Chiral basket-shaped host compounds derived from diphenylglycoluril


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(Received August 25th, 1994)

Abstract. The design and synthesis of two novel chiral receptors derived from diphenylglycoluril are described. The chirality in these molecules is due to the unsymmetrical positioning of amino functions in the crown ether rings with respect to the diphenylglycoluril subunit.

Introduction

The ability of enzymes to catalyze reactions in a stereoselective way depends to a large extent on a process of molecular recognition. The binding pocket of an enzyme has a chiral shape and, as a result of this, one particular substrate is bound and converted enantioselectively into the specified product. Recently, we have described a synthetic supramolecular catalyst consisting of a basket-shaped receptor molecule provided with a catalytically active Rh(I) complex. This system was found to mimic certain features of enzymatic catalysis, viz. selective binding of a substrate in a cavity and conversion of the bound substrate at a catalytically active center. In order to incorporate the aspect of enantioselective conversion into our supramolecular catalyst, it was felt necessary to modify the binding moiety of the receptor part in such a way that a chiral environment is obtained. Chiral recognition requires a minimum of three simultaneous interactions between the binding site and the substrate. Hydrogen bonding and electrostatic attractions are regarded to be single-point interactions, whereas e.g. dipole stacking and \( \pi-\pi \) interactions are multi-point interactions in nature. The chiral receptors described in this paper are based on the concave building block 1 (Figure 1). Earlier work in our group has shown that the binding of benzene-1,4-diol could be successfully resolved at the stage of a precursor molecule. This paper is concluded with some preliminary binding studies on 3.

Results and discussion

Strategy

As shown in Figure 1, compound 1 can be regarded as being composed of four subunits. To illustrate this, the molecule has been divided into four quadrants. Chirality can be easily built in by modifying one or two of these quadrants. As a result two chiral centers appear on the quaternary carbon atoms of the glycoluril unit, as indicated by asterisks in Figure 1. An obvious way to do this is by introducing dissymmetry in the handles of the basket compounds which can be synthesized from 1. In compound 2, only one of the handles is altered, leading to a completely asymmetric compound (\( C_1 \) symmetry). In 3, two handles are modified which results in a chiral molecule with \( C_2 \) symmetry.

First, the synthesis of basket 2 is described and an attempt made to resolve this compound into enantiomers. After that, the preparation of basket 3 is presented. This compound could be successfully resolved at the stage of a precursor molecule. This paper is concluded with some preliminary binding studies on 3.

Basket with \( C_1 \) symmetry

The synthesis of compound 2 is summarized in Scheme 1. Benzene-1,4-diol was alkylated with 1-bromo-2-chloro-ethane in acetone using \( \text{K}_2\text{CO}_3 \) as a base to yield 4-(2-chloroethoxy)phenol (4a) (30%). Subsequently, 4a was treated with 2-(2-chloroethoxy)ethyl p-toluenesulfonate and sodium hydride in DMF, resulting in 1-(2-chloroethoxy)-4-[2-(2-chloroethoxy)ethoxy]benzene (4b) (55%). Reaction of a 1:1 mixture of 4b and 1,4-bis[2-(2-chloroethoxy)ethoxy]benzene (4c) with the cyclic ether 5 in acetic anhydride and trifluoroacetic acid gave a number of products, viz. the symmetric tetrachloride 6, the meso compound 7, a racemic mixture of the target molecule 8 and the racemate 9. The molar ratio of these compounds amounted to approximately 2:1:4:1, which is close to the theoretically expected values. The compounds could be...
separated by column chromatography and the racemate of \(8\) was obtained in \(39\%\) yield. The dissymmetry in the molecule is clearly visible in its \(^1\)H-NMR spectrum. The aromatic xylylene protons on the symmetric side of the molecule are displayed as a singlet and those on the asymmetric side as an AB pattern. The methylene bridges, which link the xylylene walls to the glycoluril unit, give rise to three AX patterns, probably because two of them coincide.

Double ring closure of \(8\) with two equivalents of 4-(methoxymethoxy)benzylamine under dilute conditions in acetonitrile with \(\text{Na}_2\text{CO}_3\) as the base gave the racemate of \(2a\) (76\%). The protected phenolic hydroxyl groups in the latter compound provide functionalities for the coupling of a chiral auxiliary group or a catalytic center. In the \(^1\)H-NMR spectrum of \(2a\) the bridging methylene groups were visible as four AX patterns. The aromatic protons of the substituted benzyl groups gave rise to two different AB patterns and the xylylene wall protons displayed the same pattern as those in \(8\). For the NCH\(_2\) methylene protons in the ring, complicated signals were observed.

