Published in final edited form as:

Chembiochem. 2014 July 21; 15(11): 1584–1589. doi:10.1002/cbic.201402201.

Modulation of Amyloid- β Aggregation by Histidine-coordinating Cobalt(III) Schiff Base Complexes

Dr. Marie C. Heffern^a, Pauline T. Velasco^b, Dr. Lauren M. Matosziuk^a, Joseph L. Coomes^a, Constantine Karras^a, Prof. Mark A. Ratner^c, Prof. William B. Klein^b, Prof. Amanda L. Eckermann^{a,†,*}, and Prof. Thomas J. Meade^{a,*}

^aDepartments of Chemistry, Molecular Biosciences, Neurobiology, Biomedical Engineering, and Radiology, Northwestern University, Evanston, IL 60208-3113, USA

^bDepartment of Neurobiology, Northwestern University, Evanston, IL 60208-3113, USA

^cDepartment of Chemistry, Northwestern University, Evanston, IL 60208-3113, USA

Abstract

Oligomers of the A β 42 peptide are significant neurotoxins linked to Alzheimer's Disease (AD). Histidine (His) residues present at the N-terminus of A β 42 are believed to influence toxicity by either serving as metal-ion binding sites (that promote oligomerization and oxidative damage) or facilitating synaptic binding. Transition metal complexes that bind to these residues and modulate A β toxicity have emerged as therapeutic candidates. Cobalt(III) Schiff base complexes (Co(III)-sb) were evaluated for their ability to interact with A β peptides. HPLC-MS, NMR, fluorescence, and DFT studies demonstrated that Co(III)-sb complexes could interact with the His residues in a truncated A β 16 peptide representing the A β 42 N-terminus. Coordination of Co(III)-sb complexes altered the structure of A β 42 peptides and promoted the formation of large soluble oligomers. Interestingly, this structural perturbation of A β correlated to reduced synaptic binding to hippocampal neurons. These results demonstrate the promise of Co(III)-sb complexes in anti-AD therapeutic approaches.

Keywords

Alzheimer's Disease; Amyloid beta; Cobalt; Oligomer; Histidine

Alzheimer's Disease (AD) is a neurodegenerative disorder that manifests as impaired memory formation and cognitive decline.^[1] Progression of this devastating disease has been

*Corresponding Authors: Prof. Thomas J. Meade and Prof. Amanda L. Eckermann, Department of Chemistry, Molecular Biosciences, Neurobiology, Biomedical Engineering, and Radiology, Northwestern University, Evanston, IL 60208-3113, USA, tmeade@northwestern.edu.

†Present Addresses: Prof. Amanda Eckermann, Department of Chemistry, Hope College, Holland, MI 49422-9000, USA, eckermann@hope.edu

EXPERIMENTAL SECTION

Experimental procedures are described in the Supporting Information.

Author Notes

All authors have given approval to the final version of the manuscript. The authors declare the following competing financial interest(s): W.L.K. is co-founder of Acumen Pharmaceuticals, which has been licensed by Northwestern University to target ADDLs (A β -Derived Diffusible Ligands with dementing action) for Alzheimer's therapeutics and diagnosis

linked to the accumulation of oligomers of amyloid- β peptides ($A\beta$) in the brain.^[2] $A\beta$ 42 peptides form toxic aggregates that can target neuronal synapse and cause detrimental disruption of receptor populations, morphology, and stability.^[2d, 2e, 3] Pathologies induced by $A\beta$ oligomers include tau hyperphosphorylation, reactive oxygen species (ROS) accumulation, synapse deterioration, and ultimately, nerve cell death.^[2f, 2g, 2k, 4] Blocking formation of these species is a promising approach for slowing and even preventing AD progression.^[1a, 2a, 2b, 5]

While the exact mechanism that governs $A\beta$ -induced dysfunction is widely debated, significant research has demonstrated that the histidines (His) at residues 6, 13, and 14 in the $A\beta$ sequence influence the toxicity of the peptide.^[6] Some researchers have suggested that the His residues form a putative $A\beta$ metal-ion binding site.^[6c, 6d, 7] This type of binding activity can sequester endogenous metals (such as Cu^{2+} and Zn^{2+}) in $A\beta$, disrupting normal metalloenzyme activity and catalyzing harmful ROS generation. Studies have additionally suggested that metal-ion binding may stabilize $A\beta$ conformations that mediate the formation of toxic $A\beta$ oligomers and aggregates.^[8] Other work has shown that independent of metal-ion binding, His13 and -14 facilitate aberrant interactions of $A\beta$ peptides with neuronal synapses.^[6a, 6e, 6f] While the exact role of the His residues in $A\beta$ toxicity is debated, interfering with these residues is a promising approach to modulating toxicity.

