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Are There Strong Hydrogen Bonds in Aqueous Solutions?

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The question of the strength of hydrogen bonds has been a subject of interest and contention for most of the 20th century (*1*). By the time of the publication of Pauling's book *The Nature of the Chemical Bond* in 1939 (*2*), weak hydrogen bonds were generally accepted. Evidence for strong hydrogen bonding in HF_2^- also appeared in the decades of the 1920s through the 1950s, and this strongly hydrogen bonded ion was accepted as a special case. HF_2^- is one of a handful of species for which there is compelling evidence for symmetrical hydrogen bonding; that is, the proton is equally shared between the fluoride ions, and its gas phase strength is estimated to be 37 kcal mol^{-1} (*3*). Other strongly hydrogen bonded species have been documented. In addition to fluoride containing species, the hydrated hydronium ion $H_5O_2^+$ is regarded as a case of symmetrical hydrogen bonding. In general, the strongest hydrogen bonds are found in ionic compounds and are regarded as partially covalent (*1*, *3*, *4*). Weak hydrogen bonds are regarded as arising from weak dipolar electrostatic attractions.

In this article we consider two questions about strong hydrogen bonding. Do strong hydrogen bonds occur in organic compounds in aqueous solutions? Should the strongly basic properties of proton sponge molecules be attributed to strong hydrogen bonding or to relief of steric strain upon protonation? These questions are debatable, and the purpose of this article is to consider the currently available evidence bearing on them and to define the terms of the debate.

CHARACTERIZATION OF STRONG HYDROGEN BONDS

Physicochemical characterization of strong hydrogen bonds includes the application of X-ray crystallography, neutron diffraction, infrared spectroscopy (IR or FTIR), nuclear magnetic resonance spectroscopy (NMR), and calorimetry. The interpretation of information provided by these techniques has been reviewed (*1*, *3*). X-ray crystallography and neutron diffraction give the distances separating heteroatoms participating in hydrogen bonding, and in small molecules they give the distances separating each heteroatom from hydrogen. Very short inter-heteroatom distances imply strong hydrogen bonding (*3*). However, care must be exercised in the interpretation of these distances because hydrogen bonds are not necessarily linear, and knowledge of the position of the proton is necessary to determine

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whether the hydrogen bond is linear. The strongest hydrogen bonds are symmetrical, but most moderately strong hydrogen bonds are asymmetric. Separations of less than 2.55 Å between hydrogen bonded oxygens and less than 2.65 Å between hydrogen bonded nitrogen and oxygen are much less than van der Waals contact distances, and they are regarded as evidence of strong or moderately strong hydrogen bonding. In short hydrogen bonds, the O---H or N---H distances are longer than covalent bonds (>0.9 Å) but shorter than weak hydrogen bonds (<2.0 Å). Infrared stretching frequencies for strongly hydrogen bonded protons become very broad and they are shifted to strikingly lower frequencies. Moderately strong hydrogen bonds display deuterium isotope effects on infrared stretching frequencies, the downfield NMR chemical shifts, and low H_2O/D_2O fractionation factors (*3*). In addition, the carbonyl stretching frequencies for species like C=O----H–O are decreased by hydrogen bonding, and the magnitude of this effect is regarded as a measure of the strength of the interaction (*5*, *6*).

Protons engaged in strong hydrogen bonding display very downfield NMR chemical shifts. The range for strong hydrogen bonds is in general 16 to 21 ppm (*3*, *7*); however, the range for a given heteroatom is smaller. The chemical shift for a free proton is reported to be 30 ppm (*8*). The chemical shift range for carbon-bound hydrogen is 0–10 ppm, and for protons bonded to heteroatoms it extends from 7 to 12 ppm. Therefore, a downfield chemical shift of 18–20 ppm for a proton engaged in strong hydrogen bonding indicates that it is fairly loosely bound relative to its purely covalently bonded relatives. The low field chemical shifts for LBHBs may be rationalized on the basis of shielding. A strongly hydrogen bonding proton will be more separated form both heteroatoms than a weakly hydrogen bonding proton, as illustrated below, although the heteroatoms will be more closely spaced. The greater the separation of the proton from the shielding electrons of the heteroatoms,

