

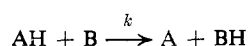
Hydrogen Exchange of Azulenes. VII. Magnitudes of the Kinetic Isotope Effects¹

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Abstract: The rates of proton transfer to and from guaiazulene, 4,6,8-trimethylazulene, and guaiazulene-2-sulfonate in dilute aqueous acid solutions (<0.5 M) have been measured using a continuous fast-flow apparatus. Combining these data with pK values from equilibrium protonation studies permits calculation of k_t and k_r , the first-order rate coefficients for protonation and deprotonation. Data are also reported on detritiation studies of these molecules in dilute acid and buffer solutions. These measurements made it possible to calculate the ratio k_2^H/k_2^T , the relative rates of loss of a proton or a triton to a base from the protonated intermediate. The resulting kinetic isotope effects, expressed as k^H/k^D ratios, range from 6.0 to 9.6. These results, together with data for other aromatic carbon bases, support a recent suggestion that highest isotope effects are observed where the proton is being transferred between bases of similar strengths.

For a general reaction



theoretical calculations have been made which predict a maximum kinetic deuterium isotope effect in the region where the transition state is symmetrical.² A limited amount of experimental confirmation of this prediction is now available, but most comparisons have so far been found to utilize data for reactions of molecules of rather different type. An attractive system for more intensive study is the substituted azulenes all of which exchange their hydrogens by an acid-catalyzed mechanism. The present study gives information on isotope effects for the base-catalyzed deprotonation of the conjugates of three azulenes as determined from a combination of rates of acid-catalyzed tritium exchange and rates of the direct protonation-deprotonation reaction.

The acid-catalyzed exchange of hydrogen atoms attached to an aromatic nucleus has been studied extensively in recent years.^{2,3} In addition, the rates of protonation and deprotonation have been determined by direct flow studies.³ These studies have confirmed that the exchange mechanism is A-SE2.⁴

In the terminology of the previous paper,² the kinetic expression for the hydronium ion catalyzed tritium exchange is

$$\frac{-d[ArT]}{dt} = k_1^T \frac{1}{1 + k_{-1}/k_2} [H_3O^+][ArT]$$

Hence using the more illustrative subscripts $k_2^H \equiv k_{-1}$ and $k_2^T \equiv k_2$, it follows that the experimental second-order rate coefficient for exchange is given by

$$k_{ex} = \frac{k_1^T}{1 + k_2^H/k_2^T} \quad (1)$$

(1) (a) Work supported by a grant from the Atomic Energy Commission; (b) presented at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) References are given in the accompanying paper: L. C. Gruen and F. A. Long, *J. Am. Chem. Soc.*, **89**, 1287 (1967).

(3) (a) For references see B. C. Challis and F. A. Long, *ibid.*, **87**, 1196 (1965); (b) B. C. Challis and F. A. Long, *Discussions Faraday Soc.*, **39**, 67 (1965).

(4) For details on this mechanism and for relevant terminology see ref 2.

where k_2^H/k_2^T is the ratio of the rates of loss of a proton and a triton from the protonated intermediate to a base. Realizing that k_1^H , the second-order rate coefficient for acid-catalyzed protonation of the azulene by the aqueous species H_3O^+ , is determined from the flow measurements and assuming that $k_1^T = k_1^H$, an assumption which will be justified later, a combination of isotope-exchange and flow data permits calculation from eq 1 of the kinetic isotope ratio, k_2^H/k_2^T . An analogous set of equations is applicable for deuterium exchange.

As most of the previously reported ratios refer to deuterium exchange, conversion for comparison purposes can be readily made by employing the relationship⁵

$$(k_2^H/k_2^D)^{1.442} = k_2^H/k_2^T \quad (2)$$

Experimental Section

Preparation of Materials. Unless specified, all materials were reagent grade and were used without further purification.

4,6,8-Trimethylazulene (TMAz) and guaiazulene (Guaiaz), supplied by Columbia Organic Chemicals Co., were purified by chromatography on a Woelm grade 1 alumina column, from a solution in heptane by eluting with ether. After evaporating the ethereal solution to dryness the azulenes were vacuum sublimed. The purity of the compounds was checked by melting point and ultraviolet-visible spectral measurements which were in good agreement with published data.

Guaiazulene-2-sulfonate (Guaiaz-2-SO₃⁻) was prepared and purified by the method of Heilbronner.⁶ The ultraviolet-visible spectrum of the purified product was identical with that previously reported.

Tritiation of 4,6,8-trimethylazulene was performed by a method similar to that of Schulze and Long⁷ using 200 mg of TMAz, 2 ml of 72% perchloric acid, 2 ml of tritiated water (100 mcuries), and 3 ml of ether. This mixture was stirred for 15 min and then neutralized with sodium carbonate. The tritiated azulene was then extracted with three 5-ml aliquots of ether. The extract was washed with water and dried over calcium sulfate. The solution was then evaporated to dryness and the compound vacuum sublimed. A spectral check proved it to be identical with the untritiated compound.

