JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 632–641 (1998)

Predicting the rates of proton transfer reactions: a simple model using equilibrium constants and distortion energies

J. Peter Guthrie*

Department of Chemistry, University of Western Ontario, London, Ontario N6A 5B7, Canada

Received 21 July 1997; revised 20 January 1998; accepted 4 February 1998

ABSTRACT: A simple model for the energy surface of a reacting system permits the calculation of the free energies of activation. A chemical reaction is analyzed in terms of the simple processes (bond making/breaking or atom transfer; geometry changes) which must take place to achieve the overall transformation. When only one (or two, or three, …) of these processes has progressed to the full extent required for reaction, one has a 'corner intermediate.' The reaction diagram is viewed as a square (2D) or cube (3D) or hypercube (4D), etc., and energies at intermediate points on the energy surface or hypersurface are calculated by interpolation. Suitable equations have been obtained for this purpose. Along any section parallel to an axis the energy is given by an upward opening parabola centered at the lower energy end. This paper deals with the application of these ideas to proton transfer reactions involving carbon acids. For mono- or dicarbonyl compounds, with pK_as ranging from 7 to 25.6, and rate constants for water or hydroxide ranging from $10^{-9.3}$ to $10^{4.6}$, rate constants can be predicted with an r.m.s. error in log k of 0.99 for 51 reactions. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: proton transfer reactions; rate prediction; equilibrium constants; distortion energies

INTRODUCTION

In his classical study of proton transfer reactions, Eigen[1] showed that whereas proton transfers between electronegative atoms such as oxygen or nitrogen were very fast, essentially at the rate of diffusion in the thermodynamically favored direction except for a narrow range of ΔpK_a values near $\Delta pK_a = 0$, proton transfers to or from carbon were generally slow, with Brønsted slopes intermediate between 0 and 1 over very wide ranges of ΔpK_a. Since then, Kresge and co-workers[2,3] have shown that for a few kinds of carbon acids, where a localized ion is formed, proton transfer can also be fast, essentially at the rate of diffusion in the thermodynamically favored direction. It has been widely accepted that the reason for the characteristically slow reactions of carbon acids is that almost invariably for such an acid to be acidic enough to react with a base such as hydroxide or something weaker, it is necessary for it to be next to a conjugating electron-withdrawing group, such as carbonyl or nitro, so that the product anion need not have the negative charge on carbon, but rather can delocalize it on to an electronegative atom. The loss of proton is imperfectly synchronized with the electronic reorganization, and thus the full potential acidity of the CH bond is not expressed at the transition state and the reaction is slow.[4–6] Although this description in terms of imperfect synchronization is widely accepted, it has not led to a straightforward and general way to predict the rates of these reactions. In this paper, an approach which permits such predictions will be presented.

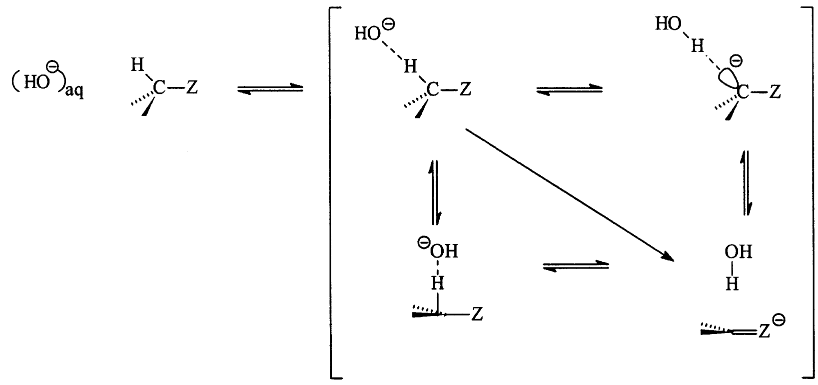
A preliminary account of this work has been published.[7] Although the approach has changed significantly, the essential idea remains, namely that for a chemical transformation where only one thing happens, there would be no kinetic barrier (intrinsic barrier in terms of Marcus theory) but rather a simple increase or decrease in energy as the process occurs. Evidence supporting this idea will be examined. For most actual chemical reactions several things have to happen simultaneously, and the resulting multi-dimensional reaction surface has a kinetic barrier separating starting materials and products. This idea was first developed as an extension of multi-dimensional Marcus theory[8] and used the mathematics developed for that theory.

With further examination of the concepts, it became clear that for processes where 'only one thing happened' there should in general be a quadratic force law, and that this simpler mathematical description should apply to all reactions described in this way. This paper presents an application of these ideas to proton transfer reactions. An application to cyanohydrin formation by addition of

---

Correspondence to: J. P. Guthrie, Department of Chemistry, University of Western Ontario, London, Ontario N6A 5B7, Canada.
Contract/grant sponsor: Natural Sciences and Engineering Research Council of Canada.

© 1998 John Wiley & Sons, Ltd. CCC 0894–3230/98/080632–10 $17.50



Scheme 1

cyanide ion to carbonyl compounds has been submitted for publication, and a number of other reactions, including covalent hydration of carbonyl compounds, hydrogensulfite adduct formation, hydration of iminium ions and aldol condensations are currently being examined in terms of these ideas.

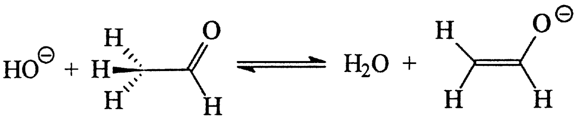
RESULTS

The method proposed in this paper requires the following postulates.

