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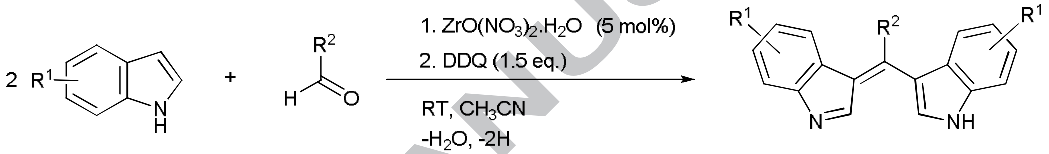

Zirconium(IV)-catalyzed one-pot synthesis and oxidation of bis- and tris(indolyl)methanes into conjugated chromophores as new pH indicators or calorimetric chemosensors for transition metals

Alireza Khorshidi*, Neda Mardazad, Zahra Shaabanzadeh

Department of Chemistry, Faculty of Sciences, University of Guilan, P.O. Box: 41335-1914, Rasht, Iran.

Abstract

Zirconium(IV) oxynitrate hydrate catalyzed efficiently the condensation reactions of indoles and aldehydes in acetonitrile, under ambient conditions. The bis- or tris(indolyl)methane products were then dehydrogenated in one pot by using a stoichiometric amount of DDQ, to give conjugated chromophores that showed feasible applications as new pH indicators with excellent sensitivity in the pH range 8-10. Hypsochromic effects were observed in the presence of transition metal cations in acetonitrile with a significant color change for cobalt(II).

Keywords: Zirconium(IV) oxynitrate hydrate; Chromophore; Dehydrogenation; pH indicator; (indolyl)methane

Numerous indole derivatives occur in many pharmacologically and biologically active compounds.[1] In particular, bis(indolyl)methanes possess a wide range of biological activity and their synthesis has received a considerable amount of interest.[2,3] Generally, bis(indolyl)methanes are prepared by

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* Corresponding author. Tel: +98 911 339 7159, Fax: +98 131 322 0066
Email-address: khorshidi@guilan.ac.ir

the condensation of indoles with various aldehydes or ketones in the presence of either protic or Lewis acids; many other methods have also been devised for their preparation.[4] Little attention however, has been paid to the dehydrogenation of bis- or tris(indolyl)methanes. Contributions in this context include a few examples and their application mainly as anion receptors.[5-8] Our interest in the study of indole-type molecules, their derivatives, and the catalytic activity of transition metal species in the synthesis of these compounds,[9-13] prompted us to evaluate the synthesis of bis- and tris(indolyl)methanes, the oxidation of the *meso* hydrogen, and the study of the spectroscopic and chromogenic behavior of the products at different pH values and toward various transition metal cations.

During our previous work on the preparation of bis- and tris(indolyl)methanes,[9] we noticed that during the purification step, the products were unstable on chromatographic silica gel plates and their color changed slightly. This observation was attributed to the possible oxidation of the products on exposure to air. Therefore, we were decided to investigate the oxidation of the aliphatic C-H bond at the *meso* position of bis- or tris(indolyl)methanes. With a one-pot procedure in mind, 2-methylindole and 3-phenoxybenzaldehyde were selected as substrates, and the reaction conditions were optimized with respect to the oxidant, solvent and temperature. Since most bis- or tris(indolyl)methanes are insoluble in alcohols such as methanol and ethanol, aprotic solvents were considered, and the best solvent was found to be CH_3CN (Table 1). The best catalyst in this solvent was found to be zirconium(IV) oxynitrate hydrate with an optimum loading of 5 mol% (entry 3).

With respect to the oxidant, the best result was obtained by using 1.5 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Finally, it was found that employing elevated temperatures had no significant effect on the yield of the target product.

<<Table 1>>

The optimized conditions for the one-pot synthesis and oxidation of bis- and tris(indolyl)methanes are summarized in Scheme 1.

<<Scheme 1>>

With optimized conditions in hand, a variety of indoles and aldehydes were used in this reaction to demonstrate the generality and scope of the process. Typical results are shown in Table 2.