The methoxymethyl protecting groups were quantitatively removed by stirring a solution of \(2a\) in tetrahydrofuran/propan-2-ol with concentrated hydrochloric acid, resulting in \(2b\cdot\text{HCl}\).

We tried to separate the enantiomers of \(2a, 2b\), and also those of \(8\) on a chiral HPLC column. Unfortunately, we were not able to find a suitable stationary phase. Subsequently, we reacted \(2b\) with chiral reagents in order to obtain diastereomers, which can be separated chromatographically. However, the coupling of \(2b\) to (+)-10-camphorsulfonyl chloride, (R)-(+)−α-methoxy−α-(trifluoromethyl)benzeneacetyl chloride (Mosher’s reagent), or (−)-menthyl chloroformate did not give separable diastereomers, as could be concluded from TLC and HPLC. Finally, we tried to achieve resolution by crystallization of the dibenzoyletartric acid salt of compound \(2a\). These attempts were also unsuccessful.

**Basket with \(C_2\) symmetry**

The synthetic route to compound \(3\) is depicted in Scheme 2. The mono-alkylated benzene-1,4-diol derivative 4-[2-(2-chloroethoxy)ethoxy]phenol (4d) was coupled to the cyclic ether \(5\) in 1,2-dichloroethane with p-toluenesulfonic acid and molecular sieves. The racemate \(10\) and the \(\text{meso}\) compound \(11\) could be separated chromatographically. Their structures were assigned on the basis of the \(^{13}\)C-NMR spectra (Figure 3): the \text{meso}
compound 11 displays two resonances for the carbonyl functionalities of the glycoluril unit, whereas the racemate gives only one signal due to the \( C_2 \) symmetry in the molecule. The bridging methylene groups in 10 form two sets which are non-equivalent and therefore give rise to two AX patterns in the \(^1\)H-NMR spectrum. The signals of the xylene wall protons appeared as an AB pattern and were shifted ca. 1 ppm to a higher field compared to the reference compounds 6–9. This feature may be explained by assuming that the phenolic hydroxyl groups are hydrogen-bonded to the carbonyl groups of the glycoluril unit. The hydrogen bond will be optimized if the xylene walls are moved towards the carbonyl groups, causing a twist in the molecule, as is shown in Figure 4. Such a twist is not unlikely and has been observed before in glycoluril derivatives. An indication for such a twist is found in the \(^{13}\)C-NMR spectrum of 10. For the carbon atoms of the phenyl groups on the convex side of the glycoluril unit several well-separated signals are observed. Normally, these carbon atoms give rise to a narrow cluster of overlapping signals (e.g. see compound 11, Figure 3). In 10, the carbon atoms will be all magnetically different as a result of the ring current shifts, caused by the twisted benzene rings. The hydrogen bonds are broken by coordinating solvent molecules, as can be concluded from the fact that the \(^1\)H-NMR signals of the xylene walls of 10 are not shifted in DMSO-\( d_6 \). In the meso compound 11, hydrogen bonds between the carbonyl groups of the glycoluril unit and the phenolic hydroxy groups are possible but these hydrogen bonds cannot be stabilized by a twist in this molecule. In line with this, only small shifts of the xylene wall protons were observed.

Rac-10 was treated with two equivalents of (–)-menthyl chloroformate to give a mixture of diastereomers (12a and 12b). The \(^1\)H-NMR spectrum of this mixture displayed several distinct sets of resonances for each of the diastereomers. After chromatographical resolution (13% yield of each diastereomer), these sets were separately visible in the \(^1\)H-NMR spectra of each of the diastereomers (see experimental section). The removal of the menthyl groups with sodium methoxide in methanol yielded each of the enantiomers of 10 in an optically pure form (74%). Reacting these enantiomers with a large excess of 1-bromo-2-chloroethane in DMSO with base, resulted in the quantitative formation of the enantiomers of 9 (\((\alpha)_{D}^{22} + 13.4^\circ\)) These compounds were also obtained as an inseparable racemate in the synthesis of 8 (see previous section). Double ring closure of 9 with two equivalents of benzylamine under dilute conditions in acetonitrile with \( \text{Na}_2\text{CO}_3 \) as a base yielded both enantiomers of the chiral basket compound 3 (\((\alpha)_{D}^{20} + 16.4^\circ\), yields 77% and 90%, respectively).