1. Reactants are in equilibrium with starting material or product at each point along each reaction coordinate. This is one of the starting assumptions of transition state theory.
2. For any process where only one elementary reaction coordinate changes, the energy will be a quadratic function of the corresponding reaction coordinate. The elementary reaction coordinates for proton transfer from carbon are the actual proton transfer between carbon and an electronegative atom and geometry change from sp^3 to sp^2 with no change in bonding. The energy will be given by an upward opening parabola centered on the lower energy end of the reaction coordinate. In the case when both ends have the same energy then the energy will be the same at all points along the coordinate. In order to obtain a logically and mathematically consistent equation for the energy surface, we will have to deviate slightly from this ideal picture, but this is the goal to be approximated. Bond breaking processes are usually shown with a bond length coordinate, in which case one has a Morse curve, but if bond order coordinates are used, then this transforms into a parabola. This follows from Pauling's bond length–log (bond order) relationship[9].
3. At each section through the reaction hypersurface for which only one reaction coordinate changes, the energy will be a quadratic function of the reaction coordinate and will depend only on the initial and final energies along it. This follows from postulates (1) and (2). Almost all chemical reactions will involve two or more elementary reaction coordinates, and thus a reaction will be described by a reaction hypersurface with two or more reaction coordinate dimensions and one energy dimension. I propose that this surface can be constructed by postulates (2) and (3), with some deviations in order to obtain a single consistent equation for the entire surface.
4. Energies of hydrogen bonds, including hydrogen bonds from O or N to CH can be estimated by the Stahl–Jencks equation.[10] This allows for loss of solvation by water when a base forms an encounter complex with a carbon acid and for changes in hydrogen bonding upon distortion of the organic compound.
5. Reaction coordinates are defined to run from 0 to 1. This means that for bond making/breaking processes bond order coordinates are used, and for geometrical distortions the reaction coordinate is the relative change in bond angle, $x = \Delta\theta/\Delta\theta_{\max}$.

The model which is used to predict the reaction rates is shown in Scheme 1.

To illustrate the way in which the model works, the example of enolate formation from acetaldehyde and hydroxide will be considered in detail. The overall reaction, corresponding to the observed rate constant, corresponds to the process



(1)

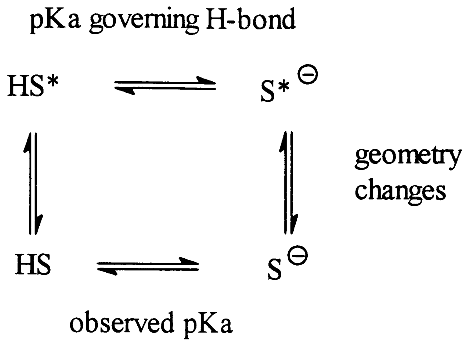
In this process several things happen: (1) the hydroxide must diffuse into contact with the CH which is to transfer its proton; (2) in the process the hydroxide loses solvation by one water and gains a very weak hydrogen bond to the CH; (3) the proton transfers within this encounter complex; and (4) the geometry changes from sp^3 to sp^2.

The first two make up the 'work term' in Marcus

© 1998 John Wiley & Sons, Ltd.

theory. The equilibrium constant for encounter complex formation, in the absence of attractive or repulsive interactions is estimated according to Hine.[11] The equilibrium constant if there is one position for a base next to an acid is 0.0085 M^{-1}. This is corrected by the symmetry numbers appropriate to the process.[12] Hydrogen bonding interactions must be explicitly accounted for, because these will change with geometry changes; the geometry changes correspond to significant changes in pK_a.

For purposes of hydrogen bonding the appropriate pK_a is for the 'vertical process' with no accompanying geometry change, including no change in bond lengths; for the actual proton transfer reaction the bond length change accompanies the proton transfer and need not be treated as a separate dimension. This approach to pK_a values appropriate to hydrogen bonding attempts to capture the electrostatic effects at the proton involved in hydrogen bonding without the electronic reorganization which would accompany proton transfer. It is straightforward to calculate the strain energies corresponding to changing the geometry to the values corresponding to the proton transferred species.



Hydrogen bond energies are calculated using the equation of Stahl and Jencks,[10] based on the appropriate pK_a values. For the carbon acids this requires examination. For the initial state of the carbon acid, with sp^3 hybridization, the pK_a was estimated[7] using a Taft $\rho^*\sigma^*$ relationship. $\rho^* = -3.09$ was evaluated from the pK_a values for CH_4 (50[13]), CH_3CH_3 (52.0[13]), $CH(CH_3)_3$ (59.7[13]) and CF_3H, taken as 27,[14] using σ^* values taken from Perrin *et al.*[15] This pK_a refers to the process whereby the carbon acid, with sp^3 geometry for the C which loses the proton, forms a tetrahedral anion in which the electron-withdrawing group is only acid strengthening to the extent measured by σ^*. We use this procedure because of uncertainties about how well we can model the distortion energy of the conjugate base. The pK_a leading directly to the corner intermediate is more important than the other pK_a values used to estimate hydrogen bond energies, although the calculation is not very sensitive even to this value.

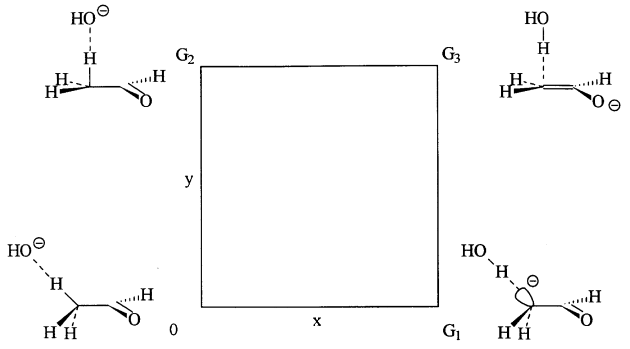
In encounter complexes with hydroxide, the hydroxide will have replaced one solvating water molecule by a hydrogen bond to CH. A CH species distorted towards the geometry of the anion will have enhanced acidity and may be expected to form a good hydrogen bond, although a CH species with the starting geometry will normally make only a very weak hydrogen bond.

The energies of species with distorted geometries were calculated by *ab initio* quantum mechanics (using Gaussian 94[16]), relative to the energy of the corresponding minimized structure, for starting material or product.

