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Solvent-Dependent Transition States for Decarboxylations

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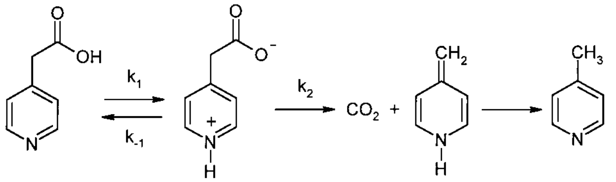
Abstract: The rate constants and kinetic isotope effects for decarboxylation of 4-pyridylacetic acid depend strongly on whether the solvent is water or dioxane, and the present paper interprets this finding. We calculate the solvent dependence of the free energy barrier and of the ^{13}C and ^{18}O kinetic isotope effects using a quantum mechanical solvation model based on class IV charges and semiempirical atomic surface tensions. The calculations provide a consistent interpretation of the experimental results, which provides a striking confirmation of the soundness of the solvation modeling. Even more significantly, the agreement of theory and experiment gives us confidence in the physical picture of the reaction provided by the model. This indicates that the location of the transition state, as measured by the length of the breaking C−C bond, is 0.24 Å later than the gas phase in dioxane and 0.37 Å later than the gas phase in water. Charge development at the transition state also depends strongly on the solvent; in particular the CO_2 moiety is 0.07 electronic charge units more negative at the transition state in dioxane than in water.

Introduction

Because of the central role played by carbon dioxide in plant physiology, the biochemistry of its fixation and enzymatic decarboxylations have been extensively studied,[1] occasionally stimulating vigorous debates.[2] Furthermore, in early studies of heavy-atom isotope effects, chemical decarboxylations were studied thoroughly because of the ease of the analysis of the products and because these reactions provided excellent models for understanding isotopic chemistry (e.g., decarboxylation of malonic acid was the first example of the comparison of intramolecular and intermolecular kinetic isotope effects[3]). Despite the availability of a large wealth of experimental data on kinetic isotope effects[4] (KIEs) of decarboxylations, the quantum mechanical modeling of these isotope effects is scarce.[5] This is because modeling of decarboxylations is not as straightforward as modeling some other well-studied classes of reactions, e.g., S_N2 reactions. Decarboxylations frequently involve zwitterionic species; the latter are usually unstable in the gas phase, and their quantitative modeling therefore requires methods for optimizing geometries in liquids. This is now possible due to recent advances in solvation modeling.[6,7]

We report here calculations of the KIEs of the decarboxylation of 4-pyridylacetic acid. This reaction is well suited for quantitative modeling. Its kinetics have been studied extensively due to the strong dependence of the rate constant on the polarity of the solvent.[8] Furthermore, kinetic isotope effects corresponding to isotopic substitutions at the carboxylic carbon[9] and oxygen[10] atoms have been measured experimentally in dioxane−water mixtures of different composition. In the case of carbon, natural abundance of ^{13}C at the carboxylic carbon was used. In the case of oxygen, one ^{16}O was replaced by ^{18}O, and the ^{18}O equilibrated between the two positions prior to reaction. The acidic form **A** is apparently unreactive. The decarboxylation is believed to proceed through the zwitterion **Z** to form carbon dioxide and 4-methylpyridine **P** as the final products:



A **Z** **P**

In water the reaction is too slow, while in pure dioxane it is too fast, to allow measurements of KIEs. Therefore the KIEs were measured in dioxane−water mixtures containing 25%, 50%, and 75% (vol %) water.[8,9] There is a systematic change in the observed KIEs as one varies the solvent through this series. The carbon KIE changes from $k_{12}/k_{13} = 1.064$ in 25% water-containing solvent to 1.056 when the water content is increased to 75%.[9] The oxygen KIE changes from a normal value (KIE larger than unity with the lighter isotope in the numerator), $k_{16}/k_{18} = 1.003$, to an inverse one, 0.995.[10]

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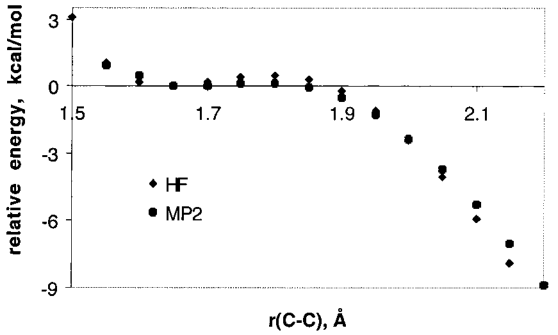

Figure 1. Energy scans along the C−C bond distance of 4-pyridylacetic acid in the gas phase for two indicated theory levels with the 6-31G(d) basis set.

