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# Synthesis and complexation properties of two new curcuminoid molecules bearing a diphenylmethane linkage

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# Abstract

Bis-curcuminoids **3** and **4**, bearing a diphenylmethane bridge for both compounds and a crown ether chain adapted to complex  $\text{Li}^+$  for compound **4**, were synthesized and characterized by mass and NMR spectroscopies. By their preorganized geometry, they represent a new class of curcuminoids able to complex transition metal cations. Their absorption spectra in DMF by comparison with those of curcumin **1** and dimethylcurcumin **2** have shown that the phenolate forms in the two halves are in interaction in compound **3** and are independent in compound **4**. Complexation studies have revealed a poor selectivity of curcuminoids for transition metals. Nevertheless complexation of Cu (II), studied by UV–visible absorption spectroscopy, has shown subtle differences between curcumin **1** and bis-curcuminoid **3**. These observations were supported by quantum mechanic calculations to establish the most probable structures of non- and complexed compounds.

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Keywords: Curcumin; Curcuminoids; UV-visible absorption; Complexation; Transition metals; Calculated structures

# 1. Introduction

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, **1**, is the main yellow compound of *Curcuma longa* rhizomes (turmeric) and is widely used as food coloring additive [1]. The medicinal activity of curcumin has been known since ancient times and this molecule has been the object of several investigations in the field of biology, medicine and pharmacology over the last decades. In addition to

\* Corresponding author. *E-mail address:* a.castellan@lcsv.u-bordeaux1.fr (A. Castellan). its powerful antioxidant activity [2–8], which was used in food system [9], curcumin has anti-inflammatory properties [10], HIV antiproteases activity [11] and cancer preventive properties [12].

Curcumin belongs to a group of naturally occurring 1,3-diketones in which the carbonyl groups are directly linked to olefinic carbons, conferring complexing properties to the molecule. Curcumin has been known for its ability to form colored complexes with other molecules [13-20]. Curcumin reacts with boric acid to form a red colored complex which is used for boron determination by visible absorption spectrometry [13,14]. Moreover, curcumin forms



strong colored chelates with transition metals ions  $Cu^{2+}$ ,  $Ni^{2+}$ ,  $Zn^{2+}$ ,  $Pd^{2+}$ ,  $Fe^{3+}$  [17–20].

#### 2. Experimental

# 2.1. Materials and methods

In our continuous effort in studying interactions between aromatic chromophore systems [21,22], curcumin offers an unique opportunity to design and study systems with some specific complexation ability in a restrained geometry. In this paper, complexation of transition metals mainly copper(II) by curcumin 1, dimethylcurcumin 2 and new curcuminoids 3 and 4 (Scheme 1) is described using molecular absorption spectroscopy. Compound 3 displays a pre-organized complexing system for transition metals whereas compound 4 also incorporates a crown ether cavity adapted to complex selectively lithium cation.



Scheme 1. Formulae of studied compounds.

The starting materials and solvents of appropriate grade (for synthesis or for spectroscopy) were obtained from Aldrich and used without further purification. Melting points were measured on a heating microscope Electrothermal 9100 Reichert. Studies by <sup>1</sup>H and <sup>13</sup>C NMR were made using Bruker WP400 and/or AC250 Fourier transform spectrometers (solvents CDCl<sub>3</sub> or DMF- $d_7$ ). J values are given in Hz. IR spectra were registered with a Paragon 1000 PC Perkin-Elmer FT-IR spectrometer. UV/Vis spectra were recorded on a Lambda 18 Perkin-Elmer spectrometer using justprepared curcuminoid solutions to avoid hydrolytic degradation [15]. Low and high-resolution mass spectra were obtained with a V.G. Micromass AutoSpec Q operating with a positive LSIMS ionization mode (Cs<sup>+</sup>, ion bombardment energy: 35 keV; matrix: 3-nitrobenzyl alcohol). The compounds were purified using Merck silica gel 60 (eluent dichloromethane-diethyl ether mixture). The purity of the synthesized compounds was confirmed by TLC analysis carried out on Fluka silica gel F<sub>254</sub> plates (thickness 0.20 mm). Also the purity of curcuminoids 2 and 3 was verified by HPLC using a Shimadzu liquid chromatography equipment (LC9 pump, SPD6A UV detector set at 280 nm and CR4A data station) equipped with a silica gel phase (Nucleosil 100, 5 µm) column (length 25 cm, internal diameter 4.6 mm, eluent CH<sub>2</sub>Cl<sub>2</sub>-methyl tbutyl ether 7v-3v). The amount of copper in the complexes was determined by atomic absorption spectroscopy (AAS) with an Instrument Laboratory (Type IL151) spectrometer. The mineralization of the complex was performed using persulfuric acid produced by action of hydrogen peroxide on concentrated sulfuric acid.

# 2.2. Syntheses

Curcumin 1 and dimethylcurcumin 2 were prepared according to a procedure described in the literature [23].

# 2.2.1. Bis{2-hydroxy-3-methoxy-5-[7-(4-hydroxy-3methoxyphenyl)-hepta-1E,6E-diene-3,5dioxo]]methane (**3**)

6-(4-Hydroxy-3-methoxyphenyl)-hex-5E-ene-2,4dione (feruloylacetone, 5). Acetylacetone (7.5 g, 75 mmol), boric anhydride (3.5 g, 54 mmol) and tri*n*-butyl borate (23 g, 100 mmol) were mixed in ethyl acetate (50 ml) at 0 °C with stirring. A solution of vanillin (3.75 g, 25 mmol) and *n*-butylamine (0.5 ml) in ethyl acetate was slowly added for 1.5 h. The reaction mixture was stirred at 0 °C for 90 min and then overnight at room temperature. Hydrochloric acid (0.4N) was then added to the solution, at 60 °C, until the pH became acid. The reaction mixture was stirred for an additional hour and then extracted with ethyl acetate. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. Feruloylacetone was obtained by column chromatography (eluent dichloromethane-diethyl ether 95:5) as a pale yellow solid (2.14 g, 37%), mp 144-147 °C (lit. [24] 146–147 °C). <sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>) δ: 2.20 (s, 3H, CH<sub>3</sub>-), 3.95 (s, 3H, CH<sub>3</sub>O-), 5.63 (s, 1H, -CH=C-OH), 6.5 (d, 1H, -CH=CH-C=O), 7.0 (m, 3H, H-Ar), 7.6 (d, 1H, -CH=CH-Ar).