<<Table 2>>

Indoles and aldehydes bearing different functional groups yielded the desired products. To the best of our knowledge, this is the first report on the one-pot application of zirconium(IV) oxynitrate hydrate in the condensation reaction of indoles with aldehydes and subsequent oxidation of the products with DDQ. Oxidation of the aliphatic C-H bond at the *meso* position of bis- and tris(indolyl)methanes is associated with deep color changes due to the formation of a highly conjugated chromophore system. Thus we can propose products **4a-j** as potential dye molecules. The structures of the products were established from their spectra (FTIR, ^{1}H-NMR and ^{13}C-NMR). Generally, the bis- and tris(indolyl)methanes exhibited a singlet for the aliphatic C-H proton (*meso* position) at about 5.5-6.0 ppm,[9] which disappeared upon oxidation. Since all of the products were soluble in DMSO-d_6, the broad singlets for the NH protons were diminished due to exchange with residual water present in DMSO. Intermolecular hydrogen bonding may be responsible for the reduced intensity of the NH stretching vibrations in the FTIR spectra. The presence of both an anion receptor subunit[5] (NH) and a cation receptor moiety (N) prompted us to evaluate the behavior of the products as potential pH indicators. Many dyes have been used as pH indicators due to the reversible action of acids and bases. It was found that our products could act as pH indicators in the range 9.0-10.5 with an extremely sharp and clear color change. For example, the color transition along with the conjugated acid-base structures of compound **4d**, are depicted in Figure 1.

<<Figure 1>>

A dilute solution of **4d** (5×10^{-6} M, EtOH 70%), appeared red in color and displayed strong absorption bands at 400 and 550 nm, which may be attributable to the intramolecular charge transfer (ICT) arising from the π-extended conjugated structure of this compound, according to Shao et al.[5] Upon addition of dilute acid (0.1 M HCl) or alkali (0.1 M NH_4OH) to this solution, however, color changes were observed. Figure 2 shows the spectroscopic behavior of **4d** at different pH values. While decreasing the pH only increased the intensities of the above mentioned bands, increasing the pH resulted in the disappearance of these bands and the appearance of a new band at 450 nm.

<<Figure 2>>

To determine the color transition range of the indicator, the absorption was measured at 450 nm with addition of dilute alkali solution (NH_4OH). The result is shown in Figure 3. As is apparent, a sharp color transition was observed in the pH range of 8.0 to 10.0, which is comparable to thymol blue and phenolphthalein.[14]

<<Figure 3>>

Encouraged by these results, we decided to study the ability of our products sense transition metal cations. It was found that these conjugated chromophores interact with transition metal cations and exhibit spectral changes. For example, compound **4d** exhibited hypsochromic effects in the presence of M^{2+} transition metal cations (where M=Ni, Co, Mn and Hg). The most intense color change was observed for Co^{2+} in acetonitrile solution. The UV-Vis spectrum of **4d** (5×10^{-6} M) and Co^{2+} (1.25×10^{-4} M) solutions in CH_3CN, before and after mixing, are shown in Figure 4. An excess amount of Co^{2+} (25 equivalents) was selected to ensure maximum interaction.

<<Figure 4>>

As is shown in Figure 4, Co^{2+} shows classic transitions of a d^7 cation in an octahedral field corresponding to transitions from the $^4T_{1g}(F)$ ground state to the $^4T_{1g}(P)$, $^4A_{2g}$ and $^4T_{2g}$ excited states of the metal cation. After mixing **4d** and Co^{2+} solutions, a blue shift of about 30 nm for the 414 nm band of **4d** was observed that might be due to N-bonding of **4d** to the metal center.

The spectral responses of **4d** to other M^{2+} transition metal cations (where M=Ni, Co, Mn and Hg) are depicted in Figure 5.

<<Figure 5>>

In order to gain insight into the interaction mechanism between the cation and the receptors, a similar experiment with Co^{2+} was conducted in acetonitrile at acidic pH (pH=2.0). In this case, the blue-shifted band was not observed upon addition of the metal, revealing that no interaction took place, due to the fact that the indol-3-ylidene moiety of **4d** was N-protonated. A 4:1 stoichiometry of the complex as indicated by the changes in the colorimetric response of **4d**, in the presence of the varying concentrations of Co^{2+} (Figure 6), is also in agreement with N-coordination of the metal.

<<Figure 6>>

In conclusion, the efficient one-pot formation and dehydrogenation of bis- and tris(indolyl)methanes catalyzed by zirconium(IV) oxynitrate hydrate as a homogeneous catalyst and DDQ as the oxidant has been described. The products showed applications as pH indicators with excellent sensitivity. The UV-Vis spectroscopy analyses of mixtures of these conjugated structures with various transition metal cations revealed that these conjugated compounds can be utilized as effective chromophores for sensing these cations. We are currently undertaking further studies on the conjugated structures shown in this work as well as similar systems.

