

DINUCLEAR COMPLEXES OF COPPER AND SILVER WITH QUININE

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SUMMARY

The following silver and copper complexes in which quinine is coordinated via the two possible donor atoms was prepared and characterized. Coordination of quinine via the hydroxyl oxygen and quinoline nitrogen is observed in $C_{20}H_{25}N_2O_2Cu_2(SO_4)_2 \cdot 6H_2O$ and $C_{20}H_{25}N_2O_2Ag_2(SO_4)$. The existence of the proton at the coordinated hydroxyl oxygen is also observed in these complexes. The coordination mode and the conformation of quinine can be derived from IR and Raman spectra and by using NMR techniques.

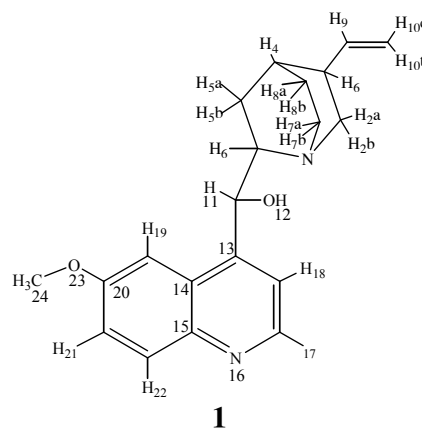
I - INTRODUCTION

Quinine - cinchona alkaloid - is a widely used antimalaria drug and its derivatives are applied as optically active auxiliaries in asymmetric synthesis [1 - 6]. In 1996 the Beck's group [7] used the Lewis acids $[(\eta^5-C_5H_5)(Ph_3P)(OC)Ru]^+$, $ClAuSMe_2$, and the chlorine-bridged complexes $[(\eta^5-C_5Me_5)MCl_2]_2$ ($M=Rh, Ir$) and $[(\eta^6-p\text{-cymene})RuCl_2]_2$ for the complexation of quinine, and obtained the coordination on tertiary N and hydroxyl O of quinine cation. Later, in 1999 the same Beck's group [8] has synthesized quinine complexes using all four potential donor sites of quinine (hydroxyl O, tertiary N and pyridine N atoms, olefinic C=C bond). In other work [9] the Fe-O, Zn-O and Ce-O bonds were evidenced to form via the quinine hydroxyl oxygen with a preservation of hydrogen bond.

In this paper we report on the synthesis of quinine complexes with silver and copper using the pyridine N atom and the hydroxyl O atom with a preservation of the quinine hydrogen bond.

II - EXPERIMENTAL

- Quinine $C_{20}H_{24}N_2O_2$ was used as supplied (Merck), with the structural formula (1).



- IR: Bruker-vector 22 spectrophotometer.
-Raman: Micro-Raman LABRAM-1B.

- All NMR measurements: Bruker AVANCE 500 MHz, the proton frequency is 500.133 MHz while the carbon frequency is at 125.758 MHz. Carbon and proton peak assignments were made using NOESY, HSQC

and HMBC spectra.

Synthesis of $C_{20}H_{25}N_2O_2Cu_2(SO_4)_2 \cdot 6H_2O$ (2). To a stirring solution of 12.507 g (0.05 mol) $CuSO_4 \cdot 5H_2O$ in 400 ml of methanol a solution of 16.227 g (0.05 mol) of quinine in 500 ml of

methanol with regulating pH value to 5.4 by H_2SO_4 was dropped at room temperature in 2.5 hours. After stirring the mixture for 30 minutes the light-blue precipitate was washed twice with MeOH and dried at 50°C.

Table 1: Carbon and proton peak assignments of NMR spectra of $C_{20}H_{25}N_2O_2Cu_2(SO_4)_2 \cdot 6H_2O$ ($CDCl_3$)

