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Zn^{2+} COMPLEXES WITH *N*-(2-PYRIDYL)CINNAMIDES: CHARACTERIZATION AND UV STUDIES

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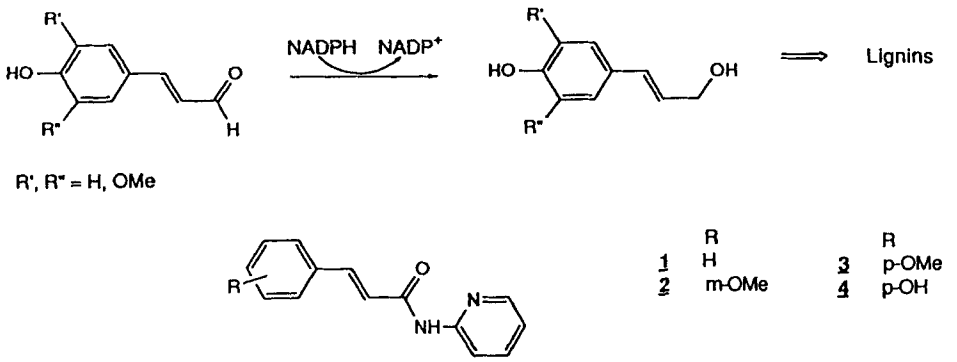
Zinc(II) complexes of *N*-pyridylcinnamides (H, *m*-OCH_3, *p*-OCH_3 and *p*-OH derivatives) were studied by spectrophotometric methods in aprotic media, and represent a chemical model inhibition by cinnamides of coniferyl alcohol dehydrogenase (CAD), a zinc enzyme involved in the lignification process. The complexation of *N*-pyridylcinnamide and *m*-methoxy-*N*-pyridylcinnamide with zinc ion is effected according to a 1 : 1 stoichiometry (ML), whereas a two-step equilibrium ($M + L \rightleftharpoons ML \rightleftharpoons ML_2$) is preferred with *p*-methoxy and *p*-hydroxy compounds. These ligands are mainly bonded through the carbonyl oxygen atom and the nitrogen of the pyridyl ring. Molar absorptivities for these complexes, not directly available, were calculated from analysis of the experiemental data. The UV complexation results are also supported by the stoichiometry of the complexes, which were synthesized and characterized.

INTRODUCTION

We are interested in the biochemical control of the lignification process through the inhibition of one enzyme involved in this process, coniferyl alcohol dehydrogenase (CAD).[1,2] This enzyme is specific to the lignification and catalyses the last step in the biosynthesis of the lignin monomers. It is a zinc enzyme, NADPH dependent, which participates in the reduction of *p*-hydroxycinnamaldehydes into alcohols; two zinc ions are present in the CAD[3] as in other zinc alcohol dehydrogenases, but one only is involved at the enzyme active site; this zinc ion, tetrahedrally ligated, acts as a Lewis acid and activates the carbonyl group of the aldehyde allowing the reduction to take place (Scheme 1).[4,5]

Attempts to control the lignification using specific enzyme inhibitors have been carried out in two ways by the synthesis of compounds designed in order to complex zinc at the enzyme active site: first, the synthesis of irreversible inactivators of the 'suicide' type, which were found to be active *in vitro* and *in vivo*;[6,7] second, the synthesis of *p*-hydroxycinnamic compounds as substrate analogues.[8] Some cinnamides are



Scheme 1

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known to show good inhibitory properties against horse liver alcohol dehydrogenase;[9] among all the cinnamic compounds that we have synthesized as substrate analogues, namely esters,[10] thioesters[11] and amides, the *N*-2-pyridylcinnamides[8] were found to be the most active compounds towards CAD.[6] No significant inhibitory effect was found when the *N*-pyridyl moiety was in another position on an *N*-alkyl chain or with the *N*-3- or -4-pyridylcinnamides. These observations prompted us to test the complexing ability of *N*-2-pyridylcinnamides towards zinc ions as a model of the complexation of zinc in CAD.