$$\mathrm{A{-}H\text{-----}B} \qquad \mathrm{A''''H''''B},$$

the more deshielded the proton and the lower the field at which it resonates. In the structure on the left, the proton is covalently bonded to atom A and is shielded by it. In the structure on the right, the proton is less strongly shielded by A but, not being fully covalently bonded by B, it is not strongly shielded by B either. It is less shielded by either atom than a typical proton and so resonates at a weaker field.

The notation used for strong hydrogen bonding in the structure on the right is intended to imply strong as distinguished from weak hydrogen bonding. It is not intended to imply perfect symmetry in the hydrogen bond.[1] There are only a few documented cases of perfectly symmetrical hydrogen bonds, whereas there are many cases of hydrogen bonding in which there is asymmetry but much stronger bonding than in weak hydrogen bonds.

[1] This practice is analogous to the use of the same bond lengths for single and double bonds in drawing structures for other organic molecules. The same bond lengths are used for convenience in describing the molecules in structural formulas and not to imply that they are the same lengths in the molecules. It is understood that strong hydrogen bonds vary in length and symmetry, just as double and single bonds vary in length and symmetry. The carbon–carbon double bond may be symmetrical in some molecules and not in others, and its length will also vary, although its length in chemical structural formulas is shown as invariant.

Proton chemical shifts of 16–21 ppm have been reported for strong hydrogen bonds (*3*). A chemical shift in the lower part of this range is not necessarily proof of strong hydrogen bonding because of variation in the differential properties of the heteroatoms. Fluorine is very different from oxygen and nitrogen in this respect. The proton chemical shift in HF_2^-, the strongest hydrogen bond, is 16 ppm, whereas chemical shifts as far downfield as 21 ppm have been observed in compounds in which oxygen or nitrogen are the heteroatoms. The size of the heteroatom and the distance of separation in the hydrogen bond may be important in determining the actual chemical shift. Fluoride is a very small ion, and the distance separating the fluorides in HF_2^- is only 2.26 Å. The shielding by fluorine in HF_2^- may be stronger than in oxygen and nitrogen compounds, owing to the small size of fluorine.

Hydrogen bonds have here been represented as weak or strong because biological molecules have until recently been regarded as containing only weak hydrogen bonds. The idea that they could incorporate strong hydrogen bonds under certain conditions is of recent origin (*7*, *9–12*). However, physical and organic chemists classify hydrogen bonds in three categories: very strong ($\geq$24 kcal mol^{-1}), moderately strong (10–24 kcal mol^{-1}), and weak (2–10 kcal mol^{-1}) (*1*, *3*). In biological molecules, hydrogen bonds are generally weak, and any bond falling in the category of moderately strong would be regarded as strong in the biological context. Only a few examples of symmetrical, very strong hydrogen bonds have been documented in simple molecules and none in biological molecules. A few examples of moderately strong hydrogen bonds have been postulated in a few proteins, notably the bridging proton in the His 57–Asp 102 diad of serine proteases (*7*, *8*, *13*) and the proton bridging Asp 99 and Tyr 14 of Δ^5-3-ketosteroid isomerase (*14*, *15*).

Hydrogen bonds classified as moderately strong are thought to differ from very strong bonds, as illustrated by qualitative potential energy diagrams in Fig. 1. The moderately strongly hydrogen bonding proton is pictured in a double minimum potential at a vibrational frequency corresponding to an energy very near the low barrier. The deuterium vibrational frequency is slightly lower, and the greater influence of the barrier upon it than hydrogen is thought to cause spectroscopic deuterium isotope effects. Bonds of this type are often known as low barrier hydrogen bonds (LBHBs). In the symmetrical, very strong hydrogen bond the vibrational frequencies for both protium and deuterium lie well above the barrier, and they are sometimes known as single well hydrogen bonds (SWHBs). In weak hydrogen bonds, the energy barrier is well above the corresponding frequencies of both protium and deuterium, and hydrogen is covalently bonded to one of the heteroatoms and electrostatically attracted to the other.