Transitional metal-containing agents that can bind to His residues have been shown to disrupt AD neuropathology.^[9] The first example was a class of platinum-phenanthroline complexes, including $Pt(1,10\text{-phenanthroline})Cl_2$ (Pt-phen, Scheme 1B).^[9a] The platinum complexes disrupted $A\beta$ aggregation and reduced ROS generation through His-coordination. Importantly, these complexes inhibited neurotoxicity and rescued long-term potentiation. Subsequently, ruthenium-, iridium-, and rhodium-based $A\beta$ binding agents were reported that exhibited similar promise for therapeutic development.^[9c-e]

Cobalt(III) Schiff base (Co(III)-sb) complexes inhibit metalloproteins by binding essential His residues through a dissociative ligand exchange at the axial positions.^[10] Hiscoordination is selective over other amino acids such as cysteine and lysine.^[11] These complexes consist of an acetylacetonatoethylenediamine (acacen) Schiff base equatorial ligand that stabilizes the cobalt(III) center. Incorporation of a peptide or oligonucleotide targeting moiety confers selectivity for the targets over proteins of the same class.^[10a, 12] The success of this approach has been demonstrated with Co(III)-sb/DNA conjugates for the selective inhibition of transcription factors relevant to development and disease.^[12a-c] In a similar manner, selective inhibition of the α -thrombin enzyme was achieved through inclusion of a peptidyl targeting domain.^[12d] Therefore, in addition to the ability to bind to His residues these complexes can be designed for targeted therapeutics.

We hypothesized that the binding of Co(III)-sb to the His residues of $A\beta$ could alter the $A\beta$ structure and alter oligomerization pathways. Through modulation of $A\beta$ activity, Co(III)-sb can serve as both an anti-AD therapeutic and a tool for understanding AD pathology. Here, the interaction between Co(III)-sb complexes and $A\beta$ peptides was investigated.

The truncated peptide A β 16 was used to evaluate the ability of the Co(III)-sb complex, Co-acacen, to bind to the A β N-terminus (Scheme 1A). A β 16 has been previously used in investigations of the putative metal binding site of A β peptides, and is believed to comprise the essential residues including the three histidines in the sequence.^[7b, 9b, 13] This peptide serves as a soluble model to evaluate small molecule binding without the complication of spontaneous aggregation of the full peptide.^[7b, 9b, 14]

A β 16 was analyzed by ESI-MS to determine the ability of the cobalt complex Co-acacen to bind the N-terminus of the peptide. The spectra of A β 16 exhibited m/z values ($m = 1955.0$, $z = 2, 3, 4$) corresponding to the peptide alone. Upon incubation of the peptide with one molar equivalent of Co-acacen, additional peaks were observed in the mass spectrum corresponding to a 1:1 peptide adduct with Co-acacen ($m = 2238.3$, observed m/z correspond to $z = 2, 3$) (SI Figure 1). This result indicates that Co(III) Schiff complexes bind to the A β N-terminus.

The incubation mixture was analyzed by HPLC (SI Figure 2, SI Figure 3). The components of the incubation mixture were separated by elution times, monitored by absorbance at 220 nm (for peptide bonds) and 330 nm (for the acacen ligand of the cobalt complex). ESI-MS spectra of the various components were deconvoluted by the m/z of the free peptide, m/z of Co-acacen (without axial ligands), and m/z of the 1:1 peptide/Co-acacen adduct. Three major components were observed corresponding to the free A β 16, free Co-acacen, and the peptide/Co-acacen adduct ((SI Figure 2, SI Figure 3B) in contrast to the single component corresponding to the free A β 16 observed in the analysis of the peptide alone (SI Figure 3A). The HPLC chromatogram corroborates that the peptide/Co-acacen adduct observed in the gas phase (direct injection by ESI-MS) exists in solution phase (SI Figure 2). Further, the eluent at the retention time corresponding to the peptide/Co-acacen adduct showed three peaks, indicating that multiple conformations may be present. Since three histidines are present that can potentially coordinate to the Co(III) center at the two axial positions, multiple conformations are possible.

