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THE SYNTHESIS AND MEMBRANE TRANSPORT CHARACTERISTICS OF MACROCYCLIC POLYETHER LIGANDS COMPOSED OF 1,10-PHENANTHROLINE AS CARRIERS FOR PRIMARY AMINE SPECIES

ZENG-RONG ZHANG*
Department of Chemistry, Hunan Teachers College, Changsha, 410006, People's Republic of China

RU-QIN YU
Department of Chemistry and Chemical Engineering, Hunan University, Changsha, 410082, People's Republic of China

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Summary—Four macrocyclic polyether derivatives of *o*-phenanthroline were synthesized and used as neutral carriers for preparing poly(vinyl chloride) (PVC) membrane electrodes to sense primary amine species. The potentiometric response characteristics of the electrodes prepared were investigated. The electrode sensitive to benzyl amine as model analyte showed a linear response range of 8.0×10^{-6}–0.1 mol/l with a detection limit of 8.9×10^{-7} mol/l and a slope of 56.5 mV/decade. The linear potentiometric response of the mexiletine-sensitive electrode was 4.7×10^{-6}–0.1 mol/l, and the detection limit was 5.0×10^{-7} mol/l with a slope of 59.0 mV/decade. The transfer behavior of amines and ammonium ions through an organic phase was investigated by means of the bulk liquid membrane transport experiment. The effects of pH, counter anions and other factors on the transfer of the amine and ammonium species were studied. The mass transfer rates of the test species facilitated by macrocyclic polyether derivatives of *o*-phenanthroline were determined and the following sequence was found: benzyl amine > ethyl amine > tetramethyl ammonium > triethyl amine > diethyl amine > K^+ > ammonium > Na^+ > Ca^{2+} > Mg^{2+}. This was exactly the potentiometric selectivity sequence of the membrane electrodes prepared by using these carriers. The mechanism of transfer of benzyl amine through a membrane phase induced by the carriers has been elucidated on the basis of experimental observations.

A transport of amines has been studied in previous work.[1] In the search for electrochemical carriers for primary amine species, we synthesized *N,N′,N″*-trimethyl-1,7,13-triaza-4,10,16-trioxacyclooctadecane and some macrocyclic polyethers with 2,2′-dinaphthyl subunits capable of forming host–guest complexes with amine species. These compounds were used as neutral carriers for the preparation of poly(vinyl chloride) (PVC) membrane electrodes sensing primary amine drug.[2,3] It has been found that macrocyclic polyether derivatives of *o*-phenanthroline are promising carrier compounds for this class of amines. In this paper, macrocyclic polyether derivatives of *o*-phenanthroline (Fig. 1), such as 1,15-(1′,10′-diazaphenanthro[2′,9′])-2,5,8,11,14-pentoxacyclon onadecane, were synthesized from the 2,9-dihydroxy-1,10-phenanthroline and polyethyleneglycol ditosylate. The potentiometric response characteristics of the electrodes based on these compounds were investigated. The transfer behavior of amine and ammonium species through an organic phase containing these macrocyclic polyethers was investigated.

*To whom correspondence should be addressed.

EXPERIMENTAL

Synthesis of macrocyclic polyether derivatives of o-phenanthroline

Synthesis of 2,9-dihydroxy-1,10-phenanthroline (I). The compound 2,9-dichloro-1,10-phenanthroline (II) was prepared from 1,10-phenanthroline(III) by a six step reaction route according to the method described by Lewis *et al.*[4] The compound II was refluxed with lithium methoxide in tetrahydrofuran (THF) for 12 hr to give 2,9-dimethoxy-1,10-phenanthroline (IV). The compound IV was dissolved in dioxane and refluxed for 16 hr after addition of

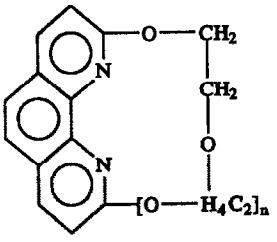

Fig. 1. The structure of carriers V $n = 1$,PHEN13C5; VI $n = 2$,PHEN16C6; VII $n = 3$,PHEN19C7; VIII $n = 4$,PHEN22C8.

anhydrous lithium iodide to give a yellow product of I.

