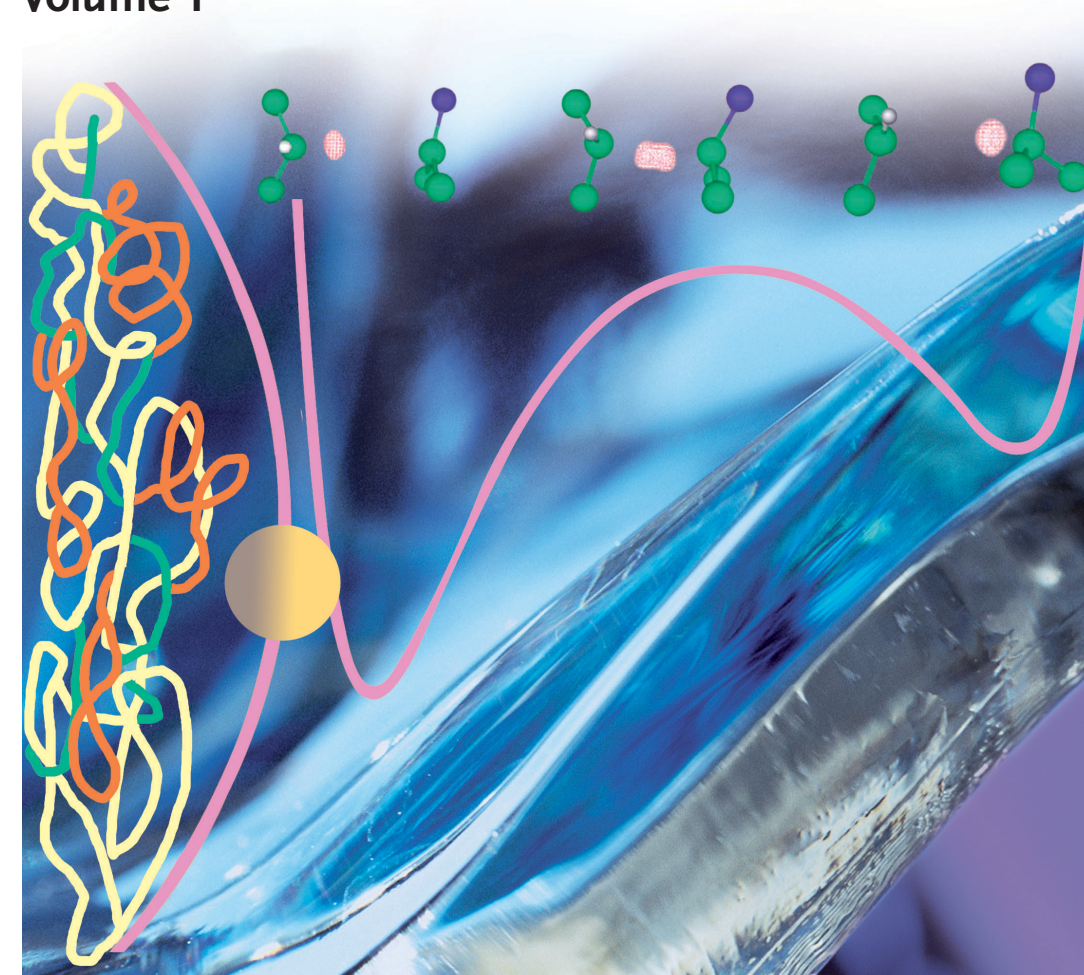


Edited by J. T. Hynes, J. P. Klinman,
H.-H. Limbach, R. L. Schowen

Hydrogen-Transfer Reactions

Foreword by Ahmed Zewail

Volume 1



Hynes · Klinman
Limbach · Schowen (Eds.)

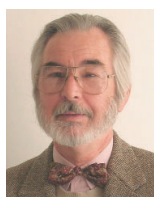
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Hydrogen-Transfer
Reactions



Hydrogen-transfer reactions, in which a proton, hydrogen atom, or hydride ion moves from a donor to an acceptor, are ubiquitous in physics, chemistry, and biology – indeed throughout the natural world. These processes occur at rates from vibrational periods to geological periods and are studied by essentially every available theory and technique. Their importance for fundamental science is enormous but they are also vital in industrial chemistry, molecular medicine, and modern pharmaceutical science.

This multivolume work provides interpretative reviews, written by the most active scientists in their fields, of hydrogen transfer in systems beginning with isolated molecules and traversing all levels of organization up to cellular biology. Beginners will find these volumes a clear and accessible introduction to a broad range of topics, while established experts will be pleased by provocative and authoritative presentations of the newest discoveries and ideas.



