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Stability constants of potent cytotoxic copper(II) complexes with furan semicarbazones in ethanolic solutions

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Abstract

Potent cytotoxic copper(II) complexes of furannic semicarbazones were studied in ethanolic solutions at 25°C. The four ligands used were synthesized in our laboratory, i.e. 2-furfural semicarbazone (FSC), 5-methyl 2-furfural semicarbazone (MFSC), 2-furfural 4-phenyl semicarbazone (FPSC) and 3-(2-furyl) prop-2-enal semicarbazone (FASC). The mathematical analysis was carried out with a recent computer program SIRKO which indicated the formation of one metal–ligand complex in each case and the logarithm of their stability constants are: $\log \beta = 2.02, 3.84, 4.58$ and 4.52 for ligands FSC, MFSC, FASC and FPSC, respectively. A relation between stability and molecular weight of the ligands is proposed which may prove to be interesting as these complexes are being investigated for their cytotoxic activities. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Copper; Cytotoxic complexes; Furan; Semicarbazones; Stability constants; Ethanolic solutions

1. Introduction

We have already reported on the subject of synthesis and physico-chemical characterization of metallic complexes with some semicarbazones [1–3]. It has been shown that the metallic complexes of oximes, semicarbazones and thiosemicarbazones have strong antiviral and cytotoxic activities [4–13]. Ceretto et al. [4] prepared certain semicarbazone derivatives from 5-nitro 2-furaldehyde of which some showed activity against *Trypanozoma cruzi*. Pandeya and Dimmock [6] reported antineoplastic and anticonvulsant properties of various cyclic and acyclic thiosemicarbazones and semicarbazones. Sidwell et al. [8] have published an interesting study of semicarbazone and thiosemicarbazone derivatives against type 2-herpes simplex virus (HSV-2) induced genitalis in mice and guinea pigs. Guo et al. [9] has also shown anti-ulcer activity of these types of compounds.

In this field of research, some furan derivatives have also been extensively studied [14–18] and we have already

reported that metallic complexes of furan oximes derivatives are potent cytotoxic agents in both murine and human cell lines and solid tumors [14,15].

We have recently prepared metallic complexes in the solid state with variety of ligands: 2-furfural semicarbazone (FSC), 5-methyl 2-furfural semicarbazone (MFSC), 2-furfural 4-phenyl semicarbazone (FPSC) and 3-(2-furyl) prop-2-enal semicarbazone (FASC) [19,20]. The formulae of these ligands are given in Table 1. Using cobalt, nickel, copper, zinc and cadmium as central metal ions, some new complexes were characterized by means of several different methods such as elemental analysis, conductometry, magnetic moment measurements, infrared spectroscopy, spectrophotometry, and X rays.

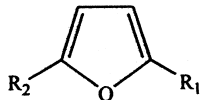
As most of these complexes are under investigation for their cytotoxic activities, they are also being studied in solution. This paper, therefore, presents the results of copper(II) complexes with the four ligands FSC, MFSC, FPSC and FASC in ethanolic solution. For a study of these complexes in solution, copper was retained as the central metal ion because we have already shown that in analogous systems the stability of the complexes with copper is highest as compared to other transition metals [21].

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Table 1
Structure of ligands studied^a

R ₁	R ₂	Systematic name	Abridged name
H	CH=N–NH–CO–NH ₂	2-Furfural semicarbazone	FSC
CH ₃	CH=N–NH–CO–NH ₂	5-Methyl 2-furfural semicarbazone	MFSC
H	CH=N–NH–CO–NH–C ₆ H ₅	2-Furfural 4-phenyl semicarbazone	FPSC
H	CH=CH–CH=N–NH–CO–NH ₂	3-(2-Furyl) prop-2-enal semicarbazone	FASC



2. Experimental

2.1. Reagents and procedure

Ethanol (Merck) was used as solvent without any further treatment. Stock solutions of all species were prepared by weighing calculated quantities of ligands, which we synthesized in our laboratory and copper(II) chloride (Fluka). Exact concentrations were determined gravimetrically. Since the mixtures are not very stable, all measurements were made immediately after the addition of the last reactant. For spectrophotometric investigation, the final analytical concentration of copper was maintained at 5×10^{-4} M in all the systems. The ligand concentrations varied from zero to their maximum concentration in ethanol, i.e. FSC = 2.6×10^{-4} , MFSC = 1.4×10^{-4} , FPSC = 7×10^{-5} and FASC = 7×10^{-5} M.