¹H NMR studies were performed with A β 16 to determine the binding site of Co-acacen in the sequence (Figure 1). The spectra were obtained in buffered D₂O to reduce signals from the exchangeable backbone amides (NH) of the peptide and simplify analysis. Assignments were made and confirmed by ¹H-¹H TOCSY NMR (SI Figure 4). Spectra of A β were acquired at increasing concentrations of Co-acacen (Co-acacen:A β 16 = 0.0 to 4.0) and the aromatic regions of the spectra (6.0–9.0 ppm) were analyzed. In the absence of Co-acacen, peaks corresponding to the CH₂ protons of the free His imidazoles are observed (7.9–8.2 ppm). With increasing equivalents of Co-acacen up to 2.0 equivalents, a concentration-dependent reduction of these free His peaks is observed, accompanied by the emergence of a new series of peaks between 6.35–6.7 ppm. The frequencies of these new peaks correspond to the resonances of the CH₅ protons of His imidazoles coordinated to Co(III)-sb complexes.^[10b] Further, the decrease in integral values of the CH₂ protons of the free His imidazoles quantitatively corresponds to rise in integral values of the new series of peaks attributed to the CH₅ protons of the Co^{III}-coordinated His upon addition of Co-acacen (SI Figure 5).

The resulting spectra exhibit lower resolution than the free peptide, likely due to conformational heterogeneity. Co-acacen can coordinate any one of the three His residues (Scheme 1C). If 1.0 eq Co-acacen is added, free His CH₂ proton peaks are still present (as Co-acacen can only coordinate two equivalents of Co-acacen at a time). Complete loss of free His protons are observed at 2.0 equivalents, indicating that all three His residues are coordinated to Co-acacen. Near complete His-coordination at 2.0 equivalents (rather than 3.0 equivalents) implies that Co-acacen is capable of coordinating two His residues simultaneously.

A further increase in concentration of Co-acacen (2.0 equivalents) resulted in the appearance of a new set of peaks at 6.4 ppm. While these new peaks are within the region of the expected chemical shifts of Co(III)-coordinated His CH₅ protons, the chemical shifts are distinct from the peaks observed at <2.0 equivalents of **1**. These observations indicate the presence of more than one species containing His coordinated to [Co(acacen)(L)₂]⁺ (Co(III)-His). The appearance of these new resonances coincides with loss of signal intensity, which correlates to an increase in conformational heterogeneity. Such heterogeneity is expected, given the multiple possible combinations of His₂ coordination to the Co-acacen (His13/His14, His6/His13, His6/His14).

The conformation and geometry of the Co^{III} center in the Co-acacen/Aβ16 adduct was evaluated by electronic absorption and compared to the Co-acacen alone ([Co(acacen)(NH₃)₂]⁺), a small molecule model of Co-acacen coordinated to two histidines, [Co(acacen)(4MeIm)₂]⁺ where the 4-methylimidazole ligands (4MeIm) mimics the histidine side chain, and the peptide alone (SI Figure 6A, D). At both 1.0 and 2.0 equivalents of Co-acacen, the resulting adduct exhibits an electronic absorption spectrum that closely resembles [Co(acacen)(4MeIm)₂]⁺, demonstrating the presence of an octahedral [Co(acacen)(His)₂]⁺ structure with the acacen in the equatorial plane and His₂-coordination at the axial positions (See SI Discussion 1 for extended discussion of electronic absorption spectra). These observations are consistent with previous observations with an established target of Co-acacen, zinc finger transcription factors.^[11]

DFT studies were performed to assess the thermodynamically favorable configuration of axial ligand coordination by the three His residues to Co-acacen. To represent possible modes of Aβ binding, several structures of cobalt complexes with varying axial ligands were located. The His13-His14 portion of the sequence was represented as two histidine side chains linked with a peptide bond.^[15] His6 was represented by 4-methylimidazole, a small molecule model of the histidine side chain.^[10c] The relative energies of the structures were compared to determine a preference for bis-coordination (both axial positions are coordinated to imidazoles) or mono-coordination (one axial position is coordinated to an imidazole and the other is coordinated to an aquo ligand) (Figure 2).

