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Kinetic and Thermodynamic Selectivity in Subcomponent Substitution

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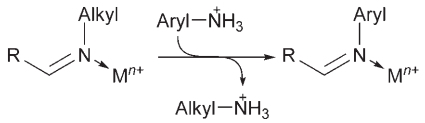
Abstract: Within assemblies prepared by metal-templated imine condensation, one amine residue (subcomponent) may be replaced with another through substitution reactions. Proton transfer from a more to a less acidic amine may be used as the driving force for substitution. Herein, we detail the development of a set of selectivity rules to predict the outcome of subcomponent substitution reactions when several different substrates are present. When both iron and copper complexes were present, substitution occurred preferentially at imines bound to copper. This preference was kinetic in nature in the absence of a chelating amine subcomponent: The different amine residues were found to scramble between the copper and iron complexes following an initial clean substitution at the copper-bound imine. When both chelating and nonchelating amine subcomponents were present, the preference became thermodynamic in nature. Only the nonchelating amine was substituted and no evidence of scrambling was found after the reaction mixture was heated to 50 °C for several days. This thermodynamic selectivity, based on the chelate effect, operated in mixtures of Cu^{I} and Fe^{II} complexes, and in systems containing only Fe^{II} complexes.

Keywords: coordination chemistry · dynamic combinatorial chemistry · ligand effects · self-assembly · substitution

Introduction

Structures prepared by means of self-assembly under thermodynamic equilibration[1] are held together through reversibly formed linkages.[2] These linkages not only allow the "annealing" processes to occur, which transform less stable kinetic products into more stable thermodynamic products,[3] but also act as potential points of dynamic reassembly. A variety of such reassembly reactions have been fruitfully investigated,[4] and dynamic reassembly also gives function to a growing array of molecular machines.[5]

We have previously shown how the subcomponent substitution reaction shown in Scheme 1 may be employed to transform one complex into another. This transformation was possible in the cases of mononuclear complexes,[6,7] helicates,[8] and macrocycles.[9] The driving force for these reactions depends not only upon the relative proton affinities of the two amines, as measured by their pK_a values, but also upon the relative metal-binding affinities of alkyl and aryl imines. In a recent study involving the acid titration of copper helicates, it was demonstrated that a helicate containing aniline residues was stable up to pH 2, whereas a helicate containing alkylamine residues was only stable up to pH 5.[8] This stability differential may provide the driving force for the imine exchange reaction.



Scheme 1. pKa-differential-driven substitution of an alkylamine residue by a protonated arylamine.

The development of more intricate functionality requires finer control over dynamic reassembly processes. A number of recent studies have demonstrated a high degree of selectivity in self-assembly, which allowed building blocks to be placed with increasing specificity within complex structures.[10,11] We have recently described systems[7,12,13] in which subcomponent self-assembly was employed to prepare pairs of structures cleanly from dynamic libraries[14,15] of subcomponents, although these subcomponents reacted to produce diverse mixtures of products in the absence of the selectivity imposed by metal template ions.[16] Herein we

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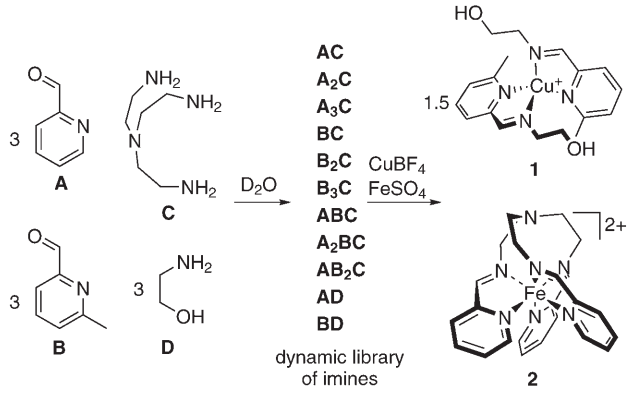
build upon these results by demonstrating selective subcomponent substitution. One may predict the site of subcomponent substitution within different "clean mixtures" of structures prepared by using parallel subcomponent self-assembly, as well as predicting whether or not the products formed initially will be thermodynamically stable through the application of selection rules we have developed.

