



How acidic are corroles and why?

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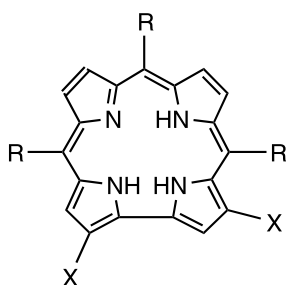
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Abstract—The pH-dependent absorption and emission spectra of the water-soluble 2,17-disulphonato-5,10,15-tris(pentafluorophenyl)corrole revealed that its inner-core nitrogen atoms can be both protonated and deprotonated, with acidity constants of 2.5 and 5.2, respectively. An analysis of the structural features of free-base corroles suggests that the quite limited pH range at which corroles remain neutral is reminiscent of the instability of mono-protonated porphyrins. © 2003 Elsevier Science Ltd. All rights reserved.

One prominent and unique feature of corroles is their unusually high N–H acidity relative to porphyrins and all other related macrocycles. This holds for both the long-known β -pyrrole-alkylated and the recently introduced *meso*-substituted derivatives.^{1–3} Specifically, corroles **1–3** of Scheme 1 were reported to be deprotonated by weak bases in non-polar organic solvents.^{4–6} Moreover, in polar solvents such as ethanol and DMF,

corroles exist as their mono-anionic forms. Acidity constants can be measured in non-aqueous solvents,⁷ but the required procedures are less straightforward and the acquired information is less meaningful than in water. In any case, quantitative measurements of acid/base equilibrium constants were not yet reported for any corrole and water-soluble derivatives were not known until very recently.



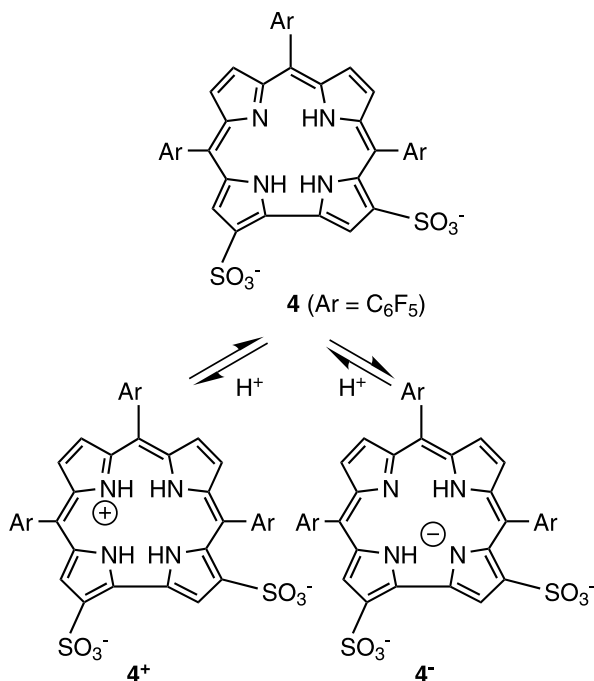
- 1:** R = C₆F₅, X = H
2: R = C₃F₇, X = H
3: R = C₆H₅, X = H
4: R = C₆F₅, X = SO₃H

Scheme 1. Structures of corroles **1–4**.

We have very recently introduced the easy and highly selective electrophilic substitution of corroles as an invaluable synthetic tool for the preparation of novel derivatives.⁸ This includes the chlorosulfonation plus hydrolysis route for transforming **1** to corrole **4**.⁹ The water-solubility of **4** allows for a straightforward determination of its acidity constants (Scheme 2). Together with the recently published X-ray structures of corroles **1** and **2**, it also provides the basis for uncovering the underlying principles that determine the unique acid–base properties of corroles.¹⁰