C No	HSQC			NOESY H ↔ H	HMBC H → C	
	^{13}C	(CH_x)	1H H assignment			
C ₂	54.92/56.98	CH ₂	3.36/2.59 3.56/3.02	1 H, dd, 2, 2.5, H _{2a} 1 H, d, 11, H _{2b}	H ₁₉ , H ₂₂	H ₆ , H ₉
C ₃	36.90/39.95	CH	2.81/2.23	1 H, br s, H ₃	H _{2b}	H _{7b} , H _{10t} , H ₉
C ₄	26.50/27.85	CH	2.23/1.77	1 H, s, H ₄	H ₃ , H ₁₈	H ₅
C ₅	24.12/27.63	CH ₂	1.97/1.47 2.26/1.74	1 H, m, H _{5a} 1 H, m, H _{5b}	H _{5b} , H _{2a} , H _{8a} H _{8b}	H ₄
C ₆	59.99/59.98	CH	3.59/3.07	1 H, m, H ₆	H ₁₁ , H ₁₉	H _{7b} , H ₄ , H _{2b} , H ₉
C ₇	18.21/21.62	CH ₂	1.50/2.62 2.17/3.45	1 H, m, H _{7a} 1 H, dd, 8.5, 8, H _{7b}	H ₄ , H ₆ , H ₉ H _{2a}	H ₆ , H ₁₁
C ₈	44.35/43.16	CH ₂	3.28/1.45 4.44/1.72	1 H, m, H _{8a} 1 H, br m, H _{8b}	H _{8b} H ₁₁	H _{2b}
C ₉	136.76/141.89	CH	5.60/5.70	1 H, m, H ₉	_____	H _{10t}
C ₁₀	117.59/114.21	CH ₂	5.10/4.89 5.13/4.93	1 H, d, 5, H _{10c} 1 H, s, H _{10t}	_____	_____
C ₁₁	66.70/71.76	CH	6.56/5.48	1 H, s, H ₁₁	H ₉	H _{7b} , H ₄ , H ₁₈
C ₁₃	155.09/147.21	C	6.45/5.57	1 H, br s, H ₁₂	_____	H ₁₁ , H ₁₉ , H ₁₇
C ₁₄	127.04/126.58	C	_____	_____	_____	_____
C ₁₅	133.85/143.86	C	_____	_____	_____	H ₁₉ , H ₂₂ , H ₁₇
C ₁₇	140.02/148.42	CH	8.94/8.40	1 H, d, 6, H ₁₇	_____	H ₁₈
C ₁₈	119.65/118.14	CH	8.26/7.45	1 H, d, 5.5, H ₁₈	H ₁₇	H ₁₁ , H ₁₇
C ₁₉	100.83/101.49	CH	7.44/7.23	1 H, d, 2.5, H ₁₉	H ₁₈	H ₂₂
C ₂₀	161.02/157.58	C	_____	_____	_____	H ₂₄ , H ₁₉ , H ₂₂ , H ₂₁
C ₂₁	123.94/121.25	CH	7.74/7.29	1 H, dd, 2.5, 2.5, H ₂₁	H ₁₇	_____
C ₂₂	127.76/131.09	CH	8.31/7.96	1 H, d, 9.5, H ₂₂	H ₂₁	H ₁₈ , H ₂₁ , H ₁₉
C ₂₄	56.70/55.60	CH ₃ O	4.60/3.88	3 H, s, H ₂₄	_____	H _{2b} , H ₉
		H	10.46	1 H, br s, $\overset{\oplus}{N}H$	_____	_____

- IR [(cm^{-1}), (complex/ligand)]: 3420 br m/3161 br s, $\nu(OH)$; 3073 m/3075 s, $\nu(=C-H)$; 2940 m/2933 s, $\nu(CH)$; 2655(new) w, $\nu(NH^+)$; 1619 m/1624 s, $\nu(=CH_2)$; 1511 m/1507 s, $\nu(C=N)$; 1313 w/1321 s, $\nu(NC_3)$; 1139 s/1132 m, $\nu(HCO-H)$ and SO_4^{2-} ; 851 w/823 s, $\delta(=CH_2)$; 619(new) m, $\nu(Cu-O)$.

- Raman spectra [(cm^{-1}) (a.u.),

(complex/ligand)]: 3079.3 (1523)/3079.4 (4500), $\nu(CH_2=CH-)$; 2857.4 (743)/2857.4 (4100), $\nu(Aryl-OCH_3)$; 1648.9 (1202)/1637.3 (8000), $\nu(C=N)$; 1431.6 (3477)/1431.7 (13000), $\nu(=CH_2)$; 1366.8 (10343)/1373.6 (52000), $\nu(NC_3)$ and $\delta(CH_3)$; 1136.8 (1296)/1136.9 (2500), $\nu(HCO-H)$; 554.0 (new, 2344), $\nu(Cu-O)$; 437.1 (new, 2155), $\nu(Cu-N)$.