Synthesis of macrocyclic polyether derivatives of o-*phenanthroline*. The syntheses were carried out in analogy to the method described by Cram *et al.*[5,6] The compound I was dissolved in THF dried by sodium. To this solution potassium *t*-butoxide and polyethyleneglycol ditosylate (one big one) were added under nitrogen, the mixture was stirred and refluxed for 5 hr. The solvent was evaporated under reduced pressure, the residue was extracted with chloroform. The organic layer was washed sequentially with a saturated sodium carbonate solution and water, then dried with anhydrous magnesium sulfate. The solvent was removed by evaporation, followed by separation of the residue by chromatography on silica gel. The product was eluted from the silica gel column with ether as a solvent.

The synthetic reactions and products (I, IV) obtained were monitored by using GC-MS system of Model GCMS-QP1000/GCMS-QP1000A (Japan). Four macrocyclic polyether derivatives of *o*-phenanthroline (V–VIII) were obtained with different polyethyleneglycol ditosylate (one big one), respectively and were all separated from the reaction mixture, and their structures were identified (Table 1). The ^1H NMR spectrum was recorded with an AC-80 spectrometer. The chemical shift for the $CDCl_3$ solution were obtained with internal tetramethylsilane(TMS). The IR(KBr) spectra were recorded with an AQS-20 spectrophotometer. The elemental analysis was carried out on a CHN-O-RAPID elemental analyzer.

Preparation of electrodes

The general procedure for the preparation of the PVC membrane[7] is as follows. A THF solution containing the carrier compound (5.8 mg), PVC (84 mg), diisooctyl sebacate (180 mg) and $KBPh_4$ (1.0 mg) was poured onto a flat glass plate (*ca* 5.3 cm^2). The THF was evaporated at room temperature to obtain a transparent, flexible membrane. A disk of 7 mm diameter was cut from the PVC membrane by using a cork borer and cemented onto the flat end of a PVC tubing with an adhesive of 5% THF solution of PVC. An internal solution of 0.1 mol/l KCl and an Ag/AgCl internal reference electrode were used. The PVC membrane electrode prepared was conditioned by soaking in 1.0×10^{-2} mol/l tested solution overnight. The external reference electrode was a saturated calomel electrode. The electrochemical cell used is: Ag/AgCl|0.1 mol/l KCl|PVC membrane|sample solution|SCE.

Electromotive force(emf) measurements

The emfs were measured at 25°C using a pH-meter of model PHS-3 (Shanghai Analytical Instruments) or a 901 Microprocessor Ionanalyzer (Orion Research, U.S.A.). The sample solutions were stirred with a magnetic stirrer in a double-walled glass container with thermostated water circulating in the water jacket.

Transport of cations through bulk liquid membranes containing the crown ethers

The transport experiment was carried out using a conventional apparatus (Fig. 2)[8] which consisted of an outer cylindrical glass vessel and a central glass tube maintained at 25°C. The source phase was 10.0 ml of an aqueous solution which contained the tested amine species

Table 1. Analytical data of carrier compounds

Polyether	Calculated (%) C	H	N	Found (%) C	H	N	IR (cm^{-1})						m/e (M^+)
I													212
IV													240
V	68.14	4.93	9.86	68.10	4.95	9.89	2940	1671	1605	1471	1131	853	282
VI	66.26	5.52	8.59	66.20	5.48	8.67	2937	1661	1599	1465	1130	843	326
VII*	64.86	5.96	7.57	64.81	5.94	7.60	2942	1600	1606	1469	1131	850	370
VIII	63.77	6.28	6.77	63.71	6.19	6.88	2947	1661	1604	1466	1131	848	414

*NMR: 3.44–3.83 (m, 16 H, OCH_2CH_2O), 7.80–8.50 (m, 6H, ArH).

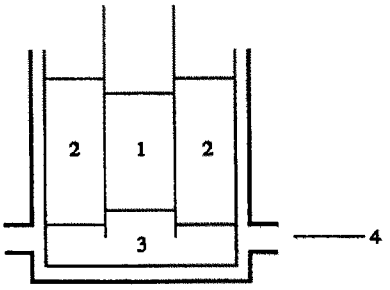

Fig. 2. Transport apparatus 1. source phase; 2. receiving phase; 3. membrane (organic) phase; 4. thermostated water (25°C).

