Educación Química

H-Bridges with OH Donors in Organic Chemistry

Donadores de Puentes de Hidrógeno con Grupos OH en Química Orgánica

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Resumen

Este artículo discute la formación de puentes de hidrógeno entre grupos funcionales con diversos grupos aceptores y OH donadores. Se presenta una serie de mallas circulares como ayuda visual para la organización y comparación de la diversidad de puentes de hidrógeno en moléculas orgánicas, haciendo énfasis en la presencia de un grupo OH (de alcoholes o fenoles, primordialmente) como donador de puente de hidrógeno. Los puentes de hidrógeno son clasificados como "poco probable", "poco significativo" y "significativo", de acuerdo con la evidencia experimental o teórica; y analizados en términos de efectos electrónicos, estéricos, termodinámicos, situacionales o de los sustituyentes. Nuestro objetivo es que el estudiante sea capaz de predecir y clasificar la probabilidad de interacción por puente de hidrógeno entre compuestos orgánicos comunes y comprender su efecto en sistemas más complejos.

Palabras clave

Pre-grado, Química orgánica, Puentes de Hidrógeno, Grupos donadores O-H, Conceptos erróneos.

Abstract

This article discusses the H-bridge formation amongst functional groups containing different H-bridge acceptors with OH donors. A series of circular grids is introduced as a visual aid for the organization and the comparison of the diversity of H-bridges present in organic molecules, emphasizing in the case where the H-bridge donor is an OH group (primarily alcohols and phenols). The H-bridges are classified as "unlikely", "less significant" and "significant" based on experimental and/or theoretical evidence, and analyzed in terms of electronic, steric, thermodynamic, substitutional, or situational effects. Using these grids, students can predict and classify the likeliness of an H-bridge interaction between common organic molecules and understand their effects in more complex systems.

Keywords

Undergraduate, Organic chemistry, Hydrogen bonds, H-bridges, O-H donor groups, Misconceptions.

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Introduction

In a previous paper, we described the important interactions in general chemistry between hydrogen-bridged (or hydrogen-bonded) acceptors (HBA) and hydrogen-bridged donors (HBD) using chemical symbols to represent the interactions (Lamoureux *et al.*, 2021). This introductory paper provided a visual organization to the many H-bridges in general chemistry, and the reasons behind the use of the phrase "H-bridge". To continue with the theme of H-bridges in organic chemistry, we present new schemes to organize the topic.

One of the greatest oversimplifications in chemistry is to assume that once students learn H-bridges in general chemistry, this knowledge will prepare them for organic chemistry. The overwhelming diversity of H-bridges in organic chemistry must be re-examined from a different viewpoint because of the complexity of the subject; the present approach causes many misconceptions to students, some of which are listed in Table 1, taken from the literature (Henderleiter *et al.*, 2001),(Schmidt *et al.*, 2009),(Underwood *et al.*, 2021).

TABLE 1. Common misconceptions about H-bridges in organic chemistry.

Misconception	Example of Error
H-bridges form to any H, regardless of if directly attached to X	$HOCH_3\bullet\bullet\bullet O$
H-bridges only form with oxygen, nitrogen, fluorine as HBA	Only $XH\bullet\bullet\bullet O$, N, F
H-bridges are the covalent bonds between H and X	RO–H *is* the H-bridge
H-bridges form with H+ (the covalent bond ionizes first in water)	$RO^- H^+\bullet\bullet\bullet OH_2$
Boiling breaks covalent bonds, including H-bridges as covalent	ROH(l) $RO^- H^+$ (g)
H-bridges only between two identical molecules	ROH no bridge con H_2O

We list below eight differences between H-bridges in introductory chemistry and organic chemistry that should be emphasized to every instructor and student during this transition. We then show how circular grids can be used to present Lewis's representations of the most common H-bridged systems in organic chemistry. Grids containing examples of intramolecular H-bridges are then shown and compared to the intermolecular cases. Practical use of these grids to predict physical properties of organic molecules is then presented.

Eight differences between H-bridges in General Chemistry and Organic Chemistry

Difference #1: Many more HBD sites (functional group differences)

Consider, for example, the O-H HBD-system. If we focus on only this system (Figure 1), there exists functional groups of alcohols (ROH), organosilanols (R_3SiOH), phenols (ArOH), organoperoxides (ROOH), carboxylic acids (RCO_2H), carboperoxy acids (RCO_3H), organosulfenic acids (RSOH), organosulfinic acids (RSO_2H), organosulfonic acids (RSO_3H), organophosphinic acid (R_2PO_2H), organophosphoric acids (RPO_3H_2), organoborinic acids (R_2BOH), organoboronic acids ($RB(OH)_2$) organohydroxylamines (R_2NOH), hydroxamic acids (R'CONROH), oximes ($R_2C{=}NOH$) and perhaps even further, more exotic, species. Further sub-divisions might be made based on the identity of R (*e.g.* aldoxime versus ketoxime) or substitution (*e.g.* primary, secondary, or tertiary alcohols). Other possible protonated oxygen functional groups (such as protonated carbonyls or protonated amine oxides) might be considered in acidic conditions. Naturally all these possible functional groups are strictly not equal; one must take into consideration the difference in structure (*e.g.* phenols are not alcohols) and properties (*e.g.* p*K*a) among functional groups.

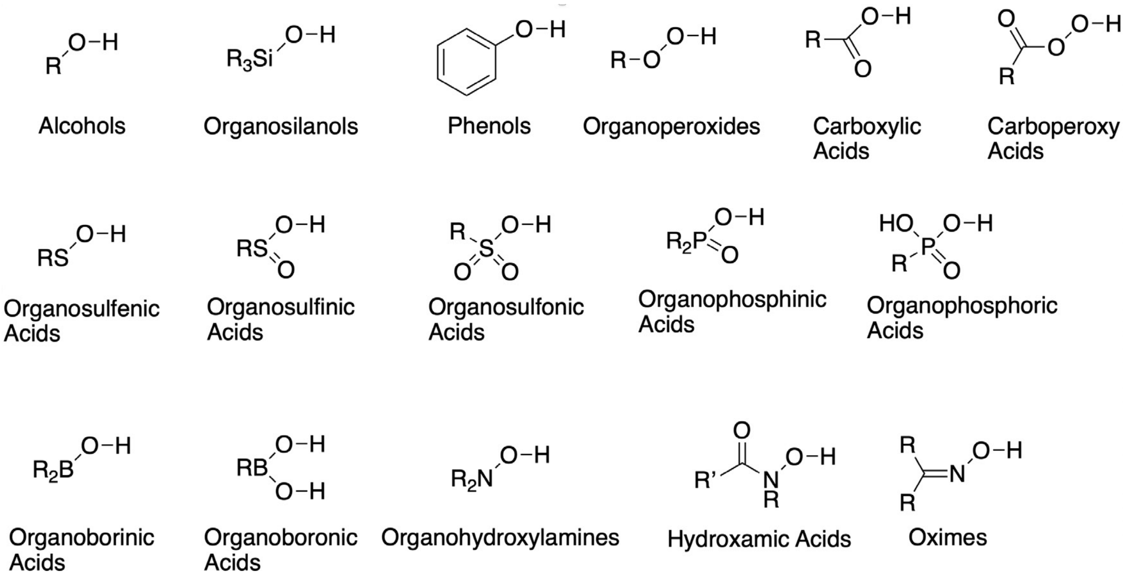


FIGURE 1. Possible O-H Hydrogen-Bridge Donors in Organic Chemistry.

Besides O-H HBD, other functional groups with C-H, N-H, S-H and P-H HBD might be analyzed in advanced courses. For introductory organic courses, the possible permutations between O-H HBD and HBA (including inorganic HBA such as water) is almost innumerable. In this article, for the sake of simplification, we take the tactic to subsume all the above O-H HBD functional groups into one system, with the caveat that there are exceptions in every system (*vide infra*). We will use alcohol and phenol O-H as HBD in specific examples, as these are the most common H-bridged systems in introductory organic chemistry.

Difference #2: Choice of HBD elements

As we indicated in a previous article, most general chemistry H-bridges can be reduced to a few HBD. Water (O-H) and ammonia (N-H) are particularly popular. The complexity for H-bridges in organic chemistry grows exponentially when one considers that the possible HBD sites present a huge variety in organic and bioorganic chemistry. Organic chemistry includes the possibilities for C-H, S-H, and P-H because organic chemistry is concerned with a wide variety of organic compounds in organic solvents.

Difference #3: Many more HBA sites for each HBD

For most of general chemistry, only a few archetypical examples of HBA and HBD systems are necessary. Nitrogen examples of HBA in introductory chemistry can be limited to ammonia. Water is the most common system presented for oxygen as HBA. This simplicity grows in complexity when a student enters organic chemistry. "Consider the atomic HBA sites (mainly O and N, but also Cπ, S, F, and even P, As, Cl, Br, I, Se, Te) multiplied by the number of organic functional groups and their possible substituents. For example, nitrogen bases may correspond to nitriles, amines, imines, amidines, pyridines, etc." (Laurence *et al.*, 2009).

Difference #4: Less dependence of significance of H-bridges on p*K*a of HBD and basicity of HBA

Restriction to simple molecules such as water or ammonia allows students to relate the significance of H-bridges to p*K*a values in general chemistry. For example, we predict from values of p*K*a that the H-bridge between O-H•••NH is more significant than N-H•••OH in comparing adduct possibilities of ammonia in water. When organic molecules are considered, however, this relationship is greatly complicated by other factors such as delocalization, functional group interactions, steric effects, and substituent effects.

