

Correlation of rates of uncatalyzed and hydroxide-ion catalyzed ketene hydration. A mechanistic application and solvent isotope effects on the uncatalyzed reaction

John Andraos and A. Jerry Kresge

Abstract: Rates of hydration of a number of ketenes were measured in neutral and basic solution using flash photolytic techniques, and rate constants for their uncatalyzed, k_{uc} , and hydroxide-ion catalyzed, k_{HO} , reactions were determined. These results, plus additional data from the literature, were found to provide the remarkably good correlation $\log k_{uc} = -3.21 + 1.14 \log k_{HO}$, which spans 10 orders of magnitude in reactivity and includes 31 ketenes. This good correlation implies that uncatalyzed and hydroxide-ion catalyzed ketene hydration occur by similar reaction mechanisms, which for the hydroxide-ion catalyzed process is known to involve nucleophilic attack on the carbonyl carbon atom of the ketene. Rate constants for phenylhydroxyketene, on the other hand, do not fit this correlation, which suggests that the mechanistic assignment upon which these rate constants are based may not be correct. Solvent isotope effects on these uncatalyzed ketene hydrations are weak; most are less than $k_H/k_D = 2$. It is argued that these isotope effects are largely, if not entirely, secondary in nature and that they are consistent with both a reaction mechanism in which nucleophilic attack of a single water molecule on the ketene carbonyl carbon atom produces a zwitterionic intermediate and also a mechanism that avoids this intermediate by passing through a cyclic transition state involving several water molecules.

Key words: ketene hydration, rate correlation, nucleophilic attack, solvent isotope effects, phenylhydroxyketene.

Résumé : Faisant appel à des techniques de photolyse éclair et opérant en solutions neutre et basiques, on a mesuré les vitesses d'hydratation d'un certain nombre de cétènes; on a aussi déterminé les constantes de vitesse de leurs réactions non catalysées, k_{uc} , et catalysées par l'ion hydroxyde, k_{OH} . On a trouvé que ces résultats, en combinaison avec des données additionnelles tirées de la littérature, permettent d'obtenir une corrélation relativement bonne, $\log k_{uc} = -3,21 + 1,14 \log k_{OH}$, qui couvre dix ordres de grandeur de réactivité et qui inclut trente et un cétènes. Cette bonne corrélation implique que les hydratations du cétène non catalysée ainsi que catalysée par l'ion hydroxyde se produisent par des mécanismes réactionnels similaires; dans le cas du processus catalysé par l'ion hydroxyde, il est admis que la réaction implique une attaque nucléophile sur l'atome de carbone du carbonyle du cétène. Par ailleurs, les constantes de vitesse du phénylhydroxycétène ne suivent pas la corrélation; ceci suggère que l'attribution mécanistique sur laquelle ces constantes de vitesse sont basées n'est peut-être pas correcte. Les effets isotopiques de solvant sur ces hydratations non catalysées du cétène sont faibles; dans la plupart des cas, $k_H/k_D \leq 2$. On croit que ces effets isotopiques sont en grande partie, si ce n'est pas totalement, de nature secondaire et qu'ils sont en accord à la fois avec un mécanisme réactionnel dans lequel l'attaque nucléophile d'une seule molécule d'eau sur l'atome de carbone du carbonyle du cétène produit un intermédiaire zwitterionique ainsi qu'avec un mécanisme qui évite cet intermédiaire en passant par un état de transition cyclique impliquant plusieurs molécules d'eau.

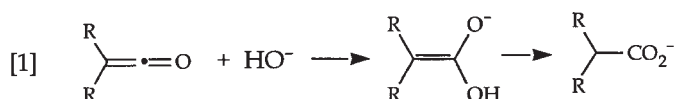
Mots clés : hydratation du cétène, corrélation de vitesse, attaque nucléophile, effets isotopiques du solvant, phénylhydroxycétène.

[Traduit par la Rédaction]

Introduction

The generally accepted reaction mechanism for the hydroxide-ion catalyzed hydration of ketenes to carboxylate ions consists of nucleophilic addition of hydroxide to the carbonyl carbon atom of the ketene, followed by ketoni-

zation of the carboxylic acid enolate ion thus formed, eq. [1] (1).

