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Are the Enol−Enolate Hydrogen Bonds at Matched PA Really Symmetrical?

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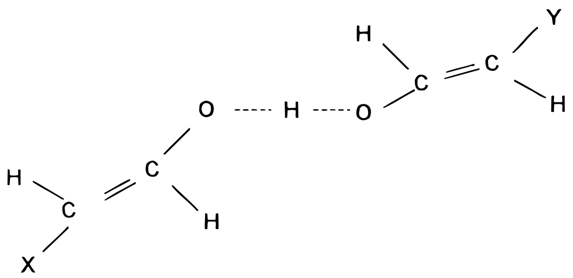
These past few years there has been growing interest in the nature of low-barrier hydrogen bonds (LBHBs) because of the presumed role of these bonds during enzyme catalysis.[1−6] Cleland and Kreevoy discussed the special stabilization arising from hydrogen bonding between proton donors and acceptors of matched pK_a and suggested that the requirement for forming low barrier hydrogen bonds appears to be the absence of a hydrogen bonding solvent, such as water, and similar pK_a values of the two heteroatoms involved in the bond.[7] For homologous series of phenol−phenolate complexes, however, no special stabilization was observed at matched pK_a.[6] As pointed out by Perrin,[8] if the two acceptor atoms are identical, it might naively be thought that the hydrogen bond must be symmetric so that the hydrogen bond would not need to choose which acceptor it will be closer to. Nevertheless, both situations have been observed, even with identical acceptor atoms. In this note, we should like to comment on the conclusions of Chen et al.[9] on enols hydrogen bonded to enolates characterized by the following structure:



where X or Y = CN, F, H, NH_2.

The hydrogen bond characteristics of homonuclear (X ≠ Y) and homomolecular (X = Y) complexes have been computed at the HF/6-31G* level. The $(OH\cdots O)^-$ bond energies vary from 16.7 to 32.2 kcal mol^{-1} when the difference between the proton affinities (PA) of the two partners (ΔPA) varies from 0 to 46 kcal mol^{-1}. Values of the energies and distances have also been calculated for the metastable complexes (ΔPA < 0) where the proton transfer is exothermic. The computed proton affinities of the enolates are 390 (X = NH_2), 377 (X = H), 372 (X = F), and 344 (X = CN) kcal mol^{-1}. Chen et al.[9] concluded that the strengths of these short hydrogen bonds are linearly related to the differences in PA of the two anions which share the proton and to the O···O distances between them. It was also shown that low-barrier hydrogen bonds with single minima after inclusion of zero-point energies occur when ΔPA is near zero, but that no special stability occurs when the double minimum becomes single-well.

1. Level of the Calculations. The optimized geometries and energies of the complexes and the proton affinities of the enolates were obtained from calculations carried out at the HF/6-31G* level. The PA of nonsubstituted vinyl alcoholate obtained at this level is 377 kcal mol^{-1}.[9] Good values of proton affinities can only be obtained when adding diffuse functions on nonhydrogen atoms.[10,11] This is clearly shown by the fact that the MP2/6-31+G** or B3LYP/6-31+G** [12] computed gas-phase acidity value of vinyl alcohol is in very good agreement with the experimental value of 355 kcal mol^{-1}. [13] Remembering that the gas-phase basicity and the PA values differ by the entropy term for a free proton, which is about 8 kcal mol^{-1}, the experimental PA should be about 363 kcal mol^{-1}. A value of 356 kcal mol^{-1} can be deduced from the experimental hydrogen bond energy of the complex $CH_2{=}CHO^-\cdots HOH$.[14] As a consequence, the PA of vinyl alcohol reported in ref 9 is at least 14 kcal mol^{-1} too high as compared with the experimental one. It is also worth mentioning that the PA of vinyl alcohol computed in this work is near the experimental PA of methanol (380.1 kcal mol^{-1}).[13] Owing to the change in hybridization at the carbon bonded to oxygen and the high polarizability of the double bond, the acidity of vinyl alcohol is expected to be higher than that of methanol.[13] Inclusion of one diffuse function in the basis set also lengthens the H···O bond, shortens the OH bond, and lowers the energies.[11] This clearly appears when one compares the experimental hydrogen bond energies in the $(H_2O)OH^-$ complex (25 kcal mol^{-1})[15] and the computed 6-31G* and the 6-311+G** energies which are respectively 34.6 and 22.8 kcal mol^{-1}.[16] It also seems that in ref 9, the energies are not corrected for the basis set superposition errors. Nevertheless, if the errors on energies and PAs are considered as constant, the correlation between energies and ΔPAs can be discussed.

