

Side Chains of Cobalt Corrinoids Control the Sensitivity and Selectivity in the Colorimetric Detection of Cyanide

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Substitution of Co^{III}-bound water by cyanide allows the rapid colorimetric detection of micromolar amounts of cyanide with cobalt corrinoids. Negatively charged side chains at the periphery of these metal-based sensors increase the selectivity of cyanide versus thiocyanate, the most disturbing anion, by a factor of 30 through additional supramolecular interactions in water.

Cyanide is produced in large quantities for different industrial applications. Normally, cyanide levels in natural water sources are negligible low, but more than 30 major accidental releases have been reported since 1975, posing a threat to the environment.¹ The toxicity of cyanide originates from its binding to cytochrome *a*₃, which inactivates cellular respiration.² Therefore, it is necessary to safely detect and remove this dangerous anion either from industrial wastewater or after an accidental release. Recently, carefully designed receptors for the *naked eye* detection³ of cyanide have attracted much attention.⁴ Their mode of action is based on either hydrogen-bonding,⁵ metal coordination,⁶ or bond-forming reactions between the nucleophilic cyanide and

either an electrophilic carbon^{3c,7} or a boron center.⁸ One major problem to overcome is still selectivity toward other disturbing anions. Here, we report an alternative in the form of a new sensor: a cobalt(III) corrinoid that modulates the sensitivity as well as the selectivity in water with its negatively charged side chains.

The affinity of cyanide to corrinoids had already been known for decades⁹ and resulted in different systems for its determination,¹⁰ but the influence of the side chains with respect to sensitivity and selectivity has not yet been investigated. We reported recently the visual detection of millimolar cyanide with vitamin B₁₂ based on the substitution of the intramolecularly bound dimethylbenzimidazole base.^{6a} X-ray structure analysis and NMR studies of different β -aquocobalamins have shown hydrogen-bonding interactions between the cobalt-coordinated water and a carbonyl oxygen of the *c*-acetamide side chain, which rotates inwardly toward the center of the macrocycle.¹¹ Therefore, we assumed that different functionalities at the periphery of corrinoids, especially at the inwardly directed side chain, could modulate the selectivity as well as the sensitivity in the substitution of cobalt-coordinated water with cyanide (Scheme 1, left).

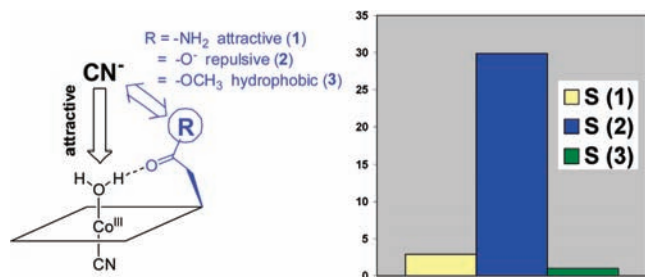
Three incomplete corrinoids with different functionalities at the rim of the molecule were chosen (Figure 1). Aquocyanocobinamide (**1**) with seven amide groups, aquocyano-

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Scheme 1. Proposed Model for Interaction of the c-Side Chain of Corrinoids **1–3** with Incoming Cyanide (left) and Selectivity (S) of Binding of CN^- vs SCN^- ($K_{(\text{CN}^-)}/K_{2(\text{CN}^-)}/K_{(\text{SCN}^-)}/K_{2(\text{SCN}^-)}$) (right)



cobyrinic acid (**2**) with seven carboxylates, and aquocyanocobester (**3**) with seven methyl ester functionalities can potentially interact with the incoming cyanide via attractive hydrogen-bonding, electrostatic repulsion, or hydrophobic interactions, respectively (Scheme 1, left).

Corrinoids **1–3** were synthesized from their corresponding dicyano forms as a pair of diastereomers through nonselective displacement of either the upper β - or α -cyanide as described elsewhere.^{9b,10b,12} Because these diastereomers convert into each other after separation,¹³ we used **1–3** as diastereomeric mixtures.^{9b,10} In a first experiment, the conditional binding constants of cyanide to **1–3** were determined by UV–vis titration experiments and analyzed with the program *Hyperquad2006*.¹⁴ Cyanide (0–45 μM) was added stepwise to a solution of **1–3** (40 μM) in water at pH 7.5 and 21 °C.