James T. "Casey" Hynes was born in Miami Beach, Florida in 1943. He received his A.B. from Catholic University in 1965 and his Ph.D. from Princeton University in 1969. He was then an NIH postdoctoral fellow at MIT and in 1971 joined the faculty at the University of Colorado, Boulder, where he is currently Professor of Chemistry and Biochemistry. Since 1999, he has also been CNRS Director of Research in the Chemistry Department at Ecole Normale Supérieure, Paris. His research interests include the theory of the rates and mechanisms of ground and excited state chemical reactions (including proton transfer), of intermolecular and intramolecular energy transfer, and of atmospheric heterogeneous reactions.



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Hans-Heinrich Limbach was born in 1943 in Brühl near Cologne, Germany. He studied Chemistry at the Universities of Bonn and Freiburg, where he obtained his Ph.D. in 1973 and his habilitation in Physical Chemistry in 1980. As a Heisenberg fellow he worked in 1984 with C. S. Yannoni at the IBM Research Laboratory, San Jose, USA and in 1984 and with Prof. C. B. Moore, UC Berkeley. In 1990 he joined the Free University of Berlin. Limbach's research interests are the study of hydrogen and deuterium transfer and bonding in organic liquids and solids, polymers, mesoporous systems, metallorganic compounds, nano-particles and enzymes. For this purpose he uses liquid and solid state Nuclear Magnetic Resonance techniques.



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Judith P. Klinman,

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Hydrogen-Transfer Reactions

Volume 1

Edited by

James T. Hynes, Judith P. Klinman,

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Cover

The cover picture is derived artistically from the potential-energy profile for the dynamic equilibrium of water molecules in the hydration layer of a protein (see A. Douhal's chapter in volume 1) and the three-dimensional vibrational wavefunctions for reactants, transition state, and products in a hydride-transfer reaction (see the chapter by S.J. Benkovic and S. Hammes-Schiffer in volume 4).

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Foreword

The Remarkable Phenomena of Hydrogen Transfer

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Life would not exist without the making and breaking of chemical bonds - chemical reactions. Among the most elementary and significant of all reactions is the transfer of a hydrogen atom or a hydrogen ion (proton). Besides being a fundamental process involving the smallest of all atoms, such reactions form the basis of general phenomena in physical, chemical, and biological changes. Thus, there is a wide-ranging scope of studies of hydrogen transfer reactions and their role in determining properties and behaviors across different areas of molecular sciences.

Remarkably, this transfer of a small particle appears deceptively simple, but is in fact complex in its nature. For the most part, the dynamics cannot be described by a classical picture and the process involves more than one nuclear motion. For example, the transfer may occur by tunneling through a reaction barrier and a quantum description is necessary; the hydrogen is not isolated as it is part of a chemical bond and in many cases the nature of the bond, "covalent" and/or "ionic" in Pauling's valence bond description, is difficult to characterize; and the description of atom movement, although involving the local hydrogen bond, must take into account the coupling to other coordinates. In the modern age of quantum chemistry, much has been done to characterize the rate of transfer in different systems and media, and the strength of the bond and degree of charge localization. The intermediate bonding strength, directionality, and specificity are unique features of this bond.

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The supreme example for the unique role in specificity and rates comes from life's genetic information, where the hydrogen bond determines the complementarities of G with C and A with T and the rate of hydrogen transfer controls genetic mutations. Moreover, the not-too-weak, not-too-strong strength of the bond allows for special "mobility" and for the potent hydrophobic/hydrophilic interactions. Life's matrix, liquid water, is one such example. The making and breaking of the hydrogen bond occurs on the picosecond time scale and the process is essential to keeping functional the native structures of DNA and proteins, and their recognition of other molecules, such as drugs. At interfaces, water can form ordered structures and with its amphiphilic character, utilizing either hydrogen or oxygen for bonding, determines many properties at the nanometer scale.

Hydrogen transfer can also be part of biological catalysis. In enzyme reactions, a huge complex structure is involved in bringing this small particle of hydrogen into the right place at the right time so that the reaction can be catalytically enhanced, with rates orders of magnitude larger than those in solution. The molecular theatre for these reactions is that of a very complex energy landscape, but with guided bias for specificity and selectivity in function. Control of reactivity at the active site has now reached the frontier of research in "catalytic antibody", and one of the most significant achievements in chemical synthesis, using heterogeneous catalysis, has been the design of site-selective reaction control.

