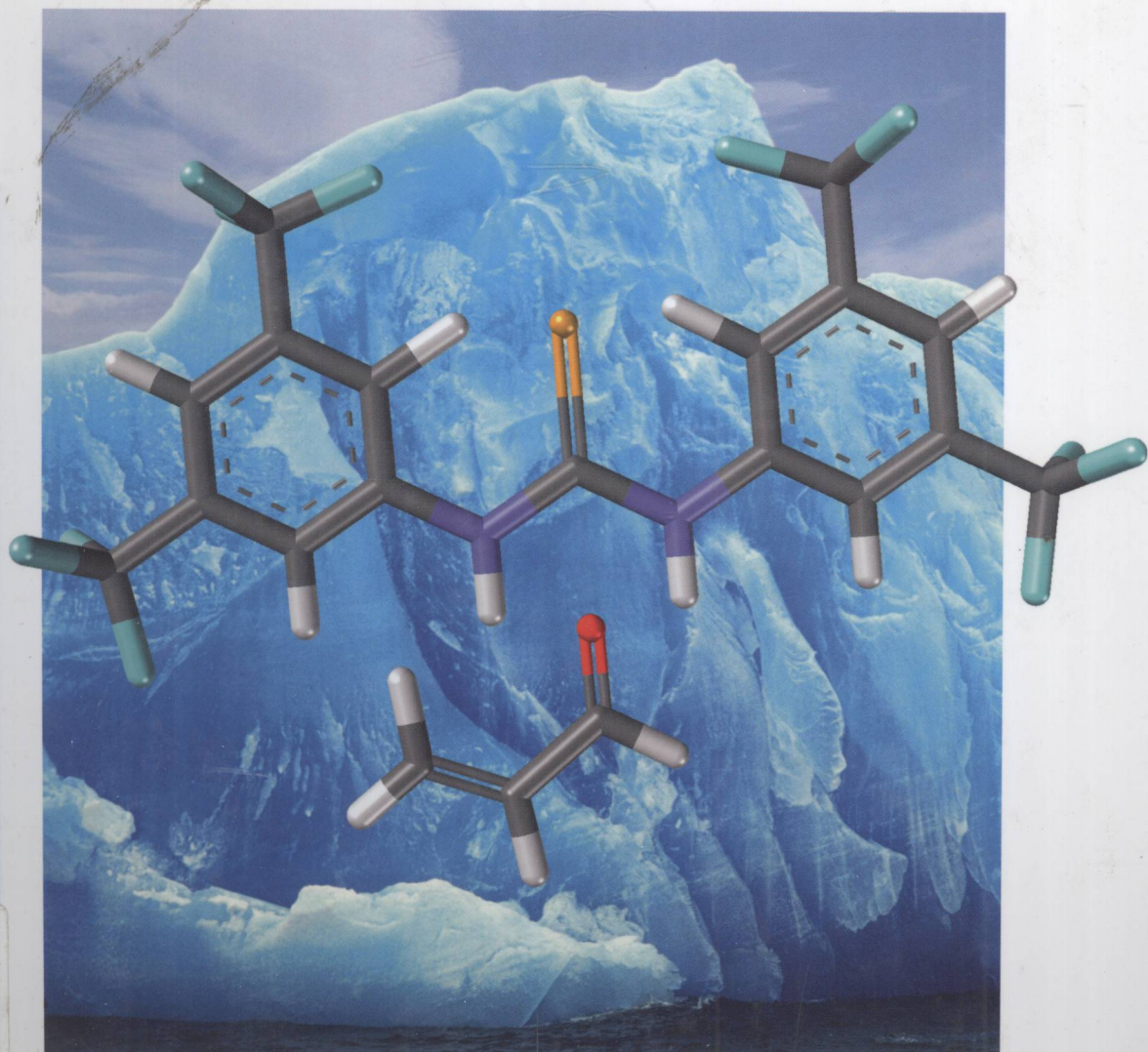


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Hydrogen Bonding in Organic Synthesis



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Petri M. Pihko

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Preface

The purpose of this book is to provide the reader with an overview of how hydrogen bonding can contribute to the advancement of the practice of organic synthesis. The field has grown explosively in recent years, as evidenced by the number of highlights and reviews devoted to hydrogen bonding in the service of organic synthesis. Advances in small-molecule catalysis, computational and experimental studies of hydrogen bonding catalysis, and structural characterization of enzymes with hydrogen bonding at the core of their catalytic activity have all contributed to the advances in the field. It is nearly impossible for practitioners of organic synthesis to keep abreast of all these developments, and I hope that covering most of these aspects within the framework of a single textbook would assist the synthetic community in assessing the current power as well as future potential of the field.

