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Hydration of Carbonyl Compounds, an Analysis in Terms of Multidimensional Marcus Theory

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Abstract: Rate constants for base-catalyzed, uncatalyzed, and acid-catalyzed additions of water to 50 compounds (aldehydes, ketones, esters, thioesters, and amides) have been calculated using Multidimensional Marcus Theory. For all of these reactions except hydroxide addition to reactive aldehydes a single average value of the intrinsic barrier (8.51 kcal/mol) can be used to give calculated values within 1 kcal/mol (root-mean-square error) of the observed values. For the addition of hydroxide to reactive aldehydes it is necessary to use an intrinsic barrier linearly related to the equilibrium constant for hydroxide addition. The work term in Marcus Theory is approximated by a detailed model of the solvation and statistical cost of bringing reactants together.

Introduction

Rate and equilibrium constants for the addition of water to carbonyl compounds have been shown to follow Marcus theory.[1−11] We have examined this reaction several times, starting with a naive and simplified version of Marcus theory[11] and gradually using more sophisticated models: first explicit inclusion of diffusion steps leading to encounter complexes within which actual reaction occurs (when there is a second reactant other than solvent);[10] then explicit allowance for the energetic cost of partially desolvating anions when they are in direct contact with the carbonyl compound.[8] In these earlier treatments different intrinsic barriers were found for the different mechanisms: different models for the work term led to different values for the intrinsic barrier, because the two parameters are correlated. In the simplest treatment, which almost ignored the work term, the intrinsic barriers were the following: uncatalyzed hydration, intrinsic barrier, $\tilde{G} < 4$ kcal/mol;[11] hydroxide addition, $\tilde{G} = 8$ kcal/mol; and acid catalyzed hydration, $\tilde{G} = 7$ kcal/mol; however, the points for aldehydes and ketones deviated from the line for esters and amides and seemed to require a different mechanism. A more sophisticated treatment applied to esters alone, which allowed for complex formation, but only took account of the entropic cost of bringing species together, led to very similar values for all three paths: uncatalyzed hydration, $\tilde{G} = 8.8$ kcal/mol; hydroxide addition, $\tilde{G} = 9.0$ kcal/mol; and acid-catalyzed hydration, $\tilde{G} = 8.8$ kcal/mol. This treatment, however, did not allow for desolvation of the hydroxide ion when it was brought into contact with a carbonyl group. We have argued that this should cost 7.1 kcal/mol.[12] Treatment of ester reactions with inclusion of the cost of desolvation led to a very similar value, $\tilde{G} = 8.5$ kcal/mol, for hydroxide addition, but this approach led to nonsensical results for formaldehyde, where the cost of encounter plus desolvation was greater than the observed free energy of activation. This suggested that for reactive compounds reaction might begin with the hydroxide separated from the carbonyl by one water molecule, thus avoiding the cost of desolvation, and that proton transfer (in effect bringing hydroxide into contact with the carbonyl carbon) would be concerted with carbon−oxygen bond formation. To test this idea required a version of Marcus theory appropriate to concerted reactions.

We have now reexamined these reactions and wish to report that a remarkable unification, giving improved predictive power, can be achieved by applying multidimensional Marcus theory[13] to carbonyl hydration reactions. 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,[14] we can fit all of the hydration data for esters, amides, and thioesters, whether hydroxide catalyzed, uncatalyzed, or acid catalyzed. Ketones and unreactive aldehydes also fit the pattern, but hydroxide additions to the more reactive aldehydes deviate from the pattern and have intrinsic barriers which are dependent on the equilibrium constant for addition.

On one hand the overall success of this approach, with a transferable intrinsic barrier, is quite striking. The intrinsic barrier for carbon−oxygen bond formation is found to be the same whether the nucleophile is hydroxide or water, and whether the carbonyl compound is protonated or unprotonated.

On the other hand, the finding that reactive aldehydes can only be described by intrinsic barriers which are a function of

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(1) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891−899.

(2) Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224−7225.

(3) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249−4256.

(4) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155−196.

(5) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701−3708.

(6) Reference 7 gives about 50 references to the application of Marcus theory to organic reactions.

(7) Guthrie, J. P. *Can. J. Chem.* **1996**, *74*, 1283−1296.

(8) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3941−3949.

(9) In refs 10 and 11 intrinsic barriers were given in units of log k, with the symbol b^5; in later work intrinsic barriers are given in units of kcal/mol, with the symbol $\tilde{G}$.

(10) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1980**, *58*, 1281−1294.

(11) Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892−5904.

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the equilibrium constant means that the hope of describing organic chemistry with a limited set of transferable intrinsic barriers has been dashed. Fortunately a new approach has been devised which avoids the need for intrinsic barriers; this is described in the accompanying paper.[15]

The practical implication of these results is that there is now a method of known generality and known limitations by which one can very easily calculate the rate of hydration for a carbonyl compound, by the acid-catalyzed, base-catalyzed, or uncatalyzed paths, provided that the equilibrium constant is known or can be estimated. Alternatively, given the rate, one could invert the calculation and calculate the equilibrium constant. The known limitation is that the intrinsic barrier for hydroxide addition becomes dependent on the equilibrium constant for highly reactive compounds.

The results reported in this paper support the case that Marcus theory, and its Multidimensional Marcus Theory variant, provide a convenient interpolation method for the approximate estimation of unknown equilibrium constants.

In this work, in common with most applications of Marcus theory, the quadratic form of the Marcus relation,[1] will be used:

$$\Delta G^{\ddagger}_{\text{corr}} = \tilde{G}\left(1 + \frac{\Delta G^{\circ}_{\text{corr}}}{4\tilde{G}}\right)^2 \qquad (1)$$

where $\Delta G^{\ddagger}_{\text{corr}}$ and $\Delta G^{\circ}_{\text{corr}}$ refer to reaction within an encounter complex, i.e., after correcting for the work terms:

$$\Delta G^{\ddagger}_{\text{corr}} = \Delta G^{\ddagger}_{\text{obs}} - w_{\text{R}}$$

$$\Delta G^{\circ}_{\text{corr}} = \Delta G^{\circ}_{\text{obs}} - w_{\text{R}} + w_{\text{P}}$$

where w_{R} = work required to bring the reactants together in the initial encounter complex and w_{P} = work required to bring the products together in the final encounter complex.

A slightly more complicated, though in practice equivalent, version of the Marcus relation, eq 2, was derived for atom transfer reactions.[1]

$$\Delta G^{\ddagger}_{\text{corr}} = \tilde{G} + {}^1\!/_2\Delta G^{\circ}_{\text{corr}} + \left(\frac{\tilde{G}}{\ln(2)}\right)\ln\left(\cosh\left(\frac{\tilde{G}}{\ln(2)}\right)(\cosh(\Delta\Delta G^{\circ}_{\text{corr}}\ln(2)/2\tilde{G})\right) \qquad (2)$$

Marcus theory provides a useful description of many simple reactions.[5] An extension of the theory, Multidimensional Marcus Theory, was developed to deal with reactions which involve two or more simple processes occurring simultaneously, as in the E2 elimination,[12] which can be regarded as a simultaneous proton abstraction and carbon-leaving group ionization, avoiding the unstable intermediates (carbanion and carbocation, respectively) in both. The theory has been generalized[13] to higher dimensional cases and applied to reactions involving proton transfers, such as the water-mediated proton switch.[14] The intrinsic barrier for proton transfer between electronegative atoms was found to be ca. 1 kcal/mol.[14]

Multidimensional Marcus Theory requires an intrinsic barrier for each of the simple process which are used as reaction dimensions. In the case of carbonyl hydration processes, one of these dimensions is carbon−oxygen bond making, and the rest are proton transfers between oxygens. For a two-dimensional case, cf. Figure 1, Multidimensional Marcus Theory leads to eq 3