Results and Discussion

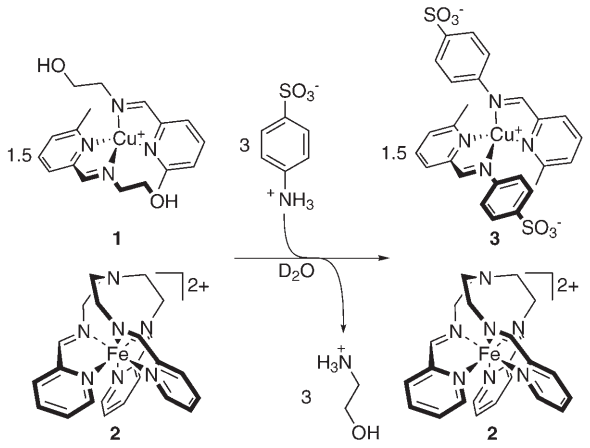
An aqueous mixture of subcomponents **A**, **B**, **C**, and **D** formed a dynamic combinatorial library[14,15] comprising all of the possible imine condensation products between the two aldehydes (**A** and **B**) and the two amines (**C** and **D**), as shown in Scheme 2. This dynamic library was observed to collapse into two unique products, $\mathbf{A_3C}$ and **BD**, upon the addition of iron(II) sulfate and copper(I) tetrafluoroborate, which resulted in the clean formation of complexes **1** and **2**. We refer to our initial communication for a detailed discussion of the driving forces behind this selectivity.[13]



Scheme 2. The formation of a dynamic combinatorial library of imines from aldehydes **A** and **B** together with amines **C** and **D**, and the subsequent sorting of this library of imines into complexes **1** and **2**, which only contain the ligands $\mathbf{A_3C}$ and **BD**.

Abstract in French: *Dans les assemblages obtenus par la formation de liaisons imine sous la direction d'un métal, il est possible de substituer un composant (en l'occurrence une amine) par un autre. Une force motrice exploitable pour cette substitution est la différence d'acidité entre deux amines. Nous détaillons ici des règles de sélectivité pour prédire le déroulement de réactions de substitution de composant dans le cas où plusieurs réactifs différents sont présents. Il a été observé que, dans un mélange de complexes de fer et de cuivre, la substitution a lieu préférentiellement au niveau des imines liées au cuivre. Cette préférence est de nature cinétique en l'absence d'amine chélatante, car elle conduit finalement à un mélange de produits. En présence d'un ligand chélatant, la préférence est de nature thermodynamique, car aucun échange de composants de ligand n'est observé, même après chauffage à 50°C pendant plusieurs jours. Cette sélectivité thermodynamique, basée sur l'effet chélate, est observée aussi bien dans des mélanges de complexes de cuivre et de fer que dans des mélanges de complexes de fer uniquement.*

The addition of sulfanilic acid to this mixture resulted in the quantitative conversion of **1** to **3** within minutes at room temperature (ca. 25°C), whereas **2** was unaltered (Scheme 3). This product mixture was unchanged after it had been heated to 50°C for 10 d, which suggested that this mixture of products was thermodynamically stable. The addition of more sulfanilic acid (3 equiv) to the mixture of **2** and **3** resulted in the partial substitution of triamine **C** by sulfanilate, which indicated the presence of a hierarchical preference in subcomponent substitution.[11,17] Progressively adding sulfanilic acid resulted in the disappearance of both **2** and **3** to give multiple products; the complete substitution of **C** by sulfanilate appeared to occur in competition with decomposition reactions. Conducting the reaction in a phosphate buffer solution (50 mM, pH 7.0) did not prevent these decomposition reactions from occurring. This observation suggested that the decomposition of **2** was a result of the presence of sulfanilate, rather than as a consequence of lower pH.



Scheme 3. Selective substitution of the alkylamine residues of **1** by sulfanilic acid in the presence of **2**.

