids), the association constants increasing with the increased number of electron-withdrawing groups (NO_2). Depending on the solvent, different factors seem to contribute to the stability of the complexes. In CD_3OD:D_2O (1:1), electron donor–acceptor interactions are the main driving forces, whereas in water, additional hydrophobic effects increase the stability of the complexes. Glycophane **12** shows chiral discrimination toward racemic mixtures of 2,4-dinitrophenyl amino acid derivatives in solid–liquid extraction experiments, with enantioselectivities ranging from 5 to 40% as deduced by integration of the aromatic proton NMR signals of both enantiomers. Cyclodextrins (CDs) under the same conditions did not show any discrimination toward these derivatives. A stereospecific carbohydrate–carbohydrate interaction in water has been shown between glycophane **12** and the 4-nitrophenyl α- and β-D-gluco-, α- and β-D-galacto- and α- and β-D-mannopyranosyl derivatives, and the contribution of this interaction to complex stability has been evaluated. The complexes of CDs and 4-nitrophenyl glycosides did not show any additional stabilization due to carbohydrate moieties.

The study of the forces between molecules is increasingly becoming the center of attention for organic chemists. Since the pioneer works of Pedersen, Cram, and Lehn,[1] organic chemists have learned to design and synthesize receptors where the nature and the arrangement of their functional groups, their degree of flexibility, and their size and shape are in accordance with a rational plan. The advantage of having available a variety of synthetic hosts with different properties for the study of molecular recognition phenomena is well emphasized in the many papers published in recent years and is clearly demonstrated by the interesting results reported therein.[2] The ability to control interactions with these small receptors will allow the chemist to quantify separately the contributions of each interaction to the total energy of complexation including also the solvation effects. The recent results of some research groups in this field allow us to speak about the emergence of a "semiquantitative supramolecular chemistry".[3]

Among the many artificial receptors, cyclodextrins (CDs)[4] and cyclophanes (CPs)[5] have been shown to be two of the most useful tools for the study of the apolar binding of neutral organic molecules in water. Cyclodextrins are α-D-glucopyranose-containing cyclic oligosaccharides. They are chiral and have a lipophilic cavity whose size and shape is determined by nature. Their water solubility is conferred by the hydroxyl groups of the glucose moiety. CDs have provided valuable insights into the hydrophobic effect and van der Waals forces,[6] and they are good models for understanding the specificity of enzyme–substrate interactions.[7] On the other hand, cyclophanes are fully synthetic compounds whose water solubility is provided by ionic centers located near to or remote from the cavity. CPs have also proven to be excellent models for studying the nature of aromatic interactions in both organic and aqueous solvents.[3,5,8]

This paper reports on the synthesis and the preliminary study of a new class of molecular receptors (Chart I) which we have named glycophanes after Wilcox[9] due to their cyclodextrin–cyclophane hybrid character. They will be constituted by sugars and aromatic segments to endow them with the requirements of

† Dedicated to Prof. E. Fernández Alvarez on occasion of his 65th birthday.

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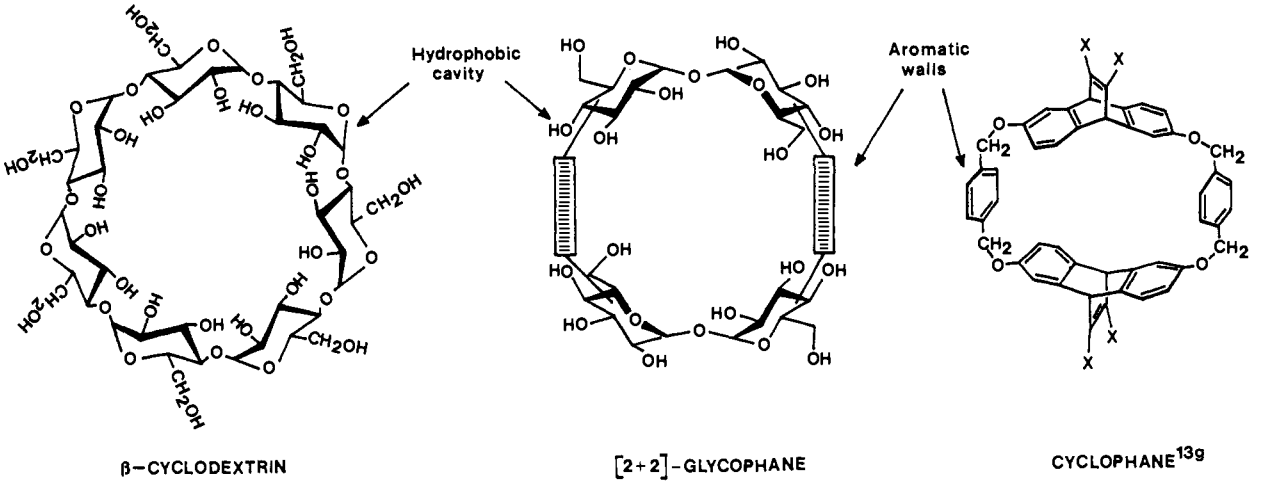
Chart I



cyclodextrins (chirality, neutrality, lipophilic cavity, and water solubility) and of cyclophanes (interactions with arenes).

The design of these receptors was inspired by different areas of research. The first one involves the evaluation and quantification of the different contributions of intermolecular forces in complexation.[3] The second area is the study of the chiral recognition phenomena, one of the functions in nature which remains difficult to understand. The last area concerns the biological carbohydrate recognition process.[10]

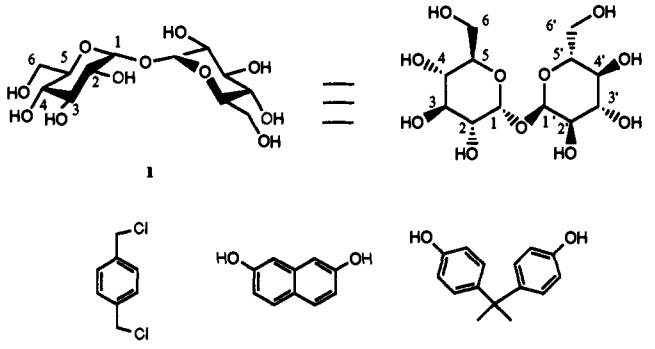
We expect these receptors (a) to allow the study of the influence of aromatic and hydrophobic interactions on the strength and the selectivity of binding in a hydrophilic surrounding; (b) to contribute to the understanding of the physical forces that govern chiral recognition in water; and (c) to demonstrate the existence of carbohydrate binding in water. Recently, two examples have been reported on the molecular recognition of monosaccharides in water using synthetic receptors.[11]

These receptors may improve the chiral recognition of organic molecules with respect to CDs, due to the directional binding introduced by their aromatic interactions. Furthermore, the amphiphilic character of these glycophanes, with a polar carbohydrate area near to an apolar surface, may be a good model to reproduce in water the interaction of carbohydrates with their natural receptors.[12]

Results and Discussion

Synthesis of Glycophanes. The synthesis of optically active cyclophanes have been reported.[13] In two cases,[13e,f] monosaccharides have been used to prepare chiral neutral cyclophanes,

Chart II



but to the best of our knowledge, no data on their complexing properties have been reported. We now have synthesized glycophanes with two sugar moieties and two aromatic segments ([2 + 2]-glycophanes). The sugar moiety is a disaccharide which is conformationally more restricted than a monosaccharide. The hydroxyl groups may behave as anchoring points to introduce the required functionality which could allow the conversion of these receptors into catalytic glycophanes.

α,α′-Trehalose (**1**) (Chart II) is a disaccharide with C_2 symmetry and a concave shape very appropriate for the preparation of highly symmetrical chiral receptors. Polar cavities, crown-ether type, using monosaccharides have been previously reported.[14a] We have also prepared crown ethers incorporating α, α′-trehalose by linking one hydroxyl group of each monosaccharide unit to a polyethyleneglycol chain.[14b] According to CPK models, a lipophilic cavity similar to that of cyclodextrins could be obtained by linking positions 6 and 6′ of α,α′-trehalose to the aromatic segment. The aromatic molecules we have used include α,α′-dichloro-*p*-xylene, 2,7-dihydroxynaphthalene, and 4,4′-isopropylidenediphenol (Chart II).

First attempts to obtain [2 + 2]-glycophanes started from 2,2′,3,3′,4,4′-hexa-*O*-allyl- α,α′-trehalose (**2**) (Scheme I).

Tritylation of the 6,6′-hydroxyl groups of α,α′-trehalose (**1**) followed by allylation of the secondary hydroxyl groups with allyl bromide and detritylation in methanol using *p*-toluensulfonic acid as catalyst gave in 45% overall yield derivative **2**. Reaction of **2** with α,α′-dichloro-*p*-xylene in THF in the presence of NaH as base gave the U-type intermediate **3** in 72% yield. Attempts to obtain the corresponding [2 + 2]-glycophanes by reaction of **3** with a second molecule of **2** were unsuccessful. However, reaction of **3** with 4,4′-isopropylidenediphenol in DMF using Cs_2-

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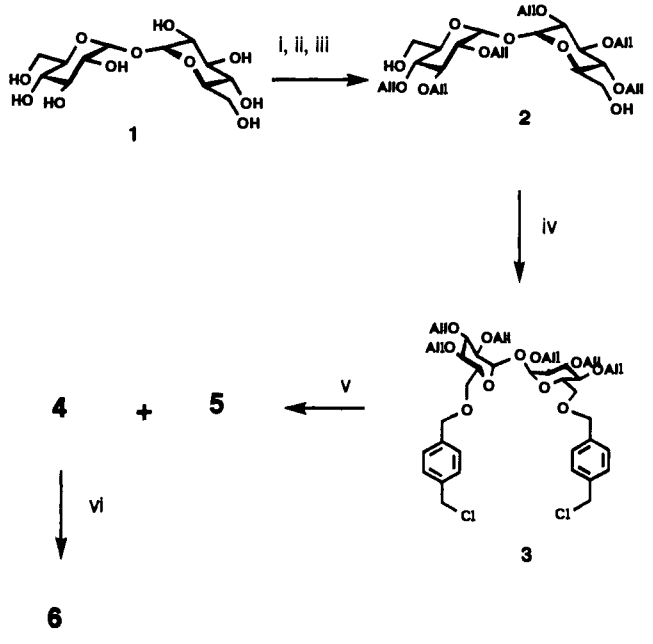
Scheme I[a]



[a]Reagents and conditions: (i) trityl chloride (TrCl), pyridine (Py), 40 °C, (ii) allyl bromide (AllBr), sodium hydride (NaH), DMF, (iii) *p*-toluenesulfonic acid (pTsOH), MeOH, 45% (from **1**), (iv) α,α'-dichloro-*p*-xylene, NaH, THF, 30 °C, 72%; (v) 4,4′-isopropylidenediphenol, Cs_2CO3, DMF (30% of **4** and 13% of **5**), and (vi) Pd/C, pTsOH, EtOH, reflux, 72%.