The field is covered from seven different angles. The first two introductory chapters, Chapter 1 (Petri Pihko) and Chapter 2 (Takahiko Akiyama), illustrate the importance of hydrogen bonding in chemistry and chemical catalysis.

The details of how hydrogen bonding contributes to catalysis are illustrated in the following chapters. Chapter 3 by Albrecht Berkessel and Kerstin Etzenbach-Effers describes computational studies of hydrogen bonding catalysts, an essential feature in analyzing the contributions of hydrogen bonding to catalysis. In Chapter 4, Pihko, Rapakko, and Wierenga provide a general overview of hydrogen bonding in enzymatic catalysis, and they go deeper into the structural features of oxy-anion holes, the powerhouses of many hydrogen bonding enzymes. The idea behind this chapter is to present an overview of the catalytic machineries of enzymes and to provide a contrast to the present status of development of small-molecule hydrogen bonding catalysts.

The small-molecule catalysts are covered in Chapters 5 and 6. In Chapter 5, Joshua Payette and Hisashi Yamamoto discuss the importance of polar Bronsted-acid-type catalysts as well as cooperative effects in hydrogen bonding catalysis. Chapter 6 by Mike Kotke and Peter Schreiner is then devoted to the single most popular small-molecule catalyst types, the thiourea catalysts. Chapter 6, the longest of all chapters, also provides an excellent overview of the history and development of the field of small-molecule hydrogen bond catalysis.

Finally, the applications of hydrogen bonding in total synthesis of complex molecules are illustrated in the concluding Chapter 7 by Mitsuru Shoji and Yujiro

Hayashi. Although the applications of hydrogen bonding catalysts in natural product synthesis are still in their infancy, hydrogen bonding has been used many times as a driving force for desired selectivity in total synthesis.

In summary, I hope that this textbook will both stimulate fruitful research in the field and also encourage practitioners of organic synthesis to use hydrogen bonding creatively as a tool to solve synthetic challenges.

Jyväskylä, Finland

Petri Pihko

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1

Introduction

Petri Pihko

1.1

Introduction

The purpose of this book is to provide the reader with an overview of how hydrogen bonding can contribute to the advancement of the practice of organic synthesis.

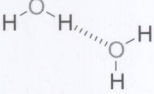
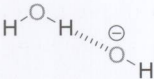
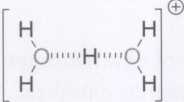
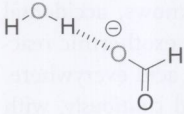
Hydrogen bonds form typically between polar or polarized X–H bonds and electronegative acceptor atoms [1–4]. The resulting weak bond, X–H·····A, is called the hydrogen bond, and it possesses a significant electrostatic character. Consistent with this, bond strengths of hydrogen bonds in the gas phase are significantly larger with charged partners than with neutral partners. Typical strengths of hydrogen bonds are indicated in Table 1.1.

In fact, a vivid demonstration of the power of hydrogen bonds is provided by the behavior of sulfuric acid. As every student of chemistry knows, accidental addition of water to concentrated sulfuric acid can lead to a very exothermic reaction that causes the water to boil and may splash concentrated acid everywhere. For this reason, students are always taught to add sulfuric acid *cautiously*, with stirring, to water—never the other way round! When mixed with water, sulfuric acid dissociates rapidly to generate strongly solvated hydrogen bonded ions. Especially the H_3O^+ ion is very strongly hydrogen bonded to water and its solvation shell in water extends beyond its three closest neighbors, giving a solvation energy of $>40\text{ kcal/mol}$. Although there is an entropic cost in orienting the water molecules toward the newly generated H_3O^+ and HSO_4^- ions, the strong hydrogen bonds that are formed can more than compensate for this and are largely responsible for the heat that is generated.¹⁾

Even between neutral molecules, hydrogen bonds are in fact quite strong forces. They are indeed strong enough to maintain strength in a variety of structures. These include ice and a vast range of other crystalline structures—in crystals,

- | | |
|--|---|
| <p>1) The enthalpy of dilution of sulfuric acid is ca. 880 kJ/mol at infinite dilution (N. N. Greenwood and A. Earnshaw (1984) <i>Chemistry of the Elements</i>. Pergamon Press, Oxford, p. 837). This value</p> | <p>compares favorably with the calculated enthalpy of hydration of H^+ (-1150 kJ/mol, see Table 1) if one assumes that the first proton of H_2SO_4 dissociates completely.</p> |
|--|---|

Table 1.1 Calculated and experimental hydrogen bond strengths.