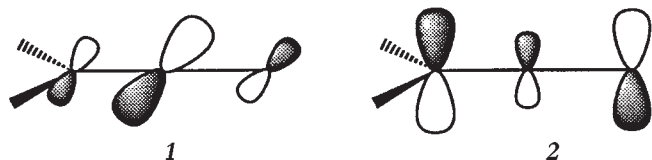


Received November 8, 1999. Published on the NRC Research Press website on April 14, 2000.

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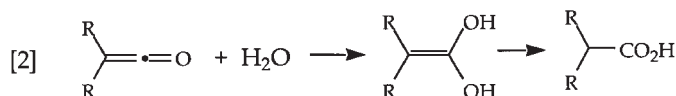
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Nucleophilic attack is directed at the lowest unoccupied molecular orbital of the ketene, **1**, which lies in the ketene

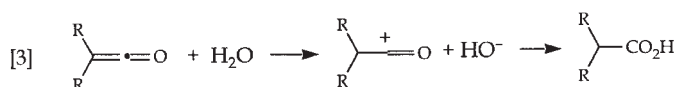


molecular plane, and large groups attached to the ketene β -carbon atom interfere substantially with approach of the nucleophile. The large steric rate retardations introduced in this way are in fact a hallmark of this reaction, and they provide some of the principal evidence upon which this reaction path is based.

A similar mechanism is believed to operate in uncatalyzed ketene hydration, with a water molecule acting as the nucleophile and enol and carboxylic acid replacing enolate and carboxylate ions, as shown in eq. [2]. Water, however, is



an acid as well as a nucleophile, and another mechanism is in principle possible, in which proton transfer from a water molecule to the ketene β -carbon atom is followed by conversion of the ensuing acylium ion to a carboxylic acid, eq. [3].



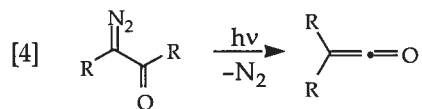
The mode of initial attack in this case is electrophilic addition to the highest occupied molecular orbital of the ketene, **2**, and, because this orbital is perpendicular to the ketene molecular plane, steric effects can be expected to be quite different from, and much less severe than, those on the nucleophilic reaction of eq. [2].

It was observed (1, 2) that substituent effects on the rate constant for uncatalyzed ketene hydration, k_{uc} , are remarkably similar to those for the hydroxide-ion catalyzed reaction, k_{HO} , and this similarity was used to support a common nucleophilic mechanism for both processes. We have now expanded the somewhat limited data upon which this earlier observation was based by determining k_{uc} and k_{HO} for a number of additional ketenes, and we have found that these values, plus data already in the literature, provide a remarkably good correlation between these two rate constants spanning ten orders of magnitude in reactivity.

We have also found a striking exception to this correlation, which suggests that the mechanistic assignment upon which this exception is based may not be correct.

The ketenes whose rate constants were measured in the present study were generated by photo-Wolff reactions of the corresponding α -diazocarbonyl compounds, eq. [4]. Be-

cause the hydration reactions were rapid, flash photolytic methods were used.



Experimental Section

Materials

The α -diazocarbonyl compounds used as photo-Wolff reaction substrates were prepared by standard methods. Their spectra conformed to their structures and agreed with literature values. Details are available in the theses of references 3 and 4.

All other materials were best-available commercial grades.

Kinetics

Flash photolytic rate measurements were made using conventional (microsecond) (5) and laser (nanosecond, $\lambda = 248$ nm) (6) systems that have already been described. The ketene hydration reactions were followed by monitoring the decrease in ketene absorbance at $\lambda = 215$ nm for the aliphatic ketenes and at $\lambda = 260$ – 300 nm for the aromatic ketenes. The temperature of all solutions upon which rate measurements were made was controlled at $25.0 \pm 0.05^\circ\text{C}$. The rate data so obtained conformed to the first-order rate law well, and observed first-order rate constants were obtained by non-linear least squares fitting of an exponential function.

Results

All rate measurements were made in wholly aqueous solution at an ionic strength of 0.10 M, maintained by adding NaClO_4 as required.



