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# Stability Constants for 18-Crown-6–Alkylammonium Ion Complexes

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**A new method of determining the stability constants for aqueous crown polyether–alkylammonium ion complexes is presented. The stability constants (log $K$) obtained are 1.22 for $NH_4^+$, 0.99 for $EtNH_3^+$, 0.87 for $Et_2NH_2^+$, 0.74 for $Et_3NH^+$, 1.13 for $MeNH_3^+$, and 0.94 for $n$-$BuNH_3^+$. While these values are qualitatively similar to those determined in organic solvents, interesting quantitative differences are observed. Specific H bonding between the crown ethers and the alkylammonium ions appears to be much less important in water than in less polar solvents.**

## Introduction

The synthesis of macrocyclic polyethers and the discovery of their ability to complex with alkali metal ions and primary ammonium ions[1] have led to a number of unique uses of compounds.[1-5] In addition, the similarity of these compounds to cyclic antibiotics and biological transport agents makes them important model compounds for the study of the effect of molecular on membrane permeability.[6-9] The ammonium moiety is an important constituent of many biologically important compounds. While the role played by these groups in membrane transport is largely unknown, the transport of organic ammonium ions is known to be affected by cyclic antibiotics[10] and organic ammonium ions are known to have important effects on the transport of other ions across biological membranes.[11]

Measurements of the aqueous stability constant sequence between dicyclohexano-18-crown-6 and alkali metal ions[12] was found to be identical with the membrane permeability sequence of this system. This work was undertaken to determine similar data for a series of alkylammonium ions in order to provide reference data relevant to their action in membrane transport.

Although qualitative data on the complexing of alkylammonium ions with macrocyclic polyethers were reported along with their original synthesis,[1] no quantitative data have been available until recently. Since the completion of this work, values have been reported between 11 alkylammonium ions and 18-crown-6 in methanol.[8] The work reported here is the first for an aqueous system and the results indicate that the solvent effects are both large and specific.

The aqueous stability constants are small and the methods applied to determine the alkali metal ion stability constants (specific ion electrodes[13] and calorimetric titration[12]) are either not available or not sensitive enough. A modified potentiometric method using a glass electrode (specific $H^+$ electrode) is described here that should be generally applicable to measuring the stability constants of macrocyclic polyethers with acidic cations.

## Experimental Section

Vacuum desiccation for 2 h of the 18-crown-6 (Aldrich Chemical Co., mp 26 °C) resulted in a material that gave a melting point of 35.5–38 °C (lit. 37 °C). The purity of this material was checked by GC–mass spectrometry, pH titrations, and conductance and found to be greater than 98% pure with no detectable acidic, basic, or ionic impurities. The ethylamine, diethylamine, and $n$-butylamine (Fisher Scientific Co., certified purity) were used without further purification. Triethylamine was vacuum distilled from a KOH solution. Concentrated solutions of ammonia and methylamine were prepared from 29% reagent grade ammonia and 40% reagent grade methylamine and were analyzed by titration with a standardized HCl solution.

Approximately 0.015 mol of the amines was weighed out and titrated to half the equivalence point with HCl and diluted to 250 mL. A 50-mL sample of this solution was then pipetted into a jacketed beaker. This beaker was covered with a Plexiglas cap that could be tightly attached to a Plexiglas lid that was glued to the lid. Four holes drilled in the lid allowed insertion of a thermometer, a glass electrode, a reference electrode, and a breaker rod. The temperature inside the beaker was controlled to ±0.1 °C by circulating water from a Haake constant-temperature bath through the jacketed beaker. Thin glass bulbs of 5–15 mL capacity contained accurately weighed samples of about 0.5 g of 18-crown-6. These bulbs could be broken on the bottom of the beaker by pushing on the breaker rod to introduce the 18-crown-6 into the solution. The pH of the solution before and after breaking the bulb was measured with a Corning Model 12 research pH meter that could be read to ±0.002 pH units. The calibration of the pH meter and electrodes were checked against commercial buffer solutions of pH 4.00, pH 7.00, pH 9.00, and a saturated solution of CaO (pH 12.45). These gave pHs that agreed to ±0.02 pH units.

## Results and Calculations

If 18-crown-6 complexes with protonated amines, introduction of the crown ether into a solution of the amine and its conjugate acid should shift the acid dissociation reaction (eq 1) to the left.

$$BH^+(aq) = B(aq) + H^+(aq) \tag{1}$$

The resulting increase in the pH of the solution could then be used to calculate the stability constant for the association of 18-crown-6 with the protonated amine (eq 2). Exact solution

$$BH^+(aq) + C(aq) = CBH^+(aq) \tag{2}$$

of this problem must also take into account the self-ionization of water (eq 3). The equilibrium equations may then be written

$$H_2O(l) = H^+(aq) + OH^-(aq) \tag{3}$$

as

$$K_1 = K_a = \frac{(B)(H^+)\gamma_\pm}{(BH^+)\gamma_\pm} \tag{4}$$

$$K_2 = K = \frac{(CBH^+)\gamma_\pm}{(BH^+)(C)\gamma_\pm} \tag{5}$$

$$K_3 = K_w = (H^+)(OH^-)\gamma_\pm \tag{6}$$

where $\gamma_\pm$ is calculated by the extended Debye–Hückel equation[11]

