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Two similar dibenzo cyclic ethers with dissimilar conformations

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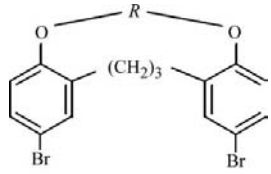
Two dibenzo cyclic ether compounds, 6,12-dibromodibenzo-[*d*,*i*]-1,2,3,6,7,8-hexahydro-1,3-dioxecin (systematic name: 8,16-dibromo-2,4-dioxatricyclo[12.4.0.0^{5,10}]octadeca-5,7,9,14,-16,18-hexaene), $C_{16}H_{14}Br_2O_2$, (II), and 8,14-dibromodibenzo[*f*,*k*]-1,5-dioxa-1,2,3,4,5,8,9,10-octahydrocyclododecene (systematic name: 7,19-dibromo-11,15-dioxatricyclo[14.4.0.0^{5,10}]-icosa-5,7,9,16,18,20-hexaene), $C_{18}H_{18}Br_2O_2$, (III), were prepared as scaffolding for phosphate-anion receptors. In both compounds, the two aromatic rings are linked by three methylene units *ortho* to the oxygen substituent of each ring. The only difference between the two compounds is the number of methylene units linking the two ether O atoms. The dibenzo cyclic ether with an ether linkage of one methylene unit adopts a chair-like conformation, where the two aromatic rings are parallel to each other. On the other hand, the dibenzo cyclic ether with an oxygen linkage of three methylene units adopts a bowl-like conformation. The latter scaffold configuration is the only structure of the two that would allow for the placement of convergent functional groups necessary for the establishment of an anion-selective binding pocket.

Comment

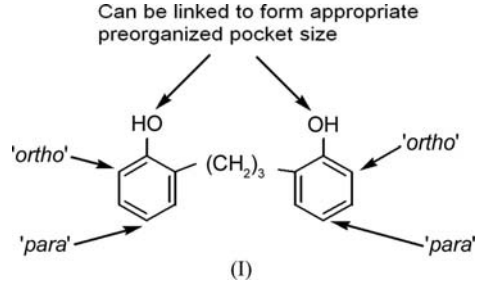
The design and fabrication of artificial anion receptors is an area of much current interest (Antonisse & Reinhoudt, 1998; Beer & Gale, 2001; Biaci *et al.*, 1997; Schmidtchen & Berger, 1997; Sessler *et al.*, 2006). This is partly due to the fact that anions are vital to the maintenance of biological systems; the large majority of protein–cofactor, protein–protein or protein–DNA interactions, for example, involve anions (Sessler *et al.*, 2006). Additionally, because the use of anions in agriculture and other industry has had a deleterious environmental impact, the need for environmental sensors or environmental remediation requiring anion receptors has increased. Particularly challenging is the preparation of receptors that exhibit a high degree of discrimination towards specific anions. To accomplish this, the binding group of a receptor must be aligned correctly in its supramolecular matrix so as to differentiate between the three-dimensional shapes (*e.g.* linear, trigonal, tetrahedral or spherical) of anions.



(II) $R = CH_2$
(III) $R = (CH_2)_3$

Our goal to prepare selective receptors for phosphatidylglycerol, an anionic phospholipid unique to bacterial membranes, dictated the synthesis of a receptor that could bind to the lipid's phosphate anion and the glycerol hydroxyl groups. The scaffold portion of the receptor had to be amenable to chemical modification that would allow for the proper positioning of binding groups during the synthetic pathway of the target molecule. Molecular modeling suggested the scaffold should be somewhat concave to best align the phosphate-anion-binding groups with the functional groups of the receptor intended to bind to the hydroxyl groups of the glycerol.

Results from our previous work suggested that the best way to bind the phosphate anion would be with two functional groups, such as neutral urea groups or charged ammonium groups (Burns *et al.*, 2005; Calderon-Kawasaki *et al.*, 2007; Jagessar *et al.*, 1997, 1998), and modeling suggested the use of two more hydrogen-bonding groups to bind to the hydroxyl groups. Based on these requirements, the scaffold chosen was bis-phenol, (I) (shown in Fig. 1). This structure is readily available in good yield by coupling appropriate Grignard and bis-tosylate reagents with the use of our soluble Cu^{I} catalyst (Burns *et al.*, 1997, 2000). The *ortho* positions on the bis-phenol can be elaborated *via* aromatic electrophilic addition to provide for the anion-binding unit, while the bromine-substituted *para* positions can be elaborated *via* organometallic reactions to provide the hydroxyl-binding unit. The phenolic O atoms can be linked to provide a preorganized binding pocket with the newly formed dibenzo cyclic ether. What was not clear *a priori* was how the length of the linkage between the two phenolic O atoms would affect the overall conformation of the molecule. Therefore, two dibenzo cyclic



(I)

Figure 1
Modular structure of the bis-phenol receptor. Facile elaboration allows iterative studies of structure–function relationships using different anion- and solvent-binding sites.

