Hydration of Carbonyl Compounds, an Analysis in Terms of No Barrier Theory: Prediction of Rates from Equilibrium Constants and Distortion Energies

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Abstract: “No Barrier Theory” postulates that when only one thing happens there is a quadratic relation between energy and reaction progress, with no kinetic barrier. The kinetic barrier seen with essentially all real chemical processes results from the need for more than one thing to happen simultaneously. This approach permits calculation of free energies of activation for covalent hydration of carbonyl compounds, over the range of reactivity for which data are available, from formaldehyde to carboxamides. Acid- and base-catalyzed and uncatalyzed reactions can be treated with no adjustable parameters, with root-mean-square errors of 1.41, 1.30, and 1.50 kcal/mol in free energy of activation. The method requires equilibrium constants and distortion energies. The latter can be calculated by molecular orbital theory using relatively low levels of theory. The calculations can be inverted to calculate equilibrium constants from experimental rate constants.

Introduction

We have devised a new approach, which we call “No Barrier Theory”,[1−3] for calculating rate constants for chemical reactions from the experimental equilibrium constants. The approach shows great promise of providing a general method for calculating the rate constants for chemical reactions with no adjustable parameters. Thus far it has been able to describe a number of reactions with root-mean-square errors less than 2 kcal/mol for rate constants in solution.

Ab initio calculation of equilibrium constants requires very high levels of theory, and even at the highest level currently practical the calculations require an empirical adjustment to give gas-phase values. Calculation of solvation energies is becoming increasingly possible but remains difficult, as shown by recent papers discussing the solvation of amines in water.[4−6] To determine the structure and energy of a transition state in solution by ab initio calculations remains an extremely challenging problem. An advantage of No Barrier Theory is that by using experimental equilibrium constants it avoids the difficult problems of calculating bonding and solvation energies, and requires only relatively easy calculations of distortion energies.

Rate and equilibrium constants for the addition of water to carbonyl compounds have been shown to follow Marcus theory.[7−10] In the accompanying paper we have examined this reaction by applying multidimensional Marcus theory.[11] With a single value of the intrinsic barrier for carbon oxygen bond formation and the value for proton transfer shown to work for both water mediated proton transfers and water mediated proton switch reactions[12] we could fit all of the data for addition of water to esters, amides, thioesters, and ketones, whether hydroxide catalyzed, uncatalyzed, or acid catalyzed.[11] Unreactive aldehydes also fit the pattern, but hydroxide additions to the more reactive aldehydes deviated from the pattern and had intrinsic barriers which were linear in the equilibrium constant for addition. The high reactivity rather than the aldehyde functional group seems to be the key thing. The most reactive ketones, esters, and thioesters also required lower intrinsic barriers for the hydroxide additions, but there were so few compounds in these families with high reactivity that no pattern could be seen. On one hand the overall success of this approach, with a transferable intrinsic barrier, was quite striking. On the other hand, the finding that reactive aldehydes can only be described by intrinsic barriers which are a function of the equilibrium constant means that the hope of describing organic chemistry with a limited set of transferable intrinsic barriers has been dashed. Recently a new approach has been devised[1−3] which avoids the need for intrinsic barriers, and allows the rate constants for all of these reactions to be calculated with no adjustable parameters. The application of this approach to carbonyl hydration is described in the present paper.

Work in progress applying No Barrier Theory to other families of reactions suggests that it will prove to be very general.

Theory

The approach to be used in this paper is based on the assumption that if only one thing happens in a chemical reaction, there is no kinetic barrier and there is a quadratic dependence of energy on the reaction coordinate: see Figure 1a. To progress from the low-energy to the high-energy end of the reaction

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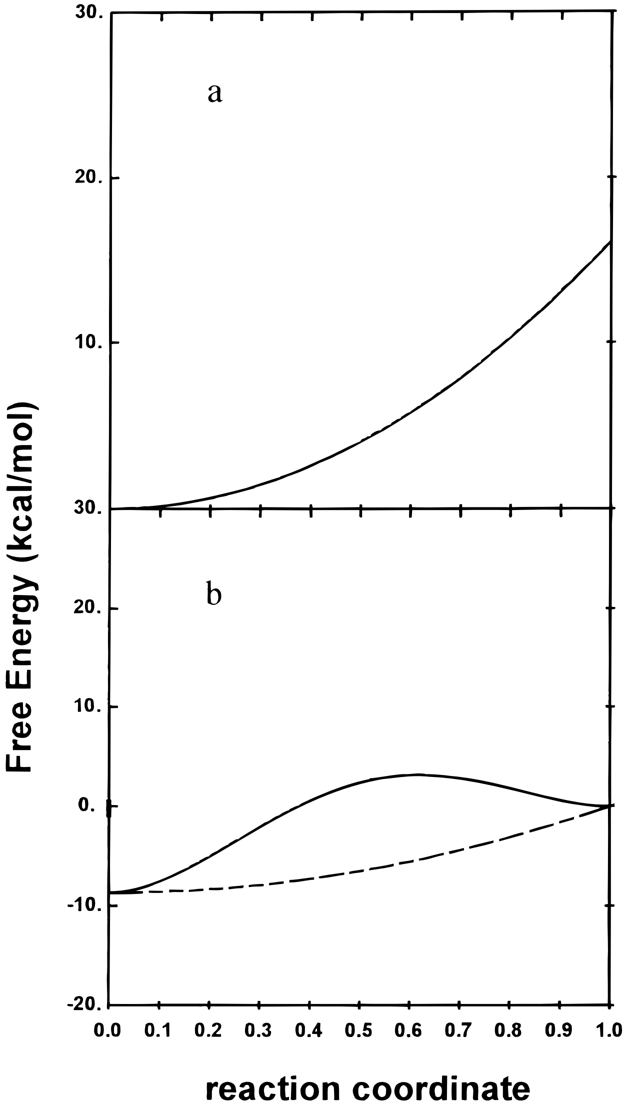

Figure 1. (a) A simple quadratic relationship between energy and reaction coordinate leads to no barrier along the reaction coordinate. (b) For most real reactions there is a barrier, which may be approximated, as here, by a quartic relationship between energy and reaction coordinate (—); the quadratic through the same initial and final points is a poor approximation to the actual behavior (- - -).

coordinate requires no extra energy, i.e., there is no kinetic barrier. This flies in the face of the common experience that for real reactions there is a kinetic barrier as illustrated in Figure 1b. This shows a kinetic barrier between the initial and final points, so that a molecule cannot go from the lower to the higher energy end of the reaction coordinate unless it has more energy than the difference between the ends, i.e., unless it has the additional energy corresponding to the kinetic barrier. For this real reaction the corresponding quadratic function passing through the energies of the initial and final species is a poor approximation to the actual energy dependence on reaction coordinate. The key is the clause “if only one thing happens”. The common occurrence of kinetic barriers is a result of the complexity of almost all chemical reactions which involve more than one simple process. In the specific case of carbonyl addition, the simple processes are bond formation to the carbonyl carbon and geometry change from sp^2 to sp^3. With two simple processes required for the observable chemical change, the assumption that any section through the energy diagram parallel to one of the edges will have an approximate quadratic dependence of energy on the reaction coordinate leads to a kinetic barrier as illustrated in Figure 2. C−O bond formation is very often accompanied by proton-transfer processes involving water molecules (or general acid or base catalysts). We have found that proton transfer from oxygen to oxygen can, to a good approximation, be treated as a simple process. These assumptions have been applied to enolate formation[3] and to cyanohydrin formation.[2] There are abundant data for carbonyl hydration reactions, so examination of this process constitutes a good test of the theory. For a convenient shorthand this theory will be referred to as “No Barrier Theory”.