We investigated the origin of the selectivity observed in the subcomponent substitution reaction shown in Scheme 3. Two key differences between complexes **1** and **2** are the metal center (pseudo-tetrahedral Cu^{I} for **1** versus pseudo-octahedral Fe^{II} for **2**) and the degree of ligand chelation (two bidentate ligands for **1** versus a single hexadentate ligand for **2**). As both of these factors would be expected to influence the relative reactivities of **1** and **2** in subcomponent substitution, we investigated a pair of systems in which the metal center and the chelate effect could be studied separately.

Initially, we hypothesized that a more electron-rich ligand, which contained alkylamine residues as opposed to aniline

residues, might bind preferentially to Fe^{II}. The metal–nitrogen bonds of **1** would be expected to be longer (mean $r_{Cu-N}=2.05$ Å in an analogue of **1**)[18] and weaker than those of **2** (mean $r_{Fe-N}=1.95$ Å).[19] Thus, a more electron-rich ligand might be more stabilizing when strongly bound to an Fe^{II} center instead of weakly bound to a Cu^{I} center. Therefore, ejection and replacement of the alkylamine residue of **2** might be thermodynamically less favorable than the corresponding **1** to **3** transformation. To test this hypothesis we carried out the experiment shown in Scheme 4, in which both the iron and copper complexes contained the same ethanolamine residue.

The aqueous reaction of aldehydes **B** and **E** with amine **D**, in the presence of copper(I) and iron(II), gave a clean mixture of pseudo-tetrahedral **1** and pseudo-octahedral **4**, as indicated by NMR and ESIMS spectra. The preferred coordination geometries of the metal ions led to the selective formation of these two complexes as the products of the reaction. Copper(I) would give rise to a "valence-frustrated" complex with a ligand derived from **E**,[20] whereas iron(II) would give a high-spin, thermodynamically unfavorable complex in the case of subcomponent **B**.[21]

The addition of sulfanilic acid to this mixture resulted in the initial conversion of **1** to **3**, whereas **4** was unaltered (>95% selectivity, as indicated by NMR and ESI spectra). However, when this reaction mixture was left at room temperature the sulfanilate and ethanolamine residues were observed by means of NMR and ESIMS techniques to scramble between the iron and copper complexes (Scheme 4). We estimate that the half-life of this process is approximately 24 h at room temperature, although the complexity of the product mixture made this difficult to determine.

The presence of iron(II) ions led to broadening of the signals in the ^{1}H NMR spectra, which made the spectra difficult to interpret in many cases (examples are provided in the Supporting Information). Greater peak separations in the ^{13}C NMR spectra generally made this nucleus more useful for monitoring the progress of reactions. Figure 1 shows ^{13}C NMR spectra for the three stages of the reaction sequence shown in Scheme 4.

We postulated that **1** reacted more rapidly with sulfanilic acid than **4** owing to the lower degree of steric crowding and longer metal–ligand bonds of **1**.[18,19] The observation of subcomponent scrambling indicated that **3** was the kinetic product of the reaction shown in Scheme 4, but that no strong enthalpic preference existed for the incorporation of sulfanilate into either Cu^{I} or Fe^{II} complexes. Thus, entropy led to the distribution of both amines among complexes of both metal ions.

