Post-Assembly Modification of Tetrazine-Edged $Fe^{II}_4L_6$ Tetrahedra

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Supporting Information Placeholder

ABSTRACT: Post-assembly modification (PAM) is a powerful tool for the modular functionalization of self-assembled structures. We report a new family of tetrazine-edged $Fe^{II}_4L_6$ tetrahedral cages, prepared using different aniline subcomponents, which undergo rapid and efficient PAM by inverse electron-demand Diels-Alder (IEDDA) reactions. Remarkably, the electron-donating or -withdrawing ability of the *para*-substituent on the aniline moiety influences the IEDDA reactivity of the tetrazine ring 11 bonds away. This effect manifests as a linear free energy relationship, quantified using the Hammett equation, between σ_{para} and the rate of the IEDDA reaction. The rate of PAM can thus be adjusted by varying the aniline subcomponent.

Covalent post-assembly modification (PAM) has recently developed into a useful tool for expanding chemical functionality in supramolecular architectures. To be most useful, a PAM reaction must proceed quantitatively under mild conditions as it is often not possible to purify supramolecular mixtures (e.g., by chromatography). Furthermore, the weaker, dynamic linkages that hold together many metallosupramolecular complexes[1] can be incompatible with the aggressive reagents associated with the formation of strong bonds under kinetic control.[2] Consequently, only a limited number of reactions have been successfully employed for supramolecular PAM, including olefin metathesis,[3] Williamson ether synthesis,[4] alkyne–azide cycloaddition,[5] acylation (acid anhydrides[6] and active esters[2b]), imine reduction,[7] Diels-Alder,[8] and nucleophile-isocyanate coupling.[2c,8] The tetrazine-based inverse electron-demand Diels-Alder (IEDDA) reaction also satisfies the requirements of efficiency and mildness necessary for successful PAM.[9] This reaction has not yet, however, been harnessed for PAM of a discrete supramolecular complex although it has found widespread use as a synthetic bioconjugation reaction[10] and, more recently, for covalently modifying polymers[11] and metal-organic frameworks.[12]

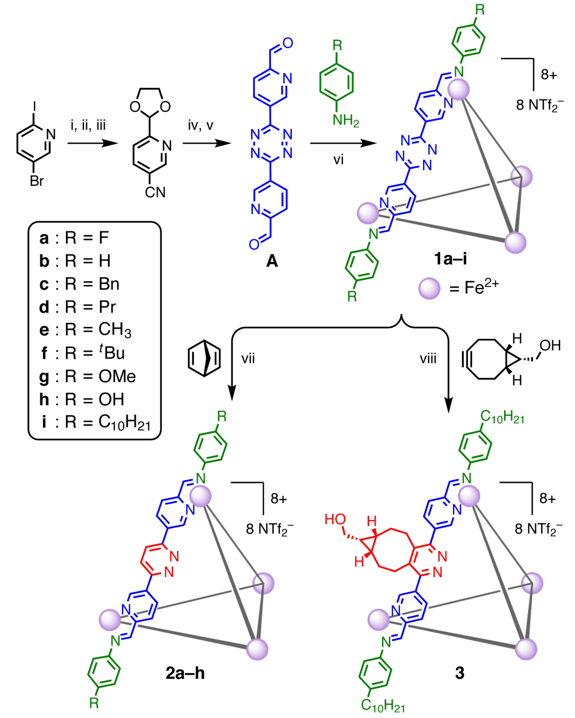
The IEDDA reaction between a 3,6-disubstituted 1,2,4,5-tetrazine and an electron-rich dienophile is an ideal reaction for PAM of a metallosupramolecular complex: it is efficient, produces N_2 as an inert by-product, does not interfere with metal–ligand coordination, and is compatible with a range of dienophiles.[9] Conveniently, the D_{2h} symmetry of the tetrazine ring allows it to be incorporated in place of the 1,4-disubstituted benzene moiety present in many existing supramolecular complexes.[13] We therefore envisaged that IEDDA reactions could be adapted to a range of existing supramolecular architectures, thus offering a general approach for the rapid and facile functionalization of supramolecular complexes through PAM.

