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Hydrogen Exchange of Azulenes. VI. Acid-Catalyzed Dedeuteration of Azulene[1]

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Abstract: The general acid catalyzed dedeuteration of azulene-1-*d* has been studied in dilute aqueous hydrochloric acid solution and also in aqueous formic acid–formate and acetic acid–acetate buffer solutions at 25°. A small positive ionic strength effect was observed on the second-order rate coefficient for hydrogen ion catalysis. For catalysis by both the strong and weak acids, the second-order rate coefficient ratio k^D/k^T for exchange is in the range 2.0–2.5. By assuming an A-SE2 mechanism for the reaction proceeding *via* a conjugate acid intermediate, and by combining the kinetic hydrogen isotope effect and solvent hydrogen isotope effect, it has been possible to calculate isotope effects characteristic of individual steps in the exchange reaction. In particular, the kinetic hydrogen isotope ratio k_2^H/k_2^D, which gives the relative rate of loss of a proton and a deuteron from the protonated intermediate to a given base, has been found to have the following values: 9.2 ± 0.8 for reaction with the base water; 6.3 ± 1.0 for reaction with formate ion; 6.1 ± 0.9 for reaction with acetate ion. These ratios are discussed in terms of current theory of isotope effects and the relative acidities of substrate and catalyst.

In recent years a good deal of attention has been focused on the acid-catalyzed rate of exchange of hydrogen atoms attached directly to the aromatic nucleus. Prime reasons for this interest have been firstly that the reaction represents the simplest possible example of electrophilic aromatic substitution, and as such its reaction mechanism has provoked considerable speculation; secondly, because the exchange reactions usually occur at a conveniently measurable rate in fairly concentrated aqueous solutions of strong acids, they are of importance in relating the observed kinetics to acidity-function data and also readily lend themselves to studies of kinetic hydrogen isotope effects in aqueous solution. Various groups have contributed to the present state of knowledge concerning these reactions.[2-9]

Early workers[10-12] suggested an A1 type of mechanism on the basis of the linear correlation between log k_{obsd} and the Hammett acidity function $-H_0$, in which a preequilibrium proton transfer to form an intermediate species was followed by a rate-determining intramolecular exchange from one form of the intermediate to the other possible form. Schematically this may be represented by eq 1. However, it was recognized[13,14] that such a linear correlation does not exclude a simple one-step, slow proton transfer exchange, *i.e.*, one following an A-SE2 type of mechanism of the form shown in eq 2;

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[1] This work was supported by a grant from the Atomic Energy Commission.

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[3] L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1959.

[4] V. Gold, R. W. Lambert, and D. P. N. Satchell, *J. Chem. Soc.*, 2641 (1960).

[5] C. Eaborn and R. Taylor, *ibid.*, 3301 (1960).

[6] (a) A. J. Kresge and Y. Chiang *J. Am. Chem. Soc.*, **83**, 2877 (1961); (b) *ibid.*, **81**, 5509 (1959); (c) *Proc. Chem. Soc.*, 81 (1961); (d) *J. Am. Chem. Soc.*, **84**, 3976 (1962).

[7] J. Colapietro and F. A. Long, *Chem. Ind.* (London), 1056 (1960).

[8] J. Schulze and F. A. Long, *J. Am. Chem. Soc.*, **86**, 327, 331 (1964).

[9] B. C. Challis and F. A. Long, *ibid.*, **87**, 1196 (1965); *Discussions Faraday Soc.*, **39**, 67 (1965).

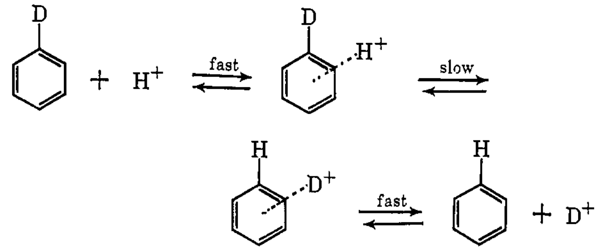
[10] V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 3609 (1955).