The crystal and molecular structures of the complexes between zinc and the carbonyl group of some aldehydes[12-14] and amides[15] have been determined; we have recently reported results on the complex between cinnamide **1** and $Zn(CF_3SO_3)_2$.[16] This paper reports the synthesis of complexes between cinnamides **1–4** and $ZnBr_2$ and complexation studies in solution by UV spectroscopy. Zinc halides have been used with some success as a model of the zinc ion in alcohol dehydrogenase; striking spectroscopic similarities have been observed for the complexes with dehydrogenase substrates. Therefore, for purposes of comparison with the literature, zinc halides were retained for this study. Zinc bromide, which shows better solubility in aprotic solvents and allows an easier determination of complexation constants, was preferred to zinc chloride.[14]

EXPERIMENTAL

Materials. The cinnamides were prepared from cinnamic acids using activation by *N,N*-dimethylchloromethyleniminium chloride and condensation with lithioaminopyridine, according to the conditions described previously.[8,10] Zinc bromide (Aldrich) was dried at 150 °C under a pressure of 10^{-2} mbar for 4 h. Diethyl ether (Et_2O) was distilled from sodium.

Preparation of complexes: method A. To 50 ml of a phenolamide solution (4.2 mM) in Et_2O a stoichiometric amount of a solution of $ZnBr_2$ (0.269 M in Et_2O) was added with a syringe under magnetic stirring, the vessel being first blown through with a stream of dry argon or nitrogen. The complexes formed immediately and precipitated. Magnetic stirring was maintained for up to 20 h without significant change, except for a slight increase in the yields. The precipitates were filtered off and the solvent was removed under reduced pressure, finally using a vacuum pump. $ZnBr_2$ solution was prepared by dissolving and diluting 1·0857 g of the dried salt with anhydrous Et_2O in a 20 ml volumetric flask.

Preparation of complexes: method B. To 20 mg of cinnamide in 2 ml of Et_2O (anhydrous) in a test-tube, a large excess of solid $ZnBr_2$ (0·1–0·2 g) was added in one portion. The mixture was homogenized by ultrasonic stirring and centrifuged. The supernatant solution was removed and the precipitate washed four times with Et_2O (2 ml) to remove excess of $ZnBr_2$. For each washing the same procedure was used: ultrasonic stirring, centrifugation and elimination of the ethereal solution.

In both methods A and B a whitish powder was obtained. Attempts to crystallize the complexes in organic solvents or by sublimation were unsuccessful. These compounds were found to be very insoluble in common organic solvents. Analytical data are given in Table 1.

IR spectroscopy. The infrared spectra of the isolated solid complexes were recorded in KBr on a Perkin-Elmer Model 783 spectrometer.

UV spectroscopy. The reactions were carried out (a) in the dark to avoid any accidental UV irradiation that might isomerize the ligands and (b) under an inert atmosphere to prevent hydration of the very hygroscopic zinc salts.

The experiments were effected under a stream of dry nitrogen and the glassware was purged with the same gas. The cells of the spectrophotometer were equipped with PTFE stoppers that permitted the introduction of the $ZnBr_2$ solution via a syringe.

The ligand was prepared at a concentration of 4×10^{-5} M in anhydrous Et_2O and aliquots of $ZnBr_2$ solution ($7{\cdot}4 \times 10^{-3}$ M in Et_2O) were added with a syringe, the mixture being rapidly homogenized in the

Table 1. Analytical data for the cinnamide complexes of zinc(II)

				Elemental analysis (%)		
no.	R	Stoichiometry		Calculated	Observed	Yield (%)
1	H	ML	C	37·41	37·49	82
			H	2·69	2·69	
			N	6·23	6·20	
2	*m*-OCH_3	ML	C	37·58	37·56	81
			H	2·94	2·87	
			N	5·84	5·88	
3	*p*-OCH_3	ML	C	37·58	36·90	74
			H	2·94	2·97	
			N	5·84	6·12	
4	*p*-OH	ML_2	C	47·66	45·95	83
			H	3·43	3·35	
			N	7·94	7·55	
4	*p*-OH	ML[a]	C	36·13	34·89	42
			H	2·60	2·71	
			N	6·02	5·51	

[a] Method B.

UV cuvette. The complexation study was stopped when a precipitate began to appear. The parameter ρ is defined as [M]/[L] (M = $ZnBr_2$, L = ligand).

Cinnamide double-bond isomerization could occur in very dilute solutions; some examples were reported previously by Lewis and co-workers;[17,18] the isomerization rate depended on the phenyl and nitrogen substitution.[19]

We decided to examine two factors that could favour the isomerization under the conditions of the UV complexation study: (a) the influence of irradiation by the spectrophotometer UV lamp on the ligand solutions, where it was found that no change of the amide chromophore appeared during a period longer than that required for the experiments; and (b) the influence of daylight, where it was found that the absorbance of the chromophore decreased by only 5–10% as equilibrium between *E* and *Z* isomers was reached in these dilute conditions. We assume that when the experiments were carried out in the dark, variations in absorbance were negligible.

