Prediction of Rate Constants for Cyanohydrin Formation Using Equilibrium Constants and Distortion Energies

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Abstract: Rate constants for cyanohydrin formation in aqueous solution can be predicted, with no use of kinetics information, by the application of a simple model requiring only equilibrium constants and distortion energies for the species involved in the reaction. The detailed model for cyanohydrin formation involves two reaction coordinates: C−C bond formation, which would lead to a cyanohydrin with an orthogonal geometry, and conversion of the carbonyl center from sp^2 to sp^3. Allowance must be made for the necessary desolvation of cyanide ion before C−C bond formation begins and for the initial partial desolvation of the newly formed cyanohydrin anion. The energies of the "corner intermediates" can be calculated, and then the rest of the surface can be deduced using an assumed interpolation formula. With distortion energies derived from semiempirical or ab initio molecular orbital calculations and overall energy changes based on experimental equilibrium constants, and with the assumption of a quadratic dependence of energy on reaction coordinates, the literature data for rate constants for cyanohydrin formation in solution can be matched for a representative selection of compounds spanning the reactivity range which has been studied.

Introduction

The lack of a reliable way to predict the rates of chemical reactions has been a serious hindrance to both the practical and theoretical development of the discipline. Although some progress has been made at predicting rates of reactions from first principles,[1−6] it remains a very difficult computational task. As a stopgap measure, rate equilibrium correlations have been used as a way to make predictions of rate constants from equilibrium constants.[7−11] This is an application of linear free energy relationships to prediction of rate constants rather than the more common use for mechanistic diagnosis. Marcus Theory has excited much interest in this regard,[12−17] even though there has been vigorous objection to its use in large classes of reactions, such as carbonyl additions, where there is no "identity reaction".[18] Despite this theoretical objection, the use of Marcus Theory has been empirically justified, by the simple observation that intrinsic barriers are often transferable for "similar" reactions.[13,15,16,19] However, the problem remains that transferability of intrinsic barriers is simply an empirical observation, and there is no assurance that such transferability will extend to a new type of compound, nor has there been any way to calculate intrinsic barriers. In fact it has been argued that intrinsic barriers will show some sensitivity to equilibrium constant.[20−22] The particular reaction discussed in this paper is cyanohydrin formation, as an example of a nucleophilic addition to a carbonyl and of a carbon−carbon bond-forming reaction. Although a Marcus correlation is possible for this reaction, the variation in intrinsic barrier is larger than one would like—that is, transferability is not as great as it sometimes is. Thus this reaction is a problem case for the methods which have been used to date.

Kreevoy[22] has argued that, at least for atom- or group-transfer reactions where there are identity reactions, the intrinsic barrier is only independent of the equilibrium constant if the "tightness" is 1.0, that is, if the sum of bond orders to the atom or group being transferred is 1.0 throughout the transfer so that the group

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acquires neither positive nor negative character at the transition state. This restrictive condition suggests that for carbonyl addition reactions (where there are no identity reactions), as in group transfer reactions (where there are), truly transferable intrinsic barriers, independent of equilibrium constant, will be rare. It remains an empirical observation that approximate constancy of intrinsic barriers is common.[23]

In this paper I wish to propose a general approach to calculating the absolute rates of chemical reactions, which in favorable cases is not computationally demanding and where the nature of the computational problem is generally recognizable. In this approach equilibrium constants are used to provide the energy contributions for processes which change the number of bonds, while molecular orbital calculations are used to supply distortion energies for bond-bending processes, for which even relatively low level calculations often give useful information. Since experimental equilibrium constants in solution are used, the effects of solvation are automatically included.

Results

The method proposed in this paper requires the following postulates, some of which are in common use.

(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*. This applies both to "edge reactions" and to any section through the reaction hypersurface for which only one reaction coordinate changes. The elementary reaction coordinates are bond making/breaking, or geometry changes 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 that both ends have the same energy, then the energy will be the same at all points along the coordinate. To get 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. The success of molecular mechanics is based on the approximately quadratic dependence of bond-bending and bond-stretching energies on the extent of distortion.

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 postulate 2, with some deviations in order to obtain a single consistent equation for the entire surface.