Results and Discussion

We initially calculated energy profiles for the gas-phase decarboxylation of the zwitterion **Z** with Hartree−Fock (HF) theory[11] and the MP2[12] perturbation theory correlated method, employing the popular 6-31G(d)[13] basis set. At each level of theory, the bond distance between the methylene and carboxylic carbons was varied systematically while all other geometrical parameters were optimized for each value of the C−C bond distance. Figure 1 summarizes the results of these scans. The local minima and maxima of the curves in Figure 1 were then used as the starting points for full optimizations of stationary points. Profiles obtained at the HF and MP2 levels are very similar, and the gas-phase stationary points were fully optimized at the HF level. These optimizations show that the C−C bond length in the zwitterion **Z** is substantially elongated, 1.64 Å compared to the 1.51 Å in the acid **A**. The transition state **T** found in these calculations is only about 0.5 kcal/mol higher in energy than the zwitterion and has a C−C bond of 1.79 Å.

Zwitterionic species are tighter and more stable in a polar or polarizable environment than in a vacuum; therefore solvent should be included to properly model decarboxylations in the liquid phase. This was accomplished by using the SM5.42/HF/6-31G(d) solvent model,[7,14] which involves calculating the Hartree−Fock orbitals and energy in the presence of a self-consistent reaction field due to the solvent to account for electrostatic interactions with the polarized dielectric medium and including atomic surface tensions to account for first-solvation-shell effects. Figure 2 shows free energy profiles for the decarboxylation of the zwitterion **Z** in pure dioxane and aqueous solution and compares them with the gas-phase energies. The stationary points were then fully optimized in solvent. These calculations show that the C−C bond length in the zwitterionic form is equal to 1.57 and 1.54 Å in dioxane and water, respectively; these structures are respectively 0.07 and 0.10 Å tighter than in the gas phase. The transition state is even more profoundly affected by the solvent. In the gas phase, the transition state C−C bond length is 1.79 Å, but it elongates to 2.03 and 2.16 Å in dioxane and water, respectively; this corresponds to loosening by 0.24−0.37 Å. Figure 2 confirms that the gas-phase calculations cannot be used for modeling the decarboxylation reaction in liquids. In related work, Gao found large differences in the calculated free energy profiles in the gas phase and the potential of mean force in water for the decarboxylation reaction of 3-carboxybenzisoxazole.[15]

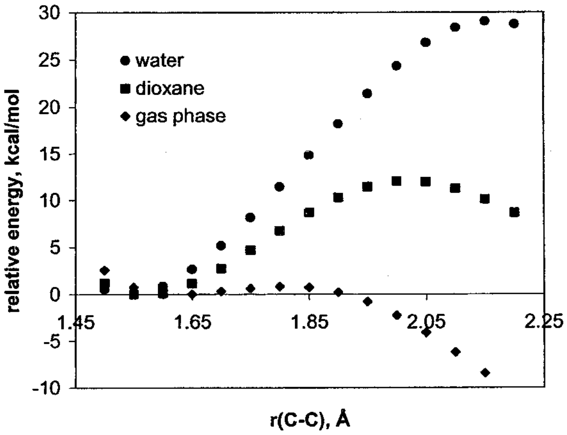

Figure 2. Energy scans along the C−C bond distance of 4-pyridylacetic acid for two solvents and in the gas phase The liquid-phase results are free energy, and the gas-phase curve is potential energy. These results were obtained by HF/6-31G(d) calculations, with the SM5.42 continuum solvent model for the liquid phase.

