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Selective Recognition of Phosphatidylcholine Lipids by a Biomimetic Calix[6]tube Receptor

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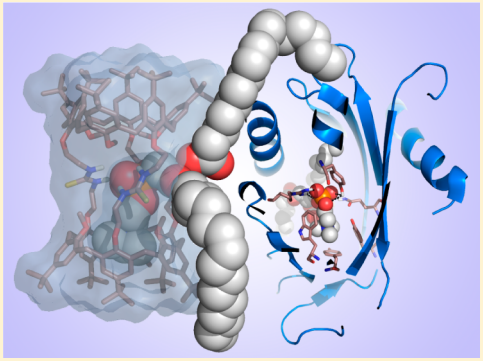
Supporting Information

ABSTRACT: Phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs) are usually the most abundant phospholipids in membranes. Only a few examples of artificial macrocyclic receptors capable of binding these zwitterionic lipids were reported, and in most cases, their mode of action differs from that of natural receptors. NMR studies show that calix[6]arenes **4**–**6** behave as heteroditopic receptors that can efficiently bind 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) in nonpolar solvents. Similarly to natural systems, the recognition proceeds through the establishment of specific interactions with the zwitterionic head of the lipid. In a protic environment, calix[6]tube **4** binds DOPC much more strongly than **5** and **6**, thanks to the higher acidity of its H-bonding thiourea groups and the better preorganization of its binding site. Moreover, **4** is reluctant to the corresponding PE, highlighting a unique selectivity for PCs over PEs. A high selectivity for DOPC over dodecylphosphocholine (DPC) was also observed, and computer modeling studies showed that it may likely originate from the curved shape of the tubular recognition system of **4**, which is well-adapted to the native conformation of DOPC. From a biomimetic point of view, the complex **4⊃DOPC** shows remarkable similarities with a natural complex formed between a PC and the human phosphatidylcholine transfer protein.



INTRODUCTION

Glycerophospholipids, sphingolipids, and cholesterol are the major lipid components of cell membranes.[1] Glycerophospholipids are amphiphilic lipids containing a hydrophobic tail and a hydrophilic head linked by a glycerol unit. The head is composed of a phosphodiester bridge that links the glycerol moiety to a polar group such as choline, ethanolamine, serine, or inositol. Zwitterionic phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs) (Figure 1, bottom) are usually the most abundant phospholipids in membranes where they serve as structural and functional components. Many hepatic functions appear to be responsive to the PCs/PEs ratio in the plasma membrane. A low ratio can adversely affect membrane permeability and decrease lipoprotein secretion, whereas abnormally high ratios can lead to steatosis, abnormal calcium homeostasis, endoplasmic reticulum stress, and enhanced lipoprotein secretion.[2] Thus, the ratio of PCs to PEs is crucial for maintaining cellular growth and survival.

In this context, artificial macrocyclic receptors capable of binding zwitterionic phospholipids are attracting targets. Surprisingly, only a few examples of such receptors based on cyclodextrins,[3] resorcinarenes,[4] or calix[4]arenes[5] have been described. In most cases, the phospholipids are recognized through an inclusion of their lipophilic chain in the hydrophobic cavity of the receptor.[3,4] This stands in contrast with natural receptors that recognize and bind phospholipids by establishing specific interactions with their zwitterionic head. Typically, the phosphate group of the phospholipid is coordinated to a metal center[6] or interacts with a positively charged Arg or Lys residue through ionic and H-bonding interactions,[7] while its ammonium head interacts with a negatively charged group and/or with aromatic residues through cation–π interactions.[8] Inspired by these natural systems, two examples of heteroditopic receptors that interact with the positively and negatively charged groups of the zwitterionic head have been developed.[9] If these biomimetic systems were found to strongly bind either the phospholipid 1,2-dioctanoyl-*sn*-glycero-3-phosphocholine or 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), the selectivity toward other classes of phospholipids was not investigated.