All possible conformations of each structure were optimized using the B3LYP density functional^[16] in conjunction with the 6-31+G(d) Pople basis set for all atoms.^[10c, 15] Frequency calculations were performed to confirm that the structures were ground-state minima and obtain thermal corrections to the electronic energy. The thermodynamic parameters of the lowest energy conformations were compared (Figure 2). These

calculations predict that the most favorable coordination geometry involves the coordination of His6 at one position and either His13 or His14 at the other position. Slightly less favorable is coordination of just one histidine (with little difference in favorability for coordination of His6, or His13/14). The least favored is the simultaneous coordination of His13 and His14. This data supports a resulting mixture of coordination, consistent with the NMR experiments.

The effects of the cobalt complex on oligomerization pathways of the full A β 42 peptide were evaluated with SDS-PAGE Western blot and silver stain analysis. Western blots were carried out with the conformation-specific antibody, NU2, that recognizes soluble A β oligomers (referred to as ADDLs). ADDLs were prepared at 100 μ M A β 42 with increasing concentrations of Co-acacen. In comparison to the untreated preparations, Co-acacen promoted the formation of large (>30kDa) SDS-stable oligomers while reducing the small oligomer population in a concentration-dependent manner (Figure 3A and SI Figure 8).

This phenomenon was analyzed in comparison to treatment with the previously studied platinum complex, Pt-phen. Although Pt-phen was previously evaluated for effects on A β plaque formation, its effects on soluble oligomer formation have not been studied. The SDS-PAGE Western blots with the NU2 antibody demonstrate that Pt-phen similarly promotes the formation of the large SDS-stable oligomer population (Figure 4). The similarity with Pt-phen in the effects on A β structure demonstrates the promise of Co-acacen in therapeutic development.

The planar aromatic scaffold contained in the 1,10-phenanthroline ligand of Pt-phen is posited to interact with the aromatic residues (Tyr10, Phe19, or Phe21) of A β through π - π stacking interactions. The non-covalent interactions of the ligand 1) targets the Pt^{II} center to the amino acids in the peptide 2) affects the reactivity of Pt^{II} center and 2) influences A β aggregation since these hydrophobic residues are associated with self-recognition of the peptide that occurs in oligomerization.^[17] This key role of the phenanthroline ligand is supported by lack of A β pathway disruption by cisplatin. In addition to non-covalent interactions, the difference in behavior may also result from a difference in binding modes; while Pt-phen coordinates up to two His residues (with preference for His6 and His14), cisplatin predominantly coordinates to Met35.^[17d] Another platinum complex lacking this aromatic scaffold, Pt(ethylenediamine)Cl₂ (Pt-en) was tested for effects on A β oligomer formation (Figure 4). Pt-en did not appear to alter oligomer formation, supporting the influential role of the N-heterocyclic aromatic scaffold on A β oligomerization pathways.

To evaluate the influence of aromatic scaffolds on A β binding a derivative of Co-acacen containing aromatic groups on the equatorial ligand, Co-benacen, was synthesized and tested for effect on A β oligomerization. Oligomerization was analyzed by SDS-PAGE Western blot probed with the oligomer-specific monoclonal antibody NU2 (Figure 3B). At the same concentrations as Co-acacen, Co-benacen demonstrated a similar stabilization of the large oligomer (Figure 3B). A slight difference in oligomer distribution is observed, possibly due to interactions between the aromatic phenyl groups of Co-benacen and the hydrophobic pocket of A β 42. This hypothesis is supported by a slight stabilization of large oligomers in the presence of the free benacen ligand that is not observed with the free acacen ligand

(Figure 3B). HPLC-MS analysis of a solution of A β 16 treated with Co-benacen demonstrated that the complex can effectively interact with the N-terminus of the A β 42 peptide that comprise the three His residues (SI Figure 3C).