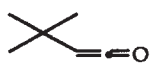
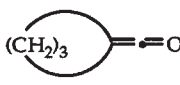
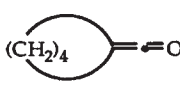
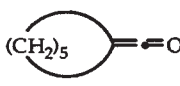
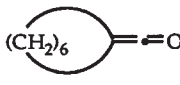

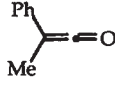
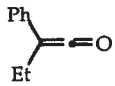
Rate profiles for ketene hydration reactions in aqueous solution typically show extensive uncatalyzed plateaus, with no base catalysis up to $\text{pH} = 10$ – 11 , and correspondingly weak, or often absent, acid catalysis. Uncatalyzed hydration rate measurements were consequently made in neutral unbuffered solutions containing no added acid or base. For each substrate, 10–25 replicate determinations were made. The results are summarized in the theses of references 3 and 4, and average values are listed in Table 1.

Some rate measurements of the uncatalyzed reaction were also made in D_2O solution. These values are also summarized in the theses of references 3 and 4, and the solvent isotope effects that they produce when combined with their H_2O counterparts, $(k_{uc})_{\text{H}_2\text{O}}/(k_{uc})_{\text{D}_2\text{O}}$, are listed in Table 1.

Rate measurements of the hydroxide-ion catalyzed ketene hydration reaction were made in dilute sodium hydroxide solutions. For each substrate, 5 to 6 different sodium hydroxide concentrations were used, spanning a 5- to 25-fold variation in $[\text{NaOH}]$, and replicate measurements were made at each concentration. The results are summarized in the theses of references 3 and 4.

In all cases, observed first-order rate constants increased linearly with hydroxide ion concentration, and the data were

Table 1. Rate constants for uncatalyzed, k_{uc} , hydroxide-ion catalyzed, k_{HO} , and hydronium-ion catalyzed, k_H , hydration of ketenes in aqueous solution at 25°C.^a

| Ketene | k_{uc}/s^{-1} | $(k_{uc})_{H_2O}/(k_{uc})_{D_2O}$ | $k_{HO}/M^{-1}s^{-1}$ | $k_H/M^{-1}s^{-1}$ | Ref |
|---|--------------------|-----------------------------------|-----------------------|--------------------|--------|
|  | 3.65×10^1 | 1.59 | 5.26×10^4 | 1.01×10^4 | 7,8 |
|  | 9.66×10^1 | 1.88 | 3.29×10^4 | 3.98×10^3 | 3,9,20 |
|  | 1.46×10^1 | 2.01 | 1.68×10^4 | 4.77×10^3 | 4,7 |
|  | 4.09×10^2 | - | - | 3.13×10^5 | 3 |
|  | 1.11×10^2 | 3.39 | 3.89×10^4 | 2.14×10^4 | 3 |
|  | 2.30×10^1 | 2.04 | 6.24×10^3 | 2.78×10^3 | 3 |
|  | 2.35×10^1 | 1.91 | 6.08×10^3 | - | 3 |
|  | 4.77×10^3 | 1.44 | 1.22×10^6 | - | 9 |
|  | 5.57×10^1 | 1.55 | 2.03×10^4 | - | 4 |
|  | 1.03×10^1 | 1.48 | 6.05×10^3 | - | 10 |

therefore analyzed by least-squares fitting of eq [5]. The resulting hydroxide-ion catalytic coefficients are listed in Table 1.

$$[5] \quad k_{obs} = k_{uc} + k_{HO} [HO^-]$$

This analysis also produced uncatalyzed reaction rate constants, k_{uc} , and these were nicely consistent with the more precise values of this rate constant determined directly in neutral solution.

Some rate measurements were also made in dilute perchloric acid solution, using several different acid concentrations of each substrate and making replicate measurements at each acid concentration. These results are summarized in reference 3. Observed first-order rate constants increased linearly with acid concentration, and the data were analyzed by least squares fitting of the H^+ analog of eq [5]. The hydronium-ion catalytic coefficients so obtained, k_H , are also listed in Table 1. The uncatalyzed reaction rate constants pro-

duced by this analysis were once again nicely consistent with results determined in neutral solution.