In this regard, we have developed calix[6]arene-based systems bearing thiourea or urea moieties **1**–**6**[10,11] (Figure 1, top) that behave as heteroditopic receptors toward charged or neutral species. Notably, receptors **1**–**3** and **6** can efficiently recognize organic contact ion pairs such as ammonium salts in a cooperative way with the three converging (thio)urea groups allowing strong binding to anions, which in turn can lead to the strong binding of an ion-paired ammonium accommodated in the calixarene cavity. The more sophisticated calix[6]tubes **4**

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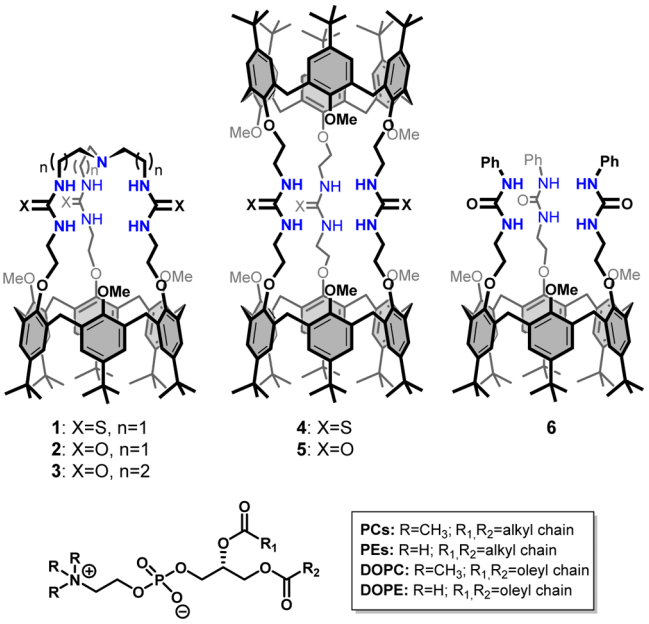

Figure 1. Top: calix[6]cryptothiourea **1**, calix[6]cryptureas **2** and **3**, calix[6]tubes **4** and **5** and calix[6]tris-urea **6**. Bottom: general structures of phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs) and structures of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) and 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE).

and **5** incorporate two divergent hydrophobic cavities triply connected by (thio)urea linkages. These tubular hosts can simultaneously bind multiple ions and are especially efficient for the complexation of organic ion triplets.[10d,e] The anionic guest is recognized through H-bonding interactions at the tris(thio)urea binding site and is thus located between the two cationic guests accommodated in the cavities. Very recently, we have shown that the heteroditopic hosts **1** and **2** can strongly encapsulate zwitterions even in a protic environment.[10a] The binding of the zwitterions proceeds through multiple H-bonding interactions between their anionic group and the tris(thio)urea cap of the host as well as through π−cationic and CH−π interactions between the cationic $(CH_3)N^+$ group and the polyaromatic calixarene cavity. Interestingly, **1** displays a remarkable selectivity for β-alanine betaine thanks to a high complementarity in terms of size, shape, and electronic structure between the two partners. From a biomimetic point of view, the host−guest complexes obtained with **1** and **2** show remarkable similarities with the complexes of betaines encountered in natural systems such as betaine-choline-carnitine transporter (BCCT) proteins. Note that, except for this recent work, the binding of zwitterions by calix[6]arenes remains quasi-unexplored to date.[12] Considering the versatile and biomimetic host−guest properties of all these previously reported heteroditopic receptors **1**−**6** toward charged and zwitterionic species, we wanted to see if these hosts could be exploited for the recognition of zwitterionic phospholipids and in particular if they could be able to distinguish between PCs and PEs.

Herein, we describe the binding properties of calix[6]arene-based hosts **1**−**6** toward zwitterionic phospholipids and notably toward 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) and DOPC, two phospholipids that only differ by the nature of their ammonium group, i.e. primary or quaternary, respectively (Figure 1, bottom). A comparative structural study with a related natural receptor that binds phospholipids is also reported.