The effect of Co-acacen on synaptic binding of ADDLs was evaluated with hippocampal neurons to correlate alterations in oligomeric structure to A β activity in cells. The Co-benacen complex was not used for these studies due to poor solubility. It has been previously determined that oligomers of particular size are able to bind the synapse.^[18] Synaptic attachment can then initiate A β -induced neurotoxicity.^[4d] Differentiated hippocampal neurons were treated with oligomers formed with 30 nM A β 42 in the presence or absence of Co-acacen. Synaptic binding was analyzed by immunolabeling the cells with NU4, a conformation-specific antibody for A β oligomers. Treatment with oligomers assembled in the presence of 100 nM of Co-acacen resulted in a marked decrease in overall binding to neurons (SI Figure 9). Specifically, this overall reduction appears to result from reduction in small NU4-sensitive clusters. These results show promise for Co(III) Schiff base complexes to reduce synaptic targeting of pathogenic A β oligomers through biochemically altering A β structure.

We have demonstrated that cobalt(III) Schiff base complexes can interact with the N-terminus of A β peptides and alter their structure and oligomerization propensities. The specific binding of the cobalt complex, Co-acacen, to the A β N-terminus was shown with the A β 16 peptide. Specifically the three histidines in the sequence were identified as the binding site of the cobalt complexes. Computational studies predict the preference for simultaneous coordination of the His6 and either the His13 or His14 imidazoles to the Co(III) center. However, NMR studies indicate the presence of multiple possible binding conformations.

The cobalt complexes altered A β oligomerization pathways, stabilizing the formation of large soluble oligomers. A similar effect was observed with Pt-phen for which promising anti-AD activity was previously demonstrated. The similarity in the effects of the cobalt complexes to Pt-phen presents the cobalt complexes as viable candidates for therapeutic development. This conclusion is validated by the reduction of A β synaptic binding induced by the cobalt complex, Co-acacen. Additionally, the stabilization of large oligomers by the natural product oleocanthal has been previously correlated to protection from synaptopathological effects of A β .^[19]

These studies reveal the potential of using cobalt(III) Schiff base complex as a platform to develop A β -binding molecules. Further, this work underscores the promise of metal-based modulators of His-residues for anti-AD applications. Finally, the cobalt complexes can be modified with an A β targeting molecule (such as a peptide or small molecule) to introduce selectivity for the A β His residues and improve overall potency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

M.C.H. and L.M.M. would like to acknowledge the National Science Foundation Graduate Research Fellowship. J.L.C. and C.K. would like to acknowledge the Northwestern University Undergraduate Research Grant with the Weinberg College of Arts and Sciences. We gratefully acknowledge funding from the National Institutes of Health under Grant R01EB005866 and Grant R21AG041953, the Center for Cancer Nanotechnology Excellence (CCNE) initiative of the National Institutes of Health's National Cancer Institute under Award U54CA151880, and the Alzheimer's Association under Award ZEN-09-133875.

