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The syntheses of phenol-containing azamacrocycles and liquid membrane transports of alkali cations

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Abstract

Two new tetra-*N*-substituted tetraazacrown ether derivatives, 4,7,13,16-tetra(2-hydroxy-3,4-dimethylbenzyl)-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane (1) and 4,7,13,16-tetra(5-*t*-butyl-2-hydroxybenzyl)-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane (2), have been synthesized *via* one-pot Mannich reaction. The compound 2 was structurally characterized. The liquid membrane transports of alkali metal cations using these two new macrocycles and the other two bisphenol-containing diaza-18-crown-6 ligands as ion-carriers were also studied. The results show that the rates of cation transport are closely related to the number of nitrogen donors and the steric effect of the substituted groups. Compared with some macrocyclic ligands, the two newly synthesized tetraazamacrocycles showed a good selectivity for Li^+, and the two diazamacrocycles showed a good selectivity for Na^+.
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Keywords: Tetraaza-crown ether; Diaza-crown ether; Crystal structure; Liquid membrane transport

1. Introduction

Transport of cations across an organic liquid membrane which separates two water phases has been extensively investigated [1]. The synthetic macrocyclic ligands, such as crown ethers, are usually used as model carriers to mimic the naturally occurring antibiotic macrocycles which have been shown to alter the permeability of biological membranes to certain cations [2,3]. Thus, they have important applications in both chemistry and biology to selective complexation of various metal cations [4,5]. It was reported that the divalent transition metal complexes of tetraazamacrocyclic ligand with four 2-cyanoethyl pendent groups exhibited antitumor activity [6]. Nitrogen–oxygen mixed donor macrocycles can form stable complexes with both alkali and transition metal ions, therefore, they have received much attention as receptors for a range of metal ions and other cations [7,8]. It has been clearly documented that the coordination properties of such ligands often span those of the well studied crown polyethers and polyaza categories of macrocycles.

These macrocycles chosen as membrane carriers should have limited water solubility to prevent loss of carrier to water phases [9]. In recent years, many macrocyclic azacrown ethers have been synthesized and their liquid membrane transports have been studied [10–12]. In our previous work, we synthesized bisphenol-containing diaza-18-crown-6 ligands 3 and 4 via one-pot Mannich reaction according to literatures [13,14], and prepared their copper complexes [15–17]. Because 1,4,10,13-tetraaza-18-crown-6 is an amphiphile, which can be soluble both in aqueous solution and organic solvent, it is not a suitable carrier in liquid membrane transport. Aiming at enhancing the lipophilic property of this kind of azacrown ether, we synthesized two new phenol-containing tetraazamacrocyclic compounds 1 and 2 and two other phenol-containing diaazamacrocycles 3 and 4. Here we report the syntheses of 1 and 2 and the crystal structure of *2* and the liquid membrane transports of alkali metal actions using these four compounds as the ion-carriers.

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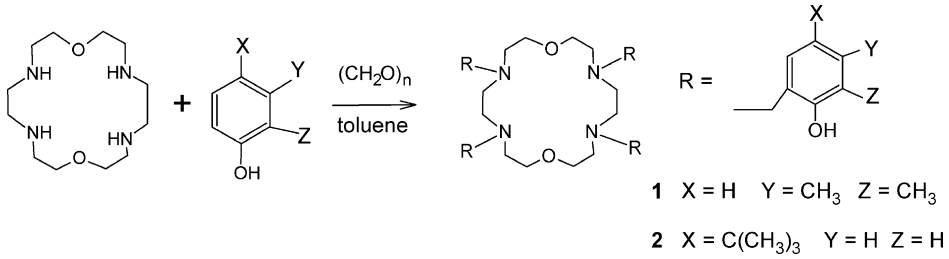


Scheme 1. The synthetic routes of 1 and 2.

2. Experimental

2.1. Materials and methods

All commercially available chemicals were of analytical grade and were used without further purification. C, H and N were determined using a Elementar vario EL elemental analyzer. UV spectra in aqueous solution were recorded on a GBC Cintra 10e UV–Visible spectrophotometer. The IR spectra were recorded on a Nicolet-AVATAR 360 FT-IR spectrometer using KBr pellets in the region of 4000–400 cm^{-1}. ^1H NMR spectra were recorded on a Varian 500 Bruker spectrometer in $CDCl_3$. Diaza-18-crown-6 and tetraaza-18-crown-6 were prepared according to literature methods [18] and [19,20], respectively.