> While this depiction [use of p*K*a] is useful for providing general guidance, substituent effects can be quite pronounced and alter these relative orderings… Steric effects are also important for hydrogen-bonding atoms within a ring. Substitution or annulation adjacent to the HBA site can reduce the hydrogen-bond basicity. However, these steric effects are often counterbalanced by favorable electronic contributions and can be difficult to predict. (Laurence *et al.*, 2009).

There are several oxygen functional groups that have significant HBA ability, but are poor Brønsted bases: sulfoxides, ureas, and phosphonamides. Common organic solvents (Figure 2) such as DMSO, DMPU, and HMPA, respectively, are examples in this anomalous grouping (Laurence *et al.*, 2021). On the other side of the coin, organic molecules that are weak HBA, but strong Brønsted bases exist: an interesting example is Proton Sponge (Figure 2) (Zheng *et al.*, 2017).

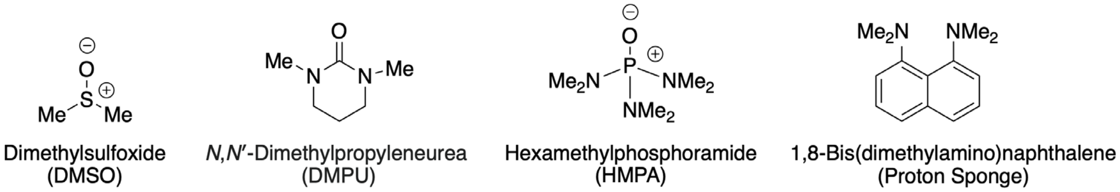


Figure 2. Specific molecules with anomalous acid/base behavior.

Difference #5: Interactions with organic solvents, not only water, is important

The purpose of presenting and organizing H-bridges in chemistry is to use these non-covalent forces to predict properties. In a previous article, we presented how simple representations of H-bridges allow students to predict the relative solubility of small inorganic molecules in water. Whereas this prediction is reasonable in general chemistry, in organic chemistry prediction is complicated by a panoply of other non-covalent forces. Moreover, the interest of organic chemists might not be the solubility of these organic molecules in water but rather in other organic solvents. The prediction of solubility of organic solutes in organic systems is an order of magnitude more difficult than aqueous solubility.

Difference #6: Acid-base chemistry is separate from H-bridges

In the previous paper in this series, we pointed out the cases where a complete proton transfer was thermodynamically preferred to an H-bridge in simple inorganic molecules. For example, it is important to reveal the thermodynamic product between HF and NH_3 is not the H-bridged structure, but rather the proton transfer species, $^+NH_4\ F^-$. In organic chemistry, the determination of H-bridges is usually considered separate from acid/base chemistry. There are a few cases of overlap (do carboxylic acids form H-bridges with amines or is there a complete proton transfer? It depends! (Heller & Silverstein, 2020)) but most students compartmentalize reactivity from non-covalent interactions (Joesten, 1982).

Difference #7: Intermolecular are as common as intramolecular H-bridges

Perhaps the greatest intellectual leap between general and organic chemistry is the realization that the HBA and the HBD might be connected by a bridge in the same organic molecule. Thus, the adduct between the two parts of the H-bridge is intramolecular. These intramolecular adducts are related to the strain revealed in cyclic hydrocarbons; just as cyclopentane, cyclohexane and cycloheptane are the most stable cyclic alkanes, below in this article we provide examples of stable 5-, 6-, and 7-membered H-bridge adducts. As we will show, these intramolecular H-bridges might differ in significance from intermolecular H-bridges depending on the situation.

Difference #8: Linear dependence of H-bridges is less important.

For X–H•••Y, one expects that the optimal angle among X, H, and Y of 180°. For small non-organic molecules, the criteria for determining the presence or absence of an H-bridge depends on this angle. "Directionality rather than energy is the discriminative attribute for a hydrogen bond." (Arunan *et al.*, 2011). In many organic systems, especially larger systems, or intramolecular systems, due to constraints of steric or electronic effects, this angle X–H•••Y often varies from 180°.

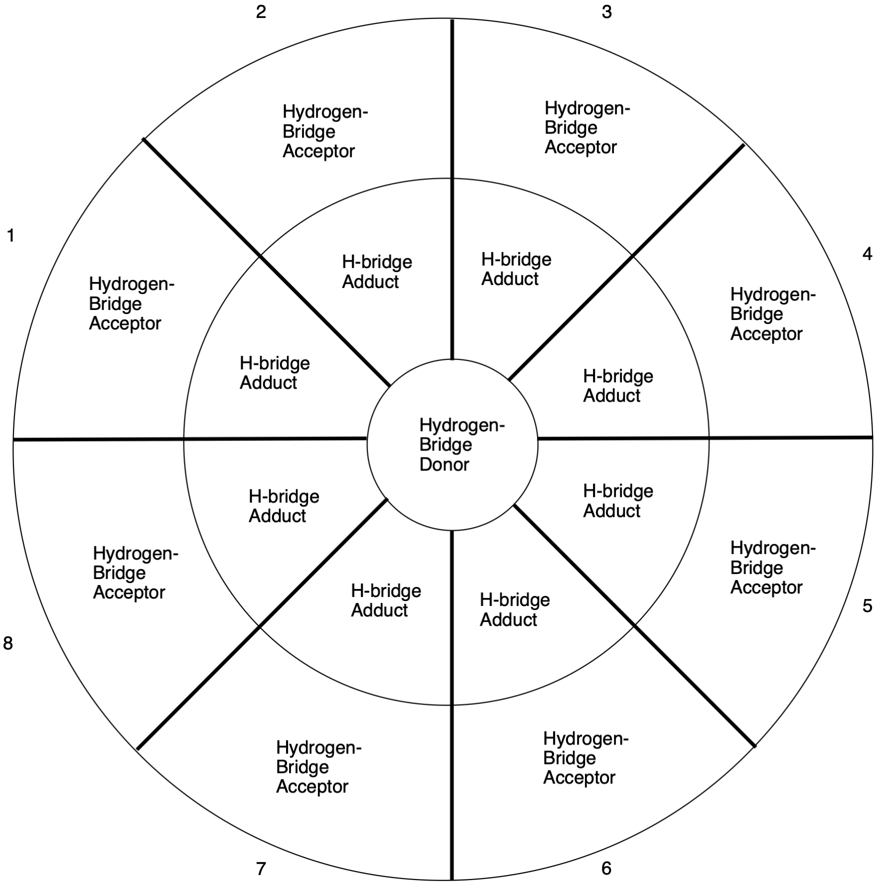


FIGURE 3. Grid based on eight HBA forming adducts with one HBD.

Putting it all Together: Grids to organize H-bridges for O-H HBD in Organic Chemistry

Figure 3 shows how one might organize the one-to-many relations between a general HBD and many HBA. The HBD is situated in the center of the circle, with the HBAs on the periphery. Up to eight adducts might be represented in the intermediate circle octants. We will separate each grid into interactions based on the significance of the H-bridge, beginning with the least significant.

Examples of hydrogen bridging with O-H HBD

We introduce the complicated world of organic H-bridges with the O-H HBD-system, which are ubiquitous and usually an archetypical example of a potent HBD. We indicated (Figure 1) there are at least 16 functional groups that use the O-H HBD-system to form H-bridges;

O-H represents the surrogate of all these functional groups. The important focus in this grid is to place O-H group in the center of the grid, which can form H-bridges with a large variety of HBA to form adducts, O–H•••Y–Z so that students can see clear examples using Lewis structures. How can students begin to understand and communicate about H-bridges, when they have never seen visual examples, only textual descriptions? "Conceiving interaction between particles is one of the most difficult aspects for students…only a few students were able to produce accurate pictures and descriptions of hydrogen bonds" (Schmidt *et al.*, 2009).

As a prelude, it is important to show that not all HBA functional groups form an adduct with O-H HBD. It should go without saying, yet important to state explicitly, that the sigma bonds in alkanes (unstrained hydrocarbon C-H or C-C) are not significant HBA and do not form an H-bridge with O-H, except in advanced theoretical studies (Olesen & Hammerum, 2009). A practical use of this knowledge is solubility; methanol is immiscible with most liquid alkanes, yet higher alcohols become miscible in hydrocarbon solvents as the H-bridge contribution diminishes relative to the London forces.

FIGURE 4. Grid showing unlikely H-bridges between O-H HBD and eight different HBA.