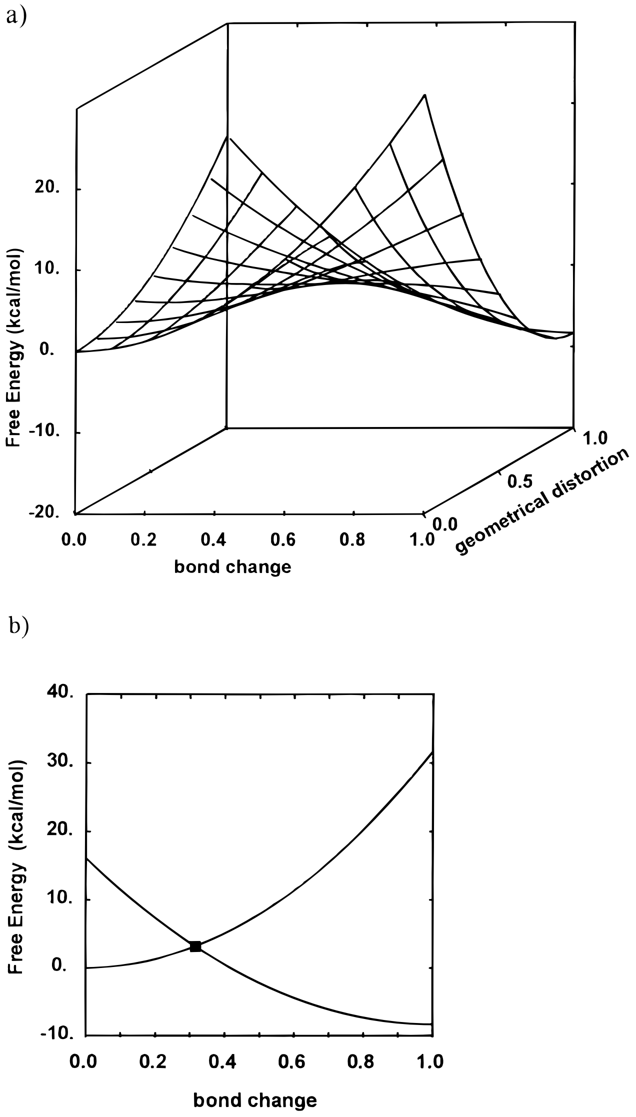

Figure 2. If a reaction requires two simple processes (each leading to a quadratic relationship) both to be completed for the overall reaction to have taken place, then the quadratic relationships in either single dimension lead to a kinetic barrier for the real, two-dimensional process. (a) A perspective drawing of the three-dimensional energy surface. (b) A projection of the same surface along the geometrical distortion dimension: (■) location of the transition state.

No Barrier Theory follows from the following postulates:[2,3]

(1) Reactants are in equilibrium with starting material or product at each point along each reaction coordinate.

(2) For any process where only one elementary reaction coordinate changes, the energy will be a quadratic function of the corresponding reaction coordinate.

(3) Heterolytic bond cleavage constitutes an elementary reaction coordinate.

(4) For an anion to react at a carbon center, it must first undergo partial desolvation so that its reactive lone pair can be in van der Waals contact with the carbon.

(5) Reaction coordinates are defined to run from 0 to 1.

That the energy cost of geometrical distortions should show a quadratic dependence on the reaction coordinate, interpreted as a suitable angle, will seem unexceptionable, since this is the behavior on which molecular mechanics is based.[13] That a similar "force law" should apply to bond breaking/bond making processes seems less intuitively reasonable. However, it is commonly accepted that for simple bond breaking (as in diatomic molecules) the energy should follow a Morse curve, which relates energy to bond length. If we transform from bond length to bond order using the Pauling relation, then the Morse curve is transformed into a quadratic in bond order. Thus with suitable choice of reaction coordinates, all "simple" one-thing-at-a-time processes should give quadratic "force laws".

To apply No Barrier Theory to these reactions, we need detailed models for the mechanisms. We have used general models which should cover all levels of reactivity. This means that the more elaborate models required in some cases are assumed at the beginning for all the molecules. Each particular system can choose to follow a simpler path, which will be a subset of the full model.

As part of creating such a model we must consider possible partial desolvation events. We assume that any carbonyl oxygen with a $\delta-$ charge will be surrounded by sufficient waters with hydrogens directed at it to provide full hydrogen bonding solvation if it becomes O^-. However, if the oxygen is initially protonated, it will be surrounded by water oxygens, with no water hydrogens pointed at it. Thus if it becomes an OH, it will initially be missing two hydrogen bonds worth of solvation. (We use an admittedly oversimplified model where each atom to be solvated is tetrahedrally surrounded by solvent or bonded atoms.) If a carbonyl oxygen is initially hydrogen bonded to hydronium ion but not protonated, then we assume that the oxygen still bears a $\delta-$ and is hydrogen bonded by two waters as well as hydronium ion, and thus when it becomes OH it will be fully solvated. These assumptions are not the same as in a recent paper on cyanohydrin formation[2] but reflect recent theoretical studies on solvation which show that carbonyl oxygens are very likely to have three solvating waters with hydrogens directed at the oxygen.[14-19] A hydroxide next to a carbonyl group is necessarily missing one hydrogen bond to solvent if it is to have a lone pair ready to attack the carbonyl; this imposes a partial desolvation energy. The energies of these desolvation events were estimated as described previously.[11]

The model for hydroxide addition is shown in Figure 3. In this figure, as for all the models discussed, we show the reaction diagram, in this case a cube, and below it, vertically displaced but in the same relative orientation, the structures corresponding to each corner. It was necessary to do this rather than putting the structures near the actual corners to avoid clutter in the higher dimensional diagrams. The simple processes which are used as reaction coordinates are the following in the present case: (000−001) proton transfer from water to hydroxide leading to a partly desolvated hydroxide next to the carbonyl carbon; (000−010) C−O bond formation, leading to a zwitterionic hydrate; and (000−100) geometry change at the carbonyl carbon, from sp^2 to sp^3. A third hydrogen-bonded water is assumed to be in contact with the carbonyl oxygen through the π-molecular orbital. Although this hydrogen bond is weak it is assumed to be present a significant fraction of the time so that the free energy cost of forming it is negligible. This model requires a cubic reaction diagram.

