The Chemistry of Alzheimer's Disease

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The Chemistry of Alzheimer's Disease

Abstract: The chemistry of Alzheimer's disease is largely centred on the amyloid beta peptide, its formation, structure, and interactions with metals, membranes, proteins and other species. This review summarizes the current state of knowledge.
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The Mechanism of Hydrogen Peroxide Production by Copper-bound Amyloid Beta Peptide: A Theoretical Study.

Abstract: The amyloid beta peptide (Ab) of Alzheimer's disease evolves hydrogen peroxide in vitro in the presence of Cu(II), external reducing agents, and molecular oxygen, without producing detectable amounts of the one-electron reduced intermediate, superoxide, O2-o. The mechanism of this process was examined by ab initio computational chemistry techniques in systems that model the binding of Cu(II) to the His13His14 fragment of Ab. The catalytic cycle begins with the reduction of the most stable Cu(II) complex to the most stable Cu(I) complex. This Cu(I)

complex forms a Cu(II)-like adduct with 3O2 that cannot dissociate in water to yield O2-o. However, it can be reduced by proton-coupled electron transfer to an adduct between HOO- and the Cu(II)-like complex, which in turn can be protonated. The protonated complex decomposes to yield H2O2 by an associative-dissociative mechanism, thus completing the cycle.

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Molecular dynamics study of the interaction of Ab(13-23) with b-sheet inhibitors

Abstract: The region encompassing residues 13-23 of the amyloid beta peptide (Ab(13-23)) of Alzheimer's disease is the self-recognition site that initiates toxic oligomerization and fibrillization, and also is the site of interaction of Ab with many other proteins. Peptidic compounds intended to act as b-sheet inhibitors targeted to Ab(13-23) have been shown to inhibit fibrillization of Ab and also to reduce its neurotoxicity. We describe herein a study by molecular dynamics (MD) of the complexes between Ab(13-23) and three (pseudo)peptidic b-sheet inhibitors, as well as its homodimer. The monomers of all systems exist predominantly as extended b-strands, with Ab(13-23) having the greatest flexibility to adopt other conformations. The dimers of all systems exist almost exclusively as stable antiparallel b-sheets anchored at the C-terminus of Ab(13-23) by salt bridges to the C-terminal residues, Glu22 and Asp23. We also employ an MD technique called "atomic force microscopy" (AFM) to examine the dynamics of dissociation of the complexes in water. Each ligand attached to Ab(13-23) begins dissociation by peeling back from its C-terminus, breaking interstrand H-bonds, and losing the b-sheet character. The salt bridges are the last to release, and presumably are the first to form in the reverse process of aggregation. The free energy profiles of the dissociation as a function of the separation of the centers-of-mass of all systems show plateau regions in which separation takes place with relatively little or no rise in free energy. For each system the dissociation profile does not have a maximum and reaches a flat plateau. By implication, the reverse process of assembly does not have a barrier. This and the plateau regions in the dissociation profile are examples of entropy-enthalpy compensation that arise naturally during the MD-AFM simulation.

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Why is the amyloid beta peptide of Alzheimer's disease neurotoxic?

Abstract: In this article, we support the case that the neurotoxic agent in Alzheimer's disease is a soluble aggregated form of the amyloid beta peptide (Ab), probably complexed with divalent copper. The structure and chemical properties of the monomeric peptide and its Cu(II) complex are discussed, as well as what little is known about the oligomeric species. Ab oligomers are neurotoxic by a variety of mechanisms. They adhere to plasma and intracellular membranes and cause lesions by a combination of radical-initiated lipid peroxidation and formation of ion-permeable pores. In endothelial cells this damage leads to loss of integrity of the blood-brain barrier and loss of blood flow to the brain. At synapses, the oligomers close neuronal insulin receptors, mirroring the effects of Type II diabetes. In intracellular membranes, the most damaging effect is loss of calcium homeostasis. The oligomers also bind to a variety of substances, mostly with deleterious effects. Binding to cholesterol is accompanied by its oxidation to products that are themselves neurotoxic. Possibly most damaging is the binding to tau, and to several kinases, that results in the hyperphosphorylation of the tau and abrogation of its microtubule-supporting role in maintaining axon structure, leading to diseased synapses and ultimately the death of neurons. Several strategies are presented and discussed for the development of compounds that prevent the oligomerization of Ab into the neurotoxic species.

