Curcumin–Benzodioxaborole Chelates

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Abstract
The reaction of substituted benzodioxaboroles with curcumin affords crystalline chelates, whose large dipole moments as well as electronic absorption and NMR spectra were studied.

Keywords: Curcumin, benzodioxaborole, chelates, dipole moment

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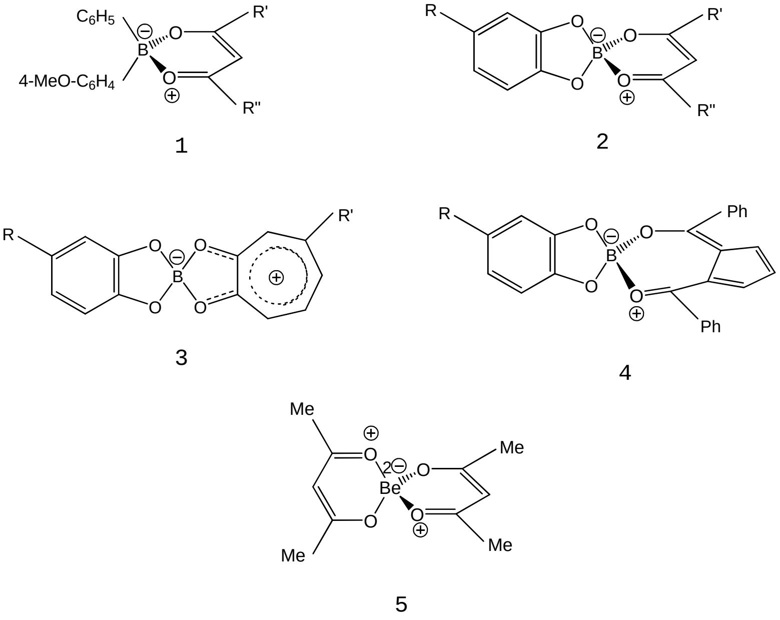
Introduction

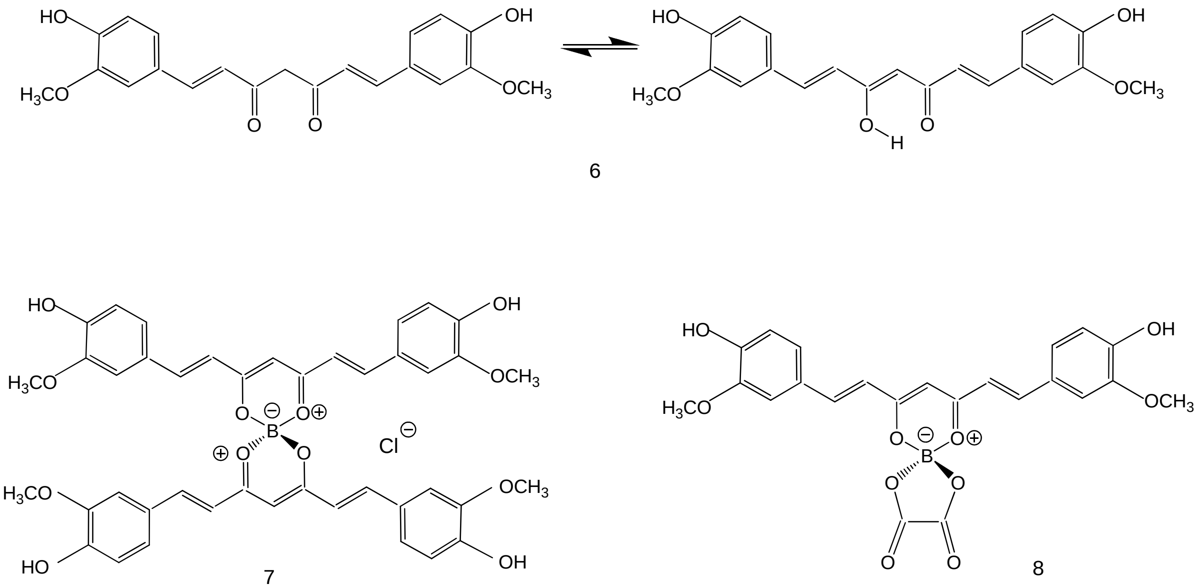
A few decades ago, it was shown in a series of papers that crystalline chelates of enolizable 1,3-diketones with borinic acid derivatives (**1**) [1–3] or of benzodioxaboroles (**2**) are easily formed.[4–10] In addition to these compounds with six-membered chelate rings, one can obtain similar chelates with equivalent oxygens from the above boron compounds with tropolones (**3,**[11–13] having five-membered chelate rings, also proved by X-ray crystallography [13]), or with dibenzoylcyclopentadiene (**4**, having seven-membered chelate rings).[7] In all these chelates the tetra-coordinate boron atom has sp^3-hybridization, as shown by investigating the enantiomerism of asymmetrically substituted spiranic structures (**2**, R ≠ H, R' ≠ R"),[14] or of chelates with diarylborinic acids with two different aryl groups (**1**, R' ≠ R").[15,16] By contrast, no stable chelates could be obtained from the above boron compounds and β-hydroxyketones or 3-hydroxypyrones, and we interpreted this negative result as being due to the fact that in this case there could be no extended conjugation between the two oxygens of the chelate ring. The electronic delocalization of boron chelates derived from tropolones (**3**) was expected to lead to high values of dipole moments, and this was confirmed by experimental data.[17,18]