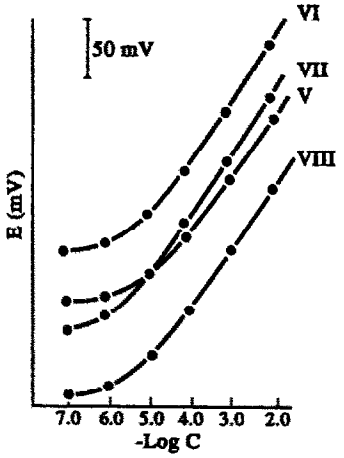

Fig. 3. Response performances of electrodes with different carriers. Membrane composition: 5.8 mg of carrier, 180 mg of diisooctyl sebacate, 84 mg of PVC and 1.0 mg of potassium tetraphenylborate. Measurement condition: 0.05 mol/l Tris solution (pH = 8.5) was used as a buffer system.

(guest), while the receiving phase was 10.0 ml of water. The pH of the source phase and the receiving phase were adjusted with HCl and 0.05 mol/l Tris to desirable values. Two aqueous phases were separated by an organic phase, which was 2.0 ml of trichloromethane solution of 0.1 mol/l crown ether (host).

The transport of amine species was initiated by the addition of the solutions. After a period of time, 1.0 ml of the solution was taken from the receiving phase and the amount of amine species was determined by the direct potentiometric method using corresponding ion-selective electrode.

RESULTS AND DISCUSSION

Performance of the electrode prepared

Four ion-selective electrodes were prepared using membranes containing different carriers and their potentiometric response performances were compared (Fig. 3). The following potentiometric response performance was found: VII > VIII > VI > V. The structure of macrocyclic polyether derivatives substantially affects the response performances of benzyl amine sensitive electrodes. It is obvious, that the sequence of cavity size provided by the carriers is as follows: V < VI < VII < VIII. Compounds with smaller (V and VI for instance) and larger (VIII) cavity sizes showed inferior performance characteristics compared with the carriers of medium size cavity (VII). It seems to mean that the size of the cavities provided by the carriers is important and one would expect better electrode performance for the carrier (VII) with cavity size sterically matching the analyte species to be sensed. By using the carrier VII an electrode sensing benzyl amine was prepared. The electrode showed a linear response to benzyl amine in the range of 8.0×10^{-6}–0.1 mol/l, with a detection limit 8.9×10^{-7} mol/l and a slope of 56.50 mV/decade (correlation coefficient 0.9998, $n = 6$, standard deviation 0.21, slope 56.50 ± 0.50) at 25°C. The stability and reproducibility of the electrode was quite satisfactory. The potentiometric selectivity coefficients were determined by the fixed interference method for the benzyl amine electrode, the concentrations of interferents were fixed at 1.0×10^{-2} mol/l (Table 2). The potentiometric selectivity coefficients toward the same cationic species were also determined when the membrane contains only the borate salt but no macrocycle (Table 3). The data shown in Tables 2 and 3 show two benefits of using the macrocyclic compounds as ionophores to prepare electrodes. First, in contrast to the electrodes based on commonly used crown ethers, the *o*-phenanthroline macrocyclic polyether

Table 2. Potentiometric selectivity coefficients of the benzyl amine electrode

Interferents (j)	K_{ij}^{pot}	Interferents (j)	K_{ij}^{pot}
Ca^{2+}	4.0×10^{-5}	Phenylamine	3.2×10^{-4}
Mg^{2+}	3.2×10^{-5}	Tetramethylammonium	1.0×10^{-2}
Na^{+}	6.6×10^{-4}	Diethylamine	8.3×10^{-3}
K^{+}	7.0×10^{-3}	Triethylamine	1.0×10^{-2}
NH_4^{+}	2.2×10^{-3}	Ethyl amine	2.0×10^{-1}

Table 3. Potentiometric selectivity coefficients of electrode based on potassium tetraphenylborate