The absorption of the solution was measured with the help of Perkin-Elmer UV–Vis–NIR spectrophotometer Lambda 19, using spectrophotometric cells of quartz of 1.0 cm. When the absorption exceeded 2.0, spectrophotometric cells of 0.5 cm were used. Identical solutions, without the presence of the metal, were used as spectrophotometric references to eliminate residual absorption due to ligands. The temperature at which the experiments were performed was maintained at $25.0 \pm 0.2^\circ\text{C}$.

2.2. Method of calculation

The equilibrium under study is:



where L is the ligand. The equilibrium is defined by the stability constant β :

$$\beta = \frac{[\text{CuL}]^{2+}}{[\text{Cu}^{2+}][\text{L}]}$$

The calculation of the stability constants is based on a recent computer program SIRKO which was conceived for the calculation of these and allied parameters from spectrophotometric, calorimetric and potentiometric experimental data [22]. The stability constants of the complexes constitute the parameters of the system and these parameters are

calculated by a least-square method, the best set of values being that which minimises the sum S :

$$S = \sum_i \sum_j W_{ij} (F_{ij}^{\text{exp}} - F_{ij}^{\text{calc}})^2$$

where i is the number of experiments, j the number of experimental points, W_{ij} takes into consideration the respective weight of each factor and F_{ij} is called the response function. To enable the program to use different physico-chemical methods such as spectrophotometry, calorimetry and potentiometry, the universal response function F is given as:

$$F = Y_0 + Y_e \sum_{k=1}^n E_k \cdot [\text{C}_k] - Y_l \cdot \log \left(\sum_{k=1}^n EH_k \cdot [\text{C}_k] \right)$$

where F is the measured value; n the number of components in the solution; $[\text{C}_k]$ the equilibrium concentration of the component k ; Y_0 a constant for a given method, depending on the properties of the solvent; Y_l is the constant for potentiometric methods; Y_e is the constant for additive methods, spectrophotometry, for example; E_k is the parameter of the k th component for the additive methods and EH_k is the parameter of the k th component for calorimetric methods.

In the case of spectrophotometry $Y_l = 0$ and $EH_k = 0$. Thus F represents absorption of the solution, E_k the molar absorption coefficient, Y_e the width of the spectrophotometric cell and Y_0 the absorption due to the solvent.

In order to test the compatibility of the theoretical model with the experimental data, the R factor is defined as:

$$R = \sqrt{\frac{S}{\sum W_i (F_i^{\text{exp}})^2}}$$

For good harmony between the experimental and the theoretical model, R must be as small as possible, certainly less than 5%.