Here we present a family of self-assembled metal-organic $Fe^{II}_4L_6$ tetrahedral cages that contain tetrazine moieties. These tetrazines react efficiently by IEDDA with alkyne or alkyne-equivalent[9b] dienophiles. The design of dialdehyde subcomponent **A**, based on an existing structural analog,[14] integrates tetrazine rings into the framework of the cage. Strong electronic coupling is thus engendered between the aniline residues incorporated into the periphery and the tetrazine cores. This coupling manifests through a linear free energy relationship (LFER) between the IEDDA rate constant and the Hammett parameter of the aniline *para*-substituent (σ_{para}). We thus demonstrate that the tetrazine moiety can serve dual roles of being both a structural element of the supramolecular architecture and a useful reactive handle for introducing new chemical functionality.

Subcomponent **A** was synthesized from commercially available 5-bromo-2-iodopyridine efficiently in five steps (Scheme 1; see SI, Section S3 for details). Cage **1a** was then prepared by subcomponent self-assembly[15] of **A** with 4-fluoroaniline and iron(II) bis(trifluoromethane)sulfonimide ($Fe(NTf_2)_2$). ESI-MS confirmed the formation of an $Fe^{II}_4L_6$ complex in solution (SI, Section S4), and NMR spectra were consistent with the expected tetrahedral symmetry (Figure 1b). Single-crystal X-ray diffraction analysis (Figure 2a) confirmed the tetrahedral structure of **1a** in the solid state.

We tested the reactivity of cage **1a** towards norbornadiene (NBD) as a model IEDDA reaction. NBD, upon reacting with a tetrazine and after retro-Diels-Alder elimination of dinitrogen (Figure 1a, **I** and **II**), gives a dihydropyridazine intermediate that spontaneously rearomatizes *via* a second retro-Diels-Alder reaction to expel a molecule of cyclopentadiene.[9b] The reaction between **1a** and NBD (2 equiv. per tetrazine) in CD_3CN resulted in the clean formation of pyridazine-paneled **2a** within 4 h at 50 °C, as verified by NMR and ESI-MS analyses (SI, Section S5), together with a stoichiometric quantity of cyclopentadiene (Figure 1). By UV-Vis spectroscopy, we found that the reaction kinetics were first-order in tetrazine (SI, Section S7), indicating that the six tetrazine sites on a given cage react non-cooperatively. It is therefore remarkable that the conversion of **1a** to **2a** occurs cleanly and without degradation of the assembled complex.

Scheme 1. Synthesis of subcomponent A, self-assembly of tetrazine-edged cages 1a-1i, and subsequent post-assembly modification by IEDDA.[a]



[a]*Conditions*: (i) ^iPrMgCl, DMF, THF, –15 °C, 99%; (ii) ethylene glycol, *p*TsOH, toluene, reflux, 99%; (iii) $K_4Fe(CN)_6$, $PdCl_2$, Na_2CO_3, DMA, 120 °C, 86%; (iv) NH_2NH_2, S_8, EtOH, reflux, then ^tBuONO, $CHCl_3$/EtOH, rt, 65%; (v) THF/$HCl_{(aq)}$, 60 °C, 45%; (vi) $Fe(NTf_2)_2$□$5H_2O$, CH_3CN, 60 °C, 5 h; (vii) CH_3CN, 50 °C, 4 h; (viii) $CDCl_3$, rt, 30 min.

During the course of PAM, desymmetrization of the cage signals was observed (Figure 1c); however, persistence of the signals from protons H_e and H_f and the absence of signals of the free subcomponents suggested that the ligands do not dissociate from the cage during the IEDDA reaction sequence. Crossover experiments using a mixture of two tetrazine-edged cages (**1a** and **1f**) revealed that the rate of ligand dissociation is much slower than the IEDDA reaction (SI, Figures S25–S27). We therefore conclude that the IEDDA reactions occur on the intact cage rather than as part of a dissociation–IEDDA–reassociation sequence. Although IEDDA reactions are known to proceed through distorted transitory bicyclic intermediates (structures **I** and **II**, Figure 1), the distortion is in a direction that is mostly perpendicular to the long-axis of the ligand in **1a** (SI, Figure S28), thus preventing strain-induced disassembly of the cage.

In order to probe the both the solvent and substrate scopes of post-assembly modification, we prepared chloroform-soluble decylaniline-substituted cage **1i**, and investigated the IEDDA reaction using commercially-available (1*R*,8*S*,9*s*)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (BCNM) as an alternative dienophile. The strained cycloalkyne of BCNM is reported to react cleanly with tetrazines to give ring-fused pyridazines, and its –OH group is a useful point of attachment for other functional groups.[16] As shown in Scheme 1, cage **1i** was observed to react with BCNM in $CDCl_3$ at 25 °C, yielding hexafunctionalised cage **3** as the major product of the reaction (SI, Section S6).