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Molecular Dynamics Study of the Beta Amyloid Peptide of Alzheimer's Disease and its Divalent Copper Complexes

Abstract: The A 1-42 monomer structure was assessed with a 790 ns molecular dynamics (MD) simulation and the results compared with the NMR experiment on A 10-35 and A 1-40. Previous theoretical work in a model of the His13-His14 region of A defined the possible Cu(II) binding geometries at this site (Raffa et al. in J Biol Inorg Chem 10:887-902, 2005). MD simulations, totalling almost 2 s, were also carried out on Cu(II)/A 1-42 systems, using the ab initio structures as templates for the copper binding site. This work finds that the copper-free A 1-42 system may stabilize after ~350 ns into a collapsed coil conformation and we find good agreement with some, but not all, of the

structural features determined experimentally for the A 10-35 and Ab1-40 peptides. The results of the Cu(II)/A 1-42 systems are compared to the Cu(II)-free A 1-42 simulation.
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The Effect of Side Chains on Competing Pathways for beta-Scission Reactions of Peptide-Backbone Alkoxyl Radicals

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Ab initio modelling of the structure and redox behaviour of copper(I) bound to a His-His model peptide: Relevance to the beta amyloid peptide of Alzheimer's disease

Abstract: A contributing factor to the pathology of Alzheimer's disease (AD) is the generation of reactive oxygen species, most probably a consequence of the -amyloid peptide (A coordinating copper ions. Experimental and theoretical results indicate that His13 and His14 are the two most firmly established ligands in the coordination sphere of Cu(II) bound to A . A 42 is known to reduce Cu(II) to Cu(I). The A -Cu(II) complex has been shown to catalytically generate H2O2 from reducing agents and O2. Cu(II) in the presence of A has been reported to have a formal reduction potential of +0.72-0.77 V (versus SHE). Quantum chemical calculations using the unrestricted B3LYP hybrid density functional method with the 6-31G(d) basis set were performed to model the reduction of previously studied Cu(II) complexes representing the His13-His14 portion of A Raffa DF, Gómez-Balderas R, Brunelle P, Rickard GA, Rauk A (2005) J Biol Inorg Chem 10:887-902). The effects of solvation were accommodated using the CPCM method. The most stable complex between Cu(I) and the model compound, 3-(5-imidazolyl)-propionylhistamine (1) involves tricoordinated Cu(I) in a distorted "T" geometry, with the N of both imidazoles as well as the oxygen of the backbone carbonyl bound to copper. This model would be the most likely representation of a Cu(I) binding site for a His-His peptide in aqueous solution. A variety of possible redox processes are discussed.
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One-Electron Oxidation of Methionine Peptides: Stability of the Three-Electron SN(Amide) Bond

Abstract: The possibility of sulfur-nitrogen (S-N) 3-electron bond formation in a 1-electron oxidized methionine peptide model was investigated computationally following the detection of such species in pulse radiolysis experiments (Schöneich, et al. J. Am. Chem. Soc. 125, 13700-13713 (2003)). Geometry optimizations were carried out at the B3LYP/6-31G(d) level of theory. Relative free energies in aqueous solution at pH = 7 were predicted for all intermediates with enthalpy evaluations at the CCSD(T)/6-31+G(d') level and free energies of solvation predicted using a continuum model, CPCM. Both the initial oxidation product and the intermediate formed at higher pH were identified as cyclic SN bonded species in which the intramolecular 3-electron interaction is between the S atom and the orbital of the amide group. TD-B3LYP calculations of the UV spectra support the assignments. A mechanism for the conversion to the most stable C-centered radical is proposed. The mechanism involves a novel deprotonation - reprotonation via an intermediate backbone-delocalized radical anion.
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Binding Affinities for Models of Biologically Available Potential Cu(II) Ligands Relevant to Alzheimer's Disease: An Ab Initio Study

Abstract: A systematic study of the binding affinities of the model biological ligands X: = (CH3)2S, CH3S-, CH3NH2, 4-CH3-imidazole, C6H5O-, and CH3CO2- to (NH3)i(H2O)3-iCu(II)-H2O (i = 3,2,1,0) complexes has been carried out using quantum chemical calculations. Geometries have been obtained at the B3LYP/6-31G(d) level of theory, and binding energies, Ho(g), relative to H2O as a ligand, have been calculated at the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) level. Solvation effects have been included using the COSMO model, and the relative binding free energies in

aqueous solution (Go'(aq)) have been determined at pH 7 for processes that are pH dependent. CH3S- (Go'(aq) = -16.0 to -53.5 kJ mol-1) and MeImid (Go'(aq) = -18.5 to -35.2 kJ mol-1) give the largest binding affinities for Cu(II). PhO- and (CH3)2S are poor ligands for Cu(II), Go'(aq) = 20.6 to -9.7 and 19.8 to -3.7 kJ mol-1 respectively. The binding affinities for CH3NH2 range from -0.8 to -15.0 kJ mol-1. CH3CO2- has Cu(II) binding affinities in the range Go'(aq) = -13.5 to -32.4 kJ mol-1 if an adjacent OH bond is available for hydrogen bonding, and Go'(aq) = 10.1 to -4.6 kJ mol-1 if this interaction is not present. In the context of copper coordination by the A peptide of Alzheimer's disease the binding affinities suggest preferential binding of Cu(II) to the three histidine residues plus a lysine or the N-terminus. For a 3N1O Cu(II) ligand arrangement it is more probable that the oxygen ligand comes from an aspartate/glutamate residue side chain than from the tyrosine at position 10. Methionine appears unlikely to be a Cu(II) ligand in A .