In determining the energies of the product, we found that it was necessary to use the enols rather than the enolates, even though we were analyzing base-catalyzed enolate formation. The problem is that in the gas phase the enolates are very flexible, with soft potentials for geometrical distortion. The enolate ion in the gas phase is less stable than the species in solution by the solvation energy, which is of the order of −100 kcal for an anion.[17–19] By contrast, the free energy of solvation of the enol is of the order of −2 kcal mol.$^{-1}$ From the data tabulated in Ref. 20, one may calculate free energies of transfer for five enols: the average value is −2.1 kcal. In solution at a pH equal to the pK_a of the enol, typically about 10,[21] the enol and enolate are at the same free energy level. Hence the gas-phase enolate differs from the species in solution by an amount of energy comparable to that for electronic excitation, and it is perhaps not surprising that the behavior of the gas-phase enolate is surprising based on prejudices from solution. We are interested in reactions in solution, and thus the enol appears to be the better model. Certainly the use of distortion energies calculated from the enolates leads to hopelessly incorrect free energies of activation for the proton transfer reactions.

Electrostatic interactions may be significant in some cases, e.g. if water is the base and the immediate product is an ion pair of H_3O^+ and the anion. Because electrostatic interactions are relatively weak in water, this is done with an approximate method[22] which takes account of the nature of the charges and the geometry.

The next two things which must happen in reaction (1) correspond to the chemical transformation within the encounter complex, and can be shown on a two-dimensional reaction coordinate diagram (two reaction dimensions, with an orthogonal energy dimension as well), which is analogous to an Albery–More O'Ferrall–Jencks[23–25] diagram:



In this diagram, the horizontal dimension corresponds to bonding changes and the vertical dimension to geometry changes. If only the geometry changes in going from one corner to another, then the corresponding energy change can be calculated by molecular orbital methods, as has already been described.

The energy of each corner intermediate is calculated from the strain energy relative to the optimized form, the pK_a change for any proton transfer which has happened, hydrogen bonding, if any, electrostatic interactions, if any, and statistical effects of encounter, if any (if the only other species is water, it is assumed to be there, and accounted for by the equilibrium constant).

Once the energies of the corner intermediates are available, the energy of the reaction surface at each point is available, and the transition state can be found.

The surface is defined beginning with the limiting curves corresponding to $\mathbf{x} = 0$ and $\mathbf{x} = 1$ or $\mathbf{y} = 0$ and $\mathbf{y} = 1$. These curves are given by

$$G_{y=0} = G_1x^2$$

$$G_{y=1} = G_3 + (G_2 - G_3)(1 - x)^2$$

$$G_{x=0} = G_2y^2$$

$$G_{x=1} = G_3 + (G_1 - G_3)(1 - y)^2$$

Although it is qualitatively easy to see how to construct the energy surface corresponding to the model used here, the mathematical details are tricky. If the qualitative description were exact, then the transition state energy would be given by the position where the isoenergetic projections of the curves for $\mathbf{x} = 0$ and $\mathbf{x} = 1$ or $\mathbf{y} = 0$ and $\mathbf{y} = 1$ cross. This is almost but not completely correct.[26] A single equation for the energy surface can be obtained as follows. The constraints imposed are: (1) that the combined equation must give the simple equations shown above for the four edges of the diagram; (2) that it should give the correct values at the four corners; and (3) that when there is no difference in energy between the two points (0, y) and (1, y) or (x, 0) and (x, 1) then the section at y (or x) should have essentially constant energy. The equation which satisfies these constraints is

$$\begin{aligned} G = {} & G_1x^2 + [G_3 + (G_2 - G_3)(1 - x)^2 - G_1x^2]y^n \\ & + G_2y^2 + [G_3 + (G_1 - G_3)(1 - y)^2 - G_2y^2]x^n \\ & - G_1x^n - G_2y^n + (G_1 + G_2 - G_3)x^ny^n \end{aligned} \tag{2}$$

with $n = 2.9$. The curves for $G_{y=0}$ and $G_{y=1}$ can be melded in a way which gives the correct value at $y = 0$ or $y = 1$ by using $G = G_1x^2 + [G_3 + (G_2 - G_3)(1 - x^2) - G_1x^2]y^n$, and similarly the curves for $G_{x=0}$ and $G_{x=1}$ can be melded in a way which gives the correct value at $x = 0$ or $x = 1$ by using $G = G_2y^2 + [G_3 + (G_1 - G_3)(1 - y^2) - G_1y^2]x^n$. Combining the two would give an equation which satisfies constraint (1), but to satisfy constraint (2) also it was necessary to add the terms $-G_1x^n - G_2y^n + (G_1 + G_2 - G_3)X^ny^n$. Finally, in order to satisfy constraint (3), the value of n was adjusted to give satisfactory behavior. It was relatively straightforward to extend this approach to higher dimensions. The principal complication is that it is not possible to make simple assumptions about the relative energy of various corners. This is in contrast to the two-dimensional case where the corner intermediates are sure to be higher in energy that the starting material and product. Therefore, a general equation contains numerous conditional statements in order to cover all possibilities.

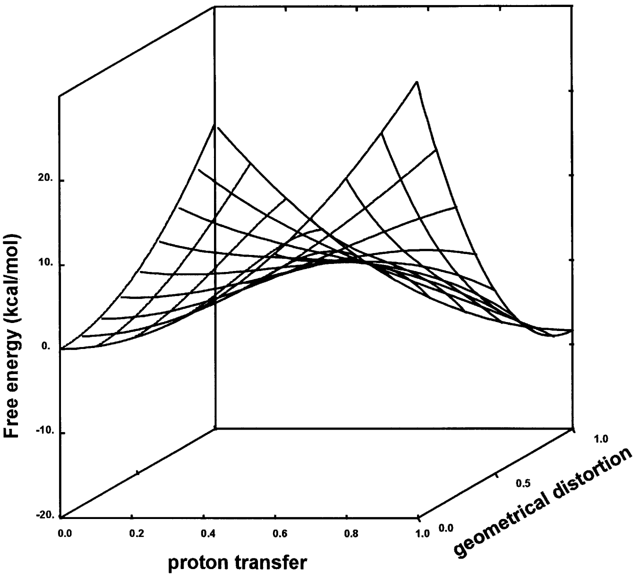


Figure 1. Energy surface for the reaction of hydroxide with acetaldehyde.