Mathematical calculation of equilibria. The stability constants of the complexes and their molar absorptivities were determined according to the method of Shapiro and Johnston,[20] neglecting the equilibria

$$M + 2L \rightleftharpoons ML_2$$
$$2M + L \rightleftharpoons M_2L$$

that require a trimolecular reaction, which is very unlikely to occur. The following equilibrium systems (1)–(3) were considered. The stability constants K, K_1, K_2, K_1' and K_2' were given as a function of x and y (the respective molar concentrations of complexes ML, M_2L or ML_2 in equilibrium) and m_0 and l_0 (the respective initial concentrations of $ZnBr_2$ and of the ligand).

$$M + L \overset{K}{\rightleftharpoons} ML \tag{1}$$

$$M + L \overset{K_1}{\rightleftharpoons} ML \overset{K_2}{\rightleftharpoons} M_2L \tag{2}$$

$$M + L \underset{+L}{\overset{K_1'}{\rightleftharpoons}} ML \overset{K_2'}{\rightleftharpoons} ML_2 \tag{3}$$

In the reaction mixture at equilibrium, for a given ratio $\rho = [ZnBr_2]/[L]$ and for the wavelength chosen (λ_i), we can write the calculated absorbance value (A_{calc}), where c_i represents the molar concentration of type i (ligand-complex) found in equilibrium with ε_i as the molar absorptivity and l being the path length of the cell:

$$A_{calc} = \sum_i \varepsilon_i l c_i \tag{4}$$

We can consider the case of the equilibrium equations between types M, L, ML and M_2L; the procedure is identical for cases (1) and (3). If $l = 1$ cm, the calculated absorbance is as follows:

$$A_{calc.} = x\varepsilon_{ML} + y\varepsilon_{M_2L} + (l_0 - x - y)\varepsilon_L + (m_0 - x - 2y)\varepsilon_M \tag{5}$$

where the last term is negligible.

Analysis of experimental data. If K_1 and K_2 are given values, x and y can be calculated for each measurement by solving the system of equations (2) and (3), which leads to a cubic equation. By substituting x and y by their values in equation (5), the values of ε_{ML} and ε_{M_2L} and the corresponding value of Q ($Q = \Sigma_i A_i^2$) are calculated after assigning relative magnitudes to the pair of equilibrium constants K_1 and K_2. By means of a computer, K_1 and K_2 are assigned iterative values ranging from $K_{1\,min}$ to $K_{1\,max}$ and $K_{2\,min}$ to $K_{2\,max}$. The complex model that will be selected will have to take into account the minimized value of Q with respect to values of ε_{ML} and ε_{M_2L} giving the best correspondence between the experimental data and the assumed mechanism.

The average relative error for a data point is given by the reliability coefficient R_e:

$$R_e = \left[\frac{\sum_{i=1}^{p} (A_{i\,exp} - A_{i\,calc})^2}{\sum_{i=1}^{p} A_{i\,exp}^2} \right]^{1/2}$$

RESULTS

Stoichiometry of the complexes and stability constants

Two types of complexes have been identified; the mono-*N*-(2-pyridyl)cinnamide complexes (ML) and the bis-*N*-(2-pyridyl)cinnamide complexes (ML_2). The formation of stoichiometrically defined complexes was demonstrated by elemental analysis (Table 1). Whereas the monoadduct (ML) was isolated for the cinnamides **1**, **2** and **3**, the cinnamide **4** gave mainly the ML or ML_2 complexes, depending on the experimental conditions. The intermediate ML_2 adduct precipitates first on adding $ZnBr_2$ solution (method A). The difference from amides **1–3** can be attributed to a lower solubility in aprotic media of the *bis-p*-hydroxycinnamic complex, owing to the presence of two phenolic functions.

The spectral properties of the cinnamide zinc complexes and their stability constants are reported in Tables 2–4.

Cinnamides **1** *and* **2**

When, zinc salts were added to the ligand, a gradual decrease in ε_L together with an increase in ε_c at the

maximum absorption of the complex ($\lambda_{c\,max}$) was observed. The presence of a sharp isosbestic point indicates that the system contains two interconvertible chromophores, the free ligand and the zinc complex (Figure 1). The plots of the variation $A_{exp} = f(\rho)$ at various wavelengths (Figure 2) show that the interaction between cinnamide **1** or **2** and zinc bromide could be described by a one-step mechanism with a stoichiometry of 1 : 1 of metal ion towards ligand (equation (1)) (Table 3). The values of the stability constants found in these cases were 5500 l mol^{-1} for **1** and 9300 l mol^{-1} for **2**.