4,4'-Dihydroxy-5,5'-dimethoxy-3,3'-methanediyldibenzaldehyde (6). Vanillin (178 g, 1.17 mol) and an aqueous solution (35%) of formaldehyde (60 g, 0.7 mol) were heated under reflux and stirring. A solution of NaOH (50 g, 1.25 mol) in 50 ml of H<sub>2</sub>O was added and the reaction mixture was refluxed for 3 h, then poured into 2.5 l of H<sub>2</sub>O at 75–80 °C before a dilute hydrochloric acid (10%) solution (0.5 l) was added dropwise. The solid was filtered, washed with water and acetone and dried under vacuum. TLC analysis indicated the presence of pure **6** (17 g, 10%), mp 255–262 °C (lit. [25] 274 °C). <sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>)  $\delta$ : 3.90 (s, 6H, CH<sub>3</sub>O–Ar); 4.0 (s, 2H, Ar–CH<sub>2</sub>–Ar); 7.3 (m, 4H, –Ar); 9.75 (s, 2H, –CHO).

*Curcuminoid* **3**. Feruloylacetone **5** (700 mg, 3.00 mmol), boric anhydride (294 mg, 4.20 mmol) and tri-*n*-butyl borate (3.22 g, 14 mmol) were heated at 80 °C, for 1 h, in DMF (30 ml). A solution of **6** (442 mg, 1.40 mmol) and *n*-butylamine (0.14 ml) in DMF (5 ml) was slowly added, for 60 min, at the same temperature. After 5 h, the reaction mixture was cooled down to 60 °C and hydrochloric acid (0.4N) was added until the pH reached

the value 2-3. The mixture was stirred for 1 h and extracted with dichloromethane. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. The solid residue was purified by column chromatography (eluent dichloromethane-diethyl ether 9:1). Compound 3 was isolated as an orange solid (360 mg, 34%), mp 149-155 °C. HPLC analysis of the isolated compound revealed only one absorption peak. FT-IR (KBr) (cm<sup>-1</sup>): 3490, 3380, 2930, 2850, 1630, 1594, 1510, 1385, 1290, 1150, 1080, 970, 830. <sup>1</sup>H NMR (400 MHz; DMF- $d_7$ )  $\delta$ : 3.90 (s, 6H, H7<sup>"</sup> and H7<sup>""</sup>), 3.92 (s, 6H, H7 and H7'), 4.02 (s, 2H, H8), 6.02 (s, 2H, Hd and Hd'), 6.77 (d, J = 15.5 Hz, 2H, Hb and Hb<sup>'</sup>), 6.81 (d, J = 15.5 Hz, 2H, Hf and Hf<sup>'</sup>), 6.90 (d, J = 7.8 Hz, 2H, H5<sup>"</sup> and H5<sup>""</sup>), 7.09 (d, J = 2.1 Hz, 2H, H6 and H6'), 7.19 (dd, J = 2.1, 7.8 Hz, 2H, H6" and H6<sup>'''</sup>), 7.33 (d, J = 2.1 Hz, 2H, H2 and H2<sup>'</sup></sup>), 7.40 (d, J = 2.1 Hz, 2H, H2<sup>"</sup> and H2<sup>""</sup>), 7.55 (d, J = 15.5 Hz, 2H, Ha and Ha'), 7.60 (d, J = 15.5 Hz, 2H, Hg and Hg'), 9.73 (br s, 4H, phenol), 16.50 (br s, enol). <sup>13</sup>C NMR (100 MHz; DMF- $d_7$ )  $\delta$ : see Table 1. The assignment was based on DEPT, COSY, HMQC and HMBC experiments (see Table 1). LSIMS-MS m/z 771 (6%, MNa<sup>+</sup>), 330 (8), 749 (6%, MH<sup>+</sup>), 329 (30), 177 (38), 176 (100); m/z 749.2630 (Found MH<sup>+</sup>); C<sub>43</sub>H<sub>41</sub>O<sub>12</sub> requires 749.2598.

# 2.2.2. 7,20-Dimethoxy-5,22-di-[7-(4-hydroxy-3methoxyphenyl)-hepta-1E,6E-diene 3,5-dioxo] {[9,12,15,18-tetraoxatricyclo[17.4.0.0<sup>3,8</sup>]tricosa-1 (23),3(8),4,6,19,21-hexaene] (**4**)

7,20-Dimethoxy-5,22-diformyl[9,12,15,18-tetraoxatricyclo[17.4.0.0<sup>3,8</sup>]tricosa-1 (23),3(8),4,6,19,21hexaene (7). Compound **6** (1 g, 3.16 mmol), sodium carbonate (1.34 g, 12.64 mmol) and 1,8-diiodo-3,6dioxaoctane (1.17 g, 5.4 mmol) in DMF (150 ml) were stirred at 100 °C, under a nitrogen atmosphere, for 30 h. The solution was filtered then evaporated. The solid residue was extracted with dichloromethane, washed by dilute hydrochloric acid and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo. The solid was purified by column chromatography (eluent dichloromethane–diethyl ether 95:5) yielding the title compound as a pale solid (650 mg, 48%), mp 171– 172 °C. FT-IR (KBr) (cm<sup>-1</sup>): 3440, 2925, 2860, 2740, 1695, 1675, 1585, 1345, 1310, 1140, 1090, 1035, 745.

