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Synthesis and Characterization of Mixed Ligand Complexes of Caffeine, Adenine and Thiocyanate with Some Transition Metal Ions

(Sintesis dan Pencirian Kompleks Ligan Campuran Kafein, Adenin dan Tiosianat dengan Beberapa Ion Logam Peralihan)

SHAYMA A. SHAKER*, YANG FARINA, SADIA MAHMMOD
& MOHEAN ESKENDER

ABSTRACT

An ethanolic solution of caffeine was added to an aqueous solution of metal salts and followed by adding ethanolic solution of adenine and an aqueous solution of potassium thiocyanate to give complexes with general formula $[M(CA)_2(Ad)X_2]$ where CA is caffeine, Ad is adenine, X is thiocyanate ion and M is Co(II), Ni(II), Cu(II), Zn(II) and Cd(II). The resulting products were characterized using UV-visible and infrared spectroscopies. Elemental analyses were performed using C, H, N analysis and atomic absorption techniques. The magnetic susceptibility and the conductivity were also measured. The results suggested that the complexes have octahedral geometry.

Keywords: Adenine complexes; caffeine complexes; mixed ligand complexes; thiocyanate complexes

ABSTRAK

Satu larutan beretanol kafein telah ditambah kepada satu larutan berakueus garam logam. Ini diikuti dengan menambahkan larutan beretanol adenina dan satu larutan akueus kalium tiosianat untuk memberi kompleks dengan formula am $[M(CA)_2(Ad)X_2]$ dengan CA ialah kafein, Ad ialah adenine, ion X ialah tiosianat dan $M=Co(II)$, $Ni(II)$, $Cu(II)$, $Zn(II)$ dan $Cd(II)$. Produk yang terhasil dicirikan menggunakan spektroskopi UL- nampak dan inframerah. Analisis unsur diusahakan menggunakan C, H, N analisis dan teknik penyerapan atom. Kebolehtahanan magnet dan kekonduksian kompleks juga diukur. Keputusan menunjukkan kompleks membentuk geometri oktahedron.

Kata kunci: Kompleks adenine; kompleks kafein; kompleks ligan bercampur; kompleks tiosianat

INTRODUCTION

Caffeine is the most widely used behavioural active substance in the world (Esimone et al. 2008; Fredholm et al. 1999; Hashimoto et al. 2004). It is well known as hydrotropic agents and has the ability to solubilize a wide variety of therapeutic drugs. Caffeine contains two aromatic rings that affect the solubility of the aromatic anti-malarial agent (Coffman & Kildsig 1996; Evstigneev et al. 2006; Jain et al. 1996; Lim & Go 2000; Rasool et al. 1991). However, scientific studies contradict the common belief that caffeine consumption causes stunted growth in children. It is confirmed that caffeine binds to receptors on the surface of heart muscle cells which leads to an increase in the level of cAMP inside the cells by blocking the enzyme that degrades cAMP (Greenberg et al. 2007).

It is essential to understand the interactions between caffeine and adenine and their constituents with metal transition ions in order to follow many biological processes (Rilavarasi et al. 1997). A few metal-caffeine and adenine complexes have shown significant antitumor activities on different animal cancer models and various types of malignant cell lines. In addition, a distinct cytostatic effect was detected for mouse liver tumours,

murine carcinogenesis, murine leukemia and leiomyosarcoma (Hall et al. 2003; Jerzy et al. 2007; Williams et al. 2004).

Several studies on adenine complexes have shown that both N1 and N3 atoms are electronically favored coordination sites for the metals. However due to tautomerization of the imidazole hydrogen atom between N7 and N9, the nitrogen N3 and N9 have been involved in metal coordination (Rilavarasi et al. 1997). But the caffeine has methyl group at the N7 site which blocks the interaction of metal ions with N7 atom. Other binding sites such as N1 and N3 are also blocked by the methyl group (Shohreh Nafisi et al. 2003). Hence, the major binding site in caffeine would be N9 as shown in Figure 1.

Thus, the aim of this paper is to synthesize and characterize mixed ligand complexes as we attempted to throw light on the coordination position for caffeine, adenine and theophylline with the transition ions.