Both NMR and IR spectra of moderately strongly hydrogen-bonded protons display spectroscopic deuterium isotope effects (*3*). The value of ν_D/ν_H is 1.4 for typical hydrogen vibrations in molecules, including weakly hydrogen bonded molecules, owing to the difference in masses between H and D. However in the case of an LBHB $\nu_D/\nu_H < 1.4$. Deuterium and protium NMR chemical shifts are typically very nearly identical. However, in LBHBs the proton chemical shift is higher than that of deuterium by up to 1 ppm, that is $0 < [\delta_H - \delta_D] \leq 1.0$. Another isotope effect that distinguishes LBHBs from weak hydrogen bonds is the fractionation

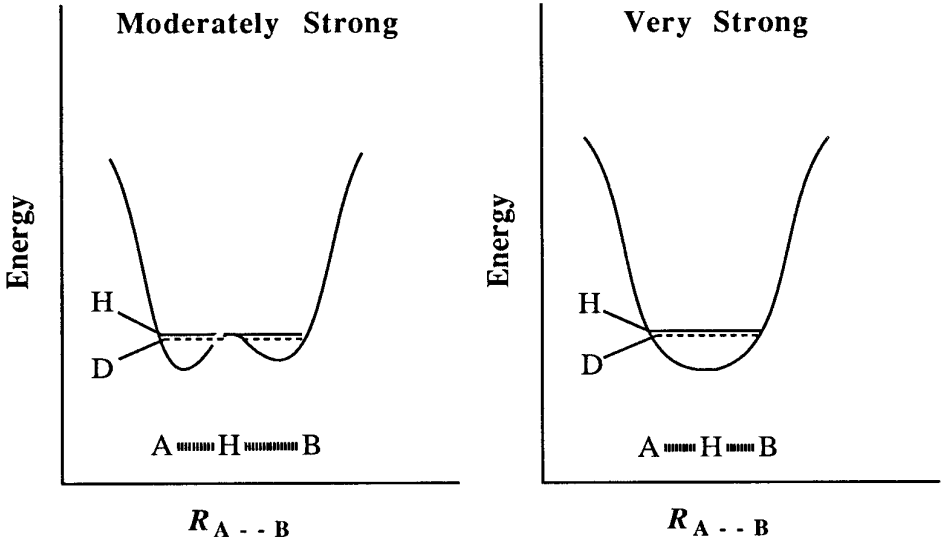
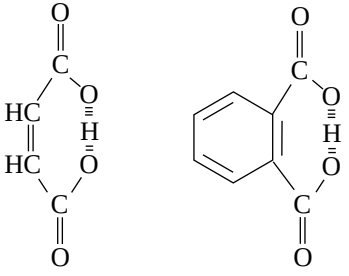


FIG. 1. Potential energy diagrams for low barrier hydrogen bonding (left) and single well hydrogen bonding (right) between two heteroatoms A and B.

factor against deuterium in H_2O/D_2O mixtures. Fractionation factors much less than 1.0; e.g., 0.3 to 0.5 are indicative of low barrier hydrogen bonding.

STRONG HYDROGEN BONDING IN CARBON COMPOUNDS

In organic chemistry, the most thoroughly studied examples of strong hydrogen bonding are the salts of hydrogen maleate **1** and hydrogen phthalate **2.** The crystalline imidazolium and potassium salts of **1** and the lithium salt of