2.2. Preparation of the compounds 1 and 2

The new tetraazamacrocyclic compounds 4,7,13,16-tetra (2-hydroxy-3,4-dimethylbenzyl)-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane (1) and 4,7,13,16-tetra(5-*t*-butyl-2-hydroxybenzyl)-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane (2) were prepared following the scheme below (Scheme 1).

2.2.1. Preparation of the compound 1

An anhydrous toluene solution (30 ml) containing 4,13-diaza-18-crown-6 (0.130 g, 0.5 mmol), paraformaldehyde (0.074 g, 2.45 mmol), and 2,3-dimethylphenol (0.259 g, 2.40 mmol) was refluxed at 383 K for 24 h. The solvent was evaporated by rotatory evaporation, and a small amount of EtOH (15 ml) was added. The mixture was ultrasonicated for 20 min. The resulting solid was collected by filtration and dried, yield, 70%, m.p. 405–406 K. Anal. calcd for $C_{48}H_{68}N_4O_6$ (M_r = 796) (%): C 72.36, H 8.54, N 7.04; found (%): C 72.04, H 8.70, N 6.85. ^1H NMR ($CDCl_3$), δ: 2.14–2.19 (m, 12H), 2.26–2.30 (m, 12H), 2.75–2.83 (m, 8H), 2.88–2.96 (m, 8H), 3.55–3.60 (m, 8H), 3.68–3.79 (m, 8H), 6.59–6.61 (d, 4H), 6.68–6.74 (m, 4H) ppm. IR (KBr): 3436(m), 2859(s), 2815(s), 1619(m), 1583(m), 1457(s), 1355(s), 1257(m), 1222(m), 1122(s), 1084(s), 1049(m), 836(w), 797(w), 763(w) cm^{-1}.

2.2.2. Preparation of the compound 2

An anhydrous toluene solution (30 m) containing 4,13-diaza-18-crown-6 (0.130 g, 0.5 mmol), paraformaldehyde (0.074 g, 2.45 mmol), and 4-*t*-butylphenol (0.374 g, 2.40 mmol) was refluxed at 383 K for 24 h. The solvent was evaporated by rotatory evaporation, and a small amount of MeOH (15 ml) was added. The mixture was ultrasonicated for 20 min. The resulting solid was collected by filtration and dried, yield, 80%, m.p. 468–469 K. Anal. calcd for $C_{56}H_{84}N_4O_6$ (M_r = 909.3) (%): C 73.90, H 9.24, N 6.16; found (%): C 73.96, H 9.35, N 6.18. ^1H NMR ($CDCl_3$), δ: 1.16–1.41 (m, 36H), 2.84 (s, 8H), 2.97 (s, 8H), 3.57 (s, 8H), 3.77 (s, 8H), 6.75–6.77 (d, 4H), 6.97 (s, 4H), 7.18–7.19 (d, 4H) ppm. IR (KBr): 3422(m), 2961(s), 2866(m), 1597(w), 1503(s), 1463(m), 1365(m), 1253(s), 1122(s), 823(m), 722(w) cm^{-1}.

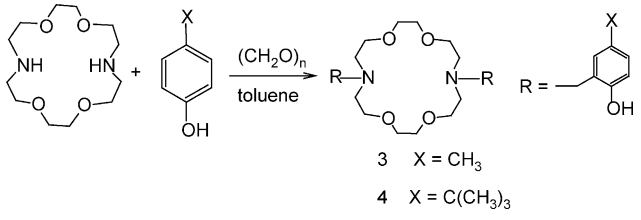
2.3. Preparation of compounds 3 and 4

The diazamacrocyclic compounds 7,16-bis(2-hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (3) and 7,16-bis(5-*t*-butyl-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane (4) were prepared according to the literature [13] following the scheme below (Scheme 2).

Elemental analysis and spectroscopy studies showed a good agreement with that reported [13].