Discussion

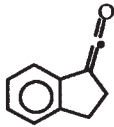
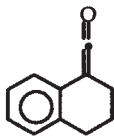

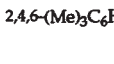
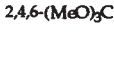
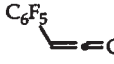


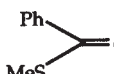
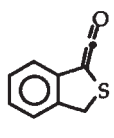
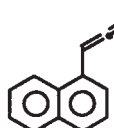
Correlation

The ketenes examined here, plus others for which aqueous solution hydration rate constants are available from the literature, are assembled in Table 1. These ketenes possess a wide variety of substituents, which produces a wide range of hydration reactivity: the range covered is 2×10^{10} in k_{HO} and 5×10^{10} in k_{uc} . And yet these widely different rate constants generate the remarkably good correlation shown in Fig. 1. Linear least squares analysis² of the data gives $\log k_{uc} = -(3.21 \pm 0.22) + (1.14 \pm 0.04) \log k_{HO}$, with a root-mean-square deviation in $\log k_{uc}$ of 0.271, which corresponds to 0.37 kcal mol⁻¹ in free energy of activation.

This good correlation implies that the various substituents present in these ketenes are affecting the uncatalyzed and

²The analysis was performed using simple weighting with both $\log k_{uc}$ and $\log k_{HO}$ subject to (the same) uncertainty (22).

Table 1 (continued).

| | | | | | |
|---|--------------------|------|--------------------|--------------------|---------|
|  | 1.96×10^3 | 1.18 | 8.42×10^5 | - | 11 |
|  | 1.03×10^2 | 1.60 | 6.30×10^4 | - | 4 |
|  | 2.90×10^3 | - | 1.13×10^6 | - | 12 |
|  | 1.10×10^2 | 1.51 | 6.78×10^4 | 4.67 | 4,12,21 |
|  | 8.28×10^0 | - | 4.34×10^3 | - | 12 |
|  | 2.76×10^3 | 1.42 | 1.13×10^6 | - | 10 |
|  | 5.76×10^3 | 2.09 | 2.31×10^6 | 2.09×10^4 | 4, 20 |
|  | 7.15×10^4 | 2.84 | 1.98×10^7 | 1.61×10^5 | 4, 20 |
|  | 1.02×10^2 | 1.59 | 1.89×10^4 | - | 10, 11 |
|  | 2.21×10^5 | 1.17 | 1.66×10^7 | - | 13 |
|  | 2.95×10^3 | - | 1.25×10^6 | - | 12 |

hydroxide-ion catalyzed reactions in the same way. As pointed out in the Introduction above, this could hardly be possible if one reaction involved nucleophilic attack and the other involved electrophilic attack. Since there is good evidence that the hydroxide-ion catalyzed reaction is a nucleophilic process (1) — it is, in fact, difficult to conceive of a different role for the hydroxide ion — it follows that the uncatalyzed reaction is a nucleophilic process as well.

This conclusion is supported by the much poorer correlation of k_{UC} with rate constants for hydronium-ion catalyzed ketene hydration, k_H , shown in Fig. 2. Linear least squares analysis³ of these data gives $\log k_{UC} = -(3.69 \pm 1.97) + (1.54 \pm 0.52) \log k_H$, with a root-mean-square deviation in

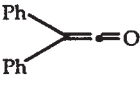

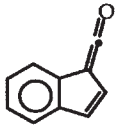
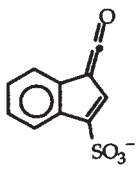
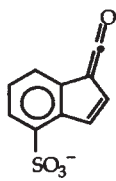
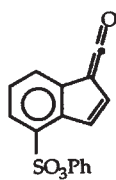
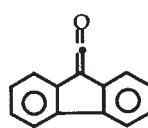
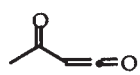
$\log k_{UC}$ of 1.08, which corresponds to 1.47 kcal mol⁻¹ in free energy of activation and is 4.0 times the deviation given by the k_{UC} - k_{HO} correlation. The hydronium-ion catalyzed reaction, of course, involves electrophilic attack on the ketene β -carbon atom and has very different steric requirements than nucleophilic attack of water or hydroxide ion on the ketene carbonyl carbon atom (1).