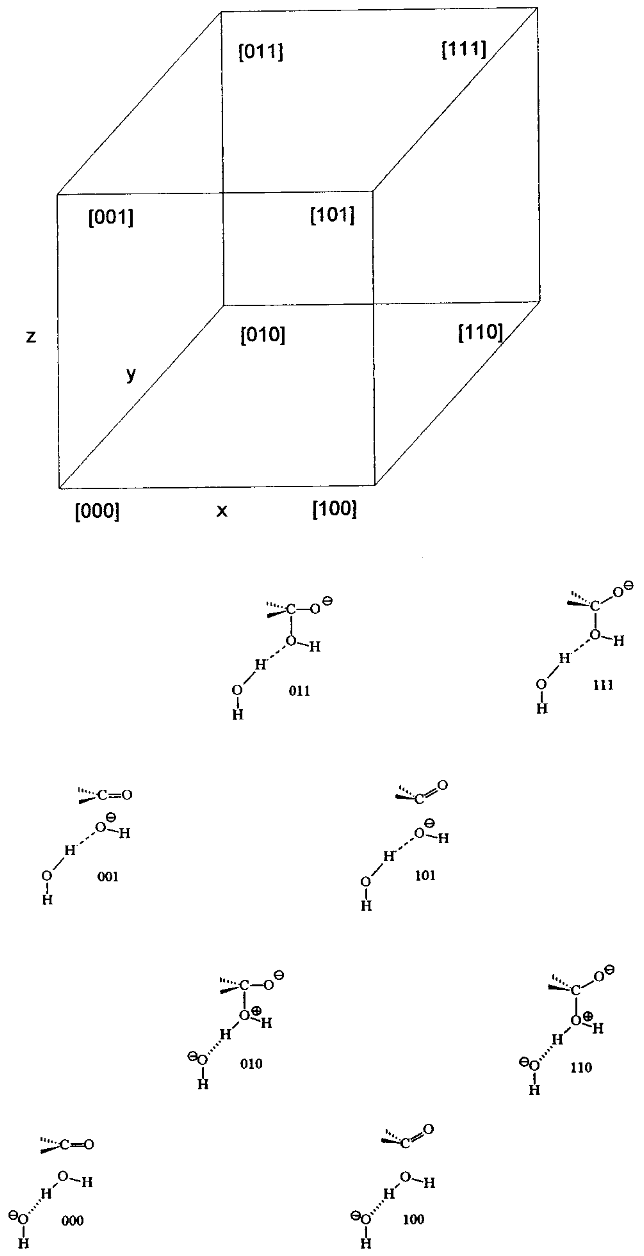

Figure 3. Cubic reaction diagram for hydroxide addition to carbonyl compounds.

Two models were explored for uncatalyzed hydration. In the first there are two water molecules, one acting as a nucleophile and the other as a general base. The zwitterion is often (though not always) more acidic than hydronium ion, so that this proton transfer is expected to be essentially barrierless if the hydrogen bond is in place. In the other the transition state is cyclic with three water molecules, one acting as nucleophile and the other

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(13) Bond length distortions might also be considered but to date we have found no cases where consideration of bond length changes accompanying but separate from bond formation/breaking is necessary or helpful in describing a reaction.

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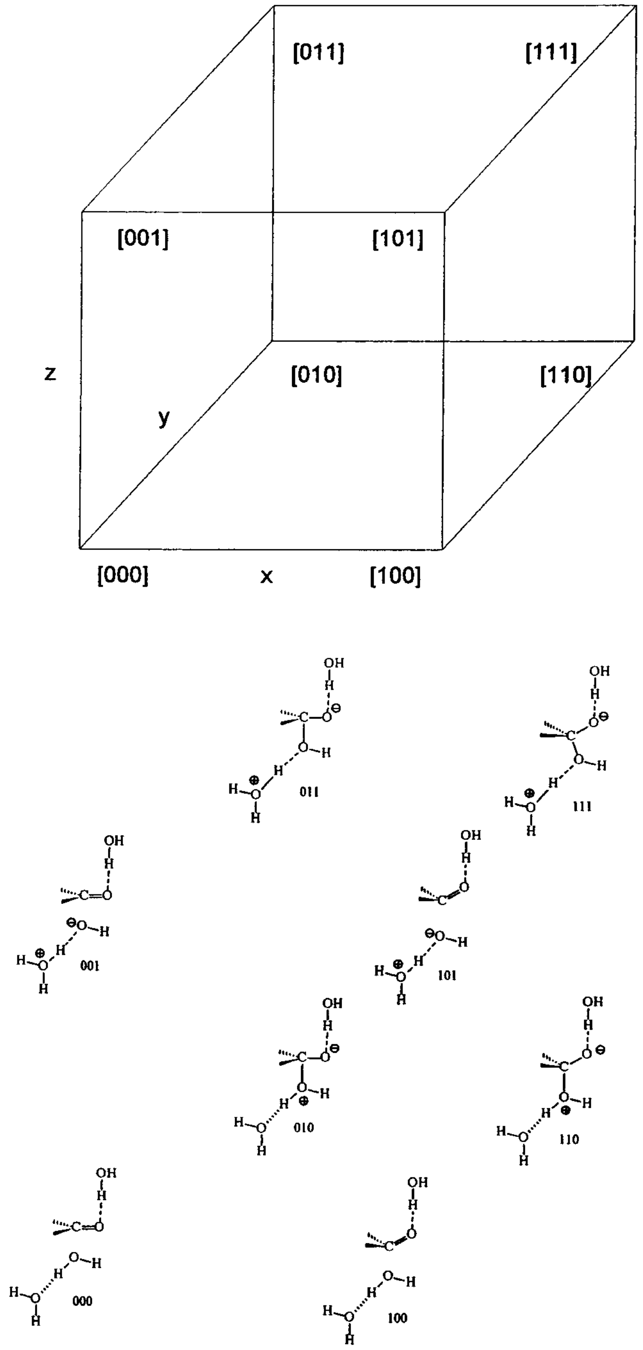

Figure 4. Cubic reaction diagram for addition of water to carbonyl compounds, assuming that one water acts as a nucleophile and a second water acts as a general base.

two in a hydrogen-bonded chain bridging the nucleophilic water to the carbonyl oxygen, so that the product is the neutral carbonyl hydrate.

The first model, with two water molecules, is shown in Figure 4. This process leads to the anionic form of the hydrate, though this will recombine with hydronium ion as soon as the latter can diffuse around to do so. Consequently the calculation used distortion energies calculated for the anion of the hydrate. This process requires a reaction cube.