General procedure for the preparation of 4a-j

Indole **1** (2.00 mmol), $ZrO(NO_3)_2.H_2O$ (12.46 mg, 0.05 mmol), aldehyde **2** (1.05 mmol) and MeCN (5 mL) were added to a flask and the resulting mixture stirred at room temperature until the disappearance of the starting indole was complete (monitored by TLC). This step typically took between 3 to 10 min. After completion of the first step, a solution of DDQ (1.5 equiv.) in MeCN was added dropwise over 10 min. Upon addition of the oxidant, the color of the solution turned deep red. After completion of the oxidation step (see Table 2, indicated by TLC), the mixture was purified by short column chromatography (*n*-hexane/EtOAc, 10:4) to provide the desired products.

*2-Methoxy-4-[(2-methyl-1H-indol-3-yl)(2-methyl-3H-indol-3-ylidene)methyl]phenol (**4a**):*

Dark red solid, m.p. 259-261 ^{o}C, IR (KBr): υ (cm^{-1}); 3408, 1483, 1371, 1346, 1226, 1120, 746. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): δ = 2.07 (s, 6H, CH_3), 3.46 (s, 3H, -OCH_3), 6.30 (d, 1H, *J* = 9.6 Hz), 6.63 (s, 1H), 6.71-6.87 (m, 4H), 7.05 (t, 2H, *J* = 7.2 Hz), 7.21 (d, 1H, *J* = 8.8 Hz), 7.38 (d, 2H, *J*= 7.8 Hz), 11.9 (bs, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): δ = 13.0, 54.4, 111.4, 112.5, 118.8, 120.3, 121.6, 124.2, 124.8, 128.5, 131.0, 135.9, 137.2, 141.0, 148.8, 151.8. Anal. Calcd. for $C_{26}H_{22}N_2O_2$; C, 79.16; H, 5.62; N, 7.10; found: C, 79.15; H, 5.65; N, 7.14.

Acknowledgements

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Table 1. The effect of experimental parameters on the one-pot condensation and oxidation reaction between 2-methylindole and 3-phenoxybenzaldehyde [a]

Entry	Catalyst	Loading (mol%)	Temp (°C)	Solvent	Oxidant	Yield (%)
1	None	-	RT	CH_3CN	DDQ	0
2	Cu^{2+}	5	RT	CH_3CN	DDQ	45
3	ZrO^{2+}	5	RT	CH_3CN	DDQ	77
4	I_2	20	RT	CH_3CN	DDQ	32
5	ZrO^{2+}	5	RT	1,4-Dioxane	DDQ	38
6	ZrO^{2+}	5	RT	CH_2Cl_2	DDQ	<5
7	ZrO^{2+}	5	RT	CH_3CN	H_2O_2	37
8	ZrO^{2+}	5	RT	CH_3CN	O_2	18
9	ZrO^{2+}	5	50	CH_3CN	DDQ	73

[a] The reaction was carried out according to the general experimental procedure.

Table 2. $ZrO(NO_3)_2.H_2O$-catalyzed formation of bis- and tris(indolyl)methanes, and their oxidation to conjugated chromophores [a]

Entry	Indole	Aldehyde	Dehydrogenated product	Time (min), Yield [b] (%)
1	2-methylindole	vanillin	**4a**	160, 73
2	2-methylindole	3-nitrobenzaldehyde	**4b**	130, 65
3	2-methylindole	3,4-dimethoxybenzaldehyde	**4c**	120, 56
4	2-methylindole	3-phenoxybenzaldehyde	**4d**	175, 77
5	2-methylindole	2-nitrobenzaldehyde	**4e**	210, 65
6	2-methylindole	4-chlorobenzaldehyde	**4f**	250, 47
7	2-methylindole	indole-3-carbaldehyde	**4g**	150, 55
8	5-nitroindole	indole-3-carbaldehyde	**4h**	150, 42
9	5-methoxyindole	indole-3-carbaldehyde	**4i**	150, 57
10	5-bromoindole	indole-3-carbaldehyde	**4j**	90, 43

[a] All products were characterized by ^1H NMR, ^{13}C NMR and IR data. [b] Isolated yields.