Earlier, Calvin and coworkers had hypothesized that the extraordinary stability of main group and transition metal chelates with 1,3-diketones (e. g. cupric acetylacetonate) might be due to aromaticity involving the metal atom.[19] Another example showing thermal stability is the distillable beryllium bis-acetylacetonate **5**. However, our results for boron chelates in which the boron atom could not be involved in an aromatic ring (because of its sp^3-hybridization) cast doubt on the above hypothesis, and allowed only the possibility of "homoaromaticity" in such chelates.[20] It should be noted that recently Krygowski et al.[21] reported a theoretical study of enolizable 1,3-diketones with intramolecular hydrogen bonding and of their lithium derivatives reviving the early ideas about electronic delocalization in the light of Clar's Rule.



Scheme 1

Curcumin (**6**) is an enolizable 1,3-diketone which has beneficial biological effects (protection against colon cancer) and is a constituent of tumeric and curry powder used in India and elsewhere for conferring its flavor and yellow color to food.[22] It has long been known that with boric acid, curcumin forms colored dicurcuminato-boronium salts (rosocyanine, with λ_{max} = 540 nm, such as the chloride **7**).[23-27] They have been used for the colorimetric determination of boron.[28] In the presence of boric and oxalic acids, the neutral chelate rubrocurcumin (**8**) is formed.[29]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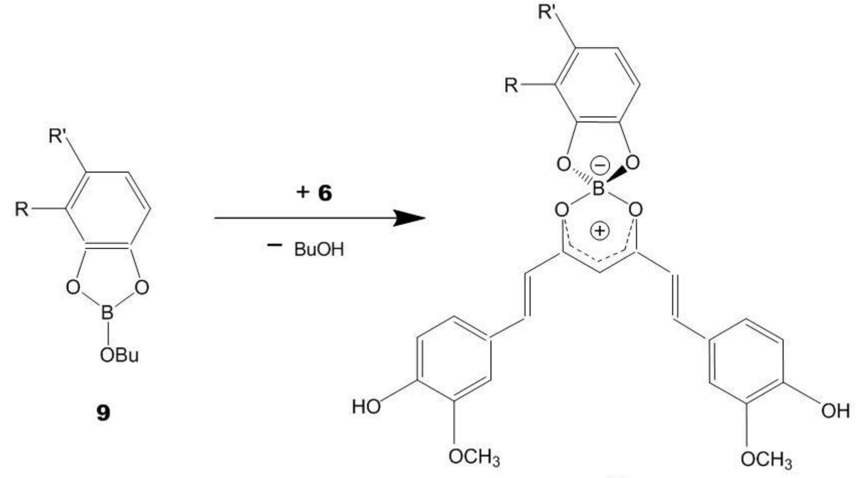
7