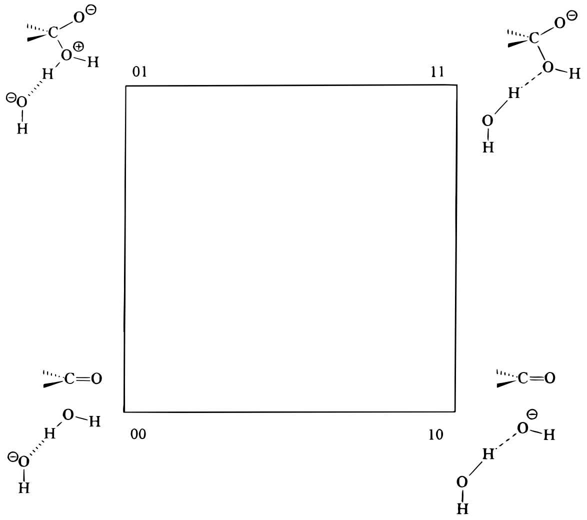

Figure 1. Reaction square for hydroxide-catalyzed hydration of a carbonyl compound.

$$G = a_1x^2 + a_2y^2 + a_3x^3 + a_4y^3 + a_5x^4 + a_6y^4 + a_7x^2y^3 + a_8x^3y^2 + a_9x^3y^3 + a_{10}x^2y^2 \qquad (3)$$

$$a_1 = 16\tilde{G}_x + 3(G_{10} - G_{00})$$

$$a_2 = 16\tilde{G}_y + 3(G_{01} - G_{00})$$

$$a_3 = -32\tilde{G}_x - 2(G_{10} - G_{00})$$

$$a_4 = -32\tilde{G}_y - 2(G_{01} - G_{00})$$

$$a_5 = 16\tilde{G}_x$$

$$a_6 = 16\tilde{G}_y$$

$$a_7 = a_8 = -6(G_{11} - G_{10} - G_{01} + G_{00})$$

$$a_9 = 4(G_{11} - G_{10} - G_{01} + G_{00})$$

$$a_{10} = 9(G_{11} - G_{10} - G_{01} + G_{00})$$

where $\tilde{G}_x$ is the intrinsic barrier for the x-direction, $\tilde{G}_y$ is the intrinsic barrier for the y-direction, G_{00} is the initial energy, G_{11} is the final energy, G_{10} is the energy after reaction along the x-reaction coordinate only, and G_{01} is the energy after reaction along the y-reaction coordinate only.

Thus the only parameters needed are the intrinsic barriers for each reaction dimension, and the input data are the corner energies for the hypothetical simple reactions (or combinations thereof in higher dimensional cases). Implicit in this derivation is the assumption that the intrinsic barrier for one direction is independent of the value of the other reaction dimensions, and in particular that the intrinsic barrier for C−O bond formation should be the same for uncatalyzed hydration, hydroxide addition, or acid-catalyzed hydration, when the reactions are treated by Multidimensional Marcus Theory. This assumption will be tested in the work reported here. The test is successfully passed in that the same intrinsic barrier does work for all three mechanism. An intrinsic barrier determined from data for

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Table 1. Equilibrium and Rate Constants for Covalent Hydration of Carbonyl Compounds

compd	log K	log k_w	log k_{OH}	log k_{H^+}
H_2CO	3.36^{a}	1.00^{b}	6.51^{b}	3.73^{b}
CH_3CHO	0.03^{c}	−2.33^{b}	4.68^{b}	2.04^{b}
CH_3CH_2CHO	−0.07^{a}	−2.46^{d}	4.7^{e}	2.69^{f}
$CH_3CH_2CH_2CHO$	−0.08^{d}	−2.46^{d}	4.7^{e}	2.65^{d}
$(CH_3)_2CHCHO$	−0.21^{a}	−2.85^{g}	2.99^{h}	2.57^{f}
				1.85^{h}
$(CH_3)_3CCHO$	−0.63^{a}	−3.46^{i}	2.54^{i}	1.36^{i}
CCl_3CHO	4.45^{j}	2.65^{k}		
X-PhCHO, X = H	−2.10^{l}	−4.00	2.5	1.25
4-Cl	−1.79^{m}	−3.48^{n}	3.49^{n}	1.30^{n}
3-Cl	−1.66^{n}	−3.28^{n}	3.82^{n}	1.04^{n}
3,4-Cl_2	−1.35^{o}	−2.95^{p}	4.23^{q}	1 × 10^{r}
4-CF_3	−1.25^{n}	−2.82^{n}	4.26^{n}	1.11^{n}
3-NO_2	−0.96^{n}	−2.43^{n}	4.68^{n}	1.05^{n}
4-NO_2	−0.77^{n}	−2.26^{n}	4.92^{n}	1.11^{n}
4-Cl-3-NO_2	−0.74^{n}	−2.24^{n}	4.86^{n}	1.00^{n}
3,5-$(NO_2)_2$	0.32^{n}	−1.00^{n}	6.20^{n}	0.90^{n}
2-Cl-5-NO_2	−0.47^{o}	−1.91^{p}	5.34^{q}	1.01^{r}
$(CH_3)_2CO$	−2.85	−5.07^{s}	2.04^{b}	1.52^{b}
$CH_2ClCOCH_3$	−1.05^{t}	−1.16^{t}		0.61^{t}
$CHCl_2COCH_3$	0.46^{u}			
$CH_2ClCOCH_2Cl$	1.0^{u}	−1.82^{v}		0.0^{w}
CH_2FCOCH_3	−0.78^{t}	0.15^{t}		1.81^{t}
$^{t}CF_3COCH_3$	1.54^{x}	0.96^{t}		
cyclohexanone	−2.16^{y}	2.15^{z}		2.04^{z}
cyclopentanone	−3.54^{y}	1.00^{z}		0.38
acetophenone	−5.18^{l}			
$PhCOCHCl_2$	−0.48^{aa}	−1.79^{aa}		−0.94^{aa}
$PhCOCF_3$	1.89^{bb}	0.51^{bb}	5.70^{bb}	
$CH_3COCOOCH_3$^{cc}	0.41^{t}	0.57^{t}		0.84^{t}
$CH_3COCH_2COCH_3$	−1.46^{dd}	−1.92^{t}		1.70^{t}
$CF_3COCH_2COCH_3$	1.89^{x}	0.18^{t}		0.63^{t}
$HCOOCH_3$	−6.6^{ee}	−6.2^{ee}	1.58^{ee}	−2.62^{ee}
CH_3COOCH_3	−8.2^{ee}	−9.5^{ee}	−0.82^{ee}	−3.95^{ee}
$CH_3CH_2COOCH_3$	−9.43^{ee}		−0.84^{ee}	−3.96^{ee}
$(CH_3)_2CHCOOCH_3$	−10.42^{ee}		−1.05^{ee}	−4.19^{ee}
CHF_2COOCH_3	−2.92^{ee}	−3.74^{ee}	3.81^{ee}	−3.93^{ee}
CF_3COOCH_3	−0.9^{ee}	−2.06^{ee}	5.53^{ee}	
$CH_2ClCOOCH_3$	−6.66^{ee}	−6.44^{ee}	1.71^{ee}	−4.12^{ee}
$CHCl_2COOCH_3$	−4.34^{ee}	−4.66^{ee}	3.09^{ee}	−3.67,^{ee} −4.91
CCl_3COOCH_3	−4.24^{ee}	−3.09^{ee}	3.57^{ee}	−3.40^{ee} −5.05
$NCCH_2COOCH_3$	−5.87^{ee}		1.61^{ee}	−4.77^{ee}
$CH_3OCH_2COOCH_3$	−9.21^{ee}		0.45^{ee}	−4.21^{ee}
$PhCOOCH_3$	−10.07^{ee}		−1.14^{ee}	−6.37^{ee}
$HCOSC_2H_5$	−3.5^{ff}	−5.57^{ff}	2.1^{ff}	−3.1^{ff}
$CH_3COSC_2H_5$	−8.2^{ff}	−7.3^{ff}	−0.92^{ff}	−4.3^{ff}
$CF_3COSC_2H_5$	−2.8^{ff}	−2.34^{ff}	3.77^{ff}	
$HCON(CH_3)_2$	−13.8^{ff}		−3.75^{ff}	−6.48^{ff}
$CH_3CON(CH_3)_2$	−14.2^{ff}		−4.75^{ff}	−6.01^{ff}
$CF_3CON(CH_3)_2$	−9.2^{gg}		−0.13^{hh}	
$HCON(CH_3)Ph$	−10.22^{ii}		−3.63^{jj}	−3.74^{ii}