The second model, the cyclic mechanism involving three water molecules, is shown in Figure 5. The five major atoms are arranged in a fashion analogous to the envelope conformation of cyclopentane. This model requires a five-dimensional hypercube reaction diagram. Such a hypercube is difficult to draw in two dimensions and difficult to interpret once drawn. The best we have been able to devise is to take two four-dimensional hypercubes displaced diagonally from each other and to join the corresponding corners. This is in effect a representation of a five-dimensional hypercube. It is unsatisfactory because the dimensions to not look equivalent as they ought to, but at least it is usable. Structures corresponding to the 32 corners are drawn below the two four-dimensional sections of the hypercube, i.e., (0xxxx) and (1xxxx). For both the four- and five-dimensional hypercubes it was necessary to draw the structures in two groups for each four-dimensional hypercube, again to avoid clutter. The corner structures for the top and bottom cubes for each hypercube are drawn in position, but slightly shifted to provide room for them while retaining a regular arrangement. The two subcubes are distinguished by the value of the *y*-coordinate.

Finally the model used for acid-catalyzed hydration is shown in Figure 6. This model is more elaborate than is needed in all cases, but should include all compounds. In some cases the reaction may involve fully protonated carbonyl compound as starting point, but in most cases the protonated carbonyl compound is more acidic than hydronium ion so that proton transfer to a hydrogen-bonded water would be essentially barrierless. This process requires a four-dimensional reaction hypercube.[20]

With all of these models the input parameters for the calculation of the transition state energy are the free energies of the corner intermediates. For each model the energies of all of the corner intermediates must be calculated. This is done by taking account of the equilibrium constant for C−O bond formation (when this has happened), the energy cost of any geometrical distortion, the equilibrium constant for any proton transfer (using the pK_a values estimated as described in the accompanying paper[11]), the energy contributions for any hydrogen bonds formed when the nonsolvent species involved in the corner intermediate come together in the geometry specified (estimated as before[12] using the Stahl−Jencks equation[22]), any electrostatic interactions between these species (estimated as before[12]), and any desolvation costs involved in generating the actual species (estimated as described above). The detailed calculations used, which in effect calculate the Marcus work term, are the same as for the application of Multidimensional Marcus Theory to these hydration reactions, and are described in more detail in the accompanying paper.[11] The only difference in the present case is that the C−O bond-making process becomes two reaction dimensions rather than one so that twice as many corner intermediates are required for each mechanism.

Distortion energies were calculated by Molecular Orbital Theory at various levels (AM1, HF/3-21+G*, B3LYP/3-21+G*) using Gaussian 94.[23] The carbonyl compound and its neutral and anionic hydrates were fully optimized at each level of theory. In the anionic hydrate of *S*-ethyl thiolformate it was necessary to lock the C−S bond length to prevent the

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[20] This representation of a hypercube was used by Gamow.[21]

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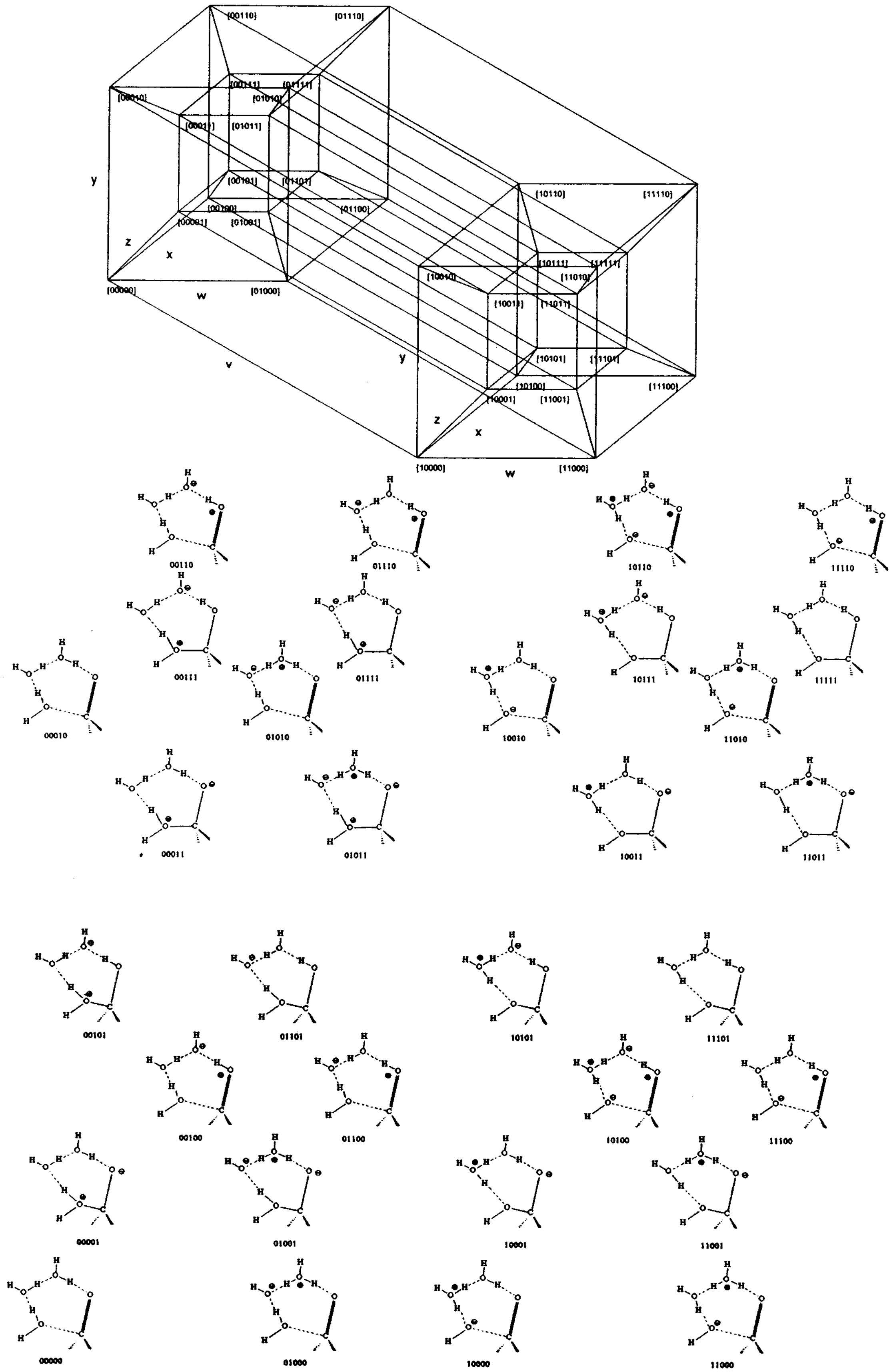