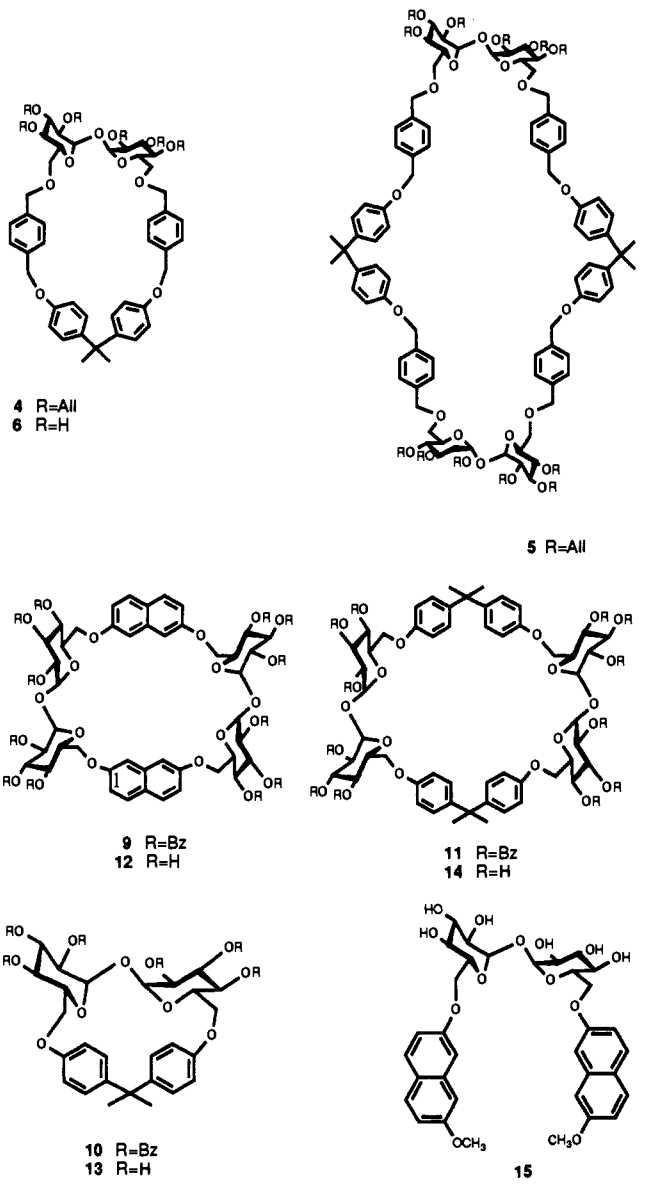
CO_3 as base gave the two cyclic compounds **4** and **5** in 30 and 13% yield, respectively (Chart III). The symmetric structures of **4** and **5** were assessed by their ^{1}H- and ^{13}C-NMR spectra, and their monomeric and dimeric nature was confirmed by FAB-mass spectroscopy. Deprotection of **4** with Pd/C in refluxing ethanol in the presence of *p*-toluensulfonic acid gave glycophane **6** in 72% yield. Although these structures do not correspond to the designed ones, they are novel chiral glycophanes which merit further investigations. By changing the synthetic strategy, we were able to synthesize in a simple and straightforward way the designed [2 + 2]-glycophanes[15] **9-14** (Chart III).

We used as starting material the 2,2′,3,3′,4,4′-hexa-*O*-benzoyl-α,α'-trehalose derivative (**7**). This derivative was obtained from **1**, following a classical sequence in carbohydrate chemistry (Scheme II). Thus, tritylation of **1** followed by benzoylation of the secondary hydroxyl groups and detritylation gave compound **7** in 65% overall yield. Reaction of diol **7** in dichloromethane (DCM) with trifluoromethanesulfonic anhydride using 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) as base gave ditriflate **8** that, without further purification, was reacted in THF in the presence of Cs_2CO_3 and DBMP with 2,7-dihydroxynaphthalene to give [2 + 2]-glycophane **9** in 12% overall yield.

Using K_2CO_3 instead of Cs_2CO_3 in the cyclization step, we observed no reaction, indicating the efficiency of Cs^+ in this type of reaction. Similarly, the cyclization of **8** with 4,4′-isopropylidenediphenol gave [1 + 1]-glycophane **10** in 15% yield together with [2 + 2]-glycophane **11** in 16% yield. Deprotection of glycophanes **9–11** with NaMeO in MeOH gave the hydroxy-free glycophanes **12–14**, respectively, in good yields. Glycophanes **12–14** are highly symmetric as indicated by their ^{1}H- and ^{13}C-NMR spectra, where only the signals corresponding to a glucose moiety and a half-aromatic molecule are present. The FAB-mass spectra of **12–14** confirmed their structures.

The U-type [1 + 2]-compound **15** (Chart III) was also synthesized in a simple and direct way in order to test the influence

Chart III



of preorganization[16] in complexation. Treatment of α,α'-trehalose in DMF with 7-methoxy-β-naphthol under Mitsunobu conditions[17] gave compound **15** in 30% yield. The structure of **15** and its C_2 symmetry were confirmed by its ^{1}H- and ^{13}C-NMR spectra.

According to CPK models, glycophane **13** presents a cavity too small to complex any organic aromatic molecule. However, the cavities of **12** and **14** are very appropriate for inclusion of benzene and naphthalene derivatives. The solubility of glycophane **12** in MeOH, MeOH:H_2O (1:1), and H_2O is 10^{-3}, 8×10^{-3}, and 3.6×10^{-4} M, respectively. However, the solubility of glycophane **14** in these solvents was too low to allow the study of complexation by NMR spectroscopy.

Structure of Glycophane 12. An observation of the CPK model of glycophane **12** shows that the receptor is relatively rigid around the glycosidic bonds C1–O1 and C1′–O1 as is expected for a disaccharide where the values of the torsion angles Φ (O5–C1–O1–C1′) and Φ′ (O5′–C1′–O1–C1) are governed by the *exo*-anomeric effect.[18] In contrast, a great number of conformational isomers are possible around the O5–C5–C6–O6, C5–C6–O6–C2(n), and C6–O6–C2(n)–O2(n) torsion angles, placing the naphthalene moieties in three different orientations giving a

(15) A preliminary communication on the synthesis is already published. See: Penadés, S.; Coterón, J. M. *J. Chem. Soc., Chem. Commun.* **1992**, 683–684.

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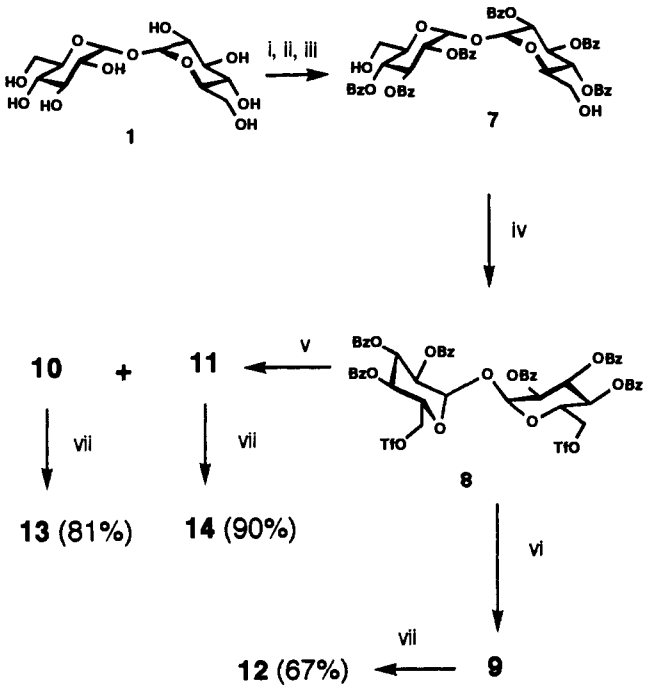
(17) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(18) Praly, J. P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213–223.

Scheme II[a]



[a]Reagents and conditions: (i) TrCl, Py, 40 °C, (ii) benzoyl chloride (BzCl), Py, (iii) pTsOH, MeOH, 65% (from **1**), (iv) triflic anhydride (Tf_2O), 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), CH_2Cl_2, 0 °C, (v) 4,4′-isopropylidenediphenol, Cs_2CO_3, DBMP, THF (16% of **10** and 15% of **11**, both from **7**), (vi) 2,7-dihydroxynaphthalene, Cs_2CO_3, DBMP, THF, 12% (from **7**), and (vii) NaMeO, MeOH.

parallel, an antiparallel, and a T-shape conformation. Besides, the ether linkages can act as hinges so that the molecule can easily pivot between a rectangular and rhomboid form. The small differences between the ^{1}H-NMR spectra of **12** and comparison compound **15** (Figure 1) indicate that minor changes take place in the conformation of the trehalose moiety upon cyclization.

The intramolecular NOEs between H1 and H5′ of the trehalose moiety accord with a conformation where the values for the torsion angles Φ and Φ′ are ca. 60 ± 20°, similar to those found for trehalose and trehalose derivatives in solution and in the solid state.[14,19] The values of the coupling constants $^3J_{H5,H6endo}$ = 2.0 Hz and $^3J_{H5,H6exo}$ = 4.7 Hz indicate that for the C5–O6 bonds of the α,α′-trehalose moiety, a population distribution of 60:40 gauche–gauche (gg):gauche–trans (gt) rotamers is present in solution.[20] Figure 2 shows some of the local minima conformations obtained in a preliminary study for glycophane **12** using the CVFF force field included in the Discover program[21] with energy differences no more than 0.5 kcal/mol.