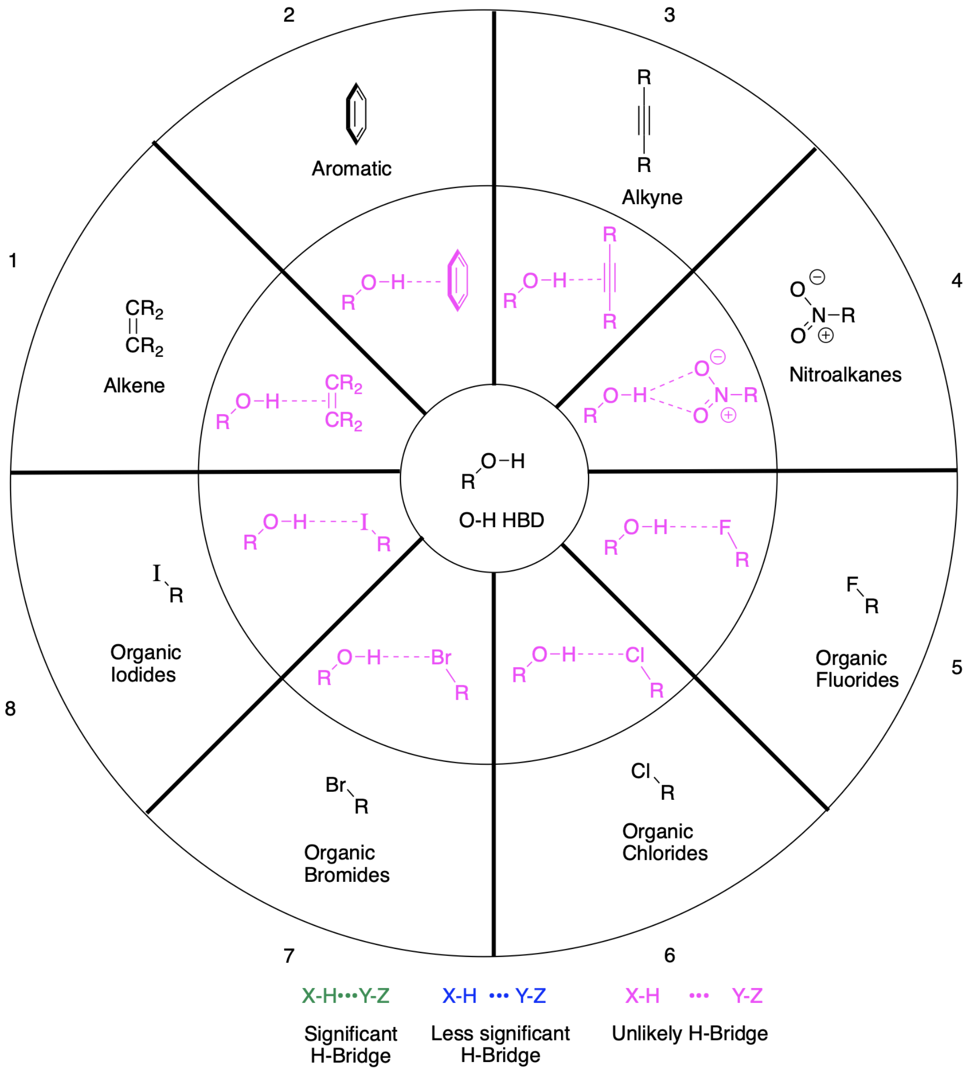


Figure 4 represents examples of very low significance or unlikely H-bridges. In choosing this category, we recognize various scenarios to determine the likelihood: **1) Experimental:** there might exist no technology today sufficiently sensitive to measure these interactions, or these interactions have yet to be experimentally confirmed. **2) Quantum-chemical:** the latest computer models show low energies of interaction. **3) Competition:** H-bridges that might exist but be overwhelmed by alternate non-covalent interactions. **4) Substitutional:** H-bridges that might not be present except where certain substituents are present. **5) Situational:** interactions that might exist under certain conditions yet be unlikely in others. This latter case will be highlighted with the discussion of intramolecular versus intermolecular H-bridges.

Some hydrocarbons, such as alkenes (octant #1), aromatics (octant #2) and alkynes (octant #3), have *pi* systems that can interact, although minimally, with O-H HBD. We represent the H-bridge with a dashed line between the O-H and the center of the *pi* system, either above or below the plane. The significance of the interaction depends on the steric and electronic effects of the HBA and HBD, a clear case of substitutional significance. More acidic HBD (*e.g.* carboxylic acids, sulfonic acids) would be expected to form a stronger H-bridge than less acidic groups. Substitution connected to the *pi* system in all three HBA shown in Figure 4 with electron-donating groups (*e.g.* -OR, -NR$_2$) provides a better acceptor, whereas electron-withdrawing groups (*e.g.* -NO$_2$, carbonyl) inhibit the formation of H-bridges (Lamoureux & Arias-Álvarez, 2020).

Students are accustomed to assign non-bonded electrons as reasonable HBA, however even functional groups with non-bonded electrons can be hard-pressed to find attraction to the HBD properties of O-H. Octant #4 in Figure 4 provides an interesting example of a visually possible but unlikely H-bridge because oxygen non-bonded electrons in the nitro functional groups are resistant to donation in most cases. In nitroalkanes, the delocalization of charge, and the strong electronegativity of the group, inhibits electron donation. It is well known that nitro-containing solvents, such as nitromethane, have poor H-bridge acceptor characteristics (Kleeberg et al., 1990).

The organic halides (octants #5, 6, 7 and 8) are also poor H-bridge acceptors (in free solution, without any constraining or competing factors). In contrast to what is often taught in general chemistry, organic F is not automatically assumed to be a good HBA. In fact, Dunitz in a review of O-H•••F-C H-bridges writes: "It seems clear that with its low polarizability and tightly contracted lone pairs, fluorine is unable to compete with stronger hydrogen-bond acceptors such as oxygen or nitrogen." (Dunitz, 2004). The title of a more recent article is more direct: "The Hydrogen Bond Between N—H or O—H and Organic Fluorine: Favourable Yes, Competitive No" (Taylor, 2017). In contrast, another review claims "it is now difficult to doubt the existence of hydrogen bonds involving organic fluorine." (Champagne *et al.*, 2015). We consider that these types of interactions are situational: to avoid confusion, let us consider that the intermolecular cases are unlikely and re-examine the case under intramolecular conditions (*vide infra*). While possible, O-H•••F-C H-bridges are only experimentally observed in extremely rare cases. From a pedagogical perspective it is therefore appropriate to include this interaction among the unlikely categories.

The general trend of the alkyl halogens as HBA is F > Cl ~ Br ~ I (Ouvrard *et al.*, 1999). If O-H•••F-C H-bridges are deemed unlikely, the O-H•••X-C H-bridges for alternative X are more so. The R group affects the HBA ability of the halogen; inductive, delocalization, and substituent effects all play a role. When the halo group is conjugated to a *pi* system, as in aryl halides Ar-X, vinyl halides C=C-X, or C≡C-X, not only are the halogen electrons reduced in donor power by delocalization, the *pi* system might compete with the halogen site as an HBA (Yang *et al.*, 2020).

In Figure 5 below, eight examples of possible, yet less significant, H-bridges are illustrated. An obvious pairing for O-H HBD might be expected to be an alcohol HBA to form the adduct O-H•••O-H (octant #1), as is found in water dimers. This adduct formation with alcohols is of less significance than the adduct formation in water for two reasons. First, steric considerations suggest that the alcohol HBD and any HBA often cannot approach each other within an optimal distance to form H-bridges. Second, the exactly linear orientation of O-H•••Y (maximum interaction) is harder to obtain when the R group in O-H and the Y group are sterically large. These arguments can also be used for ethers (octant #2) as HBA with O-H HBD. Alcohols and ethers can form H-bridges with each other, however, do not expect the same high significance of attraction that is seen when water is the HBA or HBD.

In the case of nitriles (octant #3), the nitrogen electrons are weakly attracted to an O-H hydrogen. This reluctance of interaction is usually ascribed to the electronegativity of the nitrogen in nitriles (Le Questel *et al.*, 2000).

Octant #4 and #5, showing the interaction between an O-H donor and a sulfone or sulfonamide acceptor, can also be considered as weak, yet interesting H-bridges, with a significance like alcohols, ethers, or carbonyls (Laurence *et al.*, 2009). We have illustrated the interaction as a dashed bond between the two S=O groups, a bidentate H-bridge, based on preliminary evidence (Oznobikhina *et al.*, 2009).

Some carbonyls as HBA are illustrated in octants #6-8 in Figure 5. We have grouped all these HBA in Figure 5 as approximately equal because it is difficult to form a hierarchical order. "It is common dogma to consider aliphatic ethers and alcohols as weaker hydrogen-bond acceptors than ketones or the carbonyl oxygen of esters. However, experimental measurements are consistent with these groups being equivalent." (Laurence *et al.*, 2009). Furthermore, esters (octant #7) are generally considered weaker hydrogen-bond acceptors than the analogous ketones (octant #6). Aldehydes (RCOH) should be considered like ketones (RCOR). Carbon dioxide (octant #8) is included due to the importance of supercritical CO_2 as a 'green' solvent. It has been proposed that the reasonable solubility of CO_2 in water and alcohols is due to the H-bridges formed (Raveendran *et al.*, 2005), as illustrated in octant #8.