RESULTS AND DISCUSSION

All the receptors **1**−**6** were synthesized according to previously reported procedures.[10] First, the ability of these receptors to bind DOPC was investigated by NMR spectroscopy. The ^{1}H NMR spectra of hosts **1**−**3** in $CDCl_3$ remained unaffected upon the addition of a few equivalents of DOPC, indicating an absence of binding (Table 1).[13] In strong contrast, when

Table 1. Association Constants (K_a) of Hosts 1−6 toward DOPC

	K_a (M^{-1}) in $CD_3OD/CDCl_3$ (v:v)[a]		
host	0:1	1:50	1:20
1	no inclusion	no inclusion	nd[b]
2	no inclusion	no inclusion	nd[b]
3	no inclusion	no inclusion	nd[b]
4	$>2.8 \times 10^5$	3.7×10^4	60
5	$>1.8 \times 10^5$	584	<1
6	8.5×10^3	58	nd[b]

[a]K_a determined at 298 K by integration of the different species in equilibrium; K_a is defined as [Host⊃DOPC]/([Host][DOPC]); error estimated at ±15%. [b]Not determined.

DOPC was progressively added to a $CDCl_3$ solution of **4** or **5**, the formation of a new species with well-defined signals was observed. Two sets of signals were apparent over the course of the titration, showing slow host−guest exchanges on the NMR time scale. The quantitative formation of the new species was obtained with only 1 equiv of DOPC (see Figure 2 in the case of host **4**), indicating association constants that are too high to be determined accurately by NMR (Table 1). In both cases, all the signals of the new species were attributed through 2D NMR spectra (COSY, HSQC, and HMBC)[13] and the following points allowed us to conclude that they correspond to the desired host−guest complexes (**4** or **5**)⊃DOPC (see Figure 2c for the structure of **4**⊃DOPC):

(i) the significant complexation induced shifts (CISs) of the signal corresponding to the α and β $(CH_3)N^+CH_2$ protons (Table 2 and Figure 2) attest to the inclusion of the cationic part of DOPC in the heart of the polyaromatic cavity. Moreover, integration of the singlet corresponding to the included α protons indicates a 1:1 host−guest stoichiometry;

(ii) in contrast to the other protons of the phospholipid guest, the protons in close proximity of the phosphate group $CH_2O-P(O_2)^-$-OCH_2CH exhibit positive CISs (Table 2). Besides, the (thio)urea NH protons of the hosts **4** and **5** experience significant downfield shifts upon the addition of DOPC (see Figure 2 for **4** vs **4⊃DOPC**). All these data indicate that the anionic moiety of the guest is not located in the polyaromatic cavity of the calix[6]arene subunit but is more likely bound at the level of the tris(thio)urea arms through H-bonding interactions;

(iii) both calix[6]arene subunits adopt a flattened cone conformation. The OMe groups of the calixarene subunit including the cationic head of DOPC are projected toward the outside of the cavity (δ_{OMe} = 3.86−3.93 ppm and 3.89−3.98 ppm for **4⊃DOPC** and **5⊃DOPC**,

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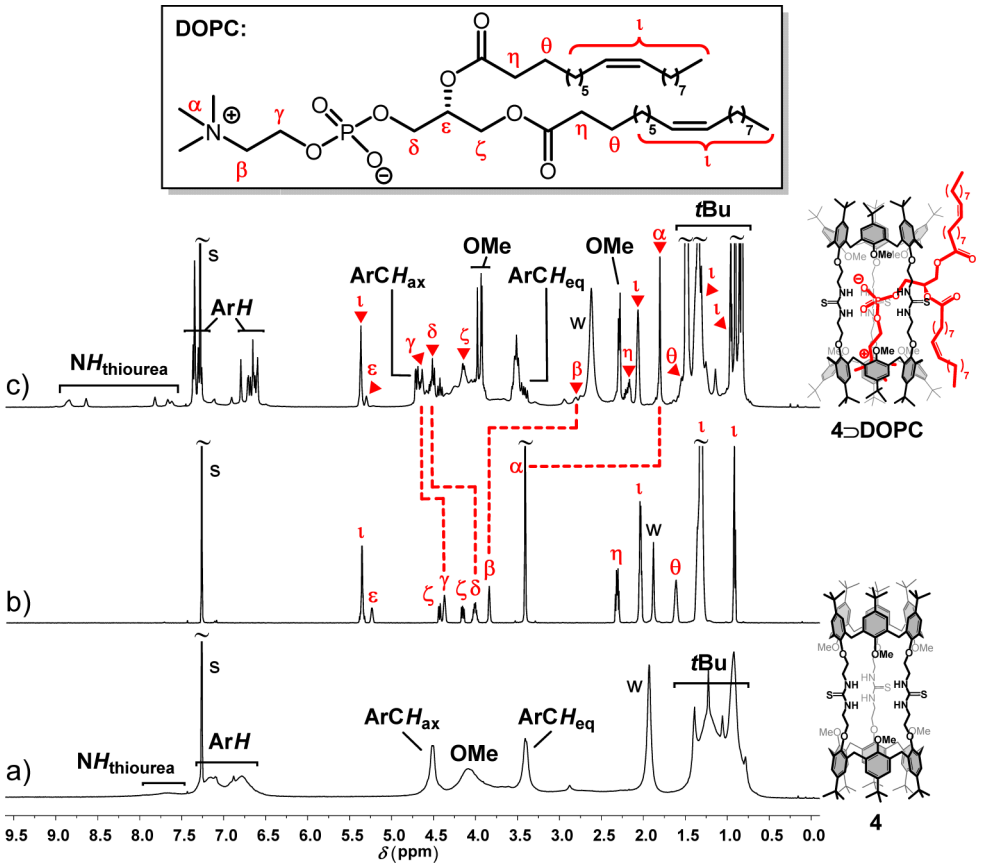