Tritiation of Guaiazulene-2-sulfonate. Owing to the high solubility of this compound in water the extraction procedure had to be modified. A mixture of 500 mg of guaiazulenesulfonate, 1 ml of

(5) C. G. Swain, E. C. Stevens, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

(6) W. Meier, D. Meuche, and E. Heilbronner, *Helv. Chim. Acta*, **46**, 1929 (1963).

(7) J. Schulze and F. A. Long, *J. Am. Chem. Soc.*, **86**, 331 (1964).

tritiated water (50 mcuries), and 2 ml of 72% perchloric acid was stirred for 30 min. The solution was then neutralized with potassium carbonate and extracted into a 50% mixture of *n*-amyl alcohol and acetone by salting out with potassium chloride. The organic layer was separated off and dried with anhydrous sodium sulfate. The preparation was then purified by chromatography using a Woelm alumina column and eluting with 95% aqueous ethanol. On drying, the compound was found to contain inorganic impurities. The residue was then extracted with acetone which dissolved the azulene, effecting a good separation. The solution was filtered and chromatographed on a Woelm activity 2 alumina column using 50% absolute ethanol plus acetone as eluent. The solution was then evaporated and the product dried in a vacuum desiccator over potassium hydroxide. Visible and ultraviolet spectral checks again were identical with those for the untritiated compound.

Preparation of Azulene Solutions. Owing to the low solubility of guaiazulene and trimethylazulene, aqueous solutions were obtained by shaking 20–30 mg of the compounds for 24 hr with 2–3 l. of water. The excess azulene was then removed by filtration through glass wool. Guaiazulene-2-sulfonate, however, is readily soluble in water and solutions could be prepared directly.

Techniques. Equilibrium Protonation Measurements. Preliminary investigations were made on each azulene in water and concentrated acid solutions using the Cary Model 14 spectrophotometer to scan the range 220–600 μ . Using these spectra, a wavelength was selected where large differences existed between the extinction coefficients of the azulene and its protonated form, at the region where optical density changes were at a maximum. This wavelength was used for the flow studies and also the equilibrium protonation measurements which were performed on a Beckman DU 2400 instrument using thermostated cells at $25 \pm 0.1^\circ$. The thermodynamic ionization constants were determined in perchloric acid using the conventional spectrophotometric technique of Long and Paul.⁸

Tritium Exchange. For trimethylazulene, the sampling procedures were identical with those of Schulze and Long,⁷ the rate of detritiation being followed by the loss of activity of the azulene. The method employed an extraction procedure with xylene. The first-order rate coefficients were obtained by plotting $\log C - C_\infty$ vs. t which gave linear plots over 90% reaction. For typical data see Thomas and Long,⁹ Figure 1. Measurements were performed both in dilute hydrochloric acid solutions and in a series of 1:1 acetic acid-acetate buffers at varying acetic acid concentrations and a constant ionic strength of 0.1. These measurements gave good linear plots which enabled rate coefficients for acetate ion catalysis to be calculated in addition to giving an extrapolated value for the hydrogen ion catalysis that was in good agreement with the value calculated from the dilute acid measurements. The hydrogen ion concentration in these buffer solutions was checked using a glass electrode. In the dilute acid solutions, the concentrations of hydrogen ion were measured by direct titration with standard 0.1 *N* alkali.

Owing to the high solubility of guaiazulene-2-sulfonate in water, a special extraction procedure had to be adopted for this compound. The sample of reacting solution was quenched with alkali in a vessel containing 10 ml of *n*-amyl alcohol and excess sodium chloride to saturate the aqueous layer. The organic layer which contained a small amount of water was then separated off and washed eight times with 10-ml aliquots of saturated sodium chloride solution to dilute any tritiated water present. This water caused problems as an aqueous layer separated on cooling in the scintillation counter. This contained most of the azulene making accurate counting difficult. Attempts to dry the amyl alcohol solutions with conventional drying agents proved unsuccessful as absorption of the azulene frequently occurred. The problem was overcome by the addition of ethanol to the counting vial which enabled a homogeneous solution to be obtained. The final mixture contained 5 ml of sample, 5 ml of normal scintillator solution in xylene, and 5 ml of ethanol. Tests showed that the presence of water and ethanol cut the counting efficiency approximately tenfold below normal. However, as guaiazulene-2-sulfonate is readily soluble in water, the initial azulene concentration could easily be increased to compensate for this. Measurements for the guaiazulene-2-sulfonate were also made in dilute acid and acetate buffer solutions.