[11] V. Gold and D. P. N. Satchell, *ibid.*, 1635, 2743 (1956).

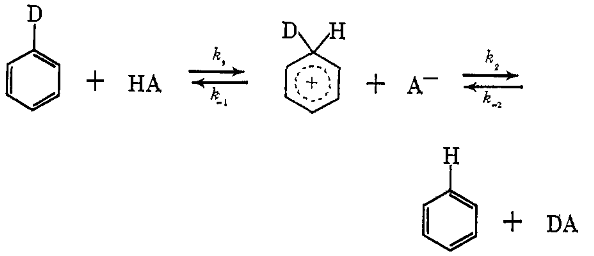
[12] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 9.

[13] F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935, (1957).

[14] L. Melander and P. C. Myhre, *Arkiv Kemi*, **13**, 507 (1959).



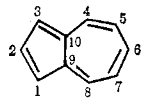
(1)



(2)

i.e., initial protonation of the neutral molecule is followed by reaction of the conjugate acid with the basic species present in the system.

An essential distinction between the two mechanisms outlined above is that the A-SE2 mechanism predicts general acid catalysis, whereas the former mechanism does not. Kresge and Chiang[6a] established that general acid catalysis occurs in the aromatic hydrogen exchange of 1,3,5-trimethoxybenzene, and other studies have shown that a similar exchange on the azulene nucleus is also subject to general acid catalysis.[7,8] Flow measurements on the rate of protonation of the azulene molecule[9] using perchloric acid have enabled the construction of a free-energy profile for the first-stage proton-transfer reaction, and this information has provided semiquantitative support for the proposed two-stage A-SE2 mechanism.



Experimental studies[15–18] have borne out the theoretical predictions[19,20] that the basicity of the azulene molecule is much greater at the equivalent 1 and 3 positions than at other sites on the molecule. Previous studies[7] on the dedeuteration of azulene were conducted under conditions where a large fraction of the 1,3-dideuterated species was present. The infrared spectrophotometric analysis involved in that work assumed that both C–D bonds make independent and equal contributions to the absorption band occurring at 13.65 μ. One of the purposes of the present work was to perform these dedeuteration reactions with an azulene species that existed predominantly in the monodeuterated form, thus minimizing any complications which may arise from nonequivalence of the two C–D bonds in regard to their infrared absorption, and also avoiding the possibility of any secondary isotope effect on the reaction rate due to the second deuterium atom (this latter effect, if present, would admittedly be expected to be small).

Considerable attention has recently been focused on the possibility of a maximum occurring in the isotope rate coefficient ratio $k^{\mathrm{H}}/k^{\mathrm{D}}$, with particular reference to the size, position, and shape of such a maximum. For the general case of the proton-transfer reaction

$$\mathrm{AH} + \mathrm{B} \longrightarrow \mathrm{A} + \mathrm{HB}$$

involving transfer of a hydrogen ion from a carbon acid AH to a base B, simple considerations of zero-point energy differences in the reactants alone lead to a predicted maximum value of $k^{\mathrm{H}}/k^{\mathrm{D}} = 6.9$[21,22] for a purely symmetrical transition state. This treatment ignores the possibility of zero-point energy occurring in the transition state. More sophisticated theoretical treatments of isotope effects have been developed and are reviewed by Bell[21] and Melander.[3] Swain[23] and Bigeleisen[24] have proposed that the $k^{\mathrm{H}}/k^{\mathrm{D}}$ ratio should be a function of the position of the "hydrogen" atom which is being transferred in the transition state. Bell[25] has suggested a more elaborate theory in which the $k^{\mathrm{H}}/k^{\mathrm{D}}$ ratio should depend on the relative basicities of the substrate and the abstracting base. Inherent in this model is a prediction that isotopic substitution must affect not only the initial energy states in proton-transfer reactions but also the transition states, and the suggestion is that the transition state involves vibrations whose frequencies (and therefore also the zero-point energies) are affected by the mass of the "hydrogen" atom involved in the transfer. Such vibrations would include contributions from bending modes. However, Bell concluded that tunneling effects would tend to cancel out the zero-point energy variations in the bending modes, and that the $k^{\mathrm{H}}/k^{\mathrm{D}}$ ratio would be relatively insensitive to the degree of "hydrogen" transfer except in limiting cases. A further recent theoretical treatment by O'Ferrall[26] considers the transfer of hydrogen from X–H to various bases. It predicts that $k^{\mathrm{H}}/k^{\mathrm{D}}$ values should pass through a maximum depending on the degree of hydrogen transfer in the transition state, though the ratios are predicted to be relatively insensitive to the bases used.

