



## Potentiometric Study Of Vanadyl (IV) Complexes Of Non-Steroidal Anti-Inflammatory Drug (NSAIDs) In Methanol At Different Temperatures And In Different Metal/Ligand Ratios



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### ABSTRACT

The reactions between flurbiprofen and  $\text{VO}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$  in 1:1, 1:2, 1:3 molar ratios in methanol was investigated at 35°C, 22°C and 0°C. The pKa values have been found as 8.52, 6.32 and 4.2 at 35°C, 8.35, 6.31 and 4.18 at 22°C, 8.34, 6.26 and 4.16 at 0°C. In various pH conditions, the different complexes which are formulated as  $\text{VO}(\text{H}_2\text{O})_3\text{L}$ ,  $\text{VO}(\text{H}_2\text{O})_2\text{L}_2$  and  $\text{VL}_3$  have been formed by titration of  $\text{VO}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$  and ligand (Flurbiprofen) mixture with NaOH. The stability constant of each complex have been calculated and general mechanism have been proposed with regard to the formation of these complexes. The order of stability is 1:1 > 1:2 > 1:3 which is justified with proposed mechanism also.

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### KEYWORDS

Vanadyl(IV) carboxylates;  
Potentiometric study;  
Stability constant.

### INTRODUCTION

It is well known that most of the anti-inflammatory drugs are carboxylic acids in which carboxylate group is available for metal-ligand interaction<sup>[1-3]</sup>. Flurbiprofen is non-steroidal anti-inflammatory drug (NSAIDs) that exhibit favourable anti-inflammatory, analgesic and antipyretic properties. The major clinical

application of NSAIDs is their action as anti-inflammatory agent in muscle skeletal diseases<sup>[4]</sup>.

Vanadium is an ultramicrotrace bioelement with interesting biological properties<sup>[5-8]</sup>. In mammals, vanadium mainly stored in bones and kidneys<sup>[9]</sup>. Vanadium has been used with great success as an oral treatment for animal model of diabetes<sup>[10]</sup>.

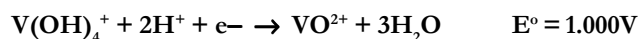
Vanadate is 6-10 times more toxic than vanadyl<sup>[11]</sup>

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but excessive applications of vanadyl is less effective than vanadate probably because of the fact that vanadate enters the living cells more rapidly<sup>[13]</sup>.

The standard potential of the vanadate ( $\text{H}_2\text{VO}_4^-$ ) to vanadyl ( $\text{VO}^{2+}$ ) is 1.31V<sup>[14]</sup>. Hence vanadyl under goes auto-oxidation to vanadate in the presence of oxygen and vanadate is reduced by reductants such as glutathione, ascorbate and NADH.

At 1M hydrogen ion concentration, aqueous solution of vanadium(V) behaves like a moderately good oxidizing agent.



In aqueous solution vanadyl ion exist either as  $\text{VO}^{2+}$  or  $[\text{VO}(\text{H}_2\text{O})_3]^{2+}$ .

The first aim of this work is to investigate the VO(IV) complexes of flurbiprofen in various molar ratios by comparing the protonation constants of the ligand. The second aim is to evaluate the stoichiometries of the complexes formed and to determine their stability constants. The stability constants of the complexes are determined by potentiometric measurement.

## EXPERIMENTAL

### Materials

All the chemical used in this research were of analytical reagent grade.  $\text{VO}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$  (Aldrich, 99% purity) was used as received. Distilled water was used for the preparation of 0.21 NaOH solution. While, methanol was used as a solvent for the preparation of 0.01M solution of vanadyl sulphate trihydrate and 0.01M solution of flurbiprofen. pH meter was calibrated by using buffer tablet of pH 4.