3. Results and discussion

3.1. Experimental spectra

The experimental spectra of the copper(II) chloride

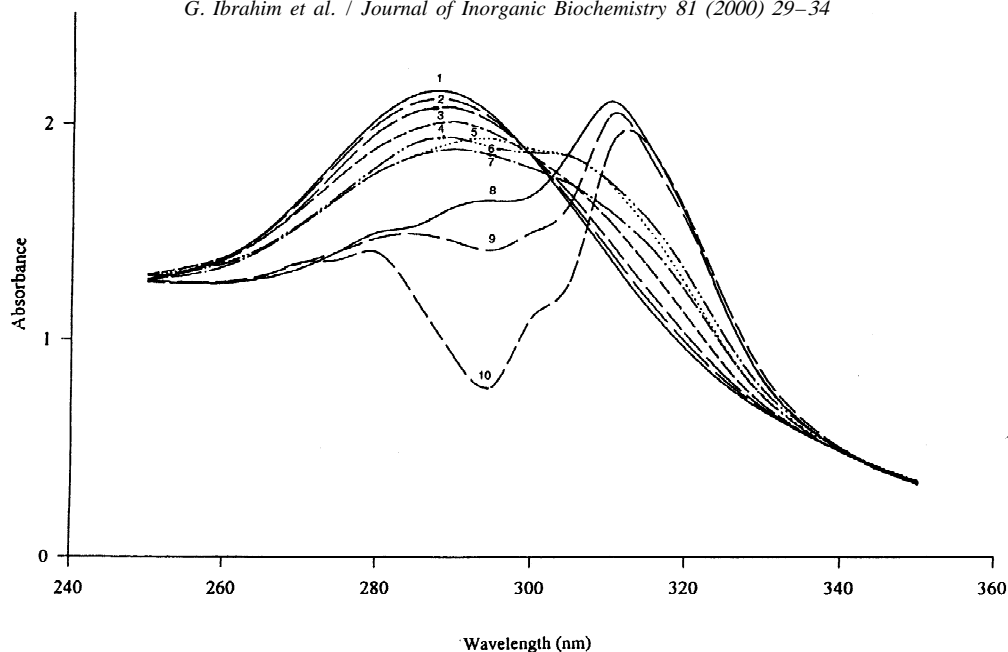


Fig. 1. Experimental spectra of copper(II) chloride solutions with FSC (ligand concentration in M: 1=0; 2= 10^{-5} ; 3= 2×10^{-5} ; 4= 4×10^{-5} ; 5= 8×10^{-5} ; 6= 10^{-4} ; 7= 1.2×10^{-4} ; 8= 1.8×10^{-4} ; 9= 2×10^{-4} ; 10= 2.4×10^{-4}).

solutions with FSC, MFSC, FPSC and FASC are presented in Figs. 1–4, respectively.

The copper(II) chloride solution in ethanol shows a maximum at 287 nm along with a shoulder peak at about 246 nm. In the UV–Vis region, the characteristic bands of the ligands are for FSC: 292 nm, MFSC: 300 nm, FPSC: 235 and 301 nm, and finally for FASC: 226 and 320 nm with a shoulder peak at about 331 nm.

Fig. 1 shows that with the increasing concentration of FSC the maximum at 290 nm diminishes and at higher concentration it appears a clear band at 314 nm with

another in the near infrared region at 890 nm (not shown in the figure). The decrease and eventual disappearance of the metal absorption maximum is evident as the concentration of the free metal ions diminishes because the metal is being engaged in complexation. In the case of MFSC (Fig. 2) the absorption band of the metal at 290 nm disappears with the appearance of other bands at 320 and 900 nm. As regards FPSC (Fig. 3), the copper(II) maximum disappears progressively in favour of another at 320 nm and in the IR region at 885 nm. A clear isosbestic point at 307 nm is observed. Finally, the addition of FASC to the copper

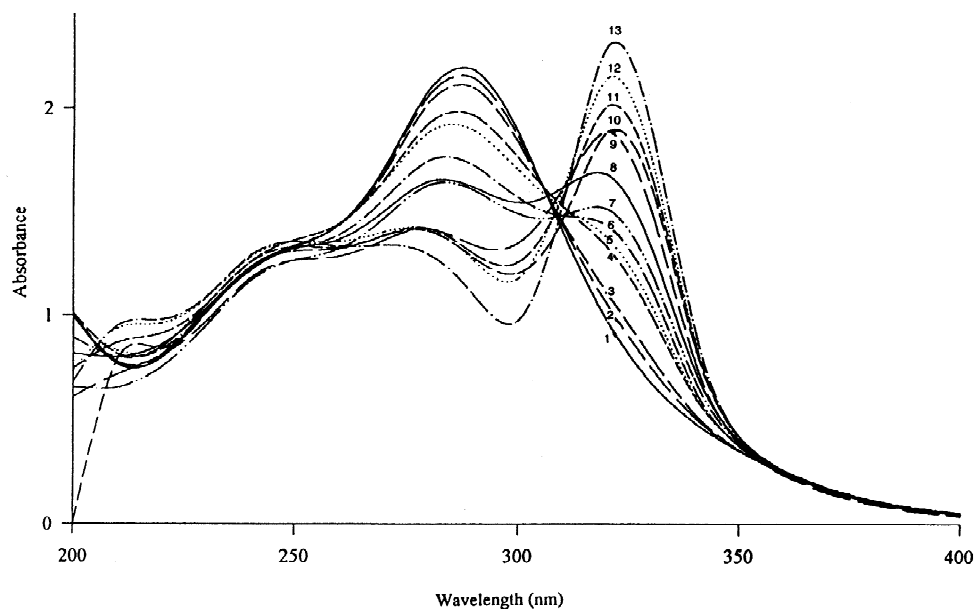


Fig. 2. Experimental spectra of copper(II) chloride solutions with MFSC (ligand concentration in M: 1=0; 2= 5×10^{-6} ; 3= 10^{-5} ; 4= 2.5×10^{-5} ; 5= 3×10^{-5} ; 6= 4×10^{-5} ; 7= 5×10^{-5} ; 8= 6×10^{-5} ; 9= 8×10^{-5} ; 10= 9×10^{-5} ; 11= 10^{-4} ; 12= 1.1×10^{-4} ; 13= 1.2×10^{-4}).

