How Do Strong Hydrogen Bonds Affect the Acidities of Carbon Acids? An ab Initio Molecular Orbital Study

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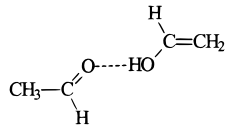
The deprotonation energies and proton affinities of acetaldehyde have been determined using ab initio molecular orbital calculations at the MP2/D95** level for the parent molecules and the hydrogen bonding dimers formed from a keto and an enol tautomer. The C−H deprotonation energies of acetic acid and its hydrogen-bonded dimer have been similarly determined. In all cases, the deprotonation energy is greatly enhanced in the dimeric form. The proton affinity is likewise enhanced for two cases studied. The current results suggest that enhancements of both acidities and basicities of 20−30 kcal/mol might be expected in enzymes where such hydrogen bonds are possible.

There has been much recent discussion about the possibility that strong hydrogen bonds might be the major contributing factor to the apparent increase in acidity of certain hydrogens in several enzymatic reactions.[1]

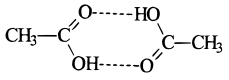
Strong hydrogen bonds have been discussed in several contexts in the chemical literature.[2] Gilli[3] has proposed that resonance-assisted hydrogen bonds (RAHB) be particularly stable, while Frey,[4] Cleland and Kreevoy,[5] and others[6] have claimed the same for low-barrier hydrogen bonds (LBHB). Frey's analysis leads to the supposition that H-bonds between acids and conjugate bases of the same pK_a should form LBHB's,[7] while Gilli's would require the existence of viable resonance structures. The two suggestions are similar in most other ways.

Among the several enzymatic mechanisms that have been proposed to involve LBHB's, probably that involving a serine−hystidine−aspartine triad in serine proteases, such as chymotrypsin, has received the most theoretical and experimental[8] attention. LBHB's have also been implicated in the mechanism of action of Δ^5-3-ketosteroid isomerase[9] and in citrate synthesis[10] which specifically involve acidity of C−H protons α to a carbonyl group. Enhanced acidity of the C−H protons of approximately 20 kcal/mol or more appears to be necessary for the viability of the LBHB rationale of this enzymatic process. Several theoretical studies of LBHB's and RAHB's have appeared. Lluch et al.[11] have reported studies involving molecules related to imidazole. McAllister et al. have reported studies involving maleate and formic acid/formate among others.[12] An interesting combined X-ray/neutron diffraction study of a related cocrystal has recently appeared.[13]

In this paper, we shall focus upon the enhancement of the acidities of C−H protons α to a carbonyl group by formation of possible LBHB's upon deprotonation. We shall also compare the basicities of the same systems where LBHB's can form upon protonation of the carbonyl group. We test the hypothesis that LBHB's sufficiently enhance these reactivities by comparing the acidities and basicities of the C−H's of acetaldehyde and acetic acid in their monomeric and H-bonding dimeric forms. While acetic acid easily forms the common cyclic dimers typical of carboxylic acids, acetaldehyde requires one of the units of the H-bonding dimer to be in the enol form. Deprotonation and protonation of the dimers of **I** leads to potentially symmetric



I



II

charged species which meet both Gilli's and Frey's criteria. Deprotonation at carbon of the dimer of **II** does not formally lead to a species that meet these criteria. Enhanced acidities of significantly less than 20 kcal/mol would cast serious doubt upon the viability of the LBHB mechanism, while enhanced acidities of 20 kcal/mol or more would be consistent with (but not proof of) the LBHB mechanism.

Methods

We performed ab initio molecular orbital calculations at the frozen core second-order Møller−Plesset (MP2) level using the D95(d,p) basis set with full optimization in all internal coordinates, using the GAUSSIAN 94 and GAUSSIAN 98 suites of computer programs. Vibrational calculations on the optimized structures confirmed the optimizations and permitted the calculation of the enthalpies and free energies at 298 K. We used constraints dictated by symmetry where appropriate. Nevertheless, we always confirmed the optimizations with vibrational calculations. As we are particularly concerned with the acidities and basicities of the monomers and dimers, we did not concentrate on the hydrogen-bonding energies of the dimeric charged and neutral species. Thus, we explicitly corrected for the basis set superposition error (BSSE) inherent in calculating the hydrogen-bonding energies only for the neutral species. This was done using a single-point counterpoise correction[14] (CP). The CP is ambiguous in the case of interactions of charged with neutral species and in the case of symmetrically charged species. For this reason, the CP corrections per hydrogen bond calculated for the neutral species are used for all the dimeric species within the same series. The CP correction is controversial.[15] When it is added as a single-point