Figure 5. Five-dimensional hypercube diagram for addition of water to carbonyl compounds, assuming a cyclic mechanism involving three water molecules.

molecule from falling apart. Partial optimizations for distorted forms of the neutral and anionic carbonyl compounds were carried out with bond angles and dihedral angles for the atoms attached to the carbonyl carbon locked at the values in the corresponding neutral or anionic forms of the hydrate. Partial optimizations for the distorted forms of the neutral and anionic

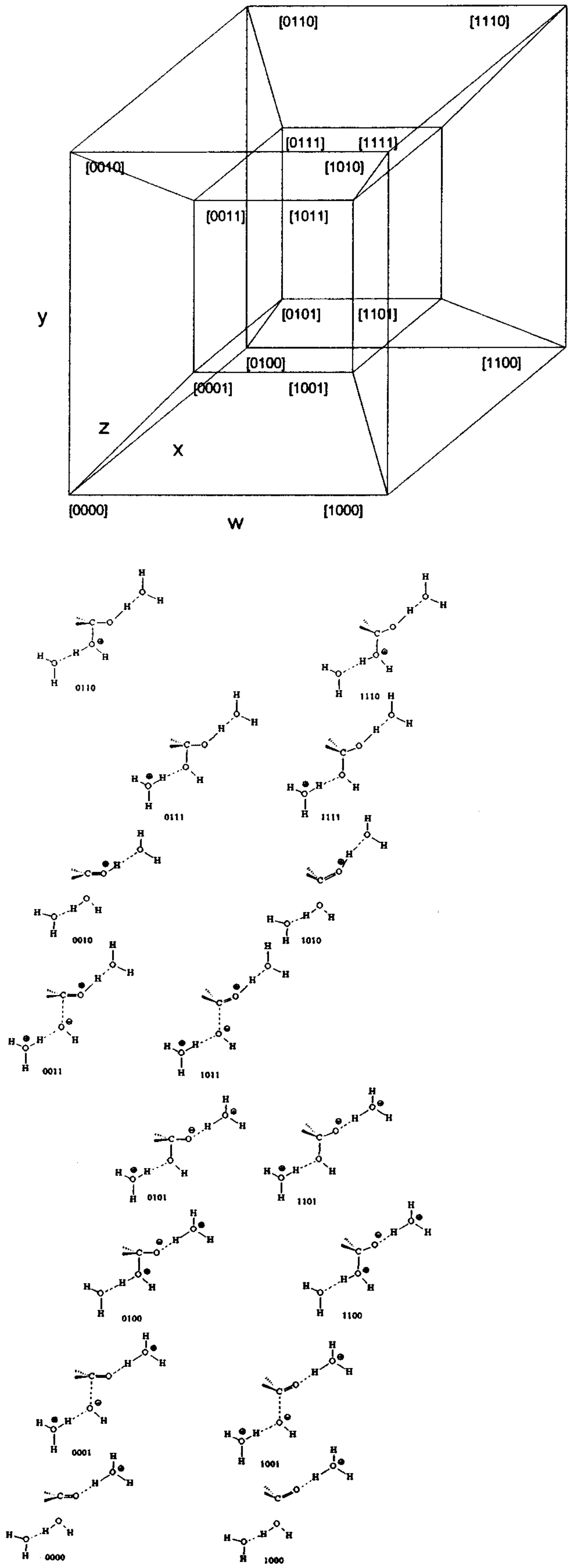

Figure 6. Four-dimensional hypercube diagram for acid-catalyzed addition of water to carbonyl compounds.

hydrates were carried out with the bond angles and dihedral angles describing the bonds from the reaction center to the atoms present in the neutral carbonyl compound locked at the values in that compound, and the bond to the nucleophile locked at the length in the optimized form of the corresponding hydrate, with angles and dihedrals locked at the values corresponding to perpendicular attack. Esters, thioesters, and their protonated forms were assumed to be in the S-trans conformations. Addition of water to carbonyls was assumed to proceed with anti stereochemistry where there were substitutents on the atom initially doubly bonded to carbon which defined the stereochemistry. Distortion energies were calculated as the difference in energy between a distorted species and the corresponding form with optimized geometry.

The method we are using to calculate rate constants for reactions involves breaking a real reaction into a series of elementary reactions simple enough to follow a quadratic law for energy vs reaction coordinate. Thus all distortions should be relative to the final product or initial starting material.

In terms of the acid-catalyzed reactions this has the following consequences in terms of how distortions should be calculated. The reaction is presumed to run from neutral starting material, hydrogen bonded to hydronium ion, to neutral product, hydrogen bonded to hydronium ion.

The base-catalyzed reaction runs from neutral starting material to anionic hydrate. The results are best if the anionic hydrate is allowed to optimize, including allowing the C−OH bond to lengthen. For the distorted form of the hydrate this bond must be locked at the optimized bond length from the equilibrium hydrate anion or else the hydroxide will fall off.

The uncatalyzed reaction (noncyclic variation) runs from neutral starting material to anionic hydrate (hydrogen bonded to hydronium ion by the OH). The distortion energies are the same as for the base-catalyzed reaction. The uncatalyzed reaction in the cyclic variation runs from the neutral starting material to the neutral hydrate. The distortion energies are the same as for the acid-catalyzed reaction.

Various algorithms have been used to find the transition state. The simplest one is based on projection. If one projects a two-dimensional reaction diagram, as in Figure 2a, along one of the reaction dimensions, which we call the "projected dimension", as in Figure 2b, one sees the two limiting quadratics, "front" and "back", for the other reaction dimension, which we call the "displayed dimension". By the central hypothesis of this work, the energy along the "projected dimension" at any point on the "displayed dimension" is a quadratic linking the points on the "front" and "back" curves. Then there is no barrier at the value of the "displayed dimension" where the curves cross, and the free energy is the same for any value of the "projected dimension". The difficulty with this simple picture is that there are, for the two-dimensional case, two ways to do the projection, and it may be shown mathematically that in general the calculated transition state free energy for the two projections will not be the same.[2] The differences are not large. Numerical exploration with a range of plausible values for the overall energy change and the energies of the corner intermediates showed that the difference in the two calculated transition state energies was at most 0.6 kcal/mol in the two-dimensional case.

To overcome this difficulty one can try to deduce an analytical expression for the surface, by melding the edge expressions in some way. We have reported one such surface,[2] and others are possible.[24] The problem with all of these surfaces is that there is an arbitrary weighting parameter controlling how the edge equations are melded. Numerical exploration allowed the weighting parameter to be chosen to minimize deviations from the idealized quadratic section behavior,[2] but no general

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(24) Dunn, B. M. *Int. J. Chem. Kinet.* **1974**, *6*, 143−159.

objective criterion has been found. Furthermore, the equation for the surface becomes increasingly complicated and difficult to program for higher dimensions. For some plausible mechanistic paths as many as six reaction dimensions are needed. Fortunately it turned out that the energy of the transition state found using the analytical surface corresponded more closely to the lower of the values found by the projection approach. Accordingly we have settled on the projection algorithm for all cases, and used the lowest of the projected transition state energies for the set of possible projections at a given level.

