Supporting Information

Molecular Crowding Effect in Hantzch Pyridine Synthesis in Polyethylene Glycol Aqueous Solution

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Figure S1. Optimized structures of chemical species for A, B, C, D, and E using density functional theory, implemented in Gaussian 16.
Figure S2. Relationship between $C_{\text{PEG}}$ and $\ln \gamma_A$. 
Derivation of the Eq. (1).

The change in the absorption upon the titration was based on the Benesi-Hildebrand equation.\(^1\) The reaction between the metal ion and HQ\(^-\) can be represented by the following reversible processes:

\[
\text{M}^{2+} + \text{HQ}^- \rightleftharpoons \text{MQ} + \text{H}^+ \\
\text{MQ} + \text{HQ}^- \rightleftharpoons \text{MQ}^2^- + \text{H}^+
\]

Thus, the equilibrium constants for the 1:1 and 1:2 complexes are given by

\[
K_1' = \frac{[\text{MQ}][\text{H}^+]}{[\text{M}^{2+}][\text{HQ}^-]}, \quad (\text{S1})
\]

\[
K_2' = \frac{[\text{MQ}^2^-][\text{H}^+]}{[\text{MQ}][\text{HQ}^-]} . \quad (\text{S2})
\]

Moreover, the total absorbance of the 1:1 and 1:2 complexes is given by the following equation according to the Lambert-Beer law.

\[
\Delta A = l\varepsilon_1 K_1'[\text{MQ}][\text{H}^+][\text{H}^+] + l\varepsilon_2 K_1'K_2'[\text{MQ}^2^-][\text{H}^+]^2 \quad (\text{S3})
\]

where \(l\) is the optical path length. The mass balance of metal ion is represented by

\[
[M^{2+}]_0 = [M^{2+}] + [MQ] + [(MQ_2)^-] = [M^{2+}] + \frac{K_1'[M^{2+}][\text{H}^+]}{[\text{H}^+]} + \frac{K_1'K_2'[M^{2+}][\text{H}^+]^2}{[\text{H}^+]^2} . \quad (\text{S4})
\]

where \([M^{2+}]_0\) is the initial concentration of metal ion. By substituting Eq. (S4) into Eq. (S3), we obtain

\[
\Delta A = \frac{l[M^{2+}]_0(K_1' \varepsilon_1[H^+][HQ^-] + K_1'K_2' \varepsilon_2[H^+]^2)}{[H^+]^2 + K_1'[H^+][HQ^-] + K_1'K_2'[HQ^-]^2} . \quad (\text{S5})
\]

Furthermore, when the acid dissociation constant of HQ\(^-\), \(K_{a2} = [Q^2^-][H^+]/[HQ^-]\), is substituted into Eq. (S5), the following equation is obtained.

\[
\Delta A = \frac{l[M^{2+}]_0(K_1K_{a2} \varepsilon_1[H^+][HQ^-] + K_1K_2K_{a2} \varepsilon_2[H^+]^2)}{[H^+]^2 + K_1K_{a2}[H^+][HQ^-] + K_1K_2K_{a2}[HQ^-]^2} . \quad (\text{S6})
\]