

Prediction of the Rate Constants for Proton Abstraction from Carbon Acids, Using a Simple Model and Multidimensional Marcus Theory

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In this paper, I wish to report that rates of proton transfer from simple carbon acids to water or hydroxide can be estimated with useful precision using a very simple model. This procedure, based on multidimensional Marcus theory,¹ permits the estimation of apparent intrinsic barriers with no input of kinetic information. The compounds studied range in acidity from ethyl acetate to acetylacetone.

Marcus correlations have been found for deprotonation of various carbon compounds by oxygen bases,^{2–6} but these correlations required different intrinsic barriers for each class of reaction (dicarbonyl with hydroxide ion, dicarbonyl with water, monocarbonyl with hydroxide, etc.).² Recently Amyes and Richard have measured rates of proton abstraction by hydroxide from ethyl acetate⁷ and ethyl thiolacetate.⁸ In combination with previously measured rates of proton abstraction from simple aldehydes and ketones,⁹ these results lead to a linear Brønsted plot extending over 14 log units in equilibrium and 5 log units in rate.⁷ This extended linearity is not consistent with a constant Marcus intrinsic barrier but could be interpreted in terms of varying intrinsic barriers.^{7,10} A rationalization of this behavior has been presented.⁷ Since the practical application of Marcus theory as a tool for correlating and predicting rate data for organic reactions depends on being able to predict intrinsic barriers, most simply by assuming a constant intrinsic barrier for a set of “similar” reactions, I looked to explain these new results in a simple way.

The model which I now propose assumes that proton abstraction involves at least three processes or reaction coordinates after the base (if it is other than water) has diffused into contact with the carbon acid. These processes are simple proton abstraction which leads to a pyramidal anion, planarization of the carbon which is going to lose the proton, and adjustment of bond lengths to those found in the final anion. Normally these three occur together in a concerted reaction, but commonly they are imperfectly synchronized.^{11–13} Energies of the “corner intermediates” corresponding to only one or two of these processes will be estimated, and the energy of the transition state will be calculated by interpolation.

The pK_a values for pyramidal anions were estimated using a Taft $\rho^*\sigma^*$ relation.¹⁴ The value of $\rho^* = -3.09$ was evaluated from the pK_a values for CH_4 , (50¹⁵), CH_3CH_3 (52.0^{15,15g}), $CH(CH_3)_3$ (59.7¹⁵), and CF_3H , taken as 27,¹⁶ using σ^* values taken from Perrin.^{17,18} The energies of species with nonequilibrium geometries were calculated by molecular mechanics (using PCMODEL²¹), relative to the energy of the corresponding minimized structure, for starting material or product. In encounter complexes with hydroxide, the hydroxide will have replaced one solvating water molecule by a hydrogen bond to CH.²² Hydrogen bond energies were estimated using the equation of Stahl and Jencks.²³ A CH species distorted toward the geometry of the anion will have enhanced acidity and may be expected form a good hydrogen bond.²⁴

For acetylacetone, the proton abstraction begins from a conformation with all carbons in a plane; the energy cost relative to the minimum-energy conformation is small. For nitromethane, an additional reaction coordinate is postulated for solvent relaxation. An aliphatic nitro group is very weakly basic, $pK_{BH^+} \approx -12$,²⁶ and hence unlikely to be hydrogen bonded;²⁷ *aci*-nitromethane has a pK_a of 3.25,³⁰ and hence nitromethide ion will be hydrogen bonded at equilibrium. The

(14) The values are given in Table S1, Supporting Information.

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(18) Here, it is assumed that fluorine acts only by a normal polar effect as measured by σ^* ; chlorine may well involve polarizability effects as well and so could be less appropriate. A referee has objected that α -fluorine may destabilize the anion by orbital repulsion, as it does in fluoro-substituted enolates. If so, fluorine would be less effective than expected from σ^* and chlorine, if it stabilizes the anion by polarizability effects will be more effective than expected from σ^* . Use of chloroform instead of fluoroform changes ρ^* by 10%. Changes of this magnitude do not affect the analysis in this paper because the tetrahedral anion is invariably a high-energy corner which is avoided by the reaction path and thus has a small effect on the transition state energy. Schleyer et al.^{19,20} examined the effect of heteroatom substituents on the stability of CH_3^- by *ab initio* calculations and concluded that lone pair repulsions were not important.