(3) *Heterolytic bond cleavage constitutes an elementary reaction coordinate*. This is simply an elaboration of postulate 2, but it seems desirable to be explicit about this important assumption. It has often been argued that there is an inherent activation barrier to simple heterolytic cleavage,[24,25] but the present assumption, that such barriers arise from accompanying geometry changes, seems to fit the data quite satisfactorily, as will be seen below.

(4) *For an anion to react at carbon, it must first undergo partial desolvation so that its reactive lone pair can be in van der Waals contact with the carbon*. An important part of the Marcus work term is represented by this effect for strongly hydrogen bonded anions. In the treatment of reactions presented here the equilibrium constant for formation of the reactive encounter complex must be calculated, so the energy cost of this desolvation must be determined, preferably from experiment.

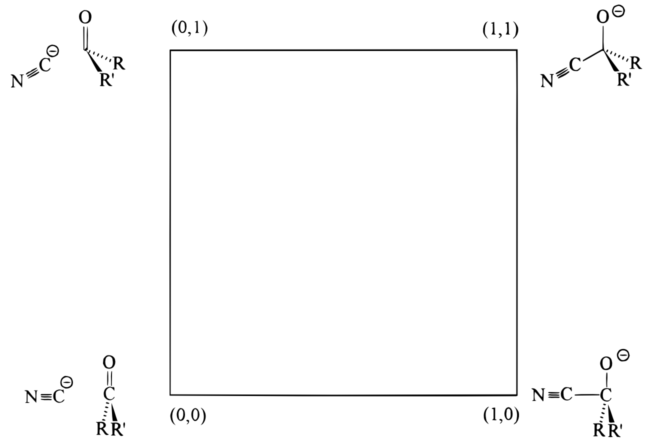

Figure 1. Model for cyanohydrin formation within an encounter complex. The two reaction coordinates are C−C bond formation and geometrical distortion.

(5) *Reaction coordinates are defined to run from 0 to 1*. This means that for bond-making/breaking processes I am using bond order coordinates and that for geometrical distortions the reaction coordinate is the relative change in bond angle, $x = \Delta\theta/\Delta\theta_{\max}$.

The corresponding model for the addition of cyanide to a carbonyl compound is shown in Figure 1. This reaction is relatively simple in that from the encounter complex only two things need to happen to proceed to product: formation of a C−C bond and a change in geometry at the reaction center from sp^2 to sp^3.

To use this model we must have the free energies, relative to reactants in solution, of the four corner species. This requires calculating the energy of the encounter complex at the origin (0,0) of Figure 1, of the initial product (1,1), and of the two "corner intermediates" at (1,0) and (0,1).

The equilibrium constant for formation of the initial encounter complex (in terms of Marcus Theory, the work term) can be calculated as the sum of the entropic cost of bringing the reactants together and the cost of initial desolvation. In order for cyanide to react with a carbonyl carbon, it must have lost hydrogen-bonding solvation to water so that the lone pair is free. The cost of partially desolvating CN^- in this way was estimated from the difference in pK_a for HCN in water, 9.21,[26] and DMSO, 12.9.[27] This procedure leads to the cost of losing hydrogen bonding both at carbon and nitrogen, 5.05 kcal/mol, since it seems probable that cyanide ion will hydrogen bond at both ends. A computational study showed that hydrogen bonding to the carbon or the nitrogen of cyanide was essentially isoenergetic.[28] The observation that cyanide in DMSO reacts with alkyl halides at carbon but in alcohols reacts at nitrogen[29] suggests that hydrogen bonding is stronger at carbon. The cyanide nitrogen must, by the end of the reaction, have lost much of the energy of hydrogen-bonded solvation. The product

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is likely to be hydrogen bonded at the nitrile nitrogen, though this is not expected to be strongly favorable. Computational studies of gas-phase hydrogen bonding suggest that the energy of the water−acetonitrile hydrogen bond is −4.6 kcal/mol[30] while the energy of a water−water hydrogen bond is −6.4 kcal/mol,[31] both calculated using the TIP4P model for water. Thus one expects that the hydrogen bond to the cyanohydrin nitrogen will make little net contribution to the free energy of the cyanohydrin anion. The above analysis imposes a limit on the rate of reaction of cyanide as a nucleophile in water because of the cost of desolvation. For proton-transfer reactions, where the C of cyanide ion will be hydrogen bonded to the acid which is about to protonate it, formation of the encounter complex requires only loss of hydrogen bonding to the nitrogen. It is observed that proton transfer to and from cyanide is fast and direct (with no intervening water),[32] which implies that the cost of losing solvation at nitrogen is small. Thus the data at hand suggest that in solution hydrogen bonding to cyanide ion is mainly to the carbon.