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TABLE 1: Deprotonation Energies (kcal/mol) of Monomeric and Dimeric Species

		dimer			
	monomer	from dimer[a]	relative to monomer[b]	from 2 monomers[c]	relative to monomer[b]
		Acetaldehyde			
energy	386.1	359.5	−26.6	366.7	−19.5
enthalpy	377.0	349.0	−28.0	356.9	−20.1
free energy	377.4	349.4	−28.0	367.6	−9.8
		Acetic Acid C			
energy	389.3	368.1	−21.2	350.7	−38.5
enthalpy	379.1	359.3	−19.8	342.5	−36.6
free energy	380.3	357.1	−26.1	354.2	−26.1
		Acetic Acid O			
energy	362.2	346.9	−15.3	329.5	−32.7
enthalpy	352.8	338.4	−14.4	321.6	−31.2
free energy	354.4	335.6	−18.8	332.7	−21.7

[a] Deprotonation of dimer. [b] Relative deprotonation energy vs single monomer. [c] Deprotonation (one proton) from two isolated monomers to form dimeric anion.

TABLE 2: Proton Affinities ($-E_{protonation}$) of Acetaldehyde and Its H-Bonding Dimer (kcal/mol)

		dimer			
	monomer	from dimer[a]	relative to monomer[b]	from 2 monomers[c]	relative to monomer[b]
energy	190.7	232.3	41.6	225.2	34.4
enthalpy	182.2	225.0	42.9	217.1	34.9
free energy	182.3	226.1	43.8	207.9	25.6

[a] Proton affinity of dimer. [b] Relative proton affinity vs single monomer. [c] Proton affinity (one proton) of two isolated monomers to form dimeric cation.

correction without further optimization, this procedure does not find the correctly optimized structure.[16] Thus, the CP calculated is an upper limit. We have previously ascertained that the D95(d,p) basis set tends to cause smaller BSSE's than the 6-31G(d,p) basis set.

Enthalpies and free energies are calculated using the vibrational frequencies that result from the standard harmonic approximations. The enthalpy and free energy values are calculated for the species indicated. In the case of the enthalpies, these are equivalent to the enthalpies of reaction for protonation or deprotonation since a proton has zero energy and no vibrations. However, the foregoing is not true for the free energies, as the number of particles changes upon protonation or deprotonation. Thus the free energies for protonation all need to be corrected by a constant, while those for deprotonation need to be corrected by the negative of the same constant. Thus, the constant will cancel in the calculations of the free energy differences between protonations or between deprotonations as well as the calculations of the free energy of autoprotolysis.

Results

The gas-phase C−H deprotonation energies for acetaldehyde and acetic acid are collected in Table 1, the protonation energies for acetaldehyde in Table 2, and the autoprotolysis energies for acetaldehyde in Table 3. Table 4 contains the hydrogen-bonding enthalpies evaluated using the CP corrections per H-bond calculated for the neutral dimers. Values appear for the monomeric and dimeric species as well as for two neutral monomers that form a dimeric anion or cation upon reaction. The last value includes the cumulative energetic of enol formation and hydrogen bonding. The H-bonding dimer formed from one keto and one enol of acetaldehyde has a deprotonation energy that is 26.6 kcal/mol less than the monomeric keto form. The deprotonation of two monomers to form the H-bonded anion requires 19.5 kcal/mol less energy than that of a single monomer. The proton affinity of the acetaldehyde dimer is 41.4 kcal/mol more than that of the monomer, while the proton affinity of two keto monomers to form a dimeric cation is 34.4 kcal/mol greater than that of a single monomer. The data clearly show that the dimeric hydrogen-bonding species have enormously enhanced acidities and basicities.

TABLE 3: Autoprotolysis Energies (Deprotonation Energy − Electron Affinity) for Acetaldehyde and Its H-Bonding Dimer (kcal/mol)

	monomer	dimer	relative to monomer[a]
energy	195.4	127.2	−68.2
enthalpy	194.9	124.0	−70.9
free energy	184.8		

[a] Relative autoprotolysis energy vs single monomer.