Both rectangular and rhomboid cavities are local minima of glycophane **12**,but some of these conformations do not have the adequate cavity for a productive binding and will not be present in the complex. The high symmetry of the ^{1}H-NMR spectrum of **12** indicates that, in solution at 30 °C, all possible conformers interconvert quickly on the NMR time scale. The rhomboid conformation of **12** (figure 2), with the antiparallel naphthalene walls ≃ 6.5–7.5-Å apart and the trehalose moieties ≃ 7–11-Å apart, seems to be well preorganized for sandwiching an aromatic guest in a face to face offset geometry.[22]

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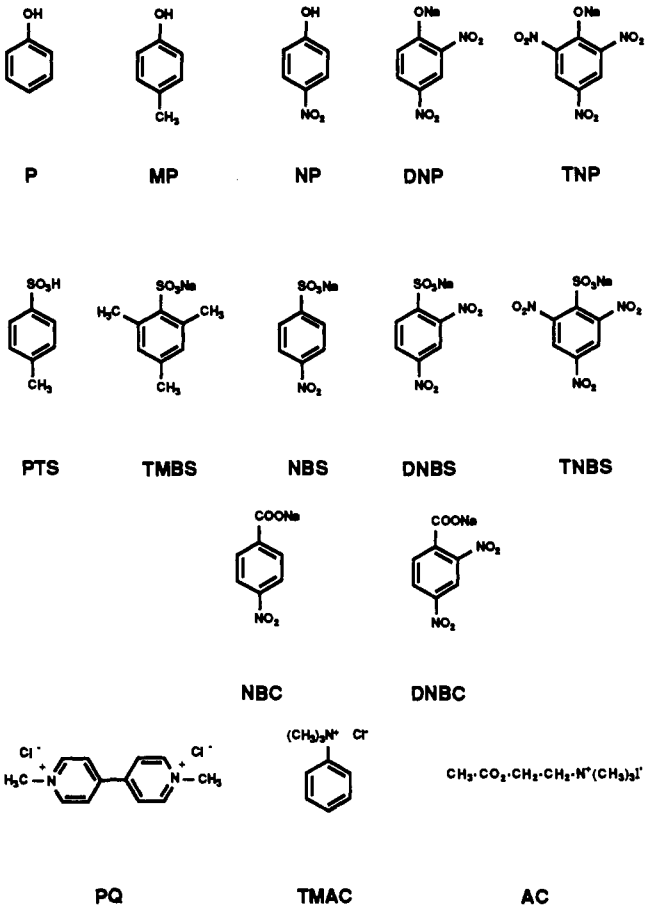
(20) Leeflang, B. R. Conformational Analysis of Oligosaccharides, Thesis; Utrech, 1991; Chapter 1, pp 19–28.

(21) Discover; Biosym, version 2.8. Although the CVFF force field is not parametrized for carbohydrates, the results agree with those obtained by us for trehalose moieties using the MM2 program.

Chart IV



Binding Studies. In CDs and CPs, a variety of factors are operative for the binding of organic molecules. The hydrophobic effect seems to be one of the driving forces in CDs, while in CPs, aromatic interactions and solvation effects may govern the binding depending on the solvent.[3e] Glycophane **12**, endowed with a lipophilic cavity and electron-rich naphthalene walls, is an appropriate model to evaluate the influence of aromatic interactions on the strength and the selectivity of binding in aqueous media in comparison with CDs and CPs. We have chosen a series of aromatic guests with different electronic properties (Chart IV). Some of them are already known to bind CDs in water. Besides, cationic organic guests (paraquat, trimethylanilinium chloride, and acetylcholine) have also been tested to see if glycophane **12** is able to complex through "cation–π" interaction as Dougherty's cyclophane does.[13g]

Preliminary tests showed that glycophane **12** binds only electron-deficient aromatic guests in CD_3OD:D_2O (1:1), indicating that electron donor–acceptor interactions[23] (EDA) should be the driving force for binding. To evaluate the binding affinities with the increasing number of electron-withdrawing groups in the guests, the association constants *K* of the mononitro-, dinitro-, and trinitro-substituted phenol (NP, DNP, and TNP), benzenesulfonic acid (NBS, DNBS, and TNBS) and benzoic acid (NBC and DNBC) derivatives were determined. All binding constants were obtained from ^{1}H-NMR titration data. The measurements were performed, as far as solubility permitted, in CD_3OD:D_2O (1:1) and borate-*d* buffer (pD = 9.7). In CD_3OD:D_2O (1:1), NaOD solution was added to the guest solutions to adjust to pD

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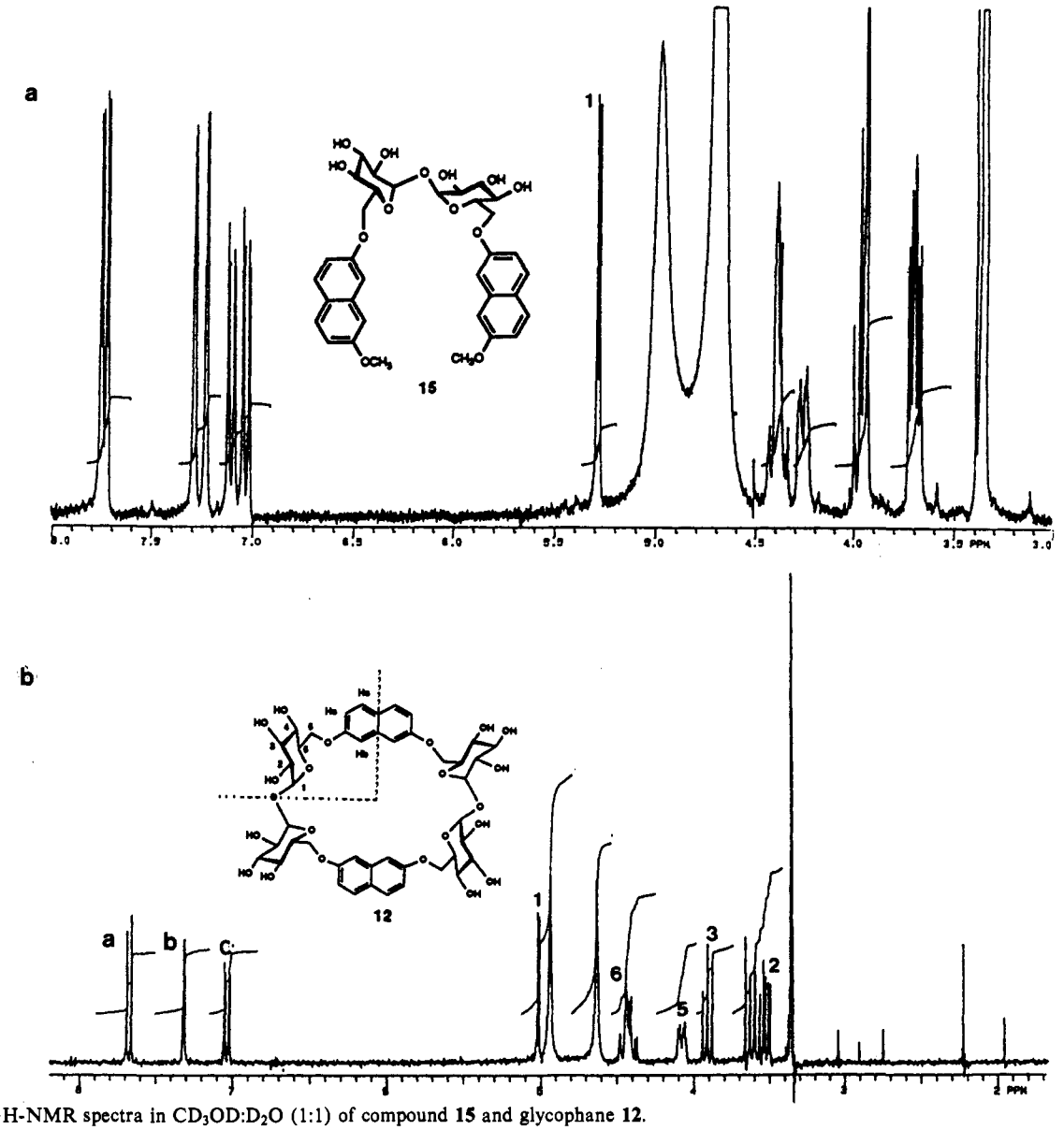


Figure 1. ^{1}H-NMR spectra in CD_3OD:D_2O (1:1) of compound **15** and glycophane **12**.

= 12. Addition of NaOD to a solution of the host did not change the chemical shifts of the protons of the glycophanes. Self-association of glycophane **12** in CD_3OD:D_2O (1:1) is negligible because no change in chemical shift of the protons of **12** was observed in a dilution experiment. In borate buffer, Hb and H1 showed, in a dilution experiment, changes below 10% of a usual calculated induced shift (CIS) and a self-association constant of less than 5 M^{-1} could be estimated. For this reason, all borate-*d* experiments were carried out at constant host concentration. Complexation constants and calculated induced shifts (CIS values at 100% binding) of glycophane **12** were obtained using two different nonlinear fitting programs,[24] depending on the experimental conditions (at varying host and guest concentration[24a] or at constant host concentration[24b]). In some experiments, both fitting programs were used and the *K* values obtained by the two methods were in good agreement.

Table I gives the *K* and CIS values of glycophane **12** upon binding with the aromatic guests. The observed variation in the chemical shift of the protons of glycophane **12** upon binding provides clear evidence for intracavity inclusion. Upon addition of the guest in CD_3OD:D_2O (1:1) or in borate-*d* buffer, aromatic protons of glycophane **12** and $H6_{endo}$ of the trehalose moiety shifted upfield, while H1, H2, and H3 of trehalose moved downfield. This shift pattern was the same for all guests, suggesting a common binding geometry for all complexes in which the guest is placed parallel to the naphthalene walls and perpendicular to the glycosidic linkages. An intermolecular NOE (2.0%) observed on the complex of **12** with TNP between H1 and the proton of the guest supports this structure. The increase of the binding affinity of glycophane upon the introduction of a new nitro group in the guest (Table I) reveals that in methanol:water (1:1), electronic complementarity is the main driving force for complexation.[23b] Charge-transfer (CT) interactions do not seem to contribute significantly since color changes were not observed after addition of the guests. α,β-, and γ-CDs were not able to complex these guests in this medium in spite of their deeper lipophilic cavity.[25] Comparison of the *K* values in CD_3OD:D_2O (1:1) (Table I) indicates a higher increase of the association constants in the phenol series ($\Delta\Delta G$ = 1.1 and 2.2 kcal/mol) with respect to those in the benzenesulfonate series ($\Delta\Delta G$ = 0.3 and

(24) (a) Schneider, H. J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442–6448. (b) Wilcox, C. S. In ref 2c, pp 123–143. We thank Prof. H. J. Schneider (University of Saarbrücken) and Prof. C. S. Wilcox (University of Pittsburgh) for their kind cession of their fitting programs.