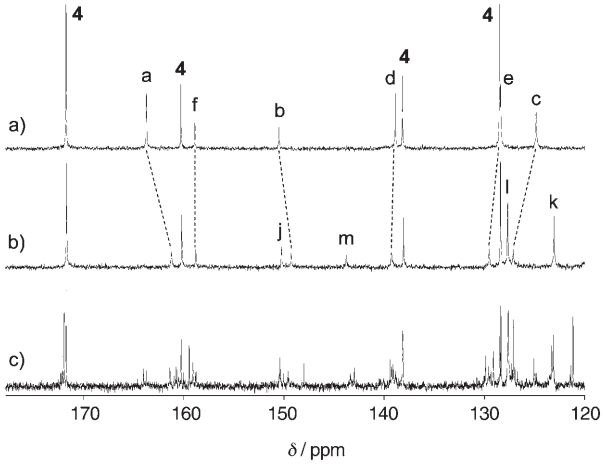
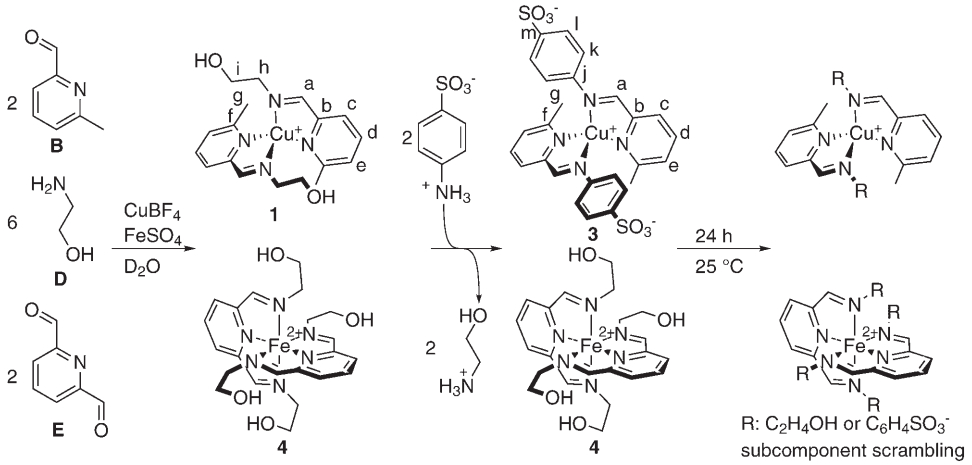


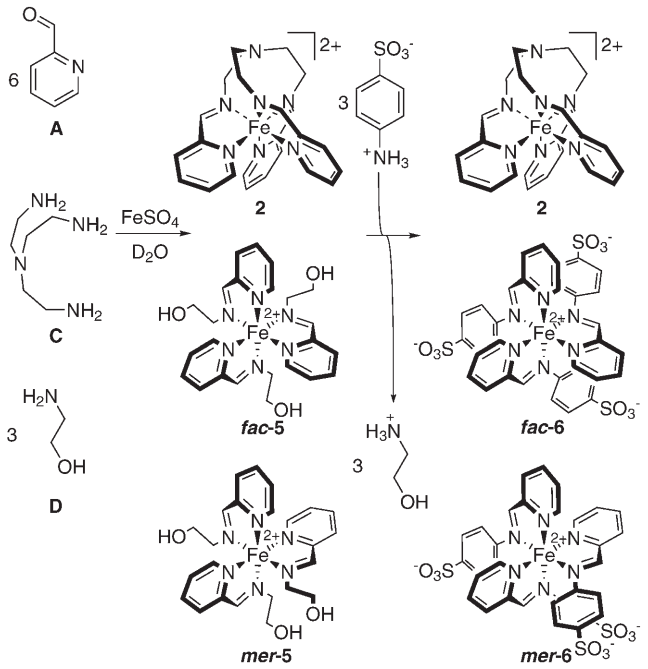
Figure 1. ^{13}C NMR spectra of the aromatic regions of the spectra of a) the mixture of **1** and **4** formed initially, b) the mixture of **3** and **4** formed after addition of sulfanilic acid, and c) the dynamic library of products formed through subcomponent scrambling. Lowercase letters correspond to the carbon atoms indicated in Scheme 4.

The observation of subcomponent scrambling in the reaction sequence shown in Scheme 4 also indicated that the chelate effect,[22] namely, the entropic penalty associated with breaking the chelating ligand of **2**, must play an important role in the selectivity observed in the substitution reaction shown in Scheme 2. To test this hypothesis, we prepared a system containing only Fe^{II} template ions,[16] but in which both chelating and non-chelating alkylamine residues were present (Scheme 5).

The addition of iron(II) sulfate to an aqueous mixture of aldehyde **A** and amines **C** and **D** resulted in the clean formation of complexes **2** and **5** (Scheme 5) as indicated by NMR and ESIMS spectra. NMR spectra indicated that complex **5** was present as a



Scheme 4. The clean simultaneous formation of complexes **1** and **4** from subcomponents **B**, **D**, and **E** followed by the reaction of this mixture with sulfanilic acid. The kinetic product **3** that formed initially underwent subcomponent scrambling with **4** over 24 h to give a mixture of Fe^{II} and Cu^{I} complexes. Lowercase letters are used to identify peaks in the ^{13}C NMR spectra of Figure 1.