Figure 2. ^{1}H NMR (600 MHz, 298 K) spectra in $CDCl_3$ of (a) **4**; (b) DOPC; and (c) **4** after addition of DOPC (1 equiv). ▼: $DOPC_{in}$. s: solvent. w: water. Inset: structure of DOPC.

Table 2. ^{1}H NMR Complexation Induced Shifts (CISs) in $CDCl_3$ in the Case of 4⊃DOPC, 5⊃DOPC, 6⊃DOPC, and 4⊃DPC

	CIS (ppm)[a]			
position[b]	4⊃DOPC	5⊃DOPC	6⊃DOPC	4⊃DPC
α	−1.64	−1.60	−1.71	−1.69
β	−1.03	−0.92	−0.68	−1.08
γ	+0.22	+0.26	+0.20	+0.23
δ	+0.47/+0.53	+0.39/+0.44	+0.27	+0.33
ε	+0.03	+0.01	+0.18	−0.34
ζ	−0.32/−0.27	−0.21/−0.11	∼0	> −0.30 and <0
η	−0.17	−0.20	∼0	∼0
θ	−0.11	−0.13	∼0	–
ι	> −0.11 and <0	> −0.13 and <0	∼0	–

[a]CIS measured at 298 K and defined as $\Delta\delta = \delta$ (complexed DOPC) − δ (free DOPC). [b]These positions are defined in Figure 2.

respectively), and as shown in the HMBC spectra,[13] the ArH and *t*Bu groups directed toward the outside of the cavity are those of the anisole moieties. The other OMe groups fill the second calixarene cavity (δ_{OMe} = 2.20−2.24 ppm and 2.27−2.37 ppm for **4⊃DOPC** and **5⊃DOPC**, respectively). In other words, the oleyl chains of the DOPC guest do not protrude from the second calixarene cavity but from one of the three macrocycles formed by the (thio)urea arms. Moreover, the weak negative CISs observed for the η and θ protons of the oleyl chains suggest that these chains are in close proximity of the aromatic moieties in order to establish CH−π interactions (Table 2);

(iv) the presence of six signals for the OMe groups and for the NH protons is characteristic of an asymmetrical C_1 structure. This lack of symmetry is due to the threading of the lipid through one of the three (thio)urea macrocycles as well as to the presence of a stereogenic center on DOPC;

(v) the structure of the **4⊃DOPC** complex was confirmed by a ROESY NMR spectrum.[13] Indeed, nuclear Overhauser effect (NOE) correlations were observed notably between the α $(CH_3)N^+$ protons of the bound DOPC and the *t*Bu protons of the calixarene subunit including the cationic head of the phospholipid as well as between the ε proton and the introverted OCH_3 of the calixarene.

All these observations show that calix[6]tubes **4** and **5** behave as heteroditopic receptors that can efficiently bind DOPC in nonpolar solvents.