- Carbon and proton peak assignments of NMR spectra of $\text{Q}\cdot 2\text{Cu}\cdot 2\text{SO}_4\cdot 6\text{H}_2\text{O}$ complex were presented in Table 1.

- $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2\text{Cu}_2(\text{SO}_4)_2\cdot 6\text{H}_2\text{O}$ (752): calcd. C 31.87, H 5.08, N 3.72, S 8.50; found C 29.92, H 5.18, N 2.84, S 8.40.

Synthesis of $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2\text{Ag}_2(\text{SO}_4)$ (3). This complex was synthesized by the same procedure of $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2\text{Cu}_2(\text{SO}_4)_2\cdot 6\text{H}_2\text{O}$. The product was milk-white.

- IR [(cm^{-1}), (complex/ligand)]: 3222 br m/3161 br s, $\nu(\text{OH})$; 3075 m/3075 s, $\nu(\text{C-H})$; 2933 s/2933 s, $\nu(\text{CH})$; 1622 m/1624 s, $\nu(\text{=CH}_2)$; 1510 m/1507 s, $\nu(\text{C=N})$; 1382 s/1360 s, $\nu(\text{NC}_3)$; 1120 s/1100 s, $\nu(\text{HCO-H})$ and SO_4^{2-} ; 859 w/823 s, $\delta(\text{=CH}_2)$; 620(new) m, $\nu(\text{Cu-O})$.

- Raman spectra [(cm^{-1}) (a.u.), (complex/ligand)]: 3079.3 (3820)/3079.4 (4500), $\nu(\text{CH}_2=\text{CH-})$; 2857.4 (3954)/2857.4 (4100), $\nu(\text{Aryl-OCH}_3)$; 1648.8 (6951)/1637.3 (8000), $\nu(\text{C=N})$; 1431.5 (7295)/1431.7 (13000), $\nu(\text{=CH}_2)$; 1366.8 (7808)/1373.6 (52000), $\nu(\text{NC}_3)$ and $\delta(\text{CH}_3)$; 1136.8 (7596)/1136.9 (2500), $\nu(\text{HCO-H})$; 456.7 (new, 10425), $\nu(\text{Ag-O})$; 429.4 (new, 9109), $\nu(\text{Ag-N})$.

- Carbon and proton peak assignments of NMR spectra were presented in table 2.

- $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2\text{Ag}_2(\text{SO}_4)$ (638): calcd. C 37.69, H 3.93, N 4.40, S 5.02; found C 36.51, H 3.70, N 4.61, S 7.10.

III - RESULTS AND DISCUSSION

The IR spectrum of free quinine shows a hydroxyl peak at 3161 cm^{-1} with percent absorption 98%, while the spectra of quinine complexes with metals show this hydroxyl peak at higher frequencies with lower percent absorption: 3420 cm^{-1} and 70% in **2**, 3222 cm^{-1} and 50% in **3**. The Raman spectra of these complexes show an existence of the O-H bond on the coordinated hydroxyl oxygen with the characteristic wavenumber 1136.8 cm^{-1} (for O-H of free quinine – 1136.9 cm^{-1}). This fact indicates that the quinine coordination with these metals was carried out via the hydroxyl O atom by means of transferring the uncoupled

electron pair on O to a $3d$ orbital of the same symmetry, and the O-H bond has been existing but percent absorption more decreased. This coordination via the hydroxyl O atom of quinine resulted in an appearance of M-O bonds in the complexes (IR: 619 for Cu-O and 620 cm^{-1} –Ag-O; Raman: 554.0 for Cu-O and 456.7 cm^{-1} –A-O).

$^1\text{H-NMR}$ spectra have also confirmed an existence of the proton (H-12) of the OH group in quinine complexes with metals by chemical shifts 6.45 and 6.63 ppm in **2** and **3**, respectively. In comparison with the δ value of H-12 in free quinine (5.60 ppm) the above protons are shifted further downfield.