[a] Reference 53. [b] Reference 54. [c] Reference 55. [d] Reference 56. [e] Assumed to be approximately equal to that for acetaldehyde. [f] Reference 57. [g] Calculated from data in ref 58. [h] Reference 58. [i] Calculated from data in ref 59 as described in the text. [j] Reference 60. [k] Reference 31. [l] Reference 61. [m] Reference 62. [n] Reference 63. [o] Estimated by interpolation using a plot of log K_{H_2O} vs log K_{OH}. [p] Estimated by interpolation using a plot of log k_{H_2O} vs log K_{OH}. [q] Reference 64. [r] Estimated by interpolation, using a plot of log k_H vs σ. [s] Reference 65. [t] Reference 56. [u] Reference 66. [v] Estimated by extrapolation of log k vs log x_{H_2O} for data from reactions in aqueous dioxane.[28,29] [w] Reference 54. [x] Reference 16. [y] Calculated from the equilibrium constants for acetal formation (and in the case of cyclcohexanone, hemiacetal formation) as described in the text. [z] Reference 67. [aa] Reference 68. [bb] Reference 69. [cc] For reaction as a ketone. Data are for the ethyl ester. [dd] Estimated using a linear free energy relationship, as described in the text. [ee] Reference 10. [ff] Reference 11. [gg] Estimated as described in the text. [hh] In 50% aqueous ethanol. Schmidt, J.; Mitzner, R. *Wiss. Z. Paedagogo. Hochsch. Potsdam* **1987**, *31*, 23−31. [ii] Reference 70. [jj] Reference 71.

hydroxide additions was used to calculate rates for uncatalyzed and acid-catalyzed reactions.

Results

Marcus Theory permits the calculation of the free energy of activation for a chemical reaction from the equilibrium free energy change for the microscopic process occurring within the encounter complex of reactants as they change into the encounter complex of products. Thus equilibrium constants are needed for the particular protonation states applicable to the reactions considered.

We begin with equilibrium constants for covalent hydration of the carbonyl compounds: measured, or calculated starting with free energies of formation of the carbonyl compound and its dimethyl acetal,[16] or estimated using rate equilibrium correlations.[10] These values are found in Table 1. 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 Appendix 1 (Supporting Information); the values are found in Table A2 (Supporting Information). With equilibrium constants for the neutral reaction and the various pK_a values in hand, the equilibrium constants for different protonation states of reactants and products can be calculated as needed.

To apply Multidimensional Marcus Theory to these reactions we need detailed models for the mechanisms. We have used general models which should cover all levels of reactivity so that the more elaborate models required in some cases are assumed at the beginning for all the molecules. Particular reactions 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. The number of hydrogen-bonding sites at oxygen changes as addition to a carbonyl takes place or as one is formed by elimination. 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. As before[8] we estimate this energy as 7.1 kcal/mol.

A carbonyl group is assumed normally to be hydrogen bonded to three water molecules. Two are likely to be directed to the locations conventionally ascribed to lone pairs, as seen on analysis of X-ray structures,[17] but there will often be a third water with a hydrogen directed at the carbonyl oxygen. Studies of solvation by molecular dynamics simulations show that in general carbonyl groups are solvated by more than two hydrogen bonding water molecules (the number depending on the system and the criteria used to decide whether to count a particular water molecule) and there is only a tendency for the waters to be directed at the lone pair positions, rather than a strong preference.[18−23] We further assume that if a hydronium ion is hydrogen bonded to the carbonyl oxygen, then there will still

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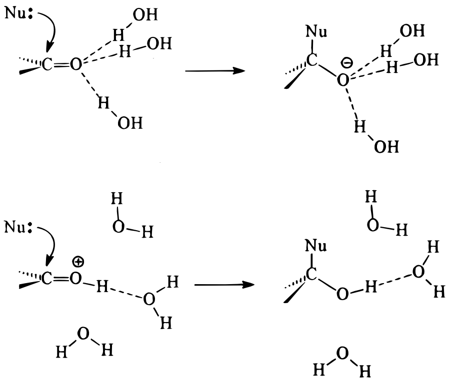
be two hydrogen bonds from water to that oxygen. On the other hand if a carbonyl is protonated, so that the oxygen bears a formal positive charge, water molecules nearby will be oriented with their hydrogens directed away from the positive oxygen, and oxygen toward it.

This implies that addition to a neutral carbonyl will lead to a fully solvated oxyanion, but that addition to a protonated carbonyl will lead to a partially desolvated OH, with the hydrogen atom hydrogen bonded to water but no water hydrogens hydrogen bonded to the new OH.

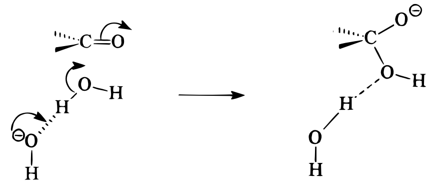


For neutral alcohols we assume that the free energy contribution of a hydrogen bond from water to an oxygen lone pair is given by half the difference in free energy of transfer (from gas at 1 atm to 1 M aqueous solution) between an ether and the analogous hydrocarbon. The value was taken from the group contributions previously reported.[24] Then the effect of electron-withdrawing substituents is calculated from the substitutent dependence of the free energy of transfer for ethers.[24] The equation so deduced for the desolvation energy is

$$\Delta G_{\mathrm{desolv}} = 1.94 - 0.212\sum\sigma^{*} \tag{4}$$

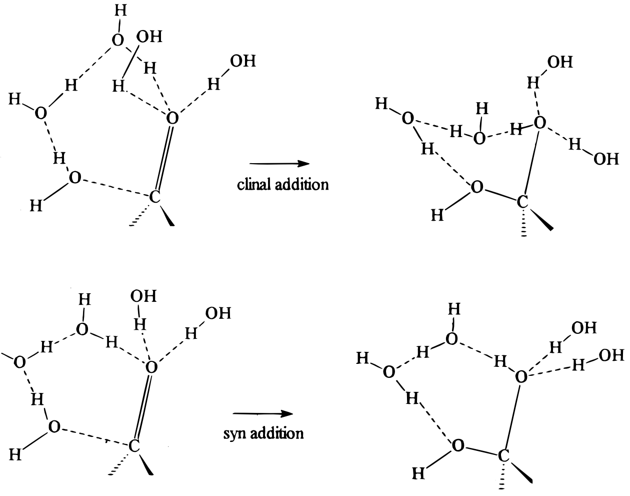
where the σ^{*} values are for the three groups attached to the carbon bearing the OH being considered.

For the hydroxide reaction, we start with an encounter complex where the hydroxide ion is separated from the carbonyl compound by one water. Depending on the reactivity of the carbonyl compound the favored reaction path may then be sequential, with a proton transfer converting this intervening water into a hydroxide ion, or concerted, with the proton transfer occurring as what was initially the intervening water forms a bond to the carbonyl. The model is as shown:

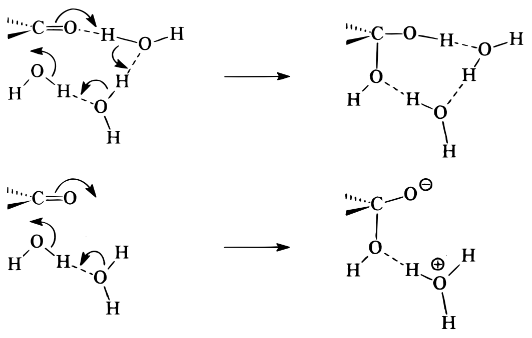


and can be described by a two-dimensional reaction diagram (an Albery−More O'Ferrall−Jencks diagram[25−27]), as shown in Figure 1.

