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Proximal Charge Effects on Coordination of Histamine by Aquocyanocobinamide

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Abstract

Coordination of histamine by aquocyanocobinamide (25 °C, μ = 1 M) causes a decrease in the pK_a of the pendant amino group of the ligand from 9.96 to 9.02 and of the endocyclic imino group from >14 to 11.34. This system provides an example of the perturbation of the acid dissociation constants of ionisable functional groups by a proximal charge interaction with the residual positive charge on the metal centre.

We have been interested in developing protein-free models to illustrate how the proximity of a metal ion to an ionisable functional group can perturb the latter's acid dissociation constant, and, conversely, how the state of ionisation of the proximal group can modulate the redox potential of the metal ion [1–6]. These proximal charge effects may be one of the key mechanistic features of the control of the Fe^{II}/Fe^{III} couple in the cytochromes [1–5] and the Co^{I}/Co^{II} couple in the reductase loop of the B_{12}-dependent methionine synthetase sytem [6].

The pK_as of the pendant amino groups of histidine and histamine (9.18 and 9.96, respectively [7]; see Fig. 1) are decreased to 7.99 and 8.89, respectively, on coordination by B_{12a}*, and the binding constants (log K) increase from 4.30 to 4.60, and from 4.43 to 4.71 on deprotonation of the pendant amino group [6]. The pK_a of coordinated histidine in $(histidine)_2Fe^{III}PPIX$ is <6.5, but increases to >11.5 on reduction to the ferrous complex [1–3]. Similarly, the pK_a of the pendant hydroxyl group of pilocarpate has a pK_a of 9.7 and *c.* 13 in the ferric and ferrous $(pilocarpate)_2FePPIX$ complexes, respectively.

We have attributed these effects to a proximal charge (coulombic) effect between the ionisable functionality and the residual positive charge at the metal centre, viz. +1 in the iron porphyrins and +2 in B_{12a}.

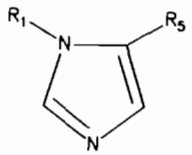

Fig. 1. Some substituted imidazoles with ionisable pendant functional groups. Histamine: R_1 = H, R_5 = $CH_2CH_2NH_3^+$; histidine: R_1 = H, R_5 = $CH_2CH(CO_2^-)NH_3^+$; pilocarpate: R_1 = CH_3, R_5 = $CH_2CHCH(CO_2^-)Et$ (with CH_2OH on the CH).

Hanania *et al.* [8] have previously reported that the pK_a of the amino group of histamine decreases to 4.49 on coordination by Factor B. This is a decrease of almost 5.5 log units (cf. a decrease on *c.* 1 log unit on coordination of histamine by B_{12a}). This very large perturbation is surprising since the presence of an axial CN^- ligand in Factor B decreases the residual positive charge on the metal centre from +2 in B_{12a} to +1 in Factor B. To resolve this apparent anomaly we have reinvestigated the histamine–Factor B system.

The pH of 50 ml of between 25 and 70 μM solution of Factor B (prepared by standard methods [9]) in the presence of between 10 and 50 mM histamine (25 °C, μ = 1.0 M (KCl)) was varied between 2 and 14 in the dark by addition of small amounts of conc. HCl. At each pH value, a sample was withdrawn and the absorbance measured at 354.0 nm, the γ-band maximum for Factor B, before returning the sample to the bulk solution. Three pK_as were found at 5.37 ± 0.02, 9.02 ± 0.02 and 11.32 ± 0.04. The pK_as were reversible and independent of the concentration of Factor B. The two higher pK_as were independent of histamine concentration, within experimental error. Figure 2 shows a non-linear least-squares fit to the titration data for these two pK_as.

The value of the most acidic pK_a depended upon the concentration of histamine in solution. Hence a value of 5.37 was obtained with [histamine] =

*Abbreviations: B_{12a}, vitamin B_{12a}, aquocobalamin; $Fe^{III}PPIX$, ferriprotoporphyrin IX; MP-8, the heme octapeptide from cytochrome *c*; Factor B, aquocyanocobinamide; Him^+, Him, Him^-, monocationic, neutral and anionic histamine.

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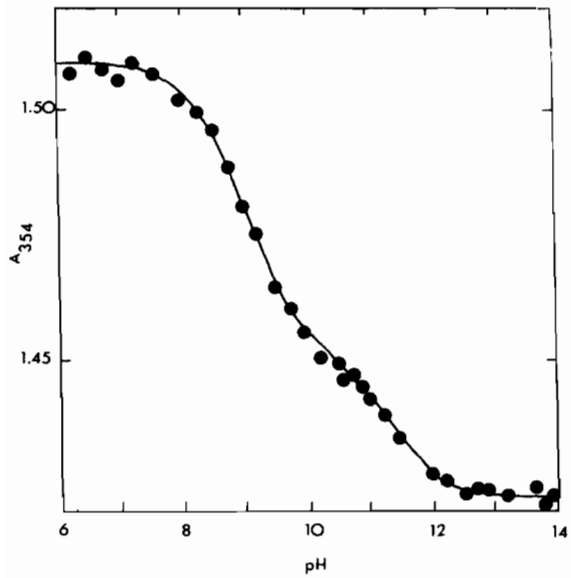

Fig. 2. Variation in A_{354} with pH for histaminecyanocobinamide (25 °C, μ = 1.0 M). The solid line was generated by non-linear least-squares fit to the data. Two pK_as occur at 9.02 ± 0.02 and 11.32 ± 0.04.