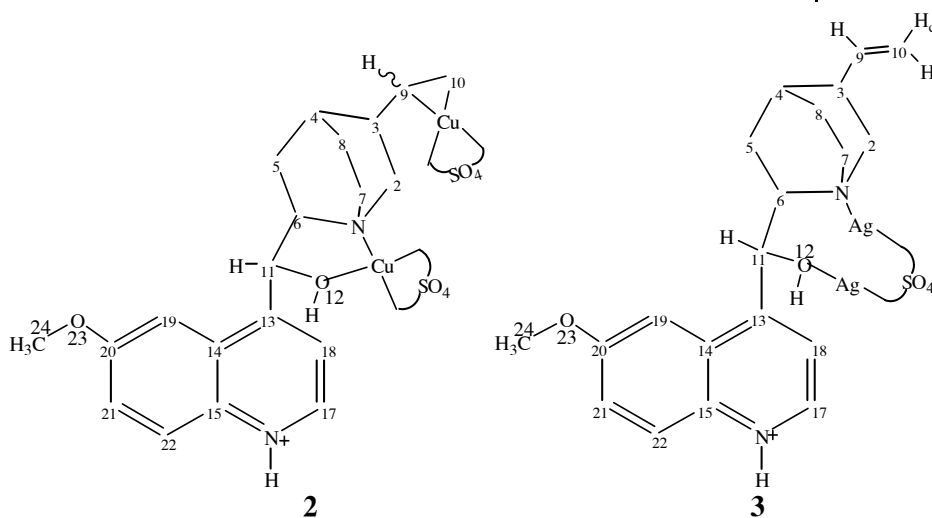
IR spectra of the complexes presented broad absorption bands with lower percent absorption in region of $2700 - 2400\text{ cm}^{-1}$ which is characteristic for NH^+ cation [10]. For **2** this band was observed at 2655 cm^{-1} . $^1\text{H-NMR}$ spectrum of this complex shows a weak and broad resonance peak at $\delta 10.46\text{ ppm}$, it is characterized for NH^+ cation. Although IR spectrum of the complex **3** did not show the characteristic peak for NH^+ but it appeared in $^1\text{H-NMR}$ spectrum at $\delta 10.61\text{ ppm}$. In each $^1\text{H-NMR}$ spectrum only one resonance peak was occurred, this indicates that the NH^+ cation was appeared only on one N atom of quinine. In our study complexes were formatted in an acidic medium, so according to [11] and [7] the NH^+ bond is assigned to the quinoline of quinine.

Comparing IR spectra of the complexes and quinine we observed large changes in absorption bands of the NC_3 group: in free quinine this band occurred at 1360 while in complexes it appeared at 1313 and 1382 cm^{-1} , respectively. Their Raman spectra also showed changes in absorption bands of this group. For example, if the free quinine absorbed energy at 1373.6 cm^{-1} with intensity of 52000 a.u., the coordinated quinine absorbed at 1366.8 and 1366.8 cm^{-1} but intensities of these bands are 10343 and 7808 a.u., respectively, in complexes. This fact shows that the quinine coordinated with metals via a

quinuclidine nitrogen atom.

Table 2: Carbon and proton peak assignments of NMR spectra of $C_{20}H_{25}N_2O_2Ag_2(SO_4)$ (DMSO)

