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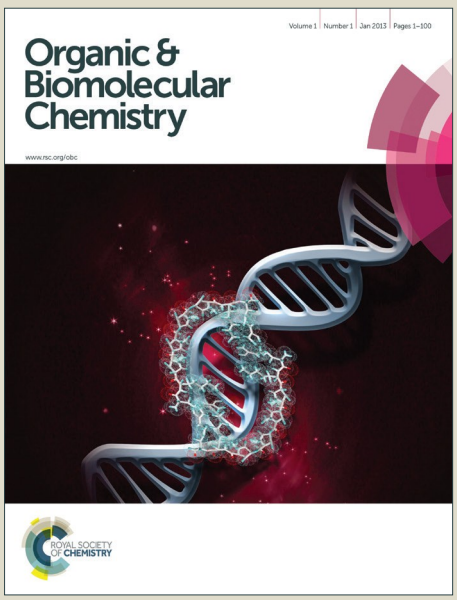

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ARTICLE

Oxacalix[2]arene[2]triazine Based Ion-pair Transporters

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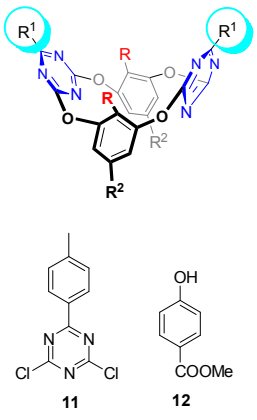
Heteracalixaromatics are a new generation of macrocyclic hosts showing unique structure and versatile recognition properties towards various guests. Amazingly, the application of heteracalixaromatics as membrane transporters or ion channels has never been explored. We reported herein the elaborated design of a series of oxacalix[2]arene[2]triazine-based derivatives **1**-**10** and their ion transport properties. Among these compounds, **3**, **8**-**10** can mediate the transport of chloride across the lipid bilayer of EYPC with activity (EC_{50}) ranging from 0.43 to 8.23 μM. These compounds serve as ion carriers during the transport process, and the transport activity is both anion- and cation-dependent, suggesting a Cl^-/M^+ ion-pair transport model. Structure-activity studies indicate that hydrogen bonding, electronic deficiency of the triazine rings, lipophilicity and macrocyclic framework are essential for the ion transport.

Introduction

Ion transport across membrane catalyzed by proteins that serve as ion channel or carriers is one of the most important processes in living cells.[1] The desire to understand the function and mechanism of the proteins has inspired the development of synthetic ion channel models.[2] Owing to their unique structure and facile functionalization, calixarenes and related resorcinarenes have a rich history as transmembrane ion channels or transporters.[3] Early work demonstrated the use of resorcinarenes and calixarenes as cation transporters or channels.[3a,3b] Later on, several groups including Davis, Izzo and Tecilla reported transport of anions through phospholipid bilayer membrane with 1,3-alternate or paco calix[4]arene derivatives.[2a,4] Very recently, Matile reported ditopic ion transport systems based on anion-π interactions and halogen bonds by taking *cone* calix[4]arene as a molecular platform.[5] Besides the largely explored classical calixarenes, other calixaromatics such as calixpyrroles, in which pyrrole instead of benzene units are incorporated in the macrocyclic framework, have been intensively studied as anion transporters by Gale's and Sessler's groups.[6] In addition to the *meta*-bridged macrocycles, Hou and coworkers[7] designed novel and versatile transmembrane channel models on the basis of pillararenes, a new type of *para*-bridged macrocycles emerged since 2008.[8]

Heteracalixaromatics, or heteroatom bridged calix(het)arenes are a new type of macrocyclic molecules.[9] In traditional calixarene the cavity itself almost shows no recognition ability. The introduction of heteroatoms as bridging linkages and heteroaromatic moieties in heteracalixaromatics, endowed the fine-tuned cavities and versatile recognition abilities. For example, these hosts can recognize various guest species, from metal ions and clusters,[10] neutral molecules,[11] to anions.[12] As the representative examples of heteracalixaromatics, oxacalix[2]arene[2]triazines, 1,3-alternate shape-persistent macrocyclic molecules bearing electron-deficient triazine rings, have been shown as unique anion acceptors based on anion-π interactions.[12] Despite of their versatile recognition properties, the application of heteracalixaromatics as transmembrane models have never been explored. Herein we report the use of a series of oxacalix[2]arene[2]triazine derivatives (Figure 1) as transmembrane transporters. Based on the fluorescence assays, we present that compounds **3**, **8**-**10** can mediate the ion pair transport across the lipid bilayers of EYPC. Hydrogen bonding, electronic deficiency of the triazine rings, lipophilicity and macrocyclic framework are considered to be essential factors in order to mediate the effective ion transport.