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 $^{13}$ C NMR data and correlated protons in HMQC and HMBC experiments of compound **3** (100 MHz, solvent: DMF- $d_7$ )



C-number	Chemical shift (ppm)	Correlated protons in HMQC	Correlated protons in HMBC
8	31.0	8	
7, 7, 7" and 7"	57.2 and 57.4	7, 7, 7" and 7"	
d and d'	102.6	d and d'	b and b'; f and f'
2 and 2'	110.3	2 and 2'	6 and $6'$ ; a and a'
2" and 2"	112.8	2" and 2"	6'' and $6'''$ , g and g'
5" and 5""	117.4	5" and 5"	
b and b'	122.7	b and b'	d and d'
f and f'	123.0	f and f'	d and d'
6" and 6""	124.9	6" and 6"	2'' and $2'''$ ; g and g'
6 and 6'	126.4	6 and 6'	8; 2 and $2'$ ; a and a'
1 and $1'$	127.5		b and b'
1'' and $1'''$	128.6		f and f'; $5''$ and $5'''$
g and g'	142.3	g and g'	2" and 2"; 6" and 6"
a and a'	142.9	a and a'	2 and 2'; 6 and 6'
5 and 5'	149.9		8; 6 and 6'
4 and 4'	150.1		2 and 2'; 6 and 6'
4" and 4""	150.1		2'' and $2'''$ ; $5''$ and $5'''$ ; $6''$ and $6'''$
3 and 3'	151.5		2 and 2'; 7 and 7'; 8
3" and 3""	151.5		2" and 2"; 5" and 5"; 7" and 7"
e and e'	185.2		d and d'; f and f'; g and g'
c and $c'$	185.6		a and a'; b and b'; d and d'

<sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>)  $\delta$ : 3.6 (m, 8H, -CH<sub>2</sub>-O-CH<sub>2</sub>-), 3.95 (s, 6H, CH<sub>3</sub>O-Ar), 4.3 (m, 4H, -CH<sub>2</sub>-O-Ar), 4.4 (s, 2H, Ar-CH<sub>2</sub>-Ar), 7.0 (m, 4H, -Ar), 9.7 (s, 2H, -CHO).

*Curcuminoid* **4**. Feruloylacetone **5** (1.31 g, 5.6 mmol), boric anhydride (294 mg, 4.2 mmol) and tri-*n*-butyl borate (2.57 g, 11.2 mmol) in DMF (30 ml) were heated at 80 °C, for 1 h. A solution of **7** (600 mg, 1.40 mmol) and *n*-butylamine (0.15 ml) in DMF (5 ml) was slowly added (60 min). After 5 h, the reaction mixture was cooled down to 60 °C and hydrochloric acid (0.4N) was added until the reaction mixture reached pH 2-3. The mixture was stirred for

1 h and extracted with dichloromethane. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. The solid residue was purified by column chromatography (eluent dichloromethane-diethyl ether 9:1) giving compound **4** as an orange solid (240 mg, 20%), mp 104–110 °C. As for compound **3**, HPLC analysis of the isolated compound revealed only one absorption peak. FT-IR (KBr) (cm<sup>-1</sup>): 3400, 2930, 2860, 1625, 1580, 1510, 1420, 1300, 1130, 960, and 850. <sup>1</sup>H NMR (400 MHz; DMF- $d_7$ )  $\delta$ : 3.60 (br s, 4H, Hu and Hu'), 3.64 (br s, 4H, Hv and Hv'), 3.90 (s, 6H, H7 and H7'), 3.99 (s, 6H, H7" and H7<sup>'''</sup>), 4.30 (br s, 4H, Hw and Hw'), 4.37 (s, 2H,



H8), 6.05 (s, 2H, Hd and Hd'), 6.79 (d, J = 15.7 Hz, 2H, Hf and Hf'), 6.80 (d, J = 1.8 Hz, 2H, H6 and H6'), 6.81 (d, J = 15.7 Hz, 2H, Hb and Hb'), 6.89 (d, J = 7.3 Hz, 2H, H5" and H5"''), 7.19 (dd, J = 1.9, 7.3 Hz, 2H, H6" and H6"''), 7.40 (d, J = 1.8 Hz, 2H, H2" and H2"'), 7.42 (d, J = 1.8 Hz, 2H, H2 and H2'), 7.53 (d, J = 15.7 Hz, 2H, Ha and Ha'), 7.62 (d, J = 15.7 Hz, 2H, Hg and Hg'), 9.73 (br s, 2H, phenol), 16.40 (br s, enol). <sup>13</sup>C NMR (100 MHz; DMF- $d_7$ )  $\delta$ : see Table 2. The assignment was based on DEPT, COSY, HMQC and HMBC experiments (see Table 2); LSIMS-MS *m*/*z* 885 (39%, MNa<sup>+</sup>), 863 (10%, MH<sup>+</sup>), 413 (100); *m*/*z* 885.3119 (Found MNa<sup>+</sup>); C<sub>49</sub>H<sub>50</sub>O<sub>14</sub>Na requires 885.3098.

#### 2.2.3. Copper(II) complex with 3

The experimental procedure was adapted from Krishnankutty's work [19]. A solution of copper(II) acetate (7.8 mg, 0.043 mmol) in methanol (20 ml) was added within 2 h, under stirring, at room temperature, to a solution of **3** (30 mg, 0.04 mmol) and sodium acetate (9.6 mg, 0.12 mmol) in methanol (20 ml).

Table 2

<sup>13</sup>C NMR data and correlated protons in HMQC and HMBC experiments of compound 4 (100 MHz, solvent: DMF-d<sub>7</sub>)



C-number	Chemical shift (ppm)	Correlated protons in HMQC	Correlated protons in HMBC
8	31.4	8	
7, 7', 7" and 7"	57.3	7, 7', 7'' and $7'''$	
u and u'	71.6	u and u'	
v and $v'$	71.6	v and $v'$	
w and w'	74.6	w and w'	
d and d'	102.8	d and d'	b and b'; f and f'
2 and 2'	111.4	2 and $2'$	6 and 6'; a and a'
2" and 2""	112.9	2" and 2"	6'' and $6'''$ ; g and g'
5" and 5""	117.4	5" and 5"	
f and f'	123.0	f and f'	d and d'
6 and 6'	124.0	6 and 6'	8; 2 and 2'; a and a'
b and b'	124.0	b and b'	d and d'
6" and 6"'	124.0	6" and 6"	2'' and $2'''$ ; g and g'
1" and 1"	128.6		f and f'; $5''$ and $5'''$
1 and 1'	132.2		b and b'
4 and 4'	136.6		8
a and $a'$	141.8	a and $a'$	2 and $2'$ ; 6 and 6'
g and g'	142.8	g and g'	2" and 2"; 6" and 6"
3 and 3'	150.1	0 0	2 and 2'; 7 and 7'; 8
5 and 5'	150.3		2 and 2'; 8; 6 and 6'
3" and 3"	151.7		2" and 2"; 7" and 7"
4" and 4"	154.4		2'' and $2'''$ ; $6''$ and $6'''$ ; $5''$ and $5'''$
c and c'	184.6		a and a'; b and b'; d and d'
e and e'	186.2		d and d'; f and f'; g and g'

