CURRICULUM VITAE
CHARLES RUSSELL HILLE

Professor
Department of Molecular and Cellular Biochemistry
The Ohio State University
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BIRTHDATE November 15, 1951

CITIZENSHIP U.S.

MARITAL STATUS Married, four children

EDUCATION

B.S. with Honors (Chemistry) Texas Tech University, Lubbock, TX, 1974.
Ph.D. (Biochemistry) Rice University, Houston, TX, 1979

PROFESSIONAL EXPERIENCE

Graduate Study (with Dr. John S. Olson, Rice University, Houston, TX), 9/74 – 8/78.
Post-doctoral Study (with Dr. Vincent Massey, University of Michigan, Ann Arbor, MI), 9/78 – 8/81.
Lecturer, Department of Biological Chemistry, University of Michigan, Ann Arbor, MI, 9/81 – 10/82.
Assistant Professor, Dept. of Biological Chemistry, University of Michigan, Ann Arbor, MI, 11/82 – 8/85.
Assistant Professor, Dept. Mol. Cell. Biochemistry, The Ohio State University, Columbus, OH, 8/85 – 8/90.
Associate Professor, Dept. Mol. Cell. Biochemistry, The Ohio State University, Columbus, OH, 9/90 – 6/95.
Professor, Dept. Mol. Cell. Biochemistry, The Ohio State University, Columbus, OH, 7/95 – present.
Professor, Department of Chemistry, The Ohio State University, Columbus, OH, 10/95 – present.

ACADEMIC AFFILIATIONS

Professor, Department of Molecular and Cellular Biochemistry (principal academic appointment); Professor, Department of Chemistry; Investigator, Dorothy Davis Heart/Lung Research Institute; The Ohio State Biochemistry Program; Biophysics Graduate Program; Integrated Biomedical Science Graduate Program; Medical Scientist Program

HONORS AND AWARDS

Phi Kappa Phi Honors Fraternity, Texas Tech University, Lubbock, TX, April 1974
Rice University Fellowship, Rice University, Houston, TX, Academic Year, 1974 - 1975
Michigan Society of Fellows, University of Michigan, Ann Arbor, MI, August 1978 - August 1981
Simson Faculty Research Award, College of Medicine and Public Health, The Ohio State University, 1997
Humboldt Research Prize, Alexander von Humboldt Foundation, Germany, 2003-2004
Fellow of the American Association for the Advancement of Science, October, 2004

PROFESSIONAL SOCIETIES

American Association for the Advancement of Science
American Society of Biochemistry and Molecular Biology
Biophysical Society
American Chemical Society

RECENT PROFESSIONAL SERVICE

Physical Biochemistry Study Section, National Institutes of Health; July 1996 – June 2000

Editorial Board, The ***Journal of Biological Chemistry***, July 1996 – June 2001; July 2002 – present

Co-organizer, Molybdenum Enzymes Meeting, University of Sussex, Brighton, UK (April 1997)

Co-organizer, Molybdenum and Tungsten Enzymes Gordon Conference, Plymouth, NH (July 1999)

Chair, Molybdenum and Tungsten Enzymes Nomenclature Committee (advisory to the IUBMB/Enzyme Commission); July 2001 – present

International Scientific Advisory Committee, 14th and 15th International Symposia on Flavins and Flavoproteins (Tokyo, Japan; Jaca, Spain) April 2003 – present

Chair, Computational Biophysics Study Section, National Institutes of Health – November, 2005

RECENT UNIVERSITY SERVICE/ADMINISTRATION

Graduate Studies Committee, The Ohio State Biochemistry Program January 1995 - June, 2001
Faculty Advisory Committee for the Molecular Life Sciences, February 1998 – June, 2001
Biochemistry Coordinating Committee, May 1998 - June, 2001
Director, The Ohio State Biochemistry Program, July 1998 – June, 2001
Search Committee for Chair of Department of Physiology and Cell Biology – 1999/2000 Academic Year
Chair, Promotion and Tenure Committee, Dept. Mol. Cell. Biochemistry, September 1997 – October 2003
Space Allocation Committee, Dept. of Molecular and Cellular Biochemistry, Sept 1999 – Oct 2003
Chair, MLS Structural Biology Search Committee, Dept. Mol. Cell. Biochemistry, 2000/01 Academic Year
Local Scientific Advisory Committee, Mathematical Biosciences Institute, June 2000 – present
Search Committee for Chair of the Department of Neuroscience, January 2001 - June 2002
Promotion and Tenure Committee, College of Medicine and Public Health, July 2002 – October 2003
Chair, Structural Biology I Search Committee, Dept. Mol. Cell. Biochemistry, 2001/02 Academic Year
Chair, Structural Biology II Search Committee, Dept. Mol. Cell. Biochemistry, 2002/03 Academic Year
Interim Chair, Department of Molecular and Cellular Biochemistry, October 1, 2003 – May, 2006
Research Committee, College of Medicine and Public Health, October 2004 – September, 2005
Steering Committee, Medical Scientist Program, College of Medicine & Public Health, Oct 2004 – present
Organizer, “Mathematical Modeling of Enzyme Dynamics and Reactivity”, Mathematical Biosciences Institute, The Ohio State University, May, 2005

RESEARCH INTERESTS

Structure/function relationships in redox-active enzymes; Inorganic biochemistry, particularly involving molybdenum; Spectroscopy of redox-active proteins; Biological electron transfer

15-YEAR GRANT HISTORY

NIH AR38917 “Studies of Xanthine Oxidase and Dehydrogenase” (R. HIlle, PI) $520,439 + 549,915 TDC, 9/88 - 8/99
NSF INT 8819821 “Pulse Radiolysis Studies of Xanthine Oxidase” (R. Hille, PI) $11,780 TDC, 4/89 - 3/93
NSF DMB8804421 “Physical Studies of Xanthine Oxidase” (R. Hille, PI) $196,000 TDC, 1/89 - 12/92
NSF MCB 9108417 “Physical Studies of Xanthine Oxidase and Trimethylamine Dehydrogenase” (R. Hille, PI) $239,000 TDC, 1/93 - 12/94
NSF MCB 9420185; “Physical Studies of Xanthine Oxidase and Trimethylamine Dehydrogenase” (R. Hille, PI) $305,000 TDC, 1/95 - 12/97
NSF INT 9513747; “Pulse radiolysis studies of xanthine oxidase and trimethylamine dehydrogenase” (R. Hille, PI) $18,000 TDC, 12/1/95 – 11/30/99
NIH R01 GM52322; “Mechanistic Studies of Oxomolybdenum enzymes” (R. Hille, PI) $565,074 TDC, 3/1/96 – 2/29/00
Monbyuso (Japanese Ministry of Science) “Structure/function studies of xanthine oxidoreductase” (T. Nishino, PI; R. Hille and E.F. Pai, additional PI’s) $18,000 TDC, 4/01 – 3/04
National Institutes of Health R01 GM59953 "Studies of Molybdenum-containing Enzymes" (R. Hille, PI) 9/1/99-12/31/04, $756,500 TDC
National Institutes of Health R01 GM58481 "Studies of Trimethylamine Dehydrogenase" (R. Hille, PI) $453,350 TDC, 1 2/1/99-12/31/04