Kinetic Protonation Measurements. The protonation reactions were studied using a Hartridge-Roughton type of continuous-flow apparatus basically similar to that described by Challis and Long.¹⁰

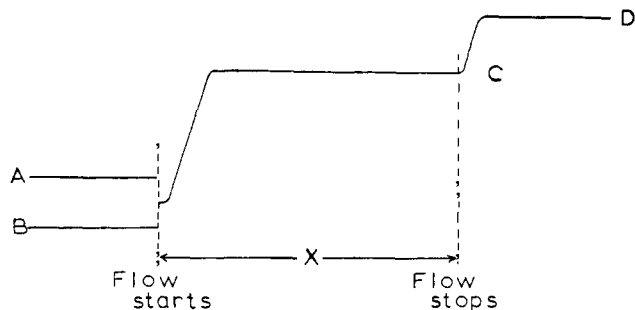


Figure 1. Schematic diagram of recorded signal observed during a measurement on the flow apparatus.

This was designed so that equal volumes of the particular azulene and perchloric acid solution could be mixed in less than 1 msec. The concentrations normally used were approximately 10^{-5} *M* in azulene. The solubility of guaiazulene in water is extremely low (0.8 mg/l. = 4×10^{-6} *M*) and, in order to make measurements possible, the solubility was increased to 2 mg/l. by the addition of 5% ethanol to the water solvent. In spite of this, the optical density changes for reaction of this compound were so small that the base line had to be stable to 0.0004, for sufficiently sensitive rate measurements. This stability was achieved by using a Deltron power supply to operate a 9 amp, 6-v, G. E. ribbon filament lamp source. The acid concentration was adjusted to give a predetermined concentration after mixing. Normally this was varied in the range 0 to 0.5 *M*.

The reactants were mixed by driving the solutions through a mixing chamber and a quartz flow tube, using mechanically operated syringes. The extent of reaction was measured spectrophotometrically. The position of observation down the flow tube was normally at a fixed distance from the mixer. Variation of the extent of reaction was achieved by varying the injection rate. A monochromator was incorporated into the optical system enabling continuous variation of the wavelength in the ultraviolet and visible regions. For study of a particular azulene a wavelength was chosen where either the azulene or protonated azulene absorbed much more strongly than its conjugate, giving a maximum spectral change when protonation occurred. As a certain amount of heat was generated in the mixing process, a High-Temperature Instrument Corp. platinum sheathed iron-constantan thermocouple probe was used for continuous monitoring of the temperature of the flowing solution.

The optical conditions used in the measurements were always in the region where the change in transmission was less than 4% so that $\log 1/T$ was equivalent to $1/T$; thus the recorded emf was linearly proportional to the absorber concentration. The rate of the reactions studied with the apparatus covered the range of half-lives from 2 to 70 msec.

In order to check the performance of the flow apparatus and hence the accuracy of the determined rate constants, measurement of the rate of the dehydration of carbonic acid was undertaken. This reaction has been studied extensively by various techniques.¹⁰ The conditions used in the experiment were identical with those of Dalziel.¹¹ The rate coefficient obtained was 23.1 sec^{-1} at 24.4° , which is in good agreement with previous measurements.

Calculation of the Rate Coefficients. The flow experiments measured the first-order rate coefficients for the approach to equilibrium

$$\text{rate} = k[\text{Az}]$$

where

$$k = \frac{2.303}{t} \log \frac{[\text{AzH}_2^+]_e - [\text{AzH}_2^+]_0}{[\text{AzH}_2^+]_e - [\text{AzH}_2^+]_t}$$

where AzH_2^+ refers to the conjugate acid and where the subscripts *e*, 0, *t* refer to equilibrium and to times 0 and *t*.

The typical chart record of a run is illustrated in Figure 1. The distance *X* is related to the time which the drive syringes were in

(8) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 1 (1957).

(9) R. J. Thomas and F. A. Long, *J. Am. Chem. Soc.*, **86**, 4770 (1964).

(10) A. Weissberger, "Techniques in Organic Chemistry. Rates and Mechanisms of Reactions," Vol. 7, Part II, A. Weissberger, Ed., Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1963, p 725.

(11) K. Dalziel, *Biochem. J.*, **55**, 79 (1953).