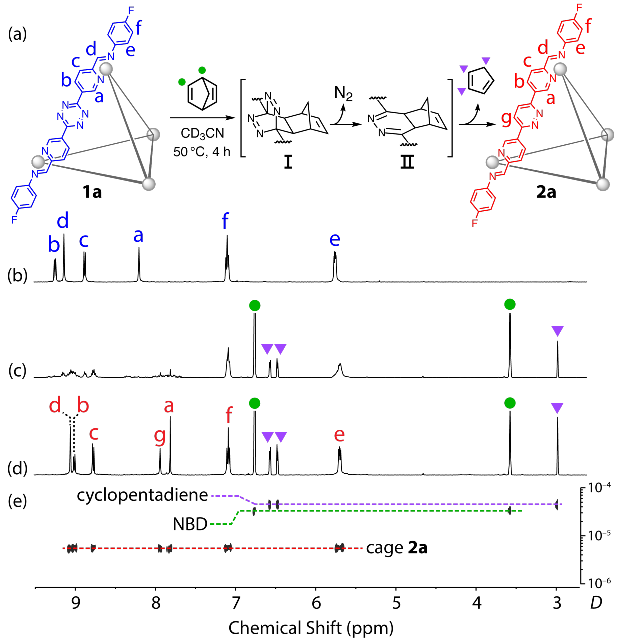


Figure 1. *In situ* ^{1}H NMR monitoring of the reaction (a) between cage **1a** (6.90×10^{-4} M) and NBD (2 equiv per tetrazine) to give cage **2a**. (b) ^{1}H NMR spectrum of **1a**. (c) ^{1}H NMR spectrum of the reaction mixture at 1 h. Green circles denote NBD signals; purple triangles denote cyclopentadiene signals. (d) ^{1}H NMR spectrum of the reaction mixture at 4 h, revealing clean formation of cage **2a** and cyclopentadiene. (e) ^{1}H DOSY spectrum of the reaction mixture after 4 h. Units of D are cm s^{-1}.

The ^{1}H NMR spectrum of **3** was broad, which we attribute to the presence of a mixture of low-symmetry diastereomers that arise from the random relative orientations of BCNM stereocenters within each cage. Variable temperature NMR studies were also consistent with a mixture of configurationally complex diastereomers (SI, Section S6). Despite the complexity, features characteristic of **3** were identified in ^{1}H and DOSY NMR spectra (SI, Figure S39), and HRMS confirmed its formation (SI, Section S41–S44). PAM with BCNM thus serves as a novel means of breaking cage symmetry,[17] where stereochemical complexity could influence cage function.[13d,18]

Cages **1a-1h** were used to elucidate the influence of the aniline *para*-substituent on the rate of the IEDDA reaction. These cages were prepared from anilines bearing *para*-substituents with Hammett constants (σ_{para}) between −0.37 (-OH) and +0.06 (-F) (SI section S5).[19] The reaction of NBD with each cage was chosen as a model system for analyzing the kinetics of IEDDA due to its moderate rate, clean conversion, and the high symmetry of the resulting product cages (**2a–2h**), which enabled facile characterization. NMR and mass spectra were consistent with the formation of pyridazine-containing $Fe^{II}_4L_6$ cages **2a–2h** (SI, Section S5), and X-ray diffraction confirmed the tetrahedral structure of product cage **2e** (Figure 2b).

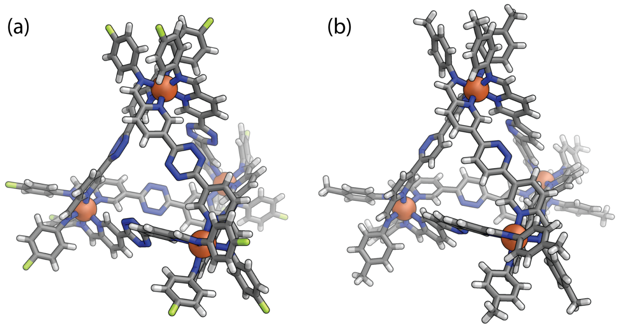


Figure 2. Depictions of the X-ray crystal structures of (a) tetrazine-edged cage **1a**, and (b) pyridazine-edged cage **2e**. *Key*: yellow = fluorine, orange = iron, blue = nitrogen. Disorder and anions have been omitted for clarity