An Exception

Figure 1 shows that the point for phenylhydroxyketene provides an apparent exception to the good k_{UC} - k_{HO} correlation. This point lies 1.77 below the correlation line, which is equivalent to 2.41 kcal mol⁻¹ in free energy of activation and

³This analysis was also performed using simple weighting with both $\log k_{UC}$ and $\log k_H$ subject to (the same) uncertainty (22).

Table 1 (continued).

| | | | | | |
|---|--------------------|------|--------------------|---|----|
|  | 2.75×10^2 | 1.27 | 6.11×10^4 | - | 9 |
|  | 9.0×10^5 | - | 4.8×10^7 | - | 14 |
|  | 1.2×10^6 | - | 3.8×10^7 | - | 15 |
|  | 1.57×10^7 | 1.39 | 2.25×10^9 | - | 6 |
|  | 2.82×10^6 | 1.22 | 8.77×10^7 | - | 6 |
|  | 9.89×10^6 | 1.17 | 2.00×10^8 | - | 6 |
|  | 1.07×10^5 | 1.35 | 3.47×10^6 | - | 16 |
|  | 1.54×10^6 | 1.10 | 1.86×10^8 | - | 17 |

is more than six times the root-mean-square deviation of the 31 points upon which this correlation is based. The probability that such a deviant point would occur by chance is ca. 10^{-9} .

The ketene providing this errant point was generated by Norrish type II photoelimination of benzoylformic acid esters, and hydration of this ketene provided the enol of mandelic acid, as shown in eq. [6] (23). In acidic and neutral solutions, ketonization of this enol is considerably slower than hydration of the ketene, and both transient species could be easily observed and a rate constant for uncatalyzed

hydration of the ketene could be quite firmly established. In basic solution, however, the rates of ketene hydration and enol ketonization became comparable. In such a situation, assignment of rate constants to molecular processes becomes notoriously difficult (24), and it now seems likely that the hydroxide-ion catalyzed process then believed to be ketene hydration was actually enol ketonization, with ketene hydration occurring only in the more basic region not investigated. The true value of k_{HO} for this ketene would consequently be less than the number assigned, and that would move the errant point closer to the correlation line.

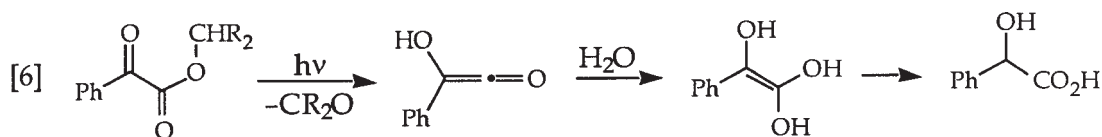
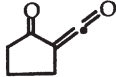
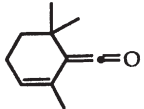