Isotope effects have been investigated for many protolytic systems and the reported $k^{\mathrm{H}}/k^{\mathrm{D}}$ values cover a wide range. Only in relatively few cases are data available which permit a study of the maximum predicted by the simple theory. Combination of the limited amount of experimental data available on the hydrogen isotope rate ratios pertaining to the protonation of carbon bases[6d,27,28] does, however, strongly suggest the possibility of a maximum in the $k^{\mathrm{H}}/k^{\mathrm{D}}$ ratio in the region where the acidities of the protonated substrate and of the catalyzing acid are similar.

Unsubstituted azulene is known to be a relatively strong base[8,9,29] and is unique in that the acidity of its

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conjugate acid ($pK_a = -1.76$) is very nearly identical with that of the hydronium ion. In line with the preceding discussion, a kinetic isotope effect close to a maximum value would be predicted for this substrate. Consequently, further studies with azulene-1-*d* and several catalysts are reported in this paper, with a view to providing information relevant to the predicted maximum in the kinetic isotope effect and to the related theoretical concepts.

Experimental Section

Materials. Azulene was obtained from the Aldrich Chemical Co., Inc., Milwaukee, Wis. It was purified by vacuum sublimation: mp 99.0–99.5°, lit.[30] mp 98.5–99.0°. Reagent grade formic acid, acetic acid, hydrochloric acid, perchloric acid, sodium chloride, sodium acetate, sodium formate, sodium hydroxide, and sodium sulfate were used without further purification. Aqueous solutions of hydrochloric acid were standardized against analytical reagent grade red mercuric oxide. CO_2-free distilled water was used in the preparation of all aqueous solutions; aqueous solutions of the above-mentioned acids and of sodium hydroxide were standardized by titration.

Deuterated Azulene. Azulene-1-*d* was prepared in a manner analogous to that adopted for azulene-1-*t*.[8] To 2 g of azulene dissolved in 30 ml of ether was added slowly a mixture of 20 ml of water (*i.e.*, H_2O–D_2O) with 4 ml of 70% aqueous perchloric acid. It should be noted that a lower amount of acid did not lead to a homogeneous solution, whereas a greater concentration tended to promote decomposition of the azulene. After stirring for several hours, the mixture was neutralized with sodium carbonate; the azulene was then extracted with ether, washed with water, dried over sodium sulfate, evaporated to dryness, and finally purified by vacuum sublimation at 50°.

Several solutions were made up in this fashion, with the deuterium content varying between 0 and 90 atom % of total "hydrogen." (Assuming that the fractionation factor for deuterium between azulene and water is unity, this percentage will also hold for each exchangeable hydrogen of the azulene.) Spectra of the resulting purified azulene-1-*d* were examined with a Perkin-Elmer Model 521 infrared spectrophotometer, using Spectroquality reagent grade 2,2,4-trimethylpentane as solvent and 1-mm potassium bromide cells.

The most satisfactory compromise between having sufficient deuterium in the azulene for infrared measurements and not too much (in order to minimize the amount of dideuteration) occurred at a deuterium content of 35 atom % of total hydrogen present in the deuteration mixture. This azulene-1-*d* sample gave a clean, uncomplicated spectrum in the region 500–4000 cm^{-1} and was used in all kinetic experiments. In particular the peak occurring at 735 cm^{-1} (13.65 μ) characterized the azulene-1-*d* species and was used in analyzing samples for deuterium content during the course of the exchange reactions.