In previous studies we have demonstrated the characteristic electronic spectra of the neutral, deprotonated, and protonated forms of corrole **1**, as well as the large increase in fluorescence-intensity upon deprotonation of the neutral macrocycle.¹¹ Both phenomena were used for the present purpose on corrole **4**, whose visible bands were very sensitive to the protonation state of the inner nitrogen atoms. Figure 1 shows the pH-dependent electronic spectra over two ranges, corresponding to the gradual transformation of 4[–] to 4 and of 4 to 4⁺. The

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Scheme 2. Protonation/deprotonation equilibria of corrole **4**.

analysis of this data provided pK_a values of 5.2 and 2.5 for deprotonation of **4** and **4⁺**, respectively.[†]

To confirm these values, the emission spectra were also recorded at various pH values (Fig. 2). A constant corrole concentration was used and excitation was performed at 420 nm, where all species had similar absorption coefficients. The data analysis provided pK_a values of 5.3 and 2.9 for deprotonation of **4** and **4⁺**, respectively.[‡] The first value is practically identical to that obtained from the absorption spectra and relies on the very large changes in intensity and only small spectral

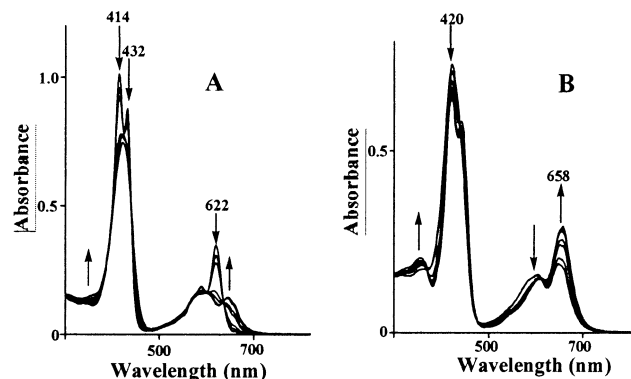


Figure 1. The electronic spectra at (A) pH 8.84–3.38 (**4⁻**→**4**) and (B) pH 2.76–1.00 (**4**→**4⁺**).

shifts. The second value is somewhat less reliable than that obtained from the visible spectra, because of small variations in absorption at the excitation wavelength.

A comparison between **4** and the water-soluble 5,10,15,20-tetra(*p*-sulphonato)porphyrin (**5**) is highly revealing. Corrole **4** is fully deprotonated at neutral pH, but **5** and all other porphyrins can not be deprotonated in water. In fact, a pK_a of 32.8 was obtained for **5** in a DMSO/water solution (80:20),¹² almost 40 orders of magnitudes higher than the pK_a of 5.2 for deprotonation of **4**. On the other hand, with acidity constants of 2.5 and 4.8 for protonation of **4** and **5**,¹³ respectively, the basicities of corroles and porphyrins appear to be quite similar: An important difference, however, is that **5** is doubly-protonated at once without an observable mono-protonated intermediate at any pH. A possible approach for explaining the very different acid/base behavior of corroles and porphyrins is to ignore the formal charges and to concentrate on the number of NH protons in each state. With this view in mind, a mono-protonated corrole corresponds to a doubly-protonated porphyrin, a neutral corrole to a mono-proto-

[†] The acidity constants for the deprotonation of **4⁺** to **4** and of **4** to **4⁻** were obtained by measuring the OD at 658 nm and 622 nm, respectively, of a constant initial concentration of **4** in buffers of different pH values (8.84–3.38 and 1.00–2.76, respectively) and analyzing the data by Eqs. (3) and (6), respectively. The OD₀ of **4⁺** and **4⁻** were obtained from the lowest and highest pHs, respectively, where only these species exist.