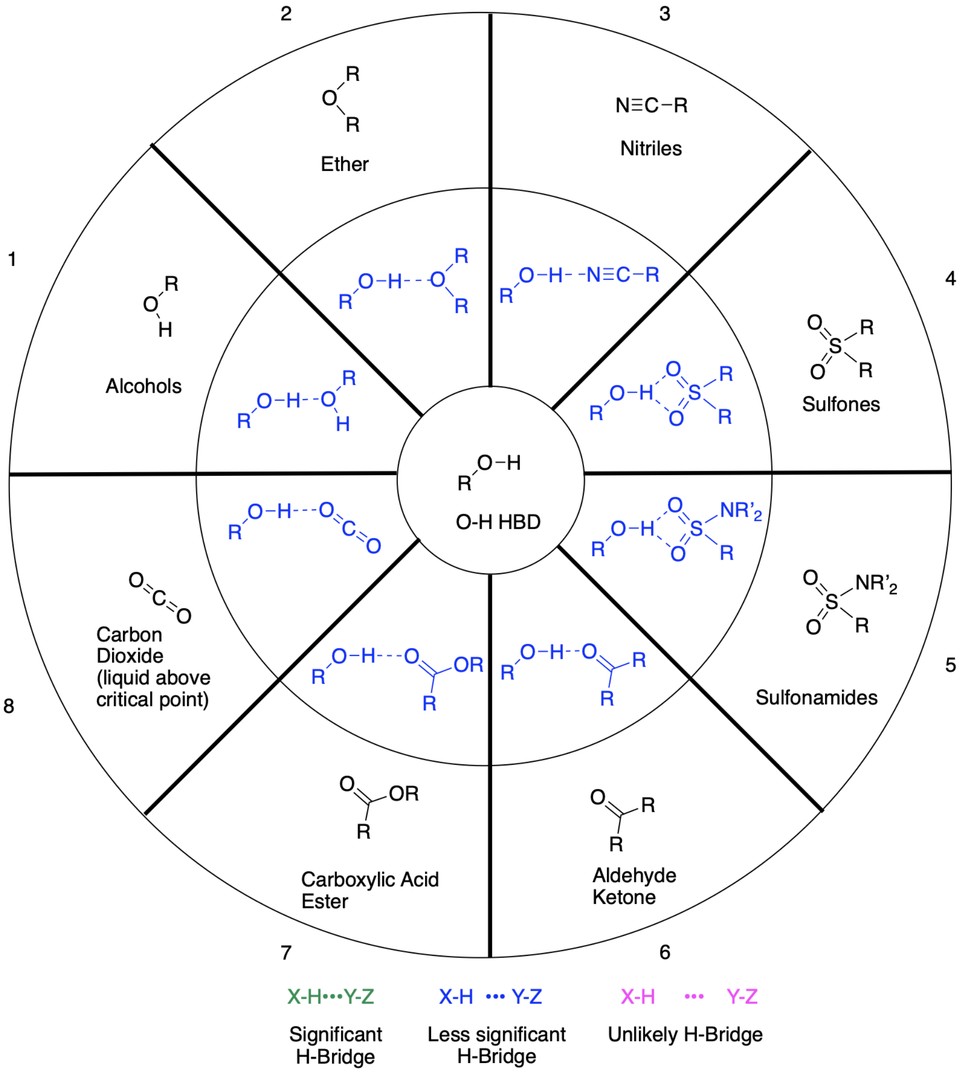


FIGURE 5. Grid showing less significant H-bridges between O-H HBD and 8 different HBA.

In contrast to the carbonyl groups in Figure 5, Figure 6 shows that the carbonyls in amides and ureas (octants #1 and #2) form significant and important H-bridges with O-H donors. To a chemist skilled in the arts of H-bridges, this difference among carbonyl groups is unmistakable, even if the structures appear similar. The presence of an amide group in peptides that can form H-bridges is important to understand the stabilization of protein secondary structures.

Amines in their various forms (octants #3-5) are also important HBA. Common examples such as triethylamine (octant #3), pyridine (octant #4) and imidazole (octant #5) are potent HBA. Note, however, that some amines such as pyrrole and indole are very weak HBA due to the nitrogen electrons being tied up in aromaticity.

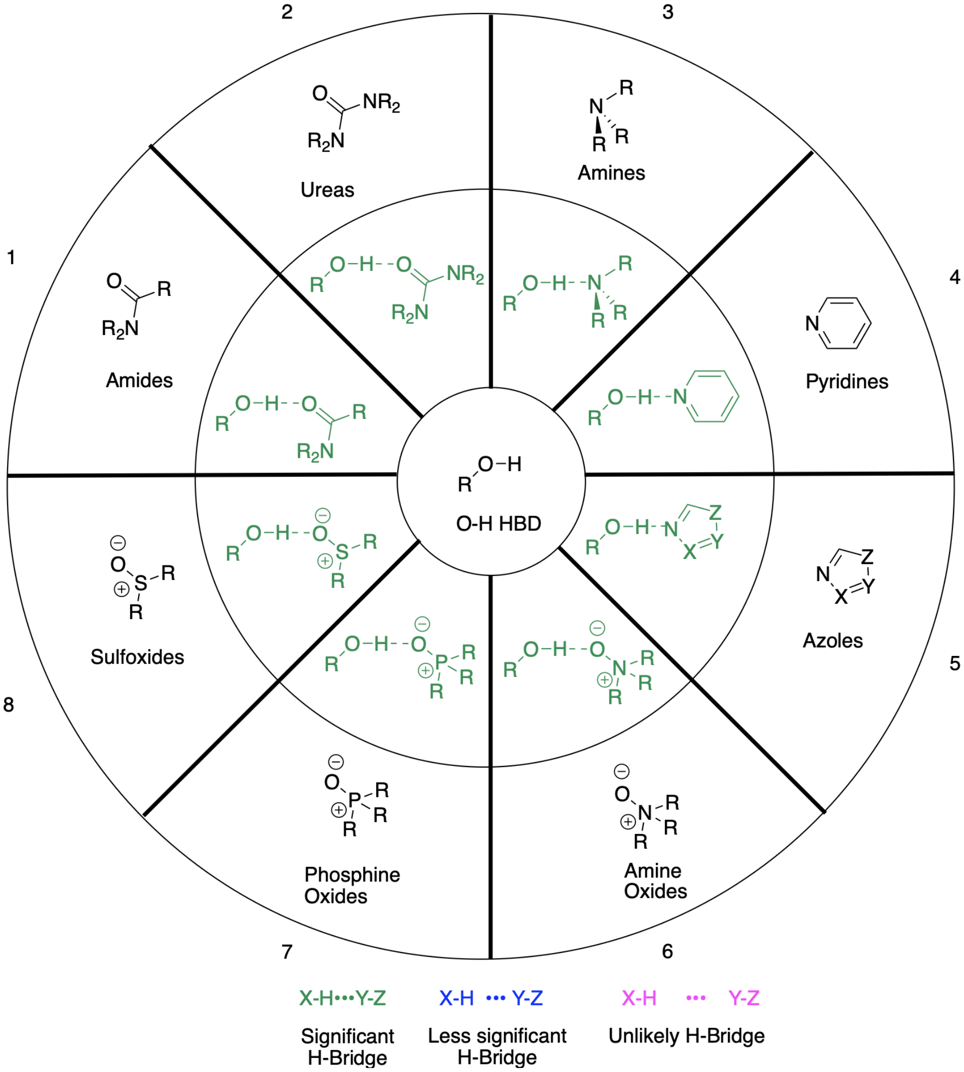


FIGURE 6. Grid showing significant H-bridges between O-H HBD and 8 different HBA.

The final group to be classified as significant HBA are shown in Figure 6 as the oxides (octants #6-8). Amine oxides (such as trimethylamine N-oxide) and phosphine oxides (such as triphenylphosphine oxide) form strong H-bridges with alcohols. The ability of triphenylphosphine oxide to create crystalline, strongly bonded H-bridged complexes with organic molecules has been utilized as a crystallization technique (Etter & Baures, 1988). Sulfoxides such as dimethylsulfoxide (DMSO) are excellent solvents for a wide variety of organic molecules. "The solubilizing properties of DMSO are well-known, and it is common to dissolve organic compounds with poor aqueous solubility in a DMSO solution prior to dilution in an aqueous buffer for biological screening. Undoubtedly the strong hydrogen-bonding ability of the sulfoxide contributes to these unique properties." (Laurence *et al.*, 2009).

Examples of intramolecular H-bridges

One of R.B. Woodward's famous expressions is "We all know that enforced propinquity often leads on to greater intimacy." (Seeman, 2017). This axiom is especially true for H-bridges. In those cases where the HBD and the HBA are linked by a tether, the interaction between the two groups might lead to greater intimacy, depending on the circumstances. The importance to continue illustrating examples of intramolecular H-bridged systems to students in organic chemistry can be emphasized by examples from multi-functional molecules, bioorganic molecules, and medicinal chemistry (Kuhn *et al.*, 2010),(Caron *et al.*, 2019).

Let us re-examine the unlikely H-bridges shown in Figure 4 within the context of intramolecular interactions (Figure 7-the tether shown by the curved line covalently links the HBD and HBA).

The intramolecular H-bridge is often more significant than the intermolecular variety (compare Figure 4 with Figure 7). This preference might be due to enthalpic or entropic considerations (Nagy, 2014). A medium ring, for example, might align the HBD and HBA within an optimized distance and angle; counting the hydrogen as one of the ring members, 5-7 membered rings are commonly observed, yet for less significant H-bridges almost all well-known examples are 6-membered rings. A rigid aromatic spacer removes rotational degrees of freedom. Thus, phenolic compounds with substituents in the *ortho*-position (Jezierska *et al.*, 2019) often illustrate a propensity for O-H•••Y-Z interactions (Figure 8).