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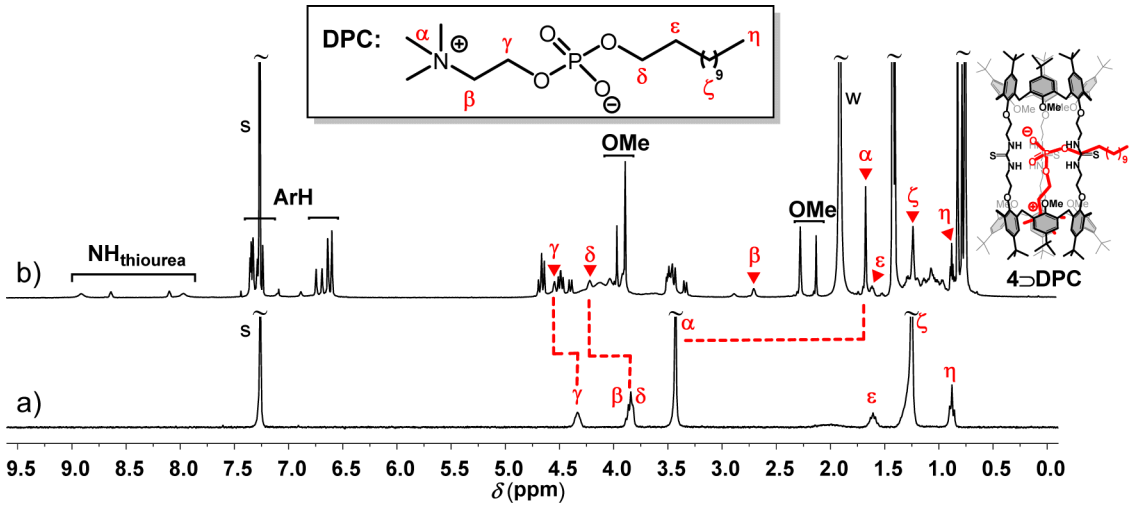

Figure 3. ^{1}H NMR (600 MHz, 298 K) spectra in $CDCl_3$ of (a) DPC and (b) **4** after addition of DPC (1 equiv). ▼: DPC_{in}. s: solvent. w: water. Inset: structure of DPC.

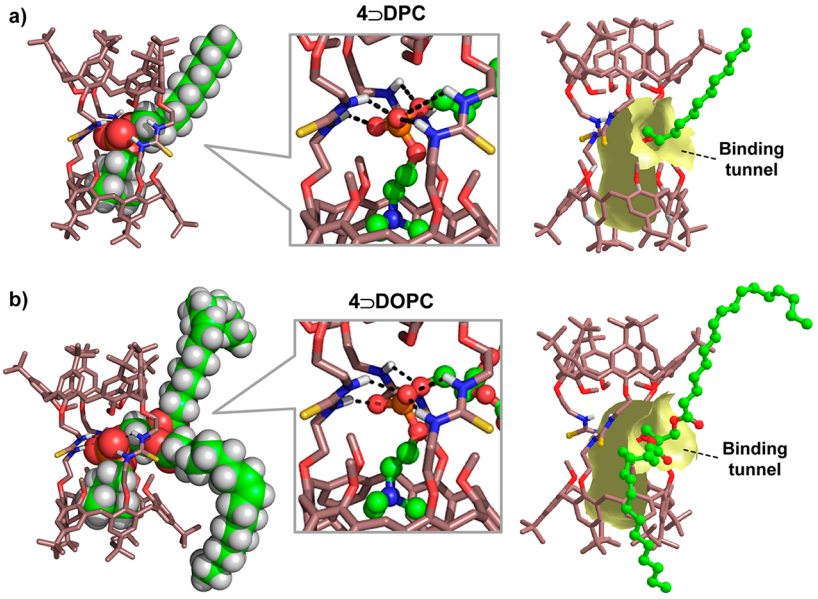

Figure 4. Energy minimized structures of (a) **4⊃DPC**, (b) **4⊃DOPC**. Hydrogen bonds are indicated by dashed lines. Binding tunnels were obtained by generating the Connolly molecular surface (radius: 1.4 Å) of the host **4** from the energy minimized structures of **4⊃DPC** and **4⊃DOPC**. With the exception of the NH, all the hydrogen atoms of the receptor **4** are omitted for clarity.