Kinetic Experiments. Aqueous solutions of hydrochloric acid and of azulene-1-*d* were separately brought to temperature (25.0° in all measurements reported in this work) and then mixed to initiate the reaction. In a typical exchange experiment 40 mg of azulene-1-*d* was present in a total volume of 3 l. Exchange was terminated by quenching a 500-ml sample with an amount of aqueous sodium hydroxide solution such that a pH value of at least 11 was achieved. The azulene was then extracted from the aqueous solution with two or three 1-ml aliquots of 2,2,4-trimethylpentane, dried overnight over sodium sulfate, and examined in the infrared spectrophotometer for the concentration of the remaining azulene-1-*d*.

No band in the infrared spectrum was found to give an adequately precise estimate of the "total" azulene concentration, so the sample was diluted by a known factor (usually a 50-fold dilution with 2,2,4-trimethylpentane) and analyzed by means of its visible spectrum, which has been well established.[31] The molar extinction coefficient for the absorption peak of azulene in 2,2,4-trimethylpentane at 278 mμ was found to be 337 ± 1. 2,2,4-Trimethylpentane was chosen because it was the only solvent that is transparent in the appropriate regions of the infrared and ultraviolet spectra. A Cary Model 14 spectrophotometer was used for the visible spectra.

Rate coefficients were calculated from plots of log [D]/[D + H] *vs.* time, where [D] and [D + H] refer to the azulene-1-*d* and total azulene concentrations, respectively. In all cases the reactions were uncomplicated and indicated that the exchange reaction exhibited first-order kinetics.

In order to investigate the general acid catalysis characteristics of the exchange, experiments were carried out in a series of formic acid–formate and acetic acid–acetate buffer solutions. As was the case for the set of experiments conducted in dilute aqueous HCl solutions, the ionic strength was adjusted to 0.1 *M* with sodium chloride in all instances. The calculated ionization constants at 25° for formic and acetic acids at this molarity (assuming that the influence of ionic strength on the dissociation constant of both acids is similar[32]) are 2.87×10^{-4} and 2.85×10^{-5}, respectively.

Results

Hydronium Ion Catalysis. Table I illustrates the effect of varying hydrochloric acid concentration on the observed first-order rate coefficient for dedeuteration at constant ionic strength (0.1 *M*). The first-order rate coefficient (k_{obsd}) is a linear function of the acid concentration (the latter being varied by more than one order of magnitude). Second-order rate coefficients (k_{H^+}) were calculated by dividing k_{obsd} by the appropriate hydronium ion concentration.

Table I. Dedeuteration of Azulene-1-*d* at 25° in HCl–NaCl Solutions (Ionic Strength = 0.1 *M*)

$[H^+]$, *M*	k_{obsd}, sec^{-1}	k_{H^+}, M^{-1} sec^{-1}
9.89×10^{-4}	4.35×10^{-4}	0.435
9.93×10^{-4}	4.44×10^{-4}	0.452
2.07×10^{-3}	1.04×10^{-3}	0.503
3.31×10^{-3}	1.44×10^{-3}	0.436
4.32×10^{-3}	1.82×10^{-3}	0.422
5.22×10^{-3}	2.33×10^{-3}	0.446
6.23×10^{-3}	2.85×10^{-3}	0.458
8.50×10^{-3}	3.77×10^{-3}	0.444
1.08×10^{-2}	4.60×10^{-3}	0.426
Mean value: $k_{H^+} = 0.45 \pm 0.02$ M^{-1} sec^{-1}		

Several kinetic experiments were also performed with dilute hydrochloric acid ($[H^+] \sim 10^{-3}$ *M*) in the absence of sodium chloride, in an endeavor to observe any ionic strength effect on the rate coefficient. These data are presented in Table II.