The hypothesis of two equilibria [as in equation (2) or (3)] cannot be completely neglected. It could occur in the complexation if two species showed the same ε value at the same wavelength.

The two-step complexation models [equation (3)] were tested (Table 4). Even though with cinnamide **2** the results give a low quadatric error, which would be acceptable for K values, the ε values are very different between the two complexes at the same wavelength ($\varepsilon_{ML} = 18100$ and $\varepsilon_{ML_2} = 6000$ l mol^{-1} cm^{-1}), and are in complete disagreement with the initial hypothesis of a two-step equilibrium model.

Finally, the presence of one isosbestic point in the UV complexation spectra, the results of the elemental analyses of the isolated complexes and the mathematical calculation of equilibria are all in agreement with the presence of an equilibrium $M + L \rightleftharpoons ML$ between cinnamide **1** or **2** and $ZnBr_2$.

Table 2. Spectral properties of zinc(II) ML complexes of cinnamides

No.	R^1	Ligand λ^L_{max} (nm)	Complex λ^C_{max} (nm)	λ_{isos}[a] (nm)
1	H	295	312	303
2	*m*-OCH_3	294	311	303
3	*p*-OCH_3	314	343	326
				331
4	*p*-OH	318	336	331
				331

[a] λ_{isos} = Wavelength of isosbestic point.

Table 3. Stability constants of zinc(II) complexes of cinnamides **1** and **2** calcualted by using the model $M + L \overset{K}{\rightleftharpoons} ML$

No.	R	K (l mol^{-1})	ε^C (l mol^{-1} cm^{-1})	Q	R_e
1	H	5500	19200	$1{\cdot}04 \times 10^{-4}$	0·004
2	*m*-OCH_3	9300	18600	$1{\cdot}52 \times 10^{-4}$	0·001

Cinnamides **3** *and* **4**

The complexation of these amides by $ZnBr_2$ differs from that for cinnamides **1** and **2**, two isosbestic points appearing in the spectra. Three phases can be distinguished. In the first the ligand L is in equilibrium with an intermediate complex I ($\lambda^I_{max} = 365$ nm), the final complex C not yet being present. An isosbestic point is observed corresponding to the first equilibrium ($\lambda_{isos\,1} = 331$ nm with **4** and 326 nm with **3**); in the second range of added $ZnBr_2$ three species L, I and C coexist. In the final part, the ligand concentration becomes negligible and complexes I and C ($\lambda^C_{max} =$ 336 nm with **4** and 343 nm with **3**) are in equilibrium and a second isosbestic point is observable ($\lambda_{isos\,2} = 331$ nm with **3** or **4**) (Figure 3).

Two theoretical models were considered to describe the phenomena [equations (2) and (3)]. The results agree better with equilibria in which the ML_2 structure is involved [equation (3)] (Table 4). The values of the complexation constants K (K_1 and K_2) are important ($0{\cdot}5$–7×10^4 l mol^{-1}) and show the ability of *N*-(2-pyridyl)cinnamides to complex zinc salts strongly.

The comparison of the plots of $A_{exp} = f(\rho)$ at two wavelengths (Figure 4), for example when the ligand disappears and when the complexes form, is interesting. Good consistency with the model is found, whatever the wavelength, when ρ lies in the range 0–1 (Figure 4). For $\rho \leqslant 1$ there is a lack of zinc salt in the solution and the preferentially formed complexes are ML_2 and ML, in

Table 4. Stability constants of $ZnBr_2$ complexes of the cinnamides calculated from the equilibria $M + L \overset{K_1}{\rightleftharpoons} ML \overset{K_2}{\rightleftharpoons} ML_2$

No.	R	λ_L (nm)	K_1 (l mol^{-1})	K_2 (l mol^{-1})	ε^C (l mol^{-1} cm^{-1}) ML	ε^C (l mol^{-1} cm^{-1}) ML_2	Q	R_e
1	H	295	20000	23000	21000	82500	$2{\cdot}28 \times 10^{-4}$	0·006
2	*m*-OCH_3	294	20000	22000	18100	6000	$8{\cdot}27 \times 10^{-6}$	0·001
3	*p*-OCH_3	314	20000	22000	4000	82800	$9{\cdot}82 \times 10^{-4}$	0·007
4	*p*-OH	318	72000	22000	16800	183000	$9{\cdot}38 \times 10^{-4}$	0·009

