Amine Mixture Separation Assisted by Macrocyclic Ligands

ELENA RUSE, ANA MARIA JOSCEANU, ELEONORA CERBU⋆ and
CONSTANTIN LUCA
*Department of Analytical Chemistry, University "Politehnica" Bucharest, 1–5 Polizu Street,
Bucharest, Romania*

Abstract. Liquid-liquid extraction and liquid membrane transport were used to separate mixtures of aliphatic and aromatic amines. Experiments showed that it is possible to discriminate between the aliphatic and aromatic amines of a given mixture. Selectivity is a result of a well-chosen aqueous pH in the biphasic system, or a suitable pH gradient in the membrane system. Results suggest that the macrocyclic ligand (18C6, DB18C6, or DCH18C6) associates with the substrate at the source phase-membrane interface, forming an aggregate of relatively low stability, that has a positive effect when transporting aniline, dibutylamine, and cyclohexylamine. Liquid-liquid extraction is very little affected by the presence of these classical compounds.

Key words: amine mixture separation, transport of aliphatic and aromatic amines

1. Introduction

Employing macrocyclic ligands is a relatively recent approach for separating neutral molecules. The complexes formed between neutral substrates and macrocyclic ligands are less stable than those formed by the same ligands with positively charged species. The interaction between the macrocyclic hosts and their neutral guests consists mainly of dipole-dipole attractions, hydrogen or hydrophobic bonding. There is extended experimental evidence for these types of interactions [1–4]. Alteration of the classical structure of the macrocyclic ring has a positive effect on the stability of complexes formed. It was noticed that aromatic rings attached to the macrocyclic core are likely to take part in π-π stacking in the presence of a suitable aromatic guest [5, 6], while cyclohexyl substituents increase the donating ability of the neighbouring macrocyclic oxygen atoms [5].

In spite of the relatively low stability of the neutral complexes, they have been involved in transport experiments through liquid membranes assisted by macrocyclic carriers. Reinhoudt and his research group reported separation yields of 90% and larger for urea and related derivatives by employing supported liquid membranes and metallomacrocyclic carriers [7].

⋆ Author for correspondence. Chemical Analysis Laboratory, ICECHIM, Bucharest, Romania.

Izatt and his group investigated the interaction between alkylammonium cations and specific macrocyclic ligands, as well as the factors that rule their transport rates through bulk liquid membranes [8–9]. Their impressive results are based on the formation of rather stable complexes between the carrier and the cationic substrate (log K values between 3.5 and 5).

The encouraging results obtained by Reinhoudt in transporting urea and the increasing interest in separation techniques that do not involve charged species prompted the idea of designing a membrane system that will allow the translocation of simple, neutral amines. This study reports the transport of aliphatic and aromatic amines through a bulk chloroform membrane, between a basic aqueous source phase and an acidic receiving phase, in the presence of 18-crown-6 (18C6), dibenzo-18-crown-6 (DB18C6), and dicyclohexyl-18-crown-6 (DCH18C6). Extraction studies were also carried out to determine the nature of the species that are likely to cross the interface. Mixtures consisting of aliphatic and aromatic amines were separated both by liquid-liquid extraction and by a liquid membrane. The importance of the pH gradient and of the macrocyclic carrier were investigated.

2. Experimental

Analytical grade chloroform was distilled, saturated with distilled water, and stocked in dark bottles to be used later in liquid-liquid extraction and transport experiments.
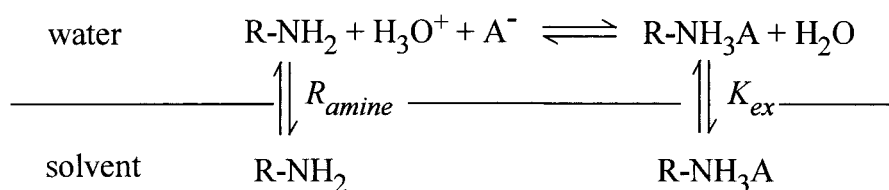
Reagent grade 18C6, DB18C6, DCH18C6 were obtained from Merck and used without further purification. Solutions of macrocyclic polyethers were prepared in water saturated chloroform. All crown ether solutions were 0.01 mol dm^{-3}.