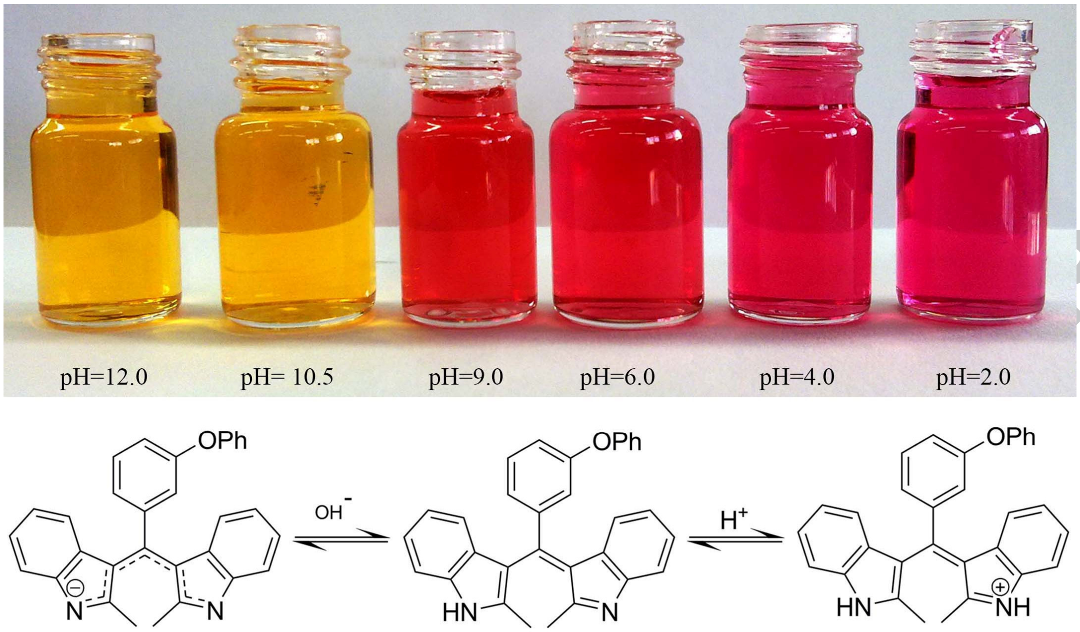


Figure 1. pH indication using **4d**

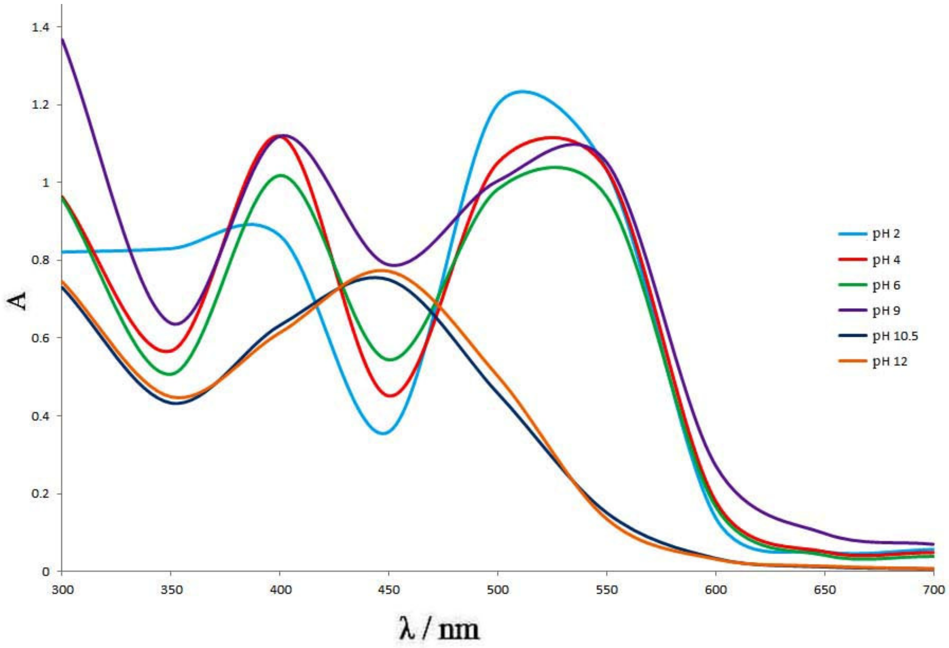


Figure 2. Spectral changes of **4d** (5×10^{-6} M, EtOH 70%) at different pH values.