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ethers were prepared, namely 6,12-dibromodibenzo[*d*,*i*]-1,2,3,6,7,8-hexahydro-1,3-dioxecin, (II), and 8,14-dibromodibenzo[*f*,*k*]-1,5-dioxa-1,2,3,4,5,8,9,10-octahydrocyclododecene, (III). Molecular modeling suggested that a linkage containing either one methylene or three methylenes would furnish a receptor with an appropriately sized binding pocket.

The X-ray crystal structures of the two linked compounds are shown in Fig. 2. (III) displays a concave structure and would act as a good scaffold for the binding groups of the receptor. In contrast, the ring in (II) adopts a chair-like conformation, with the two aromatic rings parallel to each other. With the desired concave structure, the macrocycle in (III) could be elaborated with appropriate functional groups that would be aligned correctly in space, and therefore has the potential to furnish a binding pocket that would be phosphate-anion selective. With the chair-like configuration of (II), any anion-binding functional groups would be positioned in opposite directions, precluding the correct alignment of convergent functional groups deemed necessary for selective anion binding.

Compound (II) crystallizes on a general position in the monoclinic space group $P2_1/c$. The dihedral angle between the two aromatic rings is 11.24 (13)°. The dihedral angles between the aromatic rings and the plane defined by atoms O1, O2, C7 and C9 are 74.38 (7) and 79.08 (7)°. The $-(CH_2)_3-$ and $-OCH_2O-$ chains linking the two aromatic rings essentially mirror each other. Compound (III) crystallizes on a general position in the orthorhombic space group *Pbca*. In contrast to (II), (III) adopts a concave bowl conformation, with a dihedral angle between the two aromatic rings of 61.67 (12)°, and dihedral angles between the aromatic rings and the mean plane defined by atoms O1, O2, C16 and C18 of 28.92 (11) and 32.76 (11)°. The two O atoms are both directed towards the bottom of the bowl, with an O1···O2 distance of 2.824 (4) Å. The crystal packing in both (II) and (III) shows short Br···Br contacts between the aryl bromide moieties of different molecules (Fig. 3*a*). Such interactions are recognized as a driving force in crystal packing and have been classified into two types: (i) type A, a linear arrangement with both C—Br···Br angles in the order of 150–180°; (ii) type B, a perpendicular arrangement with one linear C—Br···Br angle and the other C—Br···Br angle close to 90° (Brehmer *et al.*, 2000). In (II), the Br···Br interaction is between inversion-related Br atoms to form dimers. The Br1···Br1^{i} distance is 3.4322 (4) Å and the C1—Br1···Br1^{i} angle is 160.59 (8)° [symmetry code: (i) $2-x, 1-y, -1-z$], both of which are in the range seen for type A. In (III), the Br···Br interaction is head-to-tail, forming a chain of molecules. The Br1···Br2^{ii} distance is 3.5548 (8) Å, with C1—Br1···Br2^{i} = 156.93 (13)° [symmetry code: (ii) $x, \frac{1}{2}-y, \frac{1}{2}+z$] and C13—Br2···Br1^{iii} = 149.64 (14)° [symmetry code: (iii) $x, \frac{1}{2}-y, z-\frac{1}{2}$], also within the range for type A. The parameters of the Br···Br interaction in (III) are influenced by a C—H···Br interaction [C2···Br1^{iv} = 3.732 (5) Å; symmetry code: (iv) $\frac{3}{2}-x, \frac{1}{2}+y, z$] and a π–π interaction (3.44 Å between planes) involving the ring substituted by atom Br2.