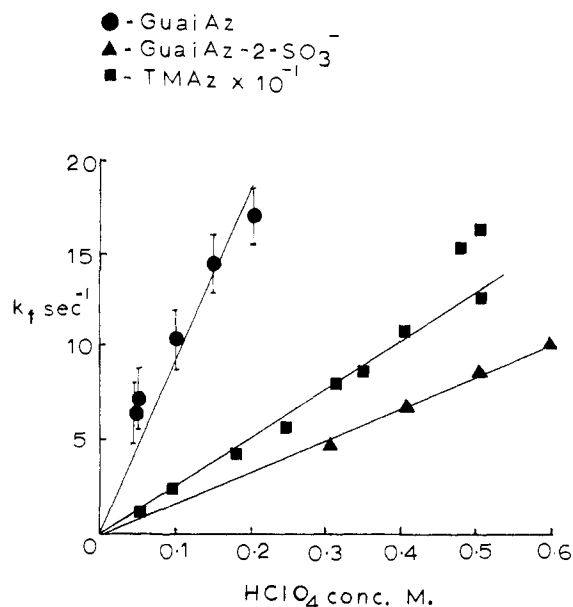


Figure 2. Plot of k_f against acid concentration for the protonation reaction.

operation. From the various physical dimensions of the apparatus, a factor (F) can be calculated which converts chart inches into reaction times in the flow tube.

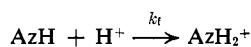
The rate coefficients were normally calculated by plotting $\log [D - 1/2(A + B)] / (D - C)$ vs. X . From this the rate coefficient can readily be calculated as

$$k = \frac{2.303 \times \text{slope}}{F} \text{ sec}^{-1}$$

where F is the conversion factor. Typical data for a kinetic run are illustrated by Challis and Long,^{3a} Table I. Now $k = k_f + k_r$, where k_f and k_r represent the individual rates for the forward and reverse reactions. These can be readily separated, provided that equilibrium protonation data are available at the appropriate acid concentration, as

$$k_f = \frac{k}{1 + \frac{[\text{AzH}]_e}{[\text{AzH}_2^+]_e}} \quad (3)$$

By dividing by the acid concentration, k_f can be converted into the bimolecular coefficient k_1^H for the following process



where

$$k_f = k_1^H[\text{H}^+] \quad (4)$$

Data for k_1^H and k_{ex} can then be used to calculate k_2^H/k_2^T ratios by using eq 1.

Results

From equilibrium protonation measurements, the variation of the ratio (BH^+/B) with acid concentration enabled pK values for the azulenes to be obtained by extrapolation⁸ (see Table I).

Table I

	pK at 25°	Wavelength, $m\mu$
Trimethylazulene	+0.48 ± 0.02	268
Guaiazulene-2-sulfonate	-0.63	292
Guaiazulene (5% ethanol)	+1.35	286

The pK for trimethylazulene is less accurate than that for the others, as at the most favorable wave-

length, 268 $m\mu$, the optical density changed only by a factor of 2 on protonation; 355 and 360 $m\mu$ were also used but these gave much lower absorption though the results were reasonably consistent. Optical density data for the solutions had to be extrapolated to zero time as the light beam caused decomposition. The extrapolated pK value of +0.48 was obtained by placing most emphasis on the data in the region where $\text{BH}^+/\text{B} = 1$, where the measurements are least sensitive to optical density errors. Measurements for guaiazulene were deliberately made with 5% ethanol in water as solvent so that the protonation data were obtained with the same solvent as used in the flow measurements. The pK of guaiazulene has previously been measured in water by Thomas and Long⁹ and found to be +1.42. The essential agreement of the present measurement with this indicates that the presence of ethanol has at most only a very small influence on the pK and the related rate coefficients.

This equilibrium data when combined with experimental measurements of k enable k_1^H to be determined by application of eq 3 and 4.

The protonation data for guaiazulene, 4,6,8-trimethylazulene, and guaiazulene-2-sulfonate are presented in Table II, and k_f data for these azulenes are illustrated in Figure 2. In this figure, it should be

Table II. Protonation Data from Flow Measurements

H^+ , M	k_{obsd} , sec^{-1}	$\text{AzH}_2^+/\text{AzH}$	k_f , sec^{-1}	$k_1^H = k_f/\text{H}^+$, $M^{-1} \text{sec}^{-1}$	k_r , sec^{-1}
4,6,8-Trimethylazulene at 26.4 ± 0.5°					
0.048	87	0.15	11.35	236	75.7
0.093	96	0.32	23.3	250	72.7
0.181	92	0.83	41.7	230	50.3
0.246	102	1.25	56.7	230	45.3
0.311	122	1.80	78.4	252	43.6
0.348	124	2.25	85.9	246	38.1
0.405	144	2.90	107.1	264	36.7
0.480	190	3.80	150.4	313	39.6
0.502	155	4.06	124.4	248	30.6
0.503	201	4.07	161.5	321	39.5
Guaiazulene-2-sulfonate at 25 ± 0.2°					
0.303	47.9	0.108	4.67	15.4	43.2
0.406	45.6	0.166	6.50	16.0	39.1
0.501	44.4	0.263	8.48	16.9	35.9
0.595	43.2	0.302	10.02	16.8	33.2
Guaiazulene in 5% Ethanol at 25 ± 0.4°					
0.0474	11.4	1.45	6.3	132	5.1
0.0492	12.8	1.52	7.2	146	5.6
0.0991	13.5	3.64	10.2	102	3.3
0.1493	17.0	6.3	14.3	96	2.7
0.2064	18.8	10.6	16.9	82	1.9

noted that, for convenience of illustration, the data for trimethylazulene have been reduced by a factor of 10. Values of k_1^H as obtained from the gradients of these lines are given in Table III. In determining k_1^H for trimethylazulene, the deviations from linearity at high acid concentrations are ignored, as the over-all rate coefficients were in the region of 300 sec^{-1} ($t_{1/2} = 2-3$ msec). It is believed that these deviations were caused by operating the apparatus at the extreme limits of its range. No measurements were possible for guaiazulene-2-sulfonate below 0.3 M acid owing to the weak basicity of the molecule. Measurements