Both experiments and theory join in the studies of hydrogen transfer reactions. In general, the approach is of two categories. The first involves the study of prototypical but well-defined molecular systems, either under isolated (microscopic) conditions or in complexes or clusters (mesoscopic) with the solvent, in the gas phase or molecular beams. Such studies over the past three decades have provided unprecedented resolution of the elementary processes involved in isolated molecules and en route to the condensed phase. Examples include the discovery of a "magic solvent number" for acid-base reactions, the elucidation of motions involved in double proton transfer, and the dynamics of acid dissociation in finite-sized clusters. For these systems, theory is nearly quantitative, especially as more accurate electronic structure and molecular dynamics computations become available.

The other category of study focuses on the nature of the transfer in the condensed phase and in biological systems. Here, it is not perhaps beneficial to consider every atom of a many-body complex system. Instead, the objective is hopefully to project the key electronic and nuclear forces which are responsible for behavior. With this perspective, approximate, but predictive, theories have a much more valuable outreach in applications than those simulating or computing bonding and motion of all atoms. Computer simulations are important, but for such systems they should be a tool of guidance to formulate a predictive theory. Similarly for experiments, the most significant ones are those that dissect complexity and provide lucid pictures of the key and relevant processes.

Progress has been made in these areas of study, but challenges remain. For example, the problem of vibrational energy redistribution in large molecules, although critical to the description of rates, statistical or not, and to the separation

of intra and intermolecular pathways, has not been solved analytically, even in an approximate but predictive formulation. Another problem of significance concerns the issue of the energy landscape of complex reactions, and the question is: what determines specificity and selectivity?

This series edited by prominent players in the field is a testimony to the advances and achievements made over the past several decades. The diversity of topics covered is impressive: from isolated molecular systems, to clusters and confined geometries, and to condensed media; from organics to inorganics; from zeolites to surfaces; and, for biological systems, from proteins (including enzymes) to assemblies exhibiting conduction and other phenomena. The fundamentals are addressed by the most advanced theories of transition state, tunneling, Kramers' friction, Marcus' electron transfer, Grote-Hynes reaction dynamics, and free energy landscapes. Equally covered are state-of-the-art techniques and tools introduced for studies in this field and including ultrafast methods of femtochemistry and femtobiology, Raman and infrared, isotope probes, magnetic resonance, and electronic structure and MD simulations.

These volumes are a valuable addition to a field that continues to impact diverse areas of molecular sciences. The field is rigorous and vigorous as it still challenges the minds of many with the fascination of how the physics of the smallest of all atoms plays in diverse applications, not only in chemistry, but also in life sciences. Our gratitude is to the Editors and Authors for this compilation of articles with new knowledge in a field still pregnant with challenges and opportunities.

Pasadena, California
August, 2006

Ahmed Zewail

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Preface

As one of the simplest of chemical reactions, pervasive on this highly aqueous planet populated by highly aqueous organisms, yet still imperfectly understood, the transfer of hydrogen as a subject of scientific attention seems hardly to require defense. This claim is supported by the readiness with which the editors of this series of four volumes on *Hydrogen-transfer Reactions* accepted the suggestion that they organize a group of their most active and talented colleagues to survey the subject from viewpoints beginning in physics and extending into biology. Furthermore, forty-nine authors and groups of authors acceded, with alacrity and grace, to the request to contribute and have then supplied the articles that make up these volumes.

Our scheme of organization involved an initial division into physical and chemical aspects on the one hand, and biological aspects on the other hand (and one might well have said biochemical and biological aspects). In current science, such a division may provide an element of convenience but no-one would seriously claim the segregation to be either easy or entirely meaningful. We have accordingly felt quite entitled to place a number of articles rather arbitrarily in one or the other category. It is nevertheless our hope that readers may find the division adequate to help in the use of the volumes. It will be apparent that the division of space between the two categories is unequal, the physical and chemical aspects occupying considerably more pages than the biological aspects, but our judgment is that this distribution of space is proper to the subjects treated. For example, many of the treatments of fundamental principles and broadly applicable techniques were classified under physical and chemical aspects. But they have powerful implications for the understanding and use of the matters treated under biological aspects.

Within each of these two broad disciplinary categories, we have organized the subject by beginning with the simple and proceeding toward the complex. Thus the physical and chemical aspects appear as two volumes, volume 1 on simple systems and volume 2 on complex systems. Similarly, the biological aspects appear as volume 3 on simple systems and volume 4 on complex systems.