ACTIVE GRANTS

NIH R01 GM075036 “Structure/activity studies of two molybdenum enzymes” (R. HIlle, PI) $650,000 TDC, 7/12/05 – 6/30/09
NIH R01 ES012658 “Studies of environmentally important molybdenum enzymes” (R. HIlle, PI)) $1,092,500 TDC, 9/1/05 – 8/31/10

PENDING GRANT

NIH R24 GM078507 “Integrative/collaborative studies of electron transfer in complex enzymes” (R. Hille, PI; G. Cecchini and R.F. Anderson, co-PI’s) $1,482,780 requested TDC (1/1/07-12/31/10)

PEER-REVIEWED JOURNAL ARTICLES

1. Hille, R., Palmer, G., & Olson, J.S. (1977) Chain equivalence in the reaction of nitric oxide with hemoglobin. ***J. Biol. Chem.*** **252**, 403-405.
2. Hille, R., Olson, J.S., & Palmer, G. (1979) Spectral transitions of nitrosyl hemes during ligand binding to hemoglobin. ***J. Biol. Chem.*** **254**, 12110-12120.
3. Hille, R., Fee, J.A., & Massey, V. (1981) Equilibrium properties of xanthine oxidase containing chemically modified flavins. ***J. Biol. Chem.*** **257**, 8933-8940.
4. Hille, R., & Massey, V. (1981) Studies on the oxidative half-reaction of xanthine oxidase. ***J. Biol. Chem.*** **257**, 9090-9095.
5. Nishino, T., Tsushima, K., Hille, R., & Massey, V. (1982) Inhibition of milk xanthine oxidase by fluorodinitrobenzene. ***J. Biol. Chem***. **257**, 7348-7353.
6. Hille, R., & Massey, V. (1982) The presence of a reducible disulfide bond in xanthine oxidase. ***J. Biol. Chem.*** **257**, 8898-8901.
7. Hille, R., Stewart, R.C., Fee, J.A., & Massey, V. (1983) The interaction of arsenite with xanthine oxidase. ***J. Biol. Chem.*** **258**, 4849-4856.
8. Hille, R., Yoshida, T., Williams, C.H., Jr., Ludwig, M.L., Fee, J.A., Kent, T.A., Hyunh, B., Day, T., & Münck, E. (1983) Studies of the ferredoxin from ***Thermus thermophilus***, ***J. Biol. Chem.*** **258**, 13008-13013.
9. Fee, J.A., Findling, K.L., Choc, M.G., Yoshida, T., Hille, R., Hearshen, D., Dunham, W.R., Kent, T.A., & Münck, E. (1984) Purification and initial characterization of a Rieske-type protein from ***Thermus thermophilus***. ***J. Biol. Chem.*** **259**, 124-133.
10. Hille, R., & Stewart, R.C. (1984) The interaction of xanthine oxidase with 8-bromoxanthine. ***J. Biol. Chem.*** **259**, 1570-1576.
11. Stewart, R.C., Hille, R., & Massey, V. (1984) Characterization of arsenite-complexed xanthine oxidase at room temperature - spectral properties and pH-dependent redox behavior of the molybdenum-arsenite Center. ***J. Biol. Chem.*** **259**, 14426-14436.
12. Stewart, R.C., Hille, R., & Massey, V. (1985) The reaction of arsenite-complexed xanthine oxidase with oxygen - evidence for an oxygen-reactive molybdenum center. ***J. Biol. Chem.*** **260**, 8892-8904.
13. Cramer, S.P., & Hille, R. (1985) Arsenite-inhibited xanthine oxidase - determination of the Mo-S-As geometry by EXAFS. ***J. Am. Chem. Soc.*** **107**, 8164-8169.
14. Hille, R., Hagen, W.R., & Dunham, W.R. (1985) Spectroscopic studies of the iron-sulfur centers in xanthine oxidase. ***J. Biol. Chem.*** **260**, 10569-10575.
15. Hille, R. & Massey, V. (1986) The equilibration of reducing equivalents within milk xanthine oxidase. ***J. Biol. Chem.*** **261**, 1241-1247.
16. Anderson, R.F., Hille, R., & Massey, V. (1986) The radical chemistry of milk xanthine oxidase as studied by radiation chemistry techniques. ***J. Biol. Chem.*** **261**, 15870-15876.
17. Hille, R., & Sprecher, H. (1987) On the mechanism of action of xanthine oxidase. ***J. Biol. Chem.*** **262**, 10914-10917.
18. Hille, R., George, G.N., Eidsness, M.K., & Cramer, S.P. (1989) EXAFS of xanthine oxidase complexes with alloxanthine, violapterin, and 6-pteridylaldehyde. ***Inorg. Chem.*** **28**, 4018-4022.
19. H.-D. Zeller, Hille, R., & Jorns, M.S. (1989) Bacterial sarcosine oxidase: identification of novel substrates and a biradical reaction intermediate. ***Biochemistry*** **28**, 5145-5154.
20. Oertling, W.A., & Hille, R. (1990) Resonance Raman spectroscopy of the molybdenum center of xanthine oxidase. ***J. Biol. Chem.*** **265**, 17446-17450.
21. Hille, R., & Anderson, R.F. (1991) Electron transfer in milk xanthine oxidase as studied by pulse radiolysis. ***J. Biol. Chem.*** **266**, 5608-5615.
22. Rohlfs, R.J., & Hille, R. (1991) Intramolecular electron transfer in trimethylamine dehydrogenase from bacterium W_3A_1. ***J. Biol. Chem.*** **266**, 15244-15252.
23. Hille, R. (1991) Electron transfer within xanthine oxidase: a solvent kinetic isotope effect study. ***Biochemistry*** **30**, 8522-8529.
24. Hille, R., & Massey, V. (1991) The kinetic behavior of xanthine oxidase containing chemically modified flavins. ***J. Biol. Chem.*** **266**, 17401-17408.