Analytical grade HCl, LiOH, LiH$_2$PO$_4$ and Li$_2$HPO$_4$ were used to vary the pH between 2 and 12, or to prepare different buffers.

All amines employed were analytical grade (Fluka) and used without further purification.

pH was measured with a combined glass/calomel electrode, using a Radiometer PM64 pH-meter. Calibration was performed before each study using standard buffered solutions of pH 4.00 ± 0.02 , 7.00 ± 0.02, and 9.20 ± 0.02.

Liquid-liquid extraction experiments were carried out in the 2–12 pH range. Increasing amounts of an aqueous solution of amine (typically 4 or 8 $\times$ 10^{-3} mol dm^{-3}) in 0.01 mol dm^{-3} LiOH were added to a solution containing the same amine (4 or 8 $\times$ 10^{-3} mol dm^{-3}) in 0.01 mol dm^{-3} HCl and extracted with an equal volume of chloroform or crown ether solution in chloroform. After 15 minutes of vigorous stirring, the two phases were allowed to settle for 5–10 minutes and separated. The content of amines was determined in both phases by gas-chromatography, using either a Perkin–Elmer or a Carlo Erba (model Fractovap 2450) instrument with FID detection. Experimental extraction data were transferred to a 586 PC for analysis with a non-linear least-squares routine.

$$\text{water} \quad \text{R-NH}_2 + \text{H}_3\text{O}^+ + \text{A}^- \rightleftharpoons \text{R-NH}_3\text{A} + \text{H}_2\text{O}$$

$$\Updownarrow R_{amine} \qquad\qquad \Updownarrow K_{ex}$$

$$\text{solvent} \quad \text{R-NH}_2 \qquad\qquad\qquad \text{R-NH}_3\text{A}$$

Scheme 1.

Transport experiments used a cell described in the literature [10]. The source phase (20 cm^3) consisted of an aqueous solution of amine or amine mixtures, 4.3×10^{-3} mol dm^{-3}, while the receiving phase (7 cm^3) was a HCl solution, 10^{-2} mol dm^{-3}. They were separated by the membrane (50 cm^3), consisting of 0.01 mol dm^{-3} crown ether solution in chloroform. All three phases were stirred at 180 r.p.m using a synchronous motor. Each experiment was repeated three times in a room thermostated at 25 ± 1 °C. A few ml of each phase were withdrawn by syringe at the end of 4 hours and analyzed chromatographically for the amine content.

3. Results and discussion

According to Scheme 1, transferring an amine from an aqueous solution into an organic solvent involves several processes that occur simultaneously.

The equilibrium constants associated with each equilibrium can be defined as:

— the repartion constant of the amine in the biphasic system,

$$R_{\text{amine}} = \frac{[\text{R} - \text{NH}_2]_s}{[\text{R} - \text{NH}_2]_w}$$

the acidity constant of the amine,

$$K_a = \frac{[\text{R} - \text{NH}_2][\text{H}_3\text{O}^+]}{[\text{R} - \text{NH}_3^+]}$$

the extraction constant of the ionic pair,

$$K_{\text{ex}} = \frac{[\text{R} - \text{NH}_3\text{A}]_s}{[\text{R} - \text{NH}_3^+]_w[\text{A}^-]_w}$$

where the subscripts w and s define aqueous and organic phase respectively. The global extraction process is quantitatively described by the distribution ratio, r, defined as:

$$r = \frac{[R - NH_2]_{t,s}}{[R - NH_2]_{t,w}} = \frac{[R - NH_2]_s + [R - NH_3A]_s}{[R - NH_2]_w + [R - NH_3^+]_w} \quad (1)$$