After 15 h, filtration of the solution, washing the solid with methanol and diethyl ether, allow isolation of the complex in the form of a brown powder (20 mg, 65%), mp > 300 °C; FT-IR (KBr) (cm<sup>-1</sup>): 3490, 3380, 2930, 2850, 1630, 1594, 1510, 1385, 1290, 1150, 1080, 970, 830; AAS Found: Cu, 9.05%.

# 3. Results and discussion

# 3.1. Synthesis of biscurcuminoids 3 and 4

Curcumin 1 and dimethylcurcumin 2 were synthesized according to a procedure patented by Krackov and Bellis [23] by reacting, in presence of *n*-butylamine, the acetylacetone boron complex (obtained by action of tributylborate and boric anhydride) with vanillin and 3,4-dimethoxybenzaldehyde, respectively. Increasing the acetylacetone content, reacting with vanillin, allowed the isolation of feruloylacetone 5 [24]. Compounds 3 and 4 were synthesized by the general procedure described in Scheme 2 using feruloylacetone 5, as 1,3-diketone, and the diphenylmethanes 6 and 7, respectively.

The structures of **3** and **4** were established mainly by mass spectrometry with Cs<sup>+</sup> SIMS ionization at low and high resolution, by UV–visible and FT-IR absorption spectroscopies in comparison with curcumin and by two-dimensional NMR techniques (see Section 2). As for curcumin and dimethylcurcumin, compounds **3** and **4** exist in their enol form [26]. Compounds **3** and **4** represent a new class of preorganized complexing system based on  $\beta$ -diketone units able to selectively complex transition metal cations.

#### 3.2. UV-visible absorption spectroscopy

Electronic absorption spectroscopy is a very useful technique to study complex formation [27]. Curcumin and curcuminoid derivatives display absorption in the ultraviolet and visible regions [28–31]. The absorption spectra of curcumin 1, dimethylcurcumin 2 and the biscurcuminoids 3 and 4 in DMF solutions are shown in Fig. 1; DMF, a polar non-protic solvent, was selected because it dissolves easily complexes of curcuminoids and transition metal cations. The influence of the presence, in large excess, of sodium acetate or sodium hydroxide is also presented because

complexation of  $\beta$ -diketone with transition metals was performed in their presence [18–20]. The position and intensity of the long-wavelength absorption bands indicate that  $\pi\pi^*$  transitions of the through-conjugated system dominate due to the conjugation of their  $\pi$ -electrons in the enolic configuration [28,29].

The UV/visible absorption of curcumin 1  $(1.8 \times 10^{-4} \text{ mol } 1^{-1})$  in DMF, in absence of sodium acetate or sodium hydroxide, displays an intense band at 430 nm due to the neutral molecule and a smaller one at 590 nm due to the deprotonated form [32]. In presence of sodium acetate or sodium hydroxide, the intensity of the band at 430 nm decreases and the one at 590 nm increases. Different assignments of the acid dissociation constants of curcumin can be found in the literature [20,31,32]. Toniolo et al. [32], in accordance with Dietze et al. [33] findings, indicate that curcumin deprotonation occurs in two steps: the easiest proton release involves both phenolic groups with little difference in the relevant dissociation constants, while the release of a proton from the enol system is more difficult (3 units  $pK_A$  difference depending on the medium). Borsari et al. [20], by means of NMR, potentiometric titrations and UV-visible absorption measurements, indicate that the enolic proton is the more acidic one. The presence of sodium acetate or sodium hydroxide in dimethylcurcumin 2 solution induces a decrease of the band intensity at 428 nm assigned to the neutral form in curcumin. This shows that formation of enolic anion does not create any new observable  $\pi\pi^*$  transitions and consequently, it indicates that the band at 590 in curcumin spectrum can be assigned to the phenolate anions. Consequently, sodium acetate in large excess in DMF solution is able, as does sodium hydroxide, to deprotonate both enolic and phenolic protons, in accordance with Borsari experiments [20].

The absorption behavior of 4 is very similar to curcumin's one: e.g. absorption maxima of neutral molecule and enolate anion at 425 nm and of phenolate anion at 580 nm. This indicates that each halves of compound 4 are acting quite independently in the ground electronic state.

Compound 3 displays UV-visible absorption spectra which are quite different compared to those of compounds 4 and 1. This is due to different behavior of the phenolate anions. The maximum absorption of



Reagents and conditions: i,  $CH_3COCH_2COCH_3$ ,  $B_2O_3$ ,  $(n-BuO)_3B$ ,  $n-BuNH_2$ , AcOEt, 80°C, then dilute HCl, Yield 37%; ii, CH2O, NaOH, H2O, 100°C, Yield 10%; iii, I(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>I, Na<sub>2</sub>CO<sub>3</sub>, DMF, 80°C, Yield 48%; iv, **5**, B<sub>2</sub>O<sub>3</sub>, (n-BuO)<sub>3</sub>B, nBuNH<sub>2</sub>, DMF, 80°C, then dilute HCl, Yield 34%; v, **5**, B<sub>2</sub>O<sub>3</sub>, (n-BuO)<sub>3</sub>B, nBuNH<sub>2</sub>, DMF, 80°C, then dilute HCl, Yield 20%.

Scheme 2. Synthetic procedure used for the preparation of the curcuminoid compounds 3 and 4.

neutral and enolate forms of 3 (433 nm) compares well with the one of biscurcuminoid 4 (425 nm), whereas the absorption maximum assigned to phenolate species in compound 3 is blue shift (538 nm). This peculiar behavior of curcuminoid 3 has to be related to some interactions between the two phenol anionic moieties through the diphenylmethane bridge.