Scheme 1

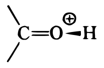


For the uncatalyzed hydration, we considered two models, with cyclic or noncyclic arrays of hydrogen bonds. In the first, cyclic model, the reaction could lead initially to a zwitterionic intermediate (if there are no concerted proton transfers), or with a concerted proton transfer could lead to the neutral intermediate. Studies of the number of water molecules involved in uncatalyzed hydration have led to the suggestion that there is a cyclic array of three waters,[28−30] though other stoichiometries have been proposed.[31] We will use a cyclic array of three waters; this is also the minimum number to give satisfactory bond angles assuming approximately linear hydrogen bonds. In the second, noncyclic model, the reaction could lead to the zwitterion or to a hydronium ion and an anionic intermediate. In the first case there are four reaction coordinates to consider, so the reaction can only be described by a reaction hypercube.[13] In the second case a square diagram is needed. The two models are:



and the reaction diagrams are shown in Figures 2 and 3.

For the cyclic mechanism there are two variations with respect to stereoelectronic factors corresponding either to syn addition, with the ═O···H−O orthogonal to the plane of the carbonyl, or to clinal[32] addition, with the ═O···H−O in the plane of the carbonyl: see Scheme 1. In the syn addition case, species with $C{=}O{-}H^{+}$ are really



and are destabilized by loss of conjugation of the C^{+} with an

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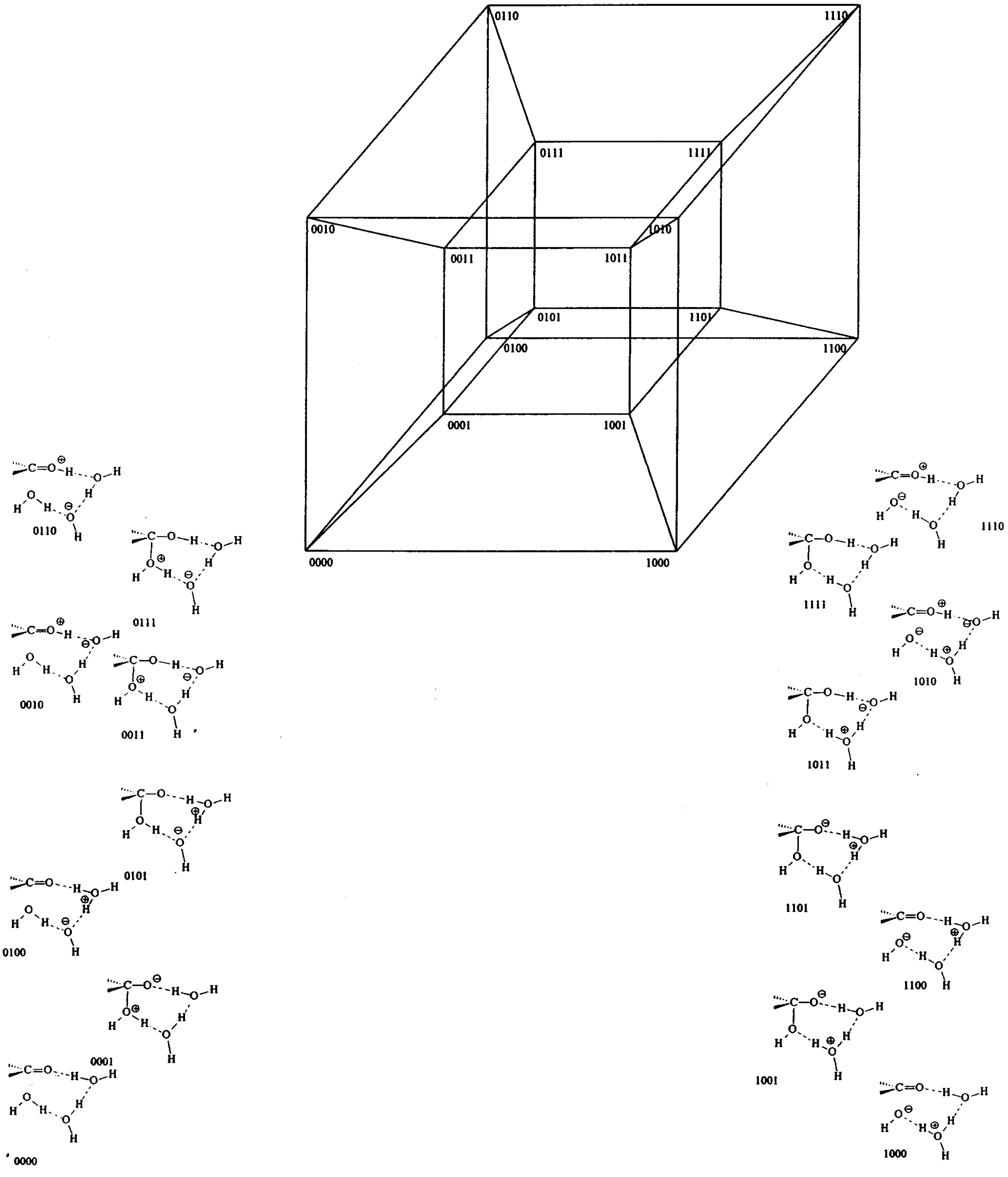

Figure 2. Reaction hypercube for the cyclic hydration mechanism for a carbonyl compound.

oxygen lone pair. Ab initio calculations[33] (B3LYP/3-21+G*) on the energies of protonated acetone in its preferred conformation and with a 90° rotation about the CO bond (with the HOC angle held fixed) gave a gas-phase distortion energy of 18.8 kcal/mol. This seems sufficient to disfavor the syn addition path for a cyclic mechanism.

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[32] (a) Addition with the angle between the two new bonds between 30° and 90° would be described as synclinal; between 90° and 150° would be anticlinal,[33b] but there seems to have been no description of the situation where the idealized angle is 90°, so I suggest clinal addition. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Sterochemistry of organic compounds*; Wiley-Interscience: New York, 1994.

[33] Gaussian 94, Revision E.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc.: Pittsburgh, PA, 1995.

Table 2. Calculations of Corner Energies for the Addition of Hydroxide to Formaldehyde[a]

				hydrogen bond							
corner structure	coord	ΔG_{eq}[b]	ΔG_{ptr}[c]	pK_{HA}[i]	pK_B[j]	ΔG_{hb}[k]	ΔG_{ip}[d]	ΔG_{enc}[e]	ΔG_{desolv}[f]	ΔG_{corner}[g]	ΔG_{corr}[h]
$HC{=}O(H),H_2O,HO^-$	00							2.01	0	2.01	0.00
$HC(O^-)(OH_2^+)(H),HO^-$	01	−4.59	16.83	0.58	16.04	−4.78	−0.69	2.42	0	9.19	7.18
$HC{=}O(H),HO^-,H_2O$	10							2.42	7.10	9.52	7.51
$HC(O^-)(OH)(H),H_2O$	11	−4.59	−1.51							−6.10	−8.11