8

Scheme 2

Arrieta and coworkers described the electronic spectra, mass spectra, and ^{1}H-NMR spectra of curcumin and its chelates with transition metals such as Cu(II) and Ni(II).[30-35] More recently, Párkányi and coworkers reported the experimental dipole moments, solvatochromic behavior, and theoretical correlations for curcuminoid dyes.[36]

Taking into account the recent interest in the extraordinary biochemical properties of curcumin, in the present paper we describe the reaction of benzodioxaboroles (**9**) with curcumin, leading to new crystalline chelates (**10**) whose NMR spectra, electronic absorption spectra, and dipole moments have been studied and are presented below.


9

10

Scheme 3. 10a, R = R' = H; **10b**, R = Me, R' = H; **10c**, R = H, R' = Me; **10d**, R = H, R' = t-Bu

Chelates of curcumin with 1,3,2-benzodioxaboroles

On distilling away 1-butanol from a mixture of catechol derivatives and tri-n-butyl borate, one obtains 2-n-butoxy-1,3,2-benzodioxaboroles, which under normal conditions are colorless liquids. By mixing a solution of curcumin (**6**) in benzene or toluene with a slight molar excess of a 2-n-butoxy-1,3,2-benzodioxaborole (**9a** – **9d**), the brick-red colored chelates **10a** – **10d** precipitated. They were purified by recrystallization from benzene – cyclohexane. Yields are in excess of 90%. The ^{1}H-NMR and ^{13}C-NMR spectral data of these chelates in $CDCl_3$ solution are presented in Table 1, and they confirm the structure **10**. Atoms are numbered as indicated in Fig. 1.

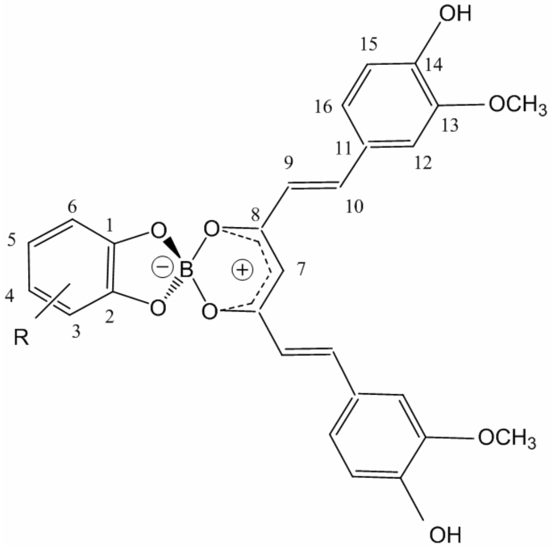


Figure 1. Numbering of atoms in boron chelates **10**.

The ^{13}C chemical shifts have been measured by indirect detection, in one-bond (gHMQC) and long-range (gHMBC) H1-C13 correlation spectra. The ^{1}H-^{13}C couplings confirmed the structural integrity of these compounds.

Table 1. NMR spectral data (δ, ppm) for boron chelates (^{1}H coupling constants *J* in Hz)