11 12

	R	R^1	R^2
1	H	Cl	H
2	H		H
3	OH		COOMe
4			COOMe
5			COOMe
6	OH	Cl	COOMe
7	OH	OMe	COOMe
8	OH		COOMe
9	OH		COOMe
10	OH		COOMe

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Fig. 1 Structures of tetraoxacalix[2]arene[2]triazine derivatives **1-10**, and the control compounds **11** and **12**.

Results and Discussion

Ion transport activity measurements

Oxacalix[2]arene[2]triazine derivatives **1**-**10** (Fig. 1) were synthesized according to our reported procedures or as described in the experimental part (Supporting Information).[11b,13] To evaluate the anion transport activities of these compounds, we chose the fluorescence assays with halide selective dye lucigenin as the probe.[2a] Briefly, egg yolk phosphatidylcholine (EYPC) lipid film was rehydrated with an aqueous solution containing 10 mM HEPES, 1 mM lucigennin and 100 mM sodium nitrate. After freeze-thaw cycles, extrusions through a membrane with 100 nm pores and size exclusion chromatography to remove the external lucigenin, EYPC large unilamellar vesicles (LUVs) containing lucigenin were prepared (for experimental details, see Supporting Information). A NaCl solution (100 mM) was added to the extravesicular buffer to create a chloride gradient. Upon addition of compounds **1**-**10**, the fluorescent emission of intravesicular lucigenin was measured over time.

Effect of substituents on the ion transport activity

The ion transport activity, as illustrated in Fig. 2, closely depends on the structure of these compounds. For example, compounds **1** and **2**, which have been previously reported as good anion-π receptors,[12a,12b,14] show little ion transport activity. The lack of activity for **1** probably owes to its poor lipophilicity and thus can't be inserted into the lipid membrane, as indicated by precipitation occurred when **1** was injected into the buffer solution. Compound **2**, with enhanced lipophilicity by introduction of *p*-tolyl groups and no precipitation observed, still can't mediate the ion transport. On contrast, compound **3** with hydroxyl groups attached on the lower rim of benzene rings, shows significant ion transport activity. Hill analysis of the dose-response curve gives an effective concentration EC_{50} = 4.31 μM and the Hill coefficient n = 2.9 (Table 1 and Supporting Information). According to our previous results,[13c] with OH groups on the lower rim, **3** can form cooperative hydrogen bonding and anion-π interactions with chloride and lead to an enhanced binding affinity. This outcome could contribute to the activity observed.

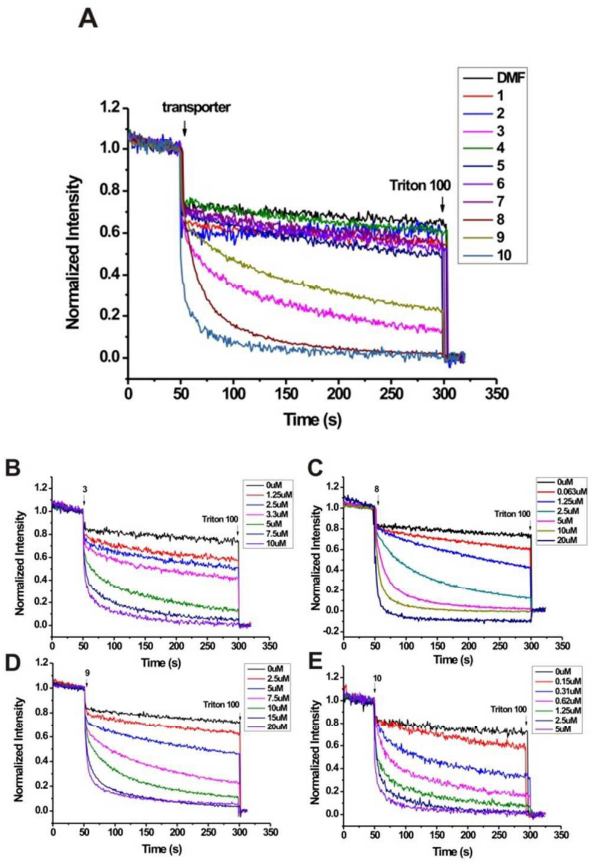

Fig. 2 Evaluation of the ion transport activity of transporters **1**-**10** by lucigenin⊂EYPC fluorescence assays. (A) All compounds and blank DMF, with concentration for each compound is 5 μM except for **9** is 7.5 μM, (B) **3**, (C) **8**, (D) **9** and (E) **10** in varied concentrations.