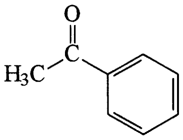
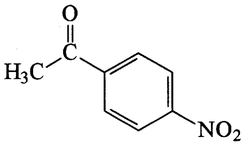
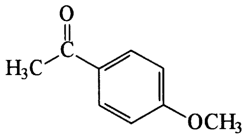
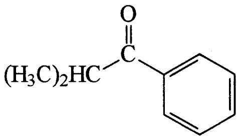
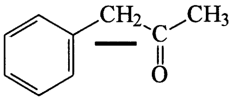
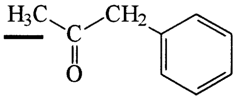
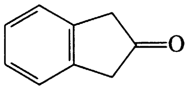
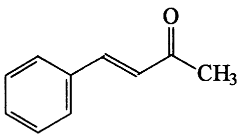
The surface obtained for the case of hydroxide and acetaldehyde is shown in Fig. 1. The figure is drawn for reaction within the encounter complex, starting with hydroxide in contact with a CH of acetaldehyde and thus partially desolvated. The entropic cost of encounter was calculated according to Hine.[11] The cost of replacing a hydrogen bond from hydroxide to water by a hydrogen bond from hydroxide to the acetaldehyde methyl CH was estimated using the Stahl–Jencks equation[10] and the pK_a for tetrahedral anion formation estimated as described above.

The transition state is constrained to lie within the reaction square or cube or hypercube. The transition state is by definition the highest energy point on the lowest energy path leading from initial to final state. To find transition states, a set of computer programs were written which systematically search the reaction space, moving out in shells from the initial state. The algorithm has been described.[8]

This model works well for monofunctional compounds as shown by the results in Tables 1 and 2, and summarized in Figure 2. The r.m.s. error in log k is

© 1998 John Wiley & Sons, Ltd.

Table 1. Rate constants for proton transfer reactions involving monofunctional compounds and hydroxide as base[a]

Compound	pK_a	Log k_{obs}	Log k_{calc}	Log k_{calc} − log k_{obs}
CH_3CHO	16.7[b]	0.07[b]	0.83	0.76
$(CH_3)_2CHCHO$	15.49[b]	−0.85[b]	−0.81	0.04
$PhCH_2CHO$	13.10[b]	1.30[b]	0.79	−0.51
Ph_2CHCHO	10.40[b]	2.40[b]	1.27	0.14
CH_3COCH_3	19.27[b]	−0.66[b]	−0.24	0.42
$(CH_3)_2C\underline{H}COCH_3$	20.33[c]	−2.43[d]	−3.81	−1.38
$(CH_3)_2CHCOC\underline{H}_3$	19.3[e]	−0.98[d]	−2.78	−1.80
$(CH_3)_2CHCOCH(CH_3)_2$	21.48[c]	−2.98[c]	−2.61	0.37
	18.30[b]	−0.60[b]	0.01	0.61
	16.60[b]	−0.37[b]	0.42	0.79
	18.90[b]	−1.35[b]	−0.15	1.20
	18.26[b]	−2.62[b]	−1.78	0.84
	15.91[c]	0.50[d]	0.12	0.38
	18.27[c]	−0.65[d]	−0.23	0.42
	12.20[b]	2.35[b]	0.81	−1.53
$ClCH_2COCH_3$	15.76[c]	0.55[c]	1.57	1.02
$Cl_2CHCOCH_3$	11.00[c]	3.24[c]	3.55	0.31
$BrCH_2COCH_3$	13.27[c]	2.21[c]	1.98	−0.23
$CH_3OC\underline{H}_2COCH_3$	18.49[c]	−1.42[c]	−0.05	1.37
$CH_3OCH_2COC\underline{H}_3$	18.29[c]	−0.77[c]	−0.01	0.76
	18.41[c]	−0.69[d]	0.14	0.83
$CH_3COOC_2H_5$	25.6[f]	−2.92[f]	−2.42	0.50
$CH_3COSC_2H_5$	21.0[g]	−1.70[g]	−1.00	0.70

[a] All in aqueous solution at 25 °C; rate constants are in M^{-1} s^{-1}. Calculated rates are based on distortion energies calculated at the 3–21 G level; some compounds were treated at the 3–21+G level but this made little difference to geometries.

[b] Ref. 21.

[c] Ref. 40.

[d] Calculated from the rate constant for detritiation,[41] assuming that the kinetic isotope effect is the same as for acetone.[42]

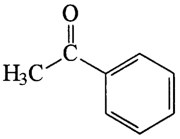
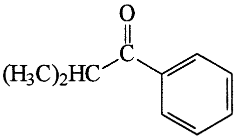
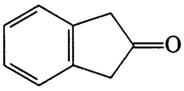
[e] Since the rate constant per hydrogen is very similar to that for acetone, the pK_a is assumed to be very similar to that for acetone.[40]

[f] Ref. 43.

[g] Ref. 44.

© 1998 John Wiley & Sons, Ltd.

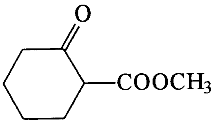
Table 2. Rate constants for proton transfer reactions involving monofunctional compounds and water as base[a]

Compound	pK_a[b]	Log k_{obs}	Log k_{calc}	Log k_{calc} − log k_{obs}
CH_3CHO	16.7	−7.62[c]	−6.00	1.62
$(CH_3)_2CHCHO$	15.49	−7.26[c]	−7.54	−0.28
$PhCH_2CHO$	12.53	−6.33[c]	−5.12	1.21
Ph_2CHCHO	10.42	−4.12[c]	−3.70	0.42
CH_3COCH_3	19.27	−9.34[c]	−8.57	0.77
	18.30	−8.73[c]	−7.60	1.13
	18.26	−9.78[c]	−9.37	0.41
	12.20	−4.50[c]	−4.39	0.11
$ClCH_2COCH_3$	15.76	−7.06[d]	−6.36	0.70
$Cl_2CHCO\text{-}CH_3$	11.00	−6.36[d]	−3.42	2.94
$BrCH_2COCH_3$	13.27	−5.55[d]	−4.98	0.57
$CH_3OC\underline{H}_2COCH_3$	18.49	−9.86[e]	−8.24	1.62
$CH_3OCH_2COC\underline{H}_3$	18.29	−9.23[e]	−7.59	1.64
$CH_3COCOOCH_3$	13.35	−5.79[f]	−4.47	1.32