MATERIAL AND MEASUREMENTS

All chemicals were obtained from commercial sources and were used without further purifications ($CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, $ZnCl_2$, $Cd(NO_3)_2 \cdot 4H_2O$

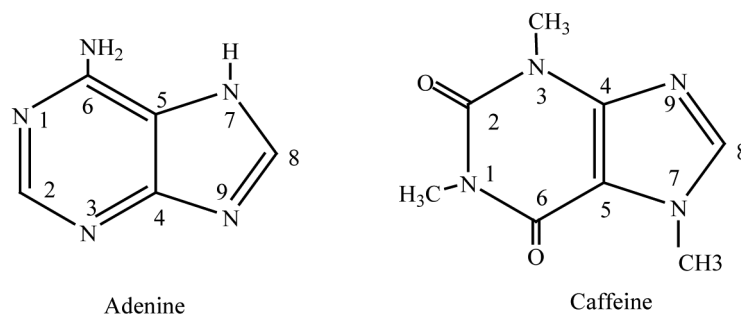


FIGURE 1. Structure of adenine and caffeine

and KSCN) from Riedel-Dehaenage. Caffeine and adenine were obtained from BDH, methanol, ethanol and dimethylsulfoxide from Fluka.

The I.R spectra in the range of 4000-400 cm^{-1} were recorded as potassium bromide discs on a Shimadzu FTIR-8300 Fourier Transform infrared spectrophotometer. UV-Visible spectra were measured in dimethylsulfoxide (DMSO) using a Shimadzu UV-Visible recorder spectrophotometer UV-160. Elemental analysis (C, H, N) was performed on a Perkin Elmer B-240 Elemental Analyzer. Determinations for metals were carried out using gravimetric methods. ^1H NMR and ^{13}C NMR spectra were recorded using the JEOL JNM-ECP 400 Spectrometer, relative to the internal standard tetramethylsilane (TMS). Conductivity measurements were carried out at 25°C in DMSO using a Philips Pw-9526 digital conductivity meter. The melting points were determined using a Stuart-Melting Point apparatus and finally the magnetic susceptibility measurements were obtained using a magnetic susceptibility balance, Model MsB-MK1.

GENERAL PROCEDURE FOR SYNTHESIS

An ethanolic solution (10 mL) of caffeine (1.33-2.75 g) was added to an aqueous solution of the metal salts. This is followed by the addition of an ethanolic solution (12 mL) of adenine (1.54-2.86 g) and an aqueous solution (10 mL) of KSCN (0.94-0.56 g). After constant stirring using appropriate amounts of materials needed as decided by the molar ratio 1:2:1:2 (M:CA:Ad:X), the resulting precipitates were filtered off, washed several times and recrystallized with 1:3 ethanol: water mixture. Then, it was dried in an oven at 65°C.

RESULTS AND DISCUSSION

The prepared complexes were found to be solids, insoluble in water but they were soluble in some organic solvents such as dimethylformamide and dimethylsulfoxide. The lower value observed of molar conductivities in DMSO indicates the non-electrolyte behavior of the complexes (Kettle 1975). Elemental analysis C, H, N and metal determination were in good agreement with general formula given for the complexes as shown in Table 1.

MAGNETIC SUSCEPTIBILITY

The magnetic moment for Co^{+2} complex should be around 3.872 B.M while the measured value of μ_{eff} were shown to be higher than the expected value. This could be related to orbital-spin coupling (David 1984). However, the values of μ_{eff} of all Ni^{+2} and Cu^{+2} complexes were found to be closer to that of spinning only models (David 1984). The complexes of Zn^{+2} , Cd^{+2} were diamagnetic as expected from their electron configuration. Physical, magnetic susceptibility and molar conductivity data are presented in Table 1.

ELECTRONIC SPECTRAL STUDIES

The electronic spectra for free ligands CA, Ad and SCN^- ion showed that the absorption bands in the UV region can be annotated as $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions. The Co(II) complex exhibited bands at 279, 408 and 981 nm which is attributed to the electronic transitions of $^4\text{T}_{1g(\text{F})} \rightarrow ^4\text{A}_{2g(\text{F})}$, $^4\text{T}_{1g(\text{F})} \rightarrow ^4\text{T}_{1g(\text{P})}$ and $^4\text{T}_{1g(\text{F})} \rightarrow ^4\text{T}_{2g(\text{F})}$ respectively. These transitions correspond for Co(II) as a distorted octahedral complex.