Pseudo-first-order rate constants (k_{obs}) for the reactions of cages **1a-1h** with excess NBD (450 equiv.) were determined by measuring the decrease in the MLCT absorption band of the tetrazine cages over the 2 h following the addition of NBD. We could not monitor the reaction directly using the weaker tetrazine $n \rightarrow \pi^*$ band ($\lambda_{lit.}$ = 510–530 nm, $\varepsilon_{lit.}$ = 1000 M^{-1} cm^{-1})[20] as it overlapped substantially with the more intense MLCT absorptions (450–650 nm). However, we observed the intensity of the MLCT band of each tetrazine cage (λ_{max} ~ 630 nm) to decrease monoexponentially during the IEDDA reaction, consistent with the *pseudo*-first-order kinetics expected for the consumption of tetrazine.[21] This observation suggests that the IEDDA reaction of a tetrazine moiety directly influences the electronics of the adjacent *tris*(2-pyridylimine)iron(II) chromophore. Consequently, we were able to use the MLCT bands of cages **1a–1h** as spectroscopic probes for the IEDDA reaction (see SI, Section S7 for details of kinetics analyses).

Measuring k_{obs} values for the set of IEDDA reactions shown in Figure 3a revealed that these reactions follow the Hammett equation, whereby $\log_{10}(k_{obs})$ increased linearly with σ_{para}: more electron-withdrawing substituents gave faster rates (Figure 3b). Weaker correlations were observed between $\log_{10}(k_{obs})$ and the Hammett resonance effect parameters (σ^+ or σ^-),[19] which is consistent with the absence of significant charge build-up at any center during the reaction (Figure S58).[9a] The positive Hammett reaction constant ($\rho = +0.47$) is consistent with a decrease in the tetrazine LUMO energy as the electron-withdrawing power of the substituent increases. Remarkably, the magnitude of ρ is comparable to values measured for IEDDA reactions in non-supramolecular systems in which the substituent is much closer to the reaction site (5 bonds[22] *vs.* 11 bonds in the present case). We attribute this sensitivity to the unimpeded conjugation pathway between the aniline *para*-substituent and the tetrazine ring—an effect also reflected in the influence of the tetrazine moiety over MLCT absorption, as noted above.

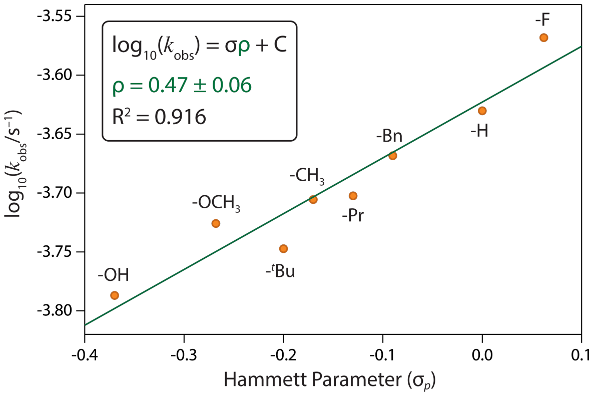


Figure 3. Plot of $\log_{10}(k_{obs})$ against σ_{para}. Aniline *para*-substituents are labeled in the diagram.

Chemical self-assembly has proven capable of generating architectures of great structural[23] and functional[24] complexity. The development of new methods to cleanly modify and transform these assemblies can expand the amount of chemical space accessible,[25] as each new reactive motif (tetrazene, in this study) may be incorporated into many previously reported structure types. Attractive features of our method are its clean "click" nature,[26] the ability to incorporate new functionality *via* BCNM, and the ability to adjust reaction rates through modular variation of the aniline subcomponent. Future work will seek to adapt this IEDDA methodology to other supramolecular architectures in order to modulate phenomena such as guest binding, reactivity and structural transformations.