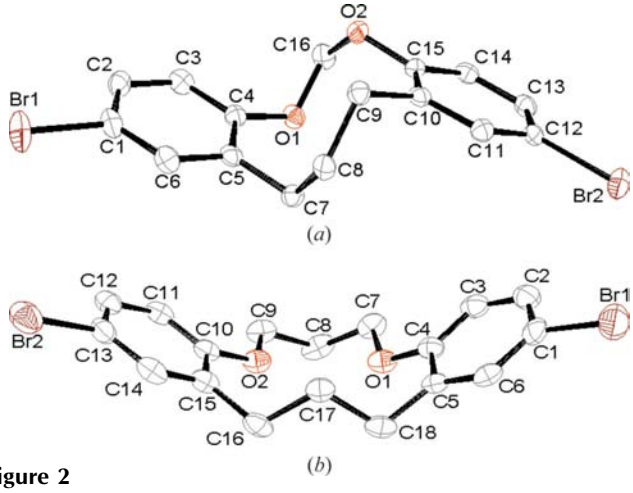

Figure 2
Displacement ellipsoid drawings (50% probability) of (*a*) (II) and (*b*) (III). H atoms have been omitted for clarity.

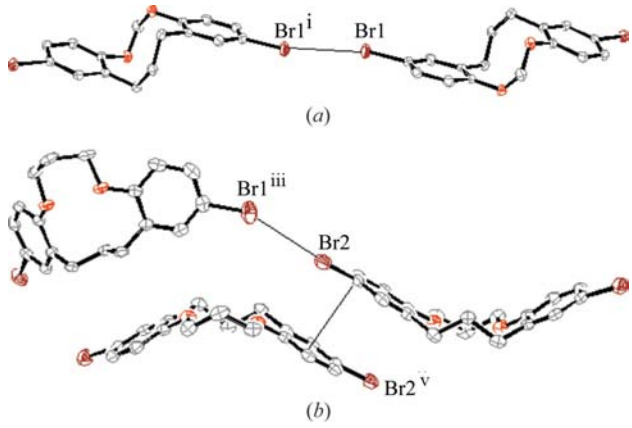

Figure 3
Drawings showing the intermolecular Br···Br and π–π interactions in (*a*) (II) and (*b*) (III). [Symmetry codes: (i) $2-x, 1-y, -1-z$; (iii) $x, \frac{1}{2}-y, -\frac{1}{2}+z$; (v) $2-x, 1-y, 1-z$.]

The two compounds in this study demonstrate quite clearly the importance of the oxygen linkage in defining the conformation of the macrocycle and in organizing the scaffold for proper alignment of functional groups for selective anion binding. Work is currently underway to further elaborate (III) with the appropriate phosphate-anion-binding functional groups and hydroxyl-binding functional groups necessary for recognition of phosphatidylglycerol.

Experimental

For the synthesis of (II), 1,1′-(1,3-propanediyl)bis(5-bromo-2-methoxybenzene) (1 g, 2.6 mmol), dried under vacuum sitting over anhydrous phosphorous oxide, was transferred along with potassium carbonate (1.1 g, 7.8 mmol) and 18-crown-6 (1 g, 3.8 mmol) into a round-bottomed flask under a nitrogen atmosphere. The flask was covered with aluminium foil, and 100 ml of tetrahydrofuran (THF) distilled from sodium was added to the reaction mixture. Diiodomethane (0.83 ml, 10.3 mmol) was added dropwise to the solution, and the reaction mixture heated to 348 K for 18 h, at which time the reaction was judged to be complete as indicated by thin-layer chro-

matography (TLC). The reaction was then quenched with 1 *M* HCl and extracted three times with methylene chloride. The combined organic fractions were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and the solvent removed under vacuum to give 1.5 g of a solid material. The crude product was recrystallized from hexanes layered upon ethyl acetate to give 0.61 g of crystals. The mother liquor was condensed and subjected to column chromatography, eluting with 35:65 methylene chloride–hexanes, furnishing 0.22 g of crystalline solid, which resulted in an overall yield of 81% (m.p. 450–451 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (*m*, 2H), 2.49 (*t*, 4H, *J* = 6.04 Hz), 5.66 (*s*, 2H), 6.98 (*d*, 2H, *J* = 4.21 Hz), 7.32–7.38 (*m*, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 24.14, 32.35, 97.66, 117.40, 120.92, 130.64, 133.25, 137.27, 154.92; MS *m*/*z*: 398 (M^+), 317, 238.