TABLE 4: Hydrogen-Bonding Enthalpies (kcal/mol)

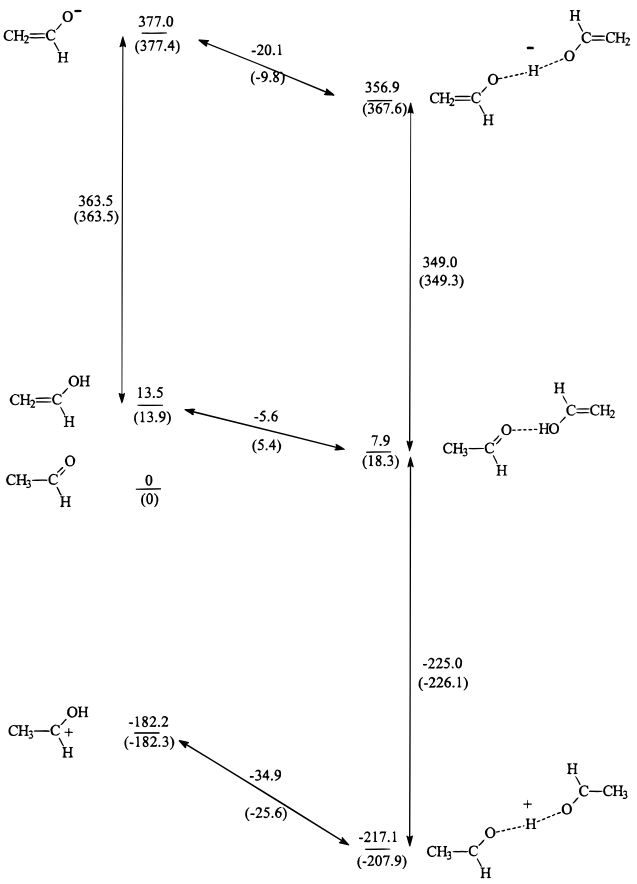
	ΔH (uncorr)	CP	ΔH (CP-corr)
$CH_3CHO + CH_2CHOH$	−5.6	2.6	−3.0
$CH_2CHO^- + CH_2CHOH$	−20.1	2.6	−17.5
$CH_3CHO + CH_3CHOH^+$	−34.9	2.6	−32.3
$2CH_3COOH$	−16.8	4.8	−12.0
$CH_3COOH + CH_3COO^-$	−31.2	2.4	−28.8
$CH_3COOH + {}^-CH_2COOH$	−36.6	4.8	−31.8

We shall use the enthalpies and free energies in the following discussion, as they account for the change in zero point vibrations and other vibrational distribution corrections. One should note that the zero-point energy differences and the effect upon the entropy and upon the free energy of changing the number of particles from two to one upon forming the dimer should be much diminished within the cavity of an enzyme due to the fact that the reactive species are likely to be already linked together in some manner.

Acetaldehyde. The data for acetaldehyde are collected in Tables 1−3, Scheme 1, and Figure 1. Acetaldehyde is predicted to have a deprotonation enthalpy of 377.0 kcal/mol. To form a H-bonding dimer, one acetaldehyde molecule must be converted to its enol form. The H-bonding dimer formed in this manner has an enthalpy of 7.9 kcal/mol higher than two acetaldehyde monomers. This value reflects both the energies of tautomerization and that of the H-bonding interaction. This dimer has a deprotonation enthalpy of 349.0 kcal/mol, 28.0 kcal/mol less than acetaldehyde, itself. Upon incorporation of the enthalpy for forming the dimer, the total enthalpy for forming the H-bonding dimeric anion from two noninteracting monomers becomes 356.9 kcal/mol, or 20.1 kcal/mol less than a monomer. At 298 K, the corresponding differences in free energies are calculated to be 28.0 and 9.8 kcal/mol vs the dimer and two monomers, respectively. The roughly 10 kcal/mol difference in enhancement between the enthalpy and free energy values vs two monomeric acetaldehydes reflects the difference in number of particles in the reference state (one for the H-bonding dimer, two for the two monomers).