Table II. Dedeuteration of Azulene-1-*d* at 25° in Dilute HCl Solutions (Ionic Strength ~ 0)

$[H^+]$, *M*	k_{obsd}, sec^{-1}	k_{H^+}, M^{-1} sec^{-1}
0.595×10^{-3}	2.41×10^{-4}	0.405
0.987×10^{-3}	4.40×10^{-4}	0.446
0.987×10^{-3}	3.75×10^{-4}	0.379
1.004×10^{-3}	4.35×10^{-4}	0.433
1.377×10^{-3}	5.72×10^{-4}	0.416
1.570×10^{-3}	6.07×10^{-4}	0.387
1.634×10^{-3}	6.45×10^{-4}	0.395
Mean value: $k_{H^+} = 0.41 \pm 0.02$ M^{-1} sec^{-1}		

Formic Acid Catalysis. Earlier studies have demonstrated conclusively that the hydrogen exchange of azulene is not catalyzed by bases and that the catalytic

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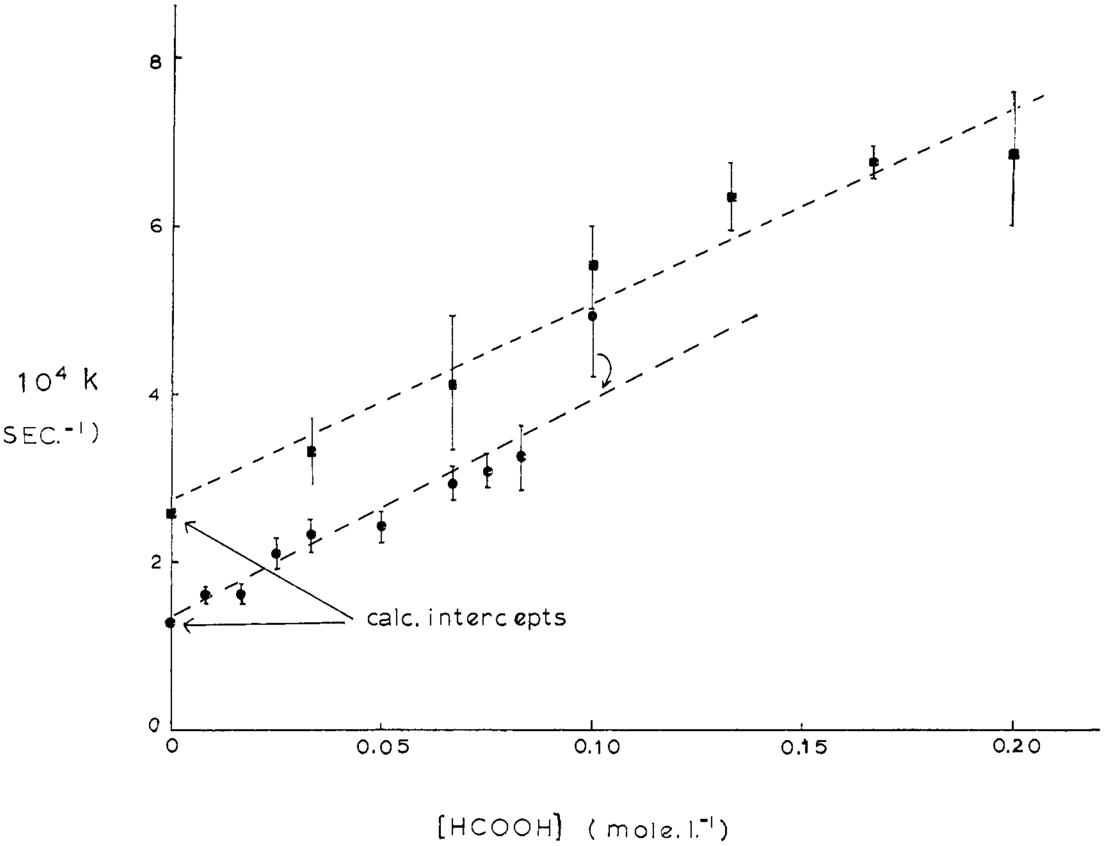