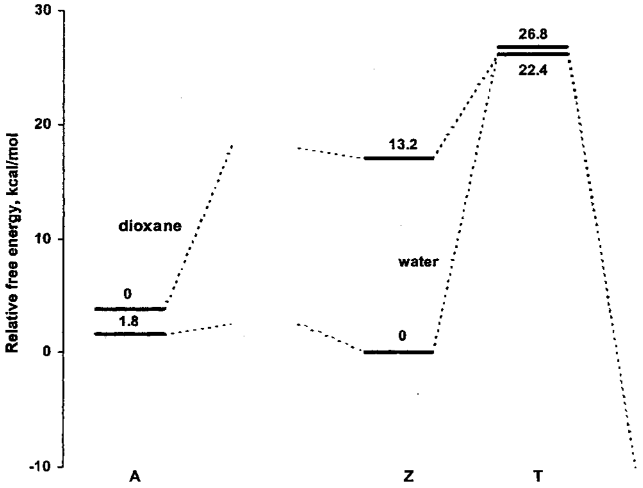

Figure 3. MC-QCISD+SM5.42/HF/6-31G(d)//SM5.42/HF/6-31G(d) energy diagrams in dioxane and water. The numerical values for each solvent are referred to the lowest energy structure for that solvent, but the two sets of energy levels are drawn in relation to each other based on the absolute energies. The transition state between acid and zwitterion is omitted since its properties do not influence the studied KIEs.

To calculate kinetic isotope effects that can be compared to experimental results, it is necessary to know the relative energy of the stationary points **A** and **Z**. To obtain a quantative estimate of this relative energy, it is essential to include electron correlation; therefore we performed single-point energy calculations for structures **A**, **Z**, and **T** in dioxane and water at a correlated level, in particular at the multi-coefficient quadratic configuration interaction with single and double excitation (MC-QCISD) level.[16] To these energies we added free energies of solvation obtained at the SM5.42/HF/6-31G(d) level. The results of these energy calculations are shown in Figure 3; all results in Figure 3 are independent of the choice of the standard state because all species involved have the same molecularity.

In dioxane the acid form **A** is calculated to be more stable than the zwitterion **Z** by 13.2 kcal/mol. The decarboxylation step in dioxane has a free energy barrier, defined as the

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difference in free energy between the transition state **T** and **A**, equal to 22.4 kcal/mol. Conversely, in water the zwitterion **Z** is more stable than the acid although the difference is only 1.6 kcal/mol. The acid in water is more stable than in dioxane by 3.8 kcal/mol. The free energy barrier, in water, relative to the zwitterion, is equal to 26.8 kcal/mol.

These relative free energies lead to different mechanisms in dioxane and water. In dioxane the reaction proceeds from the acid to the transition state, and we need not carry out calculations on a putative zwitterion intermediate (the kinetic results are independent of whether the reaction passes through a zwitterion; for example, decarboxylation and proton transfer could be simultaneous[4]). Kinetic isotope effects for this reaction can be calculated using the acid as the reactant. In the notation used in the reaction scheme, since the reverse reaction rate of the first step (with the rate constant k_{-1}) is much larger that the forward decomposition rate of the zwitterion (with the rate constant k_2), the overall rate constant in dioxane is equal to K_1k_2 where $K_1 = (k_1/k_{-1})$ is the equilibrium constant between the acid and the zwitterion. Consequently, the apparent kinetic isotope effect is given by the equation:

$$(k_L/k_H)_{app} = (K_L/K_H)_1(k_L/k_H)_2 \tag{1}$$

Subscripts L and H indicate the light and heavy isotope, respectively, and the final subscript indicates the step in the reaction scheme. Use of eq 1 is valid whether or not the system actually passes through **Z** in dioxane. In the case of the aqueous solution the isotope effect on the rate constant k_2 can be directly compared with the experimental value.

The difference in the free energy barriers between dioxane and water should also be computed in a way that takes account of the difference in mechanism in the two solvents. Thus in water one uses $G(\mathbf{T}) - G(\mathbf{Z}) = 26.8$ kcal/mol, whereas in dioxane one uses $G(\mathbf{T}) - G(\mathbf{A}) = 22.4$ kcal/mol. The difference, 4.4 kcal/mol, is in excellent agreement with the experimentally observed 4000-fold increase in rate from 75% water to pure dioxane,[8,9] which would correspond to $RT \ln 4000 = 4.9$ kcal/mol.