Substitution of R_{amine}, K_a and K_{ex} into (1) gives:

$$r = \frac{R_{amine} + K_{ex}[A^-]_w \times 10^{pK_a - pH}}{1 + 10^{pK_a - pH}}. \quad (2)$$

When a macrocyclic ligand, L, is introduced into the organic phase, the extraction scheme becomes more complicated (Scheme 2), as L can form an association with the amine:

Scheme 2.

characterized by its own association constant,

$$K_{as} = \frac{[R - NH_2L]_s}{[R - NH_2]_s[L]}.$$

In order to accommodate all equilibria considered the distribution ratio is redefined as

$$r = \frac{[R - NH_2]_s + [R - NH_2L]_s + [R - NH_3A]_s}{[R - NH_2]_w + [R - NH_3^+]_w} \quad (3)$$

After substitution, the final expression of r is given in Equation (4):

$$r = \frac{R_{amine}(1 + K_{as}[L]_s) + K_{ex}[A^-]_w \times 10^{pK_a - pH}}{1 + 10^{pK_a - pK}}. \quad (4)$$

The experimental values of the distributions ratios obtained in the $2 - 11$ pH range were fitted to Equation (2) using a non-linear least-squares routine to give the curves similar to that shown in Figure 1. The calculated pK_a, R_{amine} and K_{ex} values are presented in Table I.

The pK_a values determined in the biphasic system differ from the values reported in the literature [10]. Considering that most of the reported acidity constants
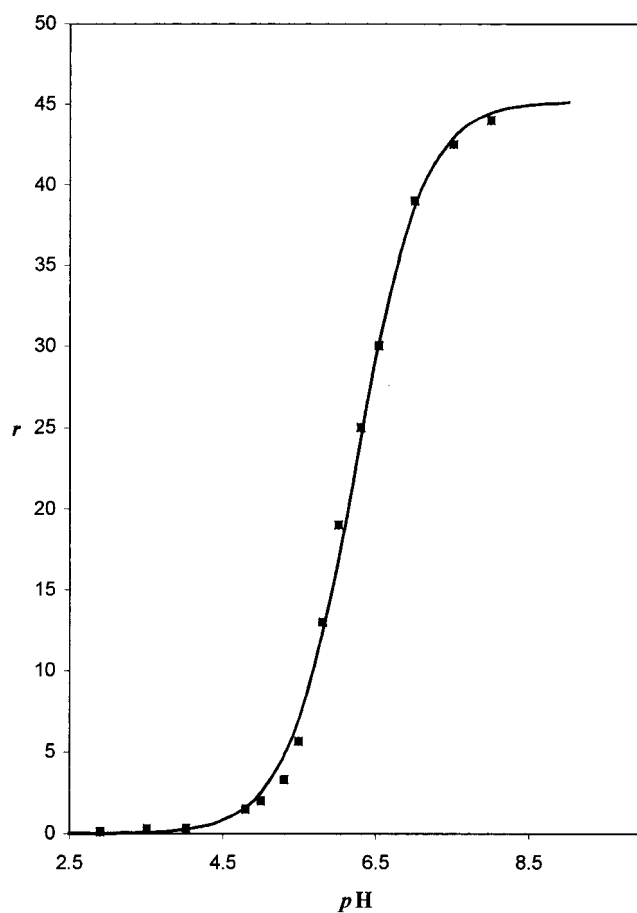
Figure 1. Extraction curve for aniline, 8.4×10^{-3} mol dm^{-3}, in chloroform at $\mu = 10^{-2}$ mol dm^{-2} and 25 °C, fitted to Equation (2).

Table I. Extraction parameters for the extraction of aromatic and aliphatic amines in a water-chloroform system at 25 °C, $\mu = 0.01$ mol dm^{-3}.

