The order with respect to H^+ ions is one at all $[H^+]$ studied. The increase in initial rate in presence of perchloric acid (or H^+ ions) is due to the fact that perchloric acid increases the rate of enolisation of carbonyl compound.

Mono and divalent metal chlorides enhance the rate many-fold. The rate is the fastest in the presence of $ZrOCl_2$.
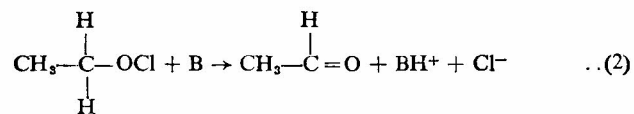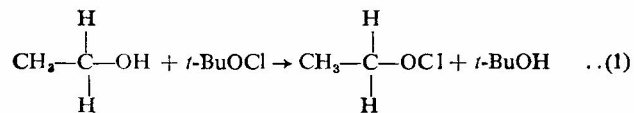
A comparison of initial rates, particularly in the case of divalent metal chlorides, reveals that there is an inverse relationship between k_0 and ionic radius. The initial rate follows the order $NiCl_2 > MnCl_2 > CaCl_2 > SrCl_2 > BaCl_2$ while ionic radii of cations follow the order $Ni^{2+}(0.78) < Mn^{2+}(0.91) < Ca^{2+}(1.06) < Sr^{2+}(1.27) < Ba^{2+}(1.43)$.

The absence of free radicals was detected by the negative test with mercurous chloride and acrylamide.

The activation parameters were calculated using Eyring's absolute reaction rate theory as described in previous paper[1]. The values of $\triangle H\ddagger$ for methanol, ethanol and n-propanol are 11.4 $\pm$ 0.22, 10.8 $\pm$ 0.38, 12.5 $\pm$ 0.03 kcal mol^{-1}, and of $\triangle S\ddagger$ 43.0, 46.5, 53.4 e. u. respectively in the absence of perchloric acid, while in presence of perchloric acid, the values of $\triangle H\ddagger$ are 10.3 $\pm$ 0.52, 9.9 $\pm$ 0.22, 11.2 $\pm$ 0.58 kcal mol^{-1} and of $\triangle S\ddagger$ 47.8, 48.9, and 47.0 e.u. respectively. The large negative entropy of activation suggests that a water molecule is involved in the rate determining step[5]. The high negative values of $\triangle S\ddagger$ also reflect a crowded transition state with hindered motion of the reaction.

The solvent isotope effects k_{H_2O}/k_{D_2O} for the oxidation of methanol, ethanol and n-propanol are 3.2, 3.4 and 3.5 respectively at 40°C. This high value suggests that rate-determining step involves the loss of proton[6] and not a hydride ion as in the latter case low values (usually below 2) should have been obtained[7].

The following polar mechanism (e. g. in the case of ethanol) may be proposed based on the results.

$$CH_3-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OH + t\text{-BuOCl} \rightarrow CH_3-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OCl + t\text{-BuOH} \quad ..(1)$$

$$CH_3-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OCl + B \rightarrow CH_3-\overset{\overset{H}{|}}{C}=O + BH^+ + Cl^- \quad ..(2)$$

where B is a base (for example water).

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Fe(II), Co(II), Ni(II) & Cu(II) Complexes of Penicillins

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Interaction of penicillins-G and -V with Fe(II), Co(II), Ni(II) and Cu(II) has been investigated in 50% aq. acetone (v/v) at 30° and an ionic strength of 0.1 M (NaClO$_4$) using Bjerrum-Calvin pH-titration technique. The stability constants of various species have been obtained by the method of Irving and Rossotti.

METAL complexes have been reported to play important part in the biological activity of drugs, as the complex formation has been suggested as one of the important mechanism for the drug action[1,2]. Although, the study of metal complexes with many therapeutic drugs have been reported including that with streptomycin[3] and tetracyclines[4], practically no work has been done to study the metal complexes of the two most common and widely used penicillins, the benzyl- (penicillin-G) and the phenoxy methyl- (penicillin-V) penicillins. We reported earlier the proton-ligand formation constants and stability constants of some alkaline earth metal complexes with these penicillins[5]. In the present note, we report the results of our studies on Fe(II), Co(II), Ni(II) and Cu(II) complexes with these penicillins in 50% aq. acetone (v/v) at 30° and an ionic strength of 0.1 M (NaClO$_4$).

All the reagents employed were of high purity. The preparation and standardisation of the metal ion and the ligand solutions and the experimental details are the same as reported earlier[5].