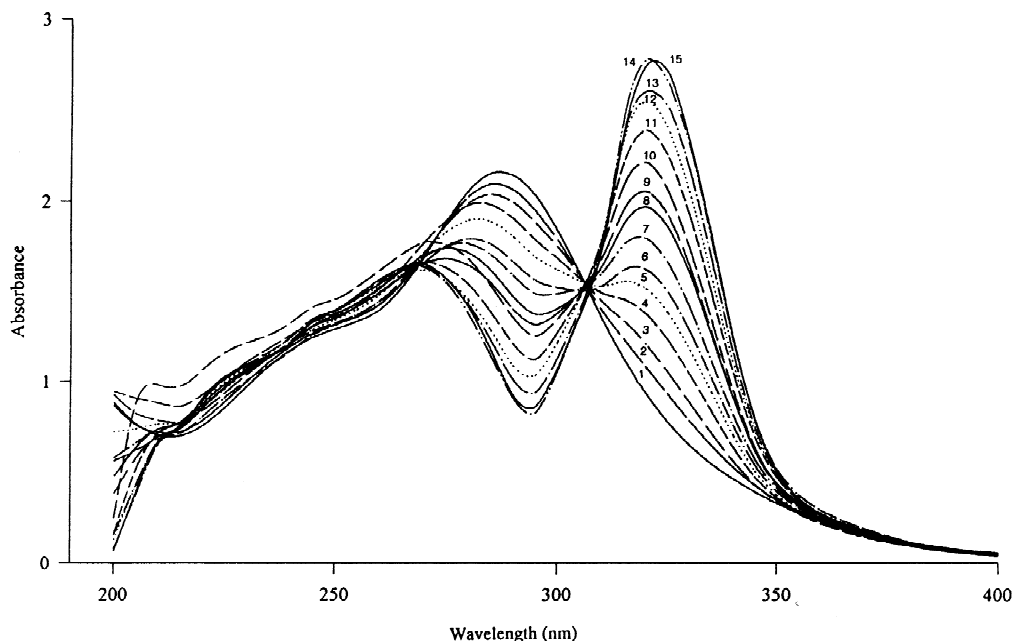


Fig. 3. Experimental spectra of copper(II) chloride solutions with FPSC (ligand concentration in M: 1=0; 2= 5×10^{-6} ; 3= 10^{-5} ; 4= 1.5×10^{-5} ; 5= 2×10^{-5} ; 6= 2.5×10^{-5} ; 7= 3×10^{-5} ; 8= 3.5×10^{-5} ; 9= 4×10^{-5} ; 10= 4.5×10^{-5} ; 11= 5×10^{-5} ; 12= 5.5×10^{-5} ; 13= 6×10^{-5} ; 14= 6.5×10^{-5} ; 15= 7×10^{-5}).

solutions shows (Fig. 4) the appearance of a new band at 355 nm and another at 885 nm. With this ligand also an isosbestic point is remarked but at 336 nm.

Table 2 presents the results in detail using the SIRKO program with FSC. For other ligands only the final results will be given.

In this presentation the theoretical model proposed is

given in the top left-hand corner CuCl_2 : 1 and FSC: 1, i.e. M:L=1:1 complex. The best value calculated for the stability constant for this complex is $\log \beta = 2.016$ with a dispersion of ± 0.091 . The molar absorption coefficients, ϵ , given at the left, are those of the complex calculated for different wavelengths λ . The numbers in parentheses are programme codes: the first number indicates the nature of