25. McWhirter, R.B., & Hille, R. (1991) The reductive half-reaction of xanthine oxidase. Spectral intermediates in the hydroxylation of 2-hydroxy-6-methylpurine. ***J. Biol. Chem.*** **266**, 23724-23731.

26. Roffey, R., Golbeck, J., Hille, R., & Sayre, R. (1991) Photosynthetic electron transport in genetically altered photosystem II reaction centers of chloroplasts. ***Proc. Natl. Acad. Sci.*** **88**, 9122-9126.

27. Anderson, G.L., Williams, J. & Hille, R. (1992) The purification and characterization of arsenite oxidase from ***Alcaligenes faecalis***: a molybdenum-containing hydroxylase. ***J. Biol. Chem.*** **267**, 23674-23682.

28. Kim, J.H., & Hille, R. (1993) The reductive half-reaction of xanthine oxidase with xanthine. Observation of a spectral intermediate attributable to the molybdenum center in the reaction of enzyme with xanthine. ***J. Biol. Chem.*** **268**, 44-51.

29. Hille, R., Kim, J.H., & Hemann, C. (1993) Reductive half-reaction of xanthine oxidase. Mechanistic role of the species giving rise to the "rapid" Mo(V) EPR signal. ***Biochemistry*** **32**, 3973-3980.

30. Ratnam, K., & Hille, R. (1993) Paradoxical stabilization of the neutral flavin semiquinone of xanthine dehydrogenase at high pH. ***Biochem. Biophys. Res. Commun.*** **194**, 1097-1102.

31. Kim, J.H., & Hille, R. (1994) Studies of substrate binding to xanthine oxidase by using a spin-labeled analog. ***J. Inorg. Biochem.*** **55**, 295-303.

32. Lorigan, G.A., Britt, R.D., Kim, J.H., & Hille, R. (1994) Electron spin echo envelope modulation spectroscopy of the molybdenum center of xanthine oxidase. ***Biochim. Biophys. Acta*** **1185**, 284-294.

33. Scrutton, N.S., Packman, L.C., Mathews, F.S., Rohlfs, & Hille, R. (1994) Assembly of redox centers in the trimethylamine dehydrogenase from bacterium W_3A_1: properties of the wild-type enzyme and a C30A mutant expressed from a cloned gene in ***Escherichia coli***. ***J. Biol. Chem.*** **269**, 13942-13950.

34. DuPlessis, E.R., Rohlfs, R.J., Hille, R., & Thorpe, C. (1994) Electron-transferring flavoprotein from pig and the methylotrophic bacterium W_3A_1 contains AMP as well as FAD. ***Biochem. Mol. Biol. Intl.,*** **32**, 195-199.

35. White, S.A., Mathews, F.S., Rohlfs, R., & Hille, R. (1994) Crystallization and preliminary crystallographic investigation of electron-transferring flavoprotein from the bacterium ***Methylophilus*** W_3A_1. ***J. Mol. Biol.*** **240**, 265-266.

36. Rohlfs, R.J., & Hille, R. (1994) The reaction of trimethylamine dehydrogenase with diethylmethylamine. ***J. Biol. Chem.*** **269**, 30869-30879.

37. Schultz, B.E., Hille, R., & Holm, R.H. (1995) Direct oxygen atom transfer in the mechanism of action of ***Rhodobacter sphaeroides*** dimethylsulfoxide reductase. ***J. Am. Chem. Soc.*** **117**, 827-828.

38. Vitale, M., Le, K.K., Hemann, C.F., Hille, R., Gustafson, T.L., & Bursten, B.E. (1995) Resonance Raman studies of $[CpFe(CO_2)]_2$ and $[Cp^*Fe(CO_2)]_2$: a probe of photoreactive states and intermediates. ***J. Am. Chem. Soc.*** **117**, 2286-2296.

39. Rohlfs, R.J., Huang, L. & Hille, R. (1995) Prototropic control of intramolecular electron transfer in trimethylamine dehydrogenase. ***J. Biol. Chem.*** **270**, 22196-22207.

40. Ryan, M.G., Ratnam, K, & Hille, R. (1995) The molybdenum centers of xanthine oxidase and xanthine dehydrogenase. Determination of the spectral change associated with reduction from the Mo^{VI} to the Mo^{IV} state. ***J. Biol. Chem.*** **270**, 19209-19212

41. Anderson, R.F., Hille, R., & Patel, K. (1996) Inactivation of xanthine oxidase by oxidative radical attack. ***Intl. J. Rad. Biol.*** **68**, 535-541.

42. Ratnam, K., Shiraishi, N., Campbell, W.H., & Hille, R. (1995) Spectroscopic and kinetic characterization of the recombinant wild-type and C242S mutant of the cytochrome ***b*** reductase fragment of nitrate reductase. ***J. Biol. Chem***. **270**, 24067-24072.

43. Brody, M.S., & Hille, R. (1995) The reaction of chicken liver sulfite oxidase with dimethylsulfite. ***Biochim. Biophys. Acta.*** **1253**, 133-135.

44. Huang, L., Rohlfs, R.J., & Hille, R. (1995) The reaction of trimethylamine dehydrogenase with electron transferring flavoprotein. ***J. Biol. Chem.*** **270**, 23958-23965.

45. Kim, J.H., Ryan, M.G., Knaut, H., & Hille, R. (1996) The reductive half-reaction of xanthine oxidase: a pH dependence and solvent kinetic isotope effect study. ***J. Biol. Chem.*** **271**, 6771-6780.

46. Sun, J., Kahlow, M.A., Kaysser, T.M., Osborne, J.P., Hill, J.J., Rohlfs, R.J., Hille, R., Gennis, R.B., & Loehr, T.M. (1996) Resonance Raman spectroscopic identification of a histidine ligand of $\boldsymbol{b}_{595}$ and the nature of the ligation of chlorin ***d*** in the fully reduced ***Escherichia coli*** cytochrome ***bd*** oxidase. ***Biochemistry*** **35**, 2403-2412.

