FORMATION CONSTANTS OF THE CHELATES OF 2-HYDROXY-1-NAPHTHALIDENE-ORTHO-BROMOANILINE WITH SOME BIVALENT METAL IONS

No systematic study of the stabilities of 2-hydroxy-1-naphthalidene-ortho-bromoaniline and its metal chelates with bivalent metal ions has been carried out so far. In the present communication the successive stability constants of the complexes of 2-hydroxy-1-naphthalidene-ortho-bromoaniline with some bivalent metal ions have been determined potentiometrically following the Calvin–Bjerrum pH titration technique as adopted by Irving and Rossotti[1].

Experimental

The Corning model 12, a precision research pH meter was used for the pH measurements. The smallest scale division on the expanded scale corresponds to 0·005 pH unit. The ligand 2-hydroxy-1-naphthalidene-ortho-bromoaniline was synthesised and repeatedly crystallised from alcohol (m.p. 150° C. Literature value 150° C)[2].

All the chemicals used were of analytical grade. The medium of titration was a dioxan-water mixture. containing 75% (v/v) of dioxan. Sodium perchlorate was added to maintain a constant ionic strength (0·1 M). The titrations were carried out in nitrogen atmosphere. All the metal perchlorate solutions were standardised complexometrically[3] by E.D.T.A. titrations.

The following solutions were titrated potentiometrically at 25° ± 0·1° against standard carbonate-free sodium hydroxide solution (1·0 M) keeping the total volume at 40 ml.

(I) 5 ml of (0·16 M) $HClO_4$ + 5 ml of (0·64 M) $NaClO_4$ + 30 ml of dioxan.

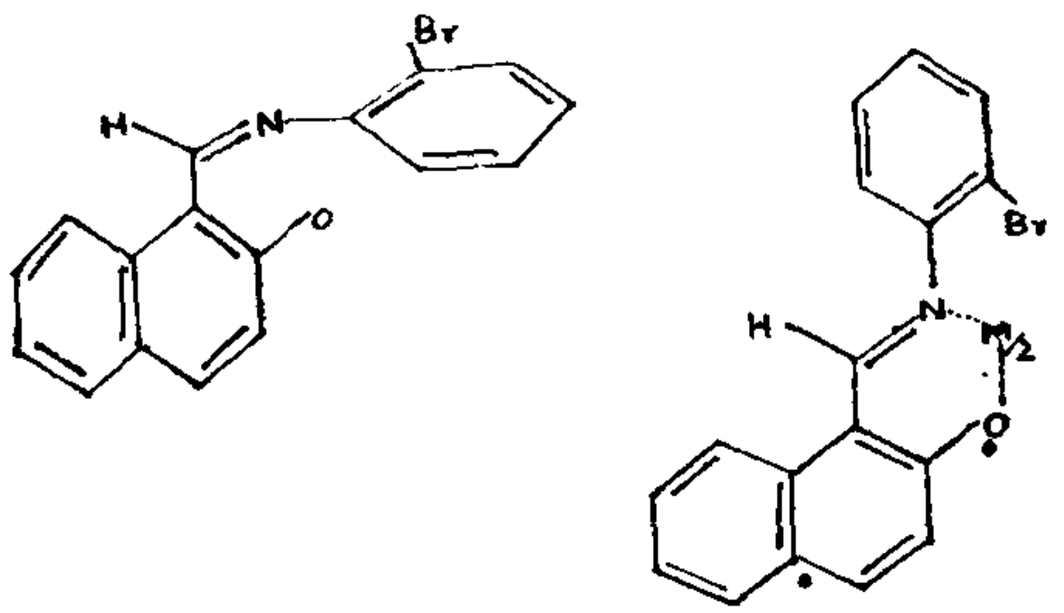
(II) 5 ml of (0·16 M) $HClO_4$ + 5 ml of (0·64 M) $NaClO_4$ + requisite amount of the ligand to give 0·004 M ligand concentration in the final solution + 30 ml of dioxan.

(III) 5 ml of (0·64 M) $NaClO_4$ + 5 ml of (0·008 M) metal salt solution in (0·16 M) $HClO_4$ + requisite amount of the ligand to give 0·004 M ligand concentration in the final solution + 30 ml of dioxan.

The experimental method of Irving and Rossotti[1] was applied to find out the values of $\bar{n}$ and pL. All titrations were performed in duplicate to test the reproducibility.

Results and Discussion

The phenolic 'OH' group in the ligand takes part in the complex formation and the proton is replaced by metal ions during complexation. Since only one proton per ligand molecule is liberated during complexation, 'Y' the number of dissociable protons attached to each ligand molecule is one. The ligand acts as bidentate. The structural formulae of the ligand and metal chelate of the Schiff base are as given below.



From the titration curves using the solutions (I) and (II), the $\bar{n}_a$ values at various 'B' values were calculated, and the curve between 'B' and $\bar{n}_a$ plotted. The formation curve extends over a range $0{\cdot}17 < \bar{n}_a < 0{\cdot}99$ and is wavelike. This indicates the formation of the species HL. The value of pK_1 was determined from the half integral point at $\bar{n}_a = 0{\cdot}5$.

From the plot of log $(\bar{n}_a/1 - \bar{n}_a)$ against 'B' the value of pK_1 was determined. The two values (half-integral and graphical) agree quite well.

From the titration curves of solutions (II) and (III) $\bar{n}$ and pL values were calculated. The $\bar{n}$ values obtained are upto 1·0 and hence only log K_1 values could be determined except in the case of UO_2^{2+} and Cu^{2+} where log K_2 values have also been determined.

The $\bar{n}$ values were plotted against the corresponding pL values and from these formation curves the values of stability constants, log K_1 were computed which correspond to pL values at $\bar{n} \equiv 0{\cdot}5$.