Scheme 5. The clean simultaneous formation of complexes **2** and **5** from subcomponents **A**, **C**, and **D** followed by the selective reaction of **5** with sulfanilic acid, which gave a stable mixture of **2** and **6**.

statistical mixture of *fac* and *mer* isomers.

Following on from the idea that the chelating triamine residue of **2** might render it less susceptible than **5** to subcomponent substitution, we added sulfanilic acid (3 equiv) to the mixture of **2** and **5**. After 12 h at room temperature, NMR and ESI spectra of the product corresponded to a mixture of **2** and **6** as expected (Scheme 5), although this reaction did not proceed as cleanly as the substitution reactions shown in Schemes 2 and 4 (see the Supporting Information). Both the *fac* and *mer* isomers of **6** were also observed. As in the system shown in Scheme 2, subcomponent scrambling was not observed after the solution was heated to 50 °C for 10 d and adding additional sulfanilic acid resulted in the decomposition of both **2** and **6** to give multiple unidentified products.

Conclusion

The behavior of the systems investigated indicated that the chelate effect[22] plays an essential role in stabilizing complex **2** against subcomponent substitution. The transformation of **2** into **6** would require the ejection of triamine **C** (1 equiv) and the incorporation of sulfanilate (3 equiv), at substantial entropic cost, and therefore does not occur. Complexes **1**, **4**, and **5** may exchange ethanolamine (1 equiv) for sulfanilate (1 equiv) with what we suspect to be a minimal change to the entropy of the system. Therefore, the kinetic formation of **3** in the system shown in Scheme 4 might be explained in terms of the lower steric hindrance and the lower metal–nitrogen bond energies in **1** than **4**. The second law of thermodynamics can thus not only be used to explain the stability of the products of the reactions shown in Schemes 2 and 5 against subcomponent scrambling, but also to explain the scrambling in the system shown in Scheme 4.

The results of this study may be of use for larger structures containing subunits similar to the structures we have described. We have established a basic set of selection rules that predict which subcomponents will undergo substitution in preference to others, and whether the selectivity will be kinetic or thermodynamic in nature. As it has been shown in other contexts[9] that pK_a-differential-driven substitution reactions may be reversed as a function of pH, the substitution chemistry described herein might be used in the generation of pH-reversible motions to do work.[5]

Experimental Section

General: All manipulations were carried out under an argon or nitrogen atmosphere with degassed solvents. Starting materials of the highest commercially available purity were used as received. The line widths of the NMR spectra of samples containing iron(II) varied greatly from sample to sample and this was attributed to small differences in stoichiometry. ^{1}H NMR spectra were referenced to 2-methyl-2-propanol at $\delta = 1.24$ ppm as the internal standard. ^{13}C NMR spectra were referenced to 2-methyl-2-propanol at $\delta = 30.29$ ppm as the internal standard.

Copper complex 1: 6-Methylpyridine-2-carbaldehyde (0.1028 g, 0.8486 mmol), ethanolamine (0.0519 g, 0.8497 mmol), and tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.1338 g, 0.4253 mmol) were added to a 50 mL Schlenk flask containing methanol (5 mL). All starting materials dissolved to give a dark red solution. The flask was sealed and the atmosphere was purged of oxygen by means of three evacuation/argon-fill cycles. Subsequently, the reaction was stirred overnight at room temperature. Volatile compounds were then removed under dynamic vacuum to give a dark red product, which was determined to be pure from its NMR spectrum (0.202 g, 99 %). ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 8.67$ (s, 2H; imine), 7.97 (t, $J = 7.6$ Hz, 2H; 4-pyridine), 7.70 (d, $J = 7.3$ Hz, 2H; 3-pyridine), 7.56 (d, $J = 7.6$ Hz, 2H; 5-pyridine), 3.96 (br s, 4H; NCH_2CH_2OH), 3.79 (br s, 4H; NCH_2CH_2OH), 2.24 ppm (s, 6H; CH_3); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 163.8$, 159.0, 150.5, 138.9, 128.4, 124.8, 61.9, 61.8, 24.6 ppm; ESIMS: *m/z*: 391.1 [M^+], 228.9 [M^+ − one ligand].