47. Ratnam, K, Brody, M. S., & Hille, R. (1996) Purification of xanthine dehydrogenase and sulfite oxidase from chicken liver. ***Prep. Biochem. Biotech.*** **26**, 143-154.

48. Huang, L., Scrutton, N.S., & Hille, R. (1996) The reaction of the C30A mutant of trimethylamine dehydrogenase with diethylmethylamine. ***J. Biol. Chem.*** **271**, 13401-13406.

49. Huber, R., Hof, P., Duarte, R.O., Moura, J.J.G., Moura, I., LeGall, J., Hille, R., Archer, M., & Romão, M. (1996) A structure-based catalytic mechanism for the xanthine oxidase family of molybdenum enzymes. ***Proc. Natl. Acad. Sci. USA*** **93**, 8846-8851.

50. Bian, S. Hemann, C.F., Hille, R., & Cowan, J.A. (1996) Mutagenesis studies to probe the role of phenylalanine 66 in defining the stability of the $[Fe_4S_4]$ center provides evidence for oxidative degradation via a $[Fe_3S_4]$ cluster. ***Biochemistry*** **35**, 14544-14552.

51. Xue Y., Traina S J., & Hille R. (1996) Stability of metal-organic complexes in acetone- and methanol-water mixtures. ***Environmental Science & Technology*** **30**, 3177-3183.

52. Winkler, W., Gonzalez, G., Wittenberg, J.B., Hille, R., Dakappagari, N., Jacob, A., Gonzalez, L.A., & Gilles-Gonzalez, M.-A. (1996) Non-steric factors dominate binding of nitric oxide, azide, imidazole, cyanide and fluoride to the rhizobial heme-based oxygen sensor FixL. ***Chem. Biol.*** **3**, 841-850.

53. Wilson, E.K., Huang, L, Sutcliffe, M.J., Mathews, F.S., Hille, R., & Scrutton, N.S. (1997) An exposed tyrosine on the surface of trimethylamine dehydrogenase facilitates electron transfer to electron transferring flavoprotein: kinetics of transfer in wild-type and mutant complexes. ***Biochemistry*** **36**, 41-48.

54. Ratnam, K., Shiraishi, N., Campbell, W.H., & Hille, R. (1997) Spectroscopic and kinetic characterization of the heme- and flavin-containing cytochrome ***c*** reductase fragment of nitrate reductase. ***J. Biol. Chem.*** **272**, 2122-2128.

55. Mewies, M., Basran, J., Packman, L.C., Hille, R., & Scrutton, N.S. (1997) Involvement of a flavin iminoquinone methide in the formation of 6-hydroxy FMN in trimethylamine dehydrogenase: a rationale for the existence of 8a-methyl- and C_6-linked covalent flavoproteins. ***Biochemistry*** **36**, 7162-7168.

56. Babu, C.R., Arudchandran, A., Hille, R., Gross, E.L., & Bullerjahn, G.S. (1997) Reconstitution and characterization of a divergent plastocyanin from the photosynthetic prokaryote ***Prochlorothrix hollandica***, expressed in ***Escherichia coli***. ***Biochem. Biophys. Res. Commun.*** **235**, 631-635.

57. Ilich, P., & Hille, R. (1997) Tautomerization of the heterocycle nucleus in the course of the reaction of xanthine oxidase with purines and pteridines. ***Inorg. Chim. Acta*** **263**, 87-94.

58. Ilich, P., Hemann, C.F., & Hille, R. (1997) Molecular vibrations of solvated uracils. ***Ab initio*** reaction field calculations and experiment. ***J. Phys. Chem.*** B **101**, 10923-10932.

59. Michaud, A.L., Herrick, J.A., Duplain, J.E., Manson, J.L., Hemann, C.F., Donohoe, R.J., Hille, R., & Oertling, W.A. (1998) FTIR characterization of heterocycles lumazine and violapterin in solution: Effects of solvent on anionic forms. ***Biospectroscopy*** **4**, 235-256.

60. Conrads, T., Hemann, C.F. & Hille, R. (1998) A tyrosyl radical generated in xanthine oxidase by reaction with ferricenium ion. ***Biochemistry*** **37**, 7787-7791.

61. Fournel, A., Gambarelli, S., Guigliarelli, B., More, C., Asso, M., Chouteau, G., Hille, R., & Bertrand, P. (1998) Magnetic interactions between a $[4Fe\text{-}4S]^{1+}$ cluster and an FMN radical in the enzyme trimethylamine dehydrogenase: a high-field EPR study. ***J. Chem. Phys.*** **109**, 10905-10913.

62. Xia, M., Dempski, R., & Hille, R. (1999) The reaction of xanthine oxidase with aldehyde substrates. ***J. Biol. Chem***. **274**, 3323-3330.

63. Huang, L., Abu-Soud, H.M., Hille, R., & Stuehr, D. (1999) Nitric oxide-generated P420 nitric oxide synthase: characterization and roles for tetrahydrobiopterin and substrate in protecting against or reversing the P420 conversion. ***Biochemistry*** **38**, 1912-1920.

64. Jang, M.-H., Basran, J., Scrutton, N.S. & Hille, R. (1999) The reaction of trimethylamine dehydrogenase with trimethylamine. ***J. Biol. Chem.*** **274**, 13147-13154.

65. Basran, J., Jang, M.-H., Sutcliffe, M.J., Hille, R., & Scrutton, N.S. (1999) The role of Tyr 169 of trimethylamine dehydrogenase in substrate oxidation and mediation of the magnetic interaction between the FMN and 4Fe/4S center. ***J. Biol. Chem***. **274**, 13155-13161.

66. Brody, M.S., & Hille, R. (1999) The kinetic behavior of chicken liver sulfite oxidase. ***Biochemistry*** **38**, 6668-6677.

67. Basran, J., Sutcliffe, M.J., Hille, R., & Scrutton, N.S. (1999) The reductive half-reaction of the H172Q mutant of trimethylamine dehydrogenase: evidence against a carbanion mechanism and assignment of kinetically influential ionizations in the enzyme-substrate complex. ***Biochem. J.*** **341**, 307-314.