References

1. a) Citron M. *Nat Rev Drug Discovery*. 2010; 9:387–398. b) Holtzman DM, John CM, Goate A. *Sci Transl Med*. 2011; 3:77sr71. c) Kenche VB, Barnham KJ. *Br J Pharmacol*. 2011; 163:211–219. [PubMed: 21232050] d) Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde ALW, Jessen F, Hoessler YC, Sanhai WR, Zetterberg H, Woodcock J, Blennow K. *Nat Rev Drug Discovery*. 2010; 9:560–574.
2. a) Ferreira ST, Klein WL. *Neurobiol Learn Mem*. 2011; 96:529–543. [PubMed: 21914486] b) Hamley IW. *Chem Rev*. 2012; 112:5147–5192. [PubMed: 22813427] c) Hung LW, Ciccotosto GD, Giannakis E, Tew DJ, Perez K, Masters CL, Cappai R, Wade JD, Barnham KJ. *J Neurosci*. 2008; 28:11950–11958. [PubMed: 19005060] d) Klein WL. *Alzheimer's Dement*. 2006; 2:43–55. [PubMed: 19595855] e) Klein W, De Felice F, Lacor PN, Lambert MP, Zhao WQ. 2008:103–132. f) Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, Wals P, Zhang C, Finch CE, Krafft GA, Klein WL. *Proc Natl Acad Sci U S A*. 1998; 95:6448–6453. [PubMed: 9600986] g) Parodi J, Sepulveda FJ, Roa J, Opazo C, Inestrosa NC, Aguayo LG. *J Biol Chem*. 2010; 285:2506–2514. [PubMed: 19915004] h) Rauk A. *Chem Soc Rev*. 2009; 38:2698. [PubMed: 19690748] i) Shankar GM, Walsh DM. *Molecular Neurodegeneration*. 2009; 4:48. [PubMed: 19930651] j) Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, Selkoe DJ. *Biochem Soc Trans*. 2002; 30:552–557. [PubMed: 12196135] k) Wang HW, Pasternak JF, Kuo H, Ristic H, Lambert MP, Chromy B, Viola KL, Klein WL, Stine WB, Krafft GA. *Brain Res*. 2002; 924:133–140. [PubMed: 11750898]
3. Gong Y. *Proc Natl Acad Sci U S A*. 2003; 100:10417–10422. [PubMed: 12925731]
4. a) Kim HJ, Chae SC, Lee DK, Chromy B, Lee SC. *The FASEB Journal*. 2003 b) Rembach A, Ryan TM, Roberts BR, Doecke JD, Wilson WJ, Watt AD, Barnham KJ, Masters CL. *Biomarkers in medicine*. 2013; 7:641–662. [PubMed: 23905901] c) Krafft GA, Klein WL. *Neuropharmacology*. 2010; 59:230–242. [PubMed: 20650286] d) Lacor PN, Buniel MC, Furlow PW, Sanz Clemente A, Velasco PT, Wood M, Viola KL, Klein WL. *J Neurosci*. 2007; 27:796–807. [PubMed: 17251419]
5. Amijee H, Scopes D. *J Alzheimer's Dis*. 2009
6. a) Arispe N, Diaz JC, Flora M. *Biophys J*. 2008; 95:4879–4889. [PubMed: 18723589] b) Diaz JC, Linnehan J, Pollard H, Arispe N. *Biol Res*. 2006 c) Liu ST, Howlett G, Barrow CJ. *Biochemistry*. 1999 d) Nakamura M, Shishido N, Nunomura A, Smith MA. *Biochemistry*. 2007 e) Poduslo JF, Gilles EJ, Ramakrishnan M, Howell KG, Wengenack TM, Curran GL, Kandimalla KK. *PLoS One*. 2010; 5:e8813. [PubMed: 20098681] f) Smith DG, Ciccotosto GD, Tew DJ, Perez K, Curtain CC, Boas JF, Masters CL, Cappai R, Barnham KJ. *Journal of Alzheimer's disease : JAD*. 2010; 19:1387–1400. g) Tickler AK, Smith DG, Ciccotosto GD, Tew DJ, Curtain CC, Carrington D, Masters CL, Bush AI, Cherny RA, Cappai R, Wade JD, Barnham KJ. *J Biol Chem*. 2005; 280:13355–13363. [PubMed: 15668252]
7. a) Lau TL, Ambroggio EE, Tew DJ, Cappai R, Masters CL, Fidelio GD, Barnham KJ, Separovic F. *J Mol Biol*. 2006; 356:759–770. [PubMed: 16403524] b) Smith DP, Smith DG, Curtain CC, Boas JF, Pilbrow JR, Ciccotosto GD, Lau TL, Tew DJ, Perez K, Wade JD, Bush AI, Drew SC, Separovic F, Masters CL, Cappai R, Barnham KJ. *J Biol Chem*. 2006; 281:15145–15154. [PubMed: 16595673]
8. a) Drew SC, Masters CL, Barnham KJ. *PLoS One*. 2010; 5:e15875. [PubMed: 21209855] b) Horikoshi Y, Mori T, Maeda M, Kinoshita N, Sato K, Yamaguchi H. *Biochem Biophys Res Commun*. 2004; 325:384–387. [PubMed: 15530403]
9. a) Barnham KJ, Kenche VB, Ciccotosto GD, Smith DP, Tew DJ, Liu X, Perez K, Cranston GA, Johanssen TJ, Volitakis I, Bush AI, Masters CL, White AR, Smith JP, Cherny RA, Cappai R. *Proc*