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THE "THEORETICAL" CHEMISTRY OF ALZHEIMER'S DISEASE: THE RADICAL MODEL

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Binding of Copper Ions to Methionine Peptide Models: Relevance to Alzheimer's Disease

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Dialkyl sulfur radical cations: competition between proton and methyl cation transfers to sulfur nucleophiles: an ab initio study

Abstract: Ab initio calculations were performed on model compounds to examine the possibility of conversion of one-electron-oxidized methionine to homocysteine radical under physiologically relevant conditions. Specifically, we studied competitive proton and methyl cation transfer from dimethyl sulfide radical cation to three neutral, closed-shell sulfur bases/nucleophiles: H2S, CH3SH, and (CH3)2S. The latter two are models for cysteine (or homocysteine) and methionine, respectively. Calculations were performed at the B3LYP/6-31G(d) and B3LYP/6-311+G(3df,2p) levels. The enthalpies of reaction and free energies were determined at 298 K in the gaseous phase and in aqueous solution. CPCM solvation calculations were employed for the solution phase to obtain free energies of solvation. For all three sulfur bases, proton transfer from oxidized (CH3)2S is endothermic and is not hindered by a barrier. Nucleophilic attack by (CH3)2S at the methyl group is strongly exothermic and is impeded by a low enthalpic barrier (DH‡(g) = 29 kJ mol-1). The entropy of activation serves to raise the barrier (DG‡(g) = 42 kJ mol-1) and unfavorable aqueous solvation of the transition structure raises it even further (DG‡(aq) = 108 kJ mol-1). It is concluded on the basis of the model systems that demethylation of oxidized methionine to give homocysteine would not be observed in an aqueous environment, but may be observable under hydrophobic conditions that exist in the beta amyloid fibrils of Alzheimer's disease.

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175. S. Roy and A. Rauk, Alzheimer's Disease and the 'ABSENT' Hypothesis: Mechanism for Amyloid Beta Synergistic Endothelial and Neuronal Toxicity

Abstract: Alzheimer's disease [AD] is the most common cause of dementia among people age 65 and older. One of the biggest stumbling blocks in developing effective drug therapy for Alzheimer's disease has been the lack of a comprehensive hypothesis that explains the mechanism behind all of the histopathological changes seen in patients suffering from Alzheimer's disease. An overview of the currently popular 'amyloid' and 'vascular' hypotheses for AD demonstrates that neither hypothesis by itself can explain all the known histopathological and biochemical lesions seen in Alzheimer's disease. The paper presents a hypothesis that tries to explain the mechanism behind almost all

the histopathological changes, and varying clinical manifestations seen in both diagnosed AD and Vascular Dementia [VaD]. The new hypothesis is based on the known dual toxicity of b amyloid to both vascular and neuronal tissue, their synergy and the resultant net effect on the onset and progression of AD. The new hypothesis therefore will be known as the Amyloid Beta Synergistic Endothelial and Neuronal Toxicity [ABSENT] hypothesis. The ABSENT hypothesis will try to show the common chemical mechanism behind almost all of the pathological changes seen in AD. According to the ABSENT hypothesis, b amyloid itself generates all the free radicals that cause both vascular dysfunction and the neuronal damage seen in AD. The chemical mechanism proposed is based on evidence from physical chemistry experiments, calculations as well as in vitro/ in vivo experiments. The ABSENT hypothesis does not favor one mode of b amyloid induced brain damage over the other, rather it considers the net effects of the neuronal stress/damage caused by both the cerebrovascular dysfunction and direct neurotoxicity caused by b amyloid. The hypothesis states that each patient has a different balance of predisposing factors that modulate the extent of neurotoxicity and cerebrovascular dysfunction caused by b amyloid and thereby explains the wide range and mixed nature of damage and dysfunction seen in the studies done on patients diagnosed with AD, VaD or 'mixed dementias'. According to the hypothesis b amyloid peptides are necessary if not sufficient to cause AD, VaD and mixed senile dementias. The hypothesis therefore proposes the term Beta Amyloid Dementias [BAD] to describe the conditions currently covered by the diagnoses of 'AD', 'VaD' and 'Mixed [senile] Dementias'. Finally the ABSENT hypothesis tries to put forth a direct chemical mechanism behind the apparent synergy and increased association between old age, pre- and coexisting vascular disease, diabetes and AD.