68. Ilich, P., & Hille, R. (1999) The mechanism of formamide hydroxylation catalyzed by a molybdenum-dithiolene complex: a model for xanthine oxidase reactivity. ***J. Phys. Chem.(B)*** **103**, 5406-5412.

69. Jones, R.M., Inscore, F.E., Hille, R., & Kirk, M.L. (1999) Freeze-quench difference magnetic circular dichroism study of a xanthine oxidase intermediate. ***Inorg. Chem.*** **38**, 4963-4970.

70. Yoon, K.-S., Hemann, C., Hille, R., &Tabita, F.R. (1999) Rubredoxin from the green sulfur bacterium ***Chlorobium tepidum*** functions as an electron acceptor for pyruvate:ferredoxin oxidoreductase. ***J. Biol. Chem.*** **274**, 29772-29778.

71. Roberts, P., Basran, J., Wilson, E.K., Hille, R., & Scrutton, N.S. (1999) Redox cycles in trimethylamine dehydrogenase and the mechanism of substrate inhibition. ***Biochemistry*** **38**, 14927-14940.

72. Jang, M.-H., Scrutton, N.S., & Hille, R. (2000) Formation of the hydroquinone of electron-transferring flavoprotein within the physiological complex with trimethylamine dehydrogenase. ***J. Biol. Chem***. **275**, 12546-12552.

73. Anderson, R.F., Jang, M.-H., & Hille, R. (2000) Radiolytic studies of trimethylamine dehydrogenase. Spectral deconvolution of the neutral and anionic semiquinone forms and determination of electron transfer rate constants in the one-electron reduced enzyme. ***J. Biol. Chem***. **275**, 30781-30786.

74. Wei, C.-C., Wang, Z.-Q., Wang, Q., Meade, A., Hemann, C., Hille, R., & Stuehr, D.J. (2001) Rapid kinetic studies link tetrahydrobiopterin oxidation, heme-dioxy reduction and arginine hydroxylation in inducible nitric oxide synthase. ***J. Biol. Chem.*** **276**, 315-319.

75. Ellis, P., Conrads, T., Hille, R., & Kuhn, P. (2001) Crystal structure of the 100 kDa arsenite oxidase from ***Alcaligenes faecalis*** in two crystal forms at 1.64 and 2.03 Å. ***Structure*** **9**, 125-132.

76. Manikandan, P, Choi, E.-Y., Hille, R., & Hoffman, B.M. (2001) 35-GHz ENDOR investigation of the "very rapid" signal of xanthine oxidase reacted with 8-[^{13}C]-2-hydroxy-6-methylpurine. ***J. Am. Chem. Soc*** **123**, 2658-2663.

77. Huhta, M.S., Chen, H.-P., Hemann, C., Hille, R. & Marsh, E.N.G. (2001) Protein-coenzyme interactions in adenosylcobalamin-dependent glutamate mutase. ***Biochem. J.*** **355**, 131-137.

78. Hille, R., & Anderson, R.F. (2001) Coupled electron transfer and protonation/deprotonation in complex flavoproteins. Solvent kinetic isotope effect studies of electron transfer in xanthine oxidase and trimethylamine dehydrogenase. ***J. Biol. Chem.*** **276**, 31193-31201.

79. Mitchell, D.J., Nikolic, D., Jang, M.-H.,van Breemen, R.V., Hille,R., & Silverman, R.B. (2001) Isolation and Mass Spectral Analysis of Flavin Adducts Produced by the Inactivation of Trimethylamine Dehydrogenase. ***Biochemistry*** **40**, 8523-8530.

80. Wang, Z.-Q., Wei, C.-C., Ghosh, S., Meade, A., Hemann, C., Hille, R., & Stuehr, D.J. (2001) A conserved tryptophan in nitric oxide synthase regulates heme-dioxy reduction by tetrahydrobiopterin. ***Biochemistry*** **40**, 12819-12825.

81. Yoon, K.-S., Bobst, C., Hemann, C.F., Hille, R., & Tabita, F.R. (2001) Spectroscopic and functional properties of novel 2[4Fe-4S] cluster-containing ferredoxins from the green sulfur bacterium ***Chlorobium tepidum***. ***J. Biol. Chem***., **276**, 44027-44036.

82. Eilers, T., Schwarz, G., Brinkmann, H., Witt, C., Richter, T., Nieder, J., Koch, B., Hille, R., Hänsch & Mendel, R.R. (2001) Identification and biochemical characterization of ***Arabidopsis thaliana*** sulfite oxidase. A new player in plant sulfur metabolism. ***J. Biol. Chem.*** **276**, 46989-46994.

83. Wei, C.-C., Wang, Z.-Q., Wang, Q., Meade, A., Hemann, C., Hille, R., & Stuehr, D.J. (2001) Rapid kinetic studies link tetrahydrobiopterin oxidation, heme-dioxy reduction and arginine hydroxylation in inducible nitric oxide synthase. ***J. Biol. Chem.*** **276**, 315-319.

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Kundu, T.K., Hille, R., Velayutham, M., & Zweier, J.L. Characterization of superoxide production from aldehyde oxidase: an important source of oxidants in biological tissues. Submitted to ***J. Biol. Chem.***

Cobb, N., Hemann, C.F., McEwan, A.G., & Hille, R. Spectroscopic and kinetic studies of Y114F and W116F mutants of DMSO reductase from ***Rhodobacter capsulatus***. To be submitted to ***J. Biol. Chem.***

Manikandan, P., Johnson, M.K., Hille, R. & Hoffman, B.M. First evidence for formaldehyde interaction of tungsten (W) containing protein: 35 GHz ENDOR spectroscopy studies. To be submitted to ***J. Am. Chem. Soc.***

Anderson, G.L., Hemann, C.F., Dunham, W.R., Ellis, P., Kuhn, P., & Hille, R. Spectroscopic studies of the iron-sulfur clusters of arsenite oxidase from ***Alcaligenes faecalis***. To be submitted to ***J. Biol. Inorg. Chem.***

Mewies, M., & Hille, R. Kinetic characterization of the bile acid inducible NADH: Flavin Oxidoreductase. To be submitted to ***Biochemistry***

Cobb, N., Hille, R., & Bell, C.E. The crystal structure of DMSO reductase from ***Rhodobacter sphaeroides***. To be submitted to ***J. Biol. Inorg. Chem.***

