5 ml of dry dioxane was allowed to react by the method previously described. Recrystallization from ether–pentane gave 110 mg (92%) of the desired material as white needles, mp 163–163.5°.

Anal. Calcd for $C_{13}H_{24}N_2S$: C, 64.95; H, 10.06; N, 11.65. Found: C, 64.99; H, 10.04; N, 11.77.

endo-**Bicyclo[3.2.1]oct-2-yl Thiocyanate (18).** A mixture of 4.20 g (0.015 mol) of Δ^4-cycloheptenylcarbinyl *p*-toluenesulfonate,[21] 1.746 g (0.018 mol) of potassium thiocyanate, and 25 ml of sulfolane was allowed to react as in the preparation of **9**, affording 2.53 g of crude Δ^4-cycloheptenylcarbinyl thiocyanate (**17**). A 1.00-g portion of the crude thiocyanate dissolved in 40 ml of sulfolane was sealed in a glass tube and heated at 150° for 32 hr. The contents of the tube were added to water and extracted with pentane. Concentration of the combined extracts, followed by distillation at 62–70° (0.15 mm), gave 400 mg of a mixture consisting of 9% **19**, 52% Δ^4-cycloheptenylcarbinyl isothiocyanate, 37% **18**, and 2% unreacted starting material. The thiocyanates were separated from the isothiocyanates by chromatography on silica gel, and the combined thiocyanate fractions were treated with a solution of bromine in carbon tetrachloride. This procedure gave 290 mg of a yellow liquid upon removal of the solvent. Distillation of this crude material at 67–70° (0.15 mm) afforded 90 mg of pure **18**: infrared spectrum (film) 2910, 2140, 1045, and 765 cm^{-1}; nmr (CCl_4) τ 6.42 (br mult), 7.33–8.93 (br mult).

Anal. Calcd for $C_9H_{13}NS$: C, 64.92; H, 7.81; N, 8.38. Found: C, 64.71; H, 7.95; N, 8.62.

endo-**Bicyclo[3.2.1]oct-2-yl Isothiocyanate (19).** A 2.93-g (0.023 mol) portion of *endo*-bicyclo[3.2.1]oct-2-ylamine[22] was treated with carbon disulfide and ethyl chloroformate by a previously described procedure,[7] giving 2.38 g (60%) of a semisolid product. Recrystallization from pentane afforded a white solid: mp 70–71°; infrared spectrum (CCl_4) 2910, 2060, and 1325 cm^{-1}; nmr (CCl_4) τ 6.28 (br tr), 7.35–9.0 (mult).

Anal. Calcd for $C_9H_{13}NS$: C, 64.62; H, 7.81; N, 8.38. Found: C, 64.74; H, 7.71; N, 8.27.

1-(*endo*-Bicyclo[3.2.1]oct-2-yl)-3-*t*-butylthiourea. The derivative was prepared by the method previously described, giving a white solid, mp 162.5–163.0°.

Anal. Calcd for $C_{13}H_{24}N_2S$: C, 64.95; H, 10.06; N, 11.65. Found: C, 64.93; H, 9.99; N, 11.60.

Isomerization of 9, 11, and 13. Solutions 0.15 *M* in pure **9**, **11**, or **13** were prepared using the various solvents. Aliquots (1 ml) were sealed in glass tubes and heated at constant temperatures for different lengths of time. The contents of the tubes were poured into 25 ml of water and the products were extracted with two 5-ml portions of pentane. The combined extracts were washed with water, dried, and concentrated. Residues were examined by gc using the following conditions: column 50 ft × 0.02 in. butanediol succinate; temperature 160°; carrier flow 65 lb He; R_t (min) **14** 6.2, **12** and **19** 6.5, **10** 7.9, **11** 9.8, **18** 10.2, **13** 10.6, **9** 11.6.

Catalyzed Isomerizations of 9, 11, and 13 in Benzene. A 0.15 *M* solution of the pure thiocyanate in benzene, which was 2% in boron trifluoride, was heated at reflux. Samples (1 ml) were withdrawn at various intervals. The samples were mixed with 10 ml of pentane, washed with saturated sodium bicarbonate solution, and dried. Upon concentration, analyses were conducted by gc using the above conditions.

Kinetic Procedure. Aliquots (5 ml) of sulfolane solutions 0.04 *M* in **11**, or 4-ml aliquots of sulfolane solutions 0.036 *M* in **13**, were sealed in glass tubes and heated at 130.0 and 150.0°. Tubes were removed at intervals and quenched by immersion in ice. The tubes were opened and the contents added to 100 ml of water. Products were extracted with pentane and the combined extracts washed with water, dried, and concentrated. The residues were examined by gc using the following conditions: column 6 ft × 0.25 in. 10% XE-60 on Diatoport S; temperature 200°; carrier flow 110 ml/min; R_t (min) **12** and **14** 5.6, **11** and **13** 8.2.