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One-Electron Oxidation of Methionine in Peptide Environments: The Effect of Three-Electron Bonding on the Reduction Potential of the Radical Cation

Abstract: The complexes between the radical cation of dimethyl sulfide 2 and models for eight biologically available electron pair donors, :X (:X = H2O (2a), H2CO (2b), HC(O)NH2 (2c), HC(O)NHCH3 (2d), HCO2- (2e), HCO3- (2f), H2PO4- (2g), CH3NH2 (2h)), were optimized at the B3LYP/6-31G(d) level of theory. S\X bond dissociation enthalpies (BDEs) were determined by single point calculations at the CBS-RAD level, a method designed for quantitative thermochemistry of free radicals. The effect of solvation was determined by application of a polarizable continuum model. Only the amine complex is predicted to be stable in water. H2O and H2PO4- make transient complexes, and the remaining complexes are predicted to dissociate spontaneously. The dissociation is driven by entropy and conformationally constrained complexes are predicted to be stable in water. Reduction potentials, E°, accurate to ±0.1 V were calculated for the complexes with dimethyl sulfide and for the amino acid, methionine, both as an isolated amino acid and incorporated into a polypeptide at the N- and C-terminals and mid-chain. Stabilization of the radical cation of Met by three-electron bonding is predicted if an S\N bond can be formed to a free amino group, as in N-terminal Met or a nearby Lys. Likewise, Met oxidation is facilitated by phosphodiesters, but not by carboxylate groups or amide groups. No lowering of E° is predicted for C-terminal Met or for mid-chain Met. The implications of the results for the redox chemistry associated with Alzheimer's disease are discussed.

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The reactions of Oxidized Methionine with Oxygen: An ab initio Study

Abstract: A one-electron oxidation of a methionine residue is thought to be a key step in the neurotoxicity of the beta amyloid peptide of Alzheimer’s disease. The chemistry of the radical cation of N-formylmethioninamide (11•+) and two model systems, dimethyl sulfide (1•+) and ethyl methyl sulfide (6•+), in the presence of oxygen, have been studied by B3LYP/6-31G(d) and CBS-RAD calculations. The stable form of 11•+ has a 3-electron bond between the sulfur radical cation and the carbonyl oxygen atom of the i – 1 residue. The radical cation may lose a proton from the methyl or methylene groups flanking the oxidized sulfur. Both 11•+ or the resultant C-centered radicals may add oxygen to form peroxy radicals. The calculations indicate that unlike C-centered radicals, the sulfur radical cation does not form a covalent bond to oxygen, but rather forms a loose ion-induced dipole complex with an S-O separation of about 2.7 Å, and bound by about 13 kJ mol-1 (based on 1•+ + O2). Direct intramolecular abstraction of an H atom from the aC-site is unlikely. It is endothermic by more than 20 kJ mol-1 and involves a high barrier (.G = 79 kJ mol-1). The a-to-S-C-centered radicals will add oxygen to form peroxy radicals. The OH BDEs of the parent hydroperoxides are in the range 352 – 355 kJ mol-1, similar to SH BDEs (360 kJ mol-1) and aC-H BDEs (345-350 kJ mol-1). Thus, the peroxy radicals are oxidizing species comparable in strength to thiyl radicals and peptide backbone aC-centered radicals. Each peroxy radical can abstract a hydrogen atom from the backbone aC-site of the Met residue to yield the corresponding aC-centered radical/hydroperoxide in a weakly exothermic process with modest

barriers in the range 64 – 92 kJ mol-1.
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172. The Structure and Reactions of the Peroxy radicals of Glycine and Alanine in Peptides - an Ab Initio Study

Abstract: Ab initio calculations at B3LYP/6-31G(d) and CBS-RAD level were carried out to investigate the reaction of aC-centered peroxy radicals of neutral, non-zwitterionic glycine and alanine (AH), and as residues in model peptides, N-formylglycinamide and N-formylalaninamide (PH). Bond dissociation enthalpies (BDEs) were calculated for the aC-O (DaCO), O-O (DOO) and O-H (DOH) bonds of glycine and alanine peroxy radicals (AOO, POO) and hydroperoxides (AOOH, POOH). The predicted BDEs at 298 K, in kJ mol-1 are: AOO(Gly), DaCO=70; AOO(Ala), DaCO=69; POO(Gly), DaCO=89; POO(Ala), DaCO=86; AOOH(Gly), DaCO=237, DOO=203, DOH=371; AOOH(Ala), DaCO=234, DOO=195, DOH=368; POOH(Gly), DaCO=266, DOO=207, DOH=380; POOH(Ala), DaCO=264, DOO=208, DOH=381. Values of BDE of the peptides in ß-sheet peptide conformations were also estimated by constraining the Ramachandran dihedral angles, F and ? to values of -150° and +150°: (S)-POO(Gly), DaCO=99; (R)-POO(Gly), DaCO=78; (S)-POO(Ala), DaCO=88; (R)-POO(Ala), DaCO=83; (S)-POOH(Gly), DaCO=258, DOO=195, DOH=362; (R)-POOH(Gly), DaCO=278, DOO=217, DOH=404; (S)-POOH(Ala), DaCO=240, DOO=192, DOH=355; (R)-POOH(Ala), DaCO=270, DOO=204, DOH=390. The reactions of aC-peroxy radicals, POO, and aC-alkoxy radicals, PO, have been studied in detail.
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171. Molecular Dynamics Simulation of a Polyunsaturated Lipid Bilayer Susceptible to Lipid Peroxidation