(25) Only changes in the chemical shifts of the H1, H2, and H4 protons of the CDs were observed by addition of the guests (NP, DNP, TNP). The association constant of α-CD and NP in water decreases 85% by adding 20% methanol.[24a]

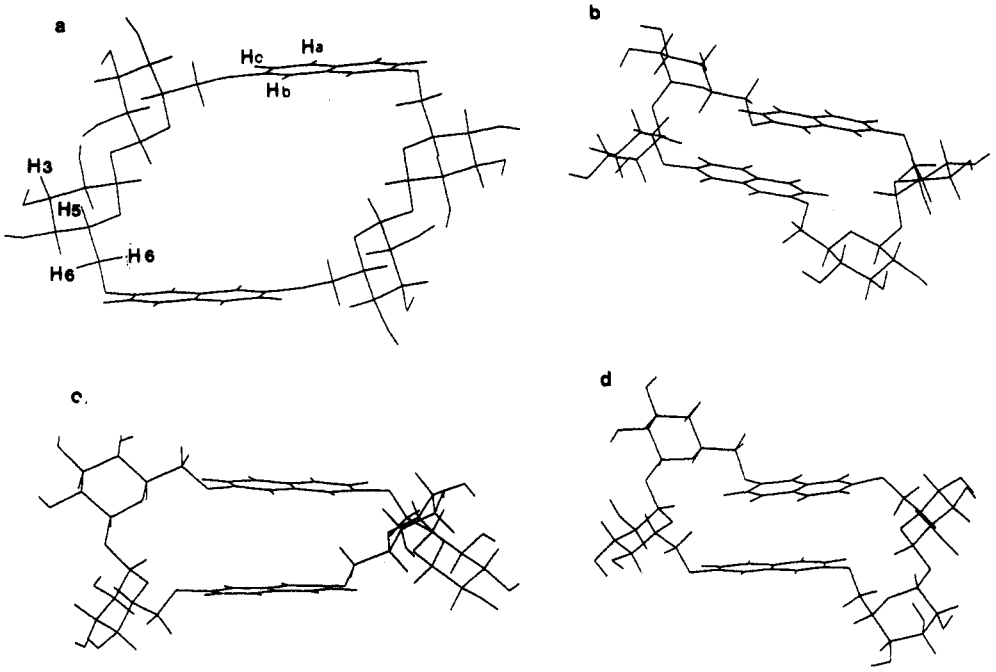


Figure 2. View of some local minima of **12** obtained by using the CVFF/Discover programm. Naphthalene–naphthalene and O1–O1 distances: (a) 7.55 and 11.2 Å, (b) 3.84 and 9.56 Å, (c) 4.76 and 11.55 Å, and (d) 4.19 and 10.51 Å.

Table I. Association Constants K (M^{-1}), Free Energies $-\Delta G$ (kcal/mol), and Calculated Induced Shifts (CIS, ppm) of Glycophane **12** with Different Guests at 303 K in CD_3OD:D_2O (1:1) and Borate-*d* Buffer

	CD_3OD:D_2O (1:1)		borate-*d*		CIS[c]		
compd	K[e,g]	$-\Delta G$[g]	K[d,g]	$-\Delta G$[g]	Hb[g]	Hc[g]	H1[g]
MP	*a*	*a*	*a*	*a*	*a*	*a*	*a*
NP	$(3.6 \pm 0.3) \times 10^0$	0.8 ± 0.10	$(1.5 \pm 0.3) \times 10^1$	1.5 ± 0.09	0.44 (0.37)		–0.22 (–0.17)
DNP	$(2.3 \pm 0.4) \times 10^1$	1.9 ± 0.11	$(4.2 \pm 0.6) \times 10^2$	3.6 ± 0.09	0.23 (0.40)	0.20	–0.17 (–0.30)
TNP	$(9.0 \pm 1.0) \times 10^2$	4.1 ± 0.09	$(1.2 \pm 0.2) \times 10^4$	5.6 ± 0.10	0.38 (0.40)	0.40	–0.30 (–0.30)
PTS	*a*	*a*	*a*	*a*	*a*	*a*	*a*
TMBS	*a*	*a*	*a*	*a*	*a*	*a*	*a*
NBS	$(1.6 \pm 0.2) \times 10^1$	1.7 ± 0.06	$(8.5 \pm 0.5) \times 10^1$	2.7 ± 0.04	0.52 (0.52)	0.40	–0.30 (–0.31)
DNBS	$(3.0 \pm 0.2) \times 10^1$	2.0 ± 0.08	$(5.5 \pm 0.9) \times 10^2$	3.8 ± 0.10	0.50 (0.45)	0.43	–0.26 (–0.26)
TNBS	$(8.9 \pm 0.4) \times 10^1$	2.7 ± 0.03	$(1.1 \pm 0.1) \times 10^4$	5.6 ± 0.07	0.42 (0.40)	0.47	–0.30 (–0.31)
NBC	$<2 \times 10^0$	<0.5	*b*	*b*	*b*	*b*	*b*
DNBC	$(1.7 \pm 0.3) \times 10^1$	1.7 ± 0.10	*b*	*b*	0.40	0.41	–0.23
PQ	$(8.5 \pm 0.2) \times 10^0$	1.3 ± 0.05	nm	nm	0.37	0.36	–0.23
NDS	nm	nm	$(4.6 \pm 0.2) \times 10^2$	3.6 ± 0.06	nm (0.71)	nm	nm (–0.49)
DHN	nm	nm	*f*	nm	nm	nm	nm

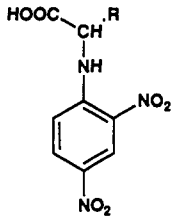
[a] No inclusion. [b] Not determined due to low solubility. [c] Numbers in brackets represent CIS in borate-*d* buffer. Positive CIS represent upfield shifts. [d] K values are the average of two different experiments and two different protons. [e] K values are the average of two different experiments and three different protons. [f] Only the shift of the H2 could be observed, and its value in a saturated solution of the guest was 2.6% of the CIS for NDS. [g] nm = not measured.

0.7 kcal/mol) by the introduction of a new nitro substituent. This result was not expected on the basis of donor–acceptor electrostatic interactions and suggests that some additional factor is involved in the preferential binding of picrate with respect to TNBS. This additional stabilization could be attributed to London dispersion forces, which are directly related to the polarizabilities of the interacting partners.[26] The phenolate ion is more polarizable than the sulfonate one so that a larger dispersion energy can contribute to the stabilization of the complexes, although hydrogen-bonding interactions between the nitro group and the methine group of the sugar moiety can not be excluded. In contrast, in aqueous solution, both substrates showed association constants in an analogous range and higher than in methanol: water (1:1), indicating a contribution of hydrophobic effects on complexation as has already been observed for CDs and CPs. The question to be addressed is whether or not hydrophobic effects are enough to establish an interaction in water. Complexation experiments in borate buffer with PTS and TMBS, having similar lipophilic areas as NBS and TNBS, respectively, did not show inclusion,[27] and association constants for these substrates could not be determined. In addition, complexation experiments with 2,6-dihydroxynaphthalene (DHN) in borate buffer showed induced shifts at less than 3% of the CIS for 2,6-naphthalenedisulfonic acid (NDS), whereas this substrate (NDS) presented, in the same medium, an association constant of 460 M^{-1}. From these results, it could be assumed that electronic complementarity (EDA) is necessary in order to establish a specific interaction with glycophane **12**, other forces (induced dipoles, hydrogen bonding, and solvation effects) contributing to the stabilization of the complexes in different degrees depending on the structure of the guest. The contribution of preorganization in glycophane **12** was assessed by complexation experiments with the [1 + 2]-compound **15** and the DNP, TNP and TNBS guests. Evidence for this inclusion was always negative, and no shifts in the proton signals of the host were observed even in the presence of a high excess of guests.

(26) Mc Curdy, A.; Jiménez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314–10321.

(27) Only upfield shifts were observed for all the protons of the host upon addition of 0.2 M TMBS solution.

Chart V



16	R = CH_2CH_3	*N*-2,4-DNP-α-amino-*n*-butyric acid
17	R = $(CH_2)_2CH_3$	*N*-2,4-DNP-norvaline
18	R = $(CH_2)_3CH_3$	*N*-2,4-DNP-norleucine
19	R = $CH_2)_5CH_3$	*N*-2,4-DNP-α-amino-*n*-caprylic acid
20	R = $(CH_2)_2SCH_3$	*N*-2,4-DNP-methionine
21	R = $(CH_2)_2S(O)CH_3$	*N*-2,4-DNP-methionine sulfoxide
22	R = $(CH_2)_2SCH_2CH_3$	*N*-2,4-DNP-ethionine
23	R = $(CH_2)_2COOH$	*N*-2,4-DNP-glutamic acid
24	R = $(CH_2)_3NHC(O)NH_2$	*N*-2,4-DNP-citrulline

Chiral Discrimination. Chiral molecular recognition is one of the most sophisticated functions of enzymes which remains difficult to mimic with artificial receptors. Cyclodextrins have been shown to be good stationary phases in chromatography for the enantioselective separation of neutral racemic guests, but their enantioselection degree in aqueous solution is quite poor.[28] Recently, optically active cyclophanes for the enantioselective binding have been prepared,[13] but the observed enantioselection in water is still moderate.[29] Better enantioselectivities have only been observed in organic solvents,[30] where oriented bonding interactions, e.g., hydrogen-bonding or electrostatic interactions, take place efficiently. It seems that it will be difficult to achieve in water chiral discrimination based only on apolar, steric, or $\pi-\pi$ interactions. We had expected our glycophanes to show good chiral discrimination in aqueous solution with racemic mixtures of 2,4-dinitrophenyl amino acid derivatives. Our expectations were based on (i) the previous results obtained with the aromatic nitro derivatives in aqueous solutions and (ii) the work of Pirkle et al.,[31] in which they established the multicenter nature of the $\pi-\pi$ interactions in the chiral recognition of aromatic amino acid derivatives, although this multicenter character has been questioned by other authors.[32] The 2,4-dinitro derivatives **16–24** (Chart V) were chosen because of the different character of the R chain.

Compounds **16–19**, with increasing aliphatic chains, should show the influence of steric interactions and hydrophobic effects in the chiral recognition. Compounds **20–24** have chains of different natures, with hydrogen-bonding acceptor or donor groups, in order to show the influence of this in the chiral discrimination.