Acknowledgments. We are grateful to the Petroleum Research Fund administered by the American Chemical Society (Grant No. 2925-A1) for partial support of this research. We also wish to thank Professor N. A. LeBel for his invaluable contributions.

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Aromatic Protonation. VI. Brønsted Relation for Aromatic Hydrogen Exchange in 1,3,5-Trimethoxybenzene[1]

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Abstract: The Brønsted relation for acid-catalyzed detritiation of 1,3,5-trimethoxybenzene-2-*t* has been reinvestigated by determining rate constants for catalysis by eight new acids and revising the value for a previously used catalyst. This change and the addition of these new catalytic coefficients do not significantly alter the exponent in the overall Brønsted relation for this reaction (original value: 0.52 ± 0.01;[4b] new value: 0.56 ± 0.03), but they do reveal striking deviations characteristic of catalyst type. Correlations based on subsets of data give Brønsted exponents ranging from 0.56 to 0.71. This suggests that the extent of proton transfer at the transition state of a proton-transfer reaction may be a function of catalyst type, and that overall Brønsted exponents can therefore provide only an approximate measure of this transition state property.

Several years ago we discovered that aromatic hydrogen exchange is subject to general acid catalysis.[4] Our interest in this reaction at that time was chiefly in its mechanism, but in the course of our work we measured several catalytic coefficients for the detritiation of 1,3,5-trimethoxybenzene-2-*t* and published a Brønsted plot.[4b] This Brønsted plot was the first ever constructed for an authentic rate-limiting proton transfer from acid to substrate (A–SE2 mechanism) and it was unusual in that it was accurately linear over the

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[1] (a) Taken from a Ph.D. Thesis submitted to the Illinois Institute of Technology by S. Slae, Jan 1969; this research was supported in part by the Atomic Energy Commission under USAEC Contract No. AT-(11-1)-1025 to the Illinois Institute of Technology; (b) part V: A. J. Kresge, D. P. Onwood, and S. Slae, *J. Amer. Chem. Soc.*, **90**, 6982 (1968).

[2] National Institutes of Health Predoctoral Fellow.

[3] National Science Foundation Summer Research Participant, High School Teachers' Program.

[4] (a) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **81**, 5509 (1959); (b) A. J. Kresge and Y. Chiang, *ibid.*, **83**, 2877 (1961).

Table I. Rates of Loss of Tritium from 1,3,5-Trimethoxybenzene-2-*t* to Aqueous Buffer Solutions at 24.62°, $\mu = 0.10\ M$[a]

10^2[HA], M[b]	$10^6 k_{obsd}$, sec^{-1}
HA = $CNCH_2CO_2H$; Buffer Ratio = 0.192[c]	
0.384	5.27
0.768	6.53
1.15	7.45
1.54	8.32
1.92	9.37
$k_1 = (5.75 \pm 0.12) \times 10^{-6} + (1.92 \pm 0.10) \times 10^{-4}$[HA][d]	
HA = $CH_3OCH_2CO_2H$; Buffer Ratio = 1.19[c]	
2.34	3.69, 4.49
4.68	4.92, 5.35
7.02	6.29
9.36	8.12
$k_1 = (2.82 \pm 0.37) \times 10^{-6} + (5.39 \pm 0.66) \times 10^{-5}$[HA][d]	
HA = HCO_2H; Buffer Ratio = 1.00[c]	
2.07	2.32
4.15	2.90
6.22	3.65
8.28	4.20
10.4	4.77
$k_1 = (1.75 \pm 0.06) \times 10^{-6} + (2.96 \pm 0.09) \times 10^{-5}$[HA][d]	
HA = $C_6H_5CH_2CO_2H$; Buffer Ratio = 1.85[c]	
0.652	0.791
1.30	0.940
1.96	1.09
2.61	1.22
3.20	1.38
$k_1 = (6.72 \pm 0.13) \times 10^{-7} + (2.16 \pm 0.06) \times 10^{-5}$ [HA][d]	
HA = CH_3CO_2H; Buffer Ratio = 1.68[c]	
3.48	0.525
6.96	0.720
10.9	0.948
13.9	1.12
17.4	1.33
$k_1 = (3.21 \pm 0.05) \times 10^{-7} + (5.77 \pm 0.04) \times 10^{-6}$[HA][d]	
HA = $(CH_3)_3CCO_2H$; Buffer Ratio = 1.73[c]	
1.34	0.231
2.67	0.282
4.00	0.369
5.34	0.429
6.67	0.495
$k_1 = (1.59 \pm 0.09) \times 10^{-7} + (5.05 \pm 0.21) \times 10^{-6}$[HA][d]	
HA = $C_6H_5NH_3^+$; Buffer Ratio = 1.00[c]	
2.00	0.504
4.00	0.863
6.00	1.23
8.00	1.50
10.0	1.85
$k_1 = (1.90 \pm 0.30) \times 10^{-6} + (1.67 \pm 0.05) \times 10^{-5}$[HA][d]	
HA + $C_5H_5NH^+$; Buffer Ratio = 1.00[c]	
1.99	0.0590
3.97	0.0833
5.96	0.0947
7.95	0.119
9.93	0.143
$k_1 = (3.92 \pm 0.42) \times 10^{-8} + (1.02 \pm 0.06) \times 10^{-6}$[HA][d]	
HA = $HO_2CCO_2^-$; Buffer Ratio = 0.94[c]	
0.582	1.43, 1.35
1.16	1.62, 1.73
1.76	1.91, 2.04
2.33	2.19, 2.32
2.91	2.51
$k_1 = (1.15 \pm 0.05) \times 10^{-6} + (4.75 \pm 0.26) \times 10^{-5}$[HA][d]	
HA = HSO_4^-; Buffer Ratio = 0.486[c]	
0.195	10.2
0.389	18.7
0.584	26.5
0.973	41.5
$k_1 = (3.20 \pm 0.01) \times 10^{-5} + (2.08 \pm 0.04) \times 10^{-3}$[HA][d]	

