

## LETTERS TO THE EDITOR

**DETERMINATION OF STABILITY CONSTANTS OF N-[5-METHYL-SALICYLIDENE]-BENZYLAMINE COMPLEXES-WITH Cu<sup>2+</sup>, Ni<sup>2+</sup>, Co<sup>2+</sup> AND Mg<sup>2+</sup>**

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In the present communication, the successive stability constants of the complexes of N-[5-methyl-salicylidene]-benzylamine with various bivalent metal ions have been determined potentiometrically following the Calvin-Bjerrum pH titration technique as adopted by Irving and Rossotti<sup>1</sup>.

The Corning Model 12, a precision research pH meter with a combined glass electrode and a calomel reference electrode was used for measuring 'B' values (pH meter readings) of the solutions. The changes in 'B' can be measured with an accuracy of 0.005 unit.

*Experimental*

The ligand N-[5-methyl-salicylidene]-benzylamine was prepared by refluxing equimolar quantities of 5-methyl-salicylaldehyde and benzylamine in methanol. The product was repeatedly crystallised to get a pure compound (observed m.p. 64°C).

Dioxan used was purified by standard methods<sup>2</sup>. The medium of titration was 75:25% (v/v) dioxan-water mixture. Sodium perchlorate was added to maintain a constant ionic strength. The titrations were carried out in nitrogen atmosphere.

The reagents were standardised complexometrically<sup>3</sup> by EDTA titrations. All the measurements were carried out at 25 ± 0.1°C by methods described in an earlier communication<sup>4</sup>. The experimental method of Irving and Rosotti<sup>1</sup> was applied to find out the values of  $\bar{n}$  and pL.

*Results and Discussion*

The reagent does not undergo hydrolysis under the experimental conditions is indicated by the rapid attainment of equilibrium without any significant drift in pH even after one hour.

The proton of the phenolic group of the ligand is replaced by the metal ion during chelation. 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 pK<sub>2</sub><sup>H</sup> which corresponds to the association of proton to imino nitrogen, and, pK<sub>1</sub><sup>H</sup> which corresponds to the association of proton to phenoxide ion of the reagent were obtained by least square method. The curve between 'B' and the corresponding  $\bar{n}_A$  values was plotted to get the formation curve. The formation curve extends over a range of 0.779 <  $\bar{n}_A$  < 1.585 and is wavelike. From this curve pK<sub>2</sub><sup>H</sup> was evaluated at  $\bar{n}_A = 1.5$ .

$\bar{n}$  and pL values were calculated and  $\bar{n}$  values were plotted against the corresponding pL values to get the formation curves of the metal complex-ion equilibria. From the formation curves, the values of stability constants log K<sub>1</sub> were evaluated which correspond to 1:1 complex at  $\bar{n} = 0.5$ . These were further corroborated by plotting

$$\log \{ \bar{n} / (1 - \bar{n}) \} \text{ vs pL.}$$

The log K<sub>2</sub> for metals could not be evaluated due to precipitation probably due to metal ion hydrolysis. The most representative values are recorded in Table I. The order of stability of bivalent metal-chelates was found to be Cu<sup>2+</sup> > Ni<sup>2+</sup> > Co<sup>2+</sup> > Mg<sup>2+</sup> and is in agreement with Mellor and Maley<sup>5</sup>.

A correlation between the stability of chelates of Cu, Ni, and Co with second ionization potential of the gaseous atoms was attempted by plotting the log K<sub>1</sub> versus the second ionization potential, as a function of atomic number. Since ionization of Cu, Ni and Co involves the removal of an electron from a 'd' orbital, the energy released in the replacement of that electron would vary in the order of Cu > Ni > Co, which is the order of stability constants observed.

TABLE I

*Stability constants of various complexes\**

Cations	$t = 25^\circ \text{C}$				
	H <sup>+</sup>	Cu <sup>2+</sup>	Ni <sup>2+</sup>	Co <sup>2+</sup>	Mg <sup>2+</sup>
log K <sub>1</sub>	11.54	11.32	7.18	6.95	5.01
log K <sub>2</sub>	8.09	..	..	..	..