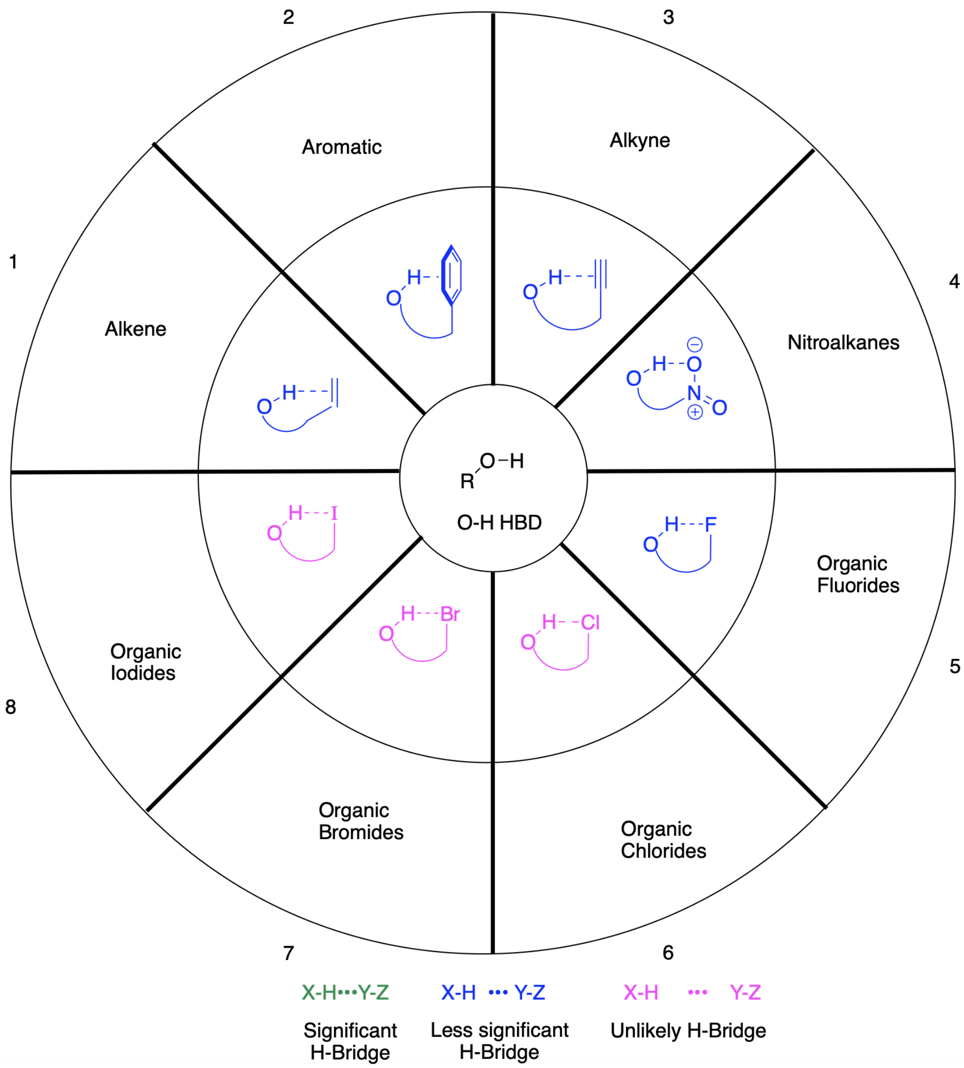


FIGURE 7. Grid showing 8 intramolecular H-bridges between O-H HBD and HBA in the same molecule.

Intramolecular H-bridges in aliphatic (Miller *et al.*, 2011) and aromatic (Berdyshev *et al.*, 2009) alkenols and alkynols are well characterized (octants #1 and #3 in Figure 7). Specifically, but-3-en-1-ol (Figure 8) has evidence of an intramolecular H-bridge (Mackeprang *et al.*, 2013). The significance of these H-bridges is situational - one of the tightest H-bridges is between a secondary O-H and alkene, forced into an optimized distance and angle by a rigid system (Struble *et al.*, 2015). The phenyl group as HBA (octant #2 in Figure 7) can be considered like an alkene, depending on the aryl substituents. 2-Phenylethan-1-ol (Figure 8) contains intramolecular H-bridge, with experimental evidence (Mons *et al.*, 2000). Further evidence of an aryl *pi* system as HBA was given in a "molecular torsion balance" (Motherwell *et al.*, 2007). Note that these systems are often overlooked by introductory students who might consider a *pi* system an unreasonable HBA, which would be an acceptable viewpoint if the circumstances (intramolecular ring size ~6, short distance between O-H and HBA, low strain) did not conspire to provide a fortuitous opportunity to interact.

We classified previously the nitro group as an unlikely HBA (octant #4 in Figure 4). When properly aligned in an intramolecular ring, however, nitro can become a possible bridging group. 2-Nitroethan-1-ol (Figure 8) is a prime example of an experimentally determined intramolecular H-bridge (Marstokk & Mollendal, 1996). *o*-Nitrophenol (Figure 8) is a special case and should be considered a significant H-bridged system (*vide infra*). Also, the intramolecular H-bridge in *o*-nitrophenol has been shown to depend on the HBA strength of the solvent (Kamlet & Taft, 1982). A strong HBA solvent will compete intermolecularly with the *o*-nitro group for the phenolic OH HBD.

The presence or absence of organic halogen as an HBA (octants #5-8 in Figure 7) is fraught with controversy. The O-H•••I-C, O-H•••Br-C and O-H•••Cl-C intramolecular

H-bridges have been proposed for o-iodo/o-bromo/o-chlorophenol and 2-iodo/2-bromo/2-chloroethan-1-ol, respectively (Kovács & Varga, 2006). These systems are very tenuous and not without controversy; the phenolic systems seem to provide more significant H-bridges than the aliphatic systems (Kovács & Varga, 2006). Intramolecular O-H•••Br-C H-bridges have also been proposed in the case of *trans*-2-bromocyclohexan-1-ol conformers (Duarte & Freitas, 2009) but not the 2-bromocyclopentan-1-ol conformers (Tormena *et al.*, 2007). For O-H•••Cl-C interactions, a crystallographic database search finds that intramolecular cases are more common than intermolecular, but the bridges are infrequent and weak. "Hydrogen bridges of the type O-H•••Cl-C occur very rarely, and even when they do, they are generally in an intramolecular situation in which the donor group is sterically hindered so that the formation of intermolecular interactions is difficult." (Banerjee *et al.*, 2004). We must assign these interactions as not significant (octants #6-#8 in Figure 7) as the evidence is not persuasive to convince students of their existence except in rare cases.

Intramolecular H-bridges with fluorine are more validated (octant #5 in Figure 7); these interactions can be identified by IR and NMR spectroscopy in solution or X-ray crystallography in the solid phase (Schneider, 2012). After many years of confusion, substantial evidence that there exists an H-bridge between O-H and F in o-fluorophenol has been published (Zeoly *et al.*, 2019),(Rosenberg *et al.*, 2020). Another recent system where H-bridges are identified is o-fluoromethylphenol (Figure 8) (Bogdan *et al.*, 2016). The presence of aliphatic cases (Figure 8) is confirmed for 3-fluoropropan-1-ol (Linclau *et al.*, 2015),(Cormanich *et al.*, 2014). "3-fluoropropanol experiences a F/HO intramolecular hydrogen bond, but the conformation exhibiting such an interaction does not dominate the conformational equilibrium amongst 12 stable structures." (Martins & Freitas, 2020). It is still unclear if 2-fluoroethanol is a certain case of intramolecular H-bridges, with evidence both against (Martins & Freitas, 2019) and for (Rosenberg, 2019) being recently presented.

The research of organic halogens as HBA is continuing, and the significance of the H-bridged structures might change, so the presentation in Figure 7 is the best compromise at this time.

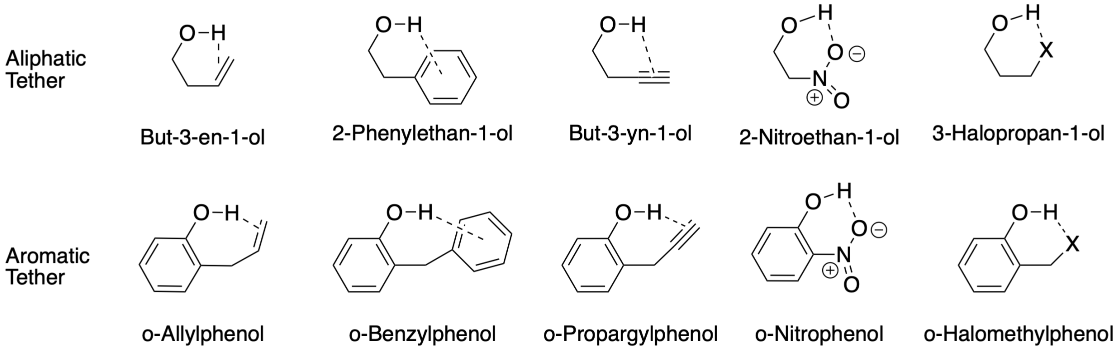


FIGURE 8. Specific examples of less significant intramolecular H-bridges in aliphatics (top row) and *ortho*-phenols (bottom row).

What happens when less significant intermolecular H-bridges are placed in an intramolecular framework? Please compare Figure 5 with Figure 9. In these intramolecular cases, the interactions are now significant. The case of nitriles (octant #3 in Figure 9) is removed because of the rigorous geometrical constraints required to form an intramolecular H-bridge (Le Questel *et al.*, 2000).