A study of the solvation of benzonitrile showed that the nitrile nitrogen was hydrogen-bonded but that the hydrogen bonding was to the π-bond and not the lone pair.[33] A study of the solvation of acetonitrile likewise showed that the nitrogen was hydrogen-bonded to water, but did not discuss the geometry.[34]

In the case of the most reactive compounds the desolvation process may be partially rate determining. The activation barrier may be estimated by assuming that the rate of formation of such hydrogen bonds from an unsolvated cyanide in an encounter complex will be limited by the reorganization time of water, which has a rate constant of 10^{11} s^{-1}.[35−37]

The entropic cost of bringing two species together to form an encounter complex was estimated following Hine's suggestion,[13] as 2.42 kcal/mol. Thus the full cost of bringing the reactants together in the encounter complex is 7.61 kcal/mol.

The initial product, (1,1), is a single molecule but will initially be partially desolvated. X-ray studies of hydrogen bonding to carbonyl groups showed that most hydrogen bonds are oriented toward the expected lone pairs for sp^2 hybridization at oxygen.[38] This implies that the initial state of the cyanohydrin will be partially desolvated at oxygen because only two of the three hydrogen bonds expected for an alkoxide ion will be present when it first forms.[39] The energetic cost of this desolvation can be estimated from the pK_a shift, from water to DMSO, for oxyanions. This pK_a shift has been shown to correlate with pK_a,[40] and the pK_a of the cyanohydrin can be estimated from the linear free energy relation between alcohol pK_a and $\sum\sigma^*$.[41,42] Thus the cost of losing one hydrogen bond to the cyanohydrin anion can be calculated and used to calculate the energy of the initial product from that of the fully solvated product, which in turn is known by means of the equilibrium constant for the overall process.

For the two "corner intermediates" we calculate the distortion energy by MO methods. For (1,0), this means calculating the distortion energy as the difference in energy between (1,1) and (1,0) and using this value to determine the energy of (1,0) from that of (1,1) in solution. For (0,1) the distortion energy is calculated as the difference in energy between (0,0) and (0,1) and is used to determine the energy of (0,1) relative to that of the encounter complex of the reactants in solution. Thus the absolute energies of the corners are based on experimental equilibrium constants and distortion energies calculated by MO methods for pairs of species differing only in geometry and not in bonding.

For the two-dimensional case it is relatively straightforward to calculate the energy for the transition state corresponding to the energy surface described above in postulates 2 and 3. Let the C−C bond-forming coordinate be x and the coordinate for rehybridization from sp^2 to sp^3 be y. Then by hypothesis the transition state will be at the energy corresponding to the crossing of the two limiting curves corresponding to $x = 0$ and $x = 1$ or $y = 0$ and $y = 1$. These curves are given by

$$G_{y=0} = G_1 x^2$$

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

$$x^* = ((G_2 - G_3) \pm \sqrt{(G_2 - G_3)^2 - G_2(G_2 - G_3 - G_1)})/(G_2 - G_3 - G_1)$$

$$G_y{}^* = G_1 x^{*2}$$

$$G_{x=0} = G_2 y^2$$

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

$$y^* = ((G_1 - G_3) \pm \sqrt{(G_1 - G_3)^2 - G_1(G_1 - G_3 - G_2)})/(G_1 - G_3 - G_2)$$

$$G_x{}^* = G_2 y^{*2}$$

The position of the transition state is given by x^*, the value of x where the two expressions for $G(x)$ cross, or y^*, the value of y where the two expressions for $G(y)$ cross. Then $G^*{}_x$ is the energy of the transition state calculated from y^* and the expression for $G_{x=0}$, and $G^*{}_y$ is the energy of the transition state calculated from x^* and the expression for $G_{y=0}$. In these expressions G_1 is the energy of the (1,0) corner, G_2 is the energy of the (0,1) corner, and G_3 is the energy of the (1,1) corner (the immediate product of the reaction). To simplify the calculations,

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[39] I thank a reviewer for suggesting that desolvation of $C-O^-$ must be included in the model if desolvation of CN^- is included. This possibility had been examined early in the development of these ideas but had been (prematurely) rejected because it led to contradictions for other reactions. With the full development of the approach presented here these contradictions disappear and inclusion of a consideration of initial partial desolvation of $C-O^-$ improves the overall agreement of calculated with experimental values. I gratefully acknowledge the help of this reviewer.