Glycophane **12** forms diastereomeric complexes in CD_3OD:D_2O (1:1) with all the guests **16–24**, as indicated by ^{1}H-NMR spectra of the 1:1 complexes obtained by liquid–solid extraction experiments (Figure 3). The observed induced ^{1}H-NMR shifts in the host upon complexation were in all cases similar to those previously found for complexes with the aromatic guests, indicating the same inclusion geometry. The degree of chiral recognition is given in Table II.

Table II. Chiral Recognition of 2,4-Dinitrophenyl Amino Acid Derivatives **16–24** by Glycophane **12** in CD_3OD:D_2O (1:1) at 303 K

compd	R	de[a] (%)
16	CH_2CH_3	<5
17	$(CH_2)_2CH_3$	<10
18	$(CH_2)_3CH_3$	40
19	$(CH_2)_5CH_3$	<5
20	$(CH_2)_2SCH_3$	15
21	$(CH_2)_2SOCH_3$	4 diastereomers
22	$(CH_2)_2SCH_2CH_3$	20
23	$(CH_2)_2CO_2H$	<5
24	$(CH_2)_3NHCONH_2$	<5

[a] These values were calculated by integration of the aromatic proton signals of both enantiomers from at least three different experiments in the same conditions (4×10^{-3} mmol of guest and 4×10^{-3} mmol of **12** in 0.6 mL of solvent).

The best enantioselectivity observed was in the case of (2,4-dinitrophenyl)norleucine (**18**) with 40% de. In the homologous series α-aminobutyric acid **16**, norvaline **17**, norleucine **18**, and caprylic acid **19**, an enantioselection maximum of 40% de was obtained for **18**, indicating that steric factors are probably at the origin of the observed enantioselectivity. Substitution of the methyl group of norvaline and norleucine in derivatives **17** and **18** by a polar group (COOH in glutamic acid and urea in citrulline) did not improve the enantioselectivity, indicating that hydrogen-bonding interactions do not play an important role. Although, due to experimental problems, we were not able to determine independently the binding affinities of each enantiomer, the present results indicate that glycophane **12** shows one of the best enantioselectivities obtained by a chiral cyclophane in aqueous solution on the basis of only steric, van der Waals, and $\pi-\pi$ interactions. When racemic **18** was complexed with β-CD, no stereoselectivity was found and only the signal corresponding to the formation of diastereoisomeric complexes was observed. These results show the superiority of a directional aromatic interaction for chiral discrimination with respect to the circular interaction in CDs and open the way to the design of other more enantioselective receptors based on this general system.

Carbohydrate–Carbohydrate Interactions. Although a large number of cellular recognition events involve specific protein–carbohydrate interactions, the exact role of the oligosaccharides and the basis for their specificity and affinity in the binding are still poorly understood.[10,12] An understanding of the factors that govern these recognition processes and, particularly, those between carbohydrates at the molecular level would be of interest. The study of sugar binding in water is difficult, since calorimetric evidences[33] suggest that carbohydrate–carbohydrate interactions between simple sugars are unfavorable in water, the stereochemical aspects of carbohydrate hydration[34] playing an important role.

The amphiphilic glycophane **12** is a good synthetic model to show carbohydrate–carbohydrate interaction in water with partially hydrophobic sugars.[35] We have used its ability to bind π-acceptor phenyl derivatives to bring both host and guest

(28) For recent studies on enantioselective binding by cyclodextrins, see: (a) Köhler, J. E. H.; Hohla, M.; Richters, M.; König, W. A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 319–320. (b) Fischer, P.; Aichholz, R.; Bölz, U.; Juza, M.; Krimmer, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 427–429. (c) Lipkowitz, K. B.; Raghothama, S.; Yang, J. *J. Am. Chem. Soc.* **1992**, *114*, 1554–1562. (d) Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457–1470 and references therein.

(29) (a) For a review on chiral molecular recognition by cyclophanes, see: Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991; pp 222–245. (b) Castro, P. P.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 6277–6280. (c) Webb, H. T.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554–8555.

(30) (a) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993–6996. (b) Sanderson, P. E. J.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314–8315. (c) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835–5838. (d) Bhattarai, K. M.; Boner-Law, R. P.; Davis, A. P.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 752–754. (e) Alcázar, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1521–1523.

(31) Pirkle, W. H.; Popapsky, T. C. *Chem. Rev.* **1989**, *89*, 347–362.

(32) (a) Topiol, S.; Sabio, M.; Moroz, J.; Caldwell, W. B. *J. Am. Chem. Soc.* **1988**, *110*, 8367–8376. (b) Ucella-Baretta, G.; Rosini, C.; Pini, D.; Salvadori, P. *J. Am. Chem. Soc.* **1990**, *112*, 2707–2710.

(33) (a) Gaffney, S. H.; Haslam, E.; Lilley, T. H.; Ward, T. R. *J. Chem. Soc., Faraday Trans. 1* **1988**, *84*, 2545–2552. (b) Barone, G.; Castronuovo, G.; Elia, V.; Savino, V. *J. Solution Chem.* **1984**, *13*, 209–219.

(34) (a) Galema, S. A.; Hoiland, H. *J. Phys. Chem.* **1991**, *95*, 5321–5326. (b) Galema, S. A.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1992**, *57*, 1995–2001.

(35) (a) Miyajima, K.; Machida, K.; Nakagaki, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2595–2599. (b) Yano, Y.; Tanaka, K.; Doi, Y.; Janado, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2963–2964. (c) Janado, M.; Yano, Y. *J. Solution Chem.* **1985**, *14*, 891–902. (d) Yano, Y.; Tanaka, K.; Doi, Y.; Janado, M. *J. Solution Chem.* **1988**, *17*, 347–358. (e) For hydrophobicity in polysaccharides, see: Balasubramanian, D.; Raman, B.; Sundari, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 74–77.

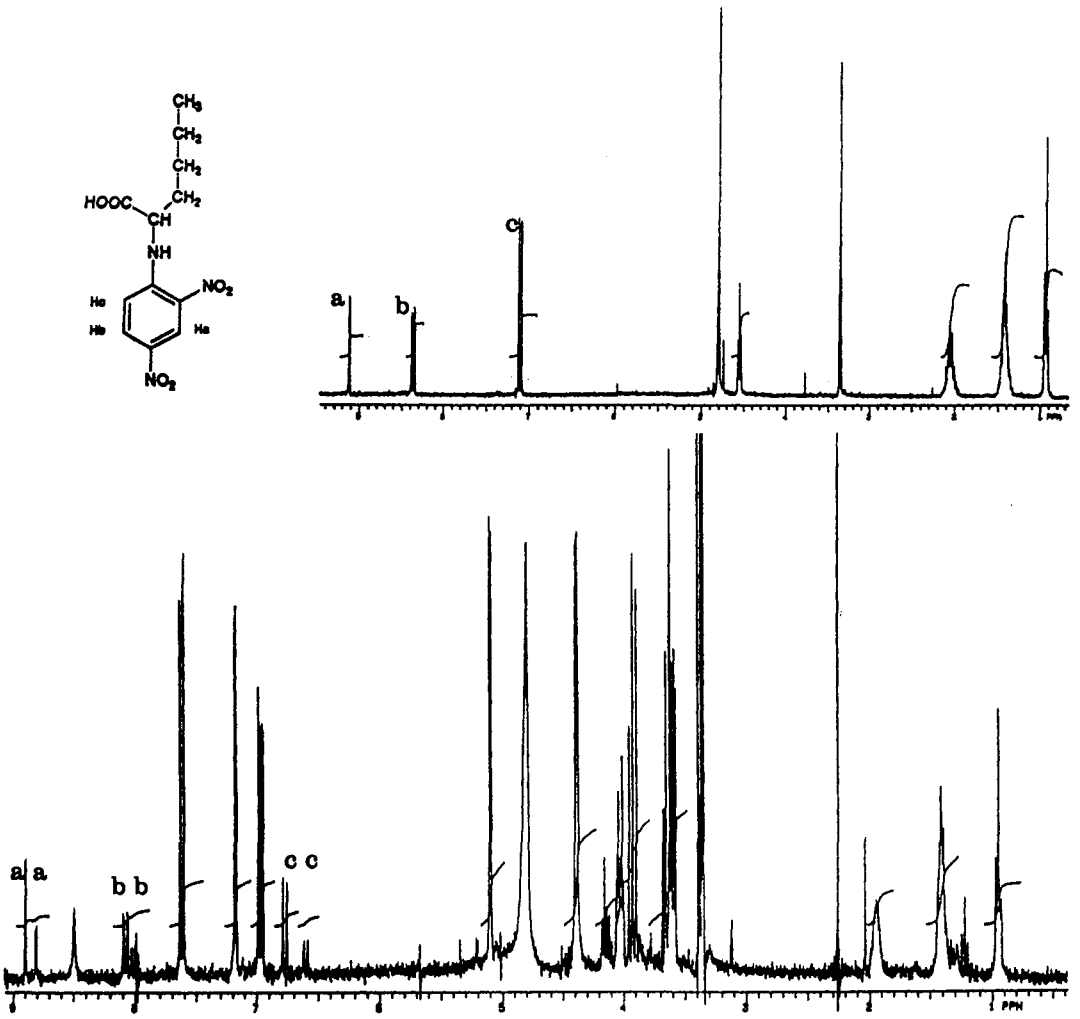


Figure 3. ^{1}H–NMR spectra in $CD_3OD:D_2O$ (1:1) of racemic **18** (saturated solution) and the **12**·**18** complex ($[12]_0 = [18]_0 = 6.66 \times 10^{-3}$ M).

carbohydrates to close proximity. The association constants[36] of the complexes formed in D_2O by **12** and the 4-nitrophenyl glycosides of α-D-gluco- (α-Glc), α-manno- (α-Man), and α-galacto- (α-Gal) pyranosides and their corresponding β-D-isomers (β-Glc, β-Gal, and β-Man) have been measured. These guest molecules were chosen because of their different hydrophobic character.[35]

The results show that **12** can complex both α- and β-derivatives of glucose, galactose, and mannose (Table III). The association constants in the α-series are all in the same range, with the highest K value corresponding to the most hydrophobic monosaccharide (mannose, $K = 265$ M^{-1}), while the lowest value was found for the less hydrophobic one (glucose, $K = 130$ M^{-1}). On the other hand, glycophane **12** does complex the β-derivatives but with smaller Ks than those of the α-derivatives and comparable to that obtained for 1-(*p*-nitrophenyl)glycerol ($K = 65$ M^{-1}). These results indicate that glycophane **12** shows an α/β stereoselectivity for these glycosides. The largest α/β stereodifferentiation was found for mannose ($K\alpha/K\beta = 3.6$, $\Delta\Delta G = -0.77$ kcal/mol), although in all cases there is a preference for the α-anomer. To our knowledge, this is the first example of α/β diasteromeric differentiation by a synthetic receptor working in aqueous media.