Table III

Temp, °C	Azulene	k_1^H , $M^{-1} \text{sec}^{-1}$
26.4 ± 0.5	Trimethylazulene	244 ± 20 ^a
25.0 ± 0.2	Guaiazulene	92 ± 10
25.0 ± 0.4	Guaiazulene-2-sulfonate	16.3 ± 0.4

^a Note for k_2^H/k_2^T calculations, k_1^H for trimethylazulene has to be divided by 2 as the compound has two equivalent sites for protonation. Uncertainties in the equilibrium protonation data have also been considered in the limits of error quoted above.

were not extended beyond 0.6 *M* as at increased acid concentrations the graph would be expected to deviate from linearity.

The measurements for guaiazulene are less precise. This is due to the extremely low solubility of the compound. The error limits represented in Figure 2 are based on the fluctuation of 0.0004 in the optical density caused by base-line fluctuation.

Tritium-exchange data for trimethylazulene and guaiazulene-2-sulfonate in acetic acid buffer solutions and in dilute hydrochloric acid solutions are illustrated in Figure 3 and Tables IV and V. The values at zero

Table IV. Detritiation of Trimethylazulene and Guaiazulene-2-sulfonate in 1:1 Acetate (Buffer Solutions) at 25° (*I* = 0.1)

HAc, <i>M</i>	$k_{\text{obsd}} \times 10^4 \text{sec}^{-1}$
Trimethylazulene	
0	1.14 ^a
0.005	1.58
0.01	1.61
0.02	2.49
0.04	3.57
0.06	5.22
0.08	5.98
0.10	6.91
$k_{\text{HAc}} = 6.4 \times 10^{-3} M^{-1} \text{sec}^{-1}$	
Guaiazulene-2-sulfonate	
	$k_{\text{obsd}} \times 10^6 \text{sec}^{-1}$
0	2.43 ^a
0.01	2.9
0.03	4.3
0.06	5.8
0.10	8.3
$k_{\text{HAc}} = 5.9 \times 10^{-4} M^{-1} \text{sec}^{-1}$	

^a Calculated from dilute HCl data.

Table V. Detritiation Studies of Trimethylazulene and Guaiazulene-2-sulfonate in Dilute HCl Solutions at 25°

$H^+ \times 10^4 M$	$k_{\text{obsd}} \times 10^3 \text{sec}^{-1}$	k_{obsd}/H^+ , $M^{-1} \text{sec}^{-1}$
Trimethylazulene		
8.9	4.0	4.50
9.5	3.75	3.97
11.4	4.54	3.98
16.9	6.35	3.82
19.5	7.52	3.84
19.6	7.80	4.00
	Mean	4.0 ± 0.2
Guaiazulene-2-sulfonate		
49.9	4.22	0.846
78.6	6.77	0.861
	Mean	0.853 ± 0.007

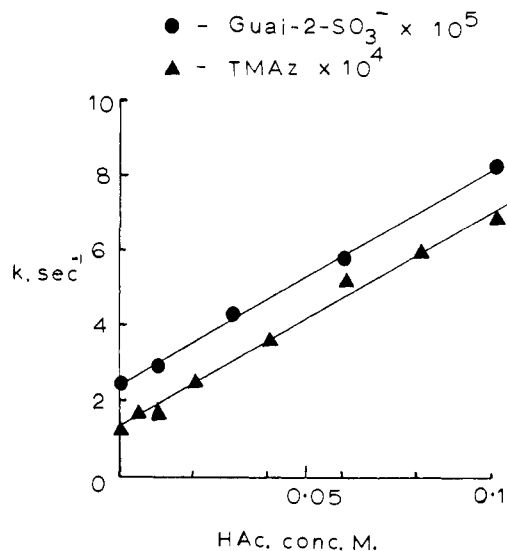


Figure 3. Tritium exchange data in 1:1 acetic acid-acetate buffer solutions at 25° (*I* = 0.1 *M*).

acetic acid concentration were calculated using the data obtained with dilute hydrochloric acid solution corrected to the appropriate hydrogen ion concentration. This concentration was calculated from *pK* and activity coefficient data.¹² For the 1:1 acetic acid-acetate buffer solutions used, the calculated c_{H^+} fell in the range 2.80 – 2.97×10^{-5} , where the spread is due to variation of the activity coefficient for sodium acetate (0.791) and sodium chloride (0.778) for solutions of 0.1 *M*. A mean value of 2.85×10^{-5} was used in the calculations which gave good agreement for the hydrogen ion catalyzed exchange rate compared to the value which extrapolates from the buffer solution data.