Abstract: Lipid peroxidation is an important part of the pathological pathway of membrane damage in membranes that have high levels of polyunsaturated fatty acids such as linoleic, linolenic, arachidonic, and docosahexaenoic acids. Neural membranes are particularly rich in polyunsaturated acids and such damage is implicated in neurological diseases, such as Alzheimer's disease. In order to obtain a bilayer model that represents the property of susceptibility to lipid peroxidation, we carried out molecular dynamics (MD) simulations of a bilayer of 1-palmitoyl-2-linoleyl-sn-glycero-3-phosphatidylcholine (PLPC). The MD simulation provided the structural properties of the system. The cis,cis- Δ□9,12 bis-allylic region of the linoleate chain induces disorder, and affects the physical properties of the membrane.
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168. H-Atom Abstraction by Thiyl Radicals from Peptides and Cyclic Dipeptides. A Theoretical Study of Reaction Rates

Abstract: The reactions of methanethiyl radicals (CH3S) with the cyclic anhydrides of glycine (1a), alanine (L,L-1b and
D,L-1b), and sarcosine (1c), and the acyclic peptides, N-formylglycinamide (3a) and N-formylalaninamide (3b), were studied by means of theoretical calculations at the B3LYP/6-311+G(d,p) level of theory. Free energies in the gas phase were determined in the classical harmonic oscillator-rigid rotator model, and used to estimate rates of H-transfer reactions at the aC-site of the peptides. The e?ects of aqueous solution were estimated by the SCIPCM procedure in combination with modi?ed experimental Arrhenius A-factors to calculate solution phase rate constants. The reactions are discussed in terms of the charge and spin polarisation in the transition state, as determined by AIM analysis. Rate constants calculated by this semiempirical Arrhenius approach are in very good agreement with available experimental data on the reaction of D3N+CH2CH2S with 1a and 1c but not 1b in D2O. The rate constants for the reaction of CH3S with 3a and 3b are also in very good agreement with experimental data on the N-acetyl analogues. Contrary to experiment, the cyclic alanine anhydrides, L,L-1b and D,L-1b, were predicted to react more than an order of magnitude more quickly than any of the other dipeptides.
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167. Conformational Analysis of Glutathione in Aqueous Solution by Molecular Dynamics

Abstract: Molecular dynamics simulations over 20 ns with the Gromacs all-atom force field, coupled with cluster analyses
of the trajectories, have been applied to the sixteen charge states of glutathione (GSH) in order to examine the distribution conformations in aqueous solution as a function of pH. The simulations show that GSH is very flexible and does not adopt a strongly preferred conformation at any pH. Comparison with limited conformational data deduced from NMR analyses shows little agreement. Contrary to the NMR results which found essentially equal populations of the three rotameric forms, the simulations reveal lower populations for gauche rotameric forms of the Cys and Glu side chains. In most species, the lowest populations were found for the sterically hindered gauche-gauche orientation about the CR-C, bond in both residues, except when electrostatic attraction between oppositely charged ends, unshielded by intervening water, was found to
dominate. In the majority of the enzyme-bound GSH structures extracted from the Brookhaven Protein Data Bank, the bound GSH has a conformation that is either the same or similar to that free in solution. In some cases, as in the case of solid-state GSH and the oxidized form, GSSG, crystal packing and intermolecular H-bonding interactions force the GSH skeleton into a conformation that is not seen in solution. The distribution of the separation of the Cys S atom from the Glu RC-H bond was monitored over the course of the 20 ns simulations to deduce conditions under which H atom transfer may occur from the Glu RC-H bond to a thiyl radical of the Cys moiety of GSH, as has been observed experimentally.
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163. Computational Studies of Cu(II)[Peptide] Binding Motifs: Cu[HGGG] and Cu[HG] as Models for Cu(II)-Binding to the Prion Protein Octarepeat Region.

Abstract: The
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163. Computational Studies of Cu(II)[Peptide] Binding Motifs: Cu[HGGG] and Cu[HG] as Models for Cu(II)-Binding to the Prion Protein Octarepeat Region.