[a] In aqueous solution at 25 °C; energies in kcal/mol. [b] Change in free energy relative to origin for neutral reactants and products. In the present case, this means $\Delta G°$ for addition of water to formaldehyde to give the neutral hydrate. [c] Free energy for proton transfer, relative to reactants in the (0,0) corner. [d] Free energy of electrostatic interaction, scaled to a value of $\Delta G_{ip} = 0.1$ kcal/mol[72] for 1:1 ion pair formation in water. Simple electrostatic calculations are used to calculate the electrostatic interaction energy for geometries other than the contact ion pair, using standard bond angles (109.5° for tetrahedral, 120° for trigonal geometries) and a single contact distance, r, for both bonding and nonbonding distances. [e] Entropic cost of bringing reactants together, calculated following Hine [5] using the equation $\Delta G_{enc} = -RT \ln(0.0085^{-(n-1)}K_\sigma)$, where $K_\sigma = 2^{(p-q)}\Pi\sigma_R/\Pi\sigma_P$, p = number of racemic products, q = number of racemic reactants, $\Pi\sigma_R$ = product of symmetry numbers of reactants, $\Pi\sigma_P$ = product of symmetry numbers of products, and n = number of nonsolvent species coming together in the encounter complex. [f] Free energy cost of partially desolvating hydroxide, estimated as previously described.[8] [g] Free energy of the corner species relative to separate reactants in solution. [h] Free energy of the corner species relative to the (0,0) corner. This gives the free energy change within the reactive encounter complex, corrected for the "work term" of Marcus Theory. [i] pK_a of acid engaged in the hydrogen bond. In the present case, this is the $-OH_2^+$ of the zwitterionic hydrate, which is hydrogen bonded to hydroxide. Only hydrogen bonds between nonsolvent species are considered. Hydrogen bonds involving solvent are assumed to be accounted for in the pK_a values used. [j] pK_a of conjugate acid of the base engaged in hydrogen bond. [k] Free energy of the hydrogen bond calculated by the Stahl−Jencks equation[39] and corrected for the entropic cost of bringing the hydrogen-bonded species together: $\Delta G_{hb} = 1.366[0.013(-1.26 - pK_B)(pK_{HA} - 16.04) - 2.04] - 2.82$.

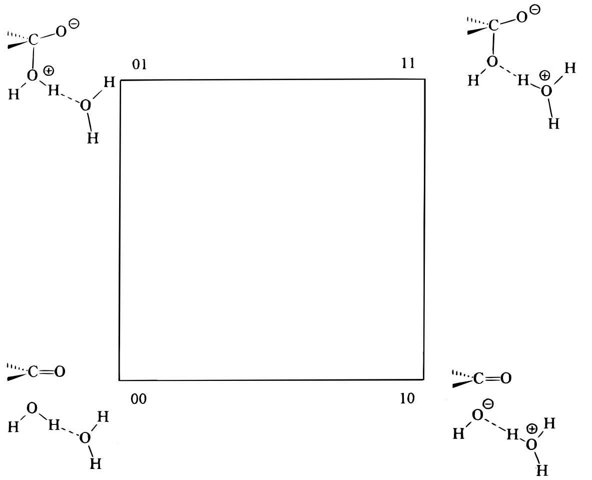
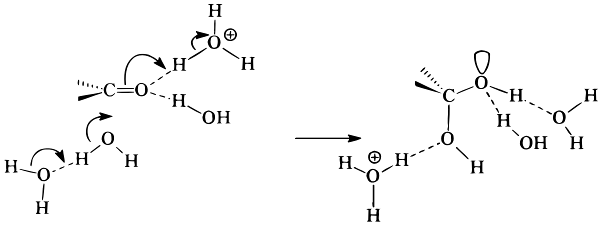


Figure 3. Reaction square for uncatalyzed hydration of a carbonyl compound by the two water molecule mechanism.

For the acid-catalyzed hydration, because the protonated carbonyl compounds are generally more acidic than hydronium ion itself, we start with the hydrogen-bonded complex of hydronium ion and the carbonyl compound. However, for amides which are relatively basic, the protonated amide is more stable than the hydrogen-bonded complex with hydronium ion, even though both are generally at least slightly less stable than the free reactants in 1 M acid.[34] Since the acid-catalyzed reactions are in general slow, there is no need to consider the encounter complex with an intervening water, because the transition state for overall addition will invariably be high in energy relative to the transition state for protonation of this last intervening water. Since the O-protonated tetrahedral intermediate is invariably acidic relative to hydronium ion, we must consider the possibility that a second water acts as a general base, removing this acidic proton concerted with the addition of water. This mechanism requires a reaction cube[36−38] to describe it, except for amides for which a reaction square suffices. The model is:



and the reaction diagram is shown in Figure 4.

With all of these models, we require Multidimensional Marcus Theory[13] to calculate the transition state energy. The input parameters for this theory are the free energies of the corner intermediates, and the intrinsic barriers for the edge reactions. We make the simplifying assumption that the intrinsic barrier for an edge reaction is independent of the value(s) of the other reaction coordinate(s). For proton transfer reactions involving electronegative atoms, the intrinsic barrier is approximately 1 kcal/mol.[14] To evaluate the intrinsic barrier for carbon−oxygen bond formation, we use the relatively straightforward reaction of hydroxide ion with carbonyl compounds.

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 equilibrium constant for any proton transfer (using the pK_a values estimated as described above), 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[14] using the Stahl−Jencks equation[39]), any electrostatic interactions between these species (estimated as before[14]), and any desolvation costs involved in generating the actual species (estimated as described above).

Equations were derived for the reaction free energy surface, based on the assumptions of Multidimensional Marcus Theory.[13]

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(34) Amides lacking electron-withdrawing substitutents have pK_{BH^+} values ≥−1.8 (see Table A2); the pK_{BH^+} of benzamide is −1.35.[35] Hydronium ion has a pK_a of −1.74. Thus for most amides the amide is more basic than water and the protonated amide will be more stable than its proton shift isomer, i.e., the hydrogen-bonded complex of amide and hydronium ion. For unusually weakly basic amides, and for most other carbonyl compounds, the hydrogen-bonded complex will be more stable than the protonated carbonyl compound.

(35) Stewart, R. *The proton: applications to organic chemistry*; Academic Press: Orlando, FL, 1985.

(36) Scudder, P. H. *J. Org. Chem.* **1990**, *55*, 4238−4240.

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(39) Stahl, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4196−4205.