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(22) This treatment is consistent with our previous use of a desolvation energy of 7.13 kcal/mol^{3,15} for loss of one hydrogen-bonded water. The value was based on the difference in the pK_a of water in water and DMSO; the predicted energy of the hydrogen bond between water and DMSO is +8.5 kcal/mol. This is the energy of the hydrogen bond alone, corrected for the entropic cost of bringing the species together.

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(24) When α_2^H values for various hydrogen bond donors (CH, NH, and OH)²⁵ were plotted vs pK_a (using pK_a values corresponding to tetrahedral anions for CH acids other than haloforms or alkynes), it was found that they fell approximately on a curve which could be fitted to a quadratic expression (see Table S3 and Figure S1, Supporting Information). If this is the correct interpretation, then a CH acid with a pK_a (for simple proton transfer without geometry change) lower than that of water should actually be better at stabilizing hydroxide by hydrogen bonding than water. The α_2^H term is a parameter which measures the hydrogen bond acidity of a molecule as a solute.²⁵

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(27) $HClO_4$ has $pK_a = -5$,²⁸ and ClO_4^- is so weakly hydrogen bonded that it tumbles almost freely in solution, while PO_4^{3-} tumbles slowly, dragging hydrogen bonded waters with it.²⁹

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Table 1. Observed and Calculated Rate Constants for Deprotonation of Carbon Acids^a

compound	p <i>K</i> _a	base	log <i>k</i> _{obsd}	<i>G</i> _{apparent} ^b	log <i>k</i> _{calcd} ^c	log <i>k</i> _{calcd} – log <i>k</i> _{obsd}
CH ₃ COOC ₂ H ₅	25.6 ^d	HO ⁻	-2.92 ^d	10.36	-3.47	-0.55
CH ₃ COSC ₂ H ₅	21.0 ^e	HO ⁻	-1.70 ^e	13.14	-0.88	0.82
CH ₃ COCH ₃	19.3 ^f	HO ⁻	-0.65 ^f	14.38	-0.76	-0.11
CH ₃ COCH ₃	19.3 ^f	H ₂ O	-9.34 ^f	13.90	-8.99 ^g	-0.45
CH ₃ CHO	16.7 ^f	HO ⁻	0.07 ^f	15.65	0.41	0.34
CH ₃ CHO	16.7 ^f	H ₂ O	-7.62 ^f	14.16	-6.42 ^g	-1.20
CH(CH ₃) ₂ CHO	15.49 ^f	HO ⁻	-0.85 ^f	17.38	-2.53	-1.68
CH(CH ₃) ₂ CHO	15.49 ^f	H ₂ O	-7.26 ^f	14.91	-6.67	0.56
CH ₃ NO ₂	10.21 ^h	HO ⁻	1.44 ⁱ	14.93	2.30	0.85
CH ₃ NO ₂	10.21 ^h	H ₂ O	-7.37	19.93	-6.92	-0.45
CH(CH ₃) ₂ NO ₂	7.74 ^h	HO ⁻	-0.50 ⁱ	20.85	0.78	1.28
CH ₂ (COCH ₃) ₂	8.87 ^j	HO ⁻	4.60 ^j	14.06	3.20	1.38
CH ₂ (COCH ₃) ₂	8.87 ^j	H ₂ O	-1.92 ^j	13.32	-2.80	-0.89