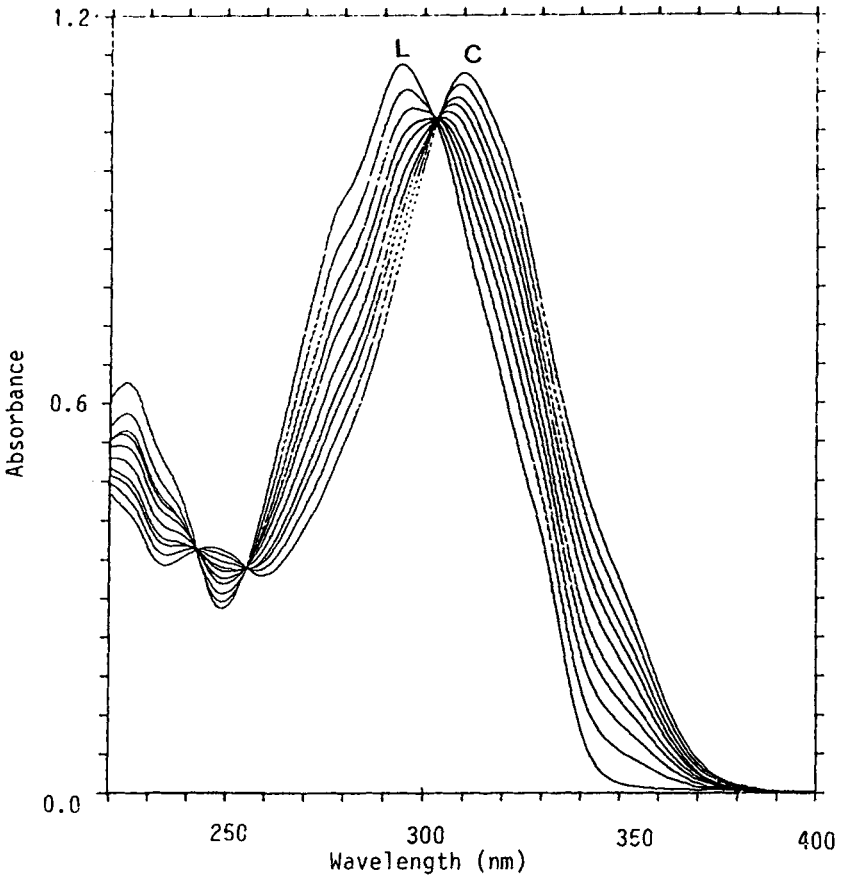


Figure 1. Complexation of *m*-methoxycinnamide **2** by addition of $ZnBr_2$ in diethyl ether at 25 °C

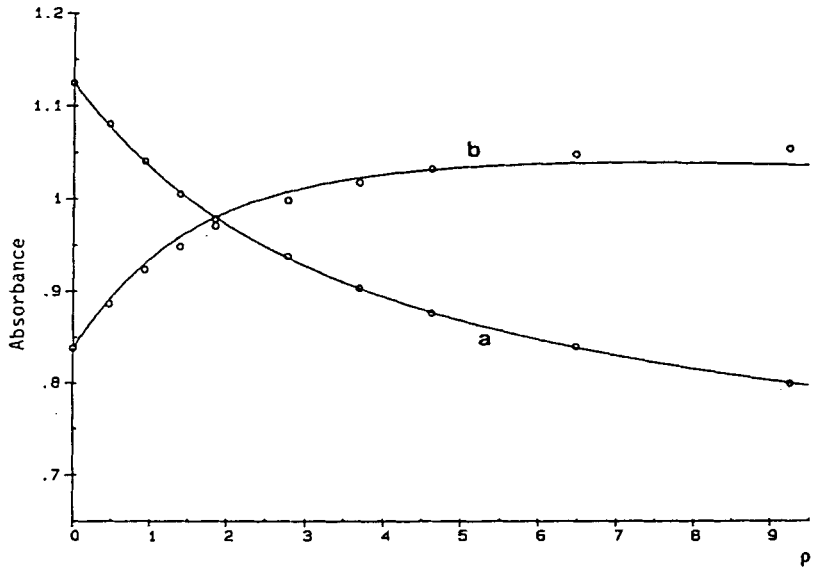


Figure 2. Graphs of $A = f(\rho)$ for the zinc(II) *m*-methoxycinnamide **2** complex: (a) at the wavelength chosen for the ligand (λ_i^L) and (b) at that for the complex (λ_i^C). Data points = A_{exp}; lines = A_{calc} for M + L ⇌ ML