Interferents (j)	K_{ij}^{pot}	Interferents (j)	K_{ij}^{pot}
Ca^{2+}	5.3×10^{-4}	Benzylamine	1.0
Mg^{2+}	6.7×10^{-4}	Tetramethylammonium	8.9
Na^{+}	4.0×10^{-2}	Diethylamine	2.3
K^{+}	7.8×10^{-3}	Triethylamine	3.7
NH_4^{+}	4.1×10^{-3}	Ethyl amine	3.0×10^{-1}

derivative-based electrodes had high potentiometric selectivity coefficients for the primary amine species with respect to alkali and alkaline earth metals, this outstanding feature might be explained by the complexing efficiency of primary amine with the azacrown ethers.[9] Macrocyclic polyethers of the 18-crown-6 are able to complex both metal cations and primary ammonium cation,[10,11] moreover, these polyethers bind the alkali cations K^+ and Rb^+ appreciably stronger than the R-NH_3^+ groups,[12] therefore these macrocyclic polyethers are not feasible to be used as selective carriers for amine or ammonium ion-selective electrodes. Since $^+$N-H ... N hydrogen bonding is stronger than the $^+$N-H ... O[13], the *o*-phenanthroline macrocyclic polyether derivatives appeared to be suitable selective carriers of primary amine drugs, the presence of the nitrogen atoms in the phenanthroline moiety of the carrier molecule increase the stability of complex formed by the protonated primary ammonium ion and carrier compound. The second feature is that the *o*-phenanthroline macrocyclic polyether derivative-based electrodes were fairly selective to the primary amine against secondary and tertiary amines and quaternary ammonium ions. For a classical drug electrode, a selectivity sequence for *N*-based drugs is found to be:[14]

$$RNH_3^+ < R_2NH_2^+ < R_3NH^+ < R_4N^+$$

in which quaternary drugs of the same carbon number are most sensitively detected. This sequence is changed by using macrocyclic polyether derivatives as carriers:

$$RNH_3^+ > R_4N^+ > R_3NH^+ > R_2NH_2^+$$

in which the primary amine drugs are most sensitively detected.

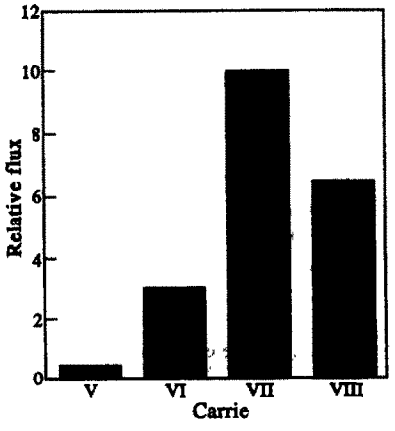

Fig. 4. Transport characteristics with different carriers for benzylamine. $[N]_s = 0.15$ mol/l, $[Cl^-]_s = 0.15$ mol/l, $[N]_r = 0$, $[Cl^-]_r = 0$, $[Tris]_s = [Tris]_r = 0.05$ mol/l, $pH_s = pH_r = 8.5$, $[Carrier]_0 = 0.1$ mol/l, $[BPh_4^-]_0 = 0.001$ mol/l.

It is possible to use the carrier VII to prepare electrodes useful for determination of primary amine drugs. For example, the linear potentiometric response of the mexiletine-sensitive electrode based on VII was 4.7×10^{-6} to 0.1 mol/l, and the detection limit was 5.0×10^{-7} mol/l with a slope of 59.0 mV/decade. The electrode was applied to the assay of mexiletine in tablets with satisfactory result. The sample solution of mexiletine were prepared according to the pharmacopoeia method[15] followed by potentiometric analysis after appropriate dilution. Direct potentiometry by calibration curve method gave an average content of 61.9% of mexiletine, with a relative standard deviation of 1.1%. The result was in fair agreement with that obtained by the standard pharmacopoeia method based on nonaqueous titrations[15] (61.3%).