[a] Except in the case of bioxalate ion where μ was 0.15 M and bisulfate ion where μ was variable. [b] Stoichiometric concentrations. [c] Buffer ratio = [acid]/[base] (stoichiometric concentrations). [d] Relationship obtained by least-squares analysis using actual (calculated) undissociated acid concentrations and observed rate constants adjusted to the hydronium ion concentration of the most concentrated buffer solution; error estimates are standard deviations.

complete range of catalyst acidity available in aqueous solution.

Since that time, other reactions proceeding by the A–SE2 mechanism have been discovered and additional Brønsted plots for this kind of process have been made.[5] These have proved to be quite different from the original relationship for trimethoxybenzene in that none is quite so linear and all show sizable deviations from a single correlation characteristic of catalyst type.[6] In view of this difference, and because it has been suggested that all Brønsted plots might in general be curved,[7] we have undertaken a more detailed examination of the Brønsted relation for aromatic hydrogen exchange in 1,3,5-trimethoxybenzene.

Results

Rates of hydrogen exchange were determined by monitoring the loss of radioactivity from 1,3,5-trimethoxybenzene-2-*t* to wholly aqueous solutions of acidic catalysts. Only in the case of catalysis by bisulfate ion, however, was this reaction fast enough to allow rate measurements to be made in a conventional way, *i.e.*, by taking samples over three to four half-lives, quenching in base, extracting trimethoxybenzene, and assaying for radioactivity by liquid scintillation counting. With all other catalysts, exchange was too slow to allow convenient sampling over more than a small fraction of one half-life, and an initial-rate method was therefore used instead. This technique took advantage of the fact that even very small extents of loss of tritium from a labeled aromatic can be measured quite accurately if the radioactive assay is performed on the aqueous portion of a kinetic sample rather than on the aromatic substrate; the aqueous fraction must of course contain little or no radioactivity at the beginning of an experiment.

With this method, sampling was generally confined to times under 2% reaction. Radioactivities at "infinite" time were also determined by adding strong acid to portions of reaction mixture, waiting for times corresponding to ten half-lives under the new conditions, and then performing the assay as usual. First-order rate constants were obtained by dividing zero-

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(5) (a) R. J. Thomas and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 4770 (1964); (b) M. M. Kreevoy, T. S. Straub, W. V. Kayser, and J. L. Melquist, *ibid.*, **89**, 1201 (1967); (c) M. M. Kreevoy and R. A. Eliason, *J. Phys. Chem.*, 72, 1313 (1968); V. Gold and D. C. A. Waterman, *Chem. Commun.*, 40 (1967); *J. Chem. Soc. B*, 839, 849 (1968); G. E. Lienhard and T. C. Wang, *J. Amer. Chem. Soc.*, **91**, 1146 (1969); A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, to be published.

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(7) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

order initial rates of appearance of aqueous radioactivity by infinity values. This method is essentially the one we have used before,[1b,4b,8] and here, as in the past, it proved to be capable of good precision.

Exchange rate constants were measured in solutions of seven carboxylic acids and two ammonium ions in addition to bisulfate ion. For the experiments with carboxylic acids and ammonium ions, catalysts were supplied as acidic components of buffer solutions. In each case, kinetic measurements were made at four to six different buffer concentrations which generally covered a fivefold variation in catalyst molarity. Buffer ratios were kept constant for a series of experiments with a given acid, and ionic strength was maintained at 0.10 *M* (0.15 *M* in the case of bioxalate ion) through the addition of inert electrolyte. The relevant data are summarized in Table I.

