

Cation Binding properties of some coumarin derivatives in acetonitrile

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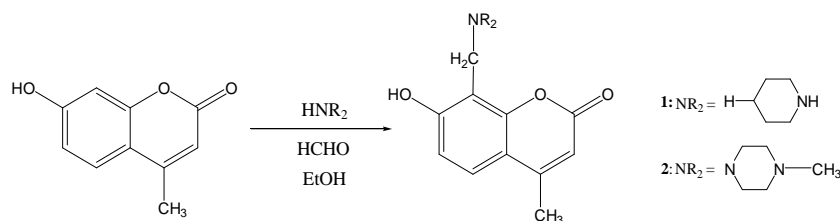
ABSTRACT: The complexation properties of some coumarin derivatives toward alkali metal, alkaline earth metal, some transition metal and some heavy metal cations have been investigated in acetonitrile by means of UV spectrophotometry absorption and conductivity. Thus, the stoichiometries of complexes formed and their stability constants were determined by digital processing of data.

Keywords: Coumarin derivatives; Stoichiometry; Complexation; Cation binding properties; Host-Guest Chemistry.

INTRODUCTION

Coumarins (2H-1-chromene-2-ones) are abundant in Nature and are common motifs found in drugs, dyes, spices, and agricultural chemicals. In particular, 3,4-unsubstituted coumarins are the most common naturally occurring coumarins, which show potential antimalarial,¹ antioxidant,²⁻⁶ antimicrobial,⁷ anti-inflammatory,⁸ and antitumor activity.⁹⁻¹¹ However, their abundance in plants is very low and the purification processes are complex. Therefore, various methods have been developed for the total synthesis of coumarins,¹¹⁻²² including the Perkin,²³ Pechmann,²⁴ and Knoevenagel reactions.²⁵ These reactions mostly lead to coumarins with substituents at the 3- or 4-position. A one-pot Wittig reaction/cyclization has been adopted by de Kimpe for the synthesis of 3,4-unsubstituted coumarins.²⁶ Herein, for mimed host-guest systems,²⁷⁻³⁰ we describe the complexation of alkali metal, alkaline earth metal and transition metal cations, and the liquid liquid extraction of metallic picrate salts by coumarin derivatives **1-3** already synthesized,³¹ also. Efforts to quantify the complexation equilibrium were based on the use of UV spectrophotometry, although conductometric measurements were also used to obtain preliminary estimates of the stoichiometry of complexes formed.

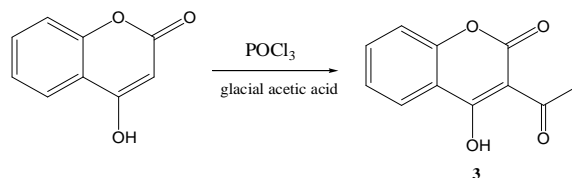
The Mannich bases **1-2** were prepared starting from 7-hydroxy 4-methyl-2H-chromen-2-one with 40% of formaldehyde and suitable secondary amines in 95% ethanol in rather good yield (Scheme 1).³²



Scheme 1: Synthetic procedure for ligands 1 & 2

The acetylation of 4-hydroxycoumarin to give 3-acetyl-4-hydroxycoumarin **3** was carried out by the method of Dholakia *et al.*³³ by using glacial acetic acid in the presence of POCl₃. The quick reaction led

to the desired product without obtaining any product from the Intramolecular condensation of 4-hydroxycoumarin.^{34, 35} (Scheme 2).



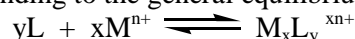
Scheme 2: Synthetic procedure for ligands 3

The structures of ligands **1-3** were confirmed via spectroscopic techniques IR,¹HNMR,¹³CNMR, Mass spectra and elemental analysis.

MATERIAL AND METHODS

General: Melting points were determined using an electrothermal apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were carried on a Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard ($\delta = 0$ ppm). IR spectra were recorded on a Perkin-Elmer 398 Spectrophotometer. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values found were within $\pm 0.3\%$ of the theoretical values. The UV spectra were recorded on a Perkin Elmer Lambda 11 spectrophotometer. Methanol (Riedel-de Haën for HPLC) and dichloromethane (Fluka, purum) were commercial and used without further purification. The supporting electrolyte used in the stability constant determinations was NEt₄Cl (Acros Organics). The metal salts chosen were chlorides (Fluka, purum).

Stability Constant Measurements: The stability constants β_{xy} being the concentration ratios $[M_xL_y^{xn+}]/[M^{n+}]^x[L]^y$ and corresponding to the general equilibrium:



(Where M^{n+} = metal ion, L = ligand) were determined in acetonitrile and methanol by UV-absorption spectrophotometry at 25°C.