Effects of the structure of crown ethers on the transport function

Four crown ethers (V–VIII), which have the same structure but different *n* values were used as carriers facilitating the transport of the primary amine species through the liquid membranes. Figure 4 shows the comparison of the transport characteristics of the carriers with benzyl amine as a model analyte, which has the typical molecular structure of a primary amine drug. Of the four polyethers V–VIII tested, VII was the best carrier for the transport of primary amine through liquid membrane, as the liquid membrane containing carrier VII exhibited the largest relative flux for benzyl amine. The

following transport rate sequence was found: VII > VIII > VI > V. The sequence of the size of the cavity provided by the carriers is as follows: VIII > VII > VI > V. The largest relative flux was provided by carriers with medium cavity size. It seems that the size of the cavity provided by the ether (host) is important and one would expect larger relative flux for the carrier with a cavity size sterically matching the primary amine molecules (guest) to be transferred. For example, compounds with smaller (V and VI, for instance) and larger (VIII) cavity sizes showed smaller relative flux compared with the carriers of medium size cavity (VII).

The selectivity of crown ether VII for primary amine with respect to the other organic or inorganic species

The relative flux of tested ions facilitated by carrier VII was determined (Fig. 5). The following transport rate sequence was found: benzyl amine > ethyl amine > tetramethyl ammonium > triethyl amine > diethyl amine > K^+ > ammonium > Na^+ > Ca^{2+} > Mg^{2+}. This sequence agrees well with the selectivity order of the corresponding species obtained by potentiometric method (Table 2). The crown ether VII showed high selectivity for primary amine over the secondary and tertiary amines and quaternary ammonium ions. This benefit was discussed as in the previous section.

The mechanism of transport of primary amine species through a liquid membrane containing crown ether VII

In analogy to the model described by Caracciolo *et al.*,[16] an equation for the total flux of protonated benzyl amine can be written as follows:

$$J_{NH^+} = \frac{DK}{l}(a_{NH^+,s}a_{x^-,s} - a_{NH^+,r}a_{X^-,r}) \quad (1)$$

where J_{NH^+} and D are the flux of protonated benzyl amine species (mol/cm²sec) and the diffusion coefficient of these species (cm²/sec) respectively, and l is the apparent thickness of the membrane(organic) phase(cm) which is kept constant during all experiments; K is a constant related with the concentration of carrier in the membrane phase and the stability of the complex formed by the protonated benzyl amine and the carrier ether. The a_{NH^+} and a_{X^-} are the concentrations (activities) of protonated benzyl amine NH^+ and the counter anion X^- at the surface of the membrane phase, respectively. The subscripts s and r refer to the surface of membrane phase contacting the source and receiving phases, respectively.

When there is no additive agent such as BPh_4^- in the membrane phase, chloride ions in aqueous phase can freely permeate into the membrane (organic) phase, the counter anion species X^- in the membrane phase are Cl^- ions:

$$a_{X^-} = k_{Cl^-}[Cl^-]$$

$$a_{NH^+} = k_{NH^+}[NH^+]$$

One can write from equation (1):

$$J_{NH^+} = \frac{DK}{l}k_{NH^+}k_{Cl^-}([NH^+]_s[Cl^-]_s - [NH^+]_r[Cl^-]_r) \quad (2)$$

where k_{NH^+} and k_{Cl^-} are the partition coefficients of the protonated benzyl amine and chloride, respectively, between the aqueous and organic

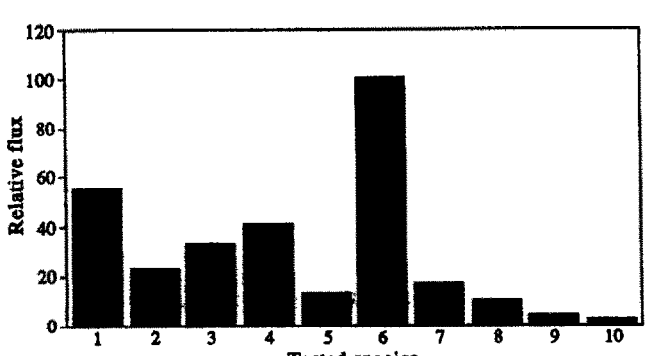

Fig. 5. Transport for different species with carrier VII. 1. Ethylamine. 2. Diethylamine. 3. Triethylamine. 4. Tetramethylammonium. 5. Ammonium. 6. Benzylamine. 7. K^+. 8. Na^+. 9. Ca^{2+}. 10. Mg^{2+}. [Tested species]$_s$ = 0.15 mol/l, $[Cl^-]_s$ = 0.15 mol/l, [Tested species]$_r$ = 0, $[Cl^-]_r$ = 0, $[Tris]_s = [Tris]_r$ = 0.05 mol/l, $pH_s = pH_r$ = 8.5, $[VII]_0$ = 0.1 mol/l, $[BPh_4^-]_0$ = 0.001 mol/l.