2.4. X-ray crystallography

A crystal with dimensions 0.30 mm × 0.25 mm × 0.20 mm was selected for X-ray diffraction experiment. The measurements were performed on a SMART 1000 CCD diffractometer at 293 K with graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXS-97 and SHELXL-97 programs [21]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located by



Scheme 2. The synthetic routes of 3 and 4.

Table 1
Results of crystal data and structure refinement of compound 2

Empirical formula	$C_{56}\ H_{84}\ N_4\ O_6$
Formula weight	909.27
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	$a=6.342(8)$ Å, $\alpha=99.17(2)°$, $b=9.808(11)$ Å, $\beta=92.01(3)°$, $c=21.79(2)$ Å, $\gamma=99.72(3)°$
Volume (Å^3)	1316(3)
Z, calculated density	1, 1.147 g/cm^3
Absorption coefficient (mm^{-1})	0.074
$F(000)$	496
Crystal size	0.30 mm × 0.25 mm × 0.20 mm
Theta range for data collection	2.14–25.03°
Limiting indices	$-6\le h\le 7$, $-11\le k\le 11$, $-25\le l\le 24$
Reflections collected/unique	5141/4368 [$R_{int}=0.0805$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9854 and 0.9782
Refinement method	Full-matrix least-squares on F^2
Final R indices [$I>2\sigma(I)$]	$R_1=0.0760$, $wR_2=0.1803$

difference Fourier synthesis and refined isotropically. A summary of the crystallographic data and details of the structure refinements are listed in Table 1.

2.5. Transport of cations across a liquid membrane

The apparatus used for the liquid membrane transport was made consulting the literature [22] as shown in Fig. 1. The transport experiments were performed at 298 (±0.5) K in a thermostatic water bath, magnetic bar: 20 mm in length and 6 mm in diameter, 160 rpm. Dichloromethane of reagent grade was shaken with deionized water four times and to saturate the solvent with water [23]. Phase 1 (the source phase): 20 ml of the mixed solution of metal hydroxide [24] (0.1 mol/l) and picrate (2×10^{-3} mol/l) [25]. Phase 2 (receiving phase): deionized water (20 ml). Phase 3 (liquid membrane): 50 ml dichloromethane solution of the macrocycle to be studied (4×10^{-4} mol/l). The concentration of the metal picrate in the receiving phase was monitored by the UV absorption of the picrate at 355.0 nm. Standard curves were obtained from the solution with known concentrations.

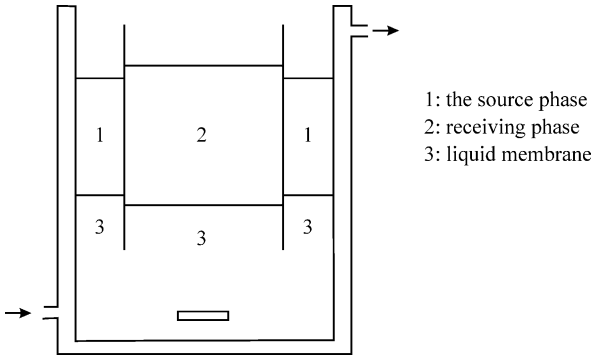


Fig. 1. Liquid membrane cell.

3. Results and discussion

3.1. Syntheses of tetraazamacrocycles

The synthetic routes of the two new tetraazamacrocycles 1 and 2 are shown in Scheme 1. The Mannich reaction is known to be a powerful method for the functionalization of diaazacrown ether with additional ligating units [13,14]. Reaction of diaza-18-crown-6, paraformaldehyde, and the appropriate phenols in refluxing toluene gave these compounds in good yields. Nearly all these compounds were purified by ultrasonication in MeOH followed by filtration and drying. However, to our knowledge, tetraaza-18-crown-6 ligands containing substituted phenol side arms have not been prepared yet. Sonication of the crude products in a small amount of MeOH followed by filtration and drying also proved to be an efficient purifying method for 2, which is similar to the syntheses of the bisphenol-containing diaza-18-crown-6 ligands. But in the synthesis of 1, when MeOH was added, because of its high solubility in MeOH, the solid cannot precipitate from it. We found that sonication of it in a small amount of EtOH enable us to obtain the compound with high purity without lowering the yield of it. The preparation of this kind of tetraazamacrocycle may assess the breadth of the synthetic approach.