### General Procedure

For potentiometric titrations, 1:1, 1:2 and 1:3 M/L ratios were prepared by mixing 25 mL of 0.01M  $\text{VO}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$  solution with 25 mL, 50 mL and 75 mL of 0.01M solution of flurbiprofen. These titrations were carried out at 35°C, 22°C and 0°C with standard 0.2M NaOH. The 35°C was room temperature while 22°C and 0°C temperatures were maintained by keeping titration flask in tap  $\text{H}_2\text{O}$  and ice, respectively.

The reaction mixture was stirred on a magnet

stirrer while the titration was carried out and pH was measured after every 0.5 mL addition of NaOH solution.

For 1:1, 1:2 and 1:3 M/L ratios, first addition of NaOH solution cause colour change of the solution from green to light yellow. As we continue the titration, colour of the reaction mixture further changed and the turbidity started appearing which means that complexation started.

Further addition of NaOH solution caused the disappearance of the colour and white precipitate of  $\text{Na}_2\text{SO}_4$  produced in colourless solution. It confirmed the reaction or complexation and complexes are formed with general formula  $[\text{VO}(\text{H}_2\text{O})_3\text{L}]$ ,  $[\text{VO}(\text{H}_2\text{O})_2\text{L}_2]$  and  $[\text{VOL}_3]$ . The general chemical reactions are given in SCHEME 1.

## RESULTS AND DISCUSSION

Physical data for the reported compounds are given in TABLE 1 (available as SUPPLEMENTARY INFORMATION).

The potentiometric titration curves for 1:1, 1:2 and 1:3 M/L ratios are given as figure 1-3. pH titration data at 35°C, 22°C and 0°C are reported in TABLE 2-4 (available as SUPPLEMENTARY INFORMATION). These figures shows that titration curves of VO(IV) complex at different temperatures were found to have less depression but more twist which showed the low stability constant values with more species present at a time.

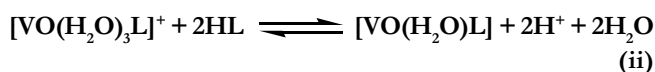
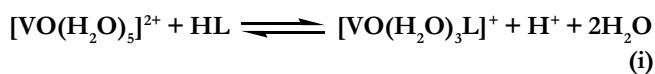
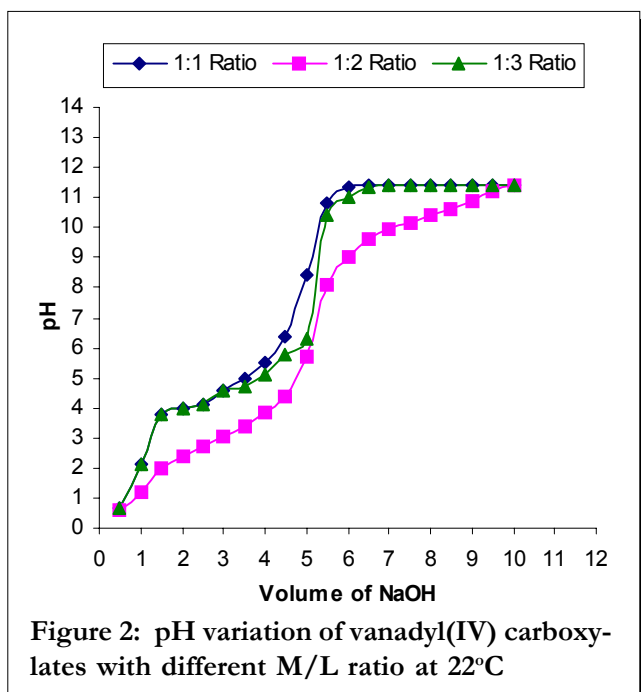
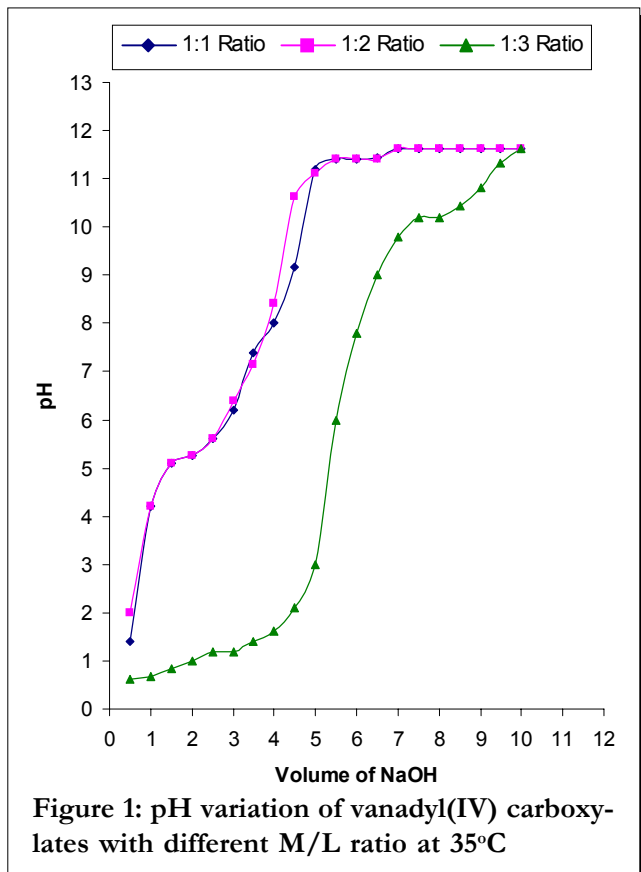
The stability of these species present was found to be more sensitive to temperature at lower pH. The deprotonation constants calculated for these complexes are given in TABLE 5 (available as SUPPLEMENTARY INFORMATION). As can be seen in this TABLE, three pKa values for each complex have been calculated.