Hood, B.L., Sandbhor, U., & Hille, R. An NMR study of sulfite oxidase. Evidence for extreme mobility of the heme domain. To be submitted to ***Biochemistry***

Sandbhor, U., Hood, B.L., & Hille, R. Direct oxygen atom transfer in sulfite oxidase. To be submitted to ***J. Am. Chem. Soc.***

Hemann, C.F., Pauff, J.L., Leimkühler, S., and Hille, R. Substrate orientation and catalysis in xanthine oxidoreductase from ***Rhodobacter capsulatus***: the role of Arg 880. To be submitted to ***J. Biol. Chem.***

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Invited Talks at National and International Meetings (since 1996)

12th International Symposium on Flavins and Flavoproteins, University of Calgary, Alberta, CA – July 1996

Inorganic Biochemistry Summer Workshop, University of Georgia, Athens GA – August 1996

Symposium on Advances Bioinorganic Chemistry, Bombay, India – October 1996

Biochemical Society Meeting, Bath, UK – April 1997

Molybdenum Enzymes Meeting, University of Sussex, Brighton, UK – April 1997

Iron-Sulfur Proteins Meeting, King's College, London, UK – April 1997

International Conference on Bioinorganic Chemistry, Okazaki, Japan – August 1997

Biochemistry and Cell Biology Symposium, Rice University, Houston, TX – October 1997

Novel Rxns & Catalytic Mechanisms in Anaerobic Microorganisms (DFG) Rothenburg, Germany – April 1998

Molybdenum and Tungsten Enzymes Gordon Conference, Portsmouth, NH – July 1999
Iron-Sulfur Proteins Meeting, King's College London, UK – May, 2000
Inorganic Biochemistry Summer Workshop, University of Georgia, Athens, GA – August, 2000
International Symposium on Bioinorganic Chemistry, Mumbai, India – November, 2000
Molybdenum and Tungsten Enzymes Gordon Conference, Oxford, UK – July, 2001
Robert C. Bray Memorial Symposium, University of Sussex, UK – September, 2002
Japanese Biochemical Society Meeting, Kyoto, Japan – October, 2002
Midwest Metals Meeting, Washington University, St. Louis – May, 2003
Molybdenum and Tungsten Enzymes Gordon Conference, Meriden, NH – July, 2003
11th International Conference on Bioinorganic Chemistry, Cairns, Australia – July, 2003
7th European Symposium on Bioinorganic Chemistry, Garmisch-Partenkirschen, Germany – August, 2004
Molybdenum and Tungsten Enzymes Gordon Conference, Oxford, UK – July, 2005
Metals in Biology Gordon Conference, Ventura, CA – January, 2006

Invited Seminars (since 1995)

Department of Chemistry, University of Auckland, New Zealand – February, 1995
Department of Chemistry, University of New Mexico – April, 1995
Department of Chemistry University of Arizona – April, 1995
Department of Biological Chemistry, University of Michigan – June, 1995
Department of Chemistry University of Michigan – June, 1995
Max-Planck Institute for Biochemistry, Munich, Germany – August, 1995
Department of Biochemistry, Virginia Tech University – February, 1996
Department of Chemistry, University of Poona, India – October, 1996
Institute for Enzyme Research, University of Wisconsin – April, 1996
Department of Chemistry, California Institute of Technology – November, 1996
Department of Biochemistry, University College, Dublin, Ireland – April, 1997
Department of Biochemistry, Nippon Medical School, Tokyo, Japan – August, 1997
Department of Chemistry and Biochemistry, University of Houston – October, 1997
Department of Chemistry, Virginia Commonwealth University – November, 1997
Department of Biochemistry, University of Minnesota – November, 1997
Department of Chemistry, University of Karlsruhe, Germany – March, 1998
Department of Chemistry, Princeton University – October, 1998
Exxon Research and Engineering Company – October, 1998
Department of Biochemistry and Biophysics, Texas A&M University – November, 1998
Department of Chemistry and Biochemistry, University of Maryland – January, 1999
Department of Biochemistry, The Ohio State University – April, 1999
Department of Biochemistry, North Dakota State University – April, 1999
Department of Chemistry and Biochemistry, Miami University (Ohio) – May, 1999
Department of Botany, University of Braunschweig, Germany – August, 1999
Department of Biochemistry, University of Rome – September, 1999
Laboratory of Bioenergetics and Protein Engineering, CNRS Marseille, France – September, 1999
Department of Chemistry, New University of Lisbon, Portugal – September, 1999
Department of Medicine, Johns Hopkins University – October, 1999
Department of Chemistry, Case Western Reserve University – November, 1999
College of Pharmacy, Ohio State University – November, 1999

Department of Biochemistry, Pennsylvania State University – January, 2000

Department of Biochemistry, The John Innis Center, Norwich, UK – May, 2000

Department of Chemistry, The University of Edinburgh, UK – May, 2000

Departments of Biochemistry and Chemistry, The University of Leicester, UK – May, 2000

Central Research Division, Pfizer Inc., Groton, CT – July, 2000

Department of Chemistry, University of New Mexico – October, 2000

Department of Biochemistry, Wright State University – January, 2001

Department of Chemistry and Biochemistry, Utah State University – January, 2001

Department of Chemistry, Duquesne University – March, 2001

Chemical Biology and Biophysics Programs, The University of Michigan, Ann Arbor – October, 2001

Biochemistry and Molecular Biology Program, University of Texas Health Sciences Center, Houston– October, 2001

Department of Microbiology, University of Brisbane – January, 2002

Department of Chemistry, University of Wisconsin (Milwaukee) – February, 2002

Department of Chemistry, University of Osaka (Japan) – October, 2002

Department of Microbiology and Immunology, University of Illinois, Chicago – November, 2002

Department of Biochemistry and Molecular Biophysics, University of Arizona – November, 2002

Department of Chemistry, University of Auckland, New Zealand – February, 2003

Department of Biochemistry, University of Texas Health Science Center, San Antonio – April, 2003

Department of Plant Biology, Technical University of Braunschweig, Germany – September, 2003
(Humboldt Lecture Series on Enzymology and Spectroscopy of Metalloenzymes)

Department of Microbiology, Technical University of Braunschweig, Germany – September, 2003

Department of Biophysics, Medical College of Wisconsin – February, 2004

Department of Biochemistry, Medical College of Wisconsin – May, 2004

Department of Microbiology, University of Halle, Germany – June, 2004

Department of Microbiology, University of Bayreuth, Germany – June, 2004

Departments of Biochemistry and Microbiology, Michigan State University – March, 2005

Department of Biochemistry, University of British Columbia – April, 2005

Department of Chemistry, University of New Mexico – September, 2005

Department of Biochemistry, University of California, Riverside – May, 2006

The subject matter of the above presentations was one of the following topics: (1) the reaction mechanism of xanthine oxidase and other molybdenum enzymes; (2) the reaction mechanism of trimethylamine dehydrogenase; (3) electron transfer in biological systems; or (4) the structure and function of arsenite oxidase.