A second remark concerns the energies computed for values of ΔPA < 0 where the proton transfer is exothermic. Starting from the free A_1^-, A_2^-, and H^+ species, one can consider two reaction paths (a) and (b).

$$A_1H\cdots A_2^- \overset{(a)}{\Leftarrow} A_1^- + H^+ + A_2^- \overset{(b)}{\Rightarrow} A_1^-\cdots A_2H$$

The hydrogen bond energies correspond to the association via path (a) when the basicity of A_1^- is higher than that

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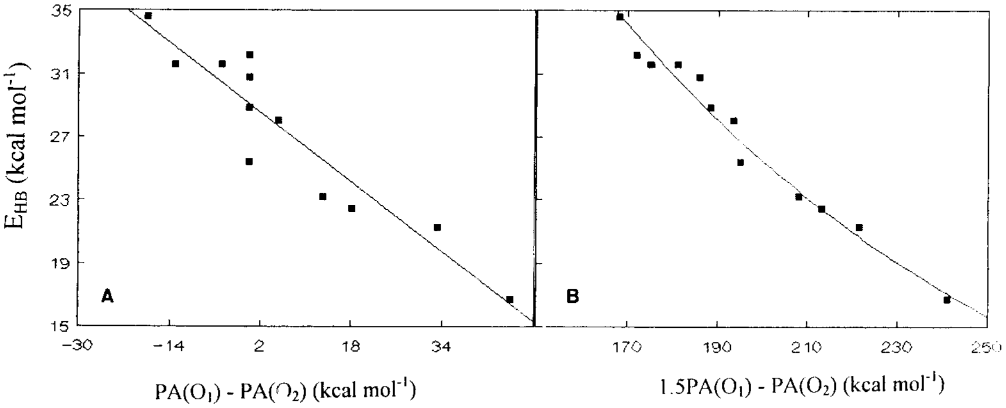

Figure 1. Hydrogen bond energies of the enol–enolate systems (A) as a function of PA(O_1) − PA(O_2) (ref 9) and (B) as a function of 1.5PA(O_1) − PA(O_2).

of A_2^- ($\Delta PA > 0$); in this case, the proton is preferentially bonded to A_1^-. One can also consider the association via path (b) where the proton is bonded to the anion having the lowest PA ($\Delta PA < 0$). The association energy for process (b) must be obtained by adding PA(A_1^-) − PA(A_2^-) to the enthalpy characterizing the (a) process. This was not obtained in ref 9. For the (NH_2, F) and (F, NH_2) complexes, the computed energies are 22.5 and 34.6 kcal mol^{-1} respectively and the computed PAs 390 and 372 kcal mol^{-1}; the energy difference (12.1 kcal mol^{-1}) does not correspond to the difference in PA of the two partners (18 kcal mol^{-1}). The same remark also holds for the (NH_2, H) and (H, NH_2) complexes characterized by energies of 23.2 and 31.6 kcal mol^{-1}, the PAs of the corresponding anions being 390 and 377 kcal mol^{-1}, respectively.

2. Correlation between Hydrogen Bond Energies and PA. Chen et al. [9] presented the following equation between the hydrogen bond energies of the enol–enolate systems:

$$E_{HB} = 29.06 - 0.275\,[PA(O_1) - PA(O_2)]\ (r = 0.9376) \quad (1)$$

Numerous correlations between the experimental hydrogen bond energies and differences in the PAs of the two partners have been established in the literature,[17–22] in agreement with the theoretical predictions of Desmeules and Allen.[23] The symmetric but not linear fall off in the hydrogen bond strength on both sides of $\Delta PA = 0$ has been discussed by Davidson et al.[17] More than 10 years ago, we have shown that, in a broad range, the correlation between the hydrogen bond energy and ΔPA takes an exponential form and that there is no discontinuity at $\Delta PA = 0$.[24] The discontinuity outlined in ref 9 is thus not a new finding. The Marcus equation,[25,26] although not reliable for high-barrier hydrogen bonds,[24] also implies a nonlinear dependence between hydrogen bond energies and ΔPA.

A simple correlation between hydrogen bond energies and ΔPA allows one to predict, in a homologous series, the same energies at the matched ΔPA value of zero. This is only a very rough estimation. Indeed, for the homomolecular enol–enolate complexes, the energy drops from 32.2 to 25.4 kJ mol^{-1} when going from the most acidic enol (X = CN) to the most basic one (X = NH_2). These results indicate that the acidity of the proton donor is a more determinant factor in determining the hydrogen bond energies than the basicity of the proton acceptor. This finding is also in very good agreement with the fact that in formally symmetric proton-held dimer cations $(BHB)^+$, the bond energies decrease as the PA of the base B increases.[27] These considerations strongly suggest that better correlations between hydrogen bond energies and difference in PAs of the two partners can be obtained when taking different coefficients for the proton donor and the proton acceptor. In this way, the following linear equation is obtained:

$$E_{HB} = 74.8 - 0.243\,[1.5PA(O_1) - PA(O_2)] \quad (r = 0.9836) \quad (2)$$

This equation shows some similarities with the dual substituent parameter equation proposed by Caldwell et al.[18] which has been overlooked in the literature. The best correlation coefficient is computed for the following exponential equation:

$$E_{HB} = 178.6e^{-0.00973[1.5PA(O1) - PA(O2)]}\ (r = 0.9885) \quad (3)$$

For the purpose of comparison, both equations 1 and 3 are illustrated in Figure 1.