Abstract: The binding of Cu(II) to the prion protein is investigated by computations at the B3LYP level of theory on models of the octarepeat domain of the prion protein. The models incorporate the functionality of the glycine (G) and histidine (H) residues which occur in the octarepeat domain, PHGGGWGQ. The copper complexes are designated Cu[HG] and Cu[HGGG]. Coordination to the metal via the imidazole ring of the histidine, the amide carbonyl groups, and the backbone nitrogen atom of the amide groups were examined, as well as several protonation/deprotonation states of each structure. EPR and CD titration experiments suggest that the octarepeat segments of the unstructured N-terminal domain of prion protein can bind Cu(II) in a 1:1 Cu-to-octarepeat ratio. The results identify the extent to which the Cu(II) facilitates peptide backbone deprotonation, and the propensity of binding in the forward (toward the C-terminus) direction from the anchoring histidine residue. A plausible mechanism is suggested for changing from amide O-atom to deprotonated amide N-atom coordination, and for assembly of the observed species in solutions of Cu[PrP] and truncated models of it. A structure is proposed which has the N2O2 coordination pattern for the minor component observed experimentally by EPR spectroscopy for the Cu[HGGG] model. The most stable neutral Cu[HGGG] structure found, with coordination environment N3O1, corresponds to that observed for Cu[HGGGW] and Cu[HGGG] both in the solid state and as the major component in solution at neutral pH.
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161. Specific Recognition of Gly29 and Gly33 by Met35 in a Model of β-Sheet Aβ: An ONIOM Study,

Abstract: The Radical Model of Alzheimer's Disease (AD) is presented in some detail. The model provides a unified picture for the role of the amyloid beta peptide (Aβ), Met35, copper ions, oxygen, beta sheet secondary structure, and the generation of hydrogen peroxide, in mediating oxidative stress in AD. It predicts a role for glycyl radicals as long-

lived species which can transport the damage into cell membranes and initiate lipid peroxidation. Previous work has established the thermodynamic and kinetic viability of most of the steps. In the present work, QM/MM and Amber calculations reveal that self assembly of antiparallel β-sheet which brings Met35 into the required close proximity to a glycine residue is more likely if the residue is Gly29 or Gly33, than any of the other four glycine residues of Aβ.
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160. H-Abstraction from Thiols by C-Centered Radicals. An Experimental and Theoretical Study,

Abstract: The hydrogen atom abstraction by a series of carbon-centered radicals from methanethiol is examined in the gas phase and in aqueous solution using quantum mechanical calculations. The gas phase reactions are modeled at the ab initio B3LYP/6311+G(d,p) level, coupled with an empirical correction to the enthalpy of reaction and activation. The solvent effects are evaluated by two different continuum models (SCIPCM, CPCM), coupled with a novel approach to the calculation of the solution phase entropy. The reaction is discussed in terms of the charge and spin polarization in the transition state, as determined by AIM analysis, and in terms of orbital interaction theory. Rate constants, calculated by transition state theory are in good agreement with the available experimental data.- Return to Selected Publications

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157. Glutathione Radical: Intramolecular H Abstraction by the Thiyl Radical

Abstract: Ab initio computations (B3LYP/6-31G(D)) were used to predict transition structures and energies of activation for intramolecular H atom transfer to a thiyl radical (RS.) from the αC-H bonds of glutathione **1** and from the model compounds, N-formylcysteinylglycine **2** and N-(2-thioethanyl)-g-glutamine **3**. For each compound, transition structures were located by in vacuo calculations on the neutral non-zwitterionic system. Thermodynamic functions derived at the same level and single point calculations at the B3LYP/6-311+G(3df,2p) level, were used to derive free energies of activation (ΔG?) and reaction (ΔG°). For abstraction of the αC-H(Gly) by the thiyl radical in the gas phase, ΔG? = 134 kJ mol-1 if the amide link to Gly is in the more stable (Z)-configuration and ΔG? = 52 kJ mol-1, if it is in the less stable (E)-configuration. The isomerization of the amide group requires about 95 kJ mol-1. Previous studies had indicated that for intramolecular reaction of the thiyl radical at αC-H(Cys), ΔG? = 110 kJ mol-1. The lowest energy pathway for intramolecular H transfer to the thiyl radical is from αC-H(Gln), Δ□G? = 37 - 42 kJ mol-1, and corresponds rather well with experimental results in solution, ΔG? = 43 kJ mol-1. The calculated free energy change for the equilibrium between thiyl and αC forms of the glutathione radical, Δ□G° = -54 kJ mol-1. The value estimated from experimental data is ΔG° = -37 kJ mol-1. The agreement between the energies from theory in the gas phase and experiment in solution suggests that the free energies of solvation of reactant thiyl radical, transition structures for H abstraction, and the product αC-centred radical, are very similar. The effects of solution were estimated by two continuum models, SCIPCM and COSMO. The SCIPCM model yields results very similar to the gas phase, predicting a modest lowering of the activation free energy. The results from the COSMO method were inconclusive as to whether a rate enhancement or decrease could be expected.- Return to Selected Publications

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156. Is Oxidative Damage By Beta Amyloid and Prion Peptides Mediated by Hydrogen Atom Transfer from Glycine Alpha-Carbon to Methionine Sulfur within Beta-Sheets?