Atom	^{1}H	NMR	chemical	shift	^{13}C	NMR	chemical	shift
Comp.	10a	10b	10c	10d	10a	10b	10c	10d
R =	H	3-Me	4-Me	4-*t*-Bu	H	3-Me	4-Me	4-*t*-Bu
1	-	-	-	-	151.1	150.6	149.0	149.0
2	-	-	-	-	151.1	149.2	151.2	151.0
3	6.67m	-	6.51d	6.74d	109.4	118.6	110.3	107.1
4	6.65m	6.51d	-	-	119.4	121.1	128.1	142.2
5	6.65m	6.55dd	6.44dd	6.63dd	119.4	119.0	119.1	115.1
6	6.67m	6.50d	6.53d	6.56d	109.4	107.1	108.7	108.1
7	6.50s	6.49s	6.49s	6.46s	102.0	102.0	102.0	102.1
8	-	-	-	-	178.1	178.0	178.2	178.1
9	7.05d	7.05d	7.04d	7.04d	118.4	118.5	118.4	118.3
10	7.88d	7.88d	7.84d	7.87d	147.5	147.5	147.4	147.5
11	-	-	-	-	126.6	126.5	126.6	126.5
12	7.45d	7.46d	7.45d	7.45d	113.2	113.2	113.2	113.2
13	-	-	-	-	148.7	148.5	148.6	148.6
14	-	-	-	-	151.9	151.9	151.9	151.8
15	6.85d	6.85d	6.85d	6.85d	116.5	116.5	116.4	116.4
16	7.33dd	7.34dd	7.32dd	7.33d	125.5	125.5	125.5	125.5
OMe	3.82s	3.82s	3.82s	3.82s	56.2	56.2	21.6	56.2
OH	10.07s	10.06s	10.07s	10.07s	-	-	-	-
R(α)	-	2.13	2.19	-	-	15.2	21.6	34.6
R(β)	-	-	-	1.23	-	-	-	32.1
J(9-10)	15.6	15.6	16.1	15.6				
J(15-16)	8.2	8.5	8.5	8.5				
J(12-16)	1.8	1.9	1.7	1.7				
J(4-5)	m	8.0	7.7	8.1				
J(x-y)	m	7.9 (3-4)	1.6 (2-4)	2.2 (2-4)				
J(x-y)	m	7.3 (3-5)	-	-				

Table 2 presents the dipole moments determined as described previously.[37] One should note that previously determined dipole moments were 3.32 D for curcumin,[36] 3.12 D for dicinnamoylmethane (the parent compound of curcumin without hydroxy and methoxy groups),[36] 2.62 D for catechol,[38,39] and 1.26 D for catecholborane.[40]

Table 2. Experimental and calculated dipole moments (in Debye units,D)

Compound	R	R’	Dipole moment, μ (D)	
			Exptl.[a]	Calcd.[b]
10a	H	H	10.85	8.34
10b	Me	H	9.85	7.65
10c	H	Me	10.10	8.20
10d	H	t-Bu	10[c]	8.09

[a] In 1,4-dioxane.

[b] Calculated by the PM3 method [45] with full geometry optimization and the use of the Polak-Ribière algorithm.

[c] Estimated value.

The relatively large dipole moments of the compounds under study are very similar. This is not surprising because the alkyl groups that constitute the difference between all compounds exert only a small effect on the overall dipole moment of the boron chelates. In addition to the experimental dipole moments, Table 2 contains calculated dipole moments. The values presented in this table were obtained by using the PM3 method. We have also carried out calculations using the AM1 and MNDO methods but the results obtained by the PM3 method seem to be most consistent and to provide the best agreement with the experimental values, although they are typically lower. This is observed quite often, because the calculations do not take into account solvent-solute interactions and other factors.

The UV-Vis spectra were measured in methanol. The absorption maxima are shown in Table 3. Electronic absorption spectra of curcuminoids were discussed in a previous publication by Párkányi et al.,[36] and also by Arrieta [33] and Chignell et al.[41] The longest-wavelength band due to the chelate as a whole does not differ appreciably between all compounds, and is situated around 510 nm. The intermediate band around 420 nm appears as a shoulder for **10a** and **10b**, and is split into two bands for **10c**, **10d**; this band corresponds to the curcumin moiety, as seen below. The band around 270 nm is characteristic for benzenoid rings.

Curcumin itself exhibits absorption maxima at 265, 422, and 436 nm (shoulder);[36] the first band at 265 nm corresponds to a $\pi\rightarrow\pi^*$ transition, whereas the band at 422 nm can be due either to an $n\rightarrow\pi^*$ transition as proposed by Balasubramanian,[42,43] or to a combination of $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions, according to our calculations. Free catechol has two absorption bands at 210 and 275 nm, both being $\pi\rightarrow\pi^*$ transitions.[44]

Table 3. Electronic absorption maxima of chelates **10** in methanol [a]