Further studies showed that host **6** was also able to complex DOPC in $CDCl_3$[13] with a similar mode of recognition for the polar head of the phospholipid (Table 2) but with a much lower affinity (Table 1). In contrast to the complexes **4⊃DOPC** and **5⊃DOPC**, the ^{1}H NMR signals of the calixarene subunit of **6⊃DOPC** are characteristic of a C_{3v} symmetrical structure even at low T (253 K).[13] Besides, no CISs are observed for the two oleyl chains of the lipid in this case (Table 2). As shown by a ROESY NMR spectrum,[13] these differences are due to the fact that the oleoyl chains of **6⊃DOPC** thread between the three phenyl groups, thus maintaining a more symmetrical structure.

If, as expected, hosts **1**–**3** were unable to bind DOPC in a mixture of $CD_3OD/CDCl_3$, it was however still possible to observe the host–guest complexes (**4**, **5** or **6**)⊃**DOPC** in this protic environment (Table 1). Remarkably, in a 1:50 mixture of $CD_3OD/CDCl_3$, **4** was found to bind the DOPC guest 2 and 3 orders of magnitude more strongly than **5** and **6**. In a 1:20 mixture, only host **4** was able to recognize the lipid. All in all, the binding affinities displayed in Table 1 indicate that the recognition of DOPC by receptors **1**–**6** depends on three key points:

(i) the nature of the anion binding group. Indeed, in comparison with the urea-based receptor **5**, the stronger ability of host **4** to bind DOPC is likely due to the higher acidity of its thiourea groups[14] and to their poorer ability to self-associate;[15]

(ii) the preorganization of the host. This is clearly illustrated by the comparison between **5** and **6**: the less preorganized host **6** displays a lower ability to bind DOPC despite the higher acidity of its phenyl-urea groups;

(iii) the size of the (thio)urea-based macrocycle from which the oleyl chains should protrude. In the case of receptors

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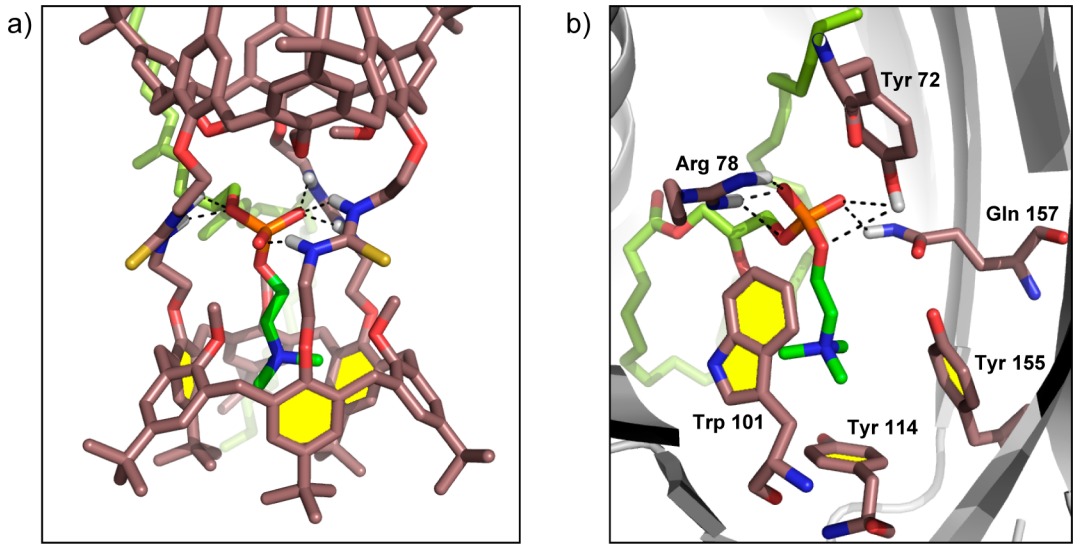

Figure 5. (a) Energy minimized structures of **4⊃DOPC**; Hydrogen bonds are indicated by dashed lines. Selected distances (Å): N(host)−O(DOPC): 2.75, 2.85, 2.90, 3.15, 3.18, 3.31; N^+(host)-(π-centroids): 4.16, 4.28, 4.31. With the exception of the N*H* of the host, all the hydrogen atoms of **4** and of DOPC are omitted for clarity. (b) XRD structure of **PC-TP⊃DLOPC** (PDB accession 1LN1). Selected distances (Å): N(host)−O(DLOPC): 2.76, 3.11, 3.12, 3.97; O(host)−O(DLOPC): 2.51, 3.46; N^+(host)-(π-centroids): 4.44, 4.51, 5.23.