The color changed from orange to violet accompanied by a large bathochromic shift ($\Delta\lambda_{\text{max}} = 51\text{--}54$ nm) with isosbestic points, indicating a conversion without any side equilibria (Figure 2).

Corrins **1** and **3** show affinities for cyanide of $K = 1.78 \times 10^6 \text{ M}^{-1}$ and $1.35 \times 10^6 \text{ M}^{-1}$ (Table 1, entries 1 and 7), respectively, while the binding to **2** is approximately one magnitude lower (Table 1, entry 4). Because different functional groups at the macrocycle have only a negligible influence on the electronic properties of the cobalt center,^{9a} we explain the lower binding constant of **2** compared to **1** and **3** with repulsive electrostatic interactions between the c-acetate side chain of **2** and cyanide.

The influence of the pH was investigated in the range between 7.5 and 11. In the absence of cyanide, **1** and **3** showed deprotonation to their hydroxo forms ($\Delta\lambda_{\text{max}} = 11\text{--}21$ nm)¹⁵ at higher pH in accordance with the pK_{a} value of 11.0 for **1**.¹⁶ However, the spectral properties of **2** remained unchanged within this pH range, indicating that

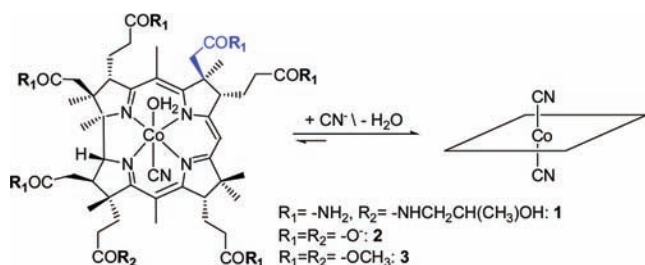


Figure 1. Structural formula of corrinoids **1–3** (left) and the schematic representation of the sensors after cyanide binding (right). The c-side chain has been drawn in blue.

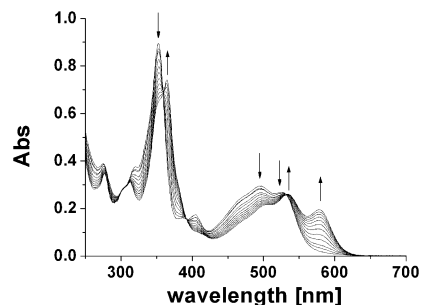


Figure 2. Absorption spectra of a solution of **2** (40 μM) upon the addition of increasing amounts of CN^- (0–45 μM) in water ([Hepes] = 20 mM; pH 7.5 \pm 0.1) at $T = 21 \pm 1$ °C.

Table 1. Binding Affinities of Sensors **1–3** to Cyanide and Thiocyanate^a

entry	sensor	anion (A^-)	pH	$K_{(\text{A}^-)} [\text{M}^{-1}]$	$K_{(\text{A}^-)}/K_{2(\text{A}^-)}$
1	1	CN^-	7.5	$1.78 \pm 0.28 \times 10^6$	15
2	1	CN^-	9.5	$1.71 \pm 0.13 \times 10^6$	3
3	1	SCN^-	7.5	55.09 ± 0.05	157
4	2	CN^-	7.5	$0.12 \pm 0.19 \times 10^6$	1
5	2	CN^-	9.5	$0.55 \pm 0.27 \times 10^6$	1
6	2	SCN^-	7.5	0.35 ± 0.24	1
7	3	CN^-	7.5	$1.35 \pm 0.16 \times 10^6$	11
8	3	CN^-	9.5	$2.73 \pm 0.22 \times 10^6$	5
9	3	SCN^-	7.5	121.35 ± 0.06	347

^a UV–vis titration: corrinoids **1–3** (40 μM); CN^- (0–45 μM), SCN^- (0–30 mM for **1** and **3**, 0–0.6 M for **2**); [Hepes] = 20 mM; pH 7.5 \pm 0.1 for entries 1, 3, 4, 6, 7, and 9 or [Ches] = 20 mM; pH 9.5 \pm 0.1 for entries 2, 5, and 8; $T = 21 \pm 1$ °C, *Hyperquad2006*.