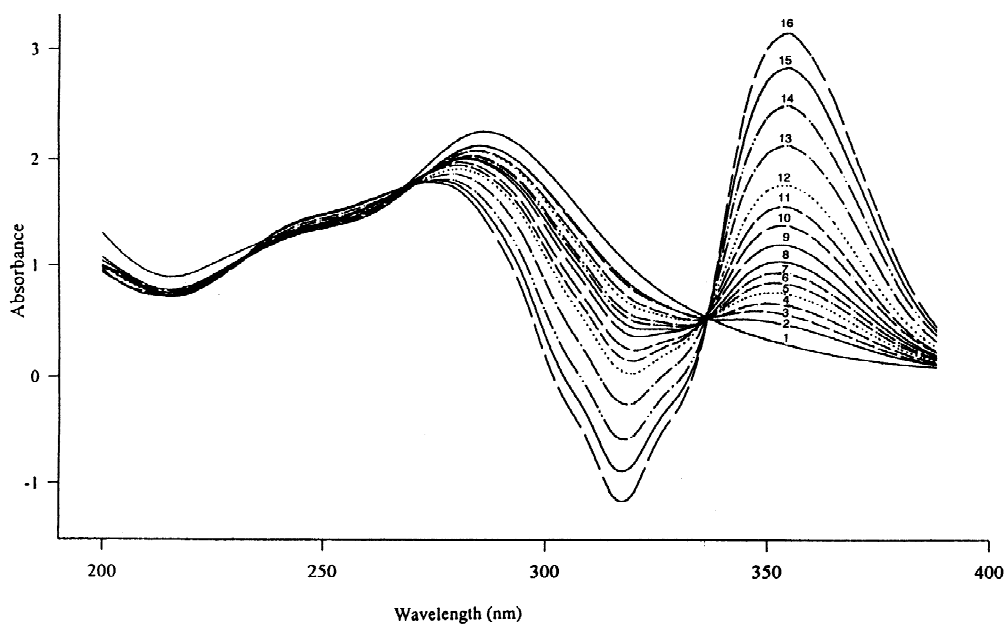


Fig. 4. Experimental spectra of copper(II) chloride solutions with FASC against individual references (ligand concentration in M: 1=0; 2= 5×10^{-6} ; 3= 7.5×10^{-6} ; 4= 10^{-5} ; 5= 1.25×10^{-5} ; 6= 1.5×10^{-5} ; 7= 1.75×10^{-5} ; 8= 2×10^{-5} ; 9= 2.5×10^{-5} ; 10= 3×10^{-5} ; 11= 3.5×10^{-5} ; 12= 4×10^{-5} ; 13= 5×10^{-5} ; 14= 6×10^{-5} ; 15= 7×10^{-5} ; 16= 8×10^{-5}).

Table 2
Detailed results for the system CuCl_2 -FSC, using the program SIRKO

Model			
CuCl_2	FSC		
1	0	$\log \beta = 0$	
0	1	$\log \beta = 0$	
1	1	$\log \beta = 2.016$	Refined
Parameters	λ		
$\epsilon(3,1) = 48131 \pm 9450$	310	$\epsilon \text{ CuCl}_2 = 2739$	
$\epsilon(3,2) = 69024 \pm 13464$	315	$\epsilon \text{ CuCl}_2 = 2289$	
$\epsilon(3,3) = 58905 \pm 11618$	320	$\epsilon \text{ CuCl}_2 = 1904$	
$\epsilon(3,4) = 36181 \pm 7491$	325	$\epsilon \text{ CuCl}_2 = 1585$	
$\epsilon(3,5) = 17508 \pm 3279$	330	$\epsilon \text{ CuCl}_2 = 1327$	
$\epsilon(3,6) = 6823 \pm 3371$	335	$\epsilon \text{ CuCl}_2 = 1117$	
$\log \beta = 2.016 \pm 0.091$			
Six iterations	$R \text{ factor} = 5.452\%$	$R\text{-lim} = 0.342\%$	

the absorbing species, i.e. 1 for the metal, 2 for the ligand, and 3 for the complex; the second indicates the code for the successive wavelengths, e.g. 1 for 310 nm, 2 for 315 nm, etc. These values are obtained after six iterations with an R factor of 5.45%.

We may remark here that the program SIRKO gave the best value of $\log \beta = 2.02$ with an initial value of $\log \beta = 2.0$. However, we further tested the reliability of the program by giving different initial values of $\log \beta$ between 1 and 6, and it always converged to the value of 2.02. Another important remark to be made here is that the absence of isosbestic points with the ligands FSC and MFSC suggests the presence of more than one complex. Different theoretical models were tested with one, two, three and four successive mononuclear complexes but the best results were always obtained with the model of one complex. We, therefore, assume that in case of these two ligands, the formation of a second complex would explain the absence of the isosbestic points but this formation is so low that for quantitative reasons it can be neglected.