1−**3**, this macrocycle is too small (i.e., 26 or 28 atoms) and thus, upon complexation, a steric clash would occur between the glycerol moiety of DOPC and the upper part of the calixarene covalent cap. In contrast, hosts **4** and **5** possess a tubular shape with a (thio)urea-based macrocycle large enough (i.e., 36 atoms) to let the glycerol moiety and the oleyl chains escape.

The best combination of these three key factors is obtained with bis-calix[6]thiourea **4**, which is thus the most efficient receptor for DOPC.

In a second set of experiments, the ability of receptor **4** to selectively recognize DOPC from other lipids was investigated by NMR spectroscopy. First, the complexation of another PC, i.e. dodecylphosphocholine (DPC), was evaluated (Figure 3). Addition of 1 equiv of DPC to a solution of **4** in $CDCl_3$ led to the quantitative formation of the complex **4⊃DPC**, indicating a binding constant $>10^5$ M^{-1}. The two calixarene subunits of this complex exhibit separate signals, with one of the calixarene cavities being filled by the methoxy groups (δ_{OMe} = 2.12−2.26 ppm), the other hosting the quaternary ammonium ion with very closed CISs in comparison with **4⊃DOPC** (Table 2), thus indicating a similar mode of recognition with the threading of the dodecyl chain between the thiourea arms. Note that the ^{1}H NMR spectrum of **4⊃DPC** is characteristic of a C_s symmetrical structure, as expected for a complex formed with an achiral lipid.

Surprisingly, in $CD_3OD/CDCl_3$ (1:50), the association constant was much lower for **4⊃DPC** (K_a = 950 M^{-1}) than for **4⊃DOPC** (3.7×10^4 M^{-1}). To tentatively rationalize this high selectivity for DOPC, computer modeling of complexes **4⊃DPC** and **4⊃DOPC** was achieved.[16] First, both optimized structures are highly compatible with what was observed in solution by NMR spectroscopy (Figure 4a,b, left). It is noteworthy that the thiourea arms wrap around the phosphate group of the phospholipids to maximize the number of H-bonding interactions (six H-bonding interactions in cases of **4⊃DPC** and **4⊃DOPC**). Moreover, the energy minimized structures nicely show the unique topology of the host **4** recognition system. Indeed, this later is constituted by a right-angled interior tunnel presenting two consecutive binding sites (i.e., the polyaromatic cavity and the multiple H-bonding thiourea groups) and an aperture delimited by the bis(thio)urea macrocycle (Figure 4a,b, right). The energy minimized structures of free DPC and DOPC were also obtained and compared to those of the corresponding complexed forms. It shows that the complexed DPC has to adopt a bent conformation in order to allow the dodecyl chain treading between the thiourea arms.[13] This conformational change takes place through rotation of the C_δ−C_ε single bond and leads to an unfavorable gauche interaction.[13] In contrast, due to the presence of the glycerol moiety, only a minor conformational change is required at the level of the C_δ−C_ε single bond of DOPC.[13] In other words, the selectivity for DOPC originates from the fact that the native conformation of this lipid is well-adapted to the curvature of the binding tunnel of receptor **4**.

The ability of **4** to bind a phosphatidylethanolamine was also evaluated. Thus, 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) was added to a solution of **4** in $CDCl_3$. However, no binding of the lipid could be detected even after the addition of a large excess (20 equiv) of DOPE. This result suggests that the polar head of the lipid must display a quaternary ammonium group in order to be recognized by **4**. Indeed, this cationic group is mandatory for the establishment of multiple CH−π and π−cationic interactions with the aromatic walls of the calix[6]arene. This absence of binding may also be due to the self-association of PEs in nonpolar solvents through H-bonding interactions between their H_3N^+ and phosphate groups.[17] Finally, the complexation of DOPC in the presence of a large excess of DOPE was investigated in $CDCl_3$ through a ^{1}H NMR competitive binding study. To our delight, only the complex **4⊃DOPC** was detected upon the addition of 1 equiv of DOPC and 20 equiv of DOPE to bis-calix[6]thiourea **4**, highlighting the remarkable selectivity of this receptor for PC-type lipids.