ASSOCIATED CONTENT

Supporting Information. Synthetic details, characterization data, NMR and mass spectra, kinetics analyses, X-ray crystallography data. Crystallographic data are deposited with the CCDC (numbers 1062282-1062283). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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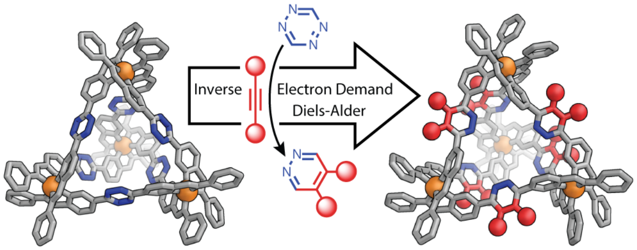
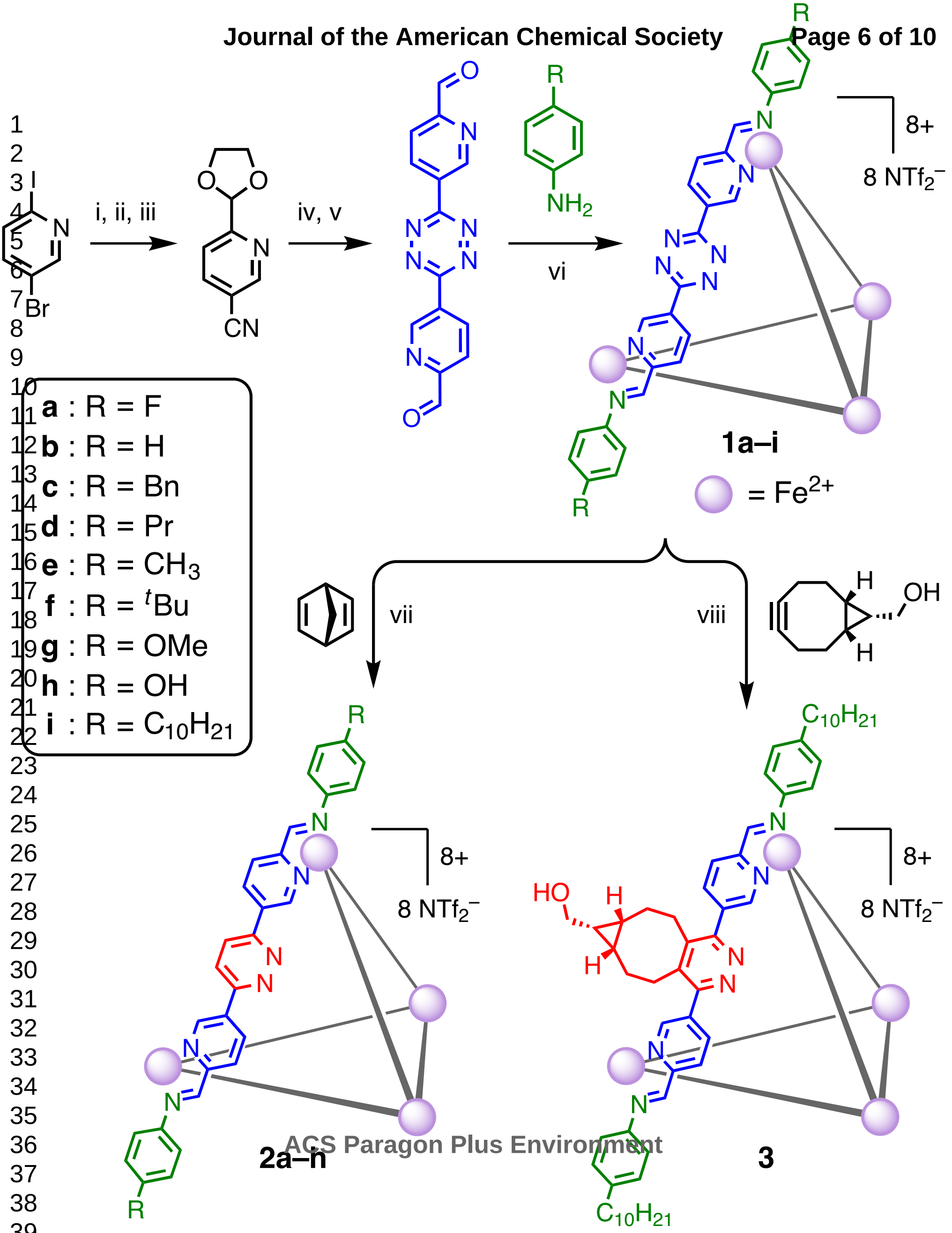
Graphical Abstract TOC Image