Iron complex 2: Tris(2-aminoethyl)amine (0.2631 g, 1.799 mmol), pyridine-2-carbaldehyde (0.5782 g, 5.398 mmol), and iron(II) sulfate heptahydrate (0.4998 g, 1.798 mmol) were added to a 100 mL Schlenk flask containing water (22 mL). All starting materials dissolved to give a dark purple solution. The flask was sealed and the atmosphere was purged of oxygen by means of three evacuation/argon-fill cycles. The reaction was stirred for 2 h at room temperature before volatile compounds were removed under dynamic vacuum to give a dark purple product, which was determined to be pure from its NMR spectrum (0.902 g, 89 %). ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 9.19$ (s, 3H; imine), 8.30 (d, $J = 7.7$ Hz, 3H; 3-pyridine), 8.17 (m, 3H; 4-pyridine), 7.48 (m, 3H; 5-pyridine), 7.09 (d, $J = 5.4$ Hz, 3H; 6-pyridine), 3.62 (m, 3H; CH_2), 3.44 (m, 3H; CH_2), 3.27 (m, 3H; CH_2), 3.12 ppm (m, 3H; CH_2); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 172.0$, 158.2, 154.5, 139.1, 128.9, 128.6, 59.5, 54.2 ppm; ESIMS: *m/z*: 234.4 [M^{2+}].

Copper complex 3: 6-Methylpyridine-2-carbaldehyde (0.0771 g, 0.636 mmol), sulfanilic acid (0.1101 g, 0.636 mmol), sodium bicarbonate (0.0534 g, 0.636 mmol), and tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.1001 g, 0.318 mmol) were added to a 50 mL Schlenk flask containing water (5 mL). All starting materials dissolved to give a dark red solution. The flask was sealed and the atmosphere was purged of oxygen by means of three evacuation/argon-fill cycles before the reaction was stir-

red overnight at room temperature. The solution was then concentrated to approximately 1 mL under dynamic vacuum and was triturated with *tert*-butanol (30 mL). The dark red solid that precipitated was filtered and dried under dynamic vacuum (0.216 g, 91 %). ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 9.01$ (s, 2H; imine), 7.95 (t, $J = 7.7$ Hz, 2H; 4-pyridine), 7.84 (d, $J = 7.6$ Hz, 2H; 3-pyridine), 7.55 (d, $J = 8.6$ Hz, 2H; phenyl), 7.46 (d, $J = 7.6$ Hz, 2H; 5-pyridine), 7.26 (d, $J = 8.6$ Hz, 2H; phenyl), 2.04 ppm (s, 6H; CH_3); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 161.3$, 159.0, 150.3, 149.5, 143.2, 139.2, 129.5, 127.6, 127.0, 123.0, 24.9 ppm; ESIMS: *m/z*: −614.1 [M^-].

Iron complex 4: Pyridine-2,6-dicarbaldehyde (0.0292 g, 0.216 mmol), ethanolamine (0.0264 g, 0.432 mmol), and iron(II) sulfate heptahydrate (0.0301 g, 0.108 mmol) were added to a 10 mL Schlenk flask containing water (3 mL). All starting materials dissolved to give a dark purple solution. The flask was sealed and the atmosphere was purged of oxygen by means of three evacuation/argon-fill cycles. The reaction was stirred for 24 h at room temperature before volatile compounds were removed under dynamic vacuum to give a dark purple product, which was determined to be pure from its NMR spectrum (0.0642 g, 99 %). ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 8.54$ (brs, 10H; imine, 3,4,5-pyridine), 3.07 (brs, 8H; NCH_2CH_2OH), 2.79 ppm (brs, 8H; NCH_2CH_2OH); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 171.8$, 160.3, 138.2, 128.5, 60.0, 59.0 ppm; ESIMS: *m/z*: 249.1 [M^{2+}].