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the energies are all relative to the (0,0) corner (the initial encounter complex), for which the energy is set at 0.0

Unfortunately there is no requirement from what has been said so far that the same value be obtained from the two possible ways to calculate ΔG^*. In fact it can be shown that the values of ΔG^* calculated in these two ways will be identical only if the corner intermediate energies are the same or the overall energy change is zero.

If $G_1 = G_2$, then

$$x^* = ((G_1 - G_3) \pm \sqrt{(G_1 - G_3)^2 + G_1G_3})/(-G_3)$$

$$y^* = ((G_1 - G_3) \pm \sqrt{(G_1 - G_3)^2 + G_1G_3})/(-G_3) = x^*$$

If $G_3 = 0$, then

$$x^* = (G_2 \pm \sqrt{G_2G_1})/(G_2 - G_1)$$

$$G_y^* = (G_1G_2^2 \pm 2G_2G_1\sqrt{G_2G_1} + G_2G_1^2)/(G_2^2 - 2G_2G_1 + G_1^2)$$

$$y^* = (G_1 \pm \sqrt{G_1G_2})/(G_1 - G_2)$$

$$G_x^* = (G_2G_1^2 \pm 2G_2G_1\sqrt{G_1G_2} + G_2^2G_1)/(G_1^2 - 2G_2G_1 + G_2^2) = G_y^*$$

Although the differences, in the general case, between the values of ΔG^* calculated in these two ways are relatively small, usually less than 1 kcal/mol, this is an unsatisfactory situation and will become more so for higher dimensional reaction surfaces. 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 it should give values at intermediate points close to those obtained by the two possible stepwise procedures (calculating the energy at a given x for $y = 0$ and $y = 1$ and then calculating the energy at (x,y) by interpolating using the appropriate quadratic expression or calculating the energy at a given y for $x = 0$ and $x = 1$ and then calculating the energy at (x,y) by interpolating using the appropriate quadratic expression). To do this, I started by writing an equation for the energy along any section parallel to the x-axis as

$$G_y = G_1x^2 + (G_3 + (G_2 - G_3)(1 - x)^2)y^n$$

$$G_x = G_2y^2 + (G_3 + (G_1 - G_3)(1 - y)^2)x^n$$

Adding the right-hand expressions and then adding suitable correction terms in x^n, y^n, and x^ny^n to force constraints 1 and 2 to be satisfied led to the following equation

$$G = G_1x^2 + (G_3 + (G_2 - G_3)(1 - x)^2 - G_1x^2)y^n + G_2y^2 + (G_3 + (G_1 - G_3)(1 - y)^2 - G_2y^2)x^n - G_1x^n - G_2y^n + (G_1 + G_2 - G_3)x^ny^n \quad (1)$$

which after simplification gives

$$G = a_1xy^n + a_2x^2 + a_3x^ny + a_4y^2 + a_5x^2y^n + a_6x^ny^2 + a_7x^ny^n$$

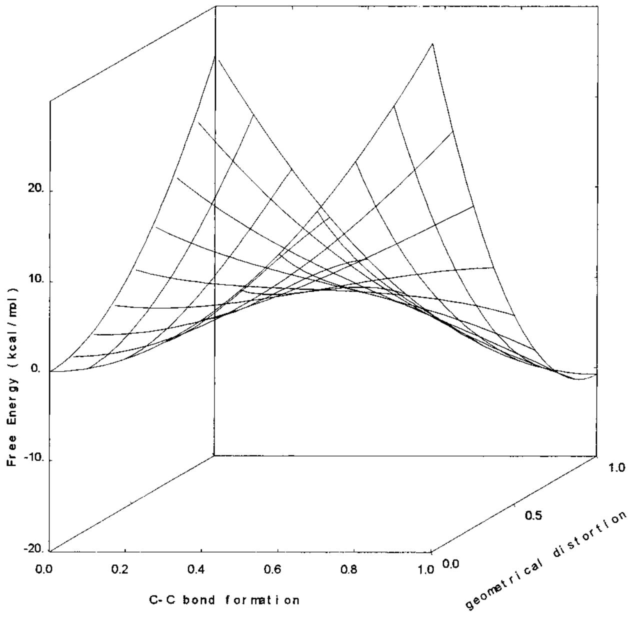

Figure 2. Surface described by eq 2; energies are calculated for the addition of cyanide to acetaldehyde, using distortion energies calculated at the 3-21G level.