Encouraged by the transport activity observed for **3**, the influence of the macrocyclic host structure on transport activity was further systematically evaluated. For example, when OH groups in **3** are replaced by perfluorophenoxy (**4**) or 3,5-dimethoxyl-1-triazinoxyl (**5**) the activity is negligible, suggesting OH groups are probably essential to mediate the ion transport. However, this speculation is argued by the little activity observed for **6** and **7**, which still contain OH groups but the *p*-tolyl groups are replaced by -Cl and -OMe respectively. Considering *p*-tolyl groups are more lipophilic than -Cl and -OCH_3, it is envisioned that ion transport occurs when both hydrogen bonding and lipophilicity take effects. To verify this hypothesis, compound **8** with *N,N*-dipropyl groups attached on the triazine rings was investigated. **8** is more lipophilic than **3** as suggested by a longer retention time (t = 20.57 *vs* 19.69 min) on an ODS-HPLC column (Table 1). Accordingly the obtained effective concentration show that **8** is more active than **3** (EC_{50} = 2.56 *vs* 4.31 μM).

The influence of the electronic nature of the substituents on ion transport activity was found to be significant. For example, when electronic donating groups *p*-OMe-phenyl were used to

replace *p*-tolyl groups in **3**, the resulting compound **9** show decreased activity (EC_{50} = 8.23 μM). However, with electronic withdrawing groups *p*-CF_3-phenyl, compound **10** gives increased activity with EC_{50} value as low as 0.43 μM, about one order of magnitude lower than **3**. According to our previous report [12a], the substituent property regulates the electronic density of the triazine rings. With electron withdrawing substituents the electronic density of triazine decreases and accordingly anion-π interactions strengthens. As listed in Table 1 and Fig. S12, the surface potential of the triazine rings increases from the electronic donating to electronic withdrawing substituents (from **9**, **3** to **10**). This clearly demonstrates the considerable substituent effect on the π-deficiency of triazine rings. The association constants between **9**, **3**, **10** and chloride (as tetrabutylammonium salt, in acetonitrile) are 1.2×10^4, 2.4×10^4 and 3.6×10^4 M^{-1} respectively (Fig. S13-16), following the order of the surface potentials of the triazine rings. As the hydrogen bonding ability of the hydroxyl groups on the benzene rings is less affected by the substituents on the triazine rings (could be judged from the very similar OH chemical shifts, δ = 10.86, 10.90, 11.00 ppm for **9**, **3**, **10**, respectively, Table 1), the increased association constant hence mainly benefits from the electronic deficiency of triazine rings. These outcomes indicate that anion-π interaction probably makes one of the main contributions to the efficient ion transport activity for **10**. In addition to the electronic withdrawing nature, the hydrophobicity of CF_3 is also considerable (retention time = 20.37 min), hence the contribution of lipophilicity to the high activity could not be excluded.

Based on the above structure-dependent ion transport activity, we believe that hydrogen bonding, lipophilicity and anion-π interactions are all essential driving forces for mediating the effective ion transport. Although it's hard to distinguish which contribution is dominant, these contributions should take effect in a subtly balanced and cooperative way. Moreover, when control compounds **11** and **12** were used negligible ion transport activity was observed (Fig. S1). This highlights the function of the cavity of this type of macrocyclic transporters.

Table 1. Summary of ion transport activity (EC_{50}), Hill coefficient (n), O*H* chemical shift, triazine ring surface potential (E), Cl^- association constant (K_a) and retention time for **3**, **8**-**10**.

	EC_{50} (μM)[a]	n	^1H NMR (ppm)[b]	E (kcal/mol)	$K_{a(1:1)}$ (L/mol)	Retention time (min)[c]
3	4.31 ± 0.60	2.9 ± 1.1	10.90	20.1	2.4×10^4	19.7
8	2.65 ± 0.62	1.9 ± 0.7	10.36	15.8	3.6×10^3	20.6
9	8.23 ± 0.68	2.8 ± 0.7	10.86	18.3	1.2×10^4	16.9
10	0.43 ± 0.19	1.5 ± 0.7	11.00	27.8	3.6×10^4	20.4

[a] effective concentration, the molar ratios of transporters to lipids are: 1:40 for **3**, 1:60 for **8**, 1:20 for **9**, 1:400 for **10**. [b] mearsured in DMSO-d_6, [c] determined by HPLC, ODS column, mobile phase is acetonitrile containing 0.1 % formic acid.