**Binding experiments**

\(^1\)H-NMR spectroscopy was used to evaluate the binding properties of the two enantiomers of 3\(^5\)\(^1\). First, the binding constant of benzene-1,3-diol was determined and found to be \( K_b = 200 \pm 25 \text{ M}^{-1} \). This value is much lower than the values normally observed\(^5\) for this type of bas-
ket-shaped compounds, \( K_a \approx 3000 \text{M}^{-1} \). The lower binding affinity may be caused by the benzyl groups which probably partially cover the cavity of \( 3 \) as a result of the restricted flexibility of the handles. A similar situation is present in a related basket compound with small handles, of which we recently reported an X-ray structure. We carried out a titration with the guest compound \( 13 \) to investigate whether receptor \( 3 \) displays any enantioselectivity in the binding of a chiral substrate. Compound \( 13 \) was prepared by the condensation of 2,4-dihydroxybenzaldehyde and \((-\)-\(\alpha\)-methylbenzylamine. Unfortunately, the affinity of \( 13 \) for both \((+)-3 \) and \((-)-3 \) was very low; the binding constants amounted to approximately \( K_a \approx 60 \text{M}^{-1} \). Probably, the cavity of the host is too shielded by the benzyl groups to accommodate a bulky substrate like \( 13 \). Another complication is the fact that in \( 13 \) an intramolecular hydrogen bond can be formed between one of the phenolic hydroxyl groups and the N atom of the imine function. This feature is also unfavourable for binding. Work is now in progress to connect ligands to the \textit{para} positions of the benzyl groups in \( 3 \). On complexation to a metal center, the benzyl groups will be lifted to a more upward position which opens the cavity of \( 3 \) and makes it more accessible for substrate molecules.

Experimental section

General

Unless otherwise indicated, commercial materials were used as received. Hexane, THF, diethyl ether, and toluene were distilled under nitrogen atmosphere from sodium ketyl. Dichloromethane was distilled from \( \text{CaCl}_2 \). All solvents were stored on molecular sieves under an inert atmosphere.

\(^1H\)-NMR spectra were recorded on Bruker WH-90, Bruker AC-100, and Bruker AM-400 instruments. Chemical shifts (\( \delta \)) are reported in ppm downfield from internal Me\(_4\)Si. Abbreviations used are \( s = \) singlet, \( d = \) doublet, \( t = \) triplet, \( q = \) quartet, \( m = \) multiplet, and \( br = \) broad. FAB mass spectra were recorded on a VG 7070E instrument, the matrix used was 3-nitrobenzyl alcohol. IR spectra were recorded on a Perkin-Elmer IRFT spectrometer 1720-X. The optical rotations were determined on a Perkin-Elmer 241 polarimeter. The HPLC columns used were a Machary Nagel Nucleosil Chiral-2, a LiChrosorb Si-100-10, and a LiChrosorb RP-18. For column chromatography Merck Silica Gel (60H) was used and for thin-layer chromatography Merck Silica Gel 60 F\(_{254}\) plates. Elemental analyses were determined with a Carlo Erba Ea 1108 instrument.

4-(2-Chloroethoxy)phenol (4a)

A mixture of 3 g (27 mmol) of benzene-1,4-diol, 10 g (70 mmol) of 1-bromo-2-chloroethane, and 10 g (72 mmol) of K\(_2\)CO\(_3\) in 50 ml of acetone was refluxed for 18 h. The mixture was filtered and the
溶剂被去除并降至大气压力。残余物被在50 ml的CH2Cl2中取上，随后溶液被随后用1M的HCl水溶液、饱和NaHCO3水溶液和NaCl水溶液洗涤。有机层被干燥（MgSO4）并被蒸发至完全干透。产品被通过色谱柱色谱法（硅胶，溶剂：CHCl3：MeOH，0.5%）来纯化，从而得到1.41 g（30%）的4a，呈白色结晶固体。

'H-NMR (100 MHz, CDCl3)
δ 6.79 (br s, 4H, ArH), 4.80 (s, 1H, OH), 4.17 (t, 2H, CH2O, J 6 Hz), 3.78 (t, 2H, CH2Cl, J 6 Hz).