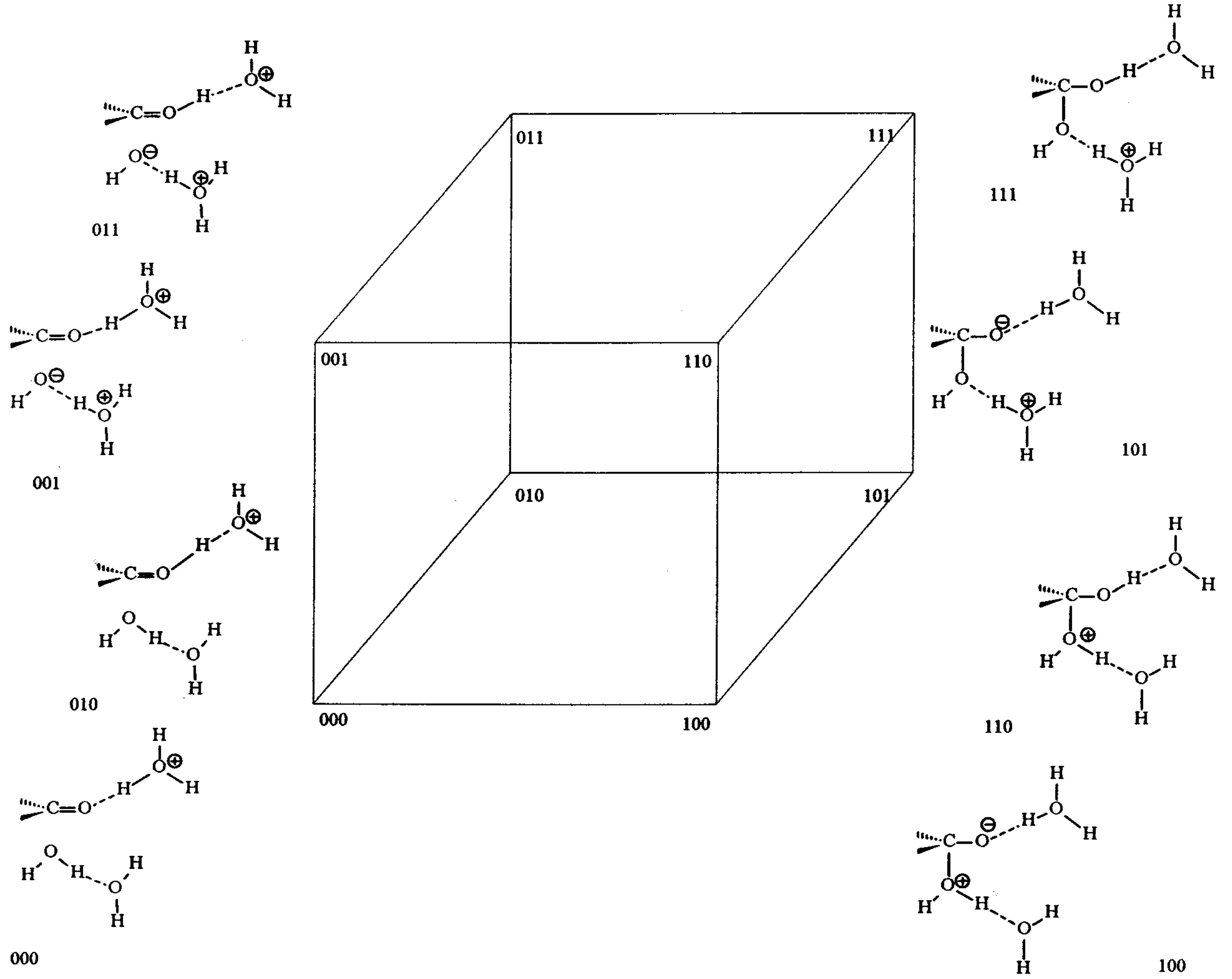

Figure 4. Reaction cube for acid-catalyzed hydration of a carbonyl compound.

These equations become complicated for high-dimensional cases but allow computer search for the lowest energy saddle point between starting material and product. For the two-dimensional case, as in hydroxide addition to a carbonyl, the equation is given above: eq 3. The calculational procedure is illustrated for the addition of hydroxide to formaldehyde, by presenting the steps of the calculation in Table 2. Similar calculations, with more corner species, will be carried out for the higher dimensional models required for other mechanisms. Once all corner energies are available and the intrinsic barriers are known, then transition states can be found by applying the computer programs previously described[13] to search for the lowest saddle point.

Applying two-dimensional Marcus theory to the hydroxide-catalyzed hydration of the compounds in Table 1 leads to the results in Table 2. We see that even though some of the reactions are concerted general base-catalyzed hydration (hydroxide as general base) and some are simple hydroxide addition all but the most reactive aldehydes are described by an intrinsic barrier of 8.51 kcal/mol for carbon oxygen bond formation.[40] For carboxylic acid derivatives, ketones, and the less reactive aldehydes, the average intrinsic barrier of 8.51 kcal/mol works very well, as shown by the results in Table S3[41] and Figure 5.

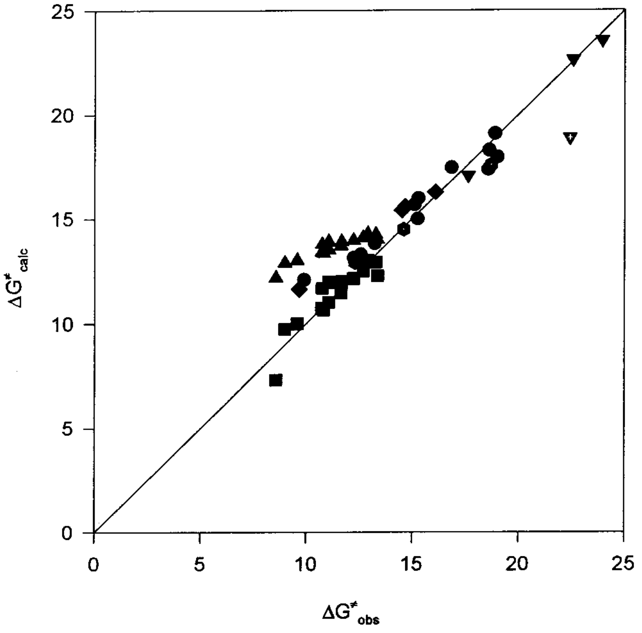

Figure 5. Calculated vs observed free energies of activation for hydroxide-catalyzed hydration of carbonyl compounds. Unless otherwise noted all calculated values are based on the average intrinsic barrier, 8.51 kcal/mol: (▲) aldehydes, using the average intrinsic barrier; (■) aldehydes using intrinsic barriers calculated using eq 5; (◆) ketones; (●) esters; (⬢) thioesters; (▼) amides; (▽) *N*-methylformanilide, for which ΔG_{obs} is not determined by hydroxide addition.

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(40) At an earlier stage in this work when a more elaborate model was used, involving assumed partial desolvation of starting materials or products, the best average value of the intrinsic barrier was 7.38, and this value was used in other calculations.[39] The intrinsic barrier and the work term in Marcus Theory generally show covariance, and different pairs of values can give similar results

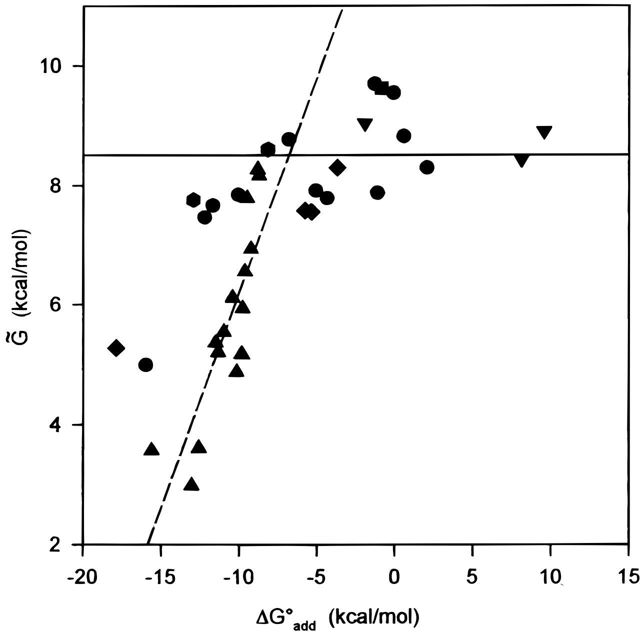

Figure 6. Best fit intrinsic barrier as a function of $\Delta G°_{add}$, the free energy change for hydroxide addition within the encounter complex: (—) average intrinsic barrier for $\Delta G°_{add} > -10$ kcal/mol; (- - -) least-squares fitted line for aldehydes; (▲) aldehydes; (◆) ketones; (●) esters; (⬢) thioesters; (▼) amides.