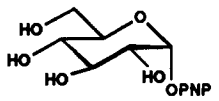
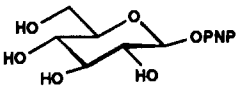
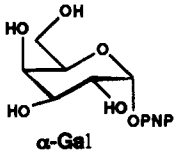
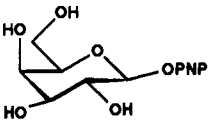
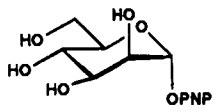
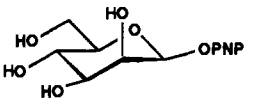
The contribution of the carbohydrate moiety to binding could be estimated by comparison of these K values with that of the complex formed by **12** and *p*-nitrophenol[37] ($K = 15$ M^{-1}). In all the α-glycosides, the K values are 1 order of magnitude higher than that of *p*-nitrophenol. The association constant of **12**–(α-Man) is 18 times higher than the K of **12** and *p*-nitrophenol which accounts for an additional stabilization of $\Delta\Delta G = -1.7$ kcal/mol. In contrast, the complexes formed between α- and β-CDs and *p*-nitrophenyl α- and β-D-mannopyranosides did not show any additional stabilization related to their complexes with *p*-nitrophenol (pH = 3) (Table IV).

These differences in complexing properties of glycophane **12** and the naturally occurring CDs must be due to the different orientation of the glucose moieties in each receptor. In α- and β-CDs, the α-face of the carbohydrate moiety of the guest will find either the hydroxymethyl groups or the 2-OH groups of the host when approaching the receptor, whereas in **12**, it is the upper-face of one glucose unit of the α,α′-trehalose which will be found by the α-face of the approaching guest (Figure 2). This different approach makes possible van der Waals contacts between both faces in the case of glycophane **12**, thus favoring desolvation of both surfaces upon binding. The observation of intermolecular NOEs[38] between the proton resonances of H3, H5, and H6ab in the upper face of Glc and looking inside the cavity of **12** and the H2 and H3 protons of the bottom face of α-Man in the complex **12**–(α-Man) shows the spatial proximity between both carbohydrate moieties. In addition, the observed intermolecular NOEs between the aromatic protons of the host and the guest showed

(36) (a) Titrations were followed by ^{1}H NMR on the H1 and Hb resonances of **12** at 500 MHz in D_2O using DMSO-d_6 as external reference. The complexation range was between 20 and 80%, except for the **12**–(α-Gal) complex where only 50% could be reached due to solubility problems. The concentration of the host was ca. 8×10^{-5} M and that of the guest ranged between 10^{-1} and 2×10^{-2} M. (b) The NMR data were adjusted using the Hostest-II, nonlinear fitting program of Wilcox.[2c]

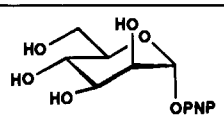
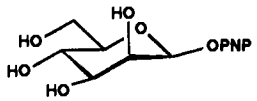
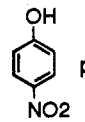
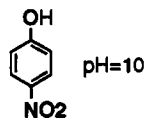
(37) K of the **12**·*p*-nitrophenol complex was measured in borate-*d* buffer, pD = 9.7, due to solubility problems in D_2O. The *p*-nitrophenolate complexes for α- and β-CDs are stronger than those of *p*-nitrophenol (see Table IV).

Table III. Stability Constants (M^{-1}) and $-\Delta G$ (kcal/mol) of the Complexes Formed by Glycophane **12** and *p*-Nitrophenyl α- and β-D-Glycosides in D_2O, T = 303 K[a]

complex	K	$-\Delta G$		K	$-\Delta G$
 α-Glc	135	2.94	 β-Glc	63	2.48
 α-Gal	150	3.00	 β-Gal	95	2.73
 α-Man	258	3.33	 β-Man	72	2.56

[a] PNP = *p*-nitrophenyl.

Table IV. Stability Constants (M^{-1}) and $-\Delta G$ (kcal/mol) of the Complexes Formed by α- and β-CD and *p*-Nitrophenyl Derivatives in D_2O, 30 °C

	α-CD		β-CD	
complex	K	$-\Delta G$	K	$-\Delta G$
 α-Man	190	3.14	263	3.34
 β-Man	333	3.48	185	3.13
 pH=3	172	3.08[a]	256	3.32
 pH=10	1639	4.44[a]	666	3.90[a]

[a] Reference 39.

the position of the π-deficient aromatic ring within the cavity.[38] There is a correlation between the K values of the α-glycosides and the number of CHs in the α-face of the monosaccharide. The mannose derivative α-Man with the smaller number of OHs in the interacting α-face of the guest forms the strongest complex, while the glucose derivative that has the higher number of OHs in the α-side has the lowest K value. These thermodynamic and structural results unambiguously indicate the existence of a carbohydrate–carbohydrate interaction in water.

Conclusions. Glycophane **12** is the first studied member of a new type of chiral receptors which were designed to show both cyclodextrin and cyclophane properties. Glycophane **12** complexes aromatic guests mainly by EDA π-interactions. Glycophane **12** shows improved chiral discrimination of amino acid derivatives with respect to that of cyclodextrins. By a rational change in either the carbohydrate or the aromatic moieties, the synthetic strategy used for glycophane **12** will allow the preparation of a variety of glycophanes with recognition sites comparable to those of cyclodextrins and cyclophanes.

An important aspect of this study concerns the use of these different glycophanes as models to determine a *carbohydrate–carbohydrate interaction in water*. We have shown evidences of a specific carbohydrate–carbohydrate interaction between glycophane **12** and 4-nitrophenyl glycosides in water, which has been found to be stereospecific for α-glycosides. The contribution to the stability of the complexes of this interaction ranges between 0.8 and 1.7 kcal/mol, while in CD complexes, this stabilization was not observed.

Although hydrogen bonding can not be excluded, it is important to remark that glycophane **12** interacts with the amphiphilic part of the glycosides through nonpolar forces, thus contributing to the stability of the complexes in a similar way as proposed first by Lemieux for the complexes between oligosaccharides and lectins and antibodies[12a,40] and more recently by Hakomori for glycolipid–glycolipid recognition.[12c] A deeper analysis of the stereochemistry of the observed carbohydrate–carbohydrate interaction and the study of the catalytic properties of glycophane **12** are underway.

Experimental Section

General. NMR spectra were recorded on Varian 300- or 500-MHz spectrometers. J coupling is reported in hertz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. Binding-event spectra in methanol–water were referenced to the methanol signal and in borate buffer, were referenced to external DMSO in a coaxial tube. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter. FAB-MS spectra were obtained in a nitrobenzyl alcohol matrix with a MS-50 Kratos instrument fitted with a 1.2-T magnet using

(38) Assignment of the ^{1}H-NMR spectra of the complex **12**–(α-Man) was done by standard COSY experiments. Steady-state NOE experiments were done using a 1:10 mixture of **12**:(α-Man) in D_2O solution at 30 °C. All the inter- and intramolecular enhancements involving the receptor were negative, indicating that the receptor is in the slow motion regime. The negative intermolecular NOE values were H6(trehalose) 5% and 2% with H2 and H3(α-mannose), H3(α-mannose) 3.4% and 1.7% with H5 and H3(trehalose), H2(α-mannose) 2.6% with H6(trehalose), Ha(naphthalene) 3.6% and 1.5% with H_{ortho} and H_{meta}(α-mannose), and Hc(naphthalene) 6% with H_{ortho}(α-mannose). The small and negative values observed for the intermolecular NOEs imply that the motion of the molecule corresponds to a value of $\omega_0\tau_c$ slightlyhigher than 1.1. This fact is not unusual for penta- and hexasaccharides in water solution, which behave as if they had correlation times higher than those expected for their molecular weights. In this regime ($\omega_0\tau_c > 1.1$), spin diffusion is not as efficient as in the typical slow-motion regime ($\omega_0\tau_c >>> 1.1$). We have also performed 2D-ROESY (CAMELSPIN) experiments which minimize spin diffusion effects. The results are quantitatively the same as in the usual laboratory frame NOESY or 1D-NOE experiments.

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a FAB 11 WF Ion Tech atom gun and with a ZAB instrument. Chromatographic eluents are given as volume to volume ratios (v/v). Solvents were distilled from drying agents: pyridine, BaO; dimethylformamide (DMF), CaO; dichloromethane (DCM), CaH_2; and tetrahydrofuran (THF), sodium/benzophenone. All reactions were stirred magnetically under an argon atmosphere unless otherwise mentioned. All guests were obtained from commercial sources. Host and guest solutions for NMR binding experiments were made up with CD_3OD:D_2O (1:1) or a borate-*d* buffer solution at pD = 9.7. All volumetric measurements were made with volumetric pipets or syringes. Binding studies were performed at 300 or 500 MHz depending on the solubility of the host and the guests used in the experiments.

2,2′,3,3′,4,4′-Hexa-*O*-allyl-α,α′-trehalose (2). Trehalose **1** (3.42 g, 10 mmol) was dissolved in dry pyridine (150 mL) at 40 °C. Trityl chloride (TrCl) (11.15 g, 40 mmol) was added, and the mixture was stirred for 6 h at 40 °C (TLC, DCM:methanol, 6:1). MeOH (15 mL) was added, and the mixture was stirred for 30 min. The crude was cooled at room temperature, and the solvents were evaporated. The residue was dissolved in DMF (200 mL) and cooled at 0 °C, NaH (4.14 g, 180 mmol) was added, and the mixture was stirred for 30 min. Allyl bromide (AllBr) (15.6 mL, 180 mmol) was added dropwise for 15 min, and the reaction mixture was stirred for 18 h (TLC, hexane:ethyl acetate, 4:1). MeOH (20 mL) was added carefully, and the solvents were evaporated. The crude was extracted with DCM (3 × 100 mL) and dried over sodium sulfate, and the solvent was evaporated. The residue was dissolved in MeOH (100 mL), and *p*-toluenesulfonic acid was added until the pH was 4. The reaction mixture was stirred for 8 h (TLC, hexane:ethyl acetate, 1:3). Triethylamine (5 mL) was added, solvents were evaporated, and the residue was purified by chromatography (hexane:ethyl acetate, 1:1), yield 2.62 g (45% in the three steps): $[\alpha]_D$ +159.1° (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.00–5.76 (m, 6H), 5.31–5.10 (m, 12H), 5.06 (d, 2H, *J* = 3.6, H1), 4.38–4.07 (m, 6H), 3.99–3.93 (m, 2H), 3.74–3.67 (m, 6H), 3.37–3.28 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 135.2, 134.8, 134.6, 116.9, 116.7, 116.2, 93.7, 80.9, 79.1, 77.1, 74.1, 73.7, 71.9, 71.2, 61.4.