Volume 1 then begins with isolated molecules, complexes, and clusters, then treats condensed-phase molecules, complexes, and crystals, and finally reaches

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Volume 3 begins with simple model (i.e., non-enzymic) reactions for proton-transfer, both to and from carbon and among electronegative atoms, hydrogen-atom transfer, and hydride transfer, as well as the extension to small, synthetic peptides. It is completed by treatments of how enzymes activate C-H bonds, multiple hydrogen transfer reactions in enzymes, and theoretical models. Volume 4 moves then into enzymic reactions and a thorough consideration of quantum tunneling and protein dynamics, one of the most vigorous areas of study in biological hydrogen transfer, then considers several specific enzyme systems of high interest, and is completed by the treatment of proton conduction in biological systems.

While we do not claim any sort of comprehensive coverage of this large subject, we believe the reader will find a representative treatment, written by accomplished and respected experts, of most of the matters currently considered important for an understanding of hydrogen-transfer reactions. I am enormously grateful to James T. (Casey) Hynes and Hans-Heinrich Limbach, who saw to the high quality of the volumes on the physical and chemical aspects, and to Judith Klinman, who gave me a nearly free pass as her co-editor of the volumes on biological aspects. We are all grateful indeed to the authors who contributed their wisdom and eloquence to these volumes. It has been a very great pleasure to be assisted, encouraged, and supported at every turn by the outstanding staff of VCH-Wiley in Weinheim, particularly (in alphabetical order) Ms. Nele Denzau, Dr. Renate Dötzer, Dr. Tim Kersebohm, Dr. Elke Maase, Ms. Claudia Zschernitz, and – of course – Dr. Peter Göllitz.

Lawrence, Kansas, USA, September 2006

Richard L. Schowen

Preface to Volumes 1 and 2

These volumes together address the subject of the physical and chemical aspects of hydrogen transfer, volume 1 focusing on comparatively simple systems and volume 2 treating relatively more complex ones.

Volume 1 comprises three parts, commencing with Part I, dealing with hydrogen transfers of polyatomic molecules and complexes in relatively isolated conditions. In the first three contributions, the transfer is a coherent tunneling process rather than a rate process, characterized by “tunnel splittings” or delocalized hydrogen nuclei, for which electronic and vibrational spectroscopies are common and potent tools. The molecular systems discussed are malonaldehyde and tropolone (Redington, Ch. 1), carboxylic acid dimers (Havenith, Ch. 2) and strongly hydrogen-bonded systems such as $(\text{H}_2\text{O}\cdots\text{H}\cdots\text{OH}_2)^+$ (Asmis, Neumark and Bauman, Ch. 3). Kühn and Gonzales (Ch. 4) consider theoretically the more active role of infrared radiation in controlling hydrogen dissociation dynamics in e.g. OHF^- .

The five contributions of Part II focus on condensed matter. If the barriers are large, the hydrogen transfer becomes a rate process which may involve incoherent tunneling. Ceulemans (Ch. 5) examines proton abstraction by alkanes from strongly acidic alkane radical cations in inert matrices. Limbach (Ch. 5) follows the kinetics of single and multiple hydrogen and deuterium transfers in liquids and solids via NMR. Optical methods are applied by Douhal (Ch. 6) to systems embedded in a nanocavity, and embedded in liquids and polymer matrices by Waluk (Ch. 7), with a contrast to coherent hydrogen transfer in supersonic jets. Finally, Vener (Ch. 9) compares theory and experiment for anharmonic vibrations of strong hydrogen bonds in crystals.

Part III, comprising four chapters, commences the examination of hydrogen transfer – here proton transfer – in polar environments. The strong electrostatic proton-environment interaction guarantees incoherent rate phenomena. Kiefer and Hynes (Ch. 10) lay out the theoretical description for such reactions. The next three chapters exploit the greatly enhanced acidity of aromatic acids in the excited electronic state. Lochbrunner, Schriever and Riedle (Ch. 11) focus on the role of the motion of the groups between which the proton transfers, Pines and Pines (Ch. 12) thoroughly examine the insight to be gained from Förster cycle and free

energy analyses, while Tolbert and Solnsteve (Ch. 13) pursue related themes for “super” photoacids in the concluding chapter of volume 1.

Volume 2 opens with Part IV dealing with hydrogen transfer in protic systems. Generally, a larger number of solvent molecules is involved, and hence multiple protons may be transferred. The first two chapters elucidate molecular details of proton transfer in solution via ultrafast infrared spectroscopy. Nibbering and Pines (Ch. 14) examine the transfer between acid-base pairs for the acid in the excited electronic state, while Elsaesser (Ch. 15) discusses coherent low frequency motions coupled to related proton transfers as well as in hydrogen-bonded complexes. The final two chapters in Part IV deal with proton transfer coupled to electron transfer, with Hammes-Schiffer (Ch. 16) expounding and illustrating the theory for these, while Hodgkiss, Rosenthal and Nocera (Ch. 17) discuss these reactions with a special emphasis on the connection to hydrogen atom transfer.