Mechanism of the transport process

In order to investigate the transport mechanism, we first set up an assay using vesicles prepared with dipalmitoyl phosphatidylcholine (DPPC). As DPPC has a gel to liquid crystalline transition phase at 41 °C, transport assays at 45 °C and 25 °C were performed respectively. The dramatically reduced transport activity caused by the decrease of membrane fluidity of DPPC at 25 °C suggests that the ion transport process is governed by a carrier mechanism (Fig. S9,a).

Then we performed a carboxyfluorescein (CF) release experiment to understand the transport process. CF is a self-quenched dye at high concentration and hence it is weakly fluorescent when entrapped in the vesicles. Enhancement of CF fluorescence could be detected if the transporters cause the membrane defects of LUVs and lead to the release of CF to the diluted extravesicular buffer solution. As illustrated in Fig. S7, addition of transporters **3**, **8**-**10** to the suspension of LUVs containing CF shows no fluorescence enhancement at all, indicating the transporters do not induce the membrane defects. To investigate whether the transport is through a Cl^- / NO_3^- anti-port process, we prepared the vesicles containing lucigenin and sodium chloride. Sodium nitrate was added to the extravesicular buffer solution. In the control experiment, sodium sulfate was applied as the external salt solution. As shown in Fig. S8, in both cases the intensity of quenched lucigenin is recovered with the release of chloride to the extravesicular buffer. Hence, the chloride efflux mediated by the transporters is independent on NO_3^- or SO_4^{2-} contained in the external solution. As sulfate is an extremely hydrophilic anion and it is normally impossible to be transported from aqueous solution to the lipid bilayer membrane, the results thus indicate the less possibility of a Cl^- / NO_3^- anti-port exchange.

The influence of the external cations (alkali metal) and anions (Cl^- and Br^-) on the transport activity was further studied. As illustrated in Fig. S6, the transport activity (EC_{50}) of **3**, **8**-**10** is both anion- and cation-dependent. For example, the chloride transport is more active than bromide except for **9**. For different cations, the activities of **3**, **9** and **10** follow an overall sequence of $Li^+ < Na^+ < K^+ < Rb^+ \approx Cs^+$. Noticeably, **8** gives the almost reversed activity sequence. Although the exact reason is not very clear, one can speculate that larger cation might be difficult to enter the cavity of 8 owing to the steric hindrance by the substitutents. These outcomes indicate that the ion transport is most probably through an X^- / M^+ ion-pair process (Figure 3). We also investigated the ion transport activity at pH 7.6 by taking compound **3** as a representative example. In principle, a higher pH value would facilitate the deprotonation of OH groups, and hence the enhancement of binding with cations. If the ion transport is dominated by cations, a decreased effective concentration should be obtained under higher pH value (pH = 7.6). However, as shown in Fig. S10, the calculated EC_{50} values are almost same at pH 7.6 and pH 7.0, respectively (EC_{50} = 4.59 *vs* 4.31 μM), suggesting the less possibility of cation-dominated ion-pair transport. In combination of the aforementioned investigations, we postulated the ion-pair transport entity as: the transporters form complex with anion through cooperative anion-π interaction and hydrogen bonding, cation as the counter ion forming compact ion-pair with the complex (Fig. 3).

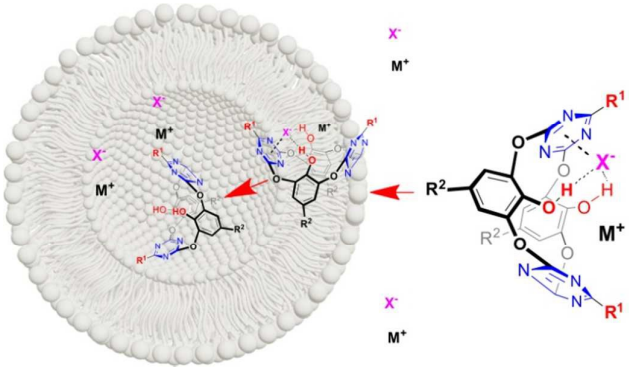

Fig. 3 Proposed schematic description of the ion-pair transport.