Figure 1. Variation of observed first-order rate coefficient with formic acid concentration for dedeuteration of azulene-1-*d* in formic acid–formate buffer solutions: ■, experimental points for $[H^+] = 5.73 \times 10^{-4}$ *M*; ●, experimental points for $[H^+] = 2.86 \times 10^{-4}$ *M*.

effect due to water is negligible.[29] Thus the general acid catalyzed behavior can be studied straightforwardly in aqueous formic acid–formate buffer solutions. Figure 1 illustrates the variation in observed rate coefficient (k_{obsd}) with formic acid concentration at constant hydrogen ion concentrations of 2.86×10^{-4} and 5.73×10^{-4} *M*, respectively. The straight line drawn in each case results fron a least-squares analysis of the experimental points. Using the k_{H^+} value determined from the studies in HCl–NaCl mixtures, the calculated intercept corresponding to zero formic acid concentration is indicated on the diagram. It is apparent that, within the limits of experimental error, the data for strong acid catalysis in Table I are internally consistent with that from buffer solution studies.

It is possible to represent such a general acid catalyzed reaction by the expression

$$k_{obsd} = k_{H^+}[H^+] + k_{HA}[HA]$$

where k_{H^+} and k_{HA} are the second-order rate coefficients for the catalyzing acids H^+ and HA, respectively. The above formic acid buffer work leads to the equation

$$k_{obsd} = 0.45[H^+] + 2.5 \times 10^{-3}[HCOOH] \qquad (3)$$

Acetic Acid Catalysis. A similar procedure to the above was adopted for the study of acetic acid catalysis. Kinetic measurements were performed in aqueous acetic acid–sodium acetate buffer solutions at constant ionic strength (0.1 *M*) in which the hydronium ion concentration was held at 2.85×10^{-5} *M*. The resulting data led to a value of 5.1×10^{-4} M^{-1} sec^{-1} for the second-order rate coefficient due to the acetic acid molecule.

Discussion

The dedeuteration of azulene-1-*d* shows general acid catalysis for each acid studied, in line with the accepted A-SE2 mechanism as outlined in eq 2.

Although the slopes of the straight lines in Figure 1 agree reasonably well with the values obtained previously,[7] the intercepts, and hence the second-order rate coefficients for the hydronium ion (k_{H^+}), are considerably higher. The k_{H^+} values reported here from both the extrapolation to zero buffer concentration and from measurements in dilute HCl are consistent within experimental error. There is no obvious explanation for the above-mentioned discrepancy, except that any complications arising from deuteration at more than one site (as was the case in the earlier studies) would be negligible in this work. A further observation is that too much reliance should not be placed on studies in buffer solutions alone; it appears that measurements in dilute acid (where feasible) are at least as useful for an accurate determination of k_{H^+}.

The experimental results in dilute aqueous hydrochloric acid solution lead to a slightly smaller k_{H^+} value than obtained from similar experiments conducted in aqueous solutions of constant ionic strength. This suggests that there is a small positive primary salt effect, of the order of a few per cent, on the reaction rate.

When the rate data presented here are combined with studies[29] on the detritiation of azulene-1-*t* in aqueous solutions, the ratios of the observed second-order rate coefficients k^D_{obsd}/k^T_{obsd} are found to be 2.5, 2.1, and 2.0, respectively, for catalysis by hydronium ion, formic acid, and acetic acid. These ratios are similar in magnitude to those reported for proton exchange in trimethoxybenzene[6d] and for similar reactions involving *p*-cresol.[4]

Application of steady-state kinetics leads to expression 4 relating the observed second-order rate coefficients to the rate coefficients for the individual steps of the A-SE2 mechanism (see eq 2). The generalized rate

$$k_{\text{obsd}} = \frac{k_1}{1 + (k_{-1}/k_2)} \tag{4}$$

coefficients k_{-1} and k_2, which refer to removal of a proton and a deuteron, respectively, from the protonated intermediate, shall be designated as k_2^{H} and k_2^{D} in the ensuing discussion.