Aqueous solutions of trimethylazulene were found to be unstable to light, which caused experimental problems in the detritiation experiments. Special procedures had to be evolved to eliminate this problem. In spite of these procedures, a number of kinetic runs had to be neglected as the ∞ count was considerably higher than that of the background. In the worst cases, this amounted to 20% of the total count. This high value is believed to be due to decomposition of the trimethylazulene to a product which did not detritiate. All the results shown in Table IV were considered satisfactory as the ∞ count was less than two to three times that of the background. The general equations for detritiation of these azulenes in acetate buffers at 25° were: for trimethylazulene

$$k_{\text{obsd}} = 4.0[H^+] + 6.4 \times 10^{-3}[HAc]$$

for guaiazulene-2-sulfonate

$$k_{\text{obsd}} = 0.853[H^+] + 5.9 \times 10^{-4}[HAc]$$

The variations in these second-order rate coefficients for detritiation of trimethylazulene and guaiazulene-2-sulfonate, as a function of the *pK* of the acid catalyst, are close to those reported for the same catalysts with azulene and guaiazulene.⁷ This implies that the

(12) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1958, p 676.

Brønsted exponents for these four compounds are almost equal, which is the expected result for such a closely related series of compounds.

Discussion

The experimental technique used in the present study to obtain k_2^H/k_2^T ratios has several limitations which affect the range of its application. If the carbon base is much weaker than guaiazulene-2-sulfonate, then the flow measurements must be performed in a relatively concentrated solution of strong acid to obtain suitable protonation. Before a calculation of k_2^H/k_2^T can be made, the k_f data must be extrapolated to dilute solution. This was done by Challis and Long^{3a} for azulene at 7.3°. However, the extrapolation causes a loss of precision which even in the case of azulene is sufficient to lead to a large uncertainty in the k_2^H/k_2^T ratio. The uncertainty also enters if the isotope effect for azulene is calculated from the data of Thomas and Long⁹ and the measurements of Challis and Long,^{3a} corrected to 25° using the reported temperature coefficient data. The value so obtained is $k_2^H/k_2^T = (3.00/0.181) - 1 = 15.6$ and $k_2^H/k_2^D(\text{calcd}) = 6.7$. More recent studies² show that this is too low. For these weaker carbon bases an alternative procedure, which can be employed to obtain the isotope ratios, is to perform parallel dedeuteration and detritiation studies under the same acid conditions. These exchange reactions can be measured in dilute acid solutions.

This second method was used by Kresge¹³ to study the hydrogen exchange of 1,3,5-trimethoxybenzene ($k_2^H/k_2^D = 6.7$). The ratio for azulene was calculated in a similar way from the dedeuteration measurements of Colapietro and Long¹⁴ and the detritiation studies of Schulze and Long⁷ ($k_2^H/k_2^D = 5.6$), but the accuracy was low, owing primarily to low precision in the dedeuteration study. For this reason, a recent reinvestigation of the dedeuteration measurements was performed in this laboratory.² The k_2^H/k_2^D ratio reported from this more precise study is 9.2, *i.e.*, considerably higher than the previously reported values for azulene.

The available data for reaction of acids of aromatic carbon bases are summarized in Table VI. For convenience of comparison k_2^H/k_2^D ratios in section A have been calculated from the k_2^H/k_2^T values obtained in the present study. Data from combined use of dedeuteration and detritiation measurements are presented in section B.

It is to be noted that the reported k_2^H/k_2^D is essentially the ratio of H and D loss from the conjugate acid AzHD⁺, whereas by strict definition the desired ratio is that for H loss from AzH₂⁺ relative to D loss from AzHD⁺. To equate these two ratios is to ignore a secondary isotope effect. At the Faraday Society Discussion, the need to correct for the secondary isotope effects present in these systems was emphasized.¹⁵ On the basis of the measurements of Streitwieser,¹⁶ Bell inquired whether a multiplication factor of 1.15 would not be appropriate to correct the k_2^H/k_2^D ratio.

(13) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **84**, 3976 (1962).

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

(15) R. P. Bell, *Discussions Faraday Soc.*, **39**, 94 (1965); V. Gold, *ibid.*, **39**, 94 (1965); see also B. D. Botts and V. Gold, *J. Chem. Soc.*, 4284 (1964).