For higher dimensional cases the projection algorithm is conceptually the same as for the two-dimensional case except that the energy along a profile perpendicular to the "front" and "back" quadratics of the "displayed dimension" is no longer a curvilinear function of the one "projected dimension" as in the two-dimensional case, but rather a surface in all of the perpendicular dimensions, and the projected energy is no longer the higher of the "front" and "back" curves, but may be higher than either, depending on the nature of the surface, and corresponds to the free energy barrier to interconversion of the points on the "front" and "back" curves. The multidimensional surface defining the energy has one less dimension than the original reaction diagram. We now proceed recursively, evaluating the energy barrier by applying projection repeatedly until we reach a two-dimensional case where energy can be determined. At each stage the lowest barrier is taken as the true one. Thus for a three-dimensional case we pick one dimension as the "displayed dimension" and for each point along this dimension calculate the barrier to progression from the front to the back quadratic of the two-dimensional reaction diagram linking them. Then the lowest energy barrier for progression from front to back quadratic will correspond to the transition state for this three-dimensional reaction diagram. This is done for all three dimensions in turn, and the lowest transition state energy is taken as the true value.

Results and Discussion

We begin with equilibrium constants for covalent hydration of the carbonyl compounds, either measured, or calculated starting with free energies of formation of the carbonyl compound and its dimethyl acetal,[25] or estimated using rate equilibrium correlations.[9] The origins of these values are documented in the accompanying paper,[11] and the values are found in Table 1 of that paper. We then estimate various pK_a values for the tetrahedral intermediates, and where necessary for the protonated carbonyl compounds. These estimation procedures are described in the accompanying paper,[11] and the values are found in Table A2 therein.

The results of these calculations are summarized in Tables S1−S4.[26] Calculations of distortion energies were carried out at various levels. AM1 required much less computer time than ab initio methods, and gave good results. Ab initio calculations either at Hartree−Fock (3-21+G*) or DFT (B3LYP/3-21+G*) levels gave similar but no better, and in fact often slightly poorer, agreement between observed and calculated free energies of activation, and required much more computer time. We conclude that at least for these hydration reactions, AM1 is quite satisfactory. All levels of calculation gave good agreement between calculated and observed free energies of activation, the root-mean-square error being in the vicinity of 1.5 kcal/mol for each set. For all reactions considered (using the cyclic mechanism for water addition) the root-mean-square errors (kcal/mol) were the following: DFT 1.53, HF 1.85, AM1 1.40. For compounds treated by all three methods, the root-mean-square errors (kcal/mol) (for all reactions) were the following: DFT 1.47, HF 1.79, AM1 1.35.

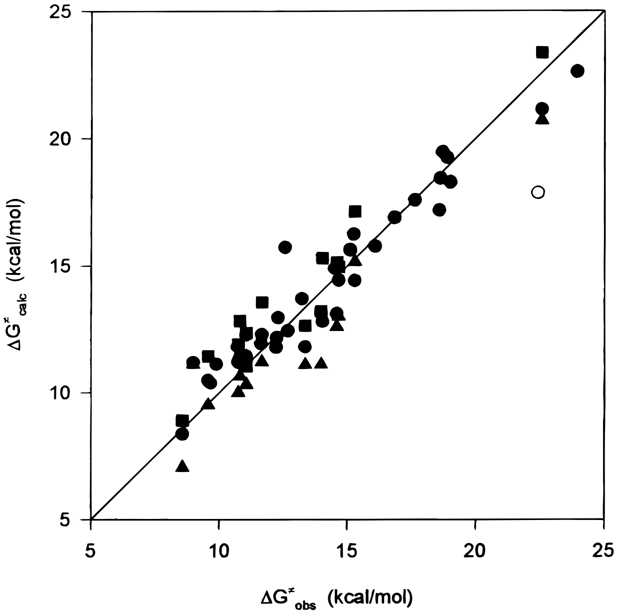

Figure 7. Calculated vs observed values of $\Delta G^{\ddagger}$ for the hydroxide-catalyzed hydration of carbonyl groups: (●) AM1 calculation of distortion energies; (■) HF/3-21+G* calculation of distortion energies; (▲) B3LYP/3-21+G* calculation of distortion energies; and (○) AM1 calculation of distortion energies for *N*-methylformanilide, for which addition is not the rate determining step for hydrolysis.

For hydroxide-catalyzed hydration, the agreement is generally very satisfactory, as shown in Figure 7. For all entries in Table S1, only six show errors greater than 2 kcal/mol, and only two are greater than 3 kcal/mol. Of these, one represents reaction of methyl trichloroacetate, where the rate constant had to be estimated from that for the ethyl ester,[9] and the equilibrium constant was estimated from the rate of the hydroxide reaction, using Marcus Theory.[9] It is now known that the assumption of a transferable intrinsic barrier breaks down for highly reactive compounds such as trihaloacetates.[11] The other serious deviation is *N*-methylformanilide, where the rate determining step for hydroxide-catalyzed hydrolysis is the breakdown of the tetrahedral intermediate and not its formation. In this case the deviation is not a failure of the method but a success.

For the uncatalyzed addition of water, two models were examined, with the results shown in Tables S2 and S3 and Figures 8 and 9. The cyclic model seems to be in better agreement with the observed free energies of activation, since the root-mean-square error (AM1 results) is 1.53 kcal/mol rather than 1.74 kcal/mol for the general base catalysis mechanism, and the average signed error[27] is −0.49 kcal/mol rather than −1.00 kcal/mol. Both models have a tendency to give calculated free energies of activation which are too low, but this is more serious for the general base model. This is awkward, because the assumptions of No Barrier Theory lead to the conclusion that the lowest calculated barrier will be the correct one. However, for all of the values calculated at the AM1 level, the root-mean-square difference between the two models is 1.73 kcal/mol, and much of this comes from the least reactive

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[25] Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898−906.

[26] These tables are available as Supporting Information.

[27] This is the simple average of calculated − observed free energy of activation, and should be zero if there were no systematic error. The negative values obtained imply calculated free energies of activation which are too low.