[a] All in aqueous solution at 25 °C; rate constants are in M^{-1} s^{-1}. Calculated rates are based on distortion energies calculated at the 3–21 G level; some compounds were treated at the 3–21+G level but this made little difference to geometries.
[b] pK_a values as in Table 1.
[c] Ref. 21.
[d] Ref. 45, corrected for hydration as described in Ref. 46.
[e] Extrapolated from measurements of de-deuteration at higher temperatures given in Ref. 47, using a value for the isotope effect calculated using the correlation in Ref. 48.
[f] Ref. 49, corrected for hydration as described in Ref. 50.

1.08 for 37 compounds. One point where the calculated and observed values differ severely dominates this r.m.s. error, and if the one outlier is removed the r.m.s. error falls to 0.97. The outlying point is the water rate constant for 1,1-dichloroacetone, which is surprisingly low considering the acceleration seen for the second chlorine on the hydroxide rate constant. The relative rates, taken from Tables 1 and 2, are catalyst, acetone, monochloro-

Table 3. Rate constants for proton transfer reactions involving polyfunctional compounds and hydroxide as base[a]

Compound	pK_a	Log k_{obs}	Log k_{calc}	Log k_{calc} − log k_{obs}
$CH_3COCH_2COCH_3$	8.87[b]	4.60[b]	4.58	−0.02
$CH_3COCH_2COOC_2H_5$	10.68[c]	3.82[d]	3.44	−0.38
$CH_3COCH(CH_3)COOC_2H_5$	12.25[d]	2.01[d]	2.32	0.31
	11.92[e]	2.35[e]	2.05	−0.30

[a] All in aqueous solution at 25 °C; rate constants are in M^{-1} s^{-1}. Calculated rates are based on distortion energies calculated at the 3–21G level; some compounds were treated at the 3–21+G level but this made little difference to geometries.
[b] Ref. 51.
[c] Ref. 52.
[d] Ref. 53.
[e] Ref. 54.

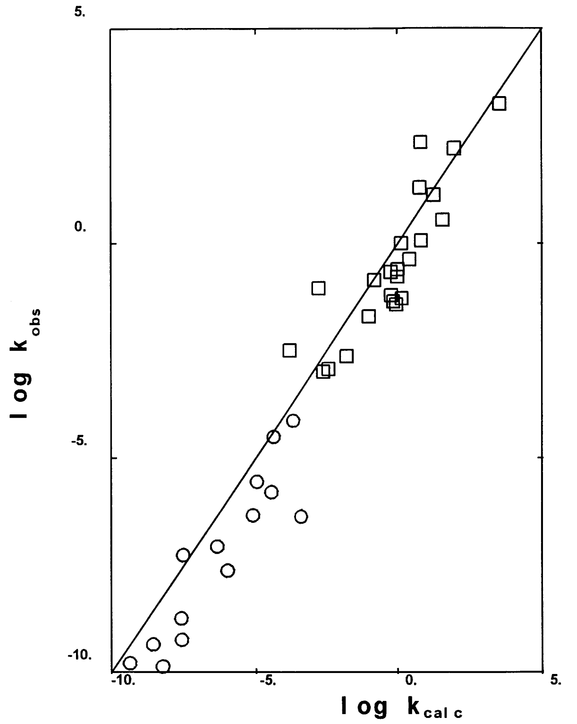


Figure 2. Observed and calculated rate constants for reactions of monocarbonyl compounds: (□) hydroxide rates (M^{-1} s^{-1}); (○) water rates (s^{-1}).

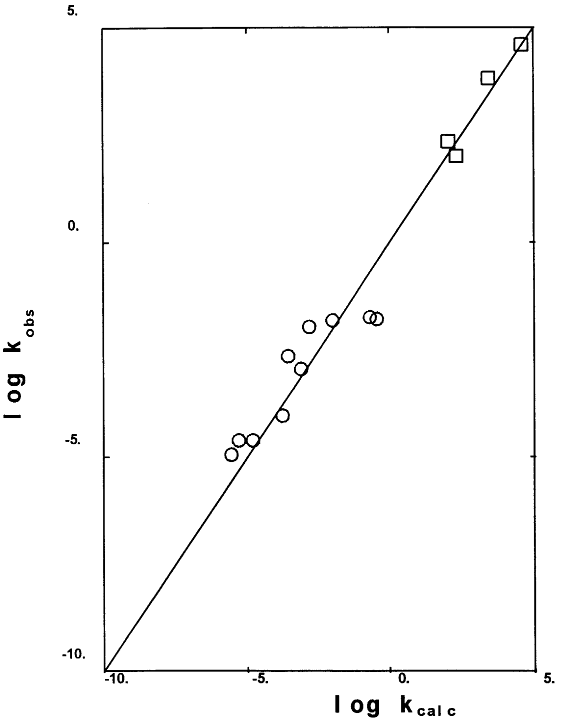
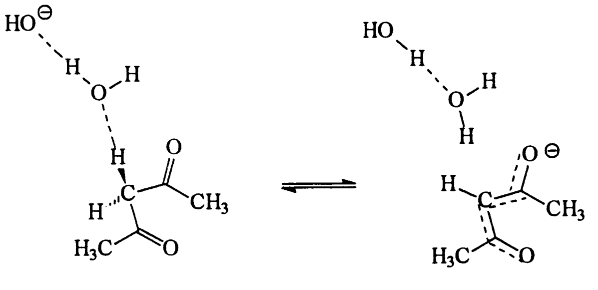


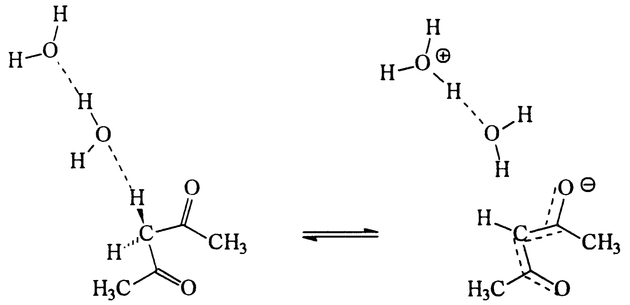
Figure 3. Observed and calculated rate constants for reactions of dicarbonyl compounds: (□) hydroxide rates (M^{-1} s^{-1}); (○) water rates (s^{-1}).

acetone, 1,1-dichloroacetone: HO— , 1.0, 16.2, 7943; H_2O, 1.0, 117, 1553.