$$\log \gamma_\pm = \frac{0.5085\sqrt{I}}{1 + \sqrt{I}}$$

The mass balance equations may be written (eq 7–9) where

$$C_1 = (BH^+) + (CBH^+) + (H^+) \tag{7}$$

$$C_2 = (B) + (BH^+) + (CBH^+) \tag{8}$$

$$C_3 = (C) + (CBH^+) \tag{9}$$

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Table I. Aqueous Stability Constants for Alkylammonium Ion-18-Crown-6 Complexes at 25 °C

| ion | runs | av $C_1$ | av $C_2$ | av $C_3$ | pH | av $K$ | log $K$ |
|---|---|---|---|---|---|---|---|
| $NH_4^+$ | 6 | 0.0296 | 0.0588 | 0.0382 | 0.166 | 17.0 | 1.22 ± 0.08 |
| $EtNH_3^+$ | 5 | 0.0298 | 0.0596 | 0.0395 | 0.100 | 9.7 | 0.99 ± 0.05 |
| $Et_2NH_2^+$ | 4 | 0.0302 | 0.0604 | 0.0370 | 0.084 | 7.4 | 0.87 ± 0.16 |
| $Et_3NH^+$ | 4 | 0.0297 | 0.0601 | 0.0384 | 0.077 | 5.5 | 0.74 ± 0.15 |
| $MeNH_3^+$ | 4 | 0.0300 | 0.050R | 0.0410 | 0.130 | 13.0 | 1.13 ± 0.03 |
| *n*-$BuNH_3^+$ | 4 | 0.0300 | 0.0564 | 0.0528 | 0.153 | 8.7 | 0.94 ± 0.05 |

$C_1$, $C_2$, and $C_3$ are the stiochiometric concentrations of HCl, parent base, and the 18-crown-6, respectively. In addition, the charge balance equation may be written as

$$(OH^-) + (Cl^-) = (H^+) + (BH^+) + (CBH^+) \qquad (10)$$

The eight unknowns in these equations can be solved from the $H^+$ concentrations before and after introduction of the 18-crown-6 into the solution. These values can be calculated from the measured pH values by the equation

$$(H^+) = \exp(-pH)/\gamma_\pm \qquad (11)$$

The values of $K$ reported in this paper were calculated by machine assisted solution of these equations. At the low $H^+$ concentrations of these experiments, even a very large stability constant for a hydronium ion–crown ether complex would have little effect on the calculated stability constants.

If $\gamma$ and $(OH^-)$ are approximated as 1 and 0, respectively, the value of stability constant may be calculated by the approximate eq 12 where $x = 10^{-\Delta pH}$. This equation gives values

$$K = \frac{1 - x}{[C_3 - C_1(1 - x)]x} \qquad (12)$$

that agree to within 2% of the exact solution of eq 4–10.

The results of these measurements and calculations are reported in Table I. Measurements were done on at least two different solution preparations. For each amine the reported uncertainties are the standard deviations of all results and are generally equivalent to an error in ΔpH of about ±0.02 pH units.

The p$K_a$ values of the amines calculated from the initial pH readings agreed to within ±0.03 units of the literature values.[14] The results for the $NH_4$–18-crown-6 interaction may be compared to values of log $K = 1.1 \pm 0.1$ arrived at from potentiometric measurements with a specific $NH_4^+$ ion electrode,[13] log $K = 1.44 \pm 0.07$ at 0 °C from freezing point depression measurements[15] and log $K = 1.23$ from calorimetric titration.[16]

## Discussion

Although there has been considerable work on the ability of various macrocyclic polyethers to differentiate between inorganic ions[12] and primary ammonium ion stereoisomers,[17-20] the previous investigations of the effects of alkyl substituents have been a qualitative study of Pederson[1] and the recent quantitative study by Izatt and co-workers.[8] The results of these investigations indicate that the stability constants decrease in the order $NH_4^+$, $RNH_3^+ > R_2NH_2^+ > R_3NH^+$. Pederson found no complexing of either secondary or tertiary ammonium ions with dibenzo-18-crown-6 in methanol. Izatt et al. found a decrease of more than 2 orders in magnitude in the stability constants between primary and secondary ammonium ions with 18-crown-6 in methanol and no measurable complexing with tertiary ammonium ions. These data and the examination of model structures have led to the conclusion that specific hydrogen bonding is responsible for the stability of the primary ammonium ion complexes.

The results presented here confirm the stability constants decrease in the order $NH_4^+ > RNH_3^+ > R_2NH_2^+$ and parallel the permeability of organic ammonium ions across biological membranes.[8,10] In water, however, the decrease is not nearly as large as that observed in methanol. The ratio of the stability constants of primary to secondary ammonium ions is only 1.7:1 in water while in methanol it is 160:1.

Apparently the strength of the hydrogen bond between the ammonium ion and water is of the same order of magnitude as that between the ammonium ion and the crown ether, so that the effect of the number of hydrogen bonds is not as dramatic. In fact the decrease in log $K$ from $NH_4^+$ to $EtNH_3^+$, where the number of hydrogen bonds is not changed, is more than that from $EtNH_3^+$ to $Et_2NH_2^+$, where at least one hydrogen bond would be disrupted.

The small decrease in the stability constant as the alkyl chain increases is the same as the trend observed in methanol.[8]

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