1-(2-Chloroethoxy)-4-[2-(2-chloroethoxy)ethoxy]benzene (4b)

将0.4 g（10 mmol）的NaH（60% 悬浮液）加入到25 ml的DMF中，并加入1.73 g（10 mmol）的4a。在气体释放完毕后，加入2.79 g（10 mmol）的2-(2-chloroethoxy)ethyl p-toluenesulfonate。混合物被搅拌18 h并在氩气下进行。混合物被用HCl水溶液中和，溶液被蒸发至干透。该有机层被用CH2Cl2提取三次。将合并的有机溶液用NaHCO3水溶液和NaCl水溶液洗涤，干燥（MgSO4），并蒸发至干透。在色谱柱色谱法（硅胶，溶剂：EtOAc:CHCl3，1:2）下，得到1.53 g（55%）的4b，呈黄色油状。

'H-NMR (100 MHz, CDCl3)
δ 6.84 (br s, 4H, ArH), 4.22-4.03 (m, 4H, CH2Cl), 3.88-3.57 (m, 8H, CH2O).

5,7,12,13b,13c,14-Hexahydro-1(1l)-(2-chloroethoxy)-4,8,11(1l)-tris[2-(2-chloroethoxy)]-13b,13c-diphenyl-6H,7H,5a,6a,12a,13a-tetraazabenzo[5,6]azulen[2,1,8-ija]benz[1]azulene-6,13-dione (rac-8)

将2.34 g（6.2 mmol）的化合物5h在Ac2O和TFAC的混合溶剂中在95°C搅拌30 min。随后，加入1.73 g（6.2 mmol）的4b和2.0 g（6.2 mmol）的4c，溶液被搅拌30 min。冷却至室温后，加入25 ml的甲醇。过滤所得产物，并用冰水迅速和缓慢地洗涤三次。产物通过色谱柱色谱法（硅胶，溶剂：EtOAc:CHCl3，1:3）分离，得到2.25 g（39%）的rac-8，呈白色固体。

'H-NMR (400 MHz, CDCl3)
δ 7.14-7.05 (m, 10H, Ar); 6.74 and 6.71 (2d, 2H, ArH, J 9 Hz), 6.73 (s, 2H, ArH); 5.57, 5.544 and 5.541 (3d, 4H, NC/7 HAr, J 16 Hz), 4.32-3.61 (m, 32H, NCH/Ar, CH2CH2); FAB MS m/z 944 (M+H); Anal. calcd. for C46H50N4O9Cl4: C 58.48, H 5.33, N 5.93; found: C 58.52, H 5.35, N 5.87%.

Racemate of compound 2a

Compound 2a was prepared according to a previously published procedure7 from 0.82 g (0.9 mmol) of 8, 0.44 g (2.6 mmol) of...
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4-(methoxy(methoxy)benzylamino)2,4-6 g of Na2CO3 (38 mmol) and 15 g of NaI in 400 ml of acetonitrile. The compound was purified by column chromatography (silica, eluent: CHCl3 with 1% MeOH). FAB MS m/z 775 (M+H+) was found.

To a solution of 0.5 g (0.44 mmol) of rac-2b in 10 ml of THF and 1.5 ml of propan-2-ol was added dropwise 2 ml of (-)-l-bis(menthylcarbonyloxy)-13b,13c-diphenyl-6a,12a,13-tetraazabenz[5,6]azuleno-2,1,8-ij[a]benz[f]aze[6,13-dione (rac-10). This compound was synthesized as described previously7 from 0.24 g (0.27 mmol) of (―)-9,89 mg (0.83 mmol) of freshly distilled benzylamine, 1 g of Na2CO3 and 2 g of NaI in 110 ml of acetonitrile. The compound was characterized by 1H-NMR (400 MHz, DMSO-d6) δ 7.35-7.31 (m, 20H, ArH), 7.65 and 7.62 (2d, 4H, NCH2Ar, CH2N). 13C-NMR (100 MHz, DMSO-d6) δ 158.6 and 157.9 (C = O), 151.5, 151.2, 139.8, 129.7, 128.8, 128.5, 126.9, 117.1, 114.5 (Ar), 85.0 (glycoluril), 71.5, 69.1, 69.0, 68.7 (CO crown), 61.0 (NCAr), 54.5 and 53.7 (NC crown), 37.6 and 36.8 (NC glycoluril). FAB MS m/z 901 (M+H+) found. Anal. calc. for C44H46N4O8C14•1.5NaCl: C 53.47, H 4.69, N 8.41%.

A solution of 0.5 g (0.45 mmol) of rac-10 in a mixture of 50 ml of MeOH and 10 ml of CH2Cl2 was brought to pH 7 (with pH paper) with concd. aqueous HCl (30%). After stirring for 3 h the solution was evaporated to dryness. The resulting emulsion was extracted three times with 1% MeOH in CHCl3, dehydrated (HCl) and evaporated to dryness. After column chromatography (silica, eluent: 4% MeOH in CHCl3), 0.25 g (74%) of white (+)-10 was obtained: [α]D 10 +38°. Starting from (+)-10, the same procedure was followed to give 0.25 g (74%) of (-)-10: [α]D 10 −30°. The spectral data of (+)-10 and (-)-10 were identical to those of rac-10.