Part V, consisting of four chapters, opens with a discussion of the kinetics and mechanisms of proton abstraction from carbon in organic systems by Koch (Ch. 18) and then turns to a presentation by Williams (Ch. 19) on free energy relationships for proton transfer, as informed by various theoretical approaches. The final two chapters are devoted to hydrogen and dihydrogen mobility in the coordination sphere of transition metal complexes, where the transition from coherent to incoherent H-tunneling can be observed, with a review of the field given by Kubas in Ch. 20 and a discussion of insights from NMR studies presented by Buntkowsky and Limbach in Ch. 21.

In the first three of the five chapters of Part VI, hydrogen transfer is examined in assorted complex solids of importance in various applications: zeolites by Sauer in Ch. 22, fuel cells by Kreuer in Ch. 23 and ice bilayers by Aoki in Ch. 24. Attention is then turned to hydrogen transfer at metal surfaces in Ch. 25 by Christmann and in metals in Ch. 26 by Hempelmann and Skripov.

Volume 2 concludes in Part VII with contributions on the variational transition state theory approach to hydrogen transfer in various contexts (Truhlar and Garrett, Ch. 27), on experimental evidence of hydrogen atom tunneling in simple systems (Ingold, Ch. 28), and finally on a theoretical perspective for multiple hydrogen transfers (Smedarchina, Siebrand and Fernández-Ramos, Ch. 29).

JTH acknowledges the support of grant CHE-0417570 from the US National Science Foundation. HHL thanks the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt, for financial support.

Boulder and Paris, September 2006
Berlin, September 2006

James T. Hynes
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Preface

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Lawrence, Kansas, USA, September 2006

Richard L. Schowen

Preface to Volumes 3 and 4

These volumes together address the rather enormous subject of hydrogen transfer in biological systems, volume 3 presenting the role of relatively simple systems in the understanding of hydrogen transfer while volume 4 considers complex systems, for the most part enzymes.

Volume 3 contains two parts that treat basic concepts and systems not limited to a single enzyme or class of enzymes in their significance. Part I consists of five chapters on the chemistry of the transfer of hydrogen in biological model systems: as a proton to and from carbon (Amyes and Richard, Ch. 1); as a proton in acid-base catalysis; i.e., largely among electronegative atoms (Kirby, Ch. 2); as a hydrogen atom (Schöneich, Ch. 3); as a hydride ion (Schowen, Ch. 4); as a proton in acid-base catalysis in designed peptides (Baltzer, Ch. 5). Part II is composed of three chapters on generally significant features of biological hydrogen-transfer reactions: in enzyme-catalyzed proton transfer from carbon (Gerlt, Ch. 6); in multiple proton transfers in enzymic systems (Spies and Toney, Ch. 7); and in computer simulations of enzymic hydrogen transfer (Braun-Sand, Olsson, Mavri, and Warshel, Ch. 8).

Volume 4, consisting of three parts, then proceeds to studies in enzyme and protein systems that for the most part serve well as paradigms for broader groups in which hydrogen transfer is important. Part III brings together seven chapters on the subject of quantum tunneling in enzymic hydrogen-transfer and its relationship to protein motions. A relative new theoretical approach is described by Schwartz (Ch. 9), leading into a general consideration of the existing evidence and its significance for the tunneling/dynamics nexus (Knapp, Meyer, and Klinman, Ch. 10), and articles by Huskey (Ch. 11) on the importance of multiple-isotope labeling for characterization of tunneling phenomena, by Kohen on kinetic isotope effects (Ch. 12) and by Basran, Hothi, Masgrau, Sutcliffe, and Scrutton on the opportunities afforded by flavoprotein systems (Ch. 13). This part is closed by articles on two important experimental approaches, isotope exchange with solvent as a probe of protein motion (Lee, Croy, Resing, and Ahn, Ch. 14) and resonance Raman spectroscopy as a probe of active-site dynamical properties (Callender and Deng, Ch. 15). Part IV brings into focus several central examples of important enzyme classes: thiamin-dependent enzymes (Ch. 16 by Hübner, Golbik, and

Tittmann), dihydrofolate reductase (Ch. 17 by Benkovic and Hammes-Schiffer), hydrolases (Ch. 18 by Stein), and vitamin B₁₂ enzymes (Ch. 19 by Banerjee, Truhlar, Dybala-Defratyka, and Paneth). The volume is closed by a one-chapter Part V on proton conduction in biology, in which Gutman and Nachliel (Ch. 20) treat the subject of proton conductance at protein surfaces and interfacial regions.

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Berkeley, California, USA, September 2006

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