However, for the most reactive aldehydes we encounter a problem, because the hydroxide rate constants are calculated to be too slow using the standard intrinsic barrier, although, as we shall see, the uncatalyzed and acid-catalyzed rate constants for all compounds are satisfactorily predicted using the average intrinsic barrier. When the intrinsic barrier is plotted as a function of the free energy change for the microscopic hydroxide addition step, we find that the deviations occur for aldehydes for which addition is very favorable, i.e., $\Delta G_{add} < -10.0$ kcal/mol; see Figure 6. Ketones or esters with very low ΔG_{add} are more satisfactorily described by intrinsic barriers lower than the standard value but there are very few such highly reactive compounds. Except for trifluoroacetophenone and methyl trifluoroacetate the average intrinsic barrier gives a satisfactory description of the reaction for esters and ketones. For aldehydes the intrinsic barrier is given by

$$\tilde{G} = (13.40 \pm 1.44) + (0.719 \pm 0.133)\Delta G°_{OH} \qquad (5)$$

where $\Delta G°_{OH}$ is the free energy change for addition of hydroxide to the carbonyl compound (all species with standard state 1 M). Figure 5 includes calculated free energies of activation for aldehydes using intrinsic barriers from eq 5. The root-mean-square error for compounds other than aldehydes was 0.91; the root-mean-square error for aldehydes, with variable intrinsic barriers, was 0.73. With the average intrinsic barrier the root-mean-square error for aldehydes was 2.50. There is a serious deviation for *N*-methylformanilide (which was not included in the calculation of the root-mean-square error), but for this compound the rate determining step is known to be breakdown of the tetrahedral intermediate and not addition of hydroxide.[42−45]

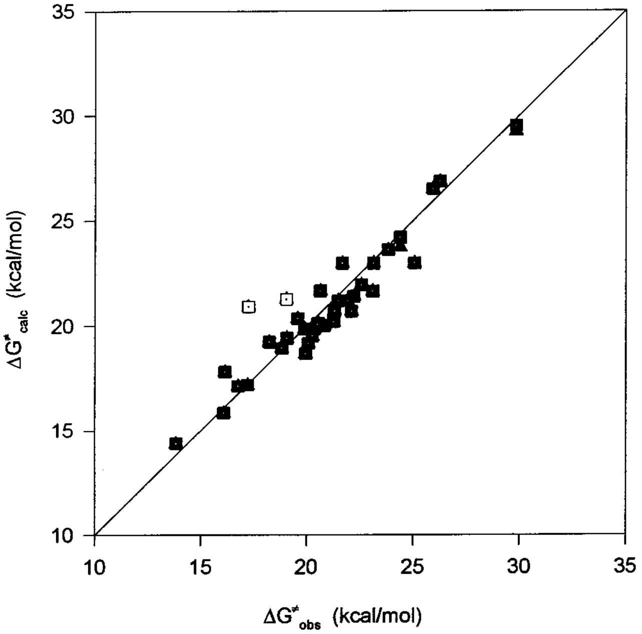

Figure 7. Calculated vs observed free energies of activation for uncatalyzed hydration of carbonyl compounds. Calculated values are based on the average intrinsic barrier, 8.51 kcal/mol: (▲) calculated for the cyclic, three water molecule mechanism; (■) calculated for the two water molecule mechanism; (△, □) monohaloketones.

We now turn to the uncatalyzed hydration of carbonyl compounds. For those compounds for which both the uncatalyzed rate constants and experimentally based equilibrium constants were available we examined both mechanisms discussed above. The results are given in Table S4[41] and Figure 7. The two models lead to very similar calculated activation energies. The root-mean-square error is slightly smaller for the two water model, at 1.14 kcal/mol, than for the cyclic model, 1.24 kcal/mol, but the calculated activation energies are somewhat lower for the cyclic model. The average signed error[46] (calculated − observed) is 0.086 for the two water model and −0.018 for the cyclic model. The clearest differences are for amides where there are no experimental rate data for comparison. Methyl acetate is disturbing because the prediction of the cyclic model seems clearly too low. This suggests that there may be deficiencies in the cyclic model as currently conceived. In general these results do not give a clear answer to the question of whether carbonyl hydration generally follows a cyclic mechanism. There are serious discrepancies between observed and calculated values for both monochloro and monofluoro acetone, but in this case examination of the experimental values for related compounds suggests that it is the experimental values which are out of line. A plot of observed rate constant against $\Sigma\sigma^*$ for acetone and mono-, di-, or trihaloacetones gives a reasonable Taft plot with only the points for monochloro and monofluoro acetone deviating seriously. A corresponding plot for the uncatalyzed hydrolysis of methyl haloacetates is nicely linear: see Figure 8. (With the monohaloketones omitted from the correlation for ketones, the two plots have indistinguishable slopes: 2.20 ± 0.45 and 2.56 ± 0.22 for ketones and esters.) The calculated rate constants are in satisfactory agreement with the line fitted to the experimental points.

Next we turn to the acid-catalyzed reactions and calculate the free energies of activation for the model described above,

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(41) These tables are available as Supporting Information.

(42) Bender, M. L.; Thomas, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4183−4189.

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(46) The average value of $\Delta G^{\ddagger}$(calcd) − $\Delta G^{\ddagger}$(obsd) (with sign retained) gives a measure of any systematic deviation in the calculated free energy of activation.

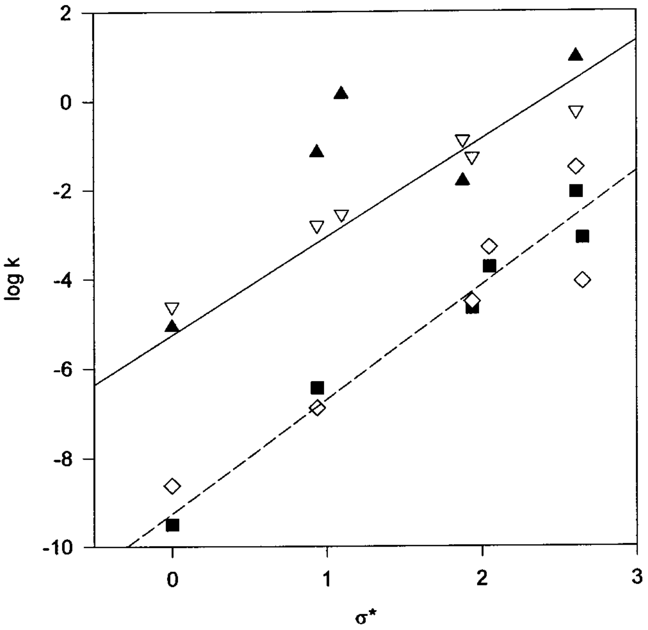

Figure 8. Logarithm of rate constant for hydration as a function of σ^* for methyl haloacetates and methyl halomethyl ketones: (■) experimental rate constants for hydration of substituted methyl acetates; (◇) calculated rate constants for hydration of substituted methyl acetates; (▲) experimental rate constants for hydration of substituted methyl ketones; (▽) calculated rate constants for hydration of substituted methyl ketones; (—) least-squares line for the experimental rate constants for methyl ketones, monohaloketones not included; (- - -) least-squares line for the experimental rate constants for methyl acetates.

using three-dimensional Marcus theory. The results of these calculations are found in Table S5.[41] The agreement is good (root-mean-square error is 1.49 kcal/mol as opposed to 1.24 for uncatalyzed hydration and 0.91 for hydroxide catalyzed hydration of compounds other than aldehydes), especially considering that these calculations depend on imperfectly known values of pK_{BH^+}, on top of the other sources of error. Figure 9 shows a comparison of experimental and calculated values.

Discussion

The results of this investigation show that, to a good approximation, the rates of acid-catalyzed, base-catalyzed, and uncatalyzed addition of water to carbonyl compounds can be described using Multidimensional Marcus Theory, using a single value of the intrinsic barrier, except for reactive aldehydes. Probably the same breakdown in transferability is occurring for other classes of compounds but there are so few such compounds of sufficient reactivity that the pattern is not yet clear. The root-mean-square deviations are as follows: base catalyzed (other than aldehydes) 0.91 kcal/mol; water reaction, cyclic model 1.24 kcal/mol; water reaction, two water model 1.14 kcal/mol; and acid catalyzed, 1.49 kcal/mol.