# 3.3. Complexation of metal cations

# 3.3.1. Curcuminoid 3

Curcumin is known to complex transition metals [17-20,34]. With Cu(II), Ni(II), Zn(II) and Pd(II) acetates, curcumin 1 forms complexes, which were isolated and characterized by elemental analysis showing two ligands for one metal cation. In contrast, with Zr(IV) oxychloride, curcumin forms a 1/1 stoichiometric complex. Its structure was established

by elemental analysis and UV-visible absorption spectroscopy, using Job's method of continuous variation [34].

The experimental procedure given by Krishnankutty and Venugopalan [19], to obtain complexes between curcuminoids and transition metals, was applied. The procedure in this study, which consists in refluxing a mixture of the curcuminoid with the metal acetate in methanol, led to a solid material with no well define crystalline structure for Cu(II), Co(II), Hg(II), Cu(I) and Fe(III). The spectra of the isolated complexes of compound **3** with a number of transition metals, in DMF solution (where they are fully soluble), are shown in Fig. 2. It is clear that complexes with Cu(II), Fe(III) and Co(II) present very different absorption curves compared to the non-complexed compound **3**. This is indicative of a strong perturbation of curcumin chromophore by the metal cation.

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Fig. 1. UV-visible absorption spectra of DMF solutions of: (A) curcumin  $\mathbf{1}$  ( $1.8 \times 10^{-4} \text{ mol } 1^{-1}$ ) in DMF (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3); (B) dimethylcurcumin  $\mathbf{2}$  ( $2.2 \times 10^{-4} \text{ mol } 1^{-1}$ ) (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3); (C) biscurcuminoid  $\mathbf{3}$  ( $10^{-4} \text{ mol } 1^{-1}$ ) (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3); (D) biscurcuminoid  $\mathbf{4}$  ( $10^{-4} \text{ mol } 1^{-1}$ ) (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3); (D) biscurcuminoid  $\mathbf{4}$  ( $10^{-4} \text{ mol } 1^{-1}$ ) (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3); (D) biscurcuminoid  $\mathbf{4}$  ( $10^{-4} \text{ mol } 1^{-1}$ ) (—1), in presence of sodium acetate ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (—2) or sodium hydroxide ( $12 \times 10^{-2} \text{ mol } 1^{-1}$ ) (--3).

In contrast, with Hg(II) and Cu(I), the spectra are not very perturbed. This is in favor of a week interaction between the ligand and the metal.

In order to examine in more details complexation of Cu(II) by curcuminoids, absorption spectra of curcuminoids (concentration  $1.3 \times 10^{-4} \text{ mol } 1^{-1}$ ) were recorded in presence of a large excess of sodium acetate ( $1.2 \times 10^{-2} \text{ mol } 1^{-1}$ ) with variable amount of cupric acetate, in DMF solution, at 20 °C. The spectra are shown in Figs. 3–5 for dimethylcurcumin **2**, curcumin **1** and curcuminoid **3**, respectively. Similar figures were obtained when sodium hydroxide was used instead of sodium acetate.

Kuhlwein et al. [17] already described the formation of 1/2 complex (ML<sub>2</sub>) between dimethylcurcumin and Cu(II). Its maximum absorption, found at 421 nm for CH<sub>2</sub>Cl<sub>2</sub> solution, compares well with



Fig. 2. UV-visible absorption spectra of isolated complexes formed between biscurcuminoid **3** and transition metal cations (see Section 2 for Cu(II) as an example) in presence of AcONa (12 mmol  $1^{-1}$ ). (—): **2**; ( $-\Box$ -): **2**/Cu(II); ( $-\Delta$ -): **2**/Co(II); ( $-\bigcirc$ -): **2**/Hg(II); ( $-\times$ -): **2**/Cu(I); (-+-): **2**/Fe(III).



Fig. 3. UV–visible absorption of compound **2**  $(1.3 \times 10^{-4} \text{ mol } l^{-1})$  in presence of AcONa  $(0.012 \text{ mol } l^{-1})$  with variable amounts of Cu(OAc)<sub>2</sub>  $(1) \text{ 0 mol } l^{-1}$ ;  $(2) 2.8 \times 10^{-5} \text{ mol } l^{-1}$ ;  $(3) 5.6 \times 10^{-5} \text{ mol } l^{-1}$ ;  $(4) 8.3 \times 10^{-5} \text{ mol } l^{-1}$ ;  $(5) 11 \times 10^{-5} \text{ mol } l^{-1}$ ;  $(6) 14 \times 10^{-5} \text{ mol } l^{-1}$ ;  $(7) 19 \times 10^{-5} \text{ mol } l^{-1}$ .

425 nm observed in this work for DMF solution (Fig. 3). The differences observed in the absorption spectra of curcuminoids, when increasing amounts of Cu(II) are added to the solution to form complexes, are much more pronounced for curcumin 1 (Fig. 4) and biscurcuminoid 3 (Fig. 5) than for dimethylcurcumin 2 (Fig. 3). This is related to the formation of phenolate anions in compounds 1 and 3 when sodium acetate or sodium hydroxide are used in large excess (see vide infra and Fig. 1). Job's method of continuous variation was not applied to determine the stoichiometry of the complex because different complexes are formed and the curves could be analyzed by a more efficient programme: the LETAGROP-SPEFO software, designed for this type of study [35,36]. It allows the determination of the stoichiometry of the complex and its binding constants. The procedure was applied to curcumin 1 and biscurcuminoid 3 due to the large differences found in the UV-visible absorption spectra compared to dimethylcurcumin 2.

A correct analysis of the absorption curves was obtained according to the following 1/2 complexation scheme:

Compound  $\mathbf{1} + \operatorname{Cu}(\operatorname{II}) \rightleftharpoons \operatorname{LCu} K_{11}$ LCu + Compound  $\mathbf{1} \rightleftharpoons \operatorname{CuL}_2 K_{12}$  $K_2 = K_{12} \times K_{11}$  The validity of the fit was verified by the good repartition of the residuals (calculated – experimental values) and the experimental  $\chi^2 = 10.92$ , compared to the theoretical expected one ( $\chi^2 = 12.60$ ). The equilibrium constants at 20 °C are log  $K_{11} = 6.53(\pm 0.23)$  and log  $K_2 = 10.88(\pm 0.22)$ , corresponding to  $K_{11} = 3.4 \times 10^6$  and  $K_{12} = 2.2 \times 10^4$ .