where

$$\begin{aligned} a_1 &= 2(G_3 - G_2) \\ a_2 &= G_1 \\ a_3 &= 2(G_3 - G_1) \\ a_4 &= G_2 \\ a_5 &= G_2 - G_3 - G_1 \\ a_6 &= G_1 - G_3 - G_2 \\ a_7 &= G_1 + G_2 - G_3 \end{aligned} \quad (2)$$

The value of n was chosen to satisfy the final constraint, namely that the energies should be close to those calculated by the stepwise procedures. Numerical exploration revealed that with $n = 2$ the surface developed spurious "valleys" where the energy fell below either the initial or final values for a given section, while with $n = 3$ the surface developed spurious "mountains" where the energy rose above either the initial or final values for a given section. Reasonable behavior was obtained with $n = 2.5$. The nature of the surface described by the final equation is shown in Figure 2.

Calculations to find the transition state positions and energies were carried out by a computer program which was a simple modification of the one used for Multidimensional Marcus Theory.[43] It was only necessary to change the input section to calculate a_1−a_7 from the corner energies and to change the functions which evaluated the energy and its derivatives at any point.

When this is done, the results in Table 1 are obtained. The calculations[44] were done at various levels. For this reaction, semiempirical (AM1) calculations gave reasonable results, with an rms deviation in ΔG^* of 1.32 kcal/mol (0.97 in log k). Ab initio calculations gave very similar results: 3-21+G, rms deviation in ΔG^* of 1.51 kcal/mol (1.11 in log k); B3LYP/3-

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Table 1. Equilibrium[a] and Rate[b] Constants for Cyanohydrin Formation in Aqueous Solution at 25 °C[c]

compound	log K_{obs}	log k_{obs}	AM1 log k_{calc}[d]	3-21+G log k_{calc}[d]	B3LYP/3-21+G log k_{calc}[d]	6-31+G** log k_{calc}[d]	B3LYP/6-31+G** log k_{calc}[d]
CH_2O	7.48	5.54	5.43[e]	4.96	5.43	5.05	5.43[e]
CH_3CHO	2.29	2.81	3.16	2.74	3.60	2.94	3.72
CH_3COCH_3	−1.84	0.60	1.11	0.73	1.91	0.95	1.88
PhCHO	0.74[f]	1.84[f]	2.29	1.82	2.77	1.97	
$PhCOCF_3$	3.98[g]	4.67[g]	2.64	2.27	3.35		
rms error in log k_{calc}			0.97	1.11	0.99	0.32	0.91

[a] $K_{obs} = [RR'C(O^-)(CN)]/[RR'C{=}O][^-CN]$. [b] $v = k_{obs}[^-CN][RR'C{=}O]$. [c] Experimental values from ref 62 unless otherwise stated. [d] Values based on distortion energies calculated by molecular orbital methods at the level indicated. [e] This reaction is predicted to have desolvation of cyanide as the rate-limiting process. [f] Reference 63. [g] Reference 64.

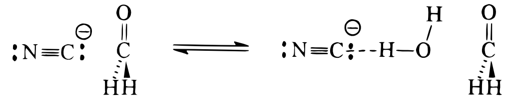
21+G, rms deviation in ΔG^* of 1.36 kcal/mol (0.99 in log k); 6-31+G** (on four reactions), rms deviation in ΔG^* of 0.43 kcal/mol (0.32 in log k); B3LYP/6-31+G** (on three reactions), rms deviation in ΔG^* of 1.24 kcal/mol (0.91 in log k). Thus relatively inexpensive calculations are quite adequate for this treatment, at least for this reaction. This seems reasonable, since the calculations are being used to determine angular distortions, in effect force constants for bond bending, and such force constants can be calculated with useful precision by AM1[45] or ab initio calculations at the 3-21G level.[45,46]