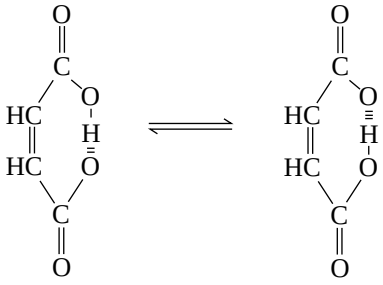


1 **2**

2 appear to incorporate symmetrical hydrogen bonds, based on neutron diffraction data (*16–18*). Data on other salts of **1** seem to show a slight asymmetry to the hydrogen bond (*1*). The low field proton chemical shift of **1** dissolved in solution is reported to be 20.2 to 20.5 ppm in five different aprotic solvents (*7*, *19*), and that

of **2** is 21.0 ppm in CD_2Cl_2 (*19*). The deuterium isotope effects on the chemical shifts are very slightly negative (−0.03 and −0.15 ppm, respectively (*19*), which is consistent with either a conventional or single well hydrogen bond, but not an LBHB.

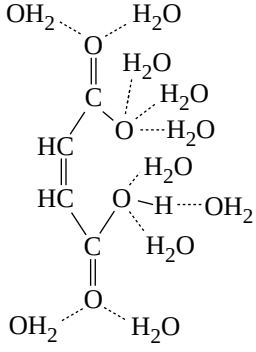
The question of whether the strong hydrogen bond in **1** is perfectly symmetrical, slightly asymmetric, or subject to isomerization according to Eq. (1) is still under debate.



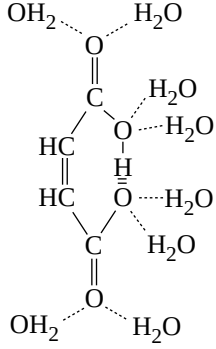
[1]

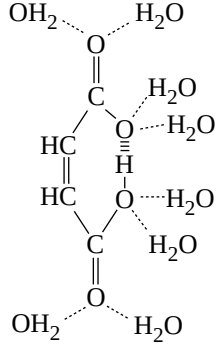
Elegant IR experiments on crystals indicate a symmetrical hydrogen bond (*20*). Carefully designed experiments on ^{18}O-perturbations of ^{13}C NMR signals indicate a symmetrical bond in aprotic solvents (*21*) and hydrogen bond isomerization in aqueous solutions (*22*). Regardless of whether these hydrogen bonds are slightly asymmetric or even subject to isomerization, they are strong. Calculations indicate an energy of −27 to −29 kcal mol^{-1} for hydrogen maleate in the gas phase (*23*, *24*). While the strength of hydrogen bonding in hydrogen maleate depends on the dielectric constant of the medium, it does not appear to become weak at high dielectric constants, decreasing to about −15 kcal mol^{-1} at the dielectric constant of water (*24*). Therefore, computations indicate that it can be moderately strong even in media of high dielectric constant.

The possibility of a moderately strong intramolecular hydrogen bond in hydrogen maleate at the dielectric constant of water does not necessarily mean that it is included in the most stable structure in aqueous solutions or that other species of comparable or greater stability do not exist. Multiply hydrogen bonded species such as that illustrated as **1a** must be considered as possible or probable in



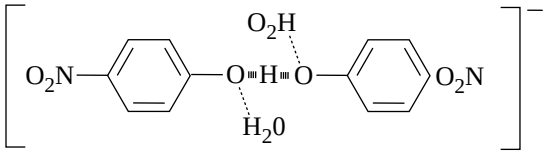
1a





1b

aqueous solutions. The multiply solvent hydrogen-bonded species could well be as stable as or more stable than the internally and strongly hydrogen bonded form. It should be noted, however, that strong hydrogen bonding does not preclude external bonding to water, as in **1b.** In fact, it is known that weak hydrogen bonds to water coexist in crystals of the strongly hydrogen bonded *p*-nitrophenol/*p*-nitrophenolate system **3**



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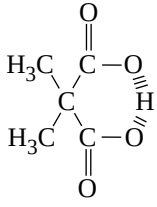
(*25*). The contact was modeled as two half-hydrogens, with an O---O separation of 2.45 Å. Many other examples of coexisting conventional and short hydrogen bonds in crystals have been tabulated (*1*). Therefore, consideration must be given to the possible importance of internally, strongly hydrogen bonded species such as **1b** in aqueous solutions. There is reason to consider that they can coexist with **1a** and may even be the dominate form, as discussed in the following section.