- Natl Acad Sci U S A. 2008; 105:6813–6818. [PubMed: 18463291] b) Ma G, Huang F, Pu X, Jia L, Jiang T, Li L, Liu Y. Chem-Eur J. 2011; 17:11657–11666. [PubMed: 21910144] c) Man BYW, Chan HM, Leung CH, Chan DSH, Bai LP, Jiang ZH, Li HW, Ma DL. Chem Sci. 2011; 2:917–921. d) Messori L, Camarri M, Ferraro T, Gabbiani C, Franceschini D. ACS Med Chem Lett. 2013; 4:329–332. [PubMed: 24900669] e) Valensin D, Anzini P, Gaggelli E, Gaggelli N, Tamasi G, Cini R, Gabbiani C, Michelucci E, Messori L, Kozłowski H, Valensin G. Inorg Chem. 2010; 49:4720–4722. [PubMed: 20459130] f) Valensin D, Gabbiani C, Messori L. Coord Chem Rev. 2012; 256:2357–2366.
10. a) Heffern MC, Yamamoto N, Holbrook RJ, Eckermann AL, Meade TJ. Curr Opin Chem Biol. 2013; 17:189–196. [PubMed: 23270779] b) Manus LM, Holbrook RJ, Atesin TA, Heffern MC, Harney AS, Eckermann AL, Meade TJ. Inorg Chem. 2013; 52:1069–1076. [PubMed: 23282130] c) Matosziuk LM, Holbrook RJ, Manus LM, Heffern MC, Ratner MA, Meade TJ. Dalton Trans. 2013; 42:4002–4012. [PubMed: 23340849]
 11. Heffern MC, Kurutz JW, Meade TJ. Chem-Eur J. 2013; 19:17043–17053. [PubMed: 24203451]
 12. a) Harney AS, Lee J, Manus LM, Wang P, Ballweg DM, LaBonne C, Meade TJ. Proc Natl Acad Sci U S A. 2009; 106:13667–13672. [PubMed: 19666616] b) Harney AS, Meade TJ, LaBonne C. PLoS One. 2012; 7:e32318. [PubMed: 22393397] Hurtado RR, Harney AS, Heffern MC, Holbrook RJ, Holmgren RA, Meade TJ. Mol Pharm. 2012; 9:c). 325–333. Takeuchi T, Böttcher A, Quezada CM, Simon MI, Meade TJ, Gray HB. J Am Chem Soc. 1998; 120:d). 8555–8556.
 13. Syme CD, Nadal RC, Rigby SEJ, Viles JH. J Biol Chem. 2004; 279:18169–18177. [PubMed: 14978032]
 14. Ma QF, Hu J, Wu WH, Liu HD, Du JT, Fu Y, Wu YW, Lei P, Zhao YF, Li YM. Biopolymers. 2006; 83:20–31. [PubMed: 16615111]
 15. Ali-Torres J, Rodríguez-Santiago L, Sodupe M, Rauk A. J Phys Chem A. 2011; 115:12523–12530. [PubMed: 21678945]
 16. a) Lee C, Yang W, Parr R. Phys Rev B Condens Matter. 1988; 37:785–789. [PubMed: 9944570] b) Becke AD. J Chem Phys. 1993; 98:5648–5652.
 17. a) Collin F, Sasaki I, Eury H, Faller P, Hureau C. Chem Commun. 2013; 49:2130–2132. b) Kenche VB, Hung LW, Perez K, Volitakes I, Ciccotosto G, Kwok J, Critch N, Sherratt N, Cortes M, Lal V, Masters CL, Murakami K, Cappai R, Adlard PA, Barnham KJ. Angew Chem, Int Ed. 2013; 52:3374–3378. c) Sasaki I, Bijani C, Ladeira S, Bourdon V, Faller P, Hureau C. Dalton Trans. 2012; 41:6404. [PubMed: 22301852] d) Streltsov VA, Chandana Epa V, James SA, Churches QI, Caine JM, Kenche VB, Barnham KJ. Chem Commun. 2013; 49:11364–11366. e) Wang X, Wang X, Zhang C, Jiao Y, Guo Z. Chem Sci. 2012; 3:1304–1312.
 18. a) Lacor PN. J Neurosci. 2004; 24:10191–10200. [PubMed: 15537891] b) Velasco PT, Heffern MC, Sebollela A, Popova IA, Lacor PN, Lee KB, Sun X, Tiano BN, Viola KL, Eckermann AL, Meade TJ, Klein WL. ACS Chem Neurosci. 2012; 3:972–981. [PubMed: 23173076]
 19. Pitt J, Roth W, Lacor P, Smith I, Amos B, Blankenship M, Velasco P, De Felice F, Breslin P, Klein WL. Toxicol Appl Pharmacol. 2009; 240:189–197. [PubMed: 19631677]
 20. Böttcher A, Takeuchi T, Hardcastle KI, Meade TJ, Gray HB, Cwikel D, Kapon M, Dori Z. Inorg Chem. 1997; 36:2498–2504.
 21. Hodges KD, Rund JV. Inorg Chem. 1975
 22. Lambert MP, Velasco PT, Chang L, Viola KL, Fernandez S, Lacor PN, Khuon D, Gong Y, Bigio EH, Shaw P, De Felice FG, Krafft GA, Klein WL. J Neurochem. 2007; 100:23–35. [PubMed: 17116235]
 23. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, Krafft GA, Klein WL. J Neurosci. 2004; 24:10191–10200. [PubMed: 15537891]