the negatively charged side chains shield the cobalt-coordinated water from deprotonation ($pK_{\text{a}} = 12.4$).¹⁵ These observations explain the different trends of the cyanide affinity of **1–3**. Although at higher pH more free cyanide¹⁷ is present in solution, **1** and **3** show no increased binding.¹⁵ At pH 9.5, their binding constants are in the same order as their values at lower pH (Table 1, entries 2 and 8). We assume that the formation of the less favorable hydroxo leaving group counterbalances the increased nucleophilicity of cyanide at basic pH.¹⁷ On the other hand, because deprotonation has not been observed for **2**, the binding constant for cyanide at pH 9.5 is approximately 5 times higher than that at pH 7.5 (Table 1, entries 4 and 5).

When we added either 1 of 14 different anions (4 mM) besides cyanide or all of them (4 mM each) to a solution of **2** (40 μM) at pH 7.5 and 21 °C (Figure 3, top), the orange color of the solution as well as the characteristic absorption bands of sensor **2** remained unaffected, indicating that no ligand displacement took place.¹⁵ After the addition of cyanide (10 μM) to these solutions, a change toward the violet-colored dicyanocobyrinic acid was observed after only 5 s (Figure 3, bottom).¹⁵ Under the same conditions, **1** and **3** showed a high tolerance toward all of these anions with the exception of SCN^- . Its coordination to the cobalt center caused a slight but visible hypsochromic shift ($\Delta\lambda_{\text{max}} = 3\text{--}7$ nm).¹⁵ On the other hand, a color change occurred only after

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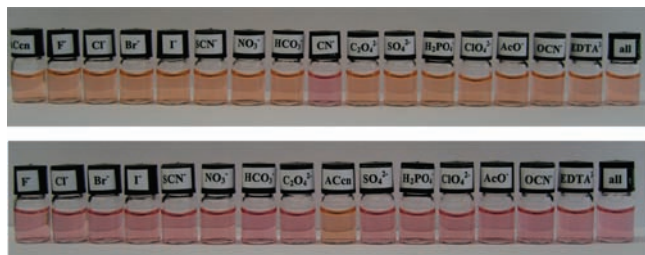


Figure 3. Color of solutions of **2** (ACcn, 40 μM) in water ([Hepes] = 20 mM; pH 7.5 \pm 0.1) at $T = 21 \pm 1$ $^{\circ}\text{C}$. (Top) In the presence of either no anion, F^- , Cl^- , Br^- , I^- , SCN^- , NO_3^- , HCO_3^- , CN^- , $\text{C}_2\text{O}_4^{2-}$, SO_4^{2-} , H_2PO_4^- , ClO_4^- , AcO^- , OCN^- , or EDTA^{4-} [4 mM besides for vial number 9: CN^- (10 μM)], or all 14 anions besides CN^- (4 mM each). (Bottom) Color change observed after the addition of CN^- (10 μM) with the exception of vial number 9 (ACcn; **2**): no CN^- added.

the addition of 200 mM of SCN^- to **2**.¹⁵ The same trend was also observed for the conditional binding constants of SCN^- to **1–3** at pH 7.5. Sensors **1** and **3** show affinities of $K = 55.09$ and 121.35 M^{-1} , whereas the affinity of **2** is 157 and 347 times lower (Table 1, entries 3 and 9 vs entry 6). Compared to the values for cyanide binding, the negatively charged side chains of **2** increase the selectivity of cyanide versus thiocyanate up to a factor of 30 (Scheme 1, right).

Apparently, for SCN^- the additional forces are more difficult to overcome. At pH 7.5, the visual detection limit of the most selective sensor **2** for cyanide is 10 μM .¹⁵ Moreover, **2** can be applied for the quantitative cyanide determination with a detection limit as low as 1.5 μM .¹⁵

In conclusion, **2** is a useful metal-based sensor for the optical detection of 10 μM cyanide in water that modulates the selectivity as well as the sensitivity through additional supramolecular interactions. Studies with three different incomplete corrinoids reveal that the negatively charged side chains of **2** have great influence on the binding specificity and magnitude.

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Supporting Information Available: Experimental data for experiments discussed but not illustrated in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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