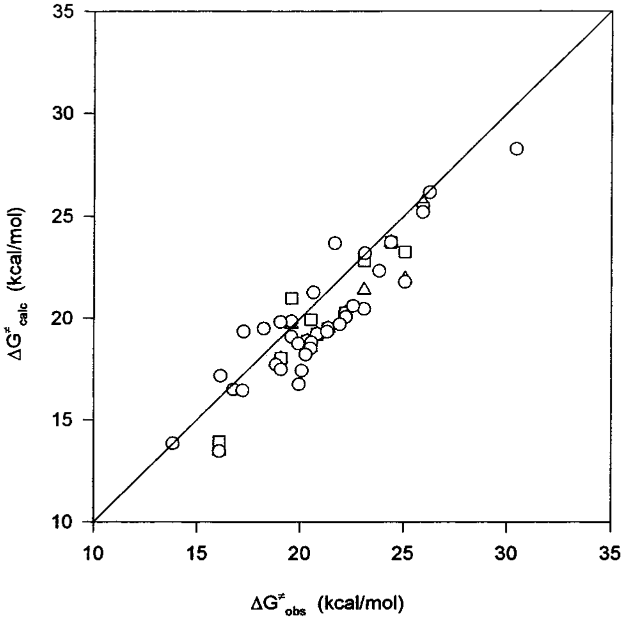

Figure 8. Calculated vs observed values of $\Delta G^{\ddagger}$ for the uncatalyzed hydration of carbonyl groups, by the two water molecule (general base) mechanism: (○) AM1 calculation of distortion energies; (□) HF/3-21+G* calculation of distortion energies; and (△) B3LYP/3-21+G* calculation of distortion energies.

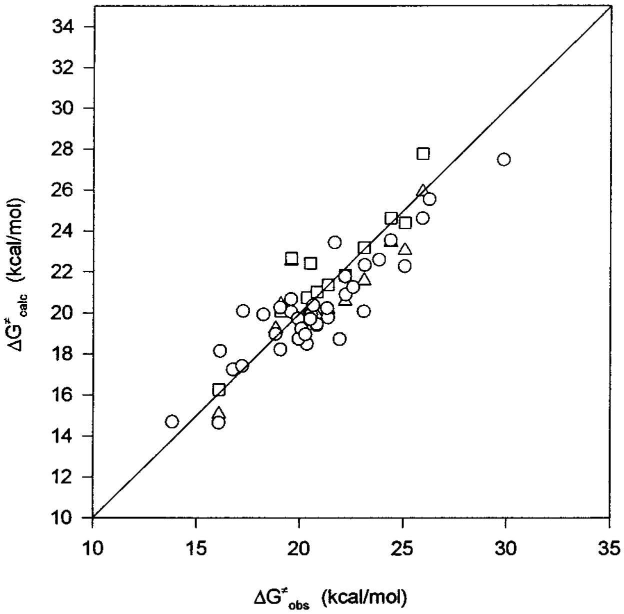

Figure 9. Calculated vs observed values of $\Delta G^{\ddagger}$ for the uncatalyzed hydration of carbonyl groups, by the three water molecule (cyclic) mechanism: (○) AM1 calculation of distortion energies; (□) HF/3-21+G* calculation of distortion energies; and (△) B3LYP/3-21+G* calculation of distortion energies.

compounds. For all compounds except amides, the root-mean-square difference is 0.93 kcal/mol, which is less than the uncertainty in the method, taken as the root-mean-square deviation seen for reactions with unambiguous models; this is generally 1.5−2.0 kcal/mol.

In fact there is little to choose between the models for aldehydes and ketones, though the general base model tends to give lower free energies of activation, and for these compounds the root-mean-square difference is 0.90 kcal/mol. However, for esters, thioesters, and amides the cyclic model most often leads to the lower predicted free energies of activation. Our calculations support the cyclic model for less reactive compounds, but do not give clear support for either with more reactive compounds. If anything, the two water, general base model is better for these substrates, but the differences are less than the inherent uncertainty in the method. For amides there are very few data for uncatalyzed hydrolysis, but the two recent reports of rate constants for amide hydrolysis at neutral pH, for resin bound-Phe-Phe-Phe- - -Gly, $\Delta G^{*} = 29.09$ kcal/mol,[28] or for N-Ac-Gly- - -Gly, $\Delta G^{*} = 31.71$ kcal/mol,[29] are close to the values calculated here for DMF or DMA using the cyclic model and much lower than the values calculated for the general base model.

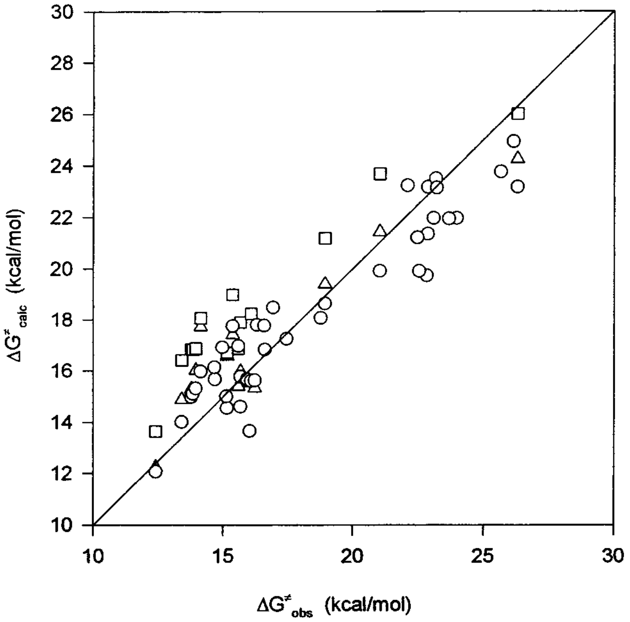

Figure 10. Calculated vs observed values of $\Delta G^{\ddagger}$ for the acid-catalyzed hydration of carbonyl groups: (○) AM1 calculation of distortion energies; (□) HF/3-21+G* calculation of distortion energies; and (△) B3LYP/3-21+G* calculation of distortion energies.

For acid-catalyzed hydration the agreement between observed and calculated $\Delta G^{\ddagger}$ is slightly poorer than that for the other pathways, as shown in Table S4 and Figure 10. This may reflect the imperfectly known pK_{BH^+} values for these substrates, which generally fall in the H_o region where there are strong activity coefficient effects, and for which correction to water as the standard state is still imperfect.

The process of calculating free energies of activation from equilibrium free energy changes can be inverted to allow calculation of equilibrium free energy changes from free energies of activation and distortion energies. This is indeed possible and the exercise is instructive. Table S5[26] shows the results of this calculation, using rate data for hydroxide-catalyzed hydration. The quality of the estimated equilibrium changes depends on the magnitude of the equilibrium free energy change, ΔG°, as shown in Figure 11. For positive values of ΔG°, the estimated values are close to those determined experimentally; the more negative ΔG° is the less reliable the estimated values become. This is a consequence of the nature of the presumed Marcus relation between free energy of activation and equilibrium free energy change.

$$\Delta G^{\ddagger} = \tilde{G}(1 + \Delta G^{\circ}/4\tilde{G})^2$$

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[28] Kahne, D.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7529−7534.