The electronic spectra of Ni(II) complex shows an absorption band at 278 nm, which is attributed to the electronic transition $^3\text{A}_{2g(\text{F})} \rightarrow ^3\text{T}_{1g(\text{P})}$ while its bands exhibited at 429 and 480 nm is caused by the electronic transition of $^3\text{A}_{2g(\text{F})} \rightarrow ^3\text{T}_{1g(\text{F})}$. The electronic transition of $^3\text{A}_{2g(\text{F})} \rightarrow ^3\text{T}_{2g(\text{F})}$ appeared at 778, 906 and 992 nm. These assignments correspond for Ni(II) as an octahedral complex.

The spectrum of Cu(II) complex show that its bands in the visible region which is attributed to the electronic transitions of $^2\text{a}_{1g(\text{D})} \rightarrow ^2\text{b}_{1g(\text{D})}$ and $^2\text{e}_{g(\text{D})} \rightarrow ^2\text{b}_{1g(\text{D})}$ appeared at 496 and 730 nm respectively. Therefore, these transitions confirmed that the Cu(II) complex has a distorted octahedral geometry (Lever 1968).

Finally Zn(II) and Cd(II) complexes with an electronic configuration of d^{10} did not show any (d-d) transitions. Instead the absorption bands in the spectra were due to charge transfer transitions which suffered from blue shift with hyper chromic effect (Lever 1968). These absorptions have been fully assigned in Table 2.

TABLE 1. The physical properties of the prepared complexes

Compound	Color	M.P. C°	Elemental Analysis Calc (Found %)			M	Magnetic moment Calc (Found)	Molar conductivity ohm ⁻¹ cm ² mol ⁻¹
			C	H	N			
[Co(CA) ₂ (Ad)X ₂]	Pink	250-252	39.543 (40.82)	3.603 (3.47)	30.072 (30.34)	8.33 (9.33)	3.872 (4.090)	17.04
[Ni(CA) ₂ (Ad)X ₂]	Green- Blue	240	39.556 (38.72)	3.604 (3.74)	30.082 (31.26)	8.33 (10)	2.828 (2.898)	19.73
[Cu(CA) ₂ (Ad)X ₂]	Gray	>300	39.284 (40.38)	3.580 (2.71)	29.875 (30.66)	9.03 (9.73)	1.732 (1.707)	23.43
[Zn(CA) ₂ (Ad)X ₂]	white	>300	39.181 (39.28)	3.570 (3.48)	29.797 (28.94)	9 (9.33)	Zero	20.27
[Cd(CA) ₂ (Ad)X ₂]	white	>300	36.732 (36.86)	3.347 (3.41)	27.934 (27.96)	14.93 (15.36)	Zero	25.86

TABLE 2. U.V-visible spectra of free ligands and their complexes 10⁻³M in DMSO

Compound	λ_{\max} n.m	ABS	Wave number cm ⁻¹	ϵ_{\max} Lmol ⁻¹ cm ⁻¹	assignment
CA	275	1.774	36363.636	1774	$\pi \rightarrow \pi^*$
	316	0.006	31645.569	6	$n \rightarrow \pi^*$
	365	0.014	27397.26	14	$n \rightarrow \pi^*$
Ad	273	1.599	36630.036	1599	$\pi \rightarrow \pi^*$
	320	0.153	31250	153	$n \rightarrow \pi^*$
KSCN	276	0.529	36231.884	529	$\pi \rightarrow \pi^*$
	360	0.329	27777.777	329	$n \rightarrow \pi^*$
[Co(CA) ₂ (Ad)X ₂]	279	1.712	35842.293	1712	${}^4T_{1g(F)} \rightarrow {}^4A_{2g(F)} (v_2)$
	408	0.020	24509.803	20	${}^4T_{1g(F)} \rightarrow {}^4T_{1g(P)} (v_3)$
	981	0.005	10193.679	5	${}^4T_{1g(F)} \rightarrow {}^4T_{2g(F)} (v_1)$
[Ni(CA) ₂ (Ad)X ₂]	278	1.728	35971.223	1728	
	429	0.007	23310.023	7	${}^3A_{2g(F)} \rightarrow {}^3T_{1g(P)} (v_3)$
	480	0.081	20833.333	81	
	778	0.012	12853.47	12	${}^3A_{2g(F)} \rightarrow {}^3T_{1g(F)} (v_2)$
	906	0.024	11037.527	24	
[Cu(CA) ₂ (Ad)X ₂]	301	2.500	33222.591	2500	${}^3A_{2g(F)} \rightarrow {}^3T_{2g(F)} (v_1)$
	351	0.819	28490.028	819	Charge transfere
	365	0.858	27397.26	858	Charge transfere
	496	0.050	20161.29	50	${}^2a_{1g(D)} \rightarrow {}^2b_{1g(D)} (v_3)$
	730	0.080	13698.63	80	${}^2e_{g(D)} \rightarrow {}^2b_{1g(D)} (v_1)$
[Zn(CA) ₂ (Ad)X ₂]	277	1.740	36101.083	1740	M \rightarrow L
	310	0.029	32258.064	29	Blue shift with hyper chromic effect
[Cd(CA) ₂ (Ad)X ₂]	274	1.622	36496.35	1622	M \rightarrow L
	347	0.013	28818.443	13	Blue shift