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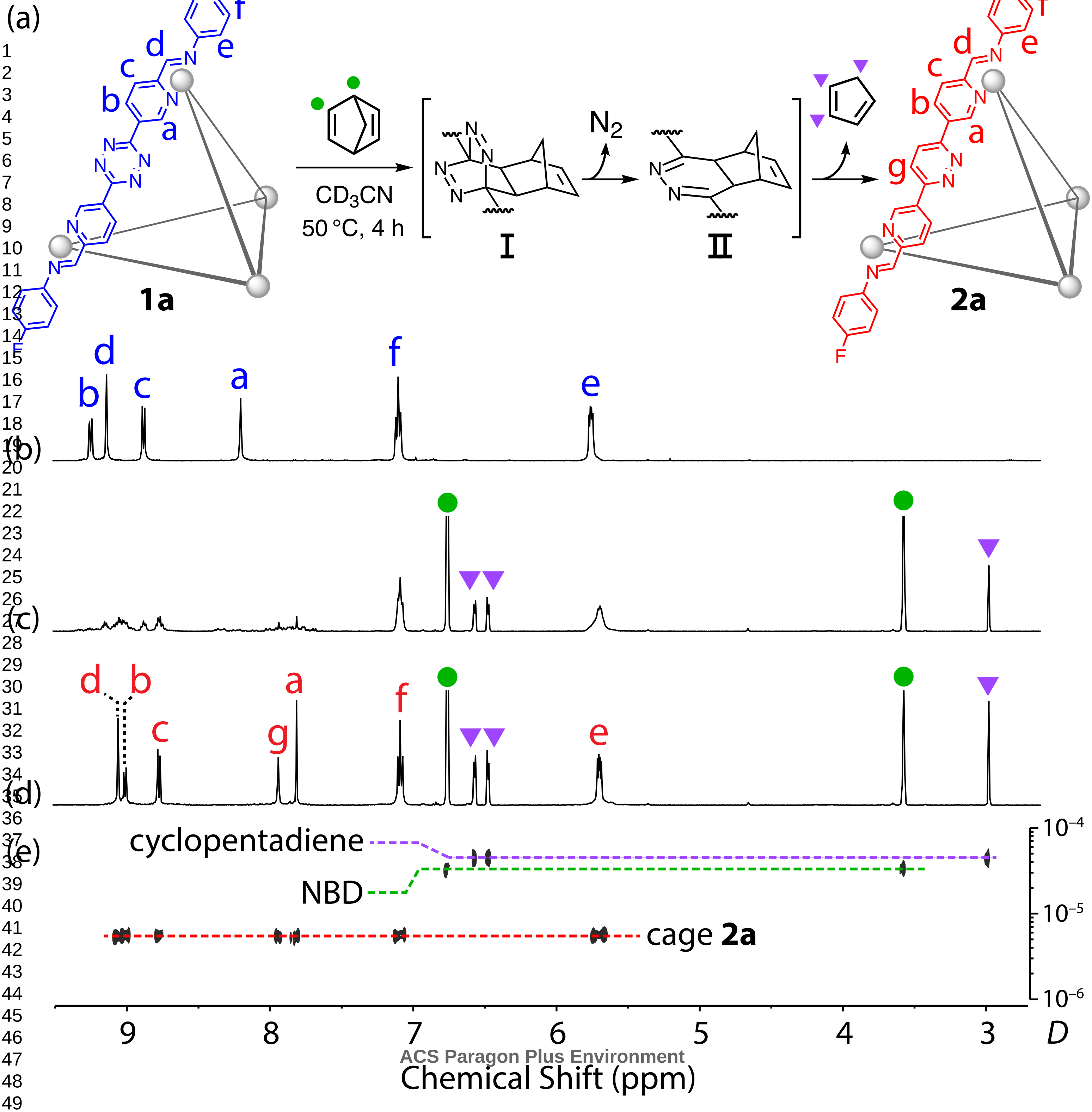
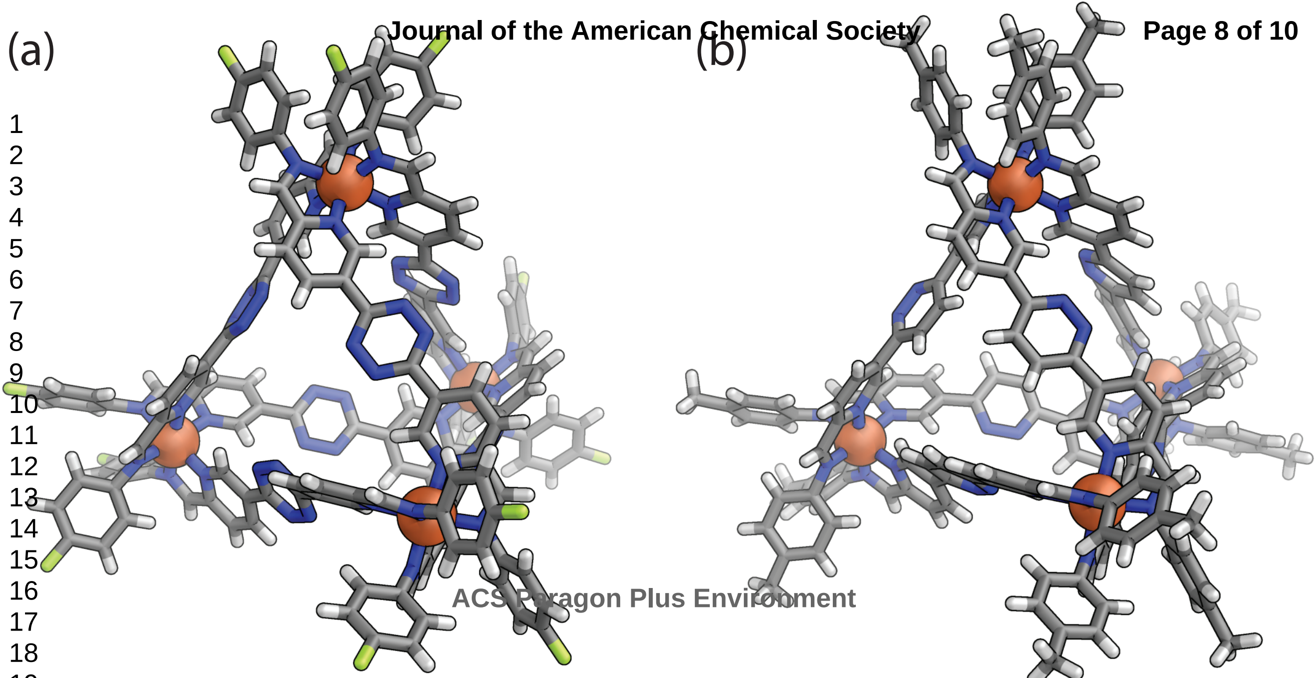
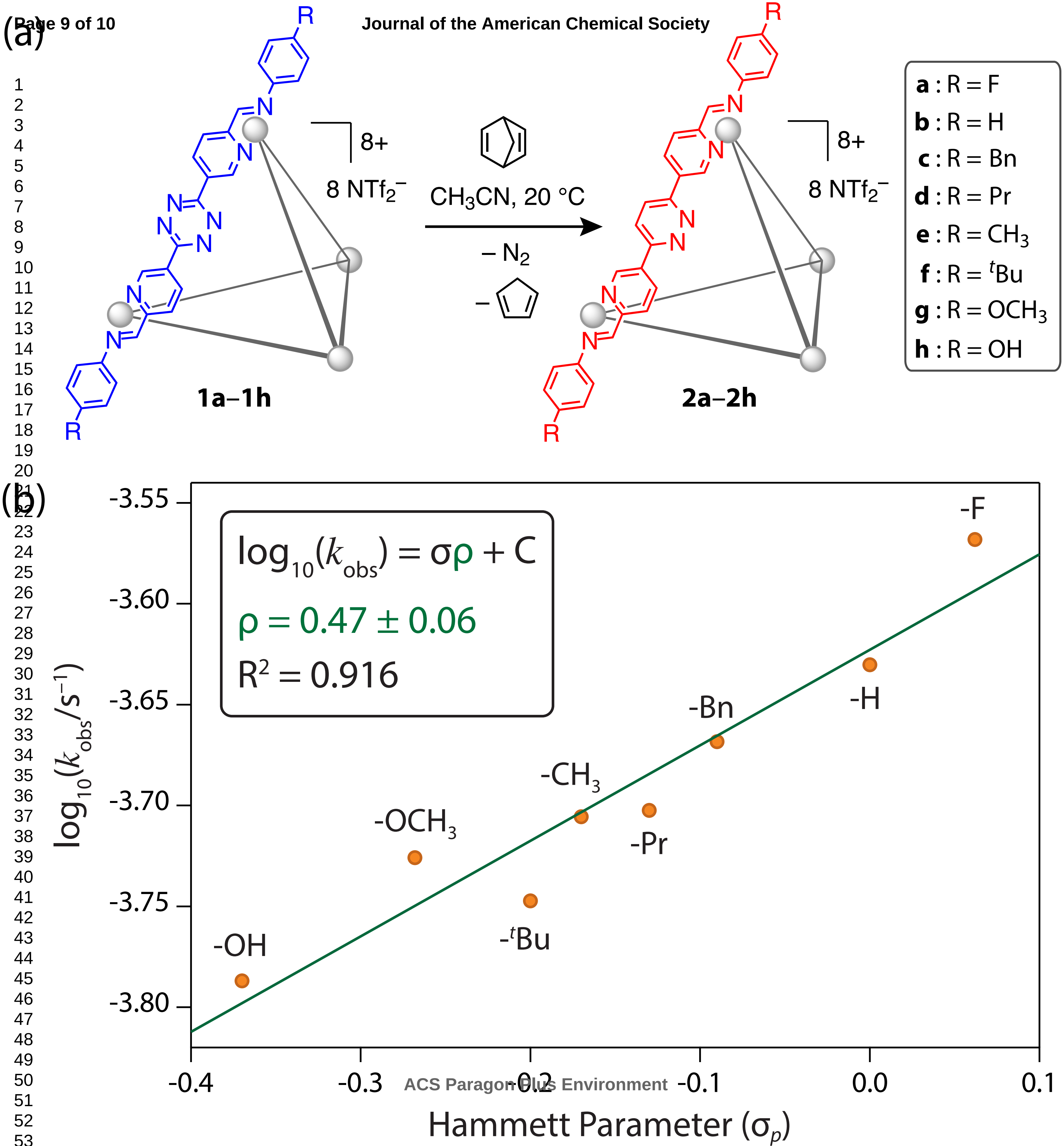
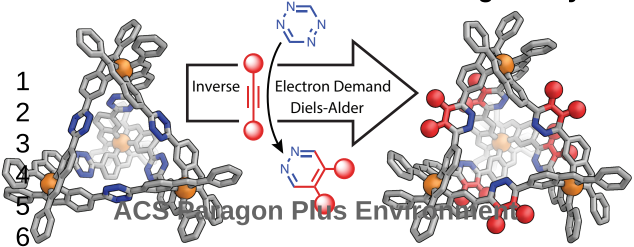
8+
8 NTf$_2^-$
1a–i
R
= Fe^{2+}
a : R = F
b : R = H
c : R = Bn
d : R = Pr
e : R = CH$_3$
f : R = ^{t}Bu
g : R = OMe
h : R = OH
i : R = C$_{10}$H$_{21}$
vii
viii
H
OH
H
R
N
N
N
N
N
8+
8 NTf$_2^-$
N
R
2a–h
C$_{10}$H$_{21}$
N
HO
H
H
N
N
N
N
N
8+
8 NTf$_2^-$
C$_{10}$H$_{21}$
3