Abstract: Methionine in glycine rich regions of both beta amyloid peptide and prion peptide is thought to be crucial to their neurotoxic properties. We postulate here a role for methionine in the propagation of oxidative damage. The S-H bond dissociation enthalpies, BDE(S-H)s, of dimethylsulfonium ion $(CH_3)_2SH^+$, and a S-protonated methionine residue of a polypeptide strand are estimated to be 351 kJ mol^{-1} and 326 - 331 kJ mol^{-1} , respectively, by the application of calculations at the B3LYP level with large basis sets. These species are direct products of H atom abstraction by radical cations of sulfides. The reactions between a glycine residue and the radical cations of $(CH_3)_2S$ and Met were investigated, and the transition structures for H atom transfer located. The results suggest that it is thermodynamically feasible for the S-ionized form of Met to cause oxidative damage at the αC-H site of almost any amino acid residue of a nearby polypeptide strand (BDE(αC-H) = 330 - 360 kJ mol^{-1}), or to nearby lipids with a bis(allylic) methylene group (BDE(C-H) = 335 kJ mol^{-1}). However, a key observation is that when the Met residue is incorporated into an antiparallel β-sheet, only a Gly residue is exposed and susceptible to oxidation at the αC-H site. Furthermore, the Gly must lie on a different strand of the β-sheet to that containing Met, and must be part of a

(5,5), rather than a (3,3) cycle. The same considerations apply to the methyl-deprotonated form of the sulfide radical cation but not the methylene-deprotonated form. These findings suggest a possible mechanism for generating and propagating oxidative damage via a Met residue of the Aβ peptide of Alzheimer's Disease and of the prion peptide of Creutzfeldt-Jakob Disease. To our knowledge, this is the first proposed mechanism that accounts for the radical damage in either of these diseases and requires peptide β-sheets, and amino acids, methionine and glycine.- Return to Selected Publications

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153. Influence of beta-Sheet Structure on the Susceptibility of Proteins to Backbone Oxidative Damage: Preference for alpha-C-Centered Radical Formation at Glycine in Antiparallel beta-Sheets

Abstract: Ab initio calculations at the B3LYP/6-31G(d) level of theory were carried out on selected cyclic hydrogen bonded dimers of glycine and alanine as models for β-sheets, and on the αC-centered radicals derived from them. The structures mirrored the cycles found in the H-bonded network of parallel and antiparallel β□-sheet secondary structure, and were optimized both with and without enforcement of constraints on the Φ,Ψ torsion angles. Transition structures for the migration of an H atom from an αC site to another αC site or to an S atom were located. It was found that the presence of a hydrogen bonded strand of a β-sheet has little effect on the αC-H bond dissociation enthalpy (BDE) of glycine, but raises the BDE of other residues by a significant amount. The parallel β-sheet structure and Φ,Ψ angles lead to a significant increase in BDE relative to the random coil structure, due to loss of captodative stabilization. The antiparallel β-sheet structure and Φ,Ψ angles do not lead to a significant increase in BDE. All residues incorporated in β-sheet secondary structure, with the exception of glycine, are protected from oxidative damage because the αC-H bond is internal to the sheet and inaccessible to oxidizing radicals. Glycine is susceptible to oxidative damage because it has a second αC-H bond which is exposed. Among residues in secondary structures, only glycine is susceptible to damage by weak oxidants such as thiyl radicals and superoxide, provided it is in an antiparallel β–sheet. Radical damage may propagate readily from one strand to another above the β-sheet, but not within the β□-sheet. β-Sheet structure narrows the difference between the glycyl αC-H BDE and S-H BDE and facilitates interstrand H atom transfer between the glycyl αC site and the S atom of cysteine.-Return to Selected Publications

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150. Effects of Structure on ºC-H Bond Enthalpies of Amino Acid Residues: Relevance to H Transfers in Enzyme Mechanisms and in Protein Oxidation