A recurrent theme about strong hydrogen bonding of organic compounds in solution is that they most often arise through intramolecular interactions when structural constraints force the heteroatoms together. Hydrogen fumarate, the *trans*-isomer of **1,** does not engage in strong hydrogen bonding under any conditions. Hydrogen 2,2-dimethylmalonate **4** displays a downfield ^{1}H NMR signal in aprotic solvents, but no downfield signal is observed in hydrogen malonate under the same conditions (*7*). A downfield ^{1}H NMR signal is observed in *cis*-urocanic acid **5** but not in *trans*-urocanic acid **6** in DMSO-d_6 (*7*).



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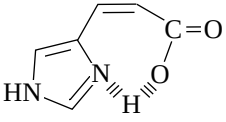

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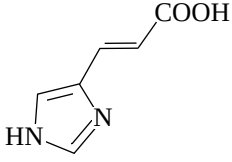

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Many similar examples have been described, including the proton sponges discussed in a later section (*3*).

Hydrogen fumarate is unable to engage in intramolecular hydrogen bonding because of structural constraints. However, it should be able to undergo intermolecular hydrogen bonding of the same groups in the same way if the low barrier hydrogen bonds are strong enough. However, in contrast to hydrogen maleate, hydrogen fumarate does not display a low field ^{1}H NMR signal when dissolved in aprotic solvents. As a carboxylic acid, it most likely forms intermolecular hydrogen bonds analogous to those of carboxylic acids in aprotic solvents (*26*), but they are not low barrier hydrogen bonds. Therefore, the structural constraints of the *cis*-

geometry in hydrogen maleate and the steric bulk in hydrogen dialkylmalonates tending to force hydrogen bonding groups together seem to be important in the formation of strong hydrogen bonds.

ACIDITIES OF DICARBOXYLIC ACIDS

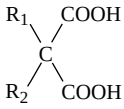
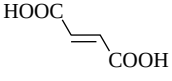
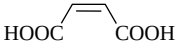
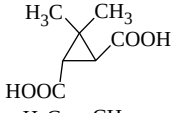
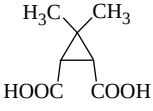
The differential acidities of the acidic groups in dicarboxylic acids are satisfactorily explained by electrostatic effects when the carboxylic acid groups are well separated. However, in molecules in which the acidic groups are separated by one or two carbon atoms, the differences between the pK_as for the two groups are often much larger than can be explained by internal inductive effects or electrostatic repulsion between the ionized groups. Values of the first and second pK_as (pK_1 and pK_2) for a collection of dicarboxylic acids are presented in Table 1. Note that structural factors such as *cis*-geometry of steric bulk tending to force the carboxylic acid groups together increases the pK_a differences. In particular, increased steric contact forces pK_1 down and pK_2 up in all cases. Internal hydrogen bonding can lead both to a decrease in pK_1 and an increase in pK_2 if the hydrogen bond is strong and provides particular stabilization to the monoanionic form. In contrast, electrostatic repulsion between two carboxylate groups upon ionization to the dianions can lead to an increase in pK_2 but not to decrease in pK_1.

The acidities of the acids in Table 1, and the differences in first and second ionization constants, were discussed more than 40 years ago (*27*). It was concluded that the steric effects on pK_1 and pK_2 could not be explained solely by electrostatic repulsion between the carboxylate groups, and intramolecular hydrogen bonding was invoked to explain part of the differences. If intramolecular hydrogen bonding in **1b** is a stabilizing interaction, it will bring about a lower value of pK_1 (1.92) than that for the *trans*-isomer (3.02). If this is true, then the same internal hydrogen bond should lead to a higher value of pK_2 than that for the *trans*-isomer, in which intramolecular hydrogen bonding is not possible. Similar arguments can be advanced to explain the remarkable effect of increasing steric bulk in the 2,2-dialkylmalonic acid series, in which pK_1 decreases from 3.17 to 2.07 with increasing sizes of alkyl groups, and pK_2 increases from 6.06 to 7.51.