Research Program

My research program focuses the reaction mechanisms of oxidoreductase enzymes - particularly those possessing molybdenum or flavin in their active sites - and biological electron transfer. The molybdenum-containing enzymes catalyze the incorporation of oxygen into a variety of organic and inorganic compounds, and constitute an important enzyme class within the oxidoreductases. These enzymes are only poorly understood in comparison to other biological systems that contain heme, flavin, non-heme iron or copper. Working with representative members of each of the three major families of molybdenum enzymes, we have successfully identified the fundamental aspects of the catalytic sequences of these enzymes. Particularly in the case of the molybdenum hydroxylase family (as represented by xanthine oxidase), work in our laboratory has elucidated the chemical course of the reaction, characterizing each of the principal intermediates in the course of the reaction. This work has demonstrated that molybdenum-based oxygen atom transfer is carried out without the generation of a highly reactive oxygenated intermediate (***e.g.***, the perferryl oxide and 4a-peroxide "oxygen guns" of heme and flavin containing enzymes, respectively), even when the reaction catalyzed involves hydroxylation of a carbon center. These studies have provided an increasingly clear picture of the chemical sequence of events that lead to oxygen atom transfer in the absence of a high-energy intermediate, and our reaction mechanism is generally accepted in the literature. Our present work in this area involves kinetic, spectroscopic and mutagenic studies to gain further insight into the basic elements of catalysis at play in these enzymes, as well as modeling of the reaction intermediates and transition states using computational approaches.

Enzymes possessing multiple redox-active centers in a single polypeptide are useful systems in which to examine the factors governing rates of biological electron transfer without the complication of protein-protein interactions. We are utilizing pH-jump stopped-flow, flash photolysis and pulse radiolysis methodologies to examine the rates of electron transfer within several such enzymes, including xanthine oxidase (possessing a molybdenum center, two [2Fe-2S] clusters and FAD), trimethylamine dehydrogenase (with FMN and a [4Fe-4S] cluster) and succinate:quinone oxidoreductase (with FAD, three different iron-sulfur centers, a b-type cytochrome and a tightly bound equivalent of ubiquinone). Our work with xanthine oxidase has shown, for example, that protonation/deprotonation of the enzyme flavin occurs concomitantly with electron transfer. By contrast, in trimethylamine dehydrogenase, protonation and electron transfer occur as discrete steps, rather than concomitantly. We have recently extended this work to studies of succinate:quinone oxidoreductase, demonstrating recently that electron equilibration involving the cytochrome of SQR is extremely rapid, despite the rather low reduction potential of the center. In each of these systems, electron transfer is generally extremely rapid and is typically not rate-limiting for turnover.

We are also interested in the reaction mechanism of TMADH and related enzymes. TMADH is a member of the amine oxidase family of flavoproteins (including monoamine oxidase) and catalyzes the oxidative deamination of a variety of tertiary amines with subsequent reduction of an electron-transferring flavoprotein (ETF). Our work has provided evidence for the formation of a covalent flavin adduct in the course of the reaction that leads to reduction of the flavin by two equivalents, and also shed important light on the interaction of the two redox-active centers in the two-electron reduced state generated upon anaerobic reaction with substrate. Other work has shown that the formation of a unique spin-interacting state between the two redox-active sites occurs much more slowly than reduction of the iron-sulfur center, indicating that the presence of flavin semiquinone and reduced iron-sulfur center is necessary but not sufficient for formation of the spin-interacting state. We have also examined the reaction of the reduced dehydrogenase with ETF, and demonstrated that this reaction takes place at the iron-sulfur center of the enzyme with the involvement of a specific tyrosine residue at the surface of the enzyme. We are presently engaged in identifying the roles of specific active-site residues in catalysis and formation of the spin-interacting state by site-directed mutagenesis.

Research Facilities

The above research program utilizes a wide range of spectroscopic techniques, including: x-ray absorption, electron paramagnetic resonance and resonance Raman. A variety of kinetic methods are also employed, including stopped-flow, freeze-quench, flash photolysis and pulse radiolysis. The principal instrumentation in the laboratory, most of which has been funded by two Shared Instrumentation Grants from NIH and one from NSF, is described below.

EPR facility. This facility consists of a computer-controlled Brüker ER300 EPR spectrometer capable of operating at 3, 9 and 34 GHz microwave frequency. The instrument is equipped with NMR gaussmeter and microwave frequency counter for the accurate determination of g-values. A variety of microwave cavities are available (including cylindrical and double-rectangular), as is cryogenic equipment for operation at both liquid nitrogen and liquid helium temperatures.

Resonance Raman facility. This instrument has been designed for optimal efficiency in the vis/NIR region. Kr^+ and Ar^+ lasers (Coherent, Inc.) provide a number of specific excitation lines and may also be used to pump either a titanium/sapphire or dye laser to provide excitation throughout the visible/NIR. The detector is a charge-coupled device whose active element is a 1024 x 1024 back-thinned element. Low-temperature capabilities are provided by an APD Cryogenics closed cycle liquid helium refrigerator. The instrument is located in a specially designed room of the laboratory that is dedicated to spectroscopic instrumentation, including an Aviv Associates CD spectrophotopolarimeter (280 - 2,000 nm spectral range) and a recently upgraded Mattson Sirius 100+ FT-IR interferometer.