Bond type	Calculated strength in the gas phase (kJ/mol)	Experimental strength in the gas phase (kJ/mol)	Calculated distance $d_{H\cdots B}$ (Å)	Calculation method/notes
	-20.6 [5]	-22.7 + -2.9 [6]	1.86	MP2
	-108.4 [7]	-111.3 + -4.2 [8]	1.30	BLAP3 Sadlej
	-104.3 [9]	-132.3 [10]	1.20	C ₂ symmetric (Zundel cation).
H ₂ OH ⁺ ...3OH ₂ (first solvation shell for H ₃ O ⁺)	-290.22 [11]	-287.7 [12]	N/A	Eigen cation MP2
H ⁺ (H ₂ O) _n	-1150.1 [13]			Commentary on values [14]
	-71.4 [15]		1.67	MP2/6-31++G** -76.0 kJ/mol for bidentate binding
CH ₃ NH ₃ ⁺ ...OH ₂	-71.0 [16]	-70.6 [17]	1.72	B3LYP/6-31+G(d)

hydrogen bonds are a very powerful directing force that keeps the molecules together. The key structures of life would be impossible without hydrogen bonding: the delicate folds of proteins, the paired and folded forms nucleic acids, DNA and different RNAs, and the fibers of cellulose are all largely dependent on hydrogen bonds for their structure.

The strength of hydrogen bond is also strongly dependent on the solvent. In polar solvents, especially solvents capable of strong intermolecular hydrogen bonds such as water, hydrogen bonds between two nonwater molecules must be relatively strong in order to compete with hydrogen bonds provided by water. Experimentally, it has been established with careful site-directed mutagenesis studies of enzymes that reasonable net binding energies, in the range of 13–20 kJ/mol, are only observed when one of the components is charged [18].

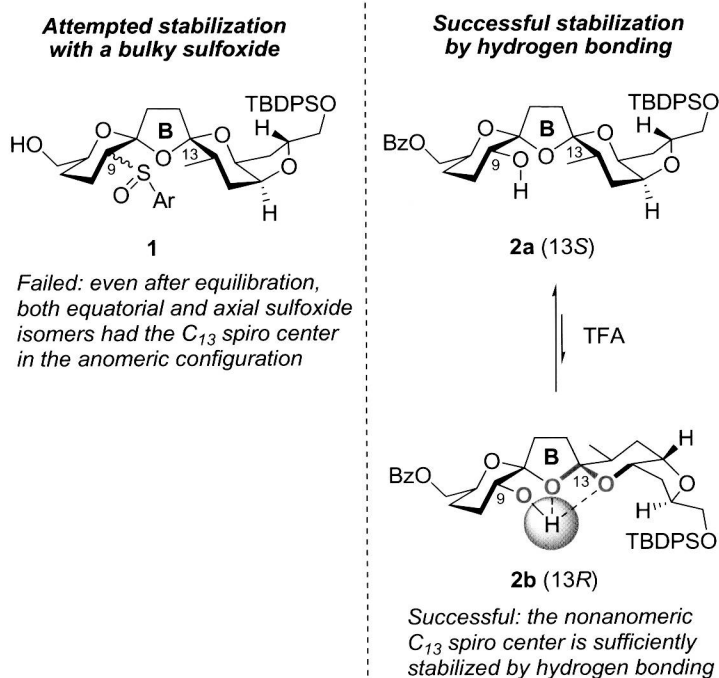
1.2

Hydrogen Bonding in Organic Synthesis

Hydrogen bonds can be used in two different ways to assist in organic synthesis. First, hydrogen bonds could be used to stabilize desired structures or intermediates. This is a *thermodynamic* method of using hydrogen bonds as an assisting force in organic synthesis. As an example, Nicolaou and co-workers used an intramolecular hydrogen bond that can be used to stabilize an otherwise unattainable thermodynamically unstable nonanomeric spiroketal structure (Scheme 1.1) [19]. These methods have been used extensively in total synthesis, and they will be reviewed in Chapter 7 by Shoji and Hayashi.

A second method to utilize hydrogen bonding in organic synthesis is to use hydrogen bonds as an assisting force in catalysis. The catalysts affect reaction rates, and therefore this is a *kinetic* way of using hydrogen bonding.

In order to accelerate reactions, a catalyst should bind the transition states more strongly than starting materials. This means that typically hydrogen bonding in catalysis functions best if partial or full negative charges are generated in the substrate during the reaction. For example, addition of nucleophiles to carbonyl groups generates negatively charged tetrahedral intermediates with a charge



Scheme 1.1 Using hydrogen bonding as a thermodynamic force to stabilize an otherwise unattainable structure.

largely residing on the oxygen atom. Such intermediates (and transition states leading to them) can be stabilized by hydrogen bonding [20]. These strategies are used by numerous enzymes and also by small-molecule catalysts and their importance in organic synthesis lies in the mildness of the conditions as well as the immense potential for selective catalysis.

These catalysts, their structures, modes of action, and uses, are discussed in the rest of the book. Both synthetic small-molecule catalysts as well as some of Nature's finest enzymes are discussed and the role of hydrogen bonding in catalysis is described in detail.

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