From a biomimetic point of view, the host−guest complex **4⊃DOPC** shows remarkable similarities with the complex formed between 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine (DLOPC) and the human phosphatidylcholine transfer protein

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(PC-TP) (Figure 5).[18] This later is a highly specific intracellular phospholipid binding protein that can transfer PC between different membranes in the cytosol, but its functions remain incompletely understood.[19] The crystallographic structure of the **PC-TP⊃DLOPC** complex shows that the lipid binding tunnel of this natural system is composed of the following:

(i) a polyaromatic cage delimited by three aromatic residues (two tyrosines and one tryptophan) that allows the formation of π−cationic interactions with the positively charged headgroup of the lipid;
(ii) multiple H-bonding donor groups (side chain groups of a tyrosine, a glutamine, and an arginine) that can interact with the phosphate group of the lipid.

As shown on the optimized structure of **4⊃DOPC**, the three aromatic moieties directed toward the inside of the cavity and the tris-thiourea arms of host **4** nicely mimic the lipid binding tunnel of PC-TP. By providing excellent models for natural receptors that recognize and bind PCs, host **4** may contribute to a better understanding of the outstanding efficiency of the phospholipid recognition processes encountered in natural systems.

CONCLUSION

In conclusion, bis-calix[6]thiourea **4** behaves like an efficient heteroditopic receptor that can strongly recognize phosphatidylcholines even in a protic environment. Under similar conditions, **4** is completely reluctant to closely related phosphatidylethanolamines. To our knowledge, such a strong and selective binding of PCs has not been described previously. Noteworthy also is the selective binding of DOPC in comparison with DPC, highlighting the role played by the unique curved shape of the binding tunnel of calix[6]tube **4**. Finally, **4** provides an interesting structural model for the PC's binding site encountered in natural systems such as human phosphatidylcholine transfer proteins (PC-TPs). Current work is directed toward the development of water-soluble bis-calix[6]thiourea-based receptors and the study of their interaction with lipids in an aqueous environment.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded at 400 and 600 MHz. Chemical shifts are expressed in ppm. The chloroform signal at 7.26 ppm was used as an internal standard. $CDCl_3$ was filtered over a short column of basic alumina to remove traces of DCl. Most of the ^{1}H NMR spectra signals were attributed to 2D NMR analyses (COSY, HSQC, HMBC). Connolly molecular surfaces (radius: 1.4 Å) were generated with ChemBio3D. Calix[6]arenes **1** to **6** were prepared as previously described.[10]

Estimation of the Association Constant K_a of 4⊃DOPC (or DPC) and 5⊃DOPC in $CDCl_3$. Association constant K_a was estimated according to the following procedure: guest G (G = DOPC or DPC) was added to a solution of host H (H = **4** or **5**; 1.4 to 2.1 × 10^{-3} M) in such a way that the corresponding ^{1}H NMR spectra recorded at 298 K revealed the total disappearance of the free receptor. The concentration of the undetectable species (i.e., H and DOPC) and the concentration of the complex were estimated to be respectively 5% and 95% of the starting host concentration. Association constant K_a was estimated according to the following equation: $K_a = [H⊃G]/([H][G])$.

Determination of the Association Constant K_a of 6⊃DOPC in $CDCl_3$ and 4, 5, and 6⊃DOPC (or DPC) in $CD_3OD/CDCl_3$. Guest G (G = DOPC or DPC) was added to host H (H = **4**, **5**, or **6**; 1.3 to 2.7 × 10^{-3} M) in such a way that the ^{1}H NMR spectrum recorded at 298 K showed the resonances of both species (the starting host H and the corresponding complex) besides the signals corresponding to the free phospholipid. Integration of the signals of the different species allowed us to calculate the association constant K_a according to the following equation: $K_a = [H⊃G]/([H][G])$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01531.

^{1}H NMR studies of the complexing properties of **1** to **6** (PDF)

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Notes

The authors declare no competing financial interest.

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