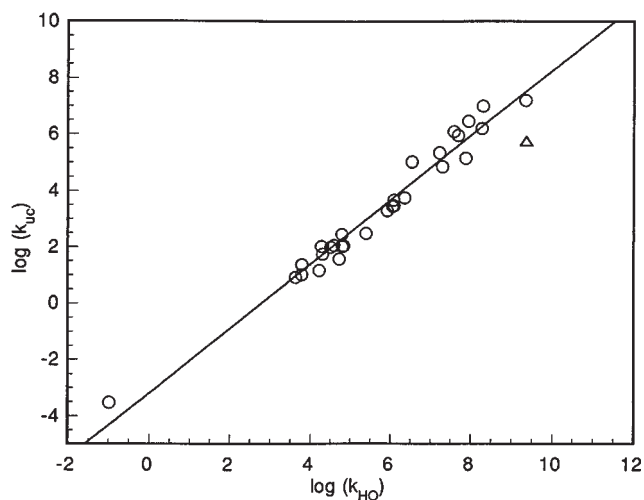


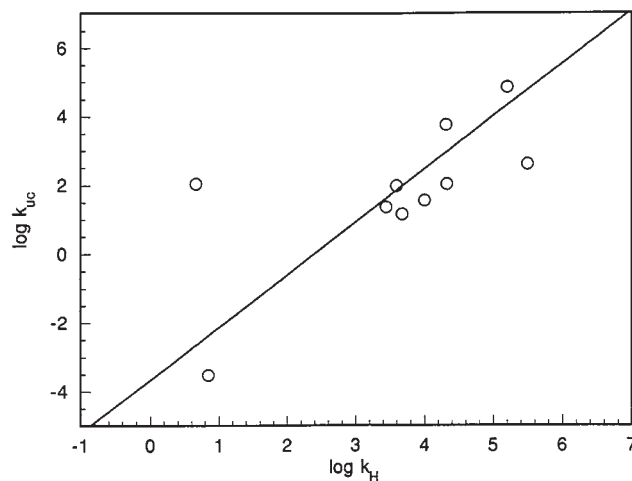
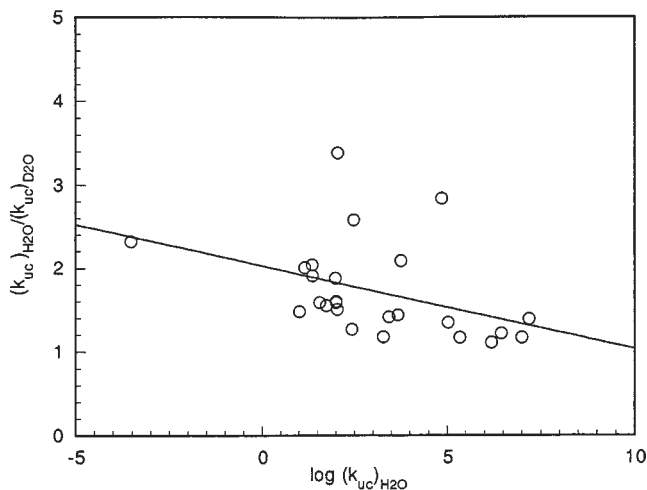
Table 1 (concluded).

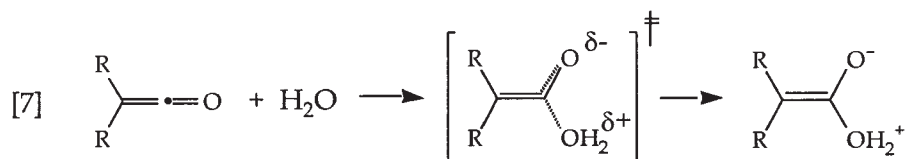
| | | | | | |
|---|-----------------------|------|-----------------------|------|----|
|  | 1.40×10^6 | - | 7.53×10^7 | - | 18 |
|  | 2.97×10^{-4} | 2.32 | 1.04×10^{-1} | 7.03 | 19 |
|  | 3.04×10^2 | 2.58 | 2.48×10^5 | - | 20 |

^aIonic strength = 0.10 M**Fig. 1.** Relationship between rate constants for the uncatalyzed, k_{uc} , and hydroxide-ion catalyzed, k_{HO} , hydration of ketenes in aqueous solution at 25°C. The triangle, representing phenylhydroxyketene, is not included in the correlation that produces the line drawn through the data.**Isotope effects**

The solvent isotope effects on uncatalyzed ketene hydration generated by the measurements made here in H_2O and D_2O solution, plus other values of this isotope effect determined in wholly aqueous solution available from the literature, are assembled in Table 1 and are displayed in Fig. 3. Although there is a fair amount of scatter, these isotope effects do appear to increase in strength with decreasing ketene reactivity as measured by $\log(k_{uc})_{H_2O}$; linear least squares analysis gives $(k_{uc})_{H_2O}/(k_{uc})_{D_2O} = (2.03 \pm 0.18) - (9.92 \pm 4.60) \times 10^{-2} \log(k_{uc})_{H_2O}$.

It may be seen that these isotope effects are all rather weak: the strongest is only $k_H/k_D = 3.4$ and most are less than $k_H/k_D = 2.0$. Much stronger isotope effects would be expected for the electrophilic reaction mechanism of eq. [3] in which water is acting as an acid delivering a proton to the β -carbon atom of the ketene. In addition to the sizeable primary isotope effect component expected for proton transfer to carbon, this mechanism would produce a secondary effect