Iron complex 5: Pyridine-2-carbaldehyde (0.2386 g, 2.228 mmol), ethanolamine (0.1366 g, 2.236 mmol), and iron(II) sulfate heptahydrate (0.2040 g, 0.734 mmol) were added to a 50 mL Schlenk flask containing methanol (5 mL). All materials dissolved to give a purple solution. The flask was sealed and the atmosphere was purged of oxygen by means of three evacuation/argon-fill cycles. The reaction was stirred overnight at room temperature before volatile compounds were removed under dynamic vacuum to give a dark purple product, which was determined to be pure from its NMR spectrum (0.441 g, 100 %). Signals corresponding to the *fac* and *mer* diastereomers of the complex were observed in the NMR spectra in an almost statistical ratio of 1:3; a slight excess of the *mer* form was noted. ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 9.25$ (s, 1H; *mer*-imine), 9.18 (s, 1H; *mer*-imine), 9.13 (s, 1H; *mer*-imine), 9.06 (s, 0.84H; *fac*-imine), 8.08–8.33 (m, 8H; *mer*, 1.68H; *fac*), 7.44–7.59 (m, 3H; *mer*, 0.84H; *fac*), 7.31 (d, 1H; *mer*), 7.12 (d, 0.84H; *fac*), 3.20–3.96 ppm (m, 12H; *mer*, 3.36H; *fac*); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 173.9$, 173.8, 173.5, 173.4, 159.3, 159.0, 158.7, 158.5, 155.8, 155.5, 155.2, 154.9, 139.5, 139.3, 139.2, 139.1, 130.03, 129.98, 129.7, 129.6, 128.8, 128.6, 128.5, 128.4, 61.2, 60.8, 60.5, 59.4, 59.1, 58.9 ppm; ESIMS: *m/z*: 253.4 [M^{2+}].

Iron complex 6: Pyridine-2-carbaldehyde (0.008 g, 0.075 mmol), sulfanilic acid (0.013 g, 0.075 mmol), sodium bicarbonate (0.0063 g, 0.075 mmol), and iron(II) sulfate heptahydrate (0.007 g, 0.025 mmol) in deuterium oxide (0.5 mL) were added to an NMR tube with a Teflon screw cap. All materials dissolved to give a purple solution. The atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The reaction was monitored by means of NMR spectroscopy, and after 24 h at room temperature only signals corresponding to complex **6** were observed in the spectra. Signals corresponding to the *fac* and *mer* diastereomers of the complex were observed in the NMR spectra in an almost statistical ratio of 1:3; a slight excess of the *mer* form was noted. ^{1}H NMR (400 MHz, 300 K, D_2O): $\delta = 9.41$ (s, 1H; *mer*-imine), 9.37 (s, 1H; *mer*-imine), 8.99 (s, 1H; *mer*-imine), 8.96 (s, 0.79H; *fac*-imine), 8.73 (d, 1H; *mer*), 8.58 (m, 1H; *mer*, 0.79H; *fac*), 8.41 (m, 1H; *mer*, 0.79H; *fac*), 8.29 (t, 1H; *mer*), 8.13 (d, 1H; *mer*), 8.07 (t, 1H; *mer*), 7.99 (m, 1H; *mer*, 0.79H; *fac*), 7.73 (m, 3H; *mer*, 1.58H; *fac*), 7.60 (m, 3H; *mer*), 7.48 (m, 3H; *mer*), 7.33 (d, 2H; *mer*), 6.95 (d, 2H; *mer*), 6.76 (m, 2H; *mer*, 0.79H; *fac*), 6.16 (d, 2H; *mer*), 5.46 ppm (d, 1.58H; *fac*); ^{13}C NMR (100.62 MHz, 300 K, D_2O): $\delta = 176.7$, 176.3, 175.4, 174.3, 158.8, 158.7, 158.4, 158.1, 156.3, 153.5, 152.5, 150.1, 149.0, 144.1, 143.5, 140.5, 139.92, 139.87, 139.6, 139.4, 132.4, 132.04, 132.01, 131.5, 130.4, 130.0, 129.8, 129.7, 128.0, 127.56, 127.59, 127.2, 127.0, 123.3, 122.8, 122.6, 122.3, 116.0 ppm.