Abstract: The bond dissociation enthalpies (BDE) of all of the amino acid residues, modelled by HC(O)NHCH(R)C(O)NH2 (PH(Res)) were determined at the B3LYP/6-31G(D) level, coupled with isodesmic reactions. The results for neutral side chains with ϕ□, ψ angles ~180º,~180º in ascending order, to an expected accuracy of " 10 kJ mol^{-1}, are: Asn 326; Cystine 330; Asp 332; Gln 334; Trp 337; Arg 340; Lys 340; Met 343; His 344; Phe 344; Tyr 344; Leu 344; Ala 345; Cys 346; Ser 349; Gly 350; Ile 351; Val 352; Glu 354; Thr 357; Pro-cis 358; Pro-trans 369. These BDEs are smaller than those of typical secondary or tertiary C-H bonds due to the phenomenon of captodative stabilisation. The stabilisation is reduced by changes in the ϕ, ψ angles. As a result the BDEs increase by about 10 kJ mol^{-1} in β-sheet and 40 kJ mol^{-1} in α-helical environments, respectively. In effect the αC-H BDEs can be "tuned" from about 345 to 400 kJ mol^{-1} by adjusting the local environment. Some very significant effects of this are seen in the current literature on H transfer processes in enzyme mechanisms and in oxidative damage to proteins. These observations are discussed in terms of the findings of the present study.- Return to Selected Publications

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140. Oxidative Damage to and by Cysteine in Proteins: an Ab Initio Study of the Radical Structures, C-H, S-H and C-C Bond Dissociation Energies, and Transition structures for H Abstraction by Thiyl Radicals

Abstract: Ab initio computations (B3LYP/6-31G(D), coupled with isodesmic reactions) were used to predict bond dissociation energies (BDEs) of aC-H (D(aC-H)) and other bonds of cysteine, both as free neutral amino acid (**AH**(Cys)) and as a residue in a model peptide (**PH**(Cys)). The latter was intended to mimic the environment in proteins. Transition structures were located for intermolecular and intramolecular H atom transfer to a thiyl radical (RS.) from a sulfhydryl group (RSH) or the aC-H bond. The predicted BDEs, at 298 K, in kJ mol-1 to an estimated

accuracy of 10 kJ mol-1 for the fully optimized system are: **AH**(Cys), D(aC-H) = 322, D(bC-H) = 390, D(aC-C)= 264, D(S-H)= 373; **PH**(Cys), D(aC-H)= 346, D(bC-H)= 392, D(aC-C)= 287, D(S-H)= 367. In **PH**(Cys) with torsional angles constrained to simulate b-sheet and a-helical secondary structure, rises to 359 and 376, respectively. Cystine in the peptide environment was modelled by replacing -SH by -SSCH3, PH(CysSCH3), D(aC-H) = 330. Enthalpies of activation for intermolecular H transfer to RS. were found to be low: from RSH, 12 kJ mol-1; from aC-H, about 25 kJ mol-1, the latter being consistent with reaction rates of the order of 105 M-1 s-1. The enthalpic barrier for intramolecular H transfer from aC-H to -S. within a single cysteine residue is too high (83 - 111 kJ mol-1) for this to be a competitive process.- Return to Selected Publications

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128. Toward Site Specificity of Oxidative Damage in Proteins: C-H and C-C Bond Dissociation Energies and the Reduction Potentials of the Radicals of Alanine, Serine, and Threonine - an Ab Initio Study

Abstract: High level ab initio computations were used to characterise the parent species and radicals for alanine, serine and threonine, both as free neutral amino acids (**AH**) and as residues in model peptides (**PH**) intended to mimic the mid chain environment in proteins. The ab initio energies were used in isodesmic reactions to predict bond dissociation energies (BDEs,) at 298 K, in kJ mol-1 to an estimated accuracy of 10 kJ mol-1. For the fully optimized systems the values of are: **AH**(Gly), 331; **AH**(Ala), 317; **AH**(Ser), 327; **AH**(Thr), 328; **PH**(Gly), 348; **PH**(Ala), 344; **PH**(Ser), 348; **PH**(Thr), 356. All of the values are less than the BDE of a typical SH bond (370 kJ mol-1), as in cysteine or glutathione (GSH), a result that suggests that oxidative damage at the site will not be repaired efficiently by the mechanism of H donation from GSH. Values of in typical peptide conformations, such as -sheet and -helical secondary structure, were estimated by constraining the Ramachandran dihedral angles *phi*, and *psi*, to values typical of these structures. Thus values are estimated as: **PH**(Gly), 361; **PH**(Ala), 359; **PH**(Ser), 347;**PH**(Thr), 356 in the *beta*-sheet conformation, and: **PH**(Gly), 402; **PH**(Ala), 384; **PH**(Ser), 381; **PH**(Thr), 363 in the *alpha*-helix conformation. Hence, these residues are also expected to be susceptible to irreparable oxidative damage in *beta*-sheet structures, but Gly, Ala and Ser residues in *alpha*-helical regions should be less susceptible to damage and should be repairable by GSH. A consideration of reduction potentials calculated from the BDEs and entropies derived from the ab initio results leads to the same conclusions and indicates that certain radicals other than OH. that occur in cells (e.g. ROO.) may also cause oxidative damage to *beta*-sheet structures. Ab initio calculations were also done for the C-centered radicals formed by removal of H from the side chains. These showed that there is a marked increase in the ease of abstraction of this H in the series Ala, Ser,Thr. - Return to Selected Publications