Comp.	R	Conc. (mol/L)	$\lambda_{max,}$ nm (log ε)		
10a	H	2.0 x 10^{-5}	272 (3.99),	421*sh* (4.36),	508 (4.65)
10b	3-Me	1.3 x 10^{-5}	271 (4.09),	417*sh* (4.43),	510 (4.82)
10c	4-Me	2.0 x 10^{-5}	273 (3.95),	432 (4.44), 440 (4.44),	507 (4.50)
10d	4-t-Bu	6.6 x 10^{-6}	267 (3.85),	418 (4.77), 440 (4.73),	510 (4.6)

Experimental Section

General Procedures. For determining the dipole moments, the dielectric constants were measured in 1,4-dioxane at 25ºC on a dipole meter model DM-01 (Wissenschaftlich-Technische Werkstätten, Weilheim, Germany). The refractive indices, *n*, were obtained with an Abbé refractometer (Bausch & Lomb, Rochester, NY).

The UV-Vis spectra were measured in methanol on a Cary 3 spectrophotometer (Varian Inc., Palo Alto, CA) using 1 cm quartz cells.

The dipole moments were calculated by MNDO, AM1, and PM3 semiempirical methods by using the HyperChem program set,[45] with full optimization geometry and use of the Polak-Ribière algorithm. A gradient norm less than 0.05 $kJ\times Å^{-1}\times mol^{-1}$ was the target.

NMR spectra were recorded on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe, operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million relative to internal TMS. The ^1H NMR and ^{13}C NMR chemical-shift assignments are based on the one-bond and long-range ^1H–^{13}C correlations seen in the gradient heteronuclear multiple-bond correlation spectra (ghmbc).

General procedure for preparation of 10a – 10d

This was carried out by treating a benzene solution of curcumin with a slight molar excess of freshly distilled 2-(n-butoxy)-1,3,2-benzodioxaborole (prepared from tri-n-butylborate and the corresponding catechol derivative). The precipitated chelate was filtered off, washed with benzene and n-hexane, and recrystallized from benzene – cyclohexane. Yields were 90% or higher.

As for other boron chelates, elemental analyses do not afford correct data because of oxygen-resistant boron carbide formation; however, high-resolution mass spectra are provided.

Chelate of curcumin with 1,3,2-benzodioxaborole (10a). $C_{27}H_{23}BO_8$. M. p. 153-155ºC. High-resolution mass spectrum: calc. *m/z* = 487.1569 (^{11}B), 486.1491 (^{10}B), found: *m/z* = 487.1508, 486.1481 (40), 456.1469 (16), 395.1333 (8), 307.0941 (33), 289.0780 (17), 177.0519 (19), 154.0504 (100).

Chelate of curcumin with 3-methyl-1,3,2-benzodioxaborole (10b). $C_{28}H_{25}BO_8$. M. p. 177-178ºC. High-resolution mass spectrum: calc. *m/z* = 500.1648 (^{10}B), found: *m/z* = 500.1638 (72), 470.1526 (29), 351.1031 (10), 307.0955 (23), 289.0802 (12), 177.0541 (34), 154.0525 (100).

Chelate of curcumin with 4-methyl-1,3,2-benzodioxaborole, $C_{28}H_{25}BO_8$ (10c). M. p. 109-111ºC. High-resolution mass spectrum: calc. *m/z* = 500.1648 (^{10}B), found: *m/z* = 500.1659 (23), 470.1595 (10), 460.1351 (6), 351.1048 (3), 307.0998 (36), 289.0835 (17), 177.0495 (9), 154.0537 (100), 137.0466 (63).

Chelate of curcumin with 4-*tert*-butyl-1,3,2-benzodioxaborole, $C_{31}H_{31}BO_8$ (10d). M. p. 175-177ºC. High-resolution mass spectrum: calc. *m/z* = 543.2196 (^{11}B), 542.2118 (^{10}B), found: *m/z* = 543.2153 (40), 542.2147 (58), 512.2003 (12), 393.1545 (5), 307.0930 (36), 289.0762 (18), 219.1695 (6), 177.0549 (22), 154.0506 (100), 137.0448 (77), 107.0545 (24).

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