INFRARED SPECTRA STUDIES

The important infrared data of the free ligands and complexes are presented in Table 3. The infrared spectra of caffeine exhibited a strong band at 1658 cm⁻¹ which is attributed to $\nu(C=N)$. This band shifted to lower wave numbers in all the complexes by 23-3 cm⁻¹, indicating that the (C=N) group is involved in complex formation.

The spectrum of adenine shows strong bands at 1672 and 1356 cm⁻¹ that may be attributed to the C=N and C-N stretching frequencies respectively (Farukh et al.

2006; John 1965; Socrates 1980). Moreover, on complex formation these bands are shifted to the lower frequencies by 37-17cm⁻¹ and 11-6 cm⁻¹ respectively. The coordination through the nitrogen atom in (C=N) and (C-N) groups are further supported by the occurrences of new bands at 475-585 cm⁻¹ in the spectra of the complexes which, may be assigned to $\nu(M-N)$ (Roger et al. 1981).

The potassium thiocyanate spectrum showed a very strong band at 2048 cm⁻¹ which is caused by the $\nu(C=N)$. However, on complex formation this band is shifted to

higher frequencies by 12-112 cm^{-1} (Kazuo 1997; Socrates 1980). Another indication for S-bonded SCN^- is the weak bands appearing at 415-450 cm^{-1} , which could be due to the bending of the absorbed thiocyanate $\delta(\text{M-SCN})$. The bending of N-bonded NCS would be expected at higher frequencies (Michael & Rudolf 1995).

^1H NMR SPECTRA

The ^1H NMR spectrum of the caffeine in $\text{DMSO-}d_6$ has shown proton signals at 3.31, 3.56, 3.92 and 8 ppm corresponding to the three methyl groups N1-CH_3 , N3-CH_3 , N7-CH_3 and C8-H respectively. In the case of the Zn and Cd complexes the signals of N1-CH_3 , N3-CH_3 and N7-CH_3 practically are not shifted since charge densities are generally affected more at the atom which is closest to the binding site. However, the signal due to the C8-H was shifted to δ 8.30 ppm on the Zn and Cd complexation, the down field shift was attributed to the involvement of N9 in complexation (Colacio et al. 1983; Satwinder et al. 1995).

The ^1H NMR spectrum of the adenine was showed δ 7.09 (2H, s, NH_2), 7.70 (1H, s, C8-H), 8.12 (1H, s, C2-H) and 13.6 (1H, s, NH). In the ^1H NMR spectra of the Zn and Cd complexes, there is no shift of the NH_2 and NH. Nevertheless, the C2-H and C8-H were deshielded to the lower field. This fact could probably be explained that the adenine is coordinated with the metal ions through N3 and N9 (Marc et al. 2002). All the chemical shifts and the assignment of the individual ^1H resonance of the free ligands and their complexes in $\text{DMSO-}d_6$ are listed in Table 4.

^{13}C NMR SPECTRA

The ^{13}C NMR spectrum of the caffeine has shown proton signals at 27.9, 29.7, 33.5, 151.7, 148.7, 107.6, 155.4 and 141.3 ppm due to the N1-CH_3 , N3-CH_3 , N7-CH_3 , C2, C4, C5, C6 and C8. All the carbon resonance are downfield shifted relative to the corresponding resonance. Moreover, the signals proton due to the C8-H and N3-CH_3 in Zn and Cd complexes were appeared higher shifting at 144.2 and 31.4, ppm respectively. These results indicate that the caffeine is coordinated with metal ions through N9 (Latif et al. 2009).

^{13}C NMR spectrum of the adenine has shown proton signals at δ 118.9, 142.5, 146.3, 149.8 and 155.5 ppm due to the C5, C8, C2, C4 and C5 respectively. However, no significant shift was observed on Zn and Cd complexes in C6, it refers that the C6-NH_2 is not coordinated with metal ions. Furthermore, the proton signals due to the C8 and C4 are shifted to the 143.3 and 150.1 ppm respectively in complexes. These signals support the involvement of N3 and N9 in complexation (Jung et al. 2007).