One can also compare the proton affinities of the monomeric acetaldehyde and its H-bonding dimer. Here the enthalpies are −182.2 and −225.0 kcal/mol for adding a proton to the monomer and dimer, respectively. The dimer is more basic by 42.9 kcal/mol (34.9 if compared to two separate monomers). The corresponding values for the free energies are 43.8 and 25.6 kcal/mol. Combining the values for deprotonation with the proton affinities, one obtains a decrease in the autoprotolysis enthalpy of 70.9 (enthalpy) and 71.9 (free energy) kcal/mol.

SCHEME 1: Relative Enthalpies and Free Energies (in Parentheses) at 298 K for Various Species in kcal/mol[a]



[a] Zero is defined as the enthalpy (free energy) of monomeric acetaldehyde. The values associated with the double-headed arrows indicate differences in enthalpy (free energy). The horizontal arrows imply adding monomeric acetaldehyde (enthalpy and free energy = zero) going from left to right.

Both the dimeric anion and cation of acetaldehyde are ideal candidates for RAHB's or LBHB's. They are also charge-assisted hydrogen bonds. Since the H-bonding hydrogen is attached to two basically identical species, they will clearly have the same pK_a's, which is the fundamental criterion for a LBHB. Similarly, resonance structures of equal energy can be drawn placing the charge on either of the acetaldehyde fragments, which is a criterion for a RAHB.

The geometries of the species and their (Mulliken) atomic charges are shown in Figure 1. Note that the dimeric anion is not planar. The two (locally planar) acetaldehyde moieties are roughly perpendicular (dihedral angle 88°) to each other. Constraining the structure to the planar D_{2h} symmetry raised the energy by 0.9 kcal/mol and produced one imaginary frequency. The bond lengths and charges did not appreciably change. The largest change was for the acyl hydrogen whose Mullikan charge decreased from 0.164 to 0.059, presumably due to the $\pi-\sigma$ interaction that occurs in the twisted system. The O···O separations are about 2.400 Å for both the dimeric anion and cation. The dimeric cation has approximate D_{2h} symmetry. The deviations from the symmetrical structure are quite small. Nevertheless, when a D_{2h} structure was input, the geometry would always converge to a C_s structure.

Acetic Acid. The data for acetic acid are collected in Table 1, Scheme 2, and Figure 2. Acetic acid differs from acetaldehyde in that the dimeric anion resulting from deprotonation at C cannot assume a structure where each monomeric unit is

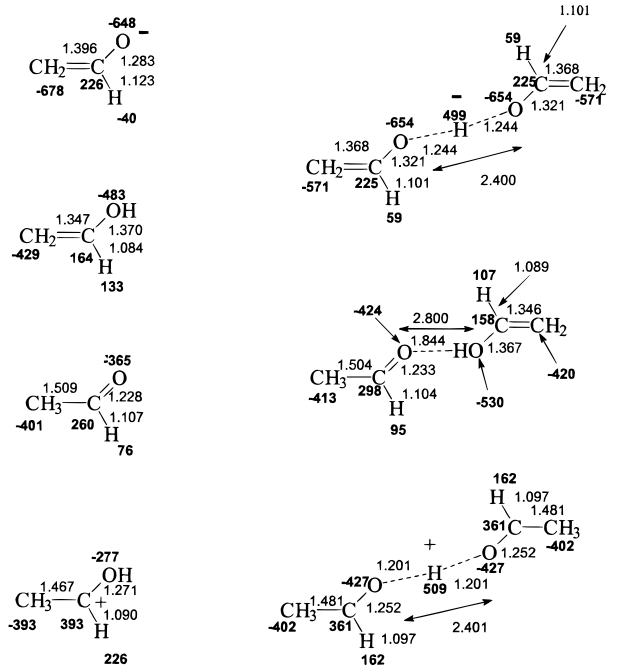
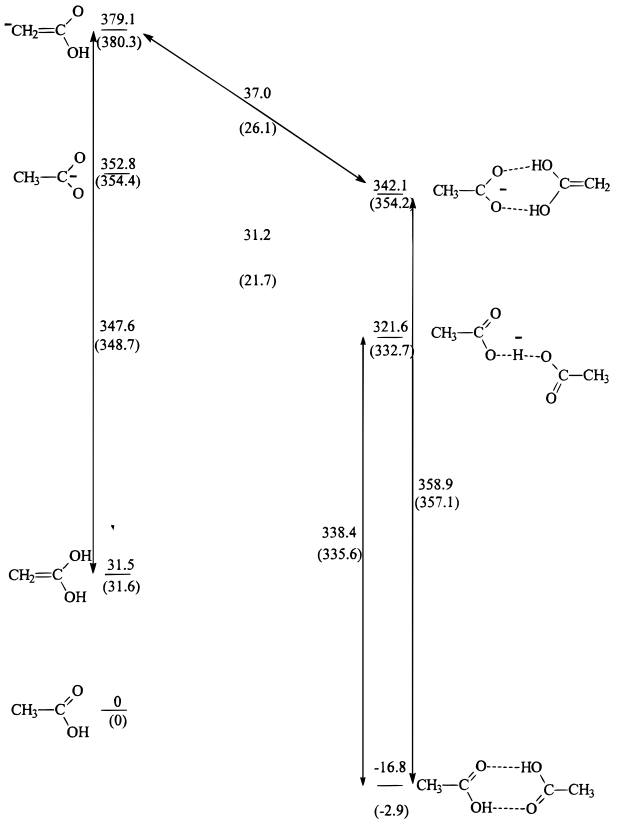