We must observe here that, in the present case, the correlation coefficients of eqs 2 and 3 do not greatly differ. In a wide range of acidities or basicities (ΔPA extending from −80 to +80 kcal mol^{-1}), the hydrogen bond energies do not obey a straight-line relationship.[17,21]

The fact that the coefficients of the PA of the proton donor and the proton acceptor are not the same, notwithstanding the similar nature of the acceptor and donor groups, may be intuitively related to the asymmetry of the hydrogen bond and to the barrier to proton transfer. It is also worth mentioning that the greater importance of the proton donor in determining the hydrogen bond

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energies has been recently outlined for the interaction between nucleobases and water and seems to be a general feature of the hydrogen bond.[28]

3. Symmetry of the Enol−Enolates Hydrogen Bonds. Chen et al.[9] have computed, for the homomolecular enol−enolate complexes, modest barriers for proton transfer, between 2.1 and 2.6 kcal mol^{-1} and after zero-point energy corrections, the barriers become negative. They have concluded that there is a single well after inclusion of zero-point energy. There is some confusion because the shape of a potential well does not depend on the zero-point energy correction. The proton can on the average occupy a central position or, in other words, the probability density function takes a maximum value at this point. In these conditions the geometry of the transition state must be the same as that of the optimized geometry, at least if the calculations are correct. But Chen et al. computed for the homomolecular complexes, O···O distances of 2.37−2.38 Å in the transition state and equilibrium distances ranging from 2.54 to 2.57 Å. Some recent calculations on $(OHO)^-$ systems carried out by the density functional or MP2 theory combined with the split-valence 6-31+G** basis set show very nicely the difference in the geometry of the transition state and of the equilibrium state as a function of the geometry of the hydrogen bond.[29] For the strong LBHB in a Kemp's triacid monoanion, the minimum energy structure is found for an O···O distance of 2.42 Å and the distance in the transition state is 2.39 Å, the small difference being only a numerical rounding effect. For this monoanion, the first vibrational level appears above the transition state and the ground vibrational state wave function has a maximum value just at the transition state region. In contrast, in hydrogen oxalate, the minimum energy structure is found at an O···O distance of 2.50 Å and the distance in the transition state is 2.33 Å. In this last system, the barrier to proton transfer is about 3 kcal mol^{-1}, the ground vibrational level is below the energy barrier separating the two minima so that the proton is found at or near the minima. As a consequence, the proton is not centralized in this system. In the enol−enolate system ($X = Y = H$), the equilibrium O···O distance (2.56 Å) (which as discussed before is probably underestimated at this level of calculation) and the O···O distance in the transition state (2.37 Å) are somewhat larger than that in hydrogen oxalate, and this strongly suggests the existence of a noncentralized proton.

The equilibrium distances of 2.54−2.57 Å computed for the enol−enolate complexes[9] also strongly suggest that the complexes are not symmetrical. A plot of the OH distance as a function of the O···O distance from selected neutron diffraction data shows indeed that when the O···O distance is 2.55 Å, the OH distance takes the value of 1.04 Å.[30] Symmetric hydrogen bonds become favored only when the O···O distance is shorter than 2.48 Å.[30] All quantum mechanical and empirical calculations indicate that there is a functional dependence between O···O distances and hydrogen bond energies, the latter increasing almost exponentially when the O···O distance tends to its minimum.[31−32] For distances shorter than 2.50 Å, there is a very strong increase of the binding energy.[33,34] The linearity observed for the enol−enolate systems indicates per se that the hydrogen bond is not centrosymmetrical.

4. Other Hydrogen Bond Properties. It must be pointed out here that other physical properties such as the isotope ratio of the OH/OD stretching frequencies can also be indicative of the symmetry of the hydrogen bond. The anomaly in the isotope frequency ratio at RO···O = 2.5 Å[34] is due to the double minimum property.[35−37] The infrared frequencies (appearance of a collapse),[38] the intensities of the absorption continuum,[39−40] the NQR resonance frequencies,[41] the NMR shifts of the proton,[42−44] and the dipole moments[45,46] also show a very strong departure from linearity for ΔpK_a values at which one expects 50% proton transfer. These ΔpK_a values are not equal to zero but vary within the limits of 1 to 5, depending on the nature of the hydrogen bond, the solvent, and the temperature.

Conclusions

Chen et al. have attempted to strip away the “Alice in Wonderland” quality of the definition related to the “low-barrier” nature of the hydrogen bonding by defining through “high level” calculations when short, strong hydrogen bonds do and do not occur. As discussed in this note, several parameters indicate that the hydrogen bonds in homomolecular enol−enolate complexes are not symmetrical. For this reason, no marked stability accrues near the PA matching. The importance of strong hydrogen bonds in enzymatic catalysis has been the subject of considerable controversy arising mainly from the fact that there is really a “no-man's land” between the specialists of the fundamental (experimental or theoretical) properties of the hydrogen bonds and people discussing the importance of these bonds in living materials.

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