Amine	pK_a	R_{amine}	$10^2 \times K_{ex}[A^-]_w$	pK_a*
Aniline	6.23 ± 0.03	45.2 ± 0.9	1.07 ± 1.35	4.6
o-Toluidine	6.37 ± 0.02	12.2 ± 1.14	2.9 ± 3.9	4.45
p-Toluidine	6.44 ± 0.14	1.8 ± 0.11	1.8 ± 0.6	5.1
Dimethylaniline	4.75 ± 0.08	2.40 ± 0.04	12.0 ± 0.4	5.1
Dibutylamine	12.91 ± 0.12	252 ± 57	0.24 ± 0.4	11.25
Cyclohexylamine	10.42 ± 0.03	4.83 ± 0.08	1.29 ± 1.5	10.6
Morpholine	10.92 ± 0.17	2.56 ± 0.37	1.73 ± 4.5	8.33
Diethylamine	12.74 ± 0.36	0.56 ± 0.01	10 ± 15	11.1

* Literature values in [11].

Table II. Percentage of amines in the two phases of a water-chloroform system at different pH values, at 25 °C and $\mu = 10^{-2}$ mol dm^{-3}.

Mixture	pH	Aqueous phase composition % amine A +% amine B	Organic phase composition % amine A +% amine B
Aniline (A)	8.21	0 + 100	100 + 0
Morpholine (B)	9.00	0 + 87.5	100 + 12
	11.08	0 + 73.5	100 + 26.4
Aniline (A)	8.20	0 + 90	100 + 10
Dibutylamine (B)	9.27	0 + 77	100 + 22.8
	10.89	0 + 37.5	100 + 61.9

were determined in homogeneous systems, under experimental conditions that differ from the present study, the lack of agreement is not a major problem.

The $K_{ex}[A^-]_w$ values show a consistent and important lack of accuracy. The chloride ion is well-known for its high free energy of hydration, so that ionic pairs formed are not particularly extractable. When the contribution of the ionic pairs to the overall process is neglected, the fit between the theoretical and experimental extraction curve is as good as that shown in Figure 1.

Using the pK_a values obtained from extraction of single amines, it is possible to optimize the experimental conditions so that certain amines are separated from mixtures. The pH of the amine mixture should be chosen so that it ensures the presence of one amine as protonated species, the second being mainly in its unprotonated form. If the two amines have pK_a values that differ by more than 4 units, then separation is achieved. The extraction data in Table II show that aniline can be separated from morpholine or dibutylamine when the pH of the aqueous solution is slightly basic. Any further increase in pH moves both amines into the organic phase.

The extraction of single amines with a chloroform solution of DB18C6 is also a *p*H dependent process in the $2 - 11$ pH range. The experimental data were fitted to Equation (4) using a non-linear least squares routine, to give curves similar to that shown in Figure 2. The complete results of this analysis are collected in Table III.

The presence of DB18C6 did not alter significantly the distribution ratio of any of the amines studied. In spite of the presence of the aromatic rings attached both to the guest and the substrate, the association between the macrocycle and the amine is relatively weak, all calculated K_{as} values being less than 100. This indicates a very weak interaction, as expected when dealing with neutral molecules and a classical crown ether.