The binding constants  $K_{11}$  and  $K_{12}$  for complex formation between curcumin **1** and Cu(II) are 7 order of magnitude lower in DMF, than those determined by Arrieta et al. [18] in water/dioxane solvent mixture by conductimetry; the ratio  $K_{12}/K_{11}$  being the same in both conditions. These differences between Arrieta's data and the present study are mainly due to different solvent effects with lesser dissociation of the ion-pairs in DMF than in dioxane/water mixtures.

For bis-curcuminoid **3**, the curves were correctly fitted using the following 2/1 complexation scheme. This scheme gives the best residual plot and the closest experimental  $\chi^2 = 14.03$  compared to the theoretical expected one ( $\chi^2 = 12.60$ ). The equilibrium constants at 20 °C were log  $K_{11} = 5.15(\pm 0.16)$  and log  $K_2 = 8.7(\pm 0.17)$ , which correspond to  $K_{11} = 1.4 \times 10^5$  and  $K_{21} = 3.6 \times 10^3$ .

Compound  $\mathbf{3} + \operatorname{Cu}(\operatorname{II}) \rightleftharpoons \operatorname{LCu} K_{11}$ 

 $LCu + Cu(II) \rightleftharpoons LCu_2 K_{21}$ 



Fig. 4. Electronic absorption of mixtures of curcumin **1**  $(1.3 \times 10^{-4} \text{ mol } 1^{-1})$  in presence of AcONa  $(0.012 \text{ mol } 1^{-1})$  with variable amounts of Cu  $(OAc)_2$  (A) (—):  $0 \text{ mol } 1^{-1}$ ;  $(-\Box)$ :  $1.43 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta-)$ :  $2.7 \times 10^{-5} \text{ mol } 1^{-1}$ ; (-O):  $5.38 \times 10^{-5} \text{ mol } 1^{-1}$ ; (-X -):  $7.92 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta)$ :  $10 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta)$ :  $12.7 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta)$ :  $12.7 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta)$ :  $12.7 \times 10^{-5} \text{ mol } 1^{-1}$ ;  $(-\Delta)$ :  $12.3 \times 10^{-5} \text{ mol } 1^{-1}$ ; (-X -):  $17 \times 10^{-5} \text{ mol } 1^{-1}$ ; (-X -):  $21.3 \times 10^{-5} \text{ mol } 1^{-1}$ .

 $K_2 = K_{21} \times K_{11}$ 

Mass spectrometry analysis of prepared complexes of curcuminoids 1 and 3 with Cu(II) did not show any molecular peaks even using soft ionization technique like LSIMS (see Section 2). This contrasts with our observations on dimethylcurcumin 2 and 1,7-diphenyl-1,6-heptadiene-3,5-dione/Cu(II) complexes (Cu(II)L<sub>2</sub> stoichiometry) and to published results by Krishnankutty and Venugopalan [19]. To confirm that the solid material isolated from curcuminoid 3 and cupric acetate is a copper complex, the copper content was measured by flame AAS. The value 9.05% (on a weight basis) obtained is between the expected value for a 1/1 and 2/1 complexes (7.8 and 11.45%), respectively. This is in favor of the formation of both complexes.



Fig. 5. UV-visible absorption of compound **3**  $(1.3 \times 10^{-4} \text{ mol } l^{-1})$ in presence of AcONa  $(0.012 \text{ mol } l^{-1})$  with variable amounts of Cu  $(OAc)_2$  (A) (—): 0 mol  $l^{-1}$ ; (——):  $1.43 \times 10^{-5} \text{ mol } l^{-1}$ ; (—A):  $2.7 \times 10^{-5} \text{ mol } l^{-1}$ ; (—O):  $5.38 \times 10^{-5} \text{ mol } l^{-1}$ ; (—A):  $7.92 \times 10^{-5} \text{ mol } l^{-1}$ ; (B) (—):  $7.92 \times 10^{-5} \text{ mol } l^{-1}$ ; (—O):  $10 \times 10^{-5} \text{ mol } l^{-1}$ ; (—A):  $12.7 \times 10^{-5} \text{ mol } l^{-1}$ ; (—O):  $17 \times 10^{-5} \text{ mol } l^{-1}$ ; (—A):  $21.3 \times 10^{-5} \text{ mol } l^{-1}$ .

The infrared spectrum of the complex (Cu(II)/3) is similar to the spectrum of compound 3 except that the intensity of the band at 1630 cm<sup>-1</sup>, due to stretching of intramolecular bonded carbonyl function, is reduced in the complex and the band at 1508 cm<sup>-1</sup>, due to the coordinated carbonyl of the  $\beta$ -diketone, is exalted. Similar observations were reported for curcumin derivatives [14,17].

The binding constant  $K_{11}$  determined for the complex of curcuminoid **3** with Cu (II) corresponds either to the formation of a 1/1 complex between one curcumin moiety of **3** and Cu (II) or to a 1/2 complex between the two curcumin halves of **3** and Cu (II). The value of  $K_{11}$  (1.4 × 10<sup>5</sup>), when compared to the value  $K_{11} \times K_{12} = 7.5 \times 10^{10}$  for a 1/2 complex between curcumin **1** and Cu (II), indicates some restrain geometry to form a 1/2 complex type between the two

halves of compound **3** and Cu(II). Also, if the two parts in compound **3** behave independently to form a 1/1 complex, the value  $K_{11}$  should be close for compounds **1** and **3**, respectively. There is one order of magnitude difference. All these observations probably indicate that the two curcumin halves in compound **3** are involved in the binding process between Cu(II) and their enol parts. Formation of the 1/2 complex involves some restrain geometry which comes from torsion of the two curcumin moieties through the diphenyl methane linkage (*vide supra*).