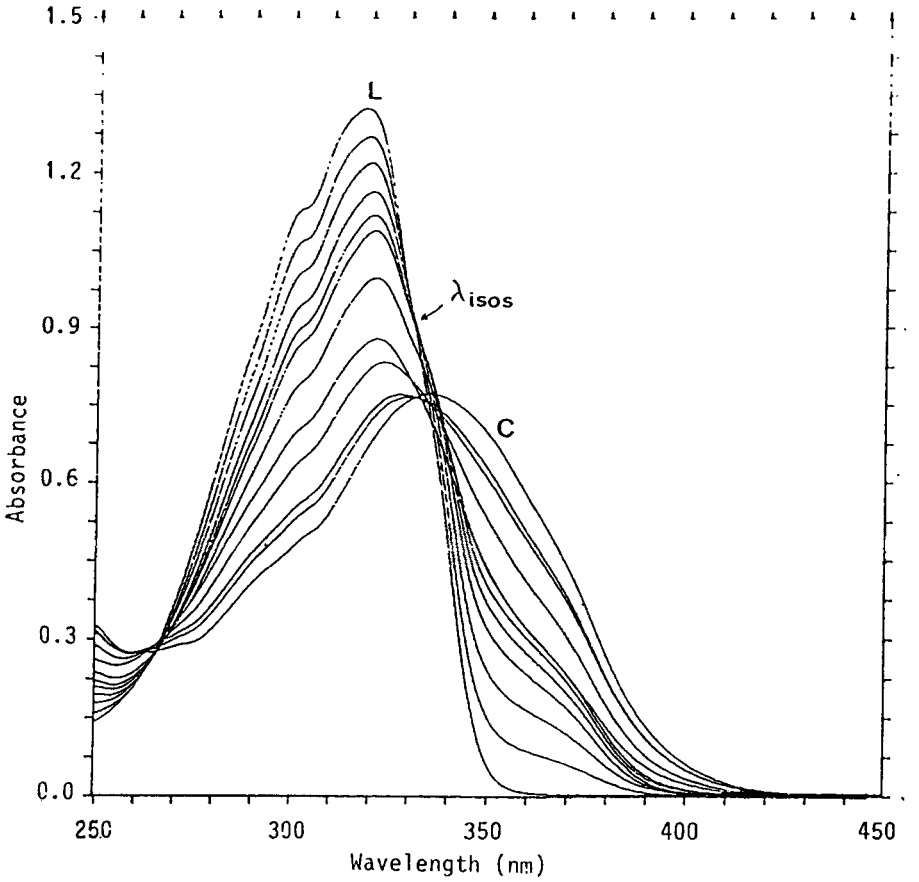


Figure 3. Complexation of *p*-hydroxycinnamide **4** by addition of $ZnBr_2$ in diethyl ether at 25 °C

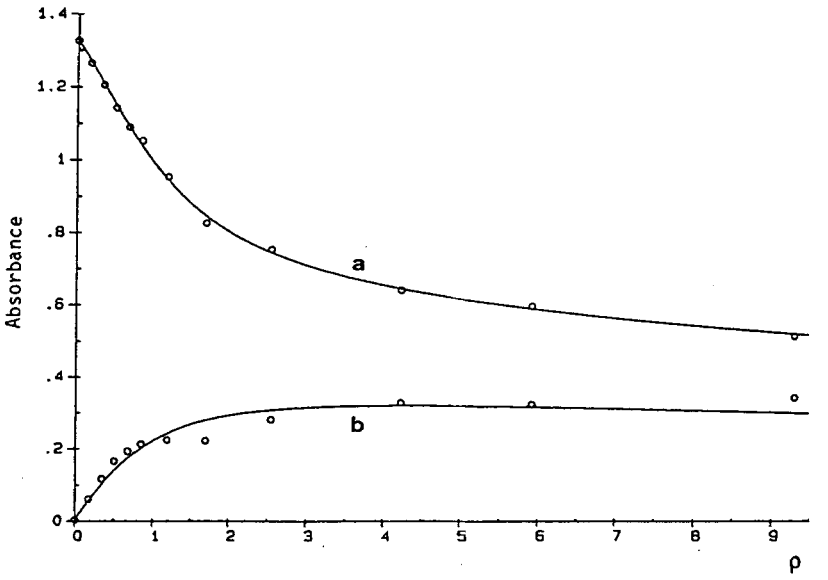


Figure 4. Graphs of $A = f(\rho)$ for the zinc(II) *p*-hydroxycinnamide **4** complex: (a) at the wavelength chosen for the ligand (λ_i^L) and (b) at that for the complex (λ_i^C). Data points = A_{exp}; lines = A_{calc} for $M + L \rightleftharpoons ML \rightleftharpoons ML_2$

good agreement with the two-equilibrium model and the stoichiometry of the isolated complexes.