For bifunctional compounds, such as acetylacetone, it is necessary to add an extra process for the reaction with hydroxide or water. The problem in this system is that the formation of the encounter complex with hydroxide in contact with the acidic CH of acetylacetone already costs 10 kcal mol^{-1} and the observed free energy of activation is only 11 kcal mol^{-1}. There simply is no room for the activation process. What can happen instead is that reaction can begin when the hydroxide is still separated from acetylacetone by one water molecule. The extra reaction dimension is a proton transfer to the hydroxide from the intervening water. Now the overall reaction within the encounter complex is described by a three dimensional reaction cube.



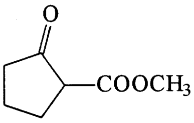
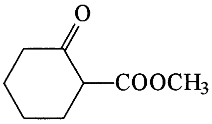
An analogous model is used for the water reaction, because a two-dimensional process leads to an unfavorable complex of H_3O^+ with the central carbon of the enolate:



Calculation of the free energy of activation for these systems also leads to good agreement with experiment, as shown by the results in Tables 3 and 4, summarized in Fig. 3. The r.m.s. error in log *k* is 0.65 for 14 reactions. The calculations were carried out using an extension of the model described for the two-dimensional case; for the three-dimensional model, *n* was 2.5. If $n = 2.5$ was used for the two-dimensional case, the agreement with experiment was poorer, though the worst deviation was less than $\Delta\log k = 2.1$ (ignoring the water reaction of dichloroacetone, which gave poor agreement even with $n = 2.9$). The need for different exponents in the two- and three-dimensional cases presumably reflects imperfections in our model, and work continues to seek a fully consistent approach.

© 1998 John Wiley & Sons, Ltd.

Table 4. Rate constants for proton transfer reactions involving polyfunctional compounds and water as base[a]

Compound	pK_a	Log k_{obs}	Log k_{calc}	Log k_{calc} − Log k_{obs}
$CH_3COCH_2COCH_3$	8.87[b]	−1.78[b]	−0.45	1.33
$CH_3COCH(CH_3)COCH_3$	10.68[c]	−4.03[d]	−3.79	0.24
$CH_3COCHBrCOCH_3$	7.0[e]	−1.47[f]	−0.70	1.04
$CH_3COCH_2COOC_2H_5$	10.68[g]	−2.94[f]	−3.14	−0.20
$CH_3COCH(CH_3)COOC_2H_5$	12.25[h]	−4.94[f]	−5.57	−0.63
$CH_3COCHBrCOOC_2H_5$	8.0[i]	−1.81[f]	−2.03	−0.22
$PhCOCH_2COCH_3$	8.53[j]	−1.96[k]	−2.85	−0.88
	10.0[l]	−2.64[f]	−3.59	−0.95
	11.92[m]	−4.61[m]	−4.82	−0.21
$CH_3OCOCH_2COOCH_3$	13.30[n]	−4.61[f]	−5.31	−0.70

[a] All in aqueous solution at 25 °C; rate constants are in s^{-1}. Calculated rates are based on distortion energies calculated at the 3–21G level; some compounds were treated at the 3–21+G level but this made little difference to geometries.
[b] Ref. 51.
[c] Ref. 52.
[d] Ref. 55.
[e] Ref. 56.
[f] Ref. 57.
[g] Ref. 52.
[h] Ref. 53.
[i] Calculated from kinetics data in Ref. 58 following the procedure described in Ref. 40.
[j] Ref. 59.
[k] Ref. 60.
[l] Ref. 61.
[m] Ref. 54.
[n] Refs 59, 62.

DISCUSSION

The central idea of the new approach to predicting rates of reactions presented in this paper is that if only one thing happens in a chemical transformation then there is no kinetic barrier. Kinetic barriers result from the need for several things to happen simultaneously for a transformation to occur. A familiar example of a reaction where there is almost no barrier is proton transfer between electronegative atoms. The intrinsic barrier from Marcus theory[27–29] provides a convenient measure of whether a reaction is inherently fast (little or no barrier except for that from thermodynamics) or inherently slow (a substantial barrier even when the thermodynamics are not unfavorable). The intrinsic barrier is the free energy of activation when the standard free energy change upon reaction is zero. There is a general prejudice among organic chemists that the intrinsic barrier for proton transfer along a hydrogen bond should be small.[11,30–33] Studies of proton transfer from acids of strength comparable to hydronium ion show that these reactions are superfast,[34,35] i.e. the actual proton transfer step is faster than diffusional encounter. This is consistent with a small intrinsic barrier.