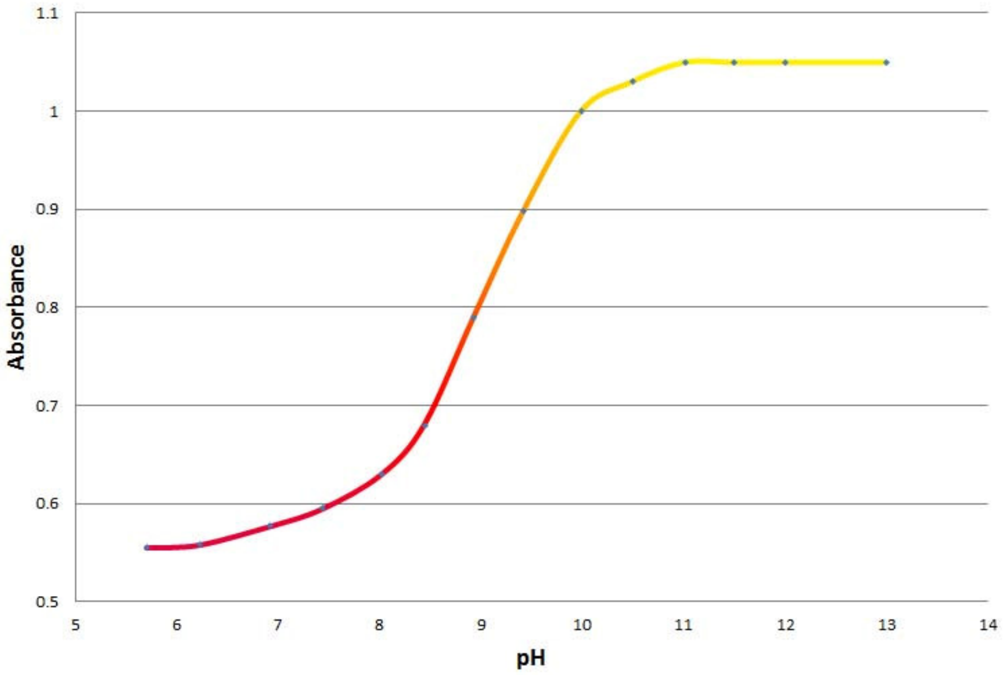


Figure 3. Effect of pH on the absorption intensity titration of **4d**: λ_{max} 450 nm.

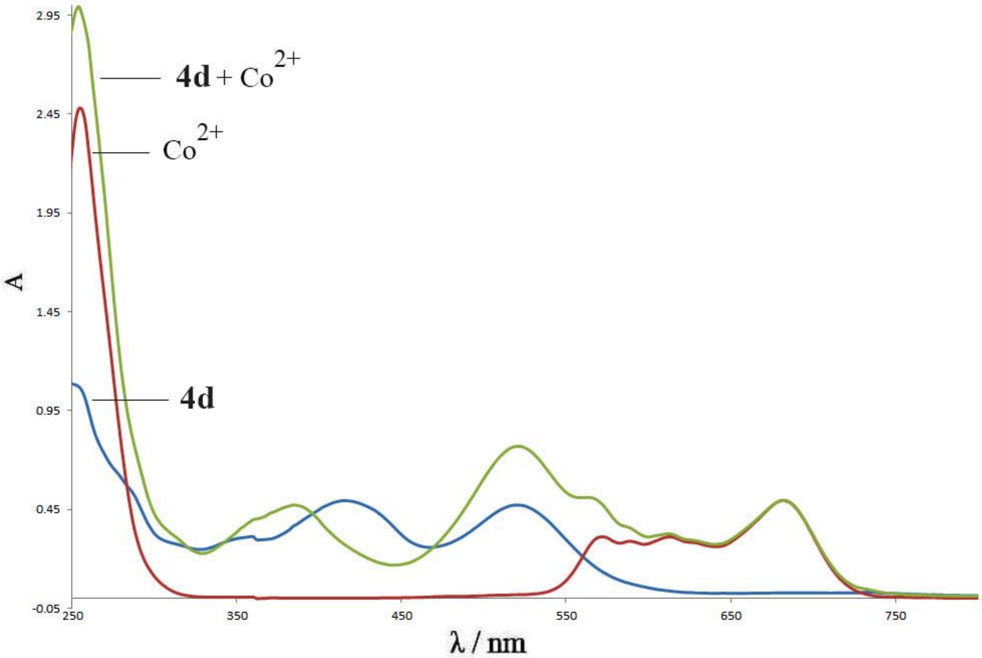


Figure 4. UV-Vis spectra of **4d** (5×10^{-6} M), Co^{2+} (1.25×10^{-4} M), and a 1:1 mixture of **4d** and Co^{2+} solutions in acetonitrile.

