

Fig. 2

The CD (upper) and UV/Vis absorption (lower) spectra of Ni(II)-albumin solutions at pH 6.9 (.....), pH 7.4 (-----), pH 8.1 (-·-·-·-), and pH 9.3 (—)

is very slow, requiring > 90 min to achieve equilibrium at 37°C and pH 7.4 (0.15 M NaCl solution), the octahedral species reacting more rapidly (via a dissociative mechanism) than the square-planar form which reacts associatively. The difference in kinetic behaviour between Ni(albumin) and Cu(albumin) could be an important factor in their different metabolic properties [4].

## REFERENCES

- [1] M.D. McNEELY, M.W. NECKAY, F.W. SUNDERMAN JR., *Clin. Chem. Winston-Salem, N.C.*, **18**, 992 (1972).
- [2] F.W. SUNDERMAN JR., *Ann. Clin. Lab. Sci.*, **7**, 377 (1977).
- [3] M. LUCASSEN, B. SARKAR, *J. Toxicol. Environ. Health*, **5**, 897 (1979).
- [4] J.D. GLENNON, B. SARKAR, *Biochem. J.*, **203**, 15 (1982).



PS6.21 — TU

ALBERT D. KOWALAK  
KAREN LeBOULLUEC  
University of Lowell  
Lowell, Massachusetts 01854  
U.S.A.

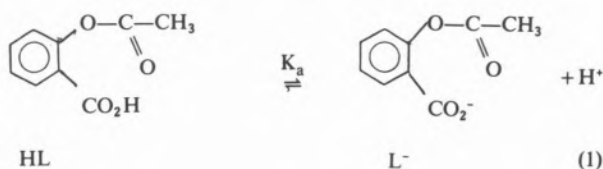
## THE STABILITY CONSTANTS FOR IRON(II)ASPIRINATE(ACETYLSALICYLATE)

The use of acetylsalicylic acid, aspirin, to relieve pain, reduce fever plus a wide variety of other ailments is well known. However, the theories to explain the effects of aspirin are vague. One theory postulates that the body under stress will have a two fold or greater increase of copper ions in the blood stream with a loss of essential copper from the organs. The role of the aspirin is the formation of a copper chelate which facilitates the return of copper to the deficient cells [1]. The chemistry of the coordination of aspirin with metal ions is therefore necessary to have a complete understanding of the therapeutic role of aspirin.

Copper(II)aspirinate has been prepared and structural studies of the solid [2] report a polymeric material of units of  $[\text{Cu}(\text{C}_9\text{H}_7\text{O}_4)_2]_2$  with the carboxylic group acting as a bridging ligand between two Cu(II) ions as well as Cu-Cu bonding. The aspirin complex in the solid state does not exhibit chelation. There are no other studies that have been reported on the interaction of aspirin with copper; in fact, very little has been reported on the interaction of aspirin with metal ions.

We wish to report the results for the determination of the stability constants for the iron(II)-aspirin system.

The aspirin as ligand is monobasic:



with the possibility of the  $L^-$  forming a chelate with  $Fe(II)$ ;



The formation of the complex affects the ligand acid dissociation and the complexation may be followed by pH titration with base. The effect of complexation on pH is independent on whether the aspirin is bound to the iron only through the carboxylate group or if a chelate is formed.

Solutions of reagent grade iron(II) chloride or perchlorate with acetylsalicylic acid of known concentrations were prepared. The ionic strength was held constant with 0.1 M  $KNO_3$ . The solutions were titrated with standardized NaOH under a nitrogen gas atmosphere. The  $[H^+]$  was calculated from the pH with correction for the  $H^+$  activity coefficient. The stability constants are based on concentrations.

The following equations were used for the determination of the stability constants:

$$\bar{n} = \frac{[FeL^+] + 2[FeL_2] + \dots}{[Fe^{2+}] + [FeL^+] + [FeL_2] + \dots} = \frac{n \Sigma \beta_n [L^-]^n}{\Sigma \beta_n [L^-]^n} \quad (4)$$

$$\bar{n}_{exp} = \frac{C_L - [L^-] - [HL]}{C_M} = \frac{C_L - [L^-]}{C_M} [1 + [H^+]/K_a] \quad (5)$$

$$[L^-] = \left[ \frac{\text{wt. HL/mol. wt.}}{V_t} - \frac{(V N)_{NaOH}}{V_t} + \frac{K_w}{[H^+]} - [H^+] \right] \frac{K_a}{[H^+]} \quad (6)$$

The stability constants were calculated by a least squares program for equation (4) with  $[L^-]$  and  $n_{exp}$  obtained by computer.  $K_1$  and  $K_2$  were also

determined graphically from plots of  $n$  vs  $pL$  at  $n=0.5$  and  $1.5$  respectively. Higher order constants were not obtained as at high pH hydroxide species must be considered. In some cases  $Fe(OH)_2$  precipitation occurs.

The  $pK_a$  of acetylsalicylic acid was determined to be 3.58. We were also concerned that hydrolysis of the ligand may have occurred. Acidification of various reaction mixtures resulted in a white solid precipitate which melted in the range  $128-132^\circ C$  characteristic of the ligand. The results for the constants are shown in the Table.