When combined with a relationship between tritium and deuterium isotope effects[33] and a knowledge of the rate of detritiation[8,29] of azulene-1-*t* in H_2O and in D_2O, it is possible to calculate the rate ratios $k_2^{\text{H}}/k_2^{\text{D}}$ and $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}}$ where the second ratio is a solvent isotope effect which compares the rate of proton and deuteron addition to the substrate in H_2O and D_2O, respectively. This procedure leads to values of $k_2^{\text{H}}/k_2^{\text{D}} = 9.2 \pm 0.8$ and $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}} = 4.3 \pm 0.3$. The $k_2^{\text{H}}/k_2^{\text{D}}$ values so obtained should properly be corrected to allow for the secondary isotope effect (*i.e.*, so that loss of a proton or a deuteron leads to an identical molecule in both cases). Streitwieser and Van Sickle[34] and Gold[35] have respectively suggested 1.15 and 1.17 would be an appropriate correction factor for $k_2^{\text{H}}/k_2^{\text{D}}$, and Bell[25b] has recently estimated a factor of 1.25 for the corresponding $k_2^{\text{H}}/k_2^{\text{T}}$ effect. However, the former would probably result in an overcorrection in this instance (see subsequent paper) and, because of its small magnitude and relative uncertainty, no adjustment of data has been made.

The $k_2^{\text{H}}/k_2^{\text{D}}$ value reported here is in excess of the maximum value (~7) which would be predicted on the basis of simple zero-point energy differences in C–H and C–D bonds for the reactant species only. However, this elementary theory does not take into account the possibility of differences in the vibrational energies occurring in the transition state, or the effect of bending modes in the initial and transition states, and also neglects the possibility of tunneling. It is clear that one or more of these effects is coming into play in this reaction.

When compared with a similar analysis made by Kresge and Chiang for trimethoxybenzene, our values of $k_2^{\text{H}}/k_2^{\text{D}} = 9.2$ and $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}} = 4.3$ are rather higher than the corresponding values of 6.7 and 2.93 reported for trimethoxybenzene.

Our $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}}$ value is appreciably lower than that predicted[6d] on the basis of simple zero-point energy differences (~7.8), yet larger than the maximum value of around 3.6 predicted when account is taken of secondary effects due to water molecules solvating the proton.[36–38] This latter figure was, however, derived from corrections to the simple theory and does not take into account the points mentioned above, in particular, contributions from vibrations in the transition-state species. It is at least satisfying to note that the calculated values of both $k_2^{\text{H}}/k_2^{\text{D}}$ and $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}}$ are higher than those reported for trimethoxybenzene and are presumably close to the maximum values in each instance, as would be expected from the similarity of the transition states in the two steps of the hydrogen isotope exchange reaction.

By following a similar line of argument to that used for the hydronium ion, it is possible to calculate $k_2^{\text{H}}/k_2^{\text{D}}$ values for other acids which catalyze the reaction. This has been done for formic acid and acetic acid and has utilized detritiation data obtained by earlier workers.[29] The results are listed below in Table III, together with a measure of the acidity difference between protonated substrate and acid catalyst ($\Delta\text{p}K = \text{p}K_{\text{protonated substrate}} - \text{p}K_{\text{catalyst}}$). The error limits given for the isotope ratios represent estimated maximum values.

Table III. Correlation of $\Delta\text{p}K$ and Kinetic Isotope Effect for Hydrogen Removal from Azulinium Ion

Catalyst	$k_2^{\text{H}}/k_2^{\text{D}}$	$\Delta\text{p}K$
H_2O	9.2 ± 0.8	−0.02
$HCOO^-$	6.3 ± 1.0	−5.51
CH_3COO^-	6.1 ± 0.9	−6.52

These data are presented graphically in the following paper and, in conjunction with data for other azulenes, lend support to the concept of a maximum kinetic isotope effect occurring in the region where the protonated substrate and acid catalyst have similar acidities.

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