Stoichiometry of the complexes formed was ascertained by potentiometric (pH) and conductometric titrations. The Bjerrum-Calvin[6] pH-titration technique as modified by Irving and Rossotti[7] was followed to determine various formation constants. For potentiometric titrations, the following mixtures (total volume 50 ml) were titrated against carbonate-free 0.2 M KOH :

(i) 5 ml of 0.04 M HClO$_4$

(ii) Mixture (i) + 10 ml of 0.02 M ligand solution (penicillin-G or V)

(iii) Mixture (ii) + 5 ml of 0.002 M metal ion solution. The ionic strength of the solution was maintained at 0.1 M by adding the required quantity

of 1.0 M NaClO$_4$ solution. Correction for pH measurements in 50% acetone-water system was done as described by Van-Uitert and Hass[8] and Irving and Rossotti[7]. On progressive addition of the alkali during the pH titrations a precipitate was obtained in each case. The pH of precipitation in the different systems is: Fe-PG/PV, 4.5; Co-PG, 7.7; Co-PV, 6.5; Ni–PG, 4.7; Ni-PV, 7.6; Cu-PG, 5.4; and Cu-PV, 4.5. Therefore, in these cases all the calculations have been done below the pH of precipitation. Further, with the use of very dilute solutions (1 $\times 10^{-4}$ M) of the metal ions, possibility of the formation of polynuclear complexes has been minimised.

The values of $\bar{n}H$, $\bar{n}$ and pL^- were calculated using the Irving-Rossotti equations[7], and the value of log k_1 and log k_2 were recorded directly from the formation curves. The refined values for the same were computed by the method of least-squares and are given in Table 1.

The conductometric and potentiometric (pH) titrations carried out using the method of Nair and Pande[9] indicated formation of 1:1 and 1:2 (M:L) complexes. The value of n in all the cases was found to be $\sim$ 2, confirming the formation of ML and ML$_2$ type of complexes (L=penicillin-G or V; abbreviated as PG and PV). A perusal of Table 1 indicates that the order of the stability constants (log k_1) of the metal complexes follows the order of the basic strengths of the ligands used in this investigation (log k_1^H for PV and PG at 30° being 3.98 and 4.77 respectively[5]). Thus, PG complexes are more stable than the PV complexes. The order obtained with reference to metal and any of the ligands: Fe(II) < Co(II) < Ni(II) < Cu(II); follows the Irving-Williams series[10] and the empirical rules given by them[11].

Low values of pK_a for these drugs ensure that they are almost entirely in the form of the complex forming species (the anion) at the physiological pH of 7.3; while the relative avidity of these drugs for the metal ions is given by the order of the stability constants cited above. Further, the value of n does not exceed 2, indicating that the most expected coordination number six for the metal ions [particularly for Fe(II), Co(II) and Cu(II)] is not attained. This may favour the attachment of the chelates with the tissue, thus resulting in the binding of these drugs with the nucleic acids via transition metal ions. The transition metal ions are present in the human body in traces and these may change the behaviour of enzyme system by replacing the essential metals. These may also affect the structure and functions of nucleic acids by binding with them. Thus, the trace metals present in the body are expected to help in the transportation of the drug to the site of its physiological action.

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A Theoretical Consideration of Potentiometric Titration of Proteins in Lower pH-region.

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On the basis of simple acid-base neutralisation, an attempt has been made to formulate a relation between number of protons bound per mole and volume of alkali added, when a protein is titrated by the method of continuous titration of Irving-Rossotti.

POTENTIOMETRIC titration has been extensively used in the study of the stability constants of proton-organic ligand interaction and proton-association in macromolecules like proteins. In practice, mainly two methods of computations are done: (i) Irving-Rossotti[1] method for organic ligands; and (ii) Tandord[2] method for macromolecules like proteins. While the method due to Irving-Rossotti involves continuous titration, that due to Tanford involves discrete or discontinuous titration. In the present paper, an attempt has been made to deduce a relation for proton-association in proteins when titrated continuously by the technique of Irving-Rossotti.

In Fig. 1, the two curves are considered with two sets of solutions, viz. (i) strong acid and (ii) strong acid + protein at constant ionic strength. The relative positions of the two curves represent binding of protons by the protein.

Let the initial volume of both the systems be

TABLE 1 — STABILITY CONSTANTS OF TRANSITION METAL COMPLEXES OF PENICILLINS

[μ = 0.1 M (NaClO$_4$); Temp. 30°]

Metal ion	PG		PV	
	log K_1	log K_2	log K_1	log K_2
Fe(II)	5.04	4.36	4.40	3.97
Co(II)	5.20	4.58	4.51	4.19
Ni(II)	5.35	4.50	4.54	4.23
Cu(II)	5.51	4.63	4.84	4.23