Nevertheless, there appears to be a substantial intrinsic barrier for this proton transfer process, and analysis of the available data in terms of Marcus theory[27–29] leads to a value of 5 kcal mol^{-1}. Fischer *et al.*[36] showed that proton transfers between oxygen and nitrogen could be fitted using reasonable assumptions about diffusion rates and a rate constant for the isoenergetic proton transfer of $10^{10.3}$ s^{-1}, which corresponds to an intrinsic barrier of 3.4 kcal mol^{-1}. Gilbert and Jencks[37] showed that proton transfers from O to O can be fitted using reasonable assumptions about diffusion rates and a rate constant for the isoenergetic proton transfer step of 10^{10} s^{-1}, which corresponds to an intrinsic barrier of 3.8 kcal mol^{-1}. Bednar and Jencks[38] showed that proton transfers involving HCN, like other ‘normal’ acids, can be fitted using reasonable assumptions about diffusion rates and a rate constant for the isoenergetic proton transfer step of 10^9 s^{-1}, which corresponds to an intrinsic barrier of 5 kcal mol^{-1}.[30]

This contradiction has been resolved: bimolecular

© 1998 John Wiley & Sons, Ltd.

reactions in solution commonly involve bridging water molecules,[39] and explicit analysis of the Eigen data in terms of a model where the acid and base never come into direct contact, but react by way of an intervening water molecule, allows the prediction of the rates of proton transfers with an intrinsic barrier less than 1 kcal mol^{-1},[22] even though analysis in terms of a model for direct proton transfer led to a barrier of 5 kcal mol^{-1}.

Hence there appears to be no problem with the assumption that there is little or no kinetic barrier associated with a reaction coordinate which is purely transfer of a proton along a preformed hydrogen bond.

The geometrical distortions used as reaction coordinates in this paper are very similar to vibrations, which are well known to be approximately harmonic.

Hence there seems to be no *a priori* reason to object to the assumption that when only one thing happens to a molecular system then the energy is a quadratic function of the corresponding reaction coordinate. It may seem surprising that this set of postulates is sufficient to lead to a method for predicting absolute rate constants, but the successful application to proton transfers from carbon reported in this paper supports the claim that it is sufficient. It should be noted that the method successfully reproduces one of the surprising features of these reactions: that for two closely related carbon acids, the thermodynamically more acidic may be the slower to react, as seen for acetaldehyde vs isobutyraldehyde, or acetophenone vs isobutyrophenone.

It is common knowledge that almost all chemical reactions are associated with a kinetic barrier, so that they occur at measurable rates even when favored by thermodynamics. The proposal in this paper, that there is no intrinsic barrier when only one thing happens, is not inconsistent with this observation, because for almost all chemical reactions more than one thing must happen in the course of a chemical transformation. For example, a reaction cannot just involve breaking a bond, there is also a geometrical reorganization. For any real chemical transformation involving several simple processes occurring more or less simultaneously, there will be an apparent intrinsic barrier. The procedure described in this paper allows this apparent intrinsic barrier to be calculated.

The model is doubtless naive, but it does seem to work, and research in progress on other reactions suggests that it is indeed very general.

Acknowledgments

I thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work. I thank Rana Ibrahim for technical assistance with many of the calculations.

APPENDIX

Calculation of rate constants for enolization from detritiation kinetics[41]

Conversion is based on the assumption that the isotope effect, k_H/k_T, will be the same as for acetone; $k_H/k_T = 19.2$ for acetone was taken from Ref. 42. Rate constants from Ref. 41 are for tracer labelled compound, and thus are per hydrogen value.

Compound	k_T	k_H per H	k_H (obs.)	Log k_H
$(CH_3)_2C\underline{H}COCH_3$	0.195×10^{-3}	3.74×10^{-3}	3.74×10^{-3}	−2.43
$(CH_3)_2CHCOC\underline{H}_3$	1.80×10^{-3}	0.0346	0.104	−0.98
$PhC\underline{H}_2COCH_3$	0.0816	1.57	3.14	0.50
$PhCH_2COC\underline{H}_3$	3.85×10^{-3}	0.0739	0.222	−0.65
$PhCH{=}CHCOC\underline{H}_3$	3.58×10^{-3}	0.0688	0.206	−0.69

REFERENCES

1. M. Eigen. *Angew. Chem., Int. Ed. Engl.* **3,** 1–72 (1964).
2. A. C. Lin, Y. Chiang, D. B. Dahlberg and A. J. Kresge. *J. Am. Chem. Soc.* **105,** 5380–5386 (1983).
3. A. J. Kresge and M. F. Powell. *J. Org. Chem.* **51,** 822–824 (1986).
4. C. F. Bernasconi. *Acc. Chem. Res.* **25,** 9–16 (1992).
5. C. F. Bernasconi. *Adv. Phys. Org. Chem.* **27,** 119 (1992).
6. F. G. Bordwell, W. J. Boyle and K. C. Yee. *J. Am. Chem. Soc.* **92,** 5926–5932 (1970).
7. J. P. Guthrie. *J. Am. Chem. Soc.* **119,** 1151–1152 (1997).
8. J. P. Guthrie. *J. Am. Chem. Soc.* **118,** 12878–12885 (1996).
9. L. Pauling. *The Nature of the Chemical Bond.* Cornell University Press, Ithaca, NY (1960).
10. N. Stahl and W. P. Jencks. *J. Am. Chem. Soc.* **108,** 4196–4205 (1986).
11. J. Hine. *J. Am. Chem. Soc.* **93,** 3701–3708 (1971).
12. J. Hine. *Structural Effects on Equilibria in Organic Chemistry.* J Wiley, New York (1975).
13. (a) J. P. Guthrie. *Can. J. Chem.* **68,** 1643–1652 (1990); calculated from results taken from the following: (b) R. Jaun, J. Schwarz and R. Breslow. *J. Am. Chem. Soc.* **102,** 5741–5748 (1980); (c) R. Breslow and J. L. Grant. *J. Am. Chem. Soc.* **99,** 7745–7746 (1977); (d) D. D. M. Wayner and D. Griller. *J. Am. Chem. Soc.* **107,** 7764–7765 (1985); (e) B. A. Sim, D. Griller and D. D. M. Wayner. *J. Am. Chem. Soc.* **111,** 754–755 (1989); (f) A. Streitwieser and D. R. Taylor. *Chem. Commun.* 1248 (1970); (g) F. G. Bordwell and D. J. Algrim. *J. Am. Chem. Soc.* **110,** 2964–2968 (1988); (h) W. L. Jorgensen and J. M. Briggs. *J. Am. Chem. Soc.* **111,** 4190–4197 (1989).
14. E. Symons and M. Clermont. *J. Am. Chem. Soc.* **103,** 3127–3130 (1981).
15. D. D. Perrin, B. Dempsey and E. P. Serjeant. *pK$_a$ Prediction for Organic Acids and Bases.* Chapman and Hall, London (1981).
16. 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 94, Revision E.1.* Gaussian, Pittsburgh, PA (1995).
17. Y. K. Kang, G. Nemethy and H. A. Scheraga. *J. Phys. Chem.* **91,** 4118–4120 (1987).
18. Y. Marcus. *Ion Solvation.* Wiley, New York (1985).
19. Y. Marcus. *Biophys. Chem.* **51,** 111–127 (1994).

