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 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,

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1) The enthalpy of dilution of sulfuric acid is ca. 880 kJ/mol at infinite dilution (N. N. Greenwood and A. Earnshaw (1984) *Chemistry of the Elements*. Pergamon Press, Oxford, p. 837). This value 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.

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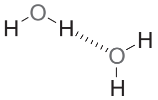
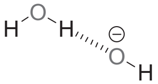
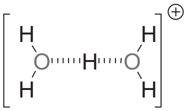
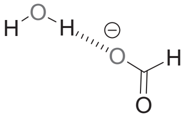
Table 1.1 Calculated and experimental hydrogen bond strengths.

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).
$H_2OH^{+}\cdots 3OH_2$ (first solvation shell for H_3O^{+})	−290.22 [11]	−287.7 [12]	N/A	Eigen cation MP2
$H^{+}(H_2O)_n$	−1150.1 [13]			Commentary on values [14]
	−71.4 [15]		1.67	MP2/6–31++G** −76.0 kJ/mol for bidentate binding
$CH_3NH_3^{+}\cdots OH_2$	−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.

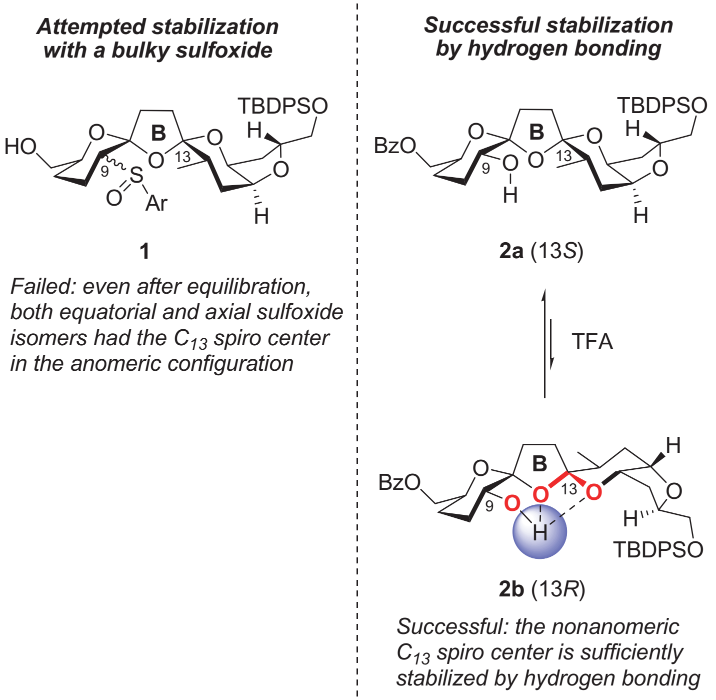
The strength of hydrogen bond is also strongly dependent on the solvent. In polar solvents, especially solvents capable of strong intermolecular hydrogen bonds such as water, hydrogen bonds between two nonwater molecules must be relatively strong in order to compete with hydrogen bonds provided by water. 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



Attempted stabilization with a bulky sulfoxide

1

Failed: even after equilibration, both equatorial and axial sulfoxide isomers had the C_{13} spiro center in the anomeric configuration

Successful stabilization by hydrogen bonding

2a (13*S*)

2b (13*R*)

Successful: the nonanomeric C_{13} spiro center is sufficiently stabilized by hydrogen bonding

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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