A plot of log $(\bar{n}/1 - \bar{n})$ against pL for the different metal systems gave straight lines from which the values of log K_1 were evaluated. A plot of log $(2 - \bar{n}/\bar{n} - 1)$ was also drawn in the case of UO_2^{2+} and Cu^{2+} and from these curves values of log K_2 were evaluated. The two values of log K_1 and log K_2 (half integral and graphical) agree quite well.

The most representative values are recorded in Table I.

TABLE I

Proton-ligand and mental-ligand stability constants

$t = 25°$ $\mu = 0{\cdot}1$

Cations	H^+	UO_2^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Mg^{2+}
log K_1	9·42	8·80	8·68	5·85	5·40	4·70	3·25
log K_2	..	6·87	5·45	..	..	..	..

H^+, K_1 correspond to the species LH of the ligand while for metal ions K_1 and K_2 correspond to the species ML and ML_2 respectively.

The order of stability of bivalent metal chelates was $UO_2^{2+} > Cu^{2+} > Zn^{2+} > Co^{2+} > Ni^{2+} > Mg^{2+}$.

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PHARMACOLOGICAL STUDIES ON MACROCYCLIC POLYETHER, 15-CROWN-5

IN view of the current interest and importance of macrocyclic polyethers, it is of interest to explore their pharmacological action. Leong *et al.* have shown[1] that rats exposed to the vapours of ethylene oxide tetramer exhibited variable degrees of anoxia, asthenia, testicular atrophy, tremors, convulsions, moribund conditicns and death. Later, the same authors reported that oral administration of the tetramer produced central nervous system (CNS) effects.[2] In this communication we report some of our results on the systematic pharmacological study of one of the crown ethers, 1, 4, 7, 10, 13-pentaoxacyclopentane, abbreviated as 15-crown-5.

The ether 15-crown-5, was prepared by the reaction of diethylene glycol with 1,8-dichloro-3,6-dioxaoctane in presence of NaOH in dioxane.[3] (BP 130°/0·2 Torr). The identification and purity was chekced by ^1H NMR spectrum of this compound. A sharp singlet was observed at 3·66 δ in $CDCl_3$ (TMS standard) which is identical with the reported value.[3] The ether was freely soluble in water. Gross behavioral effects were studied on Swiss albino mice of either sex according to the method described by Turner[4]. When administered at dose levels of 5, 50, 100, 250, 500 and 1 mg/kg. I.P. the crown ether showed profound CNS stimulation at a dose level of 50 mg/kg and above as evidenced by hyperactivity, piloerection and pronounced tremors lasting for 150 to 180 mins. LD_{50} was found to be 850 ± 25 mg/kg in mice. Pretreatment of the animals with atropine sulphate (1 mg/kg; i.p.), trihexyphenidyl HCl (1 mg/kg; i.p.) and cycrimine HCl (1 mg/kg; i.p.), afforded complete protection against the tremorogenic effect of the crown ether (50 mg/kg). Chlorpromazine HCl. (5 mg/kg; i.p.) and diphenhydramine HCl (10 mg/kg; i.p.) conferred only partial protection against the tremors induced by the crown ether (50 mg/kg), in mice and rats. 15-crown-5 at dose levels of 50 and 100 mg/kg; i.p. significantly shortened the duration of pentobarbitone sleeping time in mice While the control animals treated with 0·1 ml of normal saline 30 min. before the administration of pentobarbitone sodium (30 mg/kg; i.p.), slept for (mean–SEM) 69·2 ± 2·5 min. animals pretreated with 15-crown-5, slept only for 35·2 ± 2·6 and 21·3 ± 2 min respectively, giving a reduction of 49·1% ($P > 0·001$) and 69·2% ($P > 0·001$).

Mycocardial depression studies were carried out on frogs (*Reva hexadactyla*) weighing 80–100 g. 15-crown-5 produced a direct mycocardial depression in perfused frog's heart *in situ* at a dose level of 5 mg. Its action on the heart was not blocked by atropine (1 mg) and mycocardial stimulant effect of adrenaline (10 mg) was not altered by the crown ether. The ether did not produce any effect by itself on isolated frog's rectus abdominis muscle preparation and the contractile effect of acetylcholine (1 mg/1 ml) was not altered.

Guineapig ileum was isolated by the following procedure. Guineapigs of either sex weighing 300–350 g were killed by stunning at the back of the neck and the ileum dissected free from extraneous tissues On isolated guineapig ileum 15-Crown-5 (100 μg/ml) produced contraction which was antagonised by chlorpheniramine maleate (250 μg/ml). Administration of the crown ether (0·05 ml of 0·1% solution) into plantar aponeurosio resulted in severe oedema and inflammation in rats. The oedema volume measured plethysmographically 5 h after administration of 15-crown-5 was found to be 1·36 ± 0·12 ml. Diphenylhydramine pretreatment (10 mg/kg) afforded 31·6% inhibition ($P > 0·001$) of the oedema produced by the crown ether. Local instillation of the ether (0·1%) into rabbit's eye produced mild hyperaemia and congestion.

Additional studies on anaesthesised dog's blood pressure revealed that intravenous administration of 15-crown-5 at a dose level of 10 mg/kg produced hypotensive effect (about 30–40 mm Hg) which was antagonized by mepyramine maleate (10 mg/1 kg).

It is interesting to note that the administration of linear tetraethylene glycol does not produce the above-mentioned effects. This suggests that cyclisation of the glycol induce remarkable pharmocological effects. The above findings of the pharmacological effects of 15-crown-5 show that it may have many similarities to oxotremoxine in its actions on CNS and it may be an useful adjunct as a pharmocological tool in the evaluation of antiparkinsonism drugs. The studies