Moreover, if the two halves behaved independently in compound 3, the value of  $K_{21}$  $(=3.6 \times 10^3)$ , which represents the binding constant between the second curcumin half and Cu(II), should be close to the constant  $K_{11}$  for curcumin 1 and Cu(II) ( $= 3.4 \times 10^6$ ), though it is known that stability constants for coordination of a second ligand are generally smaller than for the first ligand. The much lower value found for  $K_{21}$  supports the hypothesis that the first atom of Cu(II) is localized between the two halves. For binding, the second Cu(II) atom should disconnect the two parts before binding with the enolate. For that reason, in the complex curcuminoid 3/Cu(II)<sub>2</sub>, the diphenylmethane structure likely adopts a head to tail conformation with the two complexed enol parts situated in a non-interacting position.

# 3.3.2. Curcuminoid 4

As indicated in Section 1, compound 4 was synthesized to form, in the same molecule, complexes with both Li<sup>+</sup> and transition metal cations. The presence of different alkaline cation acetates (Li<sup>+</sup>,  $Na^+$ ,  $K^+$ ,  $Cs^+$ ), in large excess, modifies the relative intensity of the absorption band of the phenolate species (580 nm) compared to the band at 425 nm due to the enolate and non-deprotonated molecule. With Li<sup>+</sup>, the band at 580 nm has a very low intensity. The addition of Li<sup>+</sup> in increasing quantities to a solution of compound 4 in presence of cesium or potassium acetates induces a decrease of the band at 580 nm. The same effects were observed for curcumin 1. All these observations are indicative of the absence of selective complexation of  $Li^+$  by the crown ether chain in compound 4, even though enough room is available to form the complex. The formation of tight ion pairs between phenolate and Li<sup>+</sup> appears more favored in DMF.

Complexation of compound 4 with cupric acetate in presence of a large excess of sodium acetate was also studied by UV-visible absorption spectroscopy. Different evolution of the absorption curves than for biscurcuminoid 3 was noted (results not shown). No good fitting between the calculated and experimental curves was obtained using either 1/1 or 2/1 complex schemes. This indicates that the mechanism of complex formation between compound 4 and Cu (II) is more complex than for compound 3, probably due to the involvement of Na<sup>+</sup> by the crown ether part in the complexation process.

# 3.4. Study of the geometry of complexes by quantum molecular calculations

No X-rays structures of complexes involving only curcumin derivatives and transition metal cations were published. Our attempts to obtain good crystals from curcuminoid 3 and Cu(II) were unsuccessful. Nevertheless, in order to get some insight into the structure of the complexes, we performed semiempirical quantum chemistry calculations using the AMPAC programme (AMPAC 6.0, © 1997, Semichem, 7204 Mullen, Shawnee, KS 66216 (USA)). The molecular structures were fully optimized using the SAM1d parametrization [37] that accounts for the copper element. Harmonic frequencies were determined to insure that the optimized structures are indeed minima on the potential energy surfaces. The SAM1d geometries for C-O and Cu-O bonds were confirmed against more refined Density Functional Theory [38], using a non-local B3LYP functional [39] with a DZVP2 double zeta basis set [40]. We used GAUSSIAN 98 to perform the calculation [39]. The latter was performed on a simplified model system involving a copper (II) atom complexed with two bidentate monoanions formed from hepta-1,6dien-3,5-dione. The SAM1d results were found to provide very similar geometries (bond lengths and angles). They represent conformations corresponding to the global minimum in the potential energy surface.

It was shown previously [17,19] that the complex between curcumin and Cu (II) displays a 2/1 stoichiometry involving two enolate anions. The phenol groups were chosen in their neutral form to calculate the different geometries to facilitate the calculations.







Fig. 6. (A)  $L_2Cu$  complex of curcumin 1; (B) curcuminoid 3; (C) LCu complex of curcuminoid 3.

The structure of the L<sub>2</sub>Cu complex where L is the enolate form of compound **1** is shown in Fig. 6A. The complex is centro-symmetrical, with the copper atom at the center, in a square planar environment. The Cu–O distances are 2.02 Å, very close to the observed value found in many copper oxides based crystals [41]. The C–O distances in the enolate group are stretched to 1.30 Å compared to 1.29 Å for the carbonyl group in curcumin [42] and rhodium (I) curcuminoid complexes [17].

The calculated structure for compound 3, with a Cs symmetry, is shown in Fig. 6B. The methylene bridge does not show significant strain, with a  $108^{\circ} C-C-C$ valence angle. The curcumin halves are very similar to the geometry determined for compound 1. The structure of a LCu complex in which both deprotonated enol halves are bonded to the Cu(II) cation was determined. This is shown in Fig. 6C. This complex retains a Cs symmetry. The copper site shows a quasi square planar environment and the Cu-O bond length is 2.03 Å on average, very close to that found for the  $L_2Cu$  complex of compound 1. Moreover, the methylene bridge bonding angle is barely affected (107°). Most of the necessary conformational modifications therefore occurs in each curcumin halves, with a large torsional effect at the rings junctions.

# 4. Conclusion

Curcuminoids 3 and 4 were designed and synthesized to selectively complex transition metal cations. The binding force between the transition metal cation and the central keto-enol group was found sufficient to form stable complexes and the preorganized structure given by the diphenylmethane structural element in compounds 3 and 4 does not bring additional selectivity. A better selectivity is related to higher organized systems as shown by Wong et al. [43]. For that purpose, polyaza derivatives appear more suitable than the keto-enol groups. Nevertheless, a thorough investigation of the complexation of curcumin 1 and bis-curcuminoid 3 with Cu(II) using UV-visible absorption spectroscopy combined with quantum molecular calculations led, for the first time, to new important insight on the complexation ability of curcuminoid derivatives. Such fruitful approach might be used for others

systems involving transition metal complexes, for example in the catalysis area.