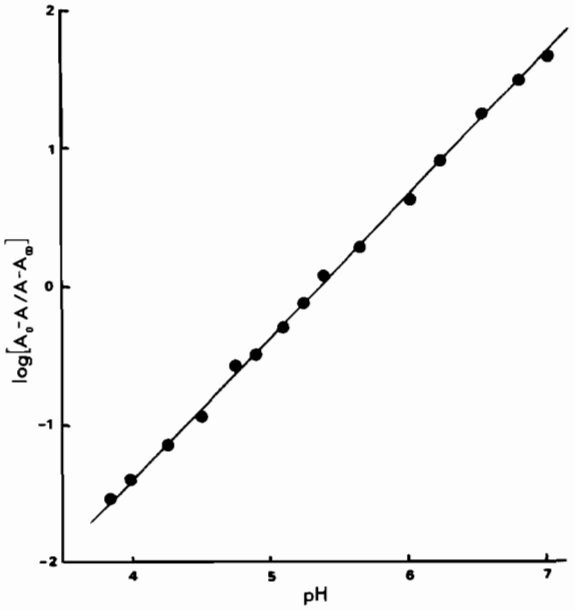

Fig. 3. Plot of $\log(A_0 - A)/(A - A_\infty)$ against pH for the titration of Factor B in the presence of 50 μM histamine at 25 °C.

50 μM, and a value of 6.00 with a concentration of 10 μM. This pK_a is associated with spectral changes from the characteristic orange colour of Factor B (354.0; 496; 526 nm) to a mauve complex (360.0; 519; 552 nm), undoubtedly the histamine–Factor B complex. A plot of $\log(A_0 - A_{345})/(A_{354} - A_\infty)$ against pH (Fig. 3) is a straight line with slope 1.02 ± 0.03. The spectral changes associated with pH changes are shown in Fig. 4.

Since at the apparent pK_a for conversion of Factor B to histaminecyanocobinamide, K = $1/[\text{Him}^+]$, where $[\text{Him}^+]$ can be calculated from the known pK_as of histamine [7], it follows that $\log K$ = 3.17 ± 0.06, since K_T, the tautomerisation constant between the 5-tautomer (which coordinates) and the 4-tautomer (which, to a first approximation, does not [6]), is 5.3 [7]. The binding constants for pyridine [10] and imidazole [11] to Factor B are $\log K$ = 2.6 and 4.1, respectively; the value for histamine deduced here is therefore reasonable.

The other two pK_as are associated with much smaller spectral changes (Fig. 3); the γ-band shifts from 360.0 to 361.2 nm as the solution is titrated through the pK_a at 9.02, and to 362.8 nm on titrating through that at 11.34. The pK_a at 9.02 is attributed to ionisation of the pendant amino group of coordinated histamine and that at 11.32 to ionisation of the endocyclic imino group. This last value is in good agreement with the value of 11.38 reported for ionisation of bound imidazole itself [11]. These pK_as can be compared to those of 8.89 and 9.89 in the analogous histamine–

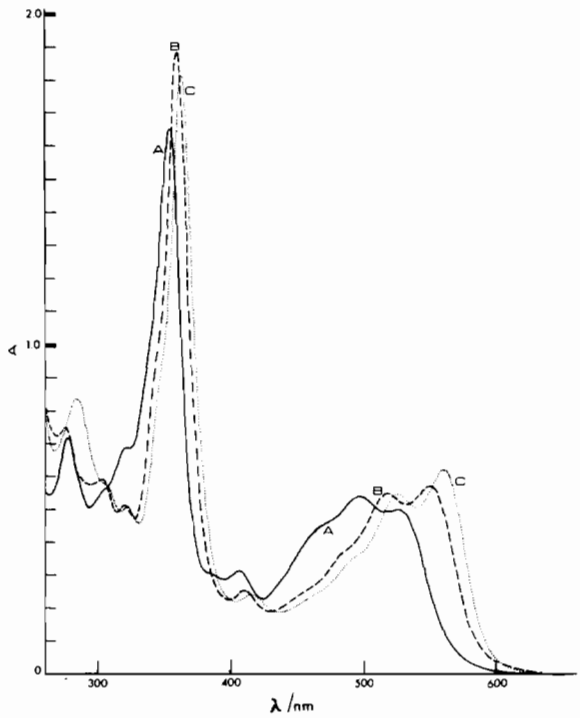

Fig. 4. UV–Vis spectra of the histamine–Factor B system: 37 mM histamine + 66 μM Factor B. A: pH 2.0; the spectrum is identical to the spectrum of Factor B in the absence of histamine in solution. B: pH 7.2; the predominant species in solution is $\text{Him}^+\cdot\text{Co}\cdot\text{CN}^-$. C: pH 13.0; the predominant species in solution is $\text{Him}^-\cdot\text{Co}\cdot\text{CN}^-$.

cobalamin complex [6]. The pK_a of the imino group of free histamine is unknown but is likely to be >14 [7]. The change in the pK_a of the amino side-chain is therefore relatively insensitive to the total residual positive charge at the metal centre, whereas that of the imino group is much more sensitive (viz. $\Delta pK_a = c.$ 5.5 for a +2 charge and *c.* 3.2 for a +1 charge). This is not surprising since the former perturbation is most likely due to a purely through-space coulombic effect, but the latter probably involves polarisation of the aromatic electron density of the coordinated heterocycle.

We therefore conclude that the ionisation of the pendant amino group of histamine on coordination to Factor B is not anomalously low. It would appear that the previously reported value of 4.49 [8] is erroneous and might have been due to protonation and loss of histamine from the coordination sphere of the metal ion. The value of this apparent pK_a will, of course, be critically dependent on the amount of ligand in solution.

The histamine complex of Factor B has provided a further example of how the pK_a of a proximal ionisable group can be perturbed by coulombic interaction with the charge on a metal ion.

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