The ionic strength was been maintained at 0.01 mol.L⁻¹ using Et₄NCl. The spectra of ligand solutions of concentrations ranging between 10⁻⁵ and 2×10⁻⁵ mol.L⁻¹ and increasing concentration of metal ion were recorded between 220 nm and 450 nm. Generally the metal to ligand ratio R at the end of the titration did not exceed 20 and the equilibriums were quasi-instantaneous for all the systems. Addition of the metal salts to the ligand induced spectra changes large enough to allow the analysis of the resulting data using the program “Letagrop”.³⁶ Best values for the formation constants β_{xy} of the various complex species and their molar absorptivity coefficients for various wavelengths, are deduced from the best fit between the experimental and calculated UV spectra.

The best fit is reflected by the lowest value of U (the sum of U values for all given lambda) corresponding to the square sum of a differences between experimental and calculated absorbances ($U = \sum (A_{cal} - A_{exp})^2$). The β_{xy} values correspond to the arithmetic means of at least three independent experiments.^{37, 38}

Conductometric studies: While complexation by a neutral ligand is not expected to dramatically alter the molar conductivity of a cationic species, the differences can usually be detected and so the measurement of conductance of a solution of a ligand into which a metal ion is added can be a useful rapid means of establishing the stoichiometry of a complex ion species. Thus, this procedure was followed to obtain preliminary estimates of the metal:ligand ratio in the complexes formed by the heterocyclic.

Synthesis of compounds 1- 2: To 20.0 mmol of 4-methyl-7-hydroxycoumarin dissolved in 50 mL of ethanol, 20.0 mmol of the appropriate amine and 2.0 mL of 40% formaldehyde were added. The resulting mixture was refluxed for 6 h. After cooling, the solvent was evaporated under reduced pressure. The pale yellow oil obtained was treated with cool acetone, leaving a white solid which was crystallized from

acetone obtaining 7-hydroxy-4-methyl-8-(piperidin-1-ylmethyl)-2H-chromen-2-one (**1**) and 7-hydroxy-4-methyl-8-((4-methylpiperazin-1-yl) methyl)-2H-chromen-2-one (**2**), respectively.³¹

7-Hydroxy-4-methyl-8-(piperidin-1-ylmethyl)-2H-chromen-2-one (1):

M.p.: 169-170 °C.

Yield: 62.0%.

FT-IR (KBr, ν , cm^{-1}): 2600, 1722, 1600, 1580.

¹H NMR (300 MHz, CDCl_3 , δ , ppm): 1.96-1.37 (m, 13H, CH_3 + Piperidinyl), 4.05 (s, 2H, CH_2), 6.09 (s, 1H, H_3), 6.77 (d, $J = 7.80$, 1H, Ar-H), 7.46 (d, $J = 7.80$, 1H, Ar-H), 12.38 (s, 1H, OH). ¹³C NMR (75 MHz, CDCl_3 , δ , ppm): 24.5 (CH_3), 25.6 (C-13,15), 26.6 (C-14), 39.5 (C11), 52.1 (C-12,16), 109.5 (C-3), 112.1 (C-6), 116.3 (C-8), 120.6 (C-10), 126.5 (C-5), 152.1 (C-9), 155.6 (C-4), 162.5 (C2), 157.2 (C-7),

7-Hydroxy-4-methyl-8-((4-methylpiperazin-1-yl)methyl)-2H-chromen-2-one (2):

M.p.: 132-134 °C.

Yield: 55%.

IR (KBr, ν , cm^{-1}): 3502, 2953, 2823, 1727, 1279.

¹H NMR (300 MHz, $\text{DMSO}-d_6$, δ , ppm): 2.65 (s, 3H, 4- CH_3), 3.25 (s, 3H, $-\text{N}-\text{CH}_3$), 4.00-4.37 (m, 8H, piperazinyl), 4.99 (s, 2H, CH_2), 6.68 (s, 1H, H_3), 7.30 (d, $J = 9$ Hz, 1H, Ar-H), 8.02 (d, $J = 9$ Hz, 1H, Ar-H), 12.25 (s, 1H, OH).

¹³C NMR (75 MHz, CDCl_3 , δ , ppm): 24.5 (CH_3), 39.5 (C11), 38.7 (N- CH_3), , 109.5 (C-3), 155.6 (C-4), 162.5 (C2), 126.5 (C-5), 112.1 (C-6), 157.2 (C-7), 116.3 (C-8), 152.1 (C-9), 120.6 (C-10), 55.1 (C-12), 58.4 (C-13).