Fig. 2. Relationship between rate constants for the uncatalyzed, k_{uc} , and hydronium-ion catalyzed, k_H , hydration of ketenes in aqueous solution at 25°C.**Fig. 3.** Solvent isotope effects on uncatalyzed ketene hydration in wholly aqueous solution at 25°C.⁴This analysis was performed using simple weighting with uncertainty in $(k_{uc})_{H_2O}/(k_{uc})_{D_2O}$ only.



in the normal direction ($k_{\text{H}}/k_{\text{D}} > 1$) generated by solvation of the hydroxide ion being formed in this reaction (25). Strong isotope effects consistent with this expectation have in fact been observed for such reactions in other systems, e.g., $k_{\text{H}}/k_{\text{D}} = 7.5$ for hydron transfer from water to the β -carbon atom of isobutyrophenone enolate ion (26), $k_{\text{H}}/k_{\text{D}} = 6.5$ to 9.1 for the corresponding reactions of a series of ynoate ions (12), and $k_{\text{H}}/k_{\text{D}} = 7.1$ for that of the enolate dianion of fluorene-9-carboxylic acid (16). The present isotope effects therefore argue against an electrophilic mechanism for uncatalyzed ketene hydration.

These isotope effects, on the other hand, are consistent with a nucleophilic mechanism. The simplest variant of such a mechanism would involve a single water molecule and give a zwitterionic product, as shown in eq. [7]. Since no bonds to isotopically substituted hydrogen are broken or made in this process, there would be no primary component in the isotope effect on such a process. There would, however, be two secondary components: one produced by solvation of the negative charge being generated on the ketene oxygen atom and another produced by the change from neutral to positively-charged oxygen-hydrogen bonds in the attacking water molecule. The maximum value of the latter secondary component can be estimated as $1/\ell^2$, where $\ell (= 0.69)$ is the fractionation factor for a fully positively charged oxygen-hydrogen bond (25*b*). This gives $(k_{\text{H}}/k_{\text{D}})_{\text{max}} = 2.1$. It is more difficult to estimate the other one of these secondary isotope effect components because, although it is known that a fully negatively charged oxygen atom, such as that in the hydroxide ion, is solvated by three water molecules whose solvating oxygen-hydrogen bonds have fractionation factors $\phi \cong 0.7$ (25), the negative charge in this case is partly delocalized into the ketene double bond and the rest of the molecule. It is likely, however, that this secondary component can contribute as much as another factor of two, raising the overall maximum value to $k_{\text{H}}/k_{\text{D}} = 4$ and easily accommodating the range of isotope effects listed in Table 1.

In addition to the reaction mechanism of [eq.] 7 giving a zwitterionic product, other nucleophilic mechanisms may be written in which the zwitterion is avoided by proton transfer from the attacking water to the ketene oxygen atom through a cyclic array of several intervening water molecules. Such mechanisms are favored by *ab initio* calculations (27) and there is evidence that the hydration of ketenes in organic solvents involves more than one water molecule (28), although, of course, in purely aqueous solution the reaction order in water cannot be determined. At any rate, protons are transferred in such mechanisms, but it is unlikely that this will add much of a primary component to the overall isotope effect. In a proton transfer such as this, where the transfer is between electronegative atoms and is accompanied by heavy-atom reorganization, protonic and heavy-atom motion appear to be uncoupled, with proton transfer taking place in a rapid step either before or after the heavy-atom reorganization; protonic motion consequently does not contribute to

the rate-determining reaction coordinate, and there is, therefore, no primary isotope effect (29). Even in situations where proton transfer is isolated and the only heavy-atom motion is diffusional encounter of proton donor and acceptor or separation of proton transfer products, proton transfer is not fully rate-determining and solvent isotope effects are small (30). Cyclic ketene hydration mechanisms avoiding zwitterionic products are therefore likely to show small, if any, primary isotope effects. Neutralization of the zwitterionic charge, moreover, will diminish the secondary effects produced by charge generation as described above, and the overall solvent isotope effects will be small, just like those for the zwitterionic mechanism. Small isotope effects should therefore be characteristic of uncatalyzed ketene hydration proceeding by nucleophilic attack of water on the ketene carbonyl carbon atom, no matter what the detailed reaction mechanism is.

Acknowledgements

We wish to thank Professor S. D. Christian for his generosity in providing us with a computer program that performs linear least squares analysis on data with both dependent and independent variables subject to error. We are also grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

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