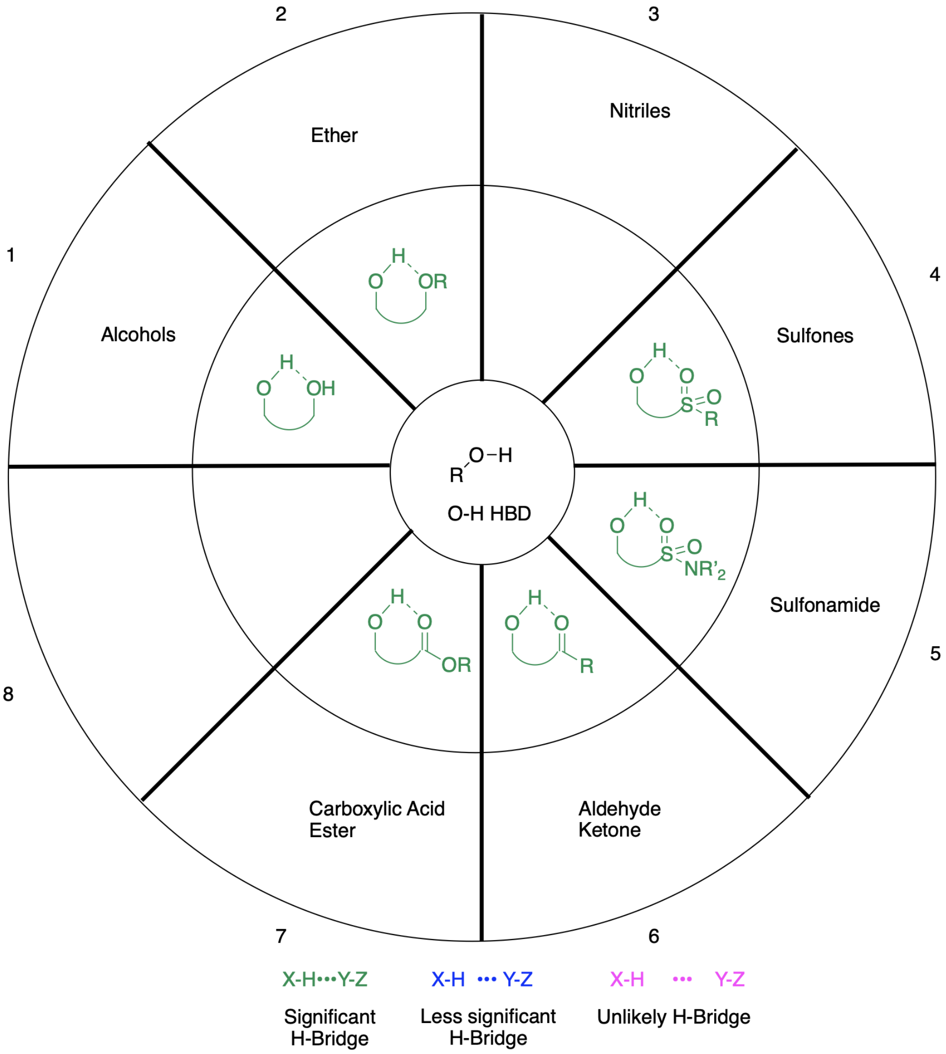


FIGURE 9. Grid showing 6 intramolecular H-bridges between O-H HBD and HBA in the same molecule.

The most common intramolecular H-bridges that should be emphasized in class are the structures shown in Figure 10 below. Both 5-membered and 6-membered rings are shown; the ring size can be varied (if possible) and still retain a significant interaction (*e.g.* formation of significant H-bridges in 1,3-propanediol - a 6-membered ring - and 1,2-dihydroxybenzene (catechol) - a 5-membered ring).

To complete the set, the significant intermolecular H-bridges shown in Figure 6 stay significant or might be improved in their intramolecular situations and need not be elaborated in another grid.

Special Cases

All the examples above show the interaction between one HBD and one HBA to simplify the visual picture. There is the possibility of cluster formation between many HBD and HBA, although in introductory courses the simplified interaction is the priority. In a few special cases, self-association between multiple HBD and HBA are important.

There is a tendency for carboxylic acids, both aliphatic and aromatic, to dimerize (Figure 11) when in the vapor state, in aprotic solvents or in the crystalline solid state (Gavezzotti, 2008). In solution, the dimer appears to be in equilibrium with the monomer, the ratio of the two species varying with concentration, temperature, and solvent. This tendency to form cyclic dimers is also present for phosphinic acids (Figure 11) (Khaikin *et al.*, 2003).

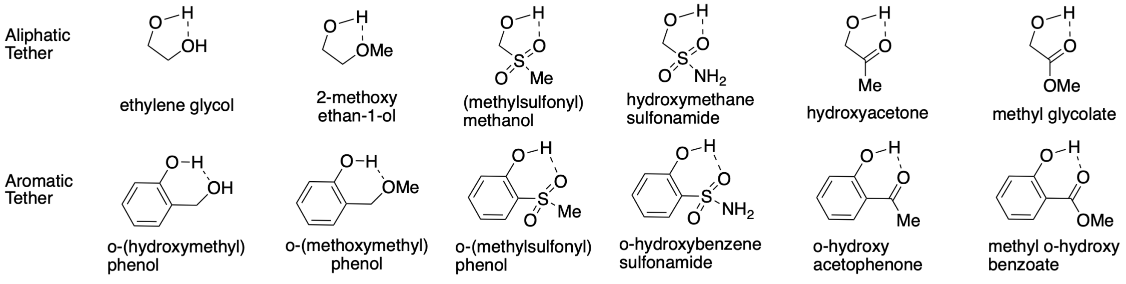
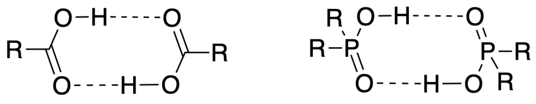


FIGURE 10. Specific examples of significant intramolecular H-bridges aliphatics (top row) and *ortho*-phenols (bottom row).



Carboxylic Acids

Phosphinic Acids

FIGURE 11. Special cases of dimeric cyclic H-bridges.

How to use grids of H-bridges to predict properties

H-bridges affect all physico-chemical properties. The presence, and significance, of an H-bridge has a large effect on the melting point (mp), boiling point (bp), solubility in water, chromatographic elution, and viscosity of many organic compounds. The presence of intermolecular H-bridges usually produces a higher mp, bp and viscosity, and generally increases aqueous solubility (non-ideal solution laws). Contrarily, the formation of intramolecular H-bridges usually produces a lower mp and bp, and generally decreases the solubility in water.

Although viscosity is a less common physical property in first-year chemistry, the importance of H-bridges that affect viscosity for organic compounds is well-known (Rajappan *et al.*, 2009). More intangible properties, such as crystallinity (Gardner & Tajvidi, 2016) or stickiness (Caldera Villalobos & Herrera González, 2019), can also be predicted in terms of the presence or absence of H-bridges.

The effect on physical properties by the presence or absence of H-bridges is most clearly seen among isomers. We provide examples below of how students can predict properties in constitutional (*i.e.* structural) isomers, regioisomers, and stereoisomers using knowledge of H-bridges.

The structural isomers of ethanol and dimethyl ether clearly show the effect of intermolecular H-bridges. Ethanol has a higher bp, mp, and solubility in water compared to dimethyl ether. Some H-bridges (combined with dipole-dipole and London forces, not shown) among several molecules of ethanol are illustrated symbolically in Figure 12, whereas dipole-dipole and London (not shown) interactions are the only forces available to dimethyl ether. Please remind students that while alcohols have both an HBD and HBA, ethers only have an HBA.

H-bridges in Ethanol

Dipole-Dipole interactions Dimethyl Ether

FIGURE 12. Comparison of representation of non-covalent forces in ethanol and in dimethyl ether

As a specific example of regioisomers, *ortho*-nitrophenol (Figure 8) has a lower mp (46 °C) and solubility in water (yet more soluble in organic solvents) than the *meta*- or *para*-nitrophenol isomers (Abraham *et al.*, 2000). Its intramolecular H-bridge allows it to be sublimed and hydrodistilled easily. Moreover, it has a lower retention on silica gel than the other regioisomers and so can be easily separated by TLC or column chromatography (Feigenbaum, 1986).

Among stereoisomers, enantiomers have the same physical properties but diastereomers might have properties that greatly differ. One pair of *E/Z* diastereomers (Figure 13) to illustrate the difference between intra- and intermolecular H-bridges are the molecules maleic acid ((2*Z*)-but-2-enedioic acid) and fumaric acid ((2*E*)-but-2-enedioic acid) (Nyasulu & Macklin, 2006). The presence of an intramolecular H-bridge in maleic acid is confirmed in its X-ray crystallographic structure (James & Williams, 1974), whereas fumaric acid is limited by its rigid geometry to intermolecular H-bridges. Fumaric has a higher mp and enthalpy of sublimation than maleic, as can be predicted by the intermolecular H-bridges increasing the interactions among fumaric molecules in the crystal form. The solubility in water cannot be predicted in these cases, however, possibly due to the significantly different values of p*K*a of these two acids.