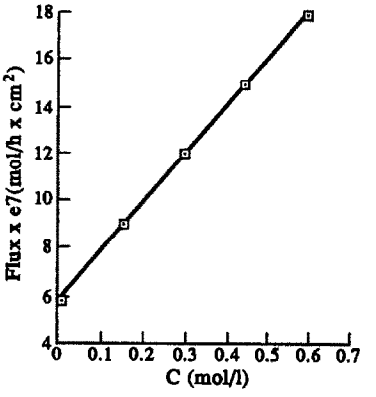

Fig. 6. Effect of the benzylamine concentration. $[Cl^-]_s = 0.15$ mol/l, $[N]_r = 0$, $[Cl^-]_r = 0$, $[Tris]_s = [Tris]_r = 0.05$ mol/l, $pH_s = pH_r = 8.5$, $[VII]_0 = 0.1$ mol/l, $[BPh_4^-]_0 = 0.001$ mol/l.

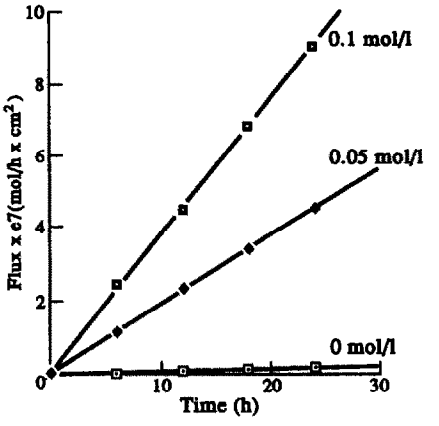

Fig. 7. Effect of carrier concentration in the membrane phase on the flux. $[N]_s = 0.15$ mol/l, $[Cl^-]_s = 0.15$ mol/l, $[N]_r = 0$, $[Cl^-]_r = 0$, $[Tris]_s = [Tris]_r = 0.05$ mol/l, $pH_s = pH_r = 8.5$, $[BPh_4^-]_0 = 0.001$ mol/l.

phase. $[NH^+]$ and $[Cl^-]$ are concentrations of the protonated benzyl amine and chloride in aqueous (source or receiving) phase, respectively.

When an additive ion such as BPh_4^- (R^-) is present in the membrane phase, preventing the transfer of anions such as chloride from aqueous phase into the membrane phase,[17] the counter anion species in the membrane phase are R^-, $a_{X^-} = a_{R^-}$, equation (1) becomes:

$$J_{NH^+} = \frac{DK}{l} k_{NH^+}([NH^+]_s a_{R_s^-} - [NH^+]_r a_{R_r^-}) \quad (3)$$

The concentration of BPh_4^- in the membrane phase is assumed to be uniform, *i.e.*, $a_{R^-s} = a_{R^-r} = a_{R^-}$, equation (3) can be rewritten as follows:

$$J_{NH^+} = \frac{DK}{l} k_{NH^+}([NH^+]_s - [NH^+]_r)a_{R^-} \quad (4)$$

At a fixed pH, the concentration of protonated benzyl amine(NH^+) is given by the following equation:

$$[NH^+] = \frac{[N][H^+]}{k_a} = k[N] \quad (5)$$

where [N] is the concentration of neutral benzyl amine in aqueous phase and k is a constant. Substituting equation (5) into (4), one obtains the total flux of protonated benzyl ammonium ion:

$$J_{NH^+} = \frac{DK}{l} k_{NH} k([N]_s - [N]_r)a_{R^-} \quad (6)$$

Considering equation (5), one obtains:

$$J_{NH^+} = \frac{DK'}{l}\left(\frac{[NH^+]_s}{[H^+]_s} - \frac{[NH^+]_r}{[H^+]_r}\right)a_{R^-} \quad (7)$$

where $K' = k_{NH^+} k k_a K$.