^a All are in aqueous solution at 25 °C; rate constants are in M⁻¹ s⁻¹ or s⁻¹. ^b Calculated from the overall equilibrium constant and the observed rate constant, corrected where appropriate for encounter complex formation, using $K_{\text{encounter}} = 0.017$ (Hine, *J. J. Am. Chem. Soc.* **1971**, *93*, 3701–3708). ^c Calculated as described in the text, with a symmetry correction for the number of equivalent acidic hydrogens. ^d Reference 8. ^e Reference 7. ^f Reference 9. ^g Calculated for diffusion controlled separation of H₃O⁺ and anion, using $k = 10^{11}$ s⁻¹; the reaction is in fact not completely diffusion controlled. ^h Reference 30. ⁱ Bell, R. P.; Goodall, D. M. *Proc. R. Soc. London Ser. A* **1966**, *294*, 273–297. ^j Ahrens, M. L.; Eigen, M.; Kruse, W.; Maas, G. *Ber. Bunsen-Ges. Phys. Chem.* **1970**, *74*, 380–385.

energy cost of this lack of solvation is taken from the difference in p*K*_a for nitromethane between water³¹ and DMSO.³² Aldehydes, ketones, esters, and thioesters are all more basic than nitro groups and are expected to be hydrogen bonded to water in solution.

In this way, one can calculate the energy of the “corner intermediates”. These “intermediates”, although normally not on the reaction path, represent the species which would form if only *one* (or *two* or ...) reaction coordinate were followed. In most real reactions of the sort considered here, the reaction proceeds along three or even more coordinates, potentially simultaneously. The essence of the method is to interpolate between the corners of known energy. To carry out the interpolation, I have used a recently developed procedure based on quartic approximations to the reaction coordinate.¹ For all processes, a “small” intrinsic barrier was assumed; “small” was arbitrarily defined as 0.01 kcal/mol. Similar results are obtained using a linear interpolation model³³ with no intrinsic barrier.

The results of the analysis just described are given in Table 1. Although the reactions considered have considerable variation in apparent intrinsic barrier, the rate of the proton abstraction can be estimated, generally within an order of magnitude, by the simple model given above. The reactions of acetone and acetaldehyde with water are predicted to be diffusion controlled, limited by separation of the enolate and H₃O⁺. The rate of diffusional encounter of an anion with H₃O⁺ was taken as 5×10^{10} M⁻¹ s⁻¹.³⁴ The rate of reaction of nitromethane with water is predicted to be limited by relaxation of water to provide hydrogen-bonding solvation of the nitronate anion. The rate of this relaxation is taken as 10^{11} s⁻¹.³⁵

The approach presented here is particularly suited for predicting the rates of reactions, which it does within the uncertainties of the corner energies. It is less suited to predicting the detailed nature of the transition state, because this may depend on the

exact energies of the corners, which are unavoidably subject to uncertainty. Analysis of the nature of a transition state in terms of an Albery–More O’Ferrall–Jencks diagram commonly assumes that the location of the transition state can shift a considerable distance within the diagram for modest changes in the relative energies of the corners; this is fully consistent with the often rather flat energy surfaces found by the method presented here. Thus, the method presented here complements more traditional treatments which have been devised to pinpoint the nature of the transition state, rather than to predict its energy.

Admittedly, the model described here is of startling naiveté. Nonetheless, it seems to work. This suggests that an exploration, using more elaborate computational methods to calculate the quantities which had to be estimated, would reward in terms of better precision and better understanding.

The success of the model suggests that it may form a pattern for a general interpretation of Marcus intrinsic barriers. It is worth noting that in the original derivation of Marcus theory for outersphere electron transfer reactions, the model used was equivalent to a two-dimensional model with no intrinsic barrier in either dimension. The two dimensions were distortion of the coordination geometry of the metal ions and transfer of electron. Thus, one can argue that the intrinsic barrier in Marcus theory arises from the need to change along several reaction coordinates for any overall chemical transformation. If the model is general, it suggests that the intrinsic barrier is not a fundamental property of a reaction but the consequence of the relative energies of the various corner intermediates. On one hand, this implies that intrinsic barriers are not necessarily transferable but, on the other hand, transferable intrinsic barriers are less necessary since rate constants can be calculated without the need for an intrinsic barrier. I intend to explore the application of these ideas to additional reactions and will report the results in due course.

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Supporting Information Available: Tables of p*K*_a and model data and acidity plot (6 pages). See any current masthead page for ordering and Internet access instructions.

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