Transport experiments were carried out under a severe pH gradient between the source and the receiving phase. The composition of each phase after the transport experiments is presented in Table IV. The best transport results were recorded when
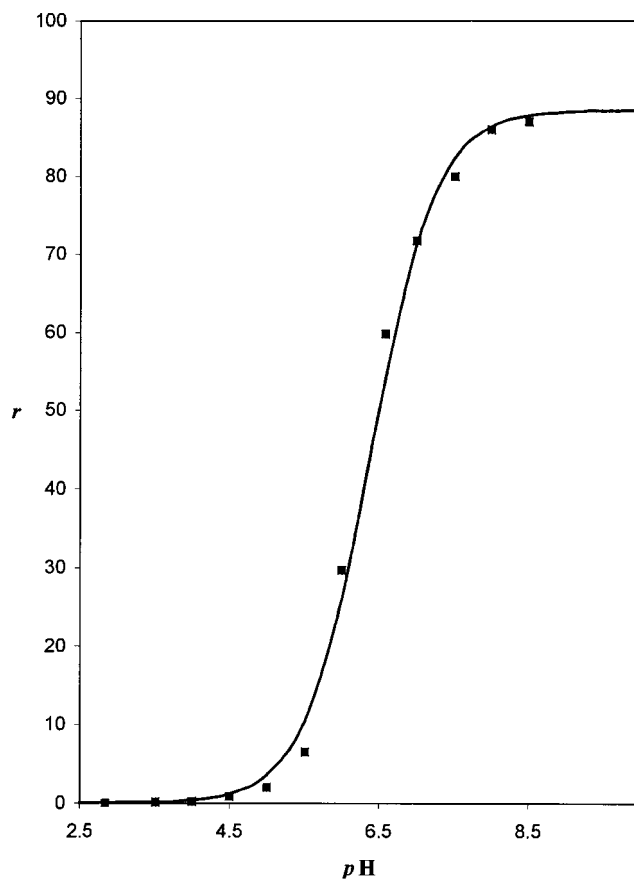
Figure 2. Extraction curve for aniline, 8.4×10^{-3} mol dm^{-3}, with DB18C6, 10^{-2} mol dm^{-3}, in chloroform at $\mu = 10^{-2}$ mol dm^{-3} and 25 °C, fitted to Equation (4).

Table III. Extraction parameters for the extraction of aromatic and aliphatic amines in a water-chloroform system with DB18C6, 10^{-2} mol dm^{-3}, at 25 °C, $\mu = 0.01$ mol dm^{-3}.

Amine	pK$_a$	R_{amine}	K_{as}/dm^3 mol^{-1}	K_{ex}/dm^6 mol^{-2}
Aniline	6.38 ± 0.03	43.5 ± 0.6	103.4 ± 2.9	6.1 ± 8.3
o-Toluidine	6.30 ± 0.02	11.8 ± 1.3	46.5 ± 0.8	5 ± 8
p-Toluidine	6.64 ± 0.02	1.4 ± 0.01	28.8 ± 0.9	20.8 ± 10
Dimethylaniline	4.81 ± 0.10	2.5 ± 0.1	76.1 ± 0.9	12.0 ± 0.4
Morpholine	10.99 ± 0.25	2.6 ± 0.3	35.3 ± 1.0	1.73 ± 4.5

Table IV. Amine distribution in the membrane system at the end of the transport experiment and the calculated transport yields.

Amine	Ligand, 10^{-2} M in CHCl$_3$	Amine molar fraction after transport			Transport yield (%)
		Source pH > 8	Membrane	Receiving pH = 2	
Aniline	–	0.17	0.19	0.64	63.5
	18C6	0.15	0.22	0.63	62.3
	DCH18C6	0	0.15	0.85	85
	DB18C6	0	0.42	0.58	58
o-Toluidine	–	0.04	0.73	0.23	23.1
	18C6	0.03	0.74	0.23	22.8
	DCH18C6	0.01	0.75	0.23	23.2
	DB18C6	0.1	0.60	04	40
p-Toluidine	–	0.25	0.46	0.28	28.3
	18C6	0.21	0.49	03	30
	DCH18C6	0.26	0.43	0.32	31.5
	DB18C6	0.22	0.53	0.25	25.4
m-Toluidine	–	0.5	0.15	0.35	35
	18C6	0.33	0.30	0.36	36
	DCH18C6	0.39	0.21	0.39	39.4
	DB18C6	0.35	0.30	0.34	34.1
Dimethylaniline	–	0.56	0.30	0.14	14
	18C6	0.58	0.28	0.14	13.8
	DCH18C6	0.5	0.33	0.17	17
	DB18C6	0.48	0.39	0.13	13.4
Dibutylamine	–	0.23	0.006	0.764	77.1
	18C6	0.18	0.05	0.76	76
	DCH18C6	0.10	0	91.9	92
	DB18C6	0.35	0	0.64	64
Cyclohexylamine	–	0.29	0.002	0.698	69.8
	18C6	0.25	0.05	0.70	70
	DCH18C6	0	0.02	0.98	98.1
	DB18C6	0.23	0.11	0.70	70