3.2. Description of the crystal structure

Fig. 2 shows the molecular structure of the compound 2. The selected bond lengths and angles are listed in Table 2. The macrocyclic compound has a crystallographic center of symmetry. In the solid state, the structure could be described as a pre-organized three-dimensional host. Four phenol groups in the molecule are roughly in a 1,2-alternate conformation with two phenol groups being above the tetraazacrown ring and the other two below it, which is similar to the structure of 4,7,13,16-tetrathenoyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane [26], in contrast to the structure of tetra *N*-substituted cyclanes where four functional groups are oriented on the same side of the ring [27].

The six donor atoms of crown ring, N1, N2, N1A, N2A, O1 and O1A, are not coplanar and adopt a chair conformation.

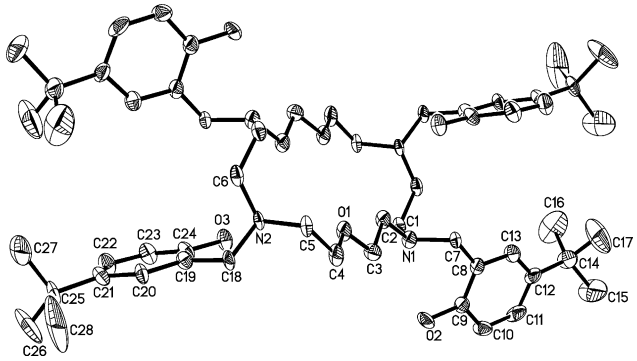


Fig. 2. Molecular structure of compound 2.

Table 2
Selected bond lengths (Å) and bond angles (°) for compound 2

Bond lengths			
O(1)–C(3)	1.412(9)	O(1)–C(4)	1.411(9)
O(2)–C(9)	1.372(10)	O(3)–C(24)	1.364(9)
N(1)–C(1)	1.448(10)	N(1)–C(2)	1.477(9)
N(1)–C(7)	1.483(9)	N(2)–C(5)	1.474(9)
N(2)–C(6)	1.502(10)	N(2)–C(18)	1.467(9)
C(1)–C(6)#1	1.533(11)	C(6)–C(1)#1	1.533(11)
Bond angles			
C(1)–N(1)–C(2)	114.7(6)	N(1)–C(2)–C(3)	110.2(7)
C(1)–N(1)–C(7)	114.5(6)	C(2)–N(1)–C(7)	113.2(6)
N(1)–C(1)–C(6)#1	120.7(7)	C(8)–C(7)–N(1)	110.7(7)
C(5)–N(2)–C(6)	110.9(6)	C(4)–C(5)–N(2)	114.4(6)
N(2)–C(6)–C(1)#1	116.2(6)	C(18)–N(2)–C(5)	110.3(6)
C(18)–N(2)–C(6)	109.0(5)	N(2)–C(18)–C(19)	112.0(6)
O(1)–C(3)–C(2)	107.4(6)	C(4)–O(1)–C(3)	115.3(6)
O(1)–C(4)–C(5)	108.7(7)	O(2)–C(9)–C(8)	119.3(7)
O(2)–C(9)–C(10)	119.2(8)	C(19)–C(24)–O(3)	122.4(8)
O(3)–C(24)–C(23)	116.2(8)		

Symmetry transformations used to generate equivalent atoms: #1 $-x$, $-y$, $-z$.

The deviations from the mean plane defined by N1, N2, N1A, N2A, O1 and O1A, are 0.1824, 0.2140, −0.1824, −0.2140, −0.3293 and 0.3293 Å, respectively. The dihedral angle between the benzene ring, C8–C13 (or C8A–C13A) and the N_4 plane, defined by N1, N2, N1A and N2A, is 133.5°. The dihedral angle between the benzene ring, C19–C24 (or C19A–C24A) and the above N_4 plane is 69.3°.

3.3. Transports of alkali metal cations

The azamacrocyclic compounds can form complexes with alkali metal picrates, so, they can be used as cation carriers. The experiment was performed through a dichloromethane membrane separating two aqueous solutions. The alkali metal picrates were transported with the aid of the ligand from an aqueous phase (phase 1) to another aqueous phase (phase 2). The picrate concentration was found to increase in phase 2, detected by UV–Vis spectrophotometry.