For the synthesis of (III), 1,1′-(1,3-propanediyl)bis(5-bromo-2-methoxybenzene) (0.3 g, 0.8 mmol), dried under vacuum sitting over anhydrous phosphorous oxide, was transferred along with potassium carbonate (0.33 g, 2.4 mmol) and 18-crown-6 (0.32 g, 1.2 mmol) into a dried round-bottomed flask under a nitrogen atmosphere. The flask was covered with aluminium foil and 25 ml of THF (distilled from sodium) was added to the reaction mixture. At this time, 1,3-dibromopropane (0.3 ml, 3 mmol) was added dropwise to the solution and the reaction mixture was heated to 348 K for 36 h, at which time the reaction was judged to be complete as indicated by TLC. The reaction was then quenched with 1 *M* HCl and extracted three times with ethyl acetate. The combined organic fractions were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and the solvent removed under vacuum to yield 0.6 g of an oily product. The crude reaction product was subjected to Chromatotron™ prep TLC (eluted with 10% ethyl acetate–hexane) to yield 0.192 g of a solid which was then recrystallized from ethanol to furnish 0.183 g (55% yield) of X-ray diffraction quality crystals (m.p. 445–446 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84–1.94 (*m*, 2H), 2.23–2.29 (*m*, 2H), 2.58 (*t*, 4H, *J* = 7.4 Hz), 4.17 (*t*, 4H, *J* = 4.84 Hz), 6.67 (*d*, 2H, *J* = 4.48 Hz), 7.22–7.26 (*m*, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.99, 29.90, 31.47, 67.97, 112.45, 129.56, 132.84, 134.18, 156.04; MS *m*/*z*: 424, 425, 426 (M^+).

Compound (II)

Crystal data

$C_{16}H_{14}Br_2O_2$
M_r = 398.09
Monoclinic, $P2_1/c$
a = 21.3204 (5) Å
b = 8.8456 (2) Å
c = 7.8155 (2) Å
β = 97.969 (1)°
V = 1459.70 (6) Å^3
Z = 4
Mo *K*α radiation
μ = 5.55 mm^{-1}
T = 150 (2) K
0.25 × 0.18 × 0.14 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.340, T_{max} = 0.500 (expected range = 0.312–0.460)
26317 measured reflections
2860 independent reflections
2415 reflections with $I > 2\sigma(I)$
R_{int} = 0.053

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.056
S = 1.08
2860 reflections
181 parameters
H-atom parameters not refined
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.46 e Å^{-3}

Compound (III)

Crystal data

$C_{18}H_{18}Br_2O_2$
M_r = 426.14
Orthorhombic, *Pbca*
a = 13.7971 (5) Å
b = 8.5744 (3) Å
c = 28.1906 (10) Å
V = 3335.0 (2) Å^3
Z = 8
Mo *K*α radiation
μ = 4.87 mm^{-1}
T = 150 (2) K
0.25 × 0.17 × 0.11 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.380, T_{max} = 0.607
81249 measured reflections
3270 independent reflections
2067 reflections with $I > 2\sigma(I)$
R_{int} = 0.156

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.100
S = 1.03
3270 reflections
199 parameters
H-atom parameters not refined
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.45 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (II).

C4—C5	1.395 (4)	C9—C10	1.506 (4)
C4—O1	1.397 (3)	C10—C15	1.392 (4)
C5—C7	1.507 (4)	C15—O2	1.396 (3)
C7—C8	1.528 (4)	C16—O1	1.407 (3)
C8—C9	1.536 (4)	C16—O2	1.413 (3)
C4—O1—C16	116.4 (2)	C15—O2—C16	115.8 (2)

Table 2
Selected geometric parameters (Å, °) for (III).

C4—O1	1.359 (5)	C9—O2	1.435 (5)
C4—C5	1.413 (6)	C10—O2	1.355 (5)
C5—C18	1.507 (6)	C10—C15	1.412 (6)
C7—O1	1.438 (5)	C15—C16	1.492 (6)
C7—C8	1.505 (6)	C16—C17	1.537 (6)
C8—C9	1.509 (6)	C17—C18	1.528 (6)
C4—O1—C7	119.5 (3)	C10—O2—C9	118.3 (3)

All H atoms were placed in geometrically calculated positions and treated as riding, with C—H = 0.97 (methylene) or 0.93 Å (aromatic) and U_{iso}(H) = 1.2U_{eq}(C).

For both compounds, data collection: *APEX2* (Bruker, 2005); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3262). Services for accessing these data are described at the back of the journal.

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