(16) A. Streitwieser, Jr., W. C. Langworth, and D. E. Van Sickle, *J. Am. Chem. Soc.*, **84**, 254 (1962).

This value is also supported by the measurements of Bell and Goodall.¹⁷ However, and in spite of this clear suggestion that secondary effects are not negligible, no such correction has been made for the data of Table VI. The reasons are twofold.

In calculating the isotope ratio data in Table VI, a further assumption is implicitly made, namely that $k_1^H = k_1^D = k_1^T$, *i.e.*, that the rate of protonation at the carbon site is entirely independent of the hydrogen isotope already present. It would be more correct to assume that secondary isotope effects are present here also, *i.e.*, present in both the protonation and deprotonation reactions. Thus correction of the data for deprotonation only would clearly be an oversimplification.

It may be shown that for values of k_2^H/k_2^D of the size considered here the secondary isotope effect can be approximated by

$$(k_2^H/k_2^D)_{\text{cor}} = (k_2^H/k_2^D)_{\text{obsd}} \frac{S_1^D S_2^H}{S_1^H S_2^D}$$

where S_1^H/S_1^D = secondary isotope effect present in the protonation reaction and S_2^H/S_2^D = secondary isotope effect present in the deprotonation reaction. Actually, there is some evidence that the secondary isotope effect for protonation S_1^H/S_1^D is small¹⁸⁻²⁰ but not negligible; *i.e.*, the k^H/k^D ratio does not differ from unity by more than 5%. However, the direction of this correction is uncertain. Recent data summarized by Baliga and Bourns²¹ show that inverse secondary isotope effects ($S_1^H/S_1^D < 1$) commonly occur in electrophilic attack on aromatic systems. In addition examples are listed where the observed S_1^H/S_1^D ratio appreciably exceeds the estimated (0.95-1.05) range mentioned previously. It is probable that in the present case the strength of the nonreacting C-H bond in the transition state lies between that of azulene and the C-H of azulinium ion. Thus the secondary isotope effect in going from reactant to transition state and transition state to product acts in the same direction. This is equivalent to stating that $S_2^H/S_2^D > 1$ if $S_1^H/S_1^D < 1$ and *vice versa*. Thus Bell's suggestion of $S_2^H/S_2^D = 1.15$, *i.e.*, a ratio of greater than unity, is consistent with the Baliga and Bourns data. If these ratios are appropriate to the present systems, the true primary kinetic isotope effect would then be greater than those calculated in Table VI. But as data exist where $S_1^H/S_1^D > 1$, even the direction of the correction is actually uncertain, let alone its magnitude. In view of the great uncertainty involved, it appears that any correction of the reported data for secondary isotope effects would not be justified at this time. Finally, it is to be noted that neglect of this correction does not influence any intercomparison of data obtained in the same way; it only affects comparison with data for systems where the secondary effect is absent.²²

(17) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc. (London)*, **A294**, 273 (1966).

(18) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).

(19) S. Olsson, *Arkiv Kemi*, **16**, 489 (1960).

(20) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960, p 89.

(21) B. T. Baliga and A. N. Bourns, *Can. J. Chem.*, **44**, 379 (1966).

(22) A. J. Kresge (private communication) reports values for the secondary isotope effects ($k^H/k^D = 0.90$, $k^H/k^T = 0.85$) for protonation of trimethoxybenzene. If one assumes that this correction factor is applicable to the closely related azulene series and that the secondary isotope effect on deprotonation is the same (which would be a reason-

The question remaining to be answered is whether the data in Table VI furnish any experimental evidence to support the theoretical prediction of a maximum isotope effect in the region where the transition state is symmetrical. In Figure 4 the k_2^H/k_2^D data of this and the preceding paper, and a single datum obtained by Kresge¹³ for the closely related compound 1,3,5-trimethoxybenzene, are presented as a function ΔpK , the difference between the pK of the substrate and that of the catalyst. This function for correlation of isotope ratio data was used by Bell and Goodall,¹⁷ who concluded on the basis of their studies that the symmetrical transition state is to be anticipated in the region close to $\Delta pK = 0$.

Table VI

Protonated substrate	Catalyst	k_2^H/k_2^T	$(k_2^H/k_2^D)_{\text{calcd}}$
Section A			
Guaiazulene ^a	H ₂ O	14.1 ± 1.6	6.0
Trimethylazulene ^b	H ₂ O	26.1 ± 1.6	9.6
Guaiazulene-2 sulfonate	H ₂ O	18.1 ± 0.5	7.4
Section B			
1,3,5-Trimethoxybenzene ^c	H ₂ O		6.7
Azulene ^d	H ₂ O		9.2
Azulene ^d	Formate ion		6.3
Azulene ^d	Acetate ion		6.1