$$K_a = \frac{[4^-][H_3O^+]}{[4]} = \frac{([4^-]_0 - [4])[H_3O^+]}{[4]} \quad (1)$$

$$[4] = (OD_0 - OD) / (\epsilon(4^-) - \epsilon(4)) = \Delta OD / \Delta \epsilon \quad (2)$$

$$\Delta OD / [H_3O^+] = -\Delta OD / K_a + \Delta \epsilon [4^-]_0 / K_a \quad (3)$$

$$K_a = \frac{[4][H_3O^+]}{[4^+]} = \frac{[4][H_3O^+]}{([4^+]_0 - [4])} \quad (4)$$

$$[4] = (OD_0 - OD) / (\epsilon(4^+) - \epsilon(4)) = \Delta OD / \Delta \epsilon \quad (5)$$

$$\Delta OD [H_3O^+] = -K_a \Delta OD + \Delta \epsilon [4^+]_0 K_a \quad (6)$$

The buffer solutions were prepared according to *Buffers for pH and Metal Ion Control*; Perrin, D. D.; Dempsey, B., Eds.; London: Chapman & Hall, 1974; pp. 48–49, table 3.9, i.e. the Universal Buffer (pH 2–12) for UV Spectrophotometry.

[‡] A constant corrole concentration was used and the excitation was performed at 420 nm, where all species had similar absorption coefficients. The acidity constants were obtained from a plot of the total fluorescence against the pH, with the two maximal changes in the total fluorescence being analyzed as reflecting the condition of $[4^-] = [4]$ and $[4^+] = [4]$, i.e. $pH = pK_a$.

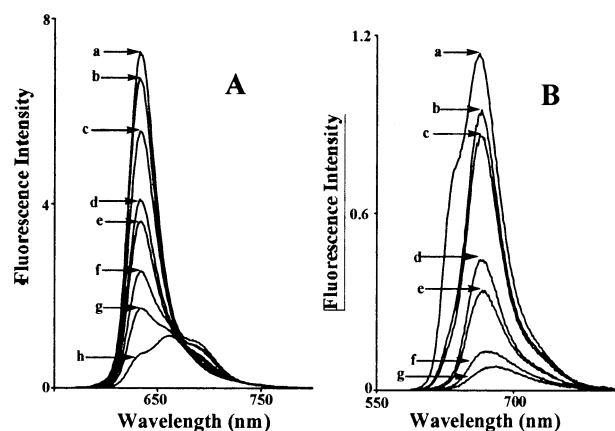


Figure 2. (A) The pH-dependent fluorescence spectra: (A) pH = (a) 8.87, (b) 7.11, (c) 5.71, (d) 5.34, (e) 5.27, (f) 4.90, (g) 4.65, (h) 4.11. (B) pH = (a) 4.11, (b) 3.42, (c) 3.11, (d) 2.60, (e) 2.24, (f) 1.62, (g) 1.30. Note the different scales in (A) and (B).

nated porphyrin, and a mono-anionic corrole to a neutral porphyrin. According to this perspective, the pH range at which mono-protonated porphyrins and neutral corroles exist is extremely limited, as both species are protonated at high pH and deprotonated at neutral pH. What remains to be explained is the instability of mono-protonated porphyrins and neutral corroles.

A unified explanation for both types of macrocycles is that a major steric penalty is paid on adding the first proton to neutral porphyrins and mono-anionic corroles. This may be appreciated by the X-ray structures of **1** and **2**, in which all three protons are in very close contact to each other and one of them deviates from the plane of its pyrrole ring by as much as 0.89 Å (in **1**) and 0.69 Å (in **2**).^{5,10} Once the inner core contains three NH protons, there is probably no large steric inhibition to adding a fourth proton leading to $[H_4(\text{por})]^{2+}$ or $[H_4(\text{cor})]^+$. On the other hand, removal of one proton from $[H_3(\text{por})]^+$ or $[H_3(\text{cor})]$ releases a significant amount of energy, hence the unusually large acidity of corroles.

Concluding, we have measured for the first time the acidity constants of a corrole and provided an explanation for its high acidity. The pK_a value of 5.2 suggests that corrole anions might be protonated and undergo large conformational changes upon association to low-pH cancer cells, similar to what has been suggested to be an important factor in the preferred accumulation of porphyrins to tumors. In addition, the very large pH-dependent changes in fluorescence-intensity might be very useful for utilization of corroles as sensors in biological systems.

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