The proper treatment of kinetics and equilibria in binary solvents presents many complex issues. The balance between the bulk electrostatic influence of the solvent and the specific first-solvent-shell interactions need not result in solvent effects that vary monotonically with solvent composition. These problems have been discussed recently for the case of an S_N2 reaction carried out in acetone–water mixtures.[17] The SM5.42 solvation model has been very successful at predicting the free energy of solvation of polar species both in pure water and in pure organic solvents.[14,18,19] It uses several properties of the solvent, such as its dielectric constant and macroscopic surface tension, as input. These properties do not necessarily change linearly or even monotonically with composition in the case of binary mixtures. One could attempt to model mixtures anyway by using experimental values for mixtures, and such data are available for the dioxane–water mixtures, at least for the dielectric constant[20] and surface tension.[21] However, it is not clear whether the SM5.42 model, as presently formulated, provides an adequate model of preferential solvation in the first solvation shell. In addition, aggregation in water–dioxane mixtures has been found to be composition-dependent by NMR studies,[22] and it is not obvious how to translate this information into the design of parameters appropriate for modeling binary solvents. For these reasons we have decided to calculate isotope effects for pure solvents (dioxane and water) only. Since the experimentally observed KIEs of carboxylic carbon and oxygen change monotonically with the solvent composition, we are assuming that experimental values obtained in mixed solvent solutions should be between the pure-solvent limits.

Table 1. Comparison of Theoretical and Experimental KIEs for Decarboxylation of 4-Pyridylacetic Acid

		% water			
	dioxane	25%	50%	75%	100%
		carbon			
$(k_{12}/k_{13})_2$	1.055				1.057[a]
$(K_{12}/K_{13})_1$	1.009				
$(K_{12}/K_{13})_1(k_{12}/k_{13})_2$	1.064[a]				
experiment[b]		1.064	1.060	1.056	
		oxygen			
$(k_{16}/k_{18})_2$	0.993				0.989[a]
$(K_{16}/K_{18})_1$	1.011				
$(K_{16}/K_{18})_1(k_{16}/k_{18})_2$	1.004[a]				
experiment[b]		1.003	1.000	0.995	

[a] The values to be compared to experiment are in the third row for dioxane and in the first row for water; see discussion in text. [b] The standard deviation of the experimental KIEs equals 0.001.

All KIEs were calculated by conventional transition state theory[23] at geometries optimized for each medium, with quantized harmonic vibrations calculated at the HF/6-31G(d) level for the gas phase and at the SM5.42/HF/6-31G(d) level for each liquid medium, with unhindered classical rotations, and with unit transmission coefficients. The KIEs are compared with the experimental values for carbon and oxygen in Table 1. The table shows excellent agreement between theory and experiment for the isotope effects calculated using the model of dioxane solution and the experimental values in the water-poor binary solvent, as well as for the values calculated for water solution and the results measured in the water-rich solvent.

As clearly seen in Figure 2, the *location* of the transition state depends strongly on the solvent. This is further clarified in Table 2, which compares the geometrical parameters of the transition states in the gas phase, in dioxane, and in water. Partial charges on selected atoms, calculated by Charge Model 2[24] (CM2), and frequencies of normal modes of vibrations are also listed. For brevity, only parameters that change substantially during the reaction or have a significant isotopic shift are included. Vibrational analysis indicates that the changes in going from the reactant to the transition state are mainly confined to the carboxylic moiety; only the C–C bond stretching vibration, involving methylene and carboxylic carbon atoms, and the asymmetric stretching mode of the O–C–O change significantly. These are also the frequencies that are perturbed the most by the ^{13}C isotopic substitution in the carboxylic carbon and