[29] Radzicka, A.; Wolfenden, R. *J. Am. Chem. Soc.* **1996**, *118*, 6105−6109.

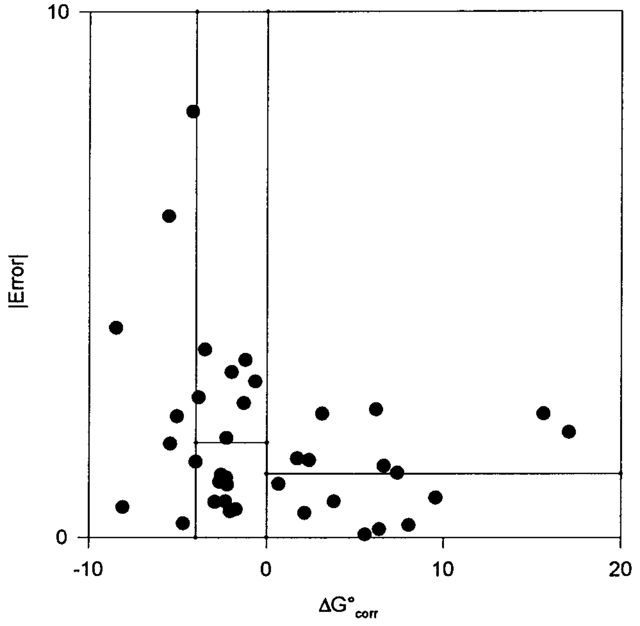

Figure 11. Error in calculated $\Delta G°$ as a function of $\Delta G°_{\mathrm{corr}}$. The absolute error is plotted and average values for two ranges of $\Delta G°_{\mathrm{corr}}$ are shown. $\Delta G°_{\mathrm{corr}}$ is the free energy change for reaction leading from the solvent-separated encounter complex of hydroxide with a carbonyl compound to the carbonyl hydrate anion; see Table S11.

From which it follows:

$$(\mathrm{d}\Delta G^{\ddagger}/\mathrm{d}\Delta G°) \approx 0.5 \text{ for } |\Delta G°| \text{ small}$$

$$(\mathrm{d}\Delta G^{\ddagger}/\mathrm{d}\Delta G°) \approx 1.0 \text{ for } \Delta G° \text{ large and positive}$$

$$(\mathrm{d}\Delta G^{\ddagger}/\mathrm{d}\Delta G°) \approx 0.0 \text{ for } \Delta G° \text{ large and negative}$$

Thus negative values of $\Delta G°$ are unlikely to be calculated with useful precision from the observed $\Delta G^{\ddagger}$ because the slope relating them is small and therefore large changes in $\Delta G°$ are needed to make small changes in $\Delta G^{\ddagger}$; conversely positive values of $\Delta G°$ are likely to be calculated with useful precision from the observed $\Delta G^{\ddagger}$ because the slope relating them is approaching unity. A factor which accentuates the effect of greater sensitivity at negative $\Delta G°$ is that $\tilde{G}$ falls for such values of $\Delta G°$ although it is approximately constant for positive $\Delta G°$. The result is that the root-mean-square error is 1.44 kcal/mol when $\Delta G° > 0$, 2.10 kcal/mol for $-4 < \Delta G° < 0$, and 3.89 kcal/mol for $\Delta G° < -4$. This analysis has the happy result that where calculation of $\Delta G°$ from $\Delta G^{\ddagger}$ is least likely to work, direct measurement is most likely to be possible, while where the calculation is most likely to work, direct measurement is likely to be difficult, and evaluation, if it is possible at all, will require indirect extrathermodynamic approaches. Thus the method is most useful where it is most needed, and should prove a valuable tool wherever the mechanism is well-known, and a tested mechanistic model is available.

The reported rate constant for uncatalyzed hydration of fluoroacetone is surprising because it is considerably faster than the analogous value for chloroacetone. Since the σ^* values are essentially identical and there should be no serious steric effects with only one substitutent added to acetone, one would have expected rather similar rate constants. The predicted values are in fact rather similar. An examination of Taft plots for haloketones and methyl haloacetates suggested that the reported rate constants for both chloroacetone and fluoroacetone were anomalously fast.[11]

Conclusions

The primary message from this investigation is that the method of calculating rate constants following No Barrier Theory works very successfully for a wide range of carbonyl compounds. Extensive tests have been carried out with a substantial body of data, spanning a wide range in reactivity and considerable variation in functional group. In particular we were able to treat hydroxide addition to all carbonyl compounds with no adjustable parameters, where Marcus Theory required variable intrinsic barriers, and thus multiple adjustable parameters, for the same data set. In effect No Barrier Theory provides a means to calculate the Marcus intrinsic barrier for reactions in solution. In principle such barriers could be calculated for a few examples and then used for similar reactions when the approximation of transferable barriers seemed likely to hold.

No Barrier Theory allowed calculation of free energies of activation for a wide range of carbonyl hydration reactions with a root-mean-square error of 1.5 kcal/mol or less for either AM1 or B3LYP/3-21+G* calculation of distortion energies or of 1.9 kcal/mol for HF/3-21+G* level calculations. This means that rate constants can be calculated with enough precision to be of practical use, provided only that the equilibrium constant is known or can be estimated.

It is known that AM1 suffices for approximate calculation of vibrational frequencies[30] so it is perhaps not surprising that it works well in the present case to calculate distortion energies which are closely related to vibrational frequencies.

The method shows promise in the reverse sense, for calculating equilibrium constants from rate constants where the equilibrium constant is unfavorable. Such attempts to extract equilibrium constants from rate data require that the mechanism be well understood.

Our results do not resolve the issue of the cyclic vs noncyclic mechanisms for uncatalyzed hydration but clearly support the cyclic mechanism for reactions where the addition is difficult. Experimental investigations leading to proposals of the cyclic mechanism have often involved reactive compounds (formaldehyde, dichloroacetone, chloral), admittedly in mixed aqueous organic solvents.

No Barrier Theory has been shown to work for an extensive series of proton-transfer reactions over a wide range of reactivity for C−H acids,[3] and now for carbonyl hydration reactions over a wide range of reactivity. The approach seems likely to be very generally applicable. Further investigations of other classes of reactions are under way, and will be reported in due course.

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Supporting Information Available: Table S1, observed and calculated free energies of activation for hydroxide catalyzed addition of water to carbonyl compounds; Table S2, uncatalyzed hydration of carbonyl compounds: two water molecule model; Table S3, uncatalyzed hydration of carbonyl compounds, cyclic mechanism; Table S4, acid-catalyzed hydration of carbonyl compounds; Table S5, calculation of equilibrium free energy changes from free energies of activation: hydroxide catalyzed hydration (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992991Q

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[30] Seeger, D. M.; Korzeniewski, W.; Kowalchyk, W. *J. Phys. Chem.* **1991**, *95*, 6871−6879.