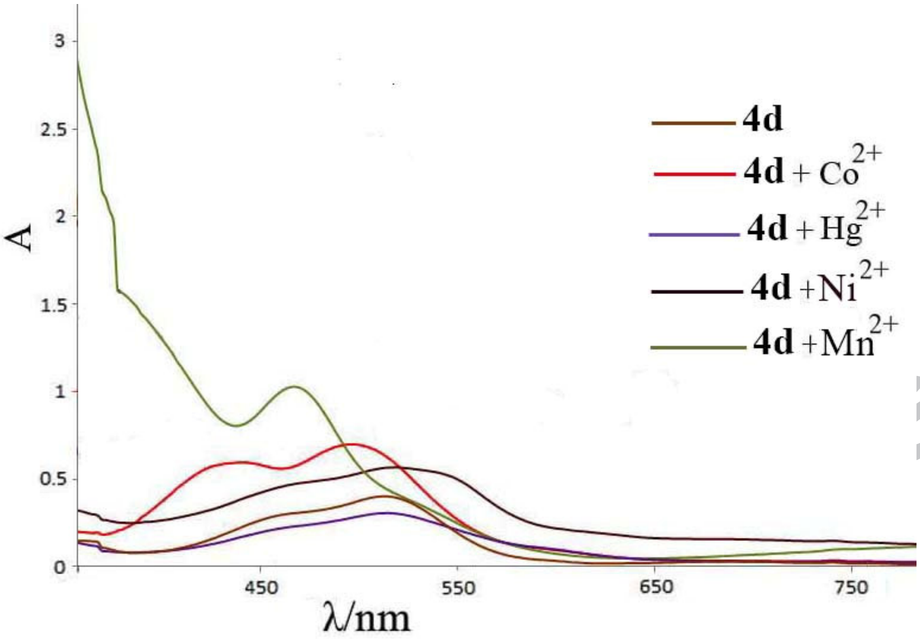


Figure 5. The spectral responses of **4d** to other M^{2+} transition metal cations (where M=Ni, Co, Mn and Hg)

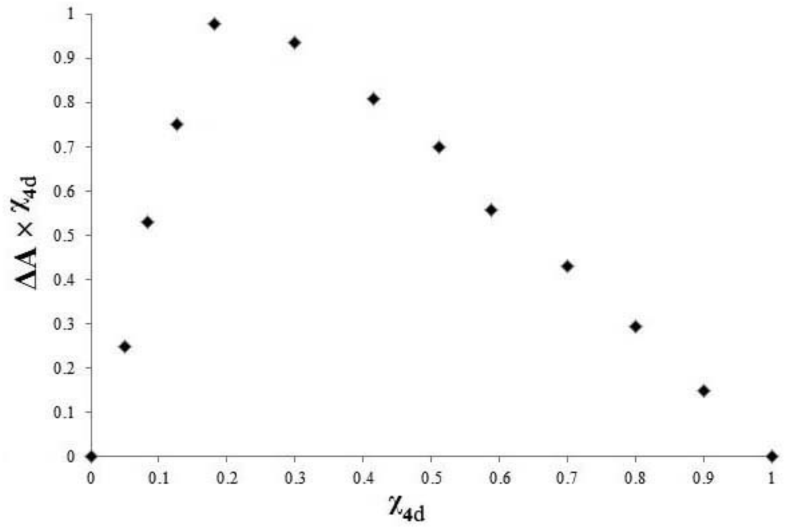
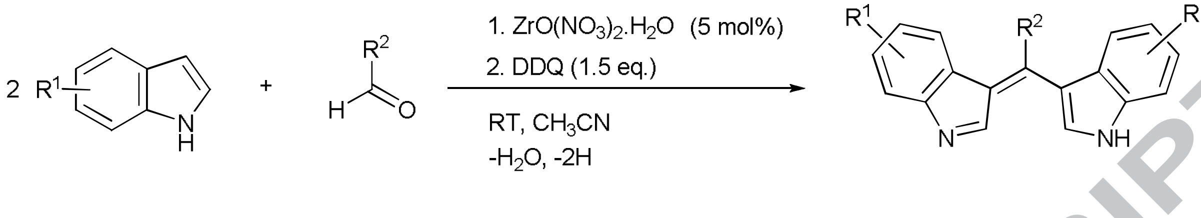


Figure 6. A Job plot for the complexation of **4d** with Co^{2+} indicating the formation of a 4:1 complex



1a-d **2a-g** **4a-j**

Scheme 1. One-pot synthesis and oxidation of bis- and tris(indolyl)methanes into π-conjugated products