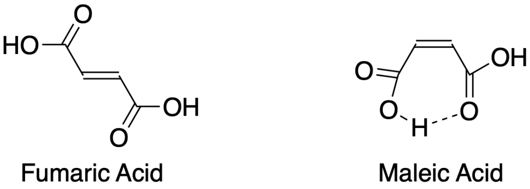


FIGURE 13. Structures of diacids fumaric (left) and maleic (right), with intramolecular H-bridge shown.

Conclusion

H-bridges in organic chemistry are complicated to learn and this article is a proposal to alleviate some of the difficulties. By presenting the interactions between O-H HBD and a series of HBA organized in 5 grids, the student can start along the path to knowledge. Especially important is the comparison between intermolecular and intramolecular cases (*i.e.* Figures 4 and 7, and Figures 5 and 9). Using the structures of specific organic compounds (*i.e.* Figures 8, 10, and 11) for practice reinforces the concepts. Isomers should be compared (Figures 12 and 13) to show how structure affects non-covalent forces. In terms of practical use, once the interactions are organized and relatively quantified, students can make predictions about the bulk properties of organic chemicals, and later apply them to the comprehension of more complex topics, for instance, biomolecular structure and interactions.

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References

Abraham, M. H., Du, C. M., & Platts, J. A. (2000). Lipophilicity of the Nitrophenols. *Journal of Organic Chemistry*, *65*(21), 7114-7118. https://doi.org/10.1021/jo000840w

Arunan, E., Desiraju, G. R., Klein, R. A., Sadlej, J., Scheiner, S., Alkorta, I., Clary, D. C., Crabtree, R. H., Dannenberg, J. J., Hobza, P., Kjaergaard, H. G., Legon, A. C., Mennucci, B., & Nesbitt, D. J. (2011). Definition of the Hydrogen Bond (IUPAC Recommendations 2011). *Pure and Applied Chemistry*, *83*(8), 1637-1641. https://doi.org/10.1351/PAC-REC-10-01-02.

Banerjee, R., Desiraju, G. R., Mondal, R., & Howard, J. A. K. (2004). Organic Chlorine as a Hydrogen-Bridge Acceptor: Evidence for the Existence of Intramolecular O-H•••Cl-C Interactions in Some gem-Alkynols. *Chemistry–A European Journal*, *10*(14), 3373-3383. https://doi.org/10.1002/chem.200400003.

Berdyshev, D. V., Glazunov, V. P., & Novikov, V. L. (2009). Conformational Analysis of o-Allylphenol by Density Functional and IR Spectroscopy Methods. *Journal of Applied Spectroscopy*, *76*(5), 630-640. https://doi.org/10.1007/s10812-009-9258-z.

Bogdan, E., Quarré de Verneuil, A., Besseau, F., Compain, G., Linclau, B., Le Questel, J.-Y., & Graton, J. (2016). alpha-Fluoro-o-cresols: The Key Role of Intramolecular Hydrogen Bonding in Conformational Preference and Hydrogen-bond Acidity. *ChemPhysChem*, *17*, 2702-2709. https://doi.org/10.1002/cphc.201600453.

Caldera Villalobos, M., & Herrera González, A. M. (2019). Polímeros Adhesivos y Formación de Uniones a Través de Reacciones de Polimerización y Fuerzas Intermoleculares. *Educación Química*, *30*(2), 2-13. https://doi.org/10.22201/fq.18708404e.2019.2.68197.

Caron, G., Kihlberg, J., & Ermondi, G. (2019). Intramolecular Hydrogen Bonding: An Opportunity for Improved Design in Medicinal Chemistry. *Medicinal Research Reviews*, *39*(5), 1707-1729. https://doi.org/10.1002/med.21562.

Champagne, P. A., Desroches, J., & Paquin, J.-F. (2015). Organic Fluorine as a Hydrogen-bond Acceptor: Recent Examples and Applications. *Synthesis*, *47*(03), 306-322. https://doi.org/10.1055/s-0034-1379537.

Cormanich, R. A., Rittner, R., Freitas, M. P., & Bühl, M. (2014). The Seeming Lack of CF... HO Intramolecular Hydrogen Bonds in Linear Aliphatic Fluoroalcohols in Solution. *Physical Chemistry Chemical Physics*, *16*(36), 19212-19217. https://doi.org/10.1039/C4CP02463J.

Duarte, C. J., & Freitas, M. P. (2009). Hydrogen Bonding and Stereoelectronic Effects in the Conformational Isomerism of trans-2-Bromocyclohexanol. *Journal of Molecular Structure*, *930*(1-3), 135-139. https://doi.org/10.1016/j.molstruc.2009.05.004.

Dunitz, J. D. (2004). Organic Fluorine: Odd Man Out. *ChemBioChem*, *5*, 614-621. https://doi.org/10.1002/cbic.200300801.

Etter, M. C., & Baures, P. W. (1988). Triphenylphosphine Oxide as a Crystallization Aid. *Journal of the American Chemical Society*, *110*, 639-640. https://doi.org/10.1021/ja00210a076.

Feigenbaum, A. (1986). Hydrogen Bonding and Retention on Silica. *Journal of Chemical Education*, *63*(9), 815-817. https://doi.org/10.1021/ed063p815.

Gardner, D., & Tajvidi, M. (2016). Hydrogen Bonding in Wood-based Materials: An Update. *Wood and Fiber Science*, *48*(4), 234-244. Retrieved from http://wfs.swst.org/index.php/wfs/article/view/2387

Gavezzotti, A. (2008). Hydrogen Bond Strength and Bond Geometry in Cyclic Dimers of Crystalline Carboxylic Acids. *Acta Crystallographica Section B: Structural Science*, *64*(3), 401-403. https://doi.org/10.1107/S0108768108007556.

Heller, S. T., & Silverstein, T. P. (2020). pKa Values in the Undergraduate Curriculum: Introducing pKa Values Measured in DMSO to Illustrate Solvent Effects. *ChemTexts*, *6*(2), 1-17. https://doi.org/10.1007/s40828-020-00112-z.

Henderleiter, J., Smart, R., Anderson, J., & Elian, O. (2001). How do Organic Chemistry Students Understand and Apply Hydrogen Bonding? *Journal of Chemical Education*, *78*(8), 1126-1130. https://doi.org/10.1021/ed078p1126.

James, M. N. G., & Williams, G. J. B. (1974). A Refinement of the Crystal Structure of Maleic Acid. *Acta Crystallographica Section B: Structural Crystallography and Crystal Chemistry*, *30*(5), 1249-1257. https://doi.org/10.1107/S0567740874004626.

Jezierska, A., Tolstoy, P. M., Panek, J. J., & Filarowski, A. (2019). Intramolecular Hydrogen Bonds in Selected Aromatic Compounds: Recent Developments. *Catalysts*, *9*(11), 909. https://doi.org/10.3390/catal9110909.

Joesten, M. D. (1982). Hydrogen Bonding and Proton Transfer. *Journal of Chemical Education*, *59*(5), 362-366. https://doi.org/10.1021/ed059p362.

Kamlet, M. J., & Taft, R. W. (1982). Linear Solvation Energy Relationships. 20. Intra-vs. Intermolecular Hydrogen Bonding by Some 2-Nitroaniline and 2-Nitrophenol Derivatives. *Journal of Organic Chemistry*, *47*(9), 1734-1738. https://doi.org/10.1021/jo00348a027.

Khaikin, L. S., Grikina, O. E., Golubinskii, A. V., Vilkov, L. V., Atavin, E. G., Asfin, R. E., & Denisov, G. S. (2003). Geometry of a Strong Hydrogen Bond As Determined by Gas-Phase Electron Diffraction: The Cyclic Dimer of Dimethylphosphinic Acid. *Doklady Physical Chemistry*, *390*(4), 158-162. https://doi.org/10.1023/A:1024402927184.

Kleeberg, H., Eisenberg, C., & Zinn, T. (1990). IR Spectroscopic Investigation of Solvent Effects and H-Bond Formation on the CD Stretching Frequency of Chloroform. *Journal of Molecular Structure*, *240*, 175-186. https://doi.org/10.1016/0022-2860(90)80508-H.

Kovács, A., & Varga, Z. (2006). Halogen Acceptors in Hydrogen Bonding. *Coordination Chemistry Reviews*, *250*(5-6), 710-727. https://doi.org/10.1016/j.ccr.2005.04.031.

Kuhn, B., Mohr, P., & Stahl, M. (2010). Intramolecular Hydrogen Bonding in Medicinal Chemistry. *Journal of Medicinal Chemistry*, *53*(6), 2601-2611. https://doi.org/10.1021/jm100087s.

Lamoureux, G., & Arias-Álvarez, C. (2020). Grids I: Electrophilic Aromatic Substitution. *Education Química*, *31*(4), 86-100. https://doi.org/10.22201/fq.18708404e.2020.4.75669.

Lamoureux, G., Chaves-Carballo, K., & Arias-Álvarez, C. (2021). Grids III: Hydrogen Bridges in Introductory Chemistry. *Educación Química*, *32*(3), 130-143. https://doi.org/10.22201/ fq.18708404e.2021.3.77705.

Laurence, C., Brameld, K. A., Graton, J., Le Questel, J.-Y., & Renault, E. (2009). The pKBHX database: Toward a Better Understanding of Hydrogen-bond Basicity for Medicinal Chemists. *Journal of Medicinal Chemistry*, *52*(14), 4073-4086. https://doi.org/10.1021/jm801331y.