2,2′,3,3′,4,4′-Hexa-*O*-allyl-6,6′-bis(4-(chloromethyl)benzyl)-α,α′-trehalose (3). Compound **2** (1.16 g, 2 mmol) was dissolved in THF (100 mL), and NaH (460 mg, 16 mmol) was added. The mixture was stirred for 30 min. α,α′-Dichloro-*p*-xylene (2.8 g, 16 mmol) in THF (50 mL) was added dropwise for 15 min. The reaction mixture was stirred at 35 °C for 24 h (TLC, hexane:ethyl acetate, 3:2). The mixture was cooled to room temperature and filtered over Celite, and the celite was washed with THF (200 mL). The solvent was evaporated with a rotatory evaporator without heating the water bath, and the product was purified by chromatography (hexane:ethyl acetate, 4:1), yield 1.24 g (72%): ^1H NMR ($CDCl_3$) δ 7.37–7.25 (m, 8H), 6.01–5.75 (m, 6H), 5.32–5.06 (m, 14H), 4.63–4.45 (m, 8H), 4.38–3.97 (m, 14H), 3.74–3.56 (m, 6H), 3.45 (t, 2H, *J* = 9.6, H4), 3.38 (dd, 2H, *J* = 3.66, *J′* = 9.6, H2); ^{13}C NMR ($CDCl_3$) δ 138.1, 137.3, 136.5, 135.1, 134.7, 134.5, 134.4, 134.3, 128.6, 128.5, 128.3, 127.2, 116.6, 116.4, 116.3, 116, 93.6, 80.9, 78.8, 77.2, 73.9, 72.7, 71.5, 70.2, 68.5, 45.6, 45.3.

Glycophanes 4 and 5. Compound **3** (1.39 g, 1.61 mmol) was dissolved in DMF (80 mL), and Cs_2CO_3 (100 mg, 0.3 mmol) was added. A solution prepared by dissolving 4,4′-isopropylidenediphenol (370 mg, 1.61 mmol) and Cs_2CO_3 (2.1 g, 6.44 mmol) in DMF (80 mL) was stirred for 12 h and then added through glass wool to the former solution for 12 h. The reaction mixture was stirred for 72 h (TLC, hexane:ethyl acetate, 3:2) and filtered through Celite. The filtrate was concentrated and the crude reaction mixture extracted with ethyl acetate (2 × 100 mL), dried over sodium sulfate, and purified by chromatography (hexane:ethyl acetate, 5:1), yield glycophane **4**, 490 mg (30%) and glycophane **5**, 210 mg (13%).

Glycophane 4: $[\alpha]_D$ +129.3° (*c* 1.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–6.75 (m, 16H), 6.03–5.69 (m, 6H), 5.33–5.01 (m, 18H), 4.62–3.40 (m, 26H), 3.34 (dd, 2H, *J* = 3.76, *J* = 9.6, H2), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.4, 143.3, 137.6, 137.1, 135.5, 135.1, 134.7, 127.6, 127.4, 126.7, 116.8, 116.7, 116.2, 114.5, 92.4, 81.2, 78.9, 77.1, 74.2, 73.8, 72.8, 71.8, 70.1, 69.7, 68.6, 41.6, 30.9. Anal. Calcd for $C_{61}H_{78}O_{13}$: C, 72.16; H, 7.35. Found: C, 72.43; H, 7.60. FAB-MS *m/z* (relative intensity) 1014 (20, M), 1037 (100, M + Na).

Glycophane 5: $[\alpha]_D$ +104.4° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–6.76 (m, 32H), 6.02–5.74 (m, 12H), 5.33–5.02 (m, 36H), 4.58–3.60 (m, 48H), 3.44 (t, 4H, *J* = 9.1), 3.37 (dd, 4H, *J* = 3.64, *J* = 9.53, H2), 1.64 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 156.5, 143.2, 137.7, 136.5, 135.4, 135.0, 134.7, 127.9, 127.7, 127.6, 127.3, 116.6, 116.5, 116.1, 114.1, 93.6, 81.1, 79.0, 77.5, 74.1, 73.7, 73.1, 71.7, 70.4, 69.6, 68.7, 41.6, 30.9. Anal. Calcd for $C_{122}H_{148}O_{26}$: C, 72.16; H, 7.35. Found: C, 71.97; H, 7.65. FAB-MS *m/z* (relative intensity) 2053 (100, M + Na).

Glycophane 6. Glycophane **4** (402 mg, 0.39 mmol) was dissolved in methanol (18 mL) and ethyl acetate (3 mL). Pd/C (45 mg) and *p*-toluenesulfonic acid (15 mg) were added, and the reaction mixture was refluxed for 90 min (TLC, DCM:methanol, 3:1). Triethylamine (1 mL) was added, the crude was filtered over Celite, and the Celite was washed with methanol (3 × 15 mL). The solvent was evaporated and the product purified by chromatography (DCM:methanol, 8:1), yield 222 mg (72%): ^1H NMR (CD_3OD) δ 7.37 (s, 8H), 7.03 (d, 4H, *J* = 8.91), 6.78 (d, 4H, *J* = 8.92), 5.16 (s, 4H), 5.10 (d, 2H, *J* = 3.78, H1), 4.56 (d, 4H), 4.00–3.95 (m, 2H, H5), 3.83 (t, 2H, *J* = 9.25), 3.82–3.76 (m, 4H, $H6_{exo}$, $H6_{endo}$), 3.50 (dd, 2H, *J* = 3.78, *J* = 9.77, H2), 3.45 (dd, 2H, *J* = 8.94, *J* = 10.04, H4), 1.60 (s, 6H); ^{13}C NMR (CD_3OD) δ 157.7, 145.1, 139.0, 129.5, 128.9, 128.3, 116.2, 94.6, 74.7, 74.3, 73.1, 72.8, 71.9, 71.8, 71.1, 70.8, 64.4, 31.5.

2,2′,3,3′,4,4′-Hexa-*O*-benzoyl-α,α′-trehalose (7). α,α′-Trehalose (**1**) (6.84 g, 20 mmol) was dissolved in pyridine (200 mL) at 40 °C. Trityl chloride (22.3 g, 80 mmol) was added, and the mixture was stirred for 6 h at 40 °C (TLC, DCM:methanol, 6:1). The crude reaction mixture was cooled at 0 °C, and benzoyl chloride (35 mL, 300 mmol) was dropped for 10 min. The reaction mixture was stirred for 10 h at room temperature (TLC, hexane:ethyl acetate, 3:2). If there was a white solid, the mixture was filtered over Celite. Pyridine was evaporated. The mixture was extracted with diethyl ether (4 × 100 mL), washed first with 0.01 N HCl (2 × 100 mL) and then with water (3 × 100 mL), and dried over sodium sulfate, and the solvents were evaporated. The residue was dissolved in methanol (100 mL) and ethyl acetate (20 mL), and *p*-toluenesulfonic acid was added until the pH was 4. The reaction mixture was stirred for 8 h (TLC, hexane:ethyl acetate, 2:3). Triethylamine (2 mL) was added, and the solvents were evaporated. The residue was extracted with ethyl acetate (3 × 100 mL), dried over sodium sulfate, and purified by chromatography (hexane:ethyl acetate, 1:1), yield 12.5 g (65% in the three steps): $[\alpha]_D$ +217.2° (*c* 1.3, $CHCl_3$) ^1H NMR ($CDCl_3$) δ 8.07–7.23 (m, 30H), 6.30 (t, 2H, *J* = 9.89, H3), 5.77 (d, 2H, *J* = 3.81, H1), 5.54 (t, 2H, *J* = 9.89, H4), 5.41 (dd, 2H, *J* = 3.79, *J* = 10.14, H2), 3.92–3.89 (m, 2H, H5), 3.20-2.95 (m, 4H, $H6_{exo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$) δ 165.8, 165.5, 165.3, 133.6, 133.1, 129.9, 129.8, 129.6, 129.0, 128.5, 128.4, 128.3, 128.2, 92.8, 71.5, 70.5, 70.0, 68.6, 59.7.

2,2′,3,3′,4,4′-Hexa-*O*-benzoyl-6,6′-bis-*O*-((trifluoromethyl)sulfonyl)-α,α′-trehalose (8). Compound **7** (483 mg, 0.5 mmol) was dissolved in DCM (40 mL), and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) (800 mg, 4 mmol) was added. The mixture was cooled at 0 °C, and trifluoromethanesulfonic anhydride (Tf_2O) (0.35 mL, 2 mmol) was carefully added. The reaction mixture was stirred at room temperature for 90 min (TLC, hexane:ethyl acetate, 3:2). The crude reaction mixture was diluted with DCM (20 mL), saturated $NaHCO_3$ solution (30 mL) was added, and the reaction mixture was stirred for 15 min. The organic phase was dried over sodium sulfate, and the solvent was evaporated. The crude reaction mixture was used without further purification.

[2 + 2]-Glycophanes 9–11. Aromatic alcohol (2,7-dihydroxynaphthalene or 4,4′-isopropylidenediphenol, 0.5 mmol) and Cs_2CO_3 (1.5 g, 4.6 mmol) were mixed in THF (50 mL), and the mixture was stirred for 2 h. The crude reaction mixture of the ditriflation of 0.5 mmol of **7** dissolved in THF (50 mL) was added dropwise for 30 min. The reaction mixture was stirred for 80 h at room temperature (TLC, hexane:ethyl acetate, 1:1). The solvent was evaporated, and the crude was extracted with DCM (2 × 100 mL), dried over sodium sulfate, and purified by chromatography.

