Iron(III) Complex Formation Equilibria of Sugar Type Ligands

I. ZAY, F. GAIZER and K. BURGER

L. Eötvös University Department of Inorganic and Analytical Chemistry, Budapest and A. József University Department of Inorganic and Analytical Chemistry, Szeged, Hungary

Received March 10, 1983

Iron(III) complexes formed with sugar type ligands (sugars, sugar acids, polyalcohols, other carbohydrates) are of vital importance in human and veterinary iron therapy [1, 2]. Their medical applicability depends – besides biological factors – on their equilibrium stability. The optimum stability is determined by chemical and biological factors.

Iron(III) containing injections are aqueous solutions of pH 4.5–7.5 containing 15–100 mg Fe/cm^3. The stability of iron(III) complexes used parenterally has to be high enough to prevent the hydrolysis of iron(III) in this pH range in such concentrated solutions and the precipitation of hydrolysis products damaging the living tissue. Too great a stability prevents, however, the utilization of iron by the living organism. Thus the experimental determination of the formation equilibrium constants of iron(III) complexes with bioligands is of great importance in the pharmacology and pharmaceutical technology of iron injections.

Iron(III) ions may coordinate the oxygen donor atoms of the sugar type ligands in pH-dependent and pH-independent processes. The coordination of iron (III) results *e.g.* in the deprotonation of carboxyl groups of sugar acids and sometimes even in that of alcoholic hydroxy groups in polyalcohols or sugars. The formation of mixed hydroxo complexes is also a general phenomenon in such systems. Both of these interactions are pH-dependent and can be examined by potentiometric equilibrium measurements using a glass electrode. The precipitation of iron(III) hydroxide at rather low pH values in solutions not containing a suitable excess of organic ligands decreases, however, the reliability of such investigations. Iron can also be coordinated in pH-independent steps by the hydroxy or aldehyde groups of the ligand. The characterization of these latter equilibria by potentiometric measurement is not feasible because no iron ion selective electrode suitable for this purpose has been developed so far. The formation of polynuclear species in the solutions makes the equilibrium study of such systems even more complicated. That is the reason why surprisingly few data have been reported in the literature on the stability of this type of iron complex [3, 4].

A UV and visible spectrophotometric equilibrium study of the iron(III) complex formation reactions of lactobionic acid, lactose and gluconic acid has been performed using a computer method for the evaluation of the experimental (absorbancy–total concentrations–pH) data and calculating the corresponding equilibrium constants. The results are reported below.

Our spectrophotometric data reflected both the pH-dependent and pH-independent steps in the complex formation processes. The measurements could be performed in an iron concentration range broad enough to cover dimerization equilibria in the systems.

Previous investigations into the stability constants of iron(III) complexes are reported only on gluconic acid so far [5]. The data of Pecsok and Sanders indicate the formation of mononuclear species only.

Experimental

Our equilibrium measurements have been performed in solutions of constant ionic strength (I = 0.30) made up with sodium perchlorate at 25.0 °C using a Specord (Zeiss, Jena) spectrophotometer with quartz cuvettes. The reagents used were of analytical purity. The iron(III) standard solution was prepared from iron(III) perchlorate (Merck *p.a.*), the solutions of the ligands from lactobionic acid (Fluka *p.a.*), α_D-lactose (Reanal *p.a.*) and α_D-gluconic acid (Fluka *p.a.*). The spectra have been recorded in the spectral range between 200 and 600 nm. For the computer evaluation absorbancies measured at 333 and 357 nm have been used for the lactobionic acid and gluconic acid systems respectively, and absorbancies measured at 270 and 280 nm for the lactose complexes. The measurements have been performed using a series of solutions with constant ligand and changing iron(III) concentrations and also with those with constant iron(III) and changing ligand concentrations. Concentration limits: iron(III) 10^{-4}–10^{-3} *M*, ligand 10^{-5}–10^{-1} *M*, pH 1.31–3.31.

Results and Discussion

In a series of preliminary experiments the iron coordination of glucose, gluconic acid, lactose, galactose and lactobionic acid, respectively, were investigated. In the absorption spectra of the glucose and galactose containing systems the interaction between iron and ligand did not cause any change indicating complex formation. Further studies have been limited, therefore, to the iron coordination of gluconic acid, lactose and lactobionic acid.

In the computer evaluation of the experimental data the presence of iron(III) hydrolysis products (hydroxo complexes) not containing the organic

0020-1693/83/$3.00

TABLE I. Composition, Stability Constants (log β values) and Molar Absorptivities (ϵ) of the Iron(III) Complexes formed with Lactobionic acid (*I*), α_D-gluconic acid (*II*) and lactose (*III*).

Composition		*I*			*II*			*III*		
		log β	ϵ (355 nm)	ϵ (333 nm)	log β	ϵ (355 nm)	ϵ (333 nm)	log β	ϵ (280 nm)	ϵ (270 nm)
FeL	$[FeL][Fe]^{-1}[L]^{-1}$	4.63	1700	1670	9.63	1464	1228	2.40	2360	1545
FeHL	$[FeHL][Fe]^{-1}[H]^{-1}[L]^{-1}$	8.49	2400	3000						
Fe_2L	$[Fe_2L][Fe]^{-2}[L]^{-1}$	13.02	3059	3418	19.08	4149	3392			
Standard deviation, absorbancy		0.02			0.01			0.02		
Number of experimental points		76			82			36		

ligand as well as the iron complexes of the sugar type ligands were taken into consideration. For the quantitative evaluation of the experimental work the potentiometrically determined hydrolysis constants of iron(III) [6] were therefore used as independent auxiliary data and the molar absorptivities of the hydrolysis products were determined by spectrophotometric measurements performed in the system used in our equilibrium studies but not containing the organic ligand.

The computer evaluations [7] based on the mass balance equations and on the additivity of the absorbancies of the species in the solutions were performed using several model assumptions. The equilibrium constants achieved with the help of these models were used for the simulation of the absorbance–concentration experimental curves. The standard deviation between experimental and calculated values was used for selecting the model most compatible with the experimental data and for determining the corresponding stability constants. The results are presented in Table I.

It can be seen that

a) the stability of the complexes decreases in the order gluconate > lactobionate > lactose;

(b) for the coordination of two iron(III) atoms by one ligand a deprotonated carboxyl group is needed in these systems (lactobionate and gluconate ions can both coordinate two iron atoms in spite of the lower chain length of the latter);

c) the presence of a non-protonated carboxylate group is not necessary for the coordination of one iron(III) if the polyalcohol has a chain length of at least 12 carbon atoms (lactose and protonated lactobionate also coordinate iron, but glucose and galactose do not).

References

1 A. Bezkorovainy, 'Biochemistry of Nonheme Iron, Plenum Press', New York, London, 1980.

2 P. K. Ku, E. R. Miller and D. E. Ullrey, *Michigan State Univ. Aes. Res., 437,* 90 (1982).

3 A. E. Martell and R. M. Smith, 'Critical Stability Constants', Vol. 3, Plenum Press, New York, London, 1977.

4 'Stability Constants of Metal Ion Complexes', The Chemical Society, London, 1964 and Supplement No. 1, 1971.

5 R. L. Pecsok and J. Sandera, *J. Am. Chem. Soc., 77,* 1489 (1955).

6 B. O. A. Hedström, *Arkiv Kemi, 6,* 1 (1953).

7 F. Gaizer and M. Máté, *Acta Chim. Hung. Acad. Sci., 103,* 355 (1980).