Synthesis of 3-acetyl-4-hydroxy-2H-chromen-2-one (3)

To a mixture of 4-hydroxy-2H-chromen-2-one (3 g, 1.86 mmol) and acetic acid (16 mL) was added phosphorus oxychloride (5.6 mL). Then, the solution was heated at reflux for 30 min. After cooling, the precipitate was collected and recrystallized from ethanol to give 3-acetyl-4-hydroxy-2H-chromen-2-one as white needles.³¹

M.p.: 135-138 °C.

Yield: 2.7 g (90%).

IR (KBr, ν , cm^{-1}): 3185, 1705, 1700.

¹H NMR (300 MHz, CDCl_3 , δ , ppm): 2.72 (s, 3H, CH_3), 7.98 (s, 1H, Ar-H), 7.95 (dd, 1H, $J = 7.80$, 8.35, $^4J = 6.80$, 1.20 Hz, Ar-H), 7.1-7.4 (m, 2H, Ar-H), 17.69 (s, 1H, OH).

¹³C NMR (75 MHz, CDCl_3 , δ , ppm): 29.9 (CH_3), 101.26 (C-3), 126.5 (C₅), 125.1 (C₆), 121.2 (C₈), 125.6 (C₇), 150.5 (C₉), 127.6 (C₁₀), 154.6 (C-2), 159.8 (C-4), 178.5 (CO).

MS (m/z , (%)): 204 (M^+ , 100), 189 (74), 161 (43).³¹

RESULTS AND DISCUSSION

Complexation of metal cations in acetonitrile: The logarithms of the stability constants $\log\beta_{xy}$ and the stoichiometries for the different complexes formed by ligand 1, 2 and 3 with alkali metal, alkaline-earth metal and some transition metal in acetonitrile are given in Tables 1 & 2.

Table 1: Stability Constants $\log\beta_{xy}$ of the Complexes of 1, 2 and 3 with Alkali and Alkaline earth cations in acetonitrile at 25 °C, $I = 10^{-2}$ M. ($0.01 \leq \sigma_{n-1} \leq 0.16$).

	M:L	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	1:1	4.13	3.73	3.43	4.21	3.93	3.20	3.85	4.23	4.03
2	1:1	3.00	2.81	3.10	3.16	3.52	3.26	4.40	4.10	4.60
3	1:1	2.80	3.20	a	3.00	a	3.60	a	2.80	4.10

a: Absorbance changes too small to enable satisfactory fitting

Table2: Stability Constants $\log \beta_{xy}$ of the Complexes of 1, 2 and 3 with some transition metals in acetonitrile at 25 °C, I = 10⁻² M. (0.01 ≤ σ_{n-1} ≤ 0.16).

	M:L	Co ²⁺	Ni ²⁺	Zn ²⁺	Cu ²⁺	Hg ²⁺
1	1:1	4.80	4.62	a	4.01	4.02
2	1:1	4.42	3.71	a	4.23	4.23
3	1:1	4.11	3.80	a	4.17	4.78