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Table 2. Selected Properties of the Transition States[a]

property	gas phase	dioxane	water
	geometry		
C−C	1.79(1.64)[b]	2.03(1.57)	2.16(1.54)
C−O	1.20(1.21)	1.18(1.23)	1.17(1.24)
O−C−O	141(135)	148(131)	151(128)
	CM2 partial charges		
C(H$_2$)	−0.29	−0.35	−0.39
C(O$_2$)	0.36	0.41	0.44
each O[c]	−0.44	−0.39	−0.37
	frequencies		
C−C str.	397*i* [−7*i*][c]	692*i* [−15*i*]	737*i* [−17*i*]
O−C−O asym. str.	2098 [−58]	2187 [−61]	2193 [−62]

[a] All bond lengths are in Å, bond angles in deg, partial charges in au, and frequencies in cm^{-1}. [b] Bond lengths and angles of the zwitterions are given in parentheses for comparison; the C−C bond length for the acid is 1.51 Å and is independent of the solvent model. [c] Although the charges on the two O are not equal by symmetry, they are the same to the number of digits shown. [d] Values in square brackets indicate the frequency shift upon ^{13}C substitution.

by the ^{18}O substitution in the carboxyl group. Table 2 illustrates this for the ^{13}C isotopic substitution. There is a systematic increase in both the absolute value of these vibrational frequencies and the magnitude of the isotopic shift on going from the gas phase to water. Similarly, systematic changes are observed for the partial charges on atoms participating in the reaction coordinate. Since the product, carbon dioxide, is a neutral molecule, and the carboxylic group bears a formal charge of −1 in the zwitterion, one can expect, if the reaction always passes through the zwitterion, that this charge decreases as the transition state structure becomes more product-like. This intuitive picture is nicely supported by the systematic change in the sum of partial charges on carboxylic atoms calculated for different environments. In the gas phase, the sum of the partial charges on carboxylic atoms is −0.52, and it drops to −0.37 in dioxane and −0.30 in water. As discussed above, the C−C bond length in the transition state increases on going from gas phase to dioxane to water.

Traditionally,[25] kinetic isotope effects have been used to provide a qualitative estimate of the extent of bond breaking in the transition state. The excellent agreement of our calculations with the experimental data allows us to provide a more quantitative interpretation using Mayer bond order analysis[26] of the quantum mechanical wave functions. This analysis indicates that the C−C bond order in the transition state is equal to 0.58, 0.48, and 0.35 in the case of gas phase, dioxane, and water, respectively, as compared to values in the zwitterions of 0.76, 0.92, and 0.94 for the gas phase, dioxane, and water, respectively.

Computational Methods

All calculations involving the SM5.42 solvation model[7,14] were performed using the MN-GSM program.[27] MC-QCISD energy calculations on SM5.42/HF/6-31G(d) optimized structures of **A**, **Z**, and **T** for dioxane and water parameters were performed using MULTILEVEL.[28] Other calculations were performed using the Gaussian98[29] and MN-GSM programs. In all cases default optimization criteria were used. Except for the scans, all geometries were fully optimized; in scan calculations, only the C−C bond distance was constrained. Vibrational analysis was performed for each stationary point; minima and transition states were confirmed to have zero and one imaginary frequency, respectively, and Hessians from these calculations were used for calculations of KIEs. The transition state theory KIEs were calculated using the complete equation of Bigeleisen[30] by means of the Isoeff98 program.[31] The oxygen isotope effect is the average of single-substitution isotope effects of the two individual oxygen atoms.

Concluding Remarks

It is widely accepted in organic chemistry that solvent effects can have a strong influence on the extent of bond breaking and bond making at transition states and thus on transition state structure. However, these effects are difficult to quantify. The present comparison of theory and experiment provides, however, a striking quantitative example of such an effect. The solvent dependence of the KIEs clearly results from the solvent dependence of the transition state frequencies, which in turn are strongly correlated to transition state bond orders and transition state geometry. The excellent agreement of theory and experiment for the solvent dependence of the KIEs of decarboxylation reactions provides strong evidence for the correctness of the transition state geometries. The C−C bond distance at the transition state in water is 0.13 Å longer than that in dioxane and 0.37 Å longer than that in the gas phase. The bond order of the breaking C−C bond is 0.58 in the gas phase, 0.48 in dioxane, and 0.35 in water. Charge analysis of the transition state wave functions is fully consistent with a reaction path through the zwitterion in all three media.

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Supporting Information Available: Gaussian input files (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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