Figure 1. Significant interatomic distances and atomic charges (**bold**, $\times 10^3$) based upon Mulliken populations for acetaldehyde species.

SCHEME 2: Relative Enthalpies and Free Energies (in Parentheses) at 298 K for Various Species in kcal/mol[a]



[a] Zero is defined as the enthalpy (free energy) of monomeric acetic acid. The values associated with the double-headed arrows indicate differences in enthalpy (free energy). The horizontal arrows imply adding monomeric acetaldehyde (enthalpy and free energy = zero) going from left to right.

equivalent. In fact, optimization leads to a species that can be thought of as an enol of acetic acid that forms two equivalent hydrogen bonds with an acetate anion. Here, the O−H of the

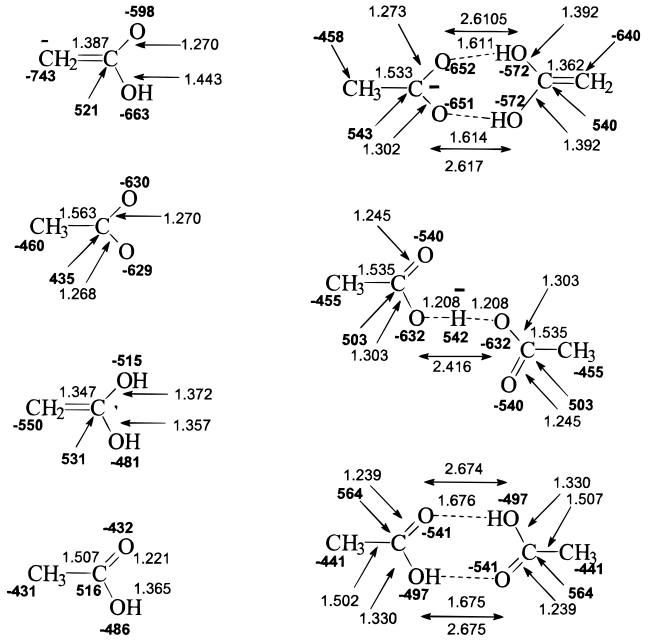
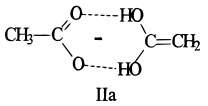


Figure 2. Significant interatomic distances and atomic charges (**bold**, $\times 10^3$) based upon Mulliken populations for acetic acid species.

neutral acid is transferred to the deprotonated acid, forming an H-bonding dimer between and acetate anion and a neutral enol, **IIa**. The process can be thought of as a "loaned" proton from



IIa

the H-bonding partner to the monomer that has been formally deprotonated. Upon reprotonation, the "loaned" proton would be expected to return to its original position. If the deprotonated methyl group reacted as a nucleophile (i.e., in an alkylation reaction), the "loaned" proton would perform a catalytic function. We have identified and discussed a similar form of catalysis (hydrogen-bond acid/base catalysis, HBA/BC) in the mechanism of alkylation of the amino group of guanine in G·C base pairs. In this case, a proton within an H-bond is transferred from the protonated guanine to the cytosine.[17]