CONCLUSIONS

In this paper, new mixed ligand complexes containing caffeine, adenine and SCN^- with the general formula $[\text{M}(\text{CA})_2(\text{Ad})\text{X}_2]$ where $\text{M}=\text{Co}(\text{II})$, $\text{Ni}(\text{II})$, $\text{Cu}(\text{II})$, $\text{Zn}(\text{II})$ and $\text{Cd}(\text{II})$ were synthesized. The molar conductivity of the complexes measured in DMSO solution showed that the complexes were non-electrolytes. The spectroscopic investigation of all complexes studied here indicate that the caffeine is coordinated as a mono dentate with metal

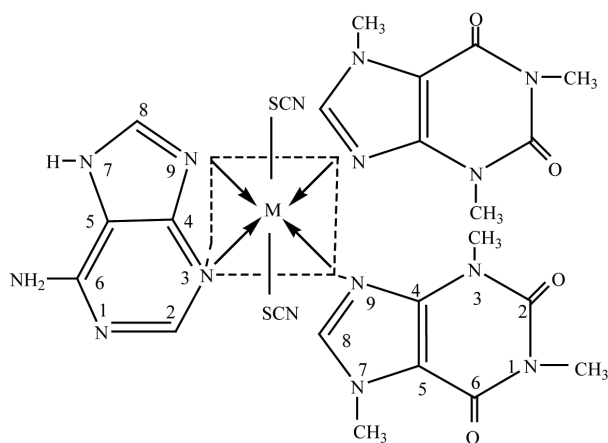
TABLE 3. The characteristic infrared absorptions of the prepared complexes

Compound	$\nu(\text{NH})$	$\nu(\text{CN})$	$\nu(\text{C=O})$	$\nu(\text{-N=C})$	$\nu(\text{-C-N})$	$\nu(\text{CS})$	$\nu(\text{M-N})$	$\delta(\text{M-SCN})$
$[\text{Co}(\text{CA})_2(\text{Ad})\text{X}_2]$	3340	2060	1690	1640	1350	730	560 505	430
$[\text{Ni}(\text{CA})_2(\text{Ad})\text{X}_2]$	3330	2110	1700	1655	1345	650	585 520	420
$[\text{Cu}(\text{CA})_2(\text{Ad})\text{X}_2]$	3320	2160	1690	1635	1350	660	540 475	415
$[\text{Zn}(\text{CA})_2(\text{Ad})\text{X}_2]$	3340	2120	1680	1640	1350	670	545 490	450
$[\text{Cd}(\text{CA})_2(\text{Ad})\text{X}_2]$	3320	2110	1705	1650	1345	675	540 500	420

TABLE 4. ^1H NMR chemical shifts (δ , ppm) of the free ligands and their complexes

Compound	N1-CH_3	N3-CH_3	N7-CH_3	C8-H	C2-H	NH_2	NH
CA	3.31	3.56	3.92	8	-	-	-
Ad	-	-	-	7.70	8.12	7.09	13.6
$[\text{Zn}(\text{CA})_2(\text{Ad})\text{X}_2]$	3.29	3.65	3.96	8.30	8.14	7	13.4
$[\text{Cd}(\text{CA})_2(\text{Ad})\text{X}_2]$	3.30	3.62	3.95	8.25	8.17	7.11	13.1

ions through the nitrogen atom N9, while adenine acts as a bidentate ligand, coordinated to metal ions through the nitrogen atoms N3 and N9. The two of thiocyanate ions are coordinated through the sulfur atom. Thus, from the results presented the metal complexes have octahedral geometry, as shown in Figure 2. Further characterisation especially the X-ray diffraction technique can be useful in elucidating the state.



M=Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)

FIGURE 2. Structure of the prepared complexes $[M(CA)_2(Ad)X_2]$

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- Shayma A. Shaker* & Yang Farina
School of Chemical Sciences & Food Technology
Universiti Kebangsaan Malaysia
43600 UKM Bangi, Selangor
Malaysia
- Sadia Mahmmod & Mohean Eskender
Chemistry Department
Ibn-Alhatham College of Education
University of Baghdad, Iraq
- *Corresponding author; email: drshaimaa611@yahoo.com

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