employing DCH18C6 in the membrane phase. Experiments run with DB18C6 in the membrane show that the amine tends to accumulate in the chloroform phase and gives slightly lower transport yields. This behaviour suggests that both macrocycles are likely to form an association with the receiving phase. It is very likely that association might orientate the amine in a position favorable for the hydronium ion attack at the membrane-receiving phase interface. This might also be true when

translocating aniline or dibutylamine, for which the transport yields are 85% and 92% respectively.

Attempts to separate a mixture of aniline and morpholine using a liquid membrane showed a the amine, that favors the transfer of the amine in the organic solvent, as supported by the results of the extraction experiments (see Table II). The associations with DCH18C6 seem less stable than those with DB18C6, as π-π stackings are possible only in the case of aromatic amines and the latter ligand.

The yield for the transport of cyclohexylamine with DCH18C6 is remarkably high at 98.1%. Thus, if there is any association between the carrier and substrate, then it also assists the release of achieving substrate in the transport yield of 93% for the first amine, and 8% for the second amine. Addition of a carrier, DCH18C6, did not bring about a significant improvement of this result, the values, 94% for aniline and 6% for morpholine, lying within the experimental error.

4. Conclusions

The extraction experiments showed that in the presence of Cl$^-$ ion the amines are extracted in chloroform only as neutral species. The contribution of ion pairs is negligible. Significantly addition of classical macrocycles does not improve the distribution ratio of the studied amines, but reveals that there is some association taking place between the ligand and the translocated amine. Separation of mixtures is achievable, but discrimination is mainly the effect of the aqueous phase pH and is not connected with a selective association of the amines with the macrocyclic compound.

The liquid membrane system can achieve reasonably good transport yields, mainly with the aid of DCH18C6 carrier. The part played by the pH gradient is more important than that of the carriers considered, even when transporting single substrates. This is connected to the reduced selectivity of the hosts investigated towards the amine substrates.

References

1. H. J. Buschmann and L. Mutihac: *Roum. Chem. Quarter. Reviews* **3**, 39 (1995).
2. M. Zinie and V. J. Skaric: *J. Org. Chem.* **53**, 2582 (1988).
3. S. A. Bryanm, R. R. Willis, and B. A. Moyer: *J. Phys. Chem.* **94**, 5230 (1990).
4. C. J. van Staveren, V. M. J. J. Aarts, P. D. J. Grootenhens, and D. N. J. Reinhoudt: *J. Am. Chem. Soc.* **110**, 8134 (1988).
5. S. R. Salman and S. M. Al-Marsumi: *Spectrochim. Acta* **49A**, 435 (1988) and Supplementary publication 13056.
6. I. F. Tsymbal, I. E. Boldeskul, V. L. Kalchenko, L. I. Atames, and N. A. Parkhomenko: *Ukr. Khim. Zh.* (Russ Ed.) **58**, 902 (1992).
7. W. F. Njenhuis, A. R. van Doorn, A. M. Reichwein, F. de Vong, and D. N. Reinhoudt: *J. Am. Chem. Soc.* **113**, 2367 (1991).
8. C. Y. Zhu, R. M. Izatt, T. M. Wang, P. Huszthy, and J. S. Bradshaw: *Pure Appl. Chem.* **63**, 275 (1992).

9. C. Y. Zhu, J. J. Bradshaw, J. L. Oscarson, and R. M. Izatt: *J. Incl. Phenom.* **12**, 275 (1992).
10. L. Mutihac, R. Mutihac, T. Constantinescu, and C. Luca: *J. Incl. Phenom.* **17**, 45 (1994).
11. The Chemical Society, *Stability Constants of Metal Ion Complexes*, Burlington House, London, special publications 17 and 25.