Glycophane 9: Eluent, hexane:ethyl acetate, 4:1; yield 65 mg (12%); ^1H NMR ($CDCl_3$) δ 8.24-6.63 (m, 72H), 6.29 (t, 4H, *J* = 9.82, H3), 5.81 (d, 4H, *J* = 3.82, H1), 5.71 (t, 4H, *J* = 9.83, H4), 5.50 (dd, 4H, *J* = 3.85, *J* = 10.06, H2), 4.21–4.08 (m, 12H, H5, $H6_{exo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$) δ 165.5, 165.4, 165.9, 157.0, 135.5, 133.4, 133.2, 133.1, 133.0, 130.1, 129.9, 129.8, 129.3, 129.0, 128.9, 128.7, 128.6, 128.3, 128.2, 124.9, 116.3, 108.1, 90.6, 71.2, 70.6, 70.0, 69.2, 66.7. Anal. Calcd for $C_{128}H_{100}O_{34}$: C, 70.45; H, 4.62. Found: C, 70.52; H, 4.92. FAB-MS *m/z* (relative intensity) 2183 (100, $[M + H]^+$), 2315 (90, $[M + H + Cs]^+$), 3274 (6, $[M + 2M + H]^+$), 3407 (6, $[M + 2M + Cs + H]^+$), 4366 (4, $[2(M + H)]^+$), 4498 (3, $[2(M + H) + Cs]^+$).

Glycophanes 10 and 11: eluent, hexane:acetone, 5:1; yield, [1+1]-glycophane **10**, 92 mg (15%), and [2+2]-glycophane **11**, 96 mg, (16%). **Glycophane 10**: ^1H NMR ($CDCl_3$) δ 8.15–6.85 (m, 38H), 5.98 (t, 2H, *J* = 10.01, H3), 5.35 (t, 2H, *J* = 10.04, H4), 5.14 (dd, 2H, *J* = 3.91, *J* = 10.13, H2), 4.72 (d, 2H, *J* = 3.91, H1), 4.13–4.05 (m, 2H, H6), 3.95–3.85 (m, 2H, H6), 3.75–3.6 (m, 2H, H5), 1.86 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.3, 165.0, 157.5, 144.5, 133.4, 133.0, 129.9, 129.7, 129.6, 129.1, 128.8, 128.7, 128.5, 128.2, 126.0, 125.9, 117.7, 89.2, 72.4,

70.5, 69.9, 68.5, 68.2, 41.2, 26.6. Anal. Calcd for $C_{69}H_{58}O_{17}$: C, 71.49; H, 5.04. Found: C, 71.12; H, 5.14. FAB-MS *m/z* (relative intensity) 1159 (100, $[M]^+$), 1182 (25, $[M+Na]^+$). **Glycophane 11**: ^1H NMR ($CDCl_3$) δ 8.14–6.65 (m, 76H), 6.24 (t, 4H, J = 9.79, H3), 5.72 (d, 4H, J = 3.88, H1), 5.67 (t, 4H, J = 10.01, H4), 5.49 (dd, 4H, J = 3.81, J = 10.13, H2), 4.18–4.14 (m, 4H, H5), 3.66–3.64 (m, 8H, $H6_{exo}$, $H6_{endo}$), 1.56 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 165.6, 165.3, 164.8, 156.3, 143.5, 133.3, 133.0, 129.9, 129.8, 129.7, 129.2, 128.9, 128.8, 128.6, 128.3, 127.8, 127.4, 114.7, 114.2, 91.1, 71.1, 70.7, 69.4, 68.7, 65.8, 41.4, 30.6. Anal. Calcd for $C_{138}H_{116}O_{34}$: C, 71.49; H, 5.04. Found: C, 71.21; H, 5.31. FAB-MS *m/z* (relative intensity) 2319 (100, $[M + H]^+$), 4640 (3, $[2(M + H)]^+$).

Glycophanes 12–14. Glycophanes **9–11** (0.112, 0.074, or 0.066 mmol, respectively) were dissolved in DCM:methanol 1:1 (10 mL), and 1 M NaMeO in methanol (0.5 mL) was added. The reaction mixture was stirred at room temperature for 3 h (TLC, DCM:methanol, 3:1) and worked up.

Glycophane 12. IR-120 H^+ Amberlite was added to the solution until pH = 7; the solvents were evaporated, and the residue was purified by chromatography (DCM:methanol, 6:1), yield 71 mg (67%): ^1H NMR (CD_3OD:D_2O, 1:1) δ 7.69 (d, 4H, J = 8.97, Ha), 7.30 (d, 4H, J = 2.23, Hb), 7.05 (dd, 4H, J = 2.38, J = 9.03, Hc), 4.98 (d, 4H, J = 3.59, H1), 4.45 (dd, 4H, J = 2.17, J = 12.33, $H6_{proS}$), 4.39 (dd, 4H, J = 4.83, J = 12.31, $H6_{proR}$), 4.1-4.0 (m, 4H, H5), 3.93 (t, 4H, J = 9.4, H3), 3.61 (t, 4H, J = 9.77, H4), 3.54 (dd, 4H, J = 3.79, J = 9.88, H2); FAB-MS *m/z* (relative intensity) 933 (100, [M]).

Glycophane 13. The solvents were evaporated, and water (20 mL) was added. The mixture was neutralized with 0.01 N HCl. The reaction mixture was filtered, and the solid was washed with acetone (50 mL) and dried, yield 32 mg (81%): ^1H NMR (DMSO-d_6) δ 7.08 (d, 4H, J = 8.67, arom), 6.75 (d, 4H, J = 8.67, arom), 4.20 (d, 2H, J = 13.21, H6), 4.11 (dd, J = 4.89, J = 13.16, H6), 3.84 (d, 2H, J = 3.72, H1), 3.38 (t, 2H, J = 9.28, H3), 3.04 (t, 2H, J = 9.11, H4), 2.89 (dd, J = 3.810, J = 9.76, H2), 1.75 (s, 6H).

Glycophane 14. The solvents were evaporated, and water (20 mL) was added. The mixture was neutralized with 0.01N HCl. The reaction mixture was filtered, and the solid was washed with acetone and dried, yield 64 mg (90%): ^1H NMR (DMSO-d_6) δ 7.02 (d, 8H, J = 8.76, arom), 6.78 (d, 8H, J = 8.76, arom), 4.75 (d, 4H, J = 3.66, H1), 4.07 (d, 4H, J = 9.5, H6), 3.97 (dd, 4H, J = 5.4, J = 10.72, H6), 3.88–3.82 (m, 4H, H5), 3.59 (t, 4H, J = 9.16, H3), 3.28–3.2 (m, 8H, H4, H2), 1.53 (s, 12H); FAB-MS *m/z* (relative intensity) 1069 (100, M).

6,6′-Bis-*O*-(7-methoxy-2-naphthyl)-α,α'-trehalose (15). α,α'-Trehalose (**1**) (116 mg, 0.34 mmol), 7-methoxy-2-hydroxynaphthalene (600 mg, 3.45 mmol), and triphenylphosphine (390 mg, 1.49 mmol) were dissolved in DMF (5 mL). Diethyl azodicarboxylate (DEAD) (0.14 mL, 0.89 mmol) was added, and the reaction mixture was stirred for 12 h. Triphenylphosphine (161 mg, 0.5 mmol) and DEAD (0.047 mL, 0.3 mmol) were added, and the reaction mixture was stirred for another 2 h (TLC, DCM:methanol, 5:1). Water (1 mL) was added, the solvents were evaporated, and the residue was purified by chromatography (DCM:methanol, 9:1), yield 63 mg (28%): ^1H NMR (CD_3OD:D_2O, 1:1) δ 7.74 (d, 2H, J = 9.03), 7.73 (d, 2H, J = 8.94), 7.28 (d, 2H, J = 2.42), 7.22 (d, 2H, J = 2.56), 7.10 (dd, 2H, J = 2.44, J = 8.91), 7.03 (dd, 2H, J = 2.56, J = 8.91), 5.28 (d, 2H, J = 3.76, H1), 4.43–4.33 (m, 4H, $H6_{exo}$, $H6_{endo}$), 4.28–4.23 (m, 2H, H5), 4.00–3.93 (m, 8H, H3, CH_3O), 3.77-3.66 (m, 4H, H2, H4).

Binding Studies. (a) CD_3OD:D_2O, 1:1. Stock solutions for guests (0.01–1 M) were prepared by dissolving the guest in the solvent mixture and adjusting the pD to 12 by adding NaOD (40% weight). Stock solutions for the host (2–8 mM) were made by dissolving the host in the solvent mixture. Binding constants were determined by performing ^1H-NMR titrations of guest added to host using the chemical shifts of the host referenced to the methanol-d_4 signal (3.35 ppm) obtained at eight different guest:host concentration ratios in an iterative least-squares fitting procedure.[24a] The temperature was kept constant at 303 ± 1 K. **(b) Borate-*d* Buffer.** Borate buffer, pD = 9.7, was prepared by mixing 50 mL of a 0.025 M $Na_2B_4O_7 \cdot 10H_2O$ solution and 13.1 mL of a 0.1 M NaOH solution. The mixture was lyophilized, D_2O (10 mL) was added, and the mixture was lyophilized again. This operation was repeated three times. D_2O (100 mL) was added to the solid residue, and it was stirred until it was a clear solution. A stock solution for the host (0.357 mM) was prepared by dissolving the host in borate-*d* buffer. Stock solutions for the guests (5–48 mM) were prepared from the stock solution of the host in order to have a constant concentration of the host during the titrations. Binding constants were determined as in the case of CD_3OD:D_2O (1:1) but using two different iterative least-squares fitting procedures.[24a,b] In this case, chemical shifts were referenced to external DMSO-d_6 (2.5 ppm) placed in a sealed capillary. Binding studies were performed at 300 MHz in the case of CD_3OD:D_2O (1:1) and at 500 MHz in the case of borate-*d* buffer.

Chiral Recognition Experiments. In a typical experiment, 4×10^{-3} mmol of the host and 4×10^{-3} mmol of 2,4-dinitrophenyl amino acid derivative were mixed in 0.6 mL of CD_3OD:D_2O (1:1) and stirred for 18 h. The mixture was filtered through glass wool and placed in a NMR tube. The spectra were recorded at 300 MHz, and diastereoselectivity was determined by careful integration of the aromatic proton signals of both enantiomers that appeared separated in the spectrum in all cases and by calculating the difference between the integral intensity of the signals. The solid–liquid extraction experiments were repeated three or four times to ensure reproducibility.

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