Figure 1.

^1H NMR of A β 16 (5mM) with increasing ratios of Co-acacen:A β 16 from 0.0 – 4.0 in D $_2$ O buffered with 100 mM phosphate buffer to pH 7.0. Spectra were acquired at on a 500 MHz spectrometer at 25 °C after 1h incubations at 37 °C. With increasing equivalents of Co-acacen, a loss of peaks corresponding to the free His CH $_2$ protons (7.9–8.2 ppm) is observed. New peaks are observed between 6.35–6.7 ppm, indicating His-coordination to Co-acacen (Co(III)-His) in a concentration-dependent manner. A complete loss of free His peaks is observed at 2.0 eq. of Co-acacen.

Figure 2.

Thermodynamic parameters of Co(III)-sb complexes coordinated to models of His6, 13, and 14. These calculations indicate the favorability of a coordination mode with the His6 and either the His13 or His14 at the axial positions of the Co(III)-sb complex. Simultaneous coordination of the His13 and His14 is the least favorable due to strain induced on the octahedral geometry (SI Figure 7).

Figure 3. SDS-PAGE Western blots of Aβ42 oligomerized in the presence of Co-acacen, Co-benacen, and the free ligands. (A) Co-acacen shifts the distribution of SDS-stable Aβ soluble oligomers to higher MW species in a concentration-dependent manner. (B) A similar effect is observed with Co-benacen but to a greater degree, possibly due to the presence of the aromatic residues. This result is confirmed by the slight stabilization of large oligomers with the free Benacen ligand. Such disruption is not observed with the free Acacen ligand.

Figure 4.

SDS-PAGE (A) silver stain profiles and (B) Western blots of Aβ42 oligomerized in the presence of Co-acacen, Pt-en and Pt-phen. In a similar manner to Co-acacen, Pt-phen shifts the distribution of SDS-stable Aβ soluble oligomers to higher MW species. This is not observed with Pt(ethylenediamine)Cl₂ (Pt-en), indicating the importance of the aromatic scaffold in Aβ structural disruption. The similarity of the effect of Co-acacen on the Aβ oligomerization to Pt-phen underscores the promise of the cobalt complexes for anti-AD therapeutic approaches.

Scheme 1.

(A) Amyloid β (A β) peptides used in these studies. A β 16 was used as a soluble peptide model to understand the interactions between Co(III)-sb complexes and the N-terminus of the A β peptide. A β 42 was used to understand the effects of Co(III)-sb complexes on peptide oligomerization and synaptic binding. (B) Transition metal complexes and naming scheme used in this chapter. Co-acacen and Co-benacen are Co(III)-sb complexes that coordinate His residues through dissociative ligand exchange of the axial amines. The behavior of Co(III)-sb on modulating A β was compared to Pt-phen, a Pt(II) complex previously shown to disrupt A β -induced neurotoxicity. (C) Proposed scheme of the modulation of A β activity by Co-acacen. Co-acacen is believed to coordinate to the His residues of A β through the two axial positions. Computational studies suggest the simultaneous coordination of His6 and either His13 or His14 as the most stable conformation. His-coordination alters the A β structure, disrupting oligomerization pathways and synaptic binding.