^a The value used for k_{ex} in this calculation ($6.1 M^{-1} \text{sec}^{-1}$) was obtained by Thomas and Long.⁹ ^b The data for 4,6,8-trimethylazulene have to be corrected to 25°. The rate constant was estimated using $\Delta H = 14,500 \text{ cal/mole}$, the value determined for azulene.^{3a} In addition, a statistical factor of 2 has to be introduced in the k_1^H value. ^c Kresge.¹³ ^d Gruen and Long.²

From Figure 4, it is evident that the data for the aromatic carbon acids reported show isotope ratios passing through a definite maximum. In locating the position of the maximum, little emphasis was placed on the datum from trimethylazulene as this compound was difficult to work with owing to instability to light, making this datum less reliable. Neglecting this value still leaves the exact position of the maximum in doubt, because of the limits of error in the other measurements, but it is clearly quite close to $\Delta pK = 0$. In Figure 4, data from aliphatic carbon acid systems are also reported. The two dotted lines show two groups of ratios for hydrogen transfer from acetone, β -carbonyl compounds, and nitroalkanes with various bases, as summarized by Bell and Goodall.¹⁷ More recent studies using ethyl 1-nitroacetate²³ have extended these measurements into the region close to the maximum. As no secondary isotope corrections have been made to the reported azulene data or to those of Bell and Goodall, the agreement between the kinetic isotope ratios for these aliphatic and aromatic carbon acid systems is surprisingly good.

able assumption for a symmetrical transition state), then corrected primary isotope ratios can be estimated. Employing this correction to the k^H/k^D data illustrated in Figure 4 would increase all values by approximately 25%, bringing them into much closer agreement with the data of Bell and Goodall for aliphatic carbon acids.

(23) R. P. Bell, private communication.

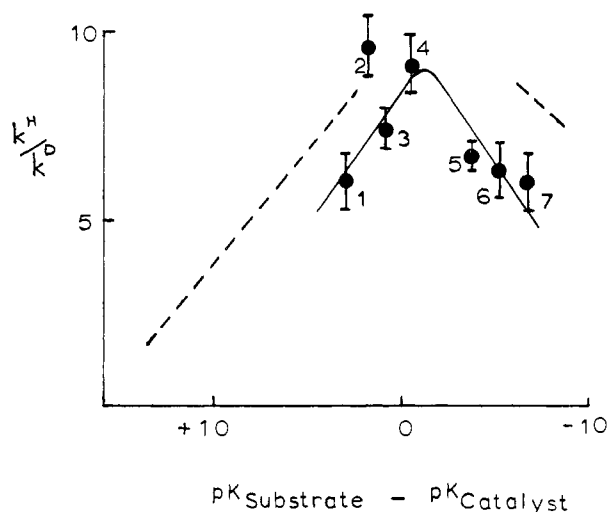


Figure 4. Summary of available data for isotope effects for C-H...X transfer reactions as a function of the pK difference between the substrate and catalyst: ---, data for aliphatic carbon acids, Bell and Goodall. Data for aromatic carbon acids: (1) Guaiaz-H₂O, (2) TMAz-H₂O, (3) Guaiaz-2-SO₃⁻-H₂O, (4) Az-H₂O,² (5) triMeOB-H₂O,¹³ (6) Az-formate ion,² (7) Az-acetate ion.²

Isotope ratios for other aromatic species were summarized by Kresge,²⁴ but since the pK 's of most of the species are unknown, these data were correlated in terms of the relative reactivity. Table VII, which is essentially Kresge's table with some extension to include recent results, gives this comparison. Since the decrease in \log (relative exchange rate) is related to decrease in ΔpK , the data show that the trend in k^H/k^D ratios continues well beyond the region illustrated in Figure 4.

Table VII

Aromatic	Ex-change position	Log (rel exchange rate)	ΔpK	k^H/k^D ^a
C ₆ H ₆	...	0	...	3.4
C ₆ H ₅ CH ₃	3	0.8	...	3.4
C ₆ H ₄ CH ₃	2	2.6	...	4.6
C ₆ H ₃ CH ₃	4	2.6	...	5.5
C ₆ H ₅ OCH ₃	2	4.3	...	7.2
C ₆ H ₄ OCH ₃	4	4.8	...	6.7
1,3,5-C ₆ H ₃ (OCH ₃) ₃	2	10.0	-3.5	6.7
Azulene	1	11.5	0	9.2
Guaiazulene-2-sulfonate	3	12.2	1.1	7.4
4,6,8-Trimethylazulene	1	12.8	2.3	9.6
Guaiazulene	3	13.0	3.3	6.0

^a No secondary isotope corrections have been made.

On the basis of the reported data, the existence of a maximum in the kinetic isotope ratio seems now for carbon acids at least to be fairly well established, confirming the theoretical predictions mentioned previously.

(24) A. J. Kresge, *Discussions Faraday Soc.*, **39**, 49 (1965).