The transports of Li^+, Na^+ and K^+ cations were studied individually from an aqueous solution which contained a mixture of metal hydroxide and picrate. The transported co-anion should be the picrate because of its lipophilic property. In the control experiment, it was shown that no transport was detectable in the absence of the carrier. In addition, the transport experiments with the standard dibenzo-18-crown-6 were also carried out and established that our apparatus gave the results in fair good agreement with those reported in the literatures [25,28]. The transport rates were calculated from the linear part of the transport curves. The transport rates and selectivity ratios are given in Table 3.

The investigation established that the nature of the species such as the ring size, the kind of donor and substituting group has an important effect on cation transport [9,29,30]. The 18-crown-6 systems preferentially transport the size-matched K^+ ion. Although a direct comparison is difficult to make with different individual experiments, dibenzo-18-crown-6 transports metal ions (especially K^+) much more efficiently under the same experimental conditions. However, the transport rates to K^+ of the four azamacrocycles, especially the two newly prepared tetraazamacrocycles, seem not high. According to the hard–soft acid–base theory, the rather soft nitrogen donors cannot coordinate as well to hard alkali metal cations as hard oxygen donors. The steric effect of four substituted phenols also affects the coordination ability. In addition, from the molecular structure of compound 2, it can be seen that the crown ether ring is twisted to result in a decrease of its efficient cavity size. From the results of the transport experiments, several conclusions can be drawn as following:

(1) The observed transport rates of Na^+ by compounds 1–4 have the following order: 1 < 2 < 3 < 4. The transport rates decreases approximately with the increase of the number of nitrogen donors and the substituted phenols and the steric effect of the side-arm phenols. As to two diaazamacrocycles 3 and 4, the bigger steric inhibition of two *t*-butyl-phenols in 4 may cause the decrease of its efficient cavity size, which preferentially transports the size-matched Na^+ and exhibits the maximum selectivity rate for Na^+.
(2) The transport rates of K^+ have the order as follows: 1 < 2 < 4 < 3. The reason may be similar to that explained in 1. The smallest steric inhibition of side-arm phenols in 3 has caused the greatest transport rate for K^+.
(3) The transport rates of Li^+ have the order as follows: 1 < 2 < 4 < 3, which coincides with that of K^+. Although the absolute value of transport rates to Li^+ by 1 and 2 is lower, the selectivity ratios for Li^+/Na^+

Table 3
Transport rates and selectivity ratios of alkali metal picrates through a liquid membrane

Compounds	Cations	Transport rates (10^{-8} mol/h)	Selectivity ratios		
			Li^+/Na^+	Li^+/K^+	Na^+/K^+
1	Li^+	1.78			
	Na^+	0.51			
	K^+	0.97	3.45	1.85	0.53
2	Li^+	3.05			
	Na^+	2.29			
	K^+	2.01	1.33	1.52	1.14
3	Li^+	9.6			
	Na^+	102			
	K^+	74.8	0.094	0.13	1.37
4	Li^+	8.8			
	Na^+	116			
	K^+	70.9	0.076	0.12	1.64
Dibenzo-18-crown-6	Li^+	1.2			
	Na^+	18.5			
	K^+	209	0.065	0.006	0.089

The source phase: 20 ml of the mixed solution of alkali metal hydroxide (0.1 M) and picrate (2×10^{-3} M). The concentration of carriers is 4×10^{-4} mol/l.

and Li^+/K^+ by 1 and 2 are greater than those by 3, 4 and dibenzo-18-crown-6, showing the good selectivity for Li^+.

Though variations in the stirring speed and other factors do not permit precise comparisons of the transport efficiency with other carriers, to our prepared compounds, the absolute rates of transport are 10^{-8}–10^{-7} mol/h, which are in fair good agreement with those obtained in other laboratories [10,24,25,28]. Compared with some macrocyclic ligands, our synthesized compounds may decrease the absolute transport rates to Li^+, Na^+ and K^+, but the two new compounds 1 and 2 may enhance the selectivity for Li^+, while compounds 3 and 4 may enhance the selectivity for Na^+, therefore providing new efficient carriers for Li^+ and Na^+ extraction, respectively.

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