A mixture of 0.25 g (0.32 mmol) of rac-10, 1 g of powdered KOH and 20 ml of 1-bromo-2-chloroethane in 5 ml of DMSO was stirred overnight. The solvent was removed under vacuum and 30 ml of water was added. The resulting emulsion was extracted three times with CH2Cl2, and the organic layer was washed with 1N aqueous HCl and a saturated aqueous solution of NaHCO3. Subsequently, this layer was concentrated to 5 ml and added dropwise to hexane with vigorous stirring. The resulting precipitate was filtered off and washed with ice-cold ether. Yield 0.27 g (93%) of white (+)-10: [α]D 10 +13.4°. 1H-NMR (400 MHz, CDCl3) δ 7.21-6.97 (m, 10H, ArH); 7.23-6.95 (m, 10H, ArH); 6.95 and 6.76 (2d, 4H, NCH2Ar, CH2N). 15C-NMR (100 MHz, CDCl3) δ 157.3 (C = O), 151.2, 150.4, 133.9, 128.8, 128.3, 128.1, 115.1, 114.5 (xylene and glycoluril), 85.3 (glycoluril), 71.6, 70.9, 70.2 (CO chain), 43.2 and 42.3 (CCl, 37.0 (NC glycoluril). FAB MS m/z 901 (M+H+) found. Anal. calc. for C44H46N4O8C14•1.5NaCl: C 53.47, H 4.69, N 8.41%; found: C 53.27, H 4.63, N 8.41%.

Starting from (+)-10 the same procedure was followed to give 0.26 g (90%) of (-)-10: [α]D 10 −13.4°. The spectral data and physical properties of (+)-10 and (-)-10 were similar to those of (+)-9.

Compound (+)-3

This compound was synthesized as described previously7 from 0.24 g (0.27 mmol) of (+)-9, 89 mg (0.83 mmol) of freshly distilled benzylamine, 1 g of Na2CO3 and 2 g of NaI in 110 ml of acetonitrile. The compound was purified by column chromatography (silica, eluent: CHCl3 with 1% MeOH and 0.5% methanol) to give 0.20 g (77%) of white (+)-3: [α]D 10 +16.4°. 1H-NMR (400 MHz, CDCl3) δ 7.38-7.04 (m, 20H, ArH); 6.74 and 6.71 (2d, 4H, ArH, J 9 Hz); 6.55 and 5.55 (2d, 4H, NCH2Ar, CH2N). 13C-NMR (100 MHz, CDCl3) δ 157.3 (C = O), 151.5, 151.2, 139.8, 129.7, 128.8, 128.5, 126.9, 117.1, 114.5 (Ar), 85.0 (glycoluril), 71.5, 69.1, 69.0, 68.7 (CO crown), 61.0 (NCAr), 54.5 and 53.7 (NC crown), 37.6 and 36.8 (NC glycoluril). FAB MS m/z 969 (M+H+) found. Anal. calc. for C44H46N4O8H12O2: C 70.57, H 6.33, N 8.51; found: C 70.60, H 6.15, N 8.41%.

Compound (-)-3

This compound was synthesized from (+)-9 as described for (+)-3. Yield 0.22 g (65%) of white product: [α]D 10 −16.4°. The spectral data of (-)-3 were identical to those of (+)-3. Anal. calc. for

An asterisk indicates that the absolute configuration of the compound

was unknown.
A solution of 1 g (7.2 mmol) of 2,4-dihydroxybenzaldehyde and 1.4 g (11.6 mmol) of (S)-(-)-α-methylbenzylamine in 50 ml of 1,2-dichloroethane was refluxed for 1 1/2 h. The reaction volume was reduced to approx. 2 ml and added dropwise to 50 ml of hexane. The resulting yellow precipitate was filtered off. The precipitation procedure was repeated four times until the excess of amine had been removed. Yield 1.3 g (73%) of a yellow powder: [α]_D^20 320°. 1H-NMR (100 MHz, CDCl_3) δ 8.00 (s, 1H, CH = N), 7.34 (m, 5H, ArH), 7.00 (d, 1H, ArH, J 8.9 Hz), 6.28-6.21 (m, 2H, ArH), 4.62 (q, 1H, CH, J 6.8 Hz), 1.65 (d, 3H, CH_3, J 6.8 Hz).

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