For the other ligands the treatment of the experimental data gives the following best values of $\log \beta$. With MFSC as ligand: $\log \beta = 3.84 \pm 0.18$ and an R factor of 3.94%. For FPSC: $\log \beta = 4.52 \pm 0.15$, R factor = 1.51% and for FASC: $\log \beta = 4.58 \pm 0.08$, R factor: 1.32%. Table 3 gives a summary of all these results.

The stability of the copper(II)-FSC complex is much lower than the one of the other complexes. It is even lower than that of the chloro complex of copper(II) in the same

Table 3
Stability and characteristic absorption bands of the copper(II) complexes with the four ligands, and the molecular weights of the ligands

Ligand	MW (ligand)	$\log \beta$	β	$\lambda \text{ max (nm)}$
FSC	153	2.02	105	314, 890
MFSC	167	3.84	6.9×10^3	320, 900
FASC	179	4.58	3.8×10^4	355, 885
FPSC	229	4.52	3.3×10^4	320, 885

medium, ethanol, as reported by Chafaa et al. [23]. This low value can be discerned on the experimental document (Fig. 1) where a saturation effect of spectra is remarked. This phenomena is only observed for FSC and also explains why only ten solutions were used with this ligand in contrast to about 15 with all other ligands. Eventually this may also be the reason that the R factor, in this case only, is high, about 5%.

3.2. Stability–ligand relationship

It appears that the stability of the complexes increases rapidly as a function of the molecular weight of the ligand and then stabilises for ligands of molecular weight around 200. The electron donor effect of the methyl substituent group at position R_1 was considered as a factor of stability. However, the methyl group has a very weak donor effect and the increase of stability from FSC to MFSC cannot be explained solely on this basis. Steric hindrance also does not explain this evolution because the stability is higher with FASC and FPSC, and in both these ligands, the substituent R_2 is bulkier than in FSC and MFSC. We, therefore, propose the explanation that molecular weight of the ligands is the correlating factor of stability. The correlation of stability with the molecular weight of the solvents used to dissolve complexes has already been reported by Bentouhami et al. [24], nevertheless, this is the first attempt at linking stability in solution with a parameter of the ligand.

It is not surprising that heavier ligands form complexes of higher stability. This has been shown to be true for the simple chloro and bromo complexes of the same copper(II) ion and in the same methanolic and ethanolic solutions [23,25]. The stability in case of FPSC and FASC is nearly the same but remains higher than that of complexes formed with the lighter ligands: FSC and MFSC. Nearly identical values with FASC and FPSC may result from the fact that these ligands use the same coordinating atoms, i.e. the carbonyl oxygen and the imine nitrogen [3,26].

The coordinating atoms in case of FSC and MFSC are the carbonyl oxygen and the ring oxygen atoms [20]. Since the coordinating mode is the same in these two ligands, the difference in their stability can not be explained on the basis that coordinating atoms determine stability. For these ligands FSC and MFSC the difference is only in the substitution of hydrogen by the methyl group. The electron donor effect of this group being weak it is proposed that it is difficult to substitute the relatively heavy ligand, MFSC, coordinated to the copper ion. This substitution is easier in case of FSC complexes. This explanation is supported by the fact that in the solid state $[\text{CuCl}_2(\text{FSC})]$ is an intermediary complex and eventually leads to $[\text{CuCl}_2(\text{FSC})_2]$ which is thermodynamically more stable [20]. Consequently, the formation of a second mononuclear successive complex in solution, especially in case of FSC, can not be ruled out. This is also indicated by the absence of

isosbestic points but as mentioned earlier, under the present experimental conditions, this formation is low and has been neglected.

This relation can be helpful in the theoretical assessment of the stability of the furan semicarbazone complexes in ethanol, or even in alcohols, without undertaking prior experimental work. However, it must be borne in mind that this will be an approximate empirical assessment for a rapid reference. For a precise information on the values of formation constants, experimental work cannot be avoided. Moreover, as this work is limited to only four ligands, it will be interesting to confirm this hypothesis with other semicarbazone ligands with molecular weights between 180 and 230.

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