As known, if the difference between two pKa values is higher, the end points of the titration curves are sharper. When pKa values are compared, it is seen that difference between two pKa ( $\Delta$  pKa) values for all the complexes are approximately 2.00 log unit. Thus the end points for 1:1, 1:2 and 1:3 M/L, pH titrations are sharper.

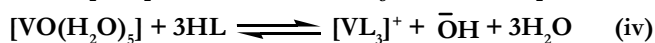
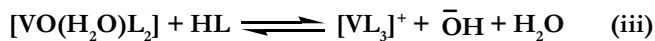
Theoretical  $\beta$  values are calculated from the ti-

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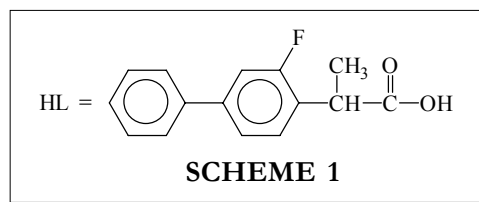
tration data and the  $\log \beta$  values obtained from these calculations for all metal ions-ligand complexes have been given in TABLE 6(available as SUPPLEMENTARY INFORMATION).



OR

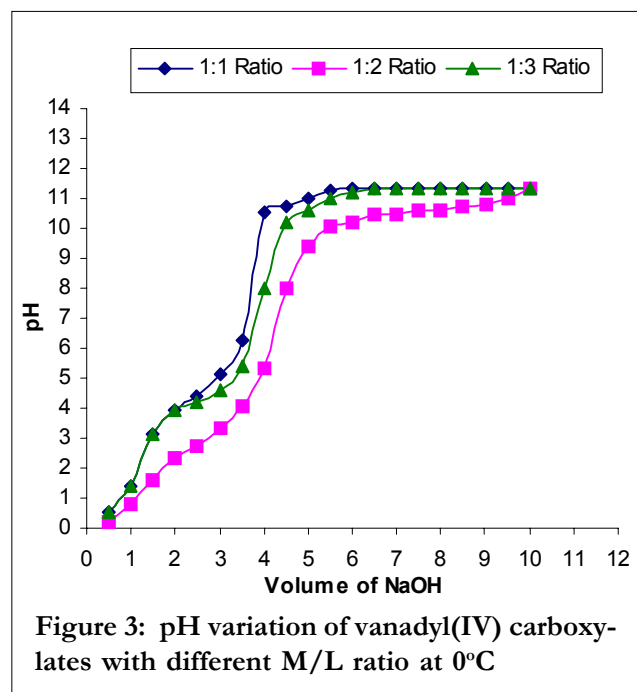


Where

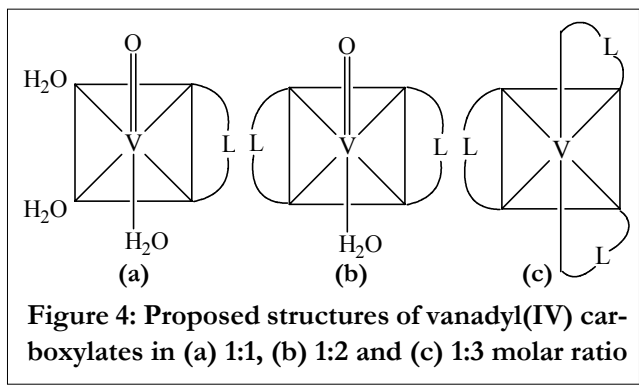
These ( $\log \beta$ ) values show that order of the sta-

bility for 1:1, 1:2 and 1:3 M/L ratios would be 1:1 > 1:3 > 1:2 which can be justified with proposed mechanism (SCHEME 1) as follows:

- Equation (i) and (iv) shows that in case of 1:1 and 1:3, the degree of hydrolysis is same or entropy should be same. Reason is that in both reactions only one  $\text{H}^+$  is produced.
- According to equation (ii) and (iii), both type of mechanism are possible for 1:2 M/L ratio. Equation (ii) shows that entropy of 1:1 and 1:2 complexes should be same but in case of second mechanism as given in equation (iii) entropy

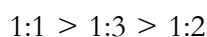


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should be in negative value.

This means that stability of 1:2 complex is less than 1:3 which is less than 1:1. We can show the stability order as