The ML_2 complex predominates for low values of ρ and is associated with the complex with the most important bathochromic effects ($\lambda^{I}_{max} = 365$ nm).

When ρ increases up to 8 the theoretical curve established for ligand disappearance still fits the experimental values correctly. However, on the curve calculated from absorption values of the incoming complexes a reproducible inflection point is observed when ρ reaches 1·5–2. The same phenomenon occurs for the two cinnamides **3** and **4** (Figure 4). At the inflection point, the ML or ML_2 monomers could associate to give new oligomers, aggregates or organized systems without significantly changing the observed transition of the chromophore. The ρ value at the inflection point on the curve could be considered as the critical concentration at which the monomers units ML or ML_2 aggregate; the presence of such aggregates will induce multi-equilibria mechanisms. In aqueous media, natural polyphenols are known to readily associate with caffeine and related heterocyclics. The complexation is polydentate and aggregates are ultimately formed sufficiently to cause precipitations.[21–23]

In our experiments with syntheses, we were unable to solubilize the isolated complexes in organic solvents, an indication that higher degrees of polymeric association of the stoichiometrically well defined ML or ML_2 complexes could exist.[24]

DISCUSSION

The nature of the binding sites in cinnamides is known to be the carbonyl oxygen in preference to the nitrogen lone pair.[18] We assume that *N*-(2-pyridyl)cinnamides **1**–**4** are bidentate ligands and that zinc is linked to the carbonyl oxygen and to the pyridyl nitrogen donors. This has been previously verified by an x-ray diffraction study on another zinc salt complex from cinnamide **1**.[16] The enone unit in that complex was also found to be in an *S-cis* conformation and all the other configurations are *trans* with respect to zinc.

Further confirmation of the participation of carbonyl oxygen in zinc bromide complexation comes from IR results. Comparison of IR data for ligands and isolated complexes[25] has shown a large decrease in the ligand carbonyl stretching frequencies (L/ML, cm^{-1}, KBr: 1694/1660 for **1**, 1690/1659 for **2**, 1685/1659 for **3** and 1678/1652 for **4**).

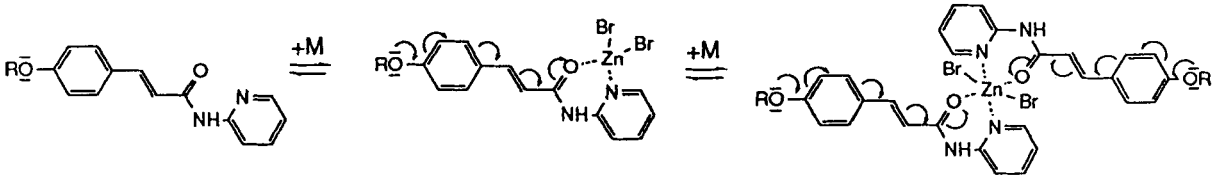
The cinnamides forms stable compounds with Zn^{2+} ions and the additional participation of the pyridyl nitrogen atom in zinc bromide complexation increases the stability of theses complexes.

The UV study indicated that complexation of the cinnamides induces red shifts. The most important bathochromic effect is associated with the intermediate complexes I, which appear with the *p*-methoxycinnamide **3** and the *p*-hydroxycinnamide **4**. A 1:2 stoichiometry (ML_2) and a λ^{I}_{max} value of 365 nm are attributed to these intermediates I.

These marked red shifts in the intermediate ML_2 complexes, compared with the λ_{max} values for the ligands **3** and **4**, are 47 and 51 nm, respectively. They are attributed to partial transfer of positive charge from zinc cation to the *para*-phenolic oxygen, with a final quinonic limiting structure participating in the phenomenon.

Although it is not completely comparable, we observed a λ_{max} value at 362 nm ($CHCl_3$) for a quinonic structure which was characterized in sinapic alcohol oxidation[26] and a similar red shift value of 48 nm in the complexation of *N,N*-dimethylaminobenzaldehyde with zinc chloride.[4] As it is difficult for such quinonic structures to intervene with cinnamides **1** and **2**, it would be tempting to correlate ML_2 intermediate formation with the more extended electronic delocalization in cinnamides **3** and **4**.