Selective simultaneous formation of complexes 1 and 2 (Scheme 2): Tris(2-aminoethyl)amine (0.0025 g, 0.017 mmol), pyridine-2-carbaldehyde (0.0055 g, 0.051 mmol), 6-methylpyridine-2-carbaldehyde (0.0062 g, 0.051 mmol), ethanolamine (0.0031 g, 0.051 mmol), iron(II) sulfate heptahydrate (0.0048 g, 0.017 mmol), and tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.0083 g, 0.026 mmol) in deuterium oxide (0.5 mL) were added to an NMR tube with a Teflon screw cap. All materials dissolved to give a dark red/purple solution. The atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The reaction was followed by using NMR spectroscopy, and the minority species present initially disappeared over the course of 12 h at 323 K. After this time, only signals corresponding to complexes **1** and **2** were observed in the NMR and ESIMS spectra.

Selective substitution of ethanolamine by sulfanilic acid within complex 1 in the presence of complex 2 (Scheme 3): Sulfanilic acid (0.0073 g, 0.042 mmol) was added to a mixture of **1** (0.0101 g, 0.021 mmol) and **2** (0.0118 g, 0.021 mmol) in deuterium oxide (0.5 mL) and the atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The tube was left overnight at room temperature, after which only signals corresponding to **2**, **3,** and protonated ethanolamine were observed in the NMR (Figures S1 and S2 in the Supporting Information) and ESIMS spectra. This mixture was stable at 50 °C for 10 d.

Selective simultaneous formation of complexes 1 and 4 (Scheme 4): Pyridine-2,6-dicarbaldehyde (0.0095 g, 0.07 mmol), 6-methylpyridine-2-carbaldehyde (0.0085 g, 0.07 mmol), ethanolamine (0.0129 g, 0.21 mmol), iron(II) sulfate heptahydrate (0.0096 g, 0.035 mmol), and tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.011 g, 0.035 mmol) in deuterium oxide (0.5 mL) were added to an NMR tube with a Teflon screw cap. All materials dissolved to give a dark red/purple solution. The atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The tube was left overnight at room temperature, after which only signals corresponding to complexes **1** and **4** were observed in the NMR spectrum (Figures S3 and S4 in the Supporting Information).

Kinetic substitution of ethanolamine by sulfanilic acid within complex 1 (Scheme 4): Sulfanilic acid (0.0121 g, 0.07 mmol) was added to the mixture of complexes **1** and **4** obtained in the previous experiment and the atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. Immediately after addition of sulfanilic acid (ca. 5 min) only signals corresponding to complexes **3** and **4** were observed in the NMR spectra (Figures S5 and S6 in the Supporting Information). These two products were observed to decrease in intensity over the course of several hours at 25 °C, with an estimated half-life of about 24 h. Multiple products were observed in the ^{13}C NMR spectrum (Figure S7 in the Supporting Information, the ^{1}H NMR spectrum was extremely broad), and peaks in the ESIMS spectrum were assigned to multiple Cu^I and Fe^{II} complexes containing mixtures of both ethanolamine and sulfanilate residues.

Selective simultaneous formation of complexes 2 and 5 (Scheme 5): Tris(2-aminoethyl)amine (0.0021 g, 0.014 mmol), pyridine-2-carbaldehyde (0.0091 g, 0.084 mmol), ethanolamine (0.0026 g, 0.042 mmol), and iron(II) sulfate heptahydrate (0.0076 g, 0.027 mmol) in deuterium oxide (0.5 mL) were added to an NMR tube with a Teflon screw cap. All materials dissolved to give a dark purple solution. The atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The tube was left overnight at room temperature, after which only signals corresponding to complexes **2** and **5** were observed in the NMR spectra (Figures S8 and S9 in the Supporting Information) and ESIMS spectra.

Selective substitution of ethanolamine by sulfanilic acid within iron complex 5 (Scheme 5): Sulfanilic acid (0.0073 g, 0.042 mmol) was added to the mixture of complexes **2** and **5** obtained in the previous experiment and the atmosphere in the tube was purged of oxygen by means of three evacuation/argon-fill cycles. The tube was left overnight at room temperature, after which, the signals corresponding to complexes **2**, **6,** and protonated ethanolamine predominated the NMR spectra (Figures S10 and S11 in the Supporting Information).

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