To verify our postulation and get deep insights on the ion transport mechanism at molecular level, we cultivated the single crystals of the complexes of the compounds and halide anions. Fortunately, single crystals of the complex between **7** and bromide were obtained through slow evaporation of the solvent. Although **7** shows no transport activity, its structural similarity with the active transporters could provide detailed information of the host-guest interactions. As revealed by the crystal structure (Fig. 4A and B), **7** interacts with bromide through cooperative anion-π interaction and hydrogen bonding. Bromide locates over one of the triazine rings with distances to the plane and centroid of the triazine ring being 3.266 Å ($d_{Br1\text{-}plane}$) and 3.315 Å ($d_{Br1\text{-}centroid}$) respectively, forming typical non-covalent anion-π interaction. Meanwhile the two hydroxyl groups interact with bromide through multiple hydrogen bonds. The tetraethylammonium cation locates outside the cavity and shows short contact with bromide and oxygen atom of one of the hydroxyl groups. Two such complexes, with aid of intermolecular C-H…Br hydrogen bonds between OCH_3 on the triazine rings and bromides, self-assemble into a dimeric structure (2+2) (Figure 4B). Based on the crystal structure, we set up DFT modeling at B3LYP/6-31G* level to speculate the complex structure of **3** and NaCl. DFT models give an energy favorable ion-pair complex (Figure 4D). The optimized model shows that **3** binds Cl^- through the aforementioned cooperative anion-π and hydrogen bonding interactions, meanwhile sodium as the counter cation seats at the outer rim of the cavity and interacts with one of oxygen atoms ($d_{Na\text{-}O}$ = 2.325 Å) through dipole-ion interaction (Fig. 4C). It is worth addressing that the ion-pair complex structure observed in both crystal structure and DFT calculation all support our hypothesized ion-pair transport entity. Moreover, from the dimeric crystal structure and the Hill coefficient (n) obtained around 2 from Hill analysis of the dose-response curve, it is likely that the transporters mediate transport of ions through a 2+2 dimeric complex.

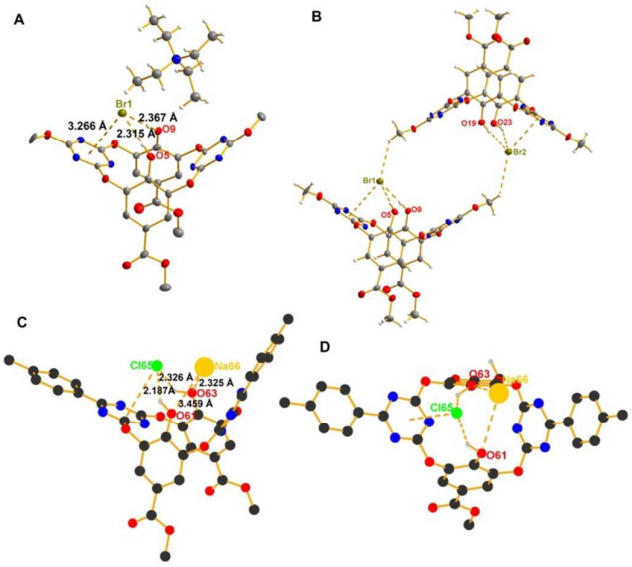

Fig. 4 Crystal structure of (A) the complex of **7** and tetraethylammonium bromide (Et_4N^+(**7**·Br^-)), (B) dimeric structure, DFT optimized structure of (C) side view and (D) top view of the complex of **3** and NaCl.

Conclusions

We have designed a series of oxacalix[2]arene[2]triazine derivatives and studied their capabilities as ion transporters through the double layer membrane of EYPC. The fluorescent assays demonstrated that compounds **3**, **8**-**10** can mediate the ion pair transport and act as transmembrane carriers. Hydrogen bonding, electronic deficiency of the triazine rings, lipophilicity and macrocyclic framework were revealed to be essential for mediating the ion transport. This work hence

provides new dimensions of heteracalixaromatics as molecular model of ion transporter or ion channel. Design of heteracalixaromatics-based ion channel is undergoing in our laboratory.

Acknowledgements

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Notes and references

‡ Crystallographic data for 2([**7**·Br^-]Et_4^+) ($CHCl_3$) (C_{65} H_{77} Br_2 Cl_3 N_{14} O_{24}): *Mr* = 1704.58, monolinic, space group P2(1)/n, a = 21.688 (6), b = 17.152 (4), c = 22.729 (5) Å, α = 90.00°, β = 115.043°, γ = 90.00°, V = 7660 (3) $Å^3$, T = 173 (2) K, full-matrix least-squares refinement on F^2 converged to R_F = 0.1495 [I > 2σ(*I*)], 0.1745 (all data) and $Rw(F^2)$ = 0.3675 [$I > 2\sigma(I)$], 0.3798 (all data), goodness of fit 1.882. CCDC 1432620.

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