Electrostatic repulsion must also contribute to the different values of pK_2 in Table 1. The dissociation of a second proton from the monoanionic form of a dicarboxylic acid introduces a second negative charge, an energetically unfavorable process that will increase the value of pK_2. It is difficult to separate the electrostatic and hydrogen bonding effects on the pK_2 values in Table 1. However, an estimate of the electrostatic contribution to $\Delta\Delta G^\circ_{\text{ion}}$ in Table 1 can be made by considering the values of pK_a for mononuclear polyhydroxy acids such as carbonic, phosphoric, and arsonic acids. Values of pK_a for successive ionizations in these acids differ by about 5.[2] Thus, the values of pK_a in the ionizations of phosphoric acid are pK_1 =

[2] The pK_a difference is (pK_2 − pK_1) = [(−log K_2) − (−log K_1)]. Because $\Delta G^\circ_{\text{ion}} = -\text{RT ln } K_a$, the difference in ionization free energies is $\Delta\Delta G^\circ_{\text{ion}} = \text{RT}[(-\ln K_2) - (-\ln K_1)] = 2.303\text{RT}(\text{p}K_2 - \text{p}K_1)$. The values of $\Delta\Delta G^\circ_{\text{ion}}$ (corr) are corrected for statistical effects in the ionization. The dissociation constants for dibasic acids must differ by a factor of at least four for statistical reasons. The ratio $K_1/K_2 = 4$ in the case of a dicarboxylic acid with identical, noninteracting carboxylic acid groups. The correction to $\Delta\Delta G^\circ_{\text{ion}}$ is −0.82 kcal mol^{-1}.

TABLE 1
Energetics of the Ionizations of Selected Dibasic Acids[a]

	pK_1	pK_2	$\Delta\Delta G^\circ_{ion}$[b]	$\Delta\Delta G^\circ_H$[c]
				
R_1, R_2 =				
Me, Me	3.17	6.06	3.02	0.4
Et, Me	2.86	6.41	4.02	1.3
Et, Et	2.21	7.29	6.11	3.4
Et, nPr	2.15	7.43	6.38	3.7
iPr, iPr	2.07	7.51	6.60	3.9
	3.02	4.38	1.04	—[d]
	1.92	6.23	5.06	2.4
	3.82	5.32	1.23	—[d]
	2.34	8.31	7.32	4.6

[a] Values of pK_1 and pK_2 are from Brown *et al.* (*27*) and Jencks and Regenstein (*28*).
[b] Differential ionization energies are reported in units of kcal mol^{-1} at 25°C. The calculation of $\Delta\Delta G^\circ_{ion}$ from the difference in pK_1 and pK_2 is described in footnote 2 and includes the correction for statistical effects in the ionization of dibasic acids.
[c] Values of $\Delta\Delta G^\circ_H$ were calculated by substracting 2.7 kcal mol^{-1}, the estimated contribution of electrostatic repulsion, from the values of $\Delta\Delta G^\circ_{ion}$ for dialkylmalonates and *cis*-isomers.
[d] The electrostatic correction of −2.7 kcal mol^{-1} does not apply to *trans*-isomers.

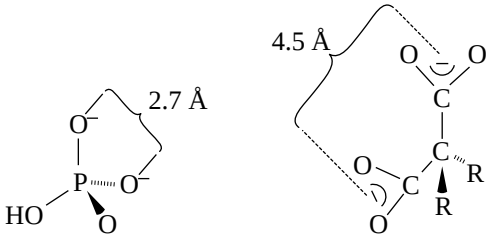
2.0, pK_2 = 7.1, and pK_3 = 12.3.[3] These differences are attributed to electrostatic destabilization attending the increase in negative charge with successive ionizations. The difference of 5 between successive pK_a values corresponds to $\Delta\Delta G^\circ_{ion}$ = 6.8 kcal mol^{-1} at 25°C. In ions of this type the oxygens are separated by about 2.8 Å. In a dicarboxylate such as maleate^{-2} or malonate^{-2}, models show that the carboxylate