© 1998 John Wiley & Sons, Ltd.

20. J. P. Guthrie. in *The Chemistry of Enols* edited by Z. Rappoport, pp. 75–93. Wiley, Chichester (1990).
21. J. R. Keeffe and A. J. Kresge. in *The Chemistry of Enols,* edited by Z. Rappoport, pp. 399–480. Wiley, Chichester (1990).
22. J. P. Guthrie. *J. Am. Chem. Soc.* **118,** 12886–12890 (1996).
23. W. J. Albery. *Prog. React. Kinet.* **4,** 353–398 (1967).
24. R. A. More O'Ferrall. *J. Chem. Soc. B* 274–277 (1970).
25. W. P. Jencks. *Chem. Rev.* **72,** 705–713 (1972).
26. J. P. Guthrie. submitted for publication
27. A. O. Cohen and R. A. Marcus. *J. Phys. Chem.* **72,** 4249–4256 (1968).
28. R. A. Marcus. *J. Am. Chem. Soc.* **91,** 7224–7225 (1969).
29. R. A. Marcus. *Annu. Rev. Phys. Chem.* **15,** 155–196 (1964).
30. F. Hibbert. *Adv. Phys. Org. Chem.* **22,** 113–212 (1986).
31. A. J. Kresge. *Chem. Soc. Rev.* **2,** 475–503 (1973).
32. A. J. Kresge. *Acc. Chem. Res.* **8,** 354–360 (1975).
33. J. Hine. *J. Am. Chem. Soc.* **94,** 5766–5771 (1972).
34. E. Grunwald. *Prog. Phys. Org. Chem.* **3,** 317–358 (1966).
35. H. Strehlow and P. Hildebrandt. *Ber. Bunsenges. Phys. Chem.* **94,** 173–179 (1990).
36. H. Fischer, F. X. DeCandis, S. D. Ogden and W. P. Jencks. *J. Am. Chem. Soc.* **102,** 1340–1347 (1980).
37. H. F. Gilbert and W. P. Jencks. *J. Am. Chem. Soc.* **99,** 7931–7947 (1977).
38. R. A. Bednar and W. P. Jencks. *J. Am. Chem. Soc.* **107,** 7117–7126 (1985).
39. E. Grunwald and D. Eustace. in *Proton Transfer Reactions,* edited by E. Caldin and V. Gold, pp. 103–120. Chapman and Hall, London (1975).
40. J. P. Guthrie. *Can. J. Chem.* **57,** 1177–1185 (1979).
41. A. Kankaanpera, L. Oinonen and P. Salomaa. *Acta Chem. Scand., Ser. A* **31,** 551–556 (1977).
42. Y. Chiang, A. J. Kresge, H. Morimoto and P. G. Williams. *J. Am. Chem. Soc.* **114,** 3981–3982 (1992).
43. T. L. Amyes and J. P. Richard. *J. Am. Chem. Soc.* **118,** 3129–3141 (1996).
44. T. L. Amyes and J. P. Richard. *J. Am. Chem. Soc.* **114,** 10297–10302 (1992).
45. R. P. Bell and O. M. Lidwell. *Proc. R. Soc. London, Ser. A* **176,** 88–113 (1940).
46. R. P. Bell and J. Hansson. *Proc. R. Soc. London, Ser. A* **255,** 214–217 (1960).
47. J. Hine, K. G. Hampton and B. C. Menon. *J. Org. Chem.* **89,** 2664–2668 (1967).
48. A. J. Kresge, D. S. Sagatys and H. L. Chen. *J. Am. Chem. Soc.* **99,** 7228–7233 (1977).
49. R. P. Bell and H. F. F. Ridgewell. *Proc. R. Soc. London, Ser. A* **298,** 178–183 (1967).
50. Y. Pocker, J. E. Meany and C. Zadorojny. *J. Phys. Chem.* **75,** 792–799 (1971).
51. M. L. Ahrens, M. Eigen, W. Kruse and G. Mass. *Ber. Bunsenges. Phys. Chem.* **74,** 380–385 (1970).
52. M. L. Eidinoff. *J. Am. Chem. Soc.* **67,** 2072–2073 (1945).
53. R. Brouillard and J. E. Dubois. *J. Org. Chem.* **39,** 1137–1142 (1974).
54. H. Groth-Andersen and P. E. Sorensen. *Acta Chem. Scand.* **43,** 32–38 (1989).
55. D. B. Dahlberg and F. A. Long. *J. Am. Chem. Soc.* **95,** 3825–3831 (1973).
56. G. Schwartzenbach and E. Felder. *Helv. Chim. Acta* **27,** 1701 (1994).
57. R. P. Bell. *Discuss Faraday Soc* **39,** 16–23 (1965).
58. K. J. Pedersen. *J. Phys. Chem.* **38,** 601–621 (1934).
59. J. W. Bunting, J. P. Kanter, R. Nelander and Z. Wu. *Can. J. Chem.* **73,** 1305–1311 (1994).
60. R. P. Bell, E. Gelles and E. Moller. *Proc. R. Soc. London, Ser. A* **310,** 308–321 (1949).
61. R. P. Bell and E. Gelles. *Proc. R. Soc. London, Ser. A* **210,** 310–321 (1952).
62. R. G. Pearson and R. L. Dillon. *J. Am. Chem. Soc.* **75,** 2439–2443 (1953).

© 1998 John Wiley & Sons, Ltd.