Laurence, C., Mansour, S., Vuluga, D., Planchat, A., & Legros, J. (2021). Hydrogen-Bond Acceptance of Solvents: A 19F Solvatomagnetic β1 Database to Replace Solvatochromic and Solvatovibrational Scales. *The Journal of Organic Chemistry*, *86*(5), 4143-4158. https://doi.org/10.1021/acs.joc.0c02964.

Le Questel, J., Berthelot, M., & Laurence, C. (2000). Hydrogen-bond Acceptor Properties of Nitriles: A Combined Crystallographic and ab initio Theoretical Investigation. *Journal of Physical Organic Chemistry*, *13*(6), 347-358. https://doi.org/0.1002/1099-1395(200006)13:6<347:AID-POC251>3.0.CO;2-E.

Linclau, B., Peron, F., Bogdan, E., Wells, N., Wang, Z., Compain, G., Fontenelle, C. Q., Galland, N., LeQuestel, J.-Y., & Graton, J. (2015). Intramolecular OH•••Fluorine Hydrogen Bonding in Saturated, Acyclic Fluorohydrins: The γ-Fluoropropanol Motif. *Chemistry A European Journal*, *21*(49), 17808. https://doi.org/10.1002/chem.201503253.

Mackeprang, K., Schrøder, S. D., & Kjaergaard, H. G. (2013). Weak Intramolecular OH… π Hydrogen Bonding in Methallyl-and allyl-carbinol. *Chemical Physics Letters*, *582*, 31-37. https://doi.org/10.1016/j.cplett.2013.07.038.

Marstokk, K.-M., & Mollendal, H. (1996). Microwave Spectrum, Conformation, Intramolecular Hydrogen Bonding and ab initio Calculations for 2-Nitroethanol. *Acta Chemica Scandinavica*, *50*(6), 505-511. https://doi.org/10.3891/acta.chem.scand.50-0505.

Martins, F. A., & Freitas, M. P. (2019). The Fluorine Gauche Effect and a Comparison with Other Halogens in 2-Halofluoroethanes and 2-Haloethanols. *European Journal of Organic Chemistry*, *2019*(37), 6401-6406. https://doi.org/10.1002/ejoc.201901234.

Martins, F. A., & Freitas, M. P. (2020). Bioconformational Modulation of a Thymidine Kinase Enzyme Ligand Through F… HO Intramolecular Hydrogen Bond. *Journal of Molecular Graphics and Modelling*, *97*, 107545. https://doi.org/10.1016/j.jmgm.2020.107545.

Miller, B. J., Lane, J. R., & Kjaergaard, H. G. (2011). Intramolecular OH… π Interactions in Alkenols and Alkynols. *Physical Chemistry Chemical Physics*, *13*(31), 14183-14193. https://doi.org/10.1039/c1cp21190k.

Mons, M., Robertson, E. G., & Simons, J. P. (2000). Intra-and Intermolecular π-Type Hydrogen Bonding in Aryl Alcohols: UV and IR– UV Ion Dip Spectroscopy. *Journal of Physical Chemistry A*, *104*(7), 1430-1437. https://doi.org/10.1021/jp993178k.

Motherwell, W. B., Moïse, J., Aliev, A. E., Nic, M., Coles, S. J., Horton, P. N., Hursthouse, M. B., Chessari, G., Hunter, C. A., & Vinter, J. G. (2007). Noncovalent Functional-Group–Arene Interactions. *Angewandte Chemie, International Edition*, *119*, 7969-7972. https://doi.org/10.1002/ange.200701463.

Nagy, P. I. (2014). Competing Intramolecular vs. Intermolecular Hydrogen Bonds in Solution. *International Journal of Molecular Sciences*, *15*(11), 19562-19633. https://doi.org/10.3390/ijms151119562.

Nyasulu, F. W., & Macklin, J. (2006). Intermolecular and Intramolecular Forces: A General Chemistry Laboratory Comparison of Hydrogen Bonding in Maleic and Fumaric Acids. *Journal of Chemical Education*, *83*(5), 770-773. https://doi.org/10.1021/ed083p770.

Olesen, S. G., & Hammerum, S. (2009). Hydrogen Bonding to Alkanes: Computational Evidence. *Journal of Physical Chemistry A*, *113*(27), 7940-7944. https://doi.org/10.1021/jp9030392.

Ouvrard, C., Berthelot, M., & Laurence, C. (1999). The First Basicity Scale of Fluoro-, Chloro-, Bromo-and Iodo-alkanes: Some Cross-comparisons with Simple Alkyl Derivatives of Other Elements. *Journal of the Chemical Society, Perkin Transactions 2*, 7), 1357-1362. https://doi.org/10.1039/a901867k.

Oznobikhina, L. P., Chipanina, N. N., Aksamentova, T. N., & Shainyan, B. A. (2009). Orientation of Hydrogen Bond in H-Complexes of Sulfones and Sulfonamides. *Russian Journal of General Chemistry*, *79*(8), 1674-1682. https://doi.org/10.1134/S1070363209080167.

Rajappan, R., Shingade, P. D., Natarajan, R., & Jayaraman, V. K. (2009). Quantitative Structure−Property Relationship (QSPR) Prediction of Liquid Viscosities of Pure Organic Compounds Employing Random Forest Regression. *Industrial & Engineering Chemistry Research*, *48*(21), 9708-9712. https://doi.org/10.1021/ie8018406.

Raveendran, P., Ikushima, Y., & Wallen, S. L. (2005). Polar Attributes of Supercritical Carbon Dioxide. *Accounts of Chemical Research*, 478-485. https://doi.org/10.1021/ar040082m.

Rosenberg, R. E. (2019). Can 2-X-Ethanols Form Intramolecular Hydrogen Bonds? *Journal of Physical Chemistry A*, *123*(35), 7651-7660. https://doi.org/10.1021/acs.jpca.9b06801.

Rosenberg, R. E., Chapman, B. K., Ferrill, R. N., Jung, E. S., & Samaan, C. A. (2020). Approximating the Strength of the Intramolecular Hydrogen Bond in 2-Fluorophenol and Related Compounds: A New Application of a Classic Technique. *Journal of Physical Chemistry A*, *124*(19), 3851-3858. https://doi.org/10.1021/acs.jpca.0c01641.

Schmidt, H.-J., Kaufmann, B., & Treagust, D. F. (2009). Students' Understanding of Boiling Points and Intermolecular Forces. *Chemistry Education Research and Practice*, *10*(4), 265-272. https://doi.org/10.1039/B920829C.

Schneider, H.-J. (2012). Hydrogen Bonds with Fluorine. Studies in Solution, in Gas Phase and by Computations, Conflicting Conclusions from Crystallographic Analyses. *Chemical Science*, *3*(5), 1381-1394. https://doi.org/10.1039/c2sc00764a.

Seeman, J. I. (2017). Woodward's Pure and Applied Chemistry Words. *Chemistry International*, *01*, 4-9. https://doi.org/10.1515/ci-2017-0103.

Struble, M. D., Holl, M. G., Coombs, G., Siegler, M. A., & Lectka, T. (2015). Synthesis of a Tight Intramolecular OH··· Olefin Interaction, Probed by IR, 1H NMR, and Quantum Chemistry. *Journal of Organic Chemistry*, *80*(9), 4803-4807. https://doi.org/10.1021/acs.joc.5b00470.

Taylor, R. (2017). The Hydrogen Bond Between N—H or O—H and Organic Fluorine: Favourable Yes, Competitive No. *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials*, *73*(3), 474-488. https://doi.org/10.1107/S2052520617005923.

Tormena, C. F., Dos Santos, F. P., Neto, A. C., Rittner, R., Yoshinaga, F., & Temistocles, J. C. T. (2007). Electronic Interactions and Their Influence on the Conformational Stability of trans-2-Halocyclopentanol. *Journal of Physical Chemistry A*, *111*(2), 295-298. https://doi.org/10.1021/jp066026f.

Underwood, S. M., Kararo, A. T., & Gadia, G. (2021). Investigating the Impact of Three-Dimensional Learning Interventions on Student Understanding of Structure–Property Relationships. *Chemistry Education Research and Practice*, *22*(2), 247-262. https://doi.org/10.1039/D0RP00216J.

Yang, Q., Chi, Z., Li, Q., & Scheiner, S. (2020). Effect of Carbon Hybridization in C—F Bond as an Electron Donor in Triel Bonds. *The Journal of Chemical Physics*, *153*(7), 0743041-0743049. https://doi.org/10.1063/5.0018950.

Zeoly, L. A., Coelho, F., & Cormanich, R. A. (2019). Intramolecular H-Bond Is Formed in 2-Fluorophenol and 2-Fluorothiophenol, but It May Not Be the Main Pathway of the J FH Coupling Constant Transmission. *Journal of Physical Chemistry A*, *123*(46), 10072-10078. https://doi.org/10.1021/acs.jpca.9b07970.

Zheng, S., Xu, S., Wang, G., Tang, Q., Jiang, X., Li, Z., Xu, Y., Wang, R., & Lin, F. (2017). Proposed Hydrogen-bonding Index of Donor or Acceptor Reflecting its Intrinsic Contribution to Hydrogen-bonding Strength. *Journal of Chemical Information and Modeling*, *57*(7), 1535-1547. https://doi.org/10.1021/acs.jcim.7b00022.