[3] An exception is boric acid, $B(OH)_3$, which ionizes by a special mechanism. The first ionization proceeds by addition of a molecule of water to boron as follows:

$$B(OH)_3 + H_2O \rightleftharpoons B(OH)_4^- + H^+.$$

The first ionization (pK_a = 9.2) is not a straightforward dissociation of a proton, and the negative charge in $B(OH)_4^-$ is formally on boron rather than oxygen. The second ionization is a proton dissociation (pK_a = 12.7).

groups would be separated by about 4.5 Å, or 1.6 times the separation in a phosphate ion.



Because electrostatic repulsion varies as the inverse square of distance, the repulsion between two carboxylate groups in a dianion such as malonate^{-2} or maleate^{-2} should be about 2.7 kcal mol^{-1}, assuming that the dielectric medium in the hydration sphere of carboxylate groups in contact is similar to that in phosphate, carbonate, arsonate, etc. This value for the electrostatic effect is smaller than the values of $\Delta\Delta G^{\circ}_{\text{ion}}$ for sterically crowded 2,2-dialkylmalonic acids and *cis*-dicarboxylic acids in Table 1.

The values of $\Delta\Delta G^{\circ}_{\text{ion}}$ in Table 1 range from 3.0 to 7.3 kcal mol^{-1}. Of this, approximately 2.7 kcal mol^{-1} must be attributed to electrostatic repulsion between vicinal or *cis*-geminal carboxylate ions, and the remaining 0.3 to 4.6 kcal mol^{-1} can be allotted to stabilization of the monoanions by other factors, primarily or exclusively intramolecular hydrogen bonding. Considering the values of $\Delta\Delta G^{\circ}_{\text{H}}$ in Table 1, the internal hydrogen bond in hydrogen maleate appears to provide about 2.4 kcal mol^{-1} more stabilization than the solvent hydrogen bonding in hydrogen fumarate. The internal hydrogen bond in hydrogen *cis*-caronate provides about 4.6 kcal mol^{-1} more stabilization than the solvent hydrogen bonds in hydrogen *trans*-caronate. These increments of stabilization should be regarded as the difference between the strengths of the internal hydrogen bonds and the combined strengths of external hydrogen bonds with water that would exist in their place.

Another way to assess the energetics of internal hydrogen bonding is to consider the differences between pK_1 for *cis*- and *trans*-isomers as attributable to internal hydrogen bonding in the *cis*-isomers. The inductive effects on pK_a should be the same for *cis*- and *trans*-isomers, so the difference is likely to be due to internal hydrogen bonding. Stabilization by internal hydrogen bonding should be symmetrical; that is, to the extent that it lowers K_1 by stabilizing the monoanionic acid, internal hydrogen bonding should also elevate K_2. That is, stabilization by internal hydrogen bonding should be as important in preventing the second ionization as it is in facilitating the first ionization. On this basis, the overall stabilizing effect of the internal hydrogen bond in hydrogen maleate should correspond to twice the difference in pK_1 for maleate and fumarate, or 2.2. In terms of standard free energy, this corresponds to 3 kcal mol^{-1}, or about 20% more than $\Delta\Delta G^{\circ}_{\text{H}}$ in Table 1. A similar analysis of *cis*- and *trans*-caronate gives an estimate of 4.0 kcal mol^{-1} for the internal hydrogen bond, or about 13% less than the value of 4.6 kcal mol^{-1} for $\Delta\Delta G^{\circ}_{\text{H}}$ in Table 1.

A third way to estimate $\Delta\Delta G^{\circ}_{\text{H}}$ for hydrogen maleate is to consider the difference between pK_1 for maleic acid and the pK_a of its monoethyl ester (2.94). The ionized