Discussion

The goal of this research has been to find a practical method for predicting rate constants. This necessarily means using a simplified model, so that there is an empirical element arising from the justification of a particular simple model, based on its success. Since the model must be explicit, it would be straightforward to try a more elaborate model, to see if it leads to better results. The key ideas are that one can, and must, analyze a reaction in terms of the "simple" processes which will follow a quadratic force law and that as a consequence of the simplicity of these force laws one can interpolate to determine the energy of the entire energy surface. If the processes used to define the reaction dimensions are not simple, then the energy at intermediate points will not be so readily determined by interpolation. In my earlier attempts at addressing this problem by Multidimensional Marcus Theory,[43] the reaction dimensions were not simple, and a quartic dependence of energy on reaction coordinate was used. The quartic expression allowed for an intrinsic barrier for each reaction dimension. This worked,[40] subject to the assumption of transferable intrinsic barriers, which had to have been evaluated separately. In the initial attempt at the approach presented here,[47] proton-transfer reactions of carbon acids were described using a quartic potential energy function[40] with the intrinsic barrier set very low because the processes were elementary reaction steps. Distortion energies were taken from molecular mechanics calculations. Although the values do change with different models or different ways of estimating the distortion energies, the results are often surprisingly insensitive to the details of how the calculations were done.

The total solvation energy of cyanide ion in water is 70.5 kcal/mol;[48] thus, the 5.2 kcal/mol lost when hydrogen bonding is removed is a small part of the overall effect of a polar solvent. Cyanide is expected to be hydrogen bonded both at carbon and nitrogen: in the gas phase the two modes of hydrogen bonding are equally favorable.[28] When cyanide becomes nitrile, it is expected to become a much weaker hydrogen bond base and consequently to compete poorly for the much more abundant water molecules for hydrogen bonding to water hydrogens.

For very reactive carbonyl compounds, in the present work formaldehyde, reaction within the encounter complex can be so fast that it becomes faster than the solvation/desolvation process and ceases to be rate-limiting. The total cost of forming the reactive encounter complex was estimated as 7.6 kcal/mol or 5.6 log units. The true reaction rate must be faster than the apparent rate by this amount if the encounter complex is indeed on the reaction path. In the case of formaldehyde, the observed rate constant is $10^{5.5}$ M^{-1} s^{-1}, so the true rate constant would be $10^{11.1}$ s^{-1}. This is similar to the rate of diffusional separation, suggesting that the rate-limiting process is before complete formation of the encounter complex. For the final desolvation process (or in the other direction the first step in the escape of cyanide from the encounter complex)



the rate constant can be estimated from the rate of reorientation of water in liquid water, that is, the dielectric relaxation time. The dielectric relaxation time seems well established as about 1 × 10^{-11} s.[35−37,49−52] Clearly this will not be exactly appropriate for the situation here, but it seems likely to be within an order of magnitude. This relaxation time imposes a limit on any diffusional separation process. Thus we expect that, for formaldehyde, desolvation will be at least partially rate limiting and could be entirely rate limiting if the actual addition process is faster.

In using the dielectric relaxation time for pure water, I am trying to set a limit on any separation process. From the complex permittivity of solutions of salts, one can extract rate constants for encounter and separation though one must impose a model for the nature of the ion pair (intimate or solvent separated). However this method requires that at least one of the ions have a charge of 2 or higher, and in these cases