Laboratory: two large chromatography refrigerators, Millipore water purification system, and centrifuges (Beckman L7-65 and J2-21 ultra- and high-speed centrifuges, Tomy MTX-150 tabletop refrigerated centrifuge). The laboratory also has a variety of equipment for handling bacterial growths (incubators, shaker-baths, Millipore cell harvester) and enzyme purification (chromatography eqpt., fraction collectors, concentrators, ***etc.***) and sample preparation (anaerobic trains, anaerobic glassware, ***etc.***); computer-controlled absorbance/fluorescence stopped-flow apparatus; three Hewlett-Packard 8452A diode-array spectrophotometers; renovated Cary 14 spectrophotometer (including computer) with a 280-3000 nm scan range; Aviv Associates spectrophotometer (280 - 2,000 nm spectral range); Beckman HPLC apparatus; EG&G 363 potentiostat and associated electrodes; two UV/vis/fluorescence stopped-flow apparatuses (Kinetic Instruments and Applied Photophysics).

Computer: The principal computational devices in the laboratory are Vaxstation 3200, Vax 4000 and DEC Alpha workstations, as well as an SGI Octane2/V10 molecular graphics workstation. Software for the simulation of rapid kinetic transients and EPR spectra, the analysis of x-ray absorption spectroscopic data and visualization of protein structure operates on these computers. The local area network utilizes the Vaxstation as central server and is connected via Ethernet to three Macintosh computers that are used in data analysis and manuscript preparation, and several PC Pentium computers used in data acquisition with laboratory instrumentation. The LAN is linked to the Ohio Supercomputer Center, which maintains a number of high-speed devices; the two used by this laboratory are Cray T90/4128 and SGI Power Challenge supercomputers.

On-going Scientific Collaborations

At Ohio State University

Charles Bell (Dept. Mol. Cell. Biochemistry) – crystallography of TMADH and DMSO reductase

James Cowan (Department of Chemistry) – Spectroscopic studies of iron-sulfur cluster assembly

Mark Foster (Department of Biochemistry) – NMR studies of sulfite oxidase

Richard Sayre (Department of Plant Biology) – Spectroscopic studies of eukaryotic photosynthetic pigments

Robert Tabita (Department of Microbiology) – Spectroscopic studies of Fe/S proteins in bacterial CO_2 fixation

Jay Zweier (Davis Heart/Lung Research Institute) – Role of xanthine oxidoreductase in ROS generation

Mark Parthun (Dept. Mol. Cell. Biochemistry) – Structure/function of histone acetylases

Nationally

John Enemark (Department of Chemistry, University of Arizona) – ENDOR and NMR studies of molybdenum enzymes

Richard Holm (Department of Chemistry, Harvard University) – Isotopic labeling studies of molybdenum-containing enzymes

Martin Kirk (Department of Chemistry, University of New Mexico) – Characterization and modeling of intermediates for molybdenum enzymes

Dennis Stuehr (Department of Immunology, Cleveland Clinic Foundation) – Spectroscopic studies of nitric oxide synthase

Gary Cecchini (Department of Biochemistry and Biophysics, University of California, San Francisco) – Kinetic studies of succinate dehydrogenase

Internationally

Robert Anderson (Department of Chemistry, University of Auckland, New Zealand) – Pulse radiolysis studies of complex oxidoreductases

Fraser Armstrong (Department of Chemistry, University of Oxford, UK) – electrochemical studies of complex redox-active enzymes

Graham George (University of Saskatchewan, Canada) – X-ray absorption studies of molybdenum-containing enzymes

Silke Leimkühler (Department of Biochemistry, University of Potsdam, Germany) – Spectroscopic and kinetic studies of xanthine dehydrogenase from ***Rhodobacter capsulatus***

Alistair McEwan (Department of Microbiology, University of Queensland, Brisbane, Australia) – mutagenesis studies of DMSO reductase

Ralf Mendel (Department of Botany, Technical University of Braunschweig, Germany) – Mechanistic studies of molybdenum enzymes from plants

Takeshi Nishino (Department of Biochemistry and Molecular Biology, Nippon Medical School, Tokyo, Japan) and Emil Pai (Department of Biochemistry, University of Toronto, Toronto, Canada) – Structure/function studies of xanthine oxidase and related enzymes

Emil F. Pai (Department of Biochemistry, University of Toronto, Canada) – Structure/function studies of xanthine oxidase and related enzymes

Günter Schwarz (Department of Biochemistry, University of Cologne) – Structure/funtion studies of nitrate reductase

Teaching

My current academic appointment is in the biochemistry unit of the medical school at Ohio State, and as a result my formal teaching obligations are minimal, amounting to four lectures a year to first- or second-year medical students on the structure and function of hemoglobin and aspects of iron nutrition. Nevertheless, I have voluntarily taken on several additional teaching responsibilities and presently give on average approximately 60 lectures each academic year. In addition to the medical instruction, this teaching load includes the graduate-level courses described below.

Molecular and Cellular Biochemistry 762 (3 cr) – This is the enzymology course in the core curriculum of the campus-wide biochemistry program at Ohio State, and is taught annually. I took over this course in 1992, and have reorganized it to reflect contemporary approaches to enzymology. The objective of this course is to take first-year graduate students from the level of an introductory biochemistry class to the literature. Enrollment varies from 30 to 50, and I am the sole instructor.

Molecular and Cellular Biochemistry 824 (3 cr) – This is an advanced enzymology course taught every other year that focuses principally on rapid reaction kinetics and related methods of elucidating enzyme reaction mechanism, along with a small set of "special topics" that varies from year to year. Enrollment has been between five and ten each time the course has been offered, and I am the sole instructor.

Chemistry 763 (3 cr) – This course is another core curriculum of the campus-wide biochemistry program at Ohio State focusing on structure and function of membranes and membrane proteins, and is taught annually. I give a three-lecture set on the mitochondrial electron transport system. Enrollment has been 30-40.

In addition, I have in the past been involved in the organization of:

Integrated Biomedical Science Program 701 – This is the core course for the Integrated Biomedical Science graduate program in the College of Medicine, and is taught annually. I initially organized and taught a five lecture set on ligand binding and enzyme kinetics. Enrollment has been 30-40.

Biophysics 702 (3 cr) – This is a course in the Biophysics Graduate Program at Ohio State that I helped organize in 1998, and is taught annually. The course is designed to give first-year graduate students in the program an introduction to the field, conveying the broad scope of molecular, cellular and sensory biophysics. The course consists of a sequence of short (2-3 lecture) presentations by a number of program faculty, my own contribution having been a three-lecture introduction to molecular biophysics and a two-lecture sequence on electron paramagnetic resonance spectroscopy. Enrollment has been 10-15 students.