Stability of 1:3 complex is greater than 1:2 due to removal of vanadyl oxygen during the formation of 6-coordinated complex from simple bidentate ligand. Proposed structures for the complexes are given as figure 4. These structures shows that ligand acts as bidentate in these complexes and 6-coordinated complexes are obtained.

Summary of experimental parameters used in this work have been given in TABLE 7 (available as SUPPLEMENTARY INFORMATION).

## CONCLUSION

- The deprotonation constant (Pka) values are determined for 1:1, 1:2 and 1:3 M/L ratio at different temperatures. Conclusion has been drawn from these Pka values that end points of the titration are sharp.
- The order of the stability is 1:1 > 1:3 > 1:2 which is justified with proposed mechanism also.
- Flurbiprofen acts as bidentate ligand and 6-coordinated complexes are obtained for 1:1, 1:2 and 1:3 M/L ratios.

## SUPPLEMENTARY INFORMATION AVAILABLE STATEMENT

Following information is available as SUPPLEMENTARY INFORMATION.

- TABLE 1: Physical parameters of vanadyl(IV) carboxylates
- TABLE 2: PH titration data for 1:1, 1:2 and 1:3 M/L ratios at 25°C.

- TABLE 3: PH titration data for 1:1, 1:2 and 1:3 M/L ratios at 22°C.
- TABLE 4: PH titration data for 1:1, 1:2 and 1:3 M/L ratios at 0°C.
- TABLE 5: Deprotonation constants for vanadyl(IV) carboxylates at 35°C, 22°C and 0°C
- TABLE 6: Stability constant data for the complexation of vanadyl(IV) with Flurbiprofen at different temperatures and in different M/L ratios.
- TABLE 7: Summary of the experimental parameters for the potentiometric stability constants measurements

## ACKNOWLEDGMENT

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