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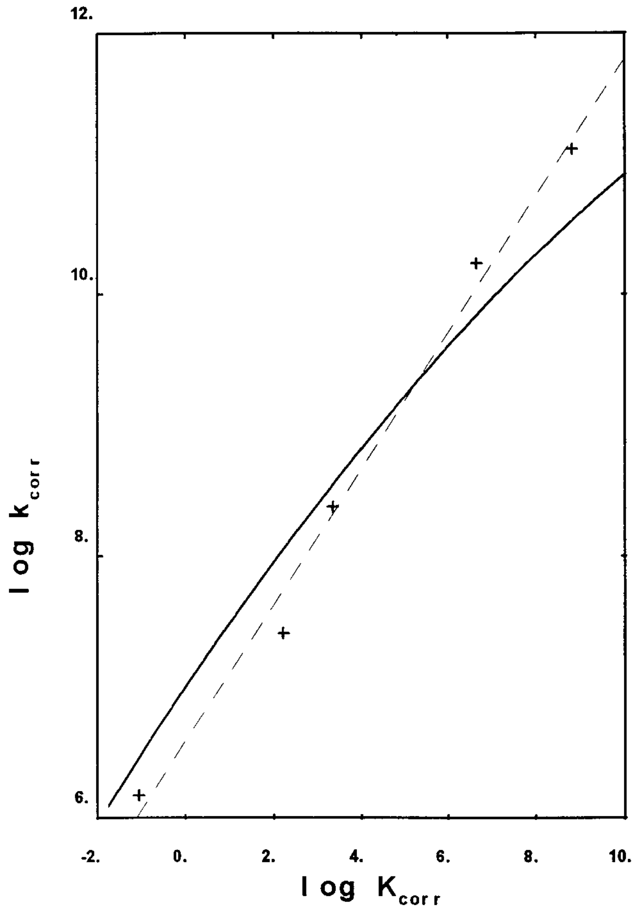

Figure 3. Rate and equilibrium constants for cyanohydrin formation, calculated for the encounter complex of desolvated cyanide ion with the carbonyl compound: (— — —) best straight line (least squares); (—) Marcus curve, using the average intrinsic barrier.

electrostatic effects retard the separation.[51,52] The method is not suited to determining rate constants for formation or separation of ion−molecule complexes.

Intuitively one might expect greater charge separation for the relatively severe distortions when a carbonyl compound is bent to tetrahedral geometry, because of an enhanced contribution from the C^+—O^- resonance contributing form at the expense of C═O. This in turn might lead to greater solvation energy, complicating the estimation of the energies of the corner intermediates. However Mulliken population analysis suggests otherwise: for all of the compounds (at the B3LYP/3-21+G level), the charge on the carbonyl oxygen changes very little upon distortion and in the direction of becoming less negative. For all but trifluoroacetophenone the charge on the carbonyl carbon changes relatively little. For trifluoroacetophenone there is a large change but there are accompanying and offsetting changes in the charges on the carbon of the trifluoromethyl group and the ipso carbon of the ring. There is little change in the charge on the peripheral atoms which would interact most directly with solvent, when the carbonyl group is distorted.

One can demonstrate a linear free energy relationship between the rate and equilibrium constants for cyanohydrin formation. This requires two empirical parameters (slope and intercept) and is of an uncertain range of validity. The slope for the compounds discussed here is 0.65; one expects this to become closer to 1.0 as the equilibrium constants become less favorable and to become closer to 0.0 as they become more favorable (though it is unlikely that there will be many compounds more reactive than formaldehyde in this context). The situation of interest is the estimation of rates of reaction for less favorable cyanohydrin formation, where the linear free energy relation is expected to break down at some unknown point, as the equilibrium becomes less favorable and the slope becomes larger. The new approach presented in this paper should be general and has no empirical parameters.

Figure 3 shows the linear free energy relation between the rate and equilibrium constants for cyanohydrin formation and the Marcus curve (with an average value of the intrinsic barrier used for all reactions) passing through the point for acetaldehyde, from which there are clearly systematic deviations.[53]

Thus, when Marcus Theory is applied to the cyanohydrin-forming reactions examined here, the intrinsic barriers calculated for reactions within the encounter complexes are similar but not constant. In fact the approximately linear relation between log k and log K over the range of data available implies that the intrinsic barrier cannot be the same for all compounds. This sort of linear free energy relationship, though it may be very useful, is strictly empirical, and over a wide enough range in reactivity it is expected to break down.[54] It should be borne in mind that a linear relationship involves two empirical parameters. A calculation procedure which involves no empirical parameters is both esthetically and practically of more value in terms of making predictions in a new situation.

For the dimension corresponding to carbon−cyanide bond formation (heterolytic cleavage in the reverse direction) we can show that the quadratic expression in bond order coordinates is equivalent to a Morse curve in bond length coordinates. We start with Pauling's[55] bond length−bond order relationship

$$r_n = r_1 + A \log(n)$$

This can readily be transformed into

$$n = e^{B(r_n - r_1)}$$

Then the expression for energy as a function of bond order coordinate becomes

$$\begin{aligned} G &= \Delta G(1 - x)^2 \\ &= \Delta G(1 - e^{B(r_n - r_1)})^2 \end{aligned}$$

which is of the form of the Morse curve, as one might expect.