a: Absorbance changes too small to enable satisfactory fitting

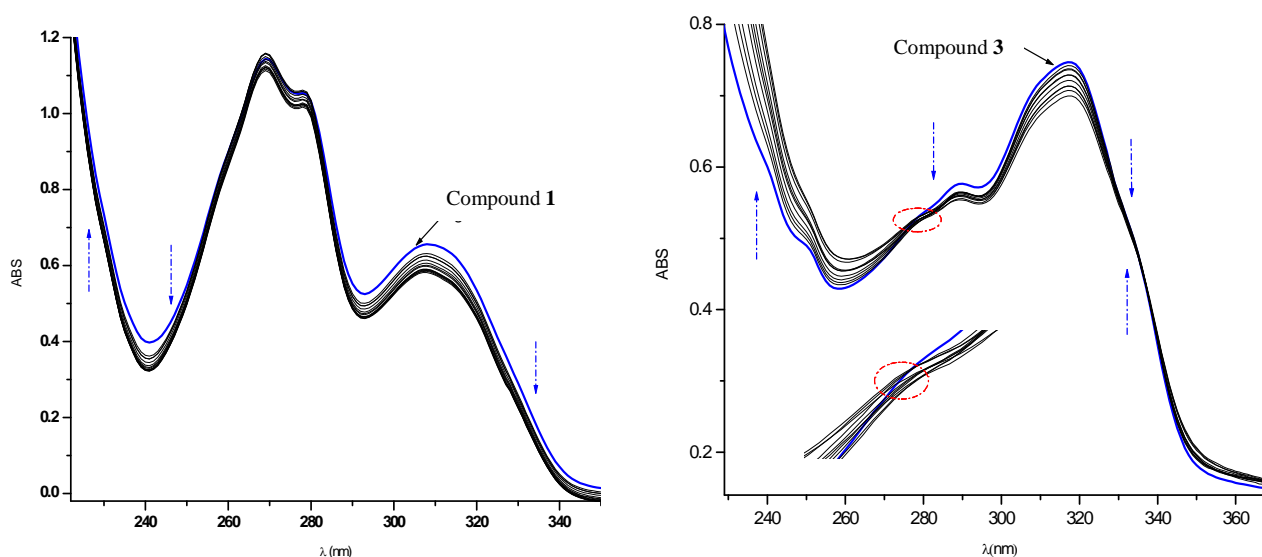


Figure 1: UV absorption spectra on complexation of (left) strontium perchlorate (Sr(ClO₄)₂) with 1 (right) Copper perchlorate (Cu(ClO₄)₂) with 3 in acetonitrile (0 ≤ R_{M/L} ≤ 7) at 25°C.

Figure 1 illustrates the titration of compound 1 by strontium perchlorate and 3 by copper perchlorate in acetonitrile at 25°C. Upon addition of the metal the absorbance recorded between 230 nm and 370 nm decreased without (figure 1 left) or with (figure 1 right) an isobestic point. The spectra changes are analyzed using the program “Letagrop”³⁶ and allows the determination of the stability constants β_{xy} of the various complex species along with their stoichiometry. Tables 1 and 2 gives the constants $\log \beta_{xy}$ corresponding to the arithmetic means of at least three independent experiments and figures 2 and 3 illustrate the trends of the stability constants $\log \beta_{11}$ (determined in acetonitrile) for alkali, alkaline-earth cations and some transition metal cations with ligands (1-3). A comparison with anterior studies has realized that methanol the stability constants appears higher in the acetonitrile than in methanol generally. This is probably due to the better solvation in acetonitrile as compared with methanol.³¹

The selectivity profile of compound 1 in the series of alkali and alkaline-earth cations shows an affinity complexation of strontium, whereas this affinity is in favor of barium with compound 2 and for magnesium with compound 3.

1 is the better complexing of alkali cation but 2 is the higher complexant in the series of alkaline earth cations. (Figure 2).³⁹

Unlike complexation results in methanol, no affinity complexation is detected in acetonitrile, with compound 3 in the case of potassium cesium and strontium. This is probably due to the ligand solvation difference in both solvents.^{31, 40}

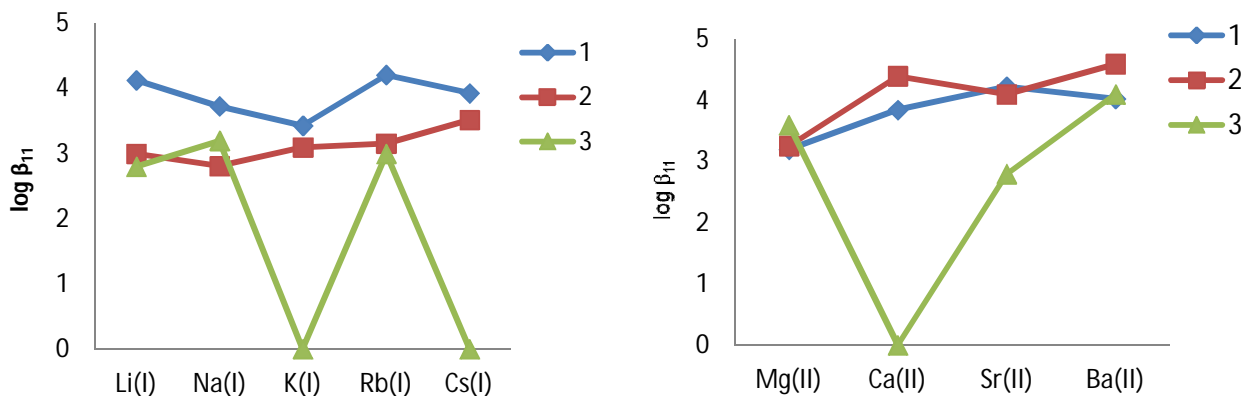


Figure 2: Trends of the stability constants $\log \beta_{11}$ (determined in acetonitrile) for (left) alkali and (right) alkaline earth cations with compounds 1, 2 and 3.