\* For proton association (H<sup>+</sup>), K<sub>1</sub> and K<sub>2</sub> correspond to the species MH and MH<sub>2</sub><sup>+</sup> respectively, while for metal ions K<sub>1</sub> correspond to the species ML<sub>1</sub>.

The authors wish to record their sincere thanks to Dr. D. G. Vartak, B.A.R.C., Bombay, for his valuable suggestions and to Prof. A. P. Rao, Vice-Principal Ramnarain Ruia College, Bombay, for his kind and continuous encouragement in accomplishing this work.

August 25, 1980.

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### SOME AMINOCOUMARIN DERIVATIVES POSSESSING LOCAL ANESTHETIC ACTIVITY

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THE general structural requirements for a local anesthetic is a lipophilic moiety containing an aromatic nucleus joined to a hydrophilic moiety containing a tertiary amino group through an intermediate alkyl chain. Since many coumarin derivatives exhibit physiological activity<sup>1-3</sup> it was thought interesting to synthesize coumarin derivatives incorporating the above structural features. The synthesis of substituted aminoacetamidocoumarins was therefore undertaken and the local anesthetic activity tested.

The first step in the synthesis of these compounds is the preparation of 3- and 6-N-chloroacetylaminocoumarins by the reaction of chloroacetyl chloride on 3- and 6-amino-coumarins<sup>4,5</sup>. 4-Aminocoumarins failed to react with chloroacetyl chloride. Treating a solution of the aminocoumarin (0.01 mole) in dioxane (minimum volume) with chloroacetyl chloride (0.02 mole) for 3 hr afforded the chloroacetyl-aminocoumarins as crystalline solid from alcohol in 70-80% yield. The IR spectrum of a typical compound is as follows: 3450, 3400, 3260 (-NH), 1660, 1620 (>C=O), 1600, 1560, 1540 cm<sup>-1</sup> (aromatic).

The chloroacetylaminocoumarin (0.01 mole) and the amine (0.015 mole) were dissolved in tetrahydrofuran and kept at 30°C for 24 hr. The filtrate was evaporated to give the aminoacetamidocoumarins in about 70% yield, crystallized from benzene-petroleum ether (100-120°). The IR spectrum of 6-N-[morpholino]-acetamidocoumarin is as follows:

3300 (-NH), 1700, 1610 (>C=O), 1540, 1490 cm<sup>-1</sup> (aromatic) (Table I).

The pharmacological testing of the substituted amino-acetamidocoumarins was carried out as follows:

The rat hemidiaphragm was mounted on a rat phrenic nerve diaphragm holder and suspended in a 40 ml bath of Kreb's solution, bubbled with oxygen and maintained at 37°C. The muscle was stimulated directly using a square wave impulse of pulse width 0.5 m sec (20-30 volts) and a frequency of 0.1 Hz. The contraction was picked up by a Force Displacement Transducer and the signal amplified using a 10 μ volt universal bio-amplifier and recorded on a 4-channel INCO-polygraph. Control tracings were obtained for 5 minutes and the drugs were added in doses of 0.5, 1.0, 2.0 and 4 mg at intervals of 5 min in a cumulative fashion. The percentage inhibition

TABLE I

Aminocoumarin	M.P. °C	Amine condensed	Acetamidocoumarin	M.P. °C
3-N-Chloroacetyl	194-96	Pyrrolidine	3-[N-pyrrolidino]-	118-20
		Piperidine	3-[N-piperidino]-	148-50
		Morpholine	3-[N-morpholino]-	152-54
6-N-Chloroacetyl	206-08	Pyrrolidine	6-[N-pyrrolidino]-	110-12
		Piperidine	6-[N-piperidino]-	152-54
		Morpholine	6-[N-morpholino]-	185-87
6-N-Chloroacetyl-7-methyl-	195-97	Pyrrolidine	7-Methyl-6-[N-pyrrolidino]-	100-02
		Piperidine	7-Methyl-6-[N-piperidino]-	128-29
		Morpholine	7-Methyl-6-[N-morpholino]-	193-94

All the compounds gave satisfactory elemental analysis.