Equations (2)–(7) lead to the following conclusions:

(1) When there is no benzyl amine in the receiving phase, that is, $[NH^+]_r = 0$, the protonated benzyl amine flux should be proportional to the product $[NH^+]_s[X^-]_s$. When the counter anion concentration is fixed (say, at 1.0×10^{-2} mol/l), the flux should be linearly proportional to the protonated benzyl amine concentration $[NH^+]_s$. This conclusion was verified experimentally as shown in Fig. 6.

(2) The benzyl amine flux should increase linearly with increase in the amount of

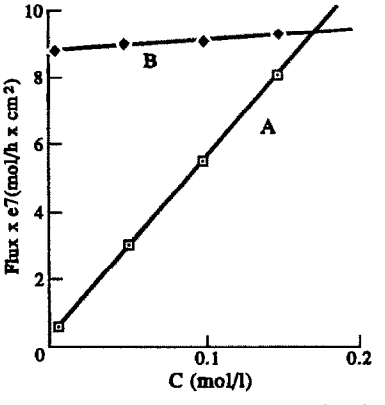

Fig. 8. Effect of counter anion concentration in aqueous phase on the flux. $[N]_s = 0.15$ mol/l, $[N]_r = 0$, $[Cl^-]_r = 0$, $[Tris]_s = [Tris]_r = 0.05$ mol/l, $pH_s = pH_r = 8.5$, $[VII]_0 = 0.1$ mol/l; A: $[BPh_4^-]_0 = 0$ B: $[BPh_4^-]_0 = 0.001$ mol/l.

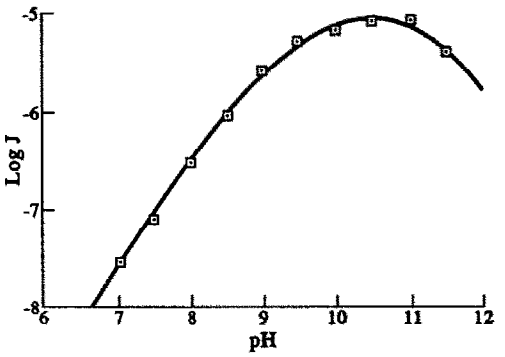

Fig. 9. Effect of pH of the source phase on the flux. $[N]_s = 0.15$ mol/l, $[Cl^-]_s = 0.15$ mol/l, $[N]_r = 0$, $[Cl^-]_r = 0$, $[Tris]_s = [Tris]_r = 0.05$ mol/l, $pH_r = 8.5$, $[VII]_0 = 0.1$ mol/l, $[BPh_4^-]_0 = 0.001$ mol/l.

carrier in the membrane phase. This was experimentally confirmed as shown in Fig. 7.

(3) When there is no additive species such as BPh_4^- (R^-) in the membrane phase, the counter anion concentration $[X^-]$ in the aqueous phases affects the benzyl amine flux. The addition of BPh_4^- could eliminate the effect of the anions in the aqueous phases on the benzyl amine flux. This was experimentally tested in Fig. 8.

(4) The pH affects the benzyl amine flux. Increasing pH value of source phase, the benzyl amine flux first increase and then decrease (Fig. 9). First, hydrogen ion may react with the polyether carrier molecules through the oxygen and nitrogen atoms, at lower pH values, a large number of hydrogen ions seep into the organic phase from the aqueous phase and react with the polyether host molecules. Increasing pH value of the source phase, the content of neutral polyether carrier molecules increase, therefore the benzyl amine flux increases. On the other hand, there is a protonation equilibrium of amine species:

$$R - NH_2 + H^+ = R - NH_3^+$$

the change of pH shifts the protonation equilibrium of amine species. At higher pH values, for example, $pH > 9.5$, the protonated ammonium ions are transformed into the neutral amine form that is not transported by the polyether host, there the benzylammonium flux decreases.

(5) The experimental results above indicated the benzylammonium ion was transported in the organic phase containing polyether host as ion-pairs.

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