Cases where the intrinsic barrier is not constant for a family of similar reactions, i.e., where the barrier is not transferable, have been reported.[47,48] Bunting proposed a linear dependence of the intrinsic barrier for proton abstraction on the equilibrium constant for the reaction.[49] An interesting implication of such a linear relation is that for extreme values of the equilibrium constant the intrinsic barrier will become zero or even negative. However, for extreme values of the equilibrium constant the intrinsic barrier ceases to be meaningful, because for $|\Delta G°| > 4\tilde{G}$ the reaction becomes diffusion controlled in the thermodynamically favored direction. The "inverted region" seen for electron-transfer reactions is not to be expected for atom transfer reactions.[1]

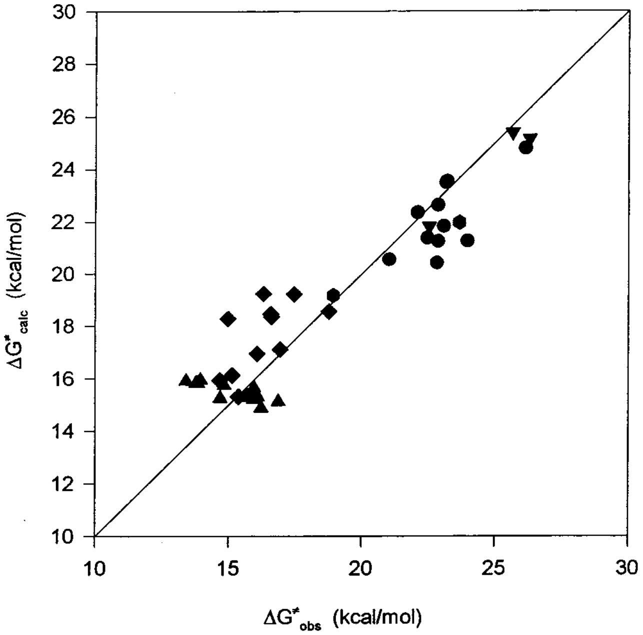

Figure 9. Calculated vs observed free energies of activation for acid-catalyzed hydration of carbonyl compounds: (▲) aldehydes; (◆) ketones; (●) esters; (⬢) thioesters; (▼) amides. Calculated values are based on the average intrinsic barrier, 8.51 kcal/mol.

For most compounds the transition state for hydroxide addition corresponds to complete proton transfer with rate-limiting C−O bond formation. However, several of the most reactive aldehydes, for which the intrinsic barrier for C−O bond formation is smaller than the average value, show concerted transition states with both C−O bond formation and proton transfer occurring simultaneously. Concerted transition states were predicted to be more likely when all intrinsic barriers are small.[13]

For most of the compounds examined, whether the cyclic or general base models for uncatalyzed hydration were used, the transition states were calculated to be essentially the same with rate limiting attack of water on the carbonyl progressing toward zwitterion formation. In some cases (less reactive compounds) the cyclic model predicts that the proton transfers would all be complete at the transition state, which would then involve attack of hydroxide ion on the protonated carbonyl compound. The general base model for less reactive compounds led to a transition state that was essentially trapping of the zwitterion by proton transfer, with complete C−O bond formation. Where both models were shifted to the unreactive compound variant, as happened for amides, the cyclic model was always the lower transition state energy. Interestingly, the available rate constants for amide hydrolysis at neutral pH, for resin-bound-Phe-Phe-Phe- - -Gly, $\Delta G^{\ddagger} = 29.09$ kcal/mol,[50] or for N−Ac-Gly-Gly, $\Delta G^{\ddagger} = 31.71$ kcal/mol,[51] are close to the values calculated here for DMF or DMA using the cyclic model and much lower than

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the values calculated for the general base model. This suggests that the cyclic model applies to the unreactive compounds, though it is impossible to tell for the more reactive compounds in aqueous solution. In any case, if the central tenet of this paper, that intrinsic barriers are generally transferable, is valid, then the model giving the lower activation barrier must be correct.

Although the transition state for uncatalyzed hydration is often calculated to involve only C−O bond formation, the zwitterion so formed is much higher in energy than the neutral hydrate formed from it by a series of proton transfers. In some cases the nature of the transition state shifts to reflect the energetics of a particular reaction. The advantage of using a model more complicated than is really needed by many cases in that the shifts in the nature of the transition state are accommodated naturally, while the lowest possible transition state within the model is always found. There is a catch when this approach is used for the two water molecule model. In a few cases the zwitterion is lower in energy than the product of addition and proton transfer by enough that the transition state for the proton transfer step would be higher than the transition state for the addition itself. One must check for this, though the difference in calculated transition state energies is usually small: at most 1.5 kcal for the compounds considered here. For the cyclic mechanism this is not a problem because the final state, the neutral hydrate, is always lower in energy than the zwitterion, and it is just a question of whether proton transfer precedes or follows the transition state.

Bell et al. concluded, from studies of the hydration of 1,3-dichloroacetone in aqueous organic solvents, that the rate determining step involved three water molecules, with a cyclic hydrogen-bonded array.[28−30] They further proposed that the reaction took place by a stepwise transfer of three protons.

For acid-catalyzed hydration, for most compounds the transition state is calculated to involve only C−O bond formation by attack of water on the protonated carbonyl, with proton transfer from the nucleophilic water not yet begun. However, for a number of molecules with strongly electron-withdrawing groups bonded to the carbonyl, the transition state involves only C−O bond formation by attack of water on the unprotonated carbonyl, and neither proton transfer has begun. Thus for these weakly basic compounds the role of hydronium ion is reduced to trapping the zwitterion by protonating it after the transition state has been passed.

Cox et al. concluded that the mechanism of acid-catalyzed hydrolysis of methyl benzoates involved rate determining attack upon the protonated ester, involving two water molecules, with the second water acting as a general base while the first acted as a nucleophile.[52] This is consistent with the conclusions drawn from the application of Multidimensional Marcus Theory to this reaction.

The conclusion from this investigation is that Multidimensional Marcus Theory works remarkably well for all but very reactive carbonyl compounds; the data span a range of about 15 kcal/mol in observed free energy of activation. By adding a linear dependence of intrinsic barrier on thermodynamic barrier, the treatment can be extended to all hydration reactions of carbonyl compounds for which data are available, for a total range of 21 kcal/mol in observed free energy of activation. With appropriate care to see that a suitable intrinsic barrier is used, this should provide a useful way to get an approximate prediction of the rate of addition of water to any carbonyl compound provided only that the equilibrium constant is known or can be estimated. Nevertheless, it is also clear that the intrinsic barrier does depend on the thermodynamic driving force, and therefore that this approach is less general than might have been hoped. New approaches are required to overcome the need for an intrinsic barrier to predict rate constants.[15]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

Supporting Information Available: Table S3, calculated and experimental transition state energies, and transition state positions, for reactions of hydroxide with carbonyl compounds; Table S4, calculated and experimental transition state energies, and transition state positions, for the uncatalyzed reaction of water with carbonyl compounds; Table S5, calculated and experimental transition state energies, and transition state positions, for acid-catalyzed hydration of carbonyl compounds; Appendix 1, estimation of pK_a values; Table A1, σ^* values used for pK_a estimation; Table A2, pK_a values estimated in this work; Table A3, estimation of pK_{BH^+} for aldehydes by comparison with pK_{BH^+} for esters; Table A4, estimation of pK_{BH^+} for ketones by comparison with pK_{BH^+} for esters; Table A5, estimation of pK_{BH^+} for cyclopentanone and cyclohexanone; Table A6, estimation of pK_{BH^+} for aromatic aldehydes; Appendix 2, equilibrium constants for hydration reactions; Table A7, difference in log $K_{hydration}$ for CF_3 vs CH_3; Appendix 3, rate constants for hydration reactions; Table A8, estimation of rate constants for uncatalyzed hydration of isobutyraldehyde; Table A9, benzaldehyde hydration rate constants; Table A10, rate constants for hydration of pivaldehyde at 25 °C; Table A11, hydration of 1,3 dichloroacetone (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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