The complexation of cinnamides with $ZnBr_2$ can be described by the theoretical model $M + L \rightleftharpoons ML$ for cinnamides **1** and **2** and by the equilibria $M + L \rightleftharpoons ML \rightleftharpoons ML_2$ for the phenolic cinnamides **3** and **4**, insofar as the ρ values are in the range 0–1. In these last examples other phenomena would probably superimpose on these equilibria for higher values. The two-equilibria model fits correctly when $\rho < 1$, a scale which is more representative of the stoichiometry range



λ_{max}	L	ML	ML_2
R = Me 3	318	336	365
R = H 4	314	343	365

encountered in the interaction of zinc with substrate at the dehydrogenase active site.

The complexing ability of cinnamaldehydes, substrates of coniferyl alcohol dehydrogenase and *N*-pyridylcinnamides, potential inhibitors toward CAD, can be correlated with inhibition activity.

Besides the enzymatic modelling process, we believe that *N*-pyridylcinnamides provide an interesting class of bidendate ligands.

REFERENCES

1. H. Grisebach, *Naturwissenschaften* **64**, 619 (1977).
2. G. G. Gross, J. Stoeckigt, R. L. Mansell and N. B. Zenk, *FEBS Lett.* **31**, 283 (1973).
3. F. Sarni, C. Grand and A. M. Boudet, *Eur. J. Biochem.* **139**, 259 (1984).
4. M. F. Dunn and J. S. Hutchison, *Biochemistry* **12**, 4882 (1973).
5. M. F. Dunn, J. F. Biellmann and G. Branlant, *Biochemistry* **14**, 3176 (1975).
6. A. M. Boudet and C. Grand, *Monogr. Br. Crop Protect Counc.* **36**, 67 (1987).
7. M. Baltas, L. Cazaux, L. Gorrichon, P. Maroni and P. Tisnès, *J. Chem. Soc., Perkin Trans. 2*, 1473 (1988).
8. H. Duran, E. Duran, M. Ben Bakkar, L. Gorrichon and C. Grand, *Bull. Soc. Chim. Fr.* 672 (1987).
9. C. Delmas, G. de Saint-Blanquat, C. Freudenreich and J. F. Biellmann, *Alcoholism Clinical and Experimental Research* **7**, 264 (1983).
10. E. Duran, L. Gorrichon, L. Cazaux and P. Tisnès, *Tetrahedron Lett.* **25**, 2755 (1984).
11. E. Duran, H. Duran, L. Cazaux, L. Gorrichon, P. Tisnès and F. Sarni, *Bull. Soc. Chim. Fr.* 143 (1977).
12. M. Bochmann, K. J. Webb, M. B. Hursthouse and M. Mazid, *J. Chem. Soc., Chem. Commun.* 1735 (1991).
13. C. T. Angelis, M. F. Dunn, D. C. Muchmore and R. M. Wing, *Biochemistry* **16**, 2922 (1977).
14. P. W. Jagodzinski and W. L. Petitcolas, *J. Am. Chem. Soc.* **103**, 234 (1981).
15. H. Sigel and R. B. Martin, *Chem. Rev.* **82**, 385 (1982).
16. A. Bouayad, N. Bitit, E. Deydier, M. J. Menu, M. Dartiguenave, Y. Dartiguenave, H. Duran, L. Gorrichon, M. Simard and A. L. Beauchamp, *Inorg. Chim. Acta* **190**, 79 (1991).
17. F. D. Lewis, J. E. Elbert, A. L. Upthagrove and P. D. Hale, *J. Am. Chem. Soc.* **110**, 5191 (1988).
18. F. D. Lewis, J. E. Elbert, A. L. Upthagrove and P. D. Hale, *J. Org. Chem.* **56**, 553 (1991).
19. F. D. Lewis, J. D. Oxman, L. L. Gibson, H. L. Hampsch and S. L. Quillen, *J. Am Chem. Soc.* **108**, 3005 (1986).
20. B. L. Shapiro and M. D. Johnston, *J. Am. Chem. Soc.* **94**, 8185 (1972).
21. M. Aplincourt, A. Debras-Bee, C. Gerard and R. L. Hugel, *J. Chem. Res. (S)* 134 (1986).
22. G. Gerard, R. Njomgang, J. P. Pierrard, J. Rimbault and R. L. Hugel, *J. Chem. Res. (S)* 294 (1987).
23. S. H. Gaffney, R. Martin, T. H. Lilley, E. Haslam and D. Magnolato, *J. Chem. Soc., Chem. Commun.* 107 (1988).
24. S. M. Nelson and T. M. Shepherd, *J. Chem. Soc.* 3276 (1965).
25. H. Duran, *Thèse* No. 1406, Toulouse III (1989).
26. A. Zanarotti, *Tetrahedron Lett.* **23**, 3815 (1982).