The energy for a bending distortion is given by[56]

$$E_\theta = 0.021914(k_\theta)\Delta\theta^2[1 - 0.014\Delta\theta + (5.6 \times 10^{-5})\Delta\theta^2 - (7.0 \times 10^{-7})\Delta\theta^3 + (9.0 \times 10^{-10})\Delta\theta^4]$$

I am using $x = \Delta\theta/\Delta\theta_{\max}$ as the reaction coordinate. Thus the energy for a bending distortion, using only the quadratic term, is given by

$$E = [0.021914(k_\theta)\Delta\theta_{\max}{}^2]x^2$$

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(53) The points are for the model with desolvated cyanide in contact with the carbonyl compound, for a total desolvation energy of 7.61 kcal/mol. Since log K and log k are corrected by the same amounts in this model, an equally good linear fit would be obtained using the direct experimental values.

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Since the molecular orbital calculations used for distortion energies refer to the gas phase, we must ask whether solvation will perturb the distortion energy. It is known that the solvent will affect the frequency of an IR absorption, though the effect is normally small (except for hydrogens which engage in hydrogen bonding). For carbonyl stretches, which have been extensively studied, the effect of solvent is less than 25 cm^{-1} for a frequency of 1700 cm^{-1},[57] corresponding to 1.5%. One thousand seven hundred inverse centimeters corresponds to 4.9 kcal/mol, while the distortions of interest here are on the order of 20−50 kcal/mol. The gas-phase values seem likely to be adequate.

Although development of this method is still in progress, some aspects of the question of when it will be computationally demanding or not are becoming clear. The necessary calculations will not be particularly demanding provided that the overall equilibrium constant is known, the pK_a or other equilibria needed to calculate the equilibrium constant for reaction in the encounter complex is known or can be estimated, the bond-making/breaking process is a simple heterolysis or a proton transfer, and other dimensions involve distortions corresponding to molecular vibrations. By using equilibrium constants in solution, we can sidestep the problem of calculating solvation energies.

The approach presented here is novel and must be tested before it can be accepted. However if it proves to be valid and general, then it offers the prospect of calculating a rate constant for a new reaction from the equilibrium constant for the microscopic rate-determining step for that reaction, with no other experimental information being required. This would be much more general than the approach based on linear free energy relations or even Marcus correlations, which require two or one parameters, respectively, evaluated from data for other ‘similar’ reactions. It would still be necessary to know the mechanism, or the plausible mechanistic possibilities, for the new reaction.

That the energy would be approximately a quadratic function of reaction coordinate for pure “edge reactions” seems to raise few objections. The question is whether simple interpolation is adequate to give the entire energy surface; including (and particularly) the region of the transition state for concerted paths is more contentious. There could be cross terms, and it is not obvious, at least to me, whether such terms might or might not be significant. A frankly empirical approach seems appropriate. The simplest model is to assume no cross terms, as has been done above. One then asks if this simple model works. My contention is that it does.

For purposes of testing the approach presented in this paper, the calculations have been restricted to cases where both rate and equilibrium constants have been directly measured. It is however possible to estimate equilibrium constants by linear free energy relations, such as the Sander and Jencks $\Delta-\gamma$ relation for carbonyl additions,[58] thermodynamic additivity procedures,[59,60] or molecular orbital or molecular mechanics calculations. In general one has more confidence in such methods than in analogous estimations of rate constants. It is also possible to determine equilibrium constants in indirect ways,[61] including equilibrium constants for formation of reactive intermediates, which are very difficult to evaluate directly. Such equilibrium constants would become the starting point for estimation of rate constants by the present method.

Although the precision of the predictions by this new method is not high, it is sufficient to be useful in considering new reactions. The method can doubtless be improved by more detailed calculations. Even as it stands, it represents for the first time a practical general method for predicting the rates of chemical reactions in solution.

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Supporting Information Available: (1) Summary of the actual calculations leading to transition state energies; (2) spreadsheet used to calculate the corner energies from distortion energies; (3) spreadsheet used to calculate the points and lines for Figure 3 (28 pages). See any current masthead page for ordering and Internet access instructions.

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