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## References

- [1] V.S. Govindarajan, Crit. Rev. Food Sci. Nutr. 12 (1980) 199.
- [2] T. Masuda, K. Hidaka, A. Shinohara, T. Maekawa, Y. Takeda, H. Yamaguchi, J. Agric. Food Chem. 47 (1999) 71.
- [3] T. Masuda, K. Hidaka, T. Toi, H. Bando, T. Maekawa, Y. Takeda, H. Yamaguchi, J. Agric. Food Chem. 50 (2002) 2524.
- [4] S.M. Khopde, K.I. Priyadarsini, P. Venkatesan, M.N.A. Rao, Biophys. Chem. 80 (1999) 85.
- [5] S.V. Jovanovic, S. Steenken, C.W. Boone, G. Simic, J. Am. Chem. Soc. 121 (1999) 9677.
- [6] L. Ross, C. Barclay, M.R. Vinqvist, Org. Lett. 2 (2000) 2841.
- [7] F. Ortica, M.A.J. Rodgers, Photochem. Photobiol. 74 (2001) 745.
- [8] Y.M. Sun, H.Y. Zhang, D.Z. Chen, C.B. Liu, Org. Lett. 4 (2002) 2909.
- [9] O.I. Aruoma, B. Halliewell, G. Williamson, in: O.L. Aruoma, S.L. Cuppet (Eds.), Antioxidant Methodology in Vivo and in Vitro Concepts, AOCS Press, Champaign, IL, 1997.
- [10] M. Ali, A. Bagati, J. Gupta, Indian J. Chem. 34B (1995) 884.
- [11] Z. Sui, R. Salto, J. Li, C. Craik, P.R.O. De Montellano, Bioorg. Med. Chem. 1 (1993) 415.
- [12] J.M. Kim, S. Araki, D.J. Kim, C.B. Park, N. Takasuka, H. Baba-Toriyama, T. Ota, Z. Nir, F. Khachik, N. Shimidzu, Y. Tanaka, T. Osawa, T. Uraji, M. Murakoshi, H. Nishino, H. Tsuda, Carcinogenesis 19 (1998) 81.
- [13] R.N. Sah, P.H. Brown, Microchem. J. 56 (1997) 285.
- [14] G.S. Spicer, J.D.H. Strickl, J. Chem. Soc. (1952) 4644.
- [15] H.H. Tonnesen, M. Masson, T. Loftsson, Intern. J. Pharm. 244 (2002) 127.
- [16] B. Tang, L. Ma, H.Y. Wang, G.Y. Zhang, J. Agric. Food Chem. 50 (2002) 1355.
- [17] F. Kuhlwein, K. Polborn, W. Beck, Z. Anorg. Allg. Chem. 623 (1997) 1211.
- [18] A. Arrieta, F. Dietze, G. Mann, L. Beyer, J. Hartung, J. Prakt. Chem. 330 (1988) 111.
- [19] K. Krishnankutty, P. Venugopalan, Synth. React. Inorg. Met. Org. Chem. 28 (1998) 1313.

- [20] M. Borsari, E. Ferrari, R. Grandi, M. Saladini, Inorg. Chim. Acta 328 (2002) 61.
- [21] A. Castellan, S. Grelier, L. Kessab, A. Nourmamode, Y. Hannachi, J. Chem. Soc. Perkin Trans. 2 (1996) 1131.
- [22] S. Guilardi-Ruggiero, A. Castellan, S. Grelier, A. Nourmamode, M. Cotrait, J. Mol. Struct. 484 (1999) 235.
- [23] M.H. Krackov, H.E. Bellis, W.O. Patent 97 16403, 1997.
- [24] P.J. Roughley, D.A. Whiting, J. Chem. Soc. Perkin Trans. 1 (1973) 2379.
- [25] J.D. Garber, US Patent, 2,775,613, 1956.
- [26] U. Pedersen, P.B. Rasmussen, S.O. Lawesson, Liebigs Ann. Chem. (1985) 1557.
- [27] J.K. Hardy, The University of Akron, http://ull.chemistry. uakron.edu/analytical/index.html, 2000.
- [28] H.H. Tonnesen, A.F. Arrieta, D. Lerner, Pharmazie 50 (1995) 689.
- [29] P.H. Bong, Bull. Kor. Chem. Soc. 21 (2000) 81.
- [30] C.F. Chignell, K.J. Reszka, A.G. Motten, R.H. Sik, T.A. Dahl, Photochem. Photobiol. 59 (1994) 295.
- [31] S.M. Khopde, K.I. Priyadarsini, D.K. Palit, T. Mukherjee, Photochem. Photobiol. 75 (2000) 625.
- [32] R. Toniolo, F. Di Narda, S. Susmel, M. Martelli, L. Martelli, G. Bontempelli, Ann. Chim. 92 (2002) 281.
- [33] F. Dietze, F. Arrieta, U. Zimmer, Pharmazie 52 (1997) 302.
- [34] P. Umapathy, D.N. Sen, Ind. J. Chem. 2 (1964) 350.
- [35] B. König, M. Pelka, H. Zieg, T. Ritter, H. Bouas-Laurent, R. Bonneau, J.P. Desvergne, J. Am. Chem. Soc. 121 (1999) 1681.
- [36] L.G. Sillen, B. Warnquist, Ark. Kemi 31 (1968) 315.

- [37] M.J.S. Dewar, C. Jie, G. Yu, Tetrahedron 23 (1993) 5003.
  [38] R.G. Parr, W. Yang, Density-Functional Theory of Atoms and Molecules, Oxford University Press, Oxford, 1989.
- [39] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, GAUSSIAN 98, Revision A.7. Edited by Gaussian Inc., Pittsburgh, PA, 1998.
- [40] N. Godbout, D.R. Salahub, J. Andzelm, E. Wimmer, Can. J. Chem. 70 (1992) 560.
- [41] I. Robertson, M. Truter, J. Chem. Soc. (1967) 309.
- [42] Y. Ishigami, M. Goto, T. Matsuda, Y. Takizawa, S. Suzuki, J. Jpn. Soc. Colour Mater. 72 (1999) 71.
- [43] E.H. Wong, G.R. Weisman, D.C. Hill, D.P. Reed, M.E. Rogers, J.S. Condon, M.A. Fagan, J.C. Calabrese, K.C. Lam, I.A. Guzei, A. Rheingold, J. Am. Chem. Soc. 122 (2000) 10531.