While, the H-bond between the monomeric units of the anion (or cation) of the dimeric acetaldehydes can be thought of as interactions between two species with matched pK_a's, this case does not obtain for the dimeric acetic acid anion as the enol will have a lower pK_a than the acid (for the H leading to the anion at C). Furthermore, the hydrogen-bonding enthalpy of stabilization of neutral acetic acid dimer calculated here is 12.0 kcal/mol (in good agreement with the previously calculated[18] to be 11.8 kcal/mol by MP2/6-31G*) and measured[19] to be 13.8−17.0 (14.2 preferred value) kcal/mol. This is in contrast to the neutral dimeric aldehydes which are destabilized relative to two monomers (see above). Thus, the deprotonation energy of the acetic acid dimer should be corrected by the dimerization energies for proper comparison with similar values for **I**. Of course, acetic acid has two H-bonds in all of the dimeric forms considered here except the anion obtained from removing a proton from one of the carboxyl groups.

The deprotonation enthalpy at carbon of the acetic acid dimer is 19.8 kcal/mol less than that of the monomer. This is about 8 kcal/mol less than the corresponding value for the acetaldehyde dimer despite the fact that there are two H-bonds in the acetic acid complex but only one for the acetaldehyde dimeric anion. The O···O distances across the hydrogen bonds in **II** are significantly longer than for **I**. (2.617 vs 2.400 Å). On the other hand, the H-bonding dimeric anion obtained by deprotonation at OH leads to an (almost) symmetric anion that contains a short H-bond (O···O, 2.416 Å), with a deprotonation enthalpy that is 14.4 less than the monomer but 31.2 kcal/mol less when taken relative to two separated monomers. The difference of 17.8 kcal/mol is somewhat higher than the expected dimerization energy due to the fact that this energy has not been corrected for BSSE. For the MP2/6-31G* calculations of this interaction, the CP correction was reported to be 5.6 kcal/mol.[14]

Hydrogen-Bonding Enthalpies. The hydrogen-bonding enthalpies of Table 4 can be derived from the values indicated in Schemes 1 and 2. The calculation of the CP correction is somewhat ambiguous since one must arbitrarily decide where to put the charge when one calculated the species in the presence of the "ghost" orbitals of the other(s). This problem becomes exacerbated when the charged species is symmetrical. For example, **I** can be thought of as a hydrogen-bonded complex of the enolate anion and the enol of acetaldehyde. The energy of the enol will be excessively lowered by the ghost orbitals of the enolate since the ghosts carry no charge. Yet, there is no clear and unambiguous way to apply the negative charge to the ghosts. For this reason, the hydrogen-binding enthalpies have been corrected for BSSE using the CP correction calculated for the neutral acetaldehyde and acetic acid dimers. The potential surfaces have not been optimized with inclusion of the CP correction. Rather, the CP corrections have been evaluated as single-point a postieri corrections. Thus, the CP corrections calculated should be taken as an upper limit. Thus, the hydrogen-bonding values of Table 4 probably are more uncertain than the relative protonation and deprotonation energies discussed above. They are included for completeness at the suggestion of a reviewer.

Conclusions

The calculations described here support the suggestion that strong hydrogen bonds, such as LBHB's, can greatly enhance the acidity of, otherwise weak, carbon acids. Greatly enhanced acidities of similar species are implicated in enzymatic mechanisms. The observed enhancement is large enough to be consistent with the LBHB hypothesis for enzymatic catalysis. However, the proton transfer within the H-bonding system that is implicit in HBA/BC can provide a similar level of stabilization without a LBHB. Thus, the current results are consistent with, but do not require, the hypothesis that LBHB's might be responsible for this behavior. Of course, enzymatic systems are much more complicated than the simple systems described here. Furthermore, there is reason to believe that the enhancement might be attenuated by the effects of a solvent or other medium with a dielectric constant greater than 1. A complete discussion of these suggestions or of the related problem of whether the solid or liquid state is the correct paradigm for interaction within proteins cannot be attempted here. However, HBA/BC would require stable H-bonds (such as those in G·C base pairs) which would not be expected to occur in solution where H-bonds continually break and form. Nevertheless, the relevance of strong hydrogen bonds (whether they be LBHB's) to enzymatic activity must consider these problems.

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