In the series of transition metal cations we observe a totally absence of complexation affinity for Zn(II) with all considered ligands. Compound 1 produces far better results with Co (II) and Ni (II) in the series of study transition metals. However, Hg(II) creates good results only when it reacts with compound 3, ($3 \cdot \text{Hg(II)}$ about 6 times more stable than $1 \cdot \text{Hg(II)}$). It is observed that the complex $1 \cdot \text{Ni(II)}$ is 10 times more stable than $2 \cdot \text{Ni(II)}$. (Figure 3). On the other hand, the stability of the complexes formed with compounds 1-3 are at the same order of magnitude, when it shows that this complexation is not affected by the size effects in the series of transition metal cations.

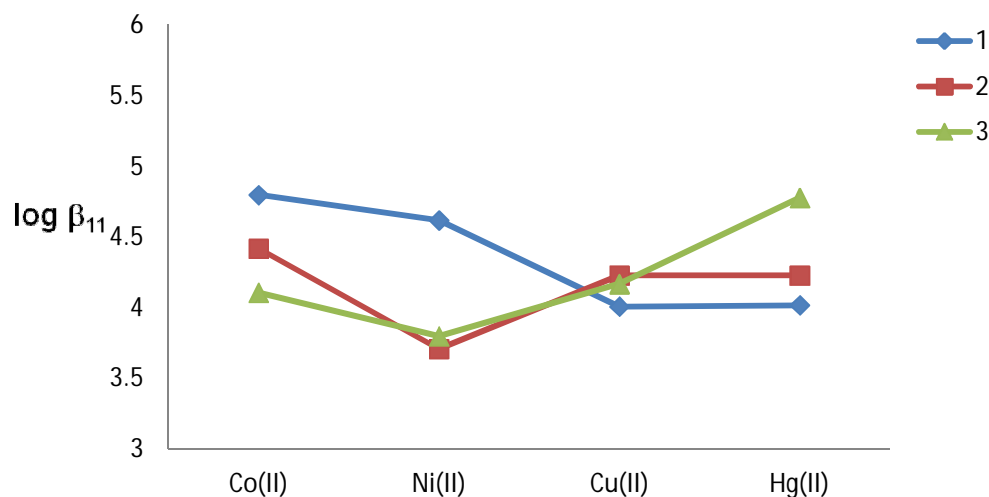


Figure 3: Trends of the Stability constants $\log \beta_{11}$ (determined in acetonitrile) for Co^{2+} , Ni^{2+} , Cu^{2+} and Hg^{2+} with ligands 1, 2 and 3.

In the other hand, the 1:1 stoichiometry of the complexes with 1, 2 and 3 were confirmed by conductometric studies (Figure 4)

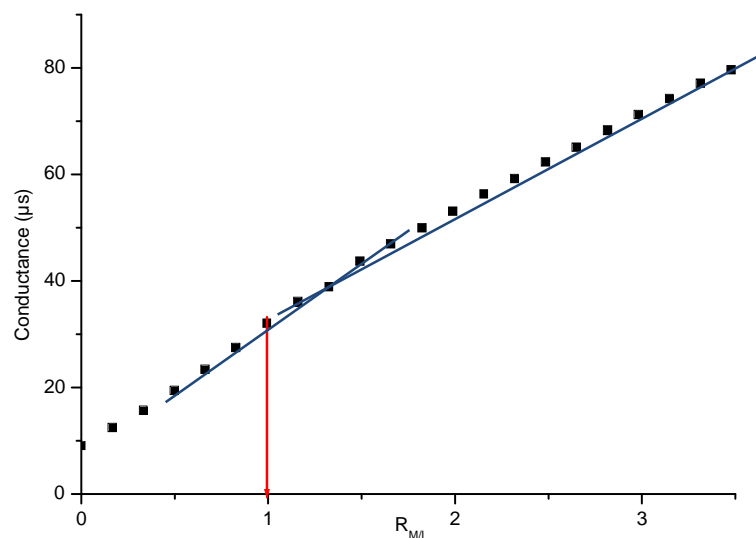


Figure 4: Conductometric titration of 2 with Ni(ClO₄)₂ in acetonitrile.

CONCLUSION

The results show the formation of mononuclear species to a ligand 1, 2 and 3 complex with metals studied. Hg(II) explain best complexation with ligand 3, we note 3·Hg(II) about 6 times more stable than 1·Hg(II). In the other hand we observe that the complex 1·Ni(II) is 10 times more stable than 2·Ni(II). The conductometric titration confirms mainly stoichiometries of complexes formed in solution with 1, 2 and 3 determined by the UV Spectrophotometry study.

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