(a)
F
f
d
e
c
N
b
N
a
N
N
N
N
N
F
1a
CD$_3$CN
50 °C, 4 h
I
N_2
II
F
f
d
e
c
N
b
N
a
g
N
N
N
N
F
2a
(b)
b
d
c
a
f
e
(c)
(d)
d
b
c
g
a
f
e
(e)
cyclopentadiene
NBD
cage 2a
10^{-4}
10^{-5}
10^{-6}
9
8
7
6
5
4
3
D
Chemical Shift (ppm)


(a)
(b)


(a)
R
N
N
N N
N N
N
N
N
R
8+
8 NTf$_2^-$
CH$_3$CN, 20 °C
– N$_2$
–
1a–1h
2a–2h
a : R = F
b : R = H
c : R = Bn
d : R = Pr
e : R = CH$_3$
f : R = ^{t}Bu
g : R = OCH$_3$
h : R = OH
(b)
log$_{10}$(k_{obs}) = σρ + C
ρ = 0.47 ± 0.06
R^2 = 0.916
-F
-H
-Bn
-CH$_3$
-Pr
-OCH$_3$
-^{t}Bu
-OH
log$_{10}$(k_{obs}/s^{-1})
-3.55
-3.60
-3.65
-3.70
-3.75
-3.80
-0.4
-0.3
-0.2
-0.1
0.0
0.1
Hammett Parameter (σ$_p$)


N
N
N
N
Inverse
Electron Demand
Diels-Alder
N
N