C No	HSQC				NOESY H ↔ H	HMBC H → C
	^{13}C	(CH _x)	1H	H assignment		
C ₂	53.17/55.90	CH ₂	3.25/2.47 3.64/2.86	1 H, m, H _{2a} 1 H, m, H _{2b}	H _{2b} , H _{8b} , H _{10c} H ₁₁ , H ₁₂ , H _{8b}	H ₆ , H ₉
C ₃	36.69/39.55	CH	2.75/2.19	1 H, br m, H ₃	H _{2b} , H _{10c}	H _{5b} , H _{7b}
C ₄	26.49/27.46	CH	2.01/1.77	1 H, m, H ₄	H ₃ , H _{8a}	H _{7a} , H _{5a} , H _{7b} , H ₃
C ₅	23.77/27.43	CH ₂	1.88/1.42 2.05/1.68	1 H, br m, H _{5a} 1 H, br m, H _{5b}	H _{5b} , H _{8a} , H ₃ H ₃ , H _{8b}	H _{7a}
C ₆	59.12/60.62	CH	3.64/3.06	1 H, m, H ₆	H _{8b} , H ₁₁	H ₄ , H _{8a} , H _{2b} , H ₁₁ , H ₁₂
C ₇	17.89/24.03	CH ₂	1.45/1.64 2.08/2.73	1 H, t, 1,3, H _{7a} 1 H, m, H _{7b}	H _{7a} , H ₆ , H ₉ , H _{2b} H _{8b} , H ₃	H _{2b} , H ₃ , H ₆ , H ₁₁
C ₈	43.18/41.75	CH ₂	3.31/2.43 4.00/3.19	1 H, m, H _{8a} 1 H, s, H _{8b}	H ₁₂	H ₄ , H _{2a} , H _{2b} , H ₆
C ₉	138.79/142.53	CH	5.81/5.87	1 H, tdd, 17, 3.5, 3.5, H ₉	H ₁₁	H ₃ , H _{2a} , H _{8a} , H _{10c} , H ₆
C ₁₀	116.25/113.95	CH ₂	5.00/4.96 5.11/5.01	1 H, d, 10.5, H _{10c} 1 H, d, 17, H _{10t}	H ₉ H ₉	H ₃
C ₁₁	66.18/70.99	CH H	5.95/5.23 6.63/5.60	1 H, s, H ₁₁ 1 H, d, 3, H ₁₂	H ₁₂ , H ₁₉	H ₁₈ , H _{5b} , H _{10c}
C ₁₃	149.01/149.26	C	_____	_____	_____	H ₁₈
C ₁₄	126.07/127.05	C	_____	_____	_____	H ₁₁ , H ₁₈ , H ₂₂
C ₁₅	142.72/147.43	C	_____	_____	_____	H ₁₉ , H ₂₁ , H ₁₇
C ₁₇	146.49/147.43	CH	8.83/8.68	1 H, d, 5, H ₁₇	_____	H ₁₁ , H ₁₉
C ₁₈	119.63/119.06	CH	7.77/7.50	1 H, d, 5, H ₁₈	_____	H ₁₁ , H ₂₂
C ₁₉	101.74/102.48	CH	7.44/7.51	1 H, d, 2.5, H ₁₉	_____	H ₂₁ , H ₂₂
C ₂₀	158.16/156.73	C	_____	_____	_____	H ₂₄ , H ₁₉ , H ₂₂ , H ₂₁
C ₂₁	122.38/120.83	CH	7.55/7.39	1 H, dd, 2.5, 3, H ₂₁	H ₂₂	H ₁₉
C ₂₂	131.60/131.09	CH	8.15/7.93	1 H, d, 9.5, H ₂₂	_____	_____
C ₂₄	56.18/55.40	CH ₃ O H	4.00/3.90 10.61	3 H, s, H ₂₄ 1 H, br m, N ⁺ H	H ₁₉ , H ₂₁	_____



The quinuclidine N donor can be unambiguously derived from the $^1\text{H-NMR}$ spectra. The signals of the hydrogen atoms situated near the NC_3 (C_2 , C_6) show a considerable downfield shift in comparison to those of the free quinine (see tables 1 and 2). The hydrogen atoms linked to C_7 are a special case: they show an upfield shift, particularly, in 2 protons H-7a and H-7b suffer a more large upfield shift.

A finding of the M-N bonds in these complexes in the Raman spectra (437.1 cm^{-1} for Cu-N and 429.4 cm^{-1} for Ag-N) together an observation of a downfield shift for the $^1\text{H-NMR}$ signals of H-17 and H-22 which indicate coordination of the metal center to the quinoline N atom.

Finally we proved the coordination of a metal ion at the C=C double bond of quinine in 2 using the $^1\text{H-NMR}$ spectrum. In the $^1\text{H-NMR}$ spectrum of this complex two sets of signals in the ratio 1:1 are observed, the characteristic coupling constants of the C-10 protons, lain in *trans* (t) and *cis* (c) positions to the proton H-9, have disappeared. By coordination of the prochiral C=C double bond the C-10 atom becomes a stereogenic centre, and two diastereoisomers are formed [8].

IV - CONCLUSION

The mode of coordination of quinine with Cu was evidenced via three donor sites: the hydroxyl O atom, the quinoline N atom and olefinic double bond, and with Ag – via two sites: the hydroxyl O atom and the quinoline N atom.

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