The values of  $\log K_1$  for the formation of  $Fe(C_9H_7O_4)^+$  appear to be reasonably precise while  $\log K_2$  is somewhat questionable particularly at higher ferrous ion concentrations. The deviations may be due to complications caused by hydroxide formation or the formation of dimeric complexes which need further study.

## REFERENCES

- [1] J. SCHUBERT, *Sci. Amer.*, **214**, 40 (1966).
- [2] L. MANOJLOVIC-MUIR, *Chem. Commun.*, **20**, 1057 (1967).

Table

$10^3 [FeCl_2], M$	$10^3 [Aspirin], M$	$\log K_1^*$	$\log K_2^*$	$\log K_1^\#$	$\log K_2^\#$
2.60	4.51				2.60
1.00	»				2.38
2.13	»				2.79
2.76	»	2.98	2.41	3.04	2.42
3.23	»	3.05		2.98	2.87
3.94	»	2.77		2.76	
3.02	4.22	2.57		2.64	1.02
3.22	»	2.74		2.74	
2.64	»	2.74		2.77	
2.78 ( $Fe(ClO_4)_2$ )	»	2.74		2.77	

\* graphical

# computer values



PS6.22 — TH

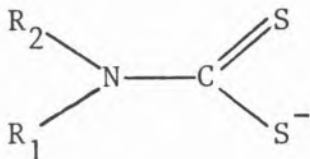
MARK M. JONES  
SHIRLEY G. JONES  
WILLIAM M. MITCHELL  
Departments of Chemistry and Pathology  
and  
Center in Molecular Toxicology  
Vanderbilt University  
Nashville, Tennessee 37235  
U.S.A.

### STRUCTURE-ACTIVITY RELATIONSHIPS IN THERAPEUTIC CHELATING AGENTS

The examination of the action of a number of structurally related dithiocarbamates as antagonists for acute and chronic cadmium intoxication reveals a number of relationships involving structural parameters and various measures of antagonist efficacy. The structural features also have a pronounced effect on the histopathology of the liver and kidney in treated animals.

The report by GALE *et al.* [1] of the ability of sodium diethyldithiocarbamate to antagonize the acute toxicity of cadmium chloride led us to examine this action in some detail [2-6]. We found that while sodium diethyldithiocarbamate was, in fact, an effective antagonist, its use led to increased levels of cadmium in the brain. Subsequently, preparation and testing of a large number of structurally related dithiocarbamates led to the discovery that alterations in the brain levels of cadmium were strongly dependent on the groups attached to the dithiocarbamate moiety and that the transport of cadmium into the brain could be reduced by the use of substituents with more polar components.

All of the compounds examined had the chelating group



present, with  $R_1$  and  $R_2$  varied. The differences in the relative polarities of compounds in this series were estimated as roughly equivalent to the differences in the sums of the  $\pi$  constants for the groups  $R_1$  and  $R_2$ . Each compound was thus characterized by the term  $(\pi_1 + \pi_2)$  where  $\pi_1$  is the  $\pi$  constant of HANSCH and LEO [7] for  $R_1$  and  $\pi_2$  that for  $R_2$ . It was found that compounds with strongly polar (or ionic groups) as well as those with very non-polar substituents were both less effective as antagonists than compounds whose R groups were of intermediate polarity (*i.e.* those bearing  $-OH$  groups). The measures of activity used include the following: survival ratios in acute cadmium chloride intoxication and relative cadmium levels in various organs (brain, liver or kidney) as well as composite measures which had two or more of these factors given various relative weights.

The pathological changes (in animals with chronic cadmium intoxication) subsequent to the use of these chelating agents to mobilize the cadmium are also very strongly dependent upon the structure of the chelating agent utilized to effect the mobilization.

Because the organ distribution of various toxic metals is not identical, different relationships between structure and activity of chelating agents can be anticipated, and indeed are found [8,9] for other toxic metallic species.

### REFERENCES

- [1] G.R. GALE, A.B. SMITH, E.M. WALKER JR., *Ann. Clin. Lab. Med.*, **11**, 476 (1981).
- [2] S.G. JONES, M.A. BASINGER, M.M. JONES, S.J. GIBBS, *Res. Commun. Chem. Pathol. Pharmacol.*, **38**, 271 (1982).
- [3] S.G. JONES, M.M. JONES, M.A. BASINGER, L.T. BURKA, L.A. SHINOBU, *Res. Commun. Chem. Pathol. Pharmacol.*, **40**, 155 (1983).
- [4] L.A. SHINOBU, S.G. JONES, M.M. JONES, *Acta Pharmacol. Toxicol.*, **54**, 189 (1984).
- [5] L.A. SHINOBU, S.G. JONES, M.M. JONES, *Arch. Toxicol.*, **54**, 235 (1983).
- [6] S.G. JONES, M.M. JONES, *Environ. Health Persp.*, **54**, 285 (1984).
- [7] C. HANSCH, A. LEO, «Substituent Constants for Correlation Analysis in Chemistry and Biology», John Wiley & Sons, New York, 1979.
- [8] G.R. GALE, L.M. ATKINS, A.B. SMITH, E.M. WALKER JR., M.M. JONES, *Res. Commun. Chem. Pathol. Pharmacol.*, **45**, 119 (1984).
- [9] G.R. GALE, L.M. ATKINS, A.B. SMITH, M.M. JONES, *Res. Commun. Chem. Pathol. Pharmacol.*, in press.