With some of the stronger acids, this procedure failed to hold the hydrogen ion concentration exactly constant. In these cases, allowance for resultant changes in the amount of hydronium ion catalysis was made by employing the known hydronium ion catalytic coefficient for this reaction[8a] to adjust observed rate constants within a given buffer series to a common hydrogen ion concentration. Hydronium ion concentrations were calculated for this purpose using the thermodynamic dissociation constants listed in Table II and activity coefficients obtained by the Debye–Hückel formula[9] with an ion-size parameter of 5.5*A*; no activity coefficient correction was applied in the case of ammonium ions. At an ionic strength of 0.10 *M*, hydronium ion concentrations obtained in this way are somewhat sensitive to the choice of ion-size parameter, but the corrections to observed rate constants never amounted to more than a few per cent, and reasonable changes in ion-size parameter were found to have no significant effect on catalytic coefficients. The latter were evaluated as slopes of plots of adjusted first-order exchange rate constants *vs.* catalyst concentration (also adjusted for any changes produced by dissociation); best values of slopes and their uncertainties were calculated by the method of least squares. Intercepts in such plots represent contributions to observed rates made by hydronium ion catalysis, and hydronium ion catalytic coefficients calculated from these intercepts and the known hydronium ion concentrations of the buffers (Table II) agreed well, on the whole, with the directly measured value of (6.20 ± 0.05) × 10^{-3} M^{-1} sec^{-1};[8a] the average value obtained from the seven carboxylic acid and the two ammonium ion series of buffers is (6.55 ± 0.73) × 10^{-3} M^{-1} sec^{-1}.

Table II. Summary of Catalytic Coefficients and Related Data for Detritiation of 1,3,5-Trimethoxybenzene-2-*t* in Aqueous Solution at 25°

Catalyst	pK_a	$10^5 k_{HA}$, M^{-1} sec^{-1}	$10^3 k_{H^+}$, M^{-1} sec^{-1} [a]
H_3O^+	−1.74	620[b]	
$CNCH_2CO_2H$	2.47[c]	19.2	5.86
FCH_2CO_2H	2.72[d]	9.43[e]	6.29[e]
$CH_3OCH_2CO_2H$	3.57[f]	5.39	5.55
HCO_2H	3.75[g]	2.96	6.14
$C_6H_5CH_2CO_2H$	4.31[h]	2.16	5.96
CH_3CO_2H	4.76[i]	0.577	6.76
$(CH_3)_3CCO_2H$	5.03[j]	0.505	7.05
$C_6H_5NH_3^+$	4.61[k]	1.67	7.58
$C_5H_5NH^+$	5.22[l]	0.102	6.52
NH_4^+	9.25[m]	0.00050[n]	
HSO_4^-	1.98[o]	208	6.18
$HO_2CCO_2^-$	4.27[p]	4.75	7.81
$H_2PO_4^-$	7.20[q]	0.0375[r]	
H_2O	15.74	9.5 × 10^{-7} [n]	

[a] From intercept of rate constant *vs.* buffer acid concentration plot. [b] Reference 8a. [c] F. S. Feates and D. J. G. Ives, *J. Chem. Soc.*, 2798 (1956); D. J. G. Ives and P. D. Marsden, *ibid.*, 649 (1965). [d] References 5b and 12. [e] From reanalysis of the data in ref 4b using the dissociation constant of ref 5b and 12. [f] E. J. King, *J. Amer. Chem. Soc.*, **82**, 3575 (1960). [g] H. S. Harned and N. D. Embree, *ibid.*, **56**, 1042 (1934). [h] J. F. Dippy and F. R. Williams, *J. Chem. Soc*, 166 (1934); G. H. Jeffrey and A. I. Vogel, *ibid.*, 166 (1934); W. L. German and A. I. Vogel, *ibid.*, 912 (1935). [i] H. S. Harned and R. W. Ehlers, *J. Amer. Chem. Soc.*, **55**, 652 (1933). [j] D. H. Everett, D. A. Landsman, and B. R. W. Pinsent, *Proc. Roy. Soc.*, *Ser. A.*, **215**, 403 (1952). [k] A. I. Biggs, *J. Chem. Soc.*, 2572 (1961). [l] I. R. Bellobono and P. Baltrame, *ibid.*, 620 (1969); C. T. Mortimer and K. J. Laidler, *Trans. Faraday Soc.*, **55**, 1731 (1959). [m] R. D. Bates and G. D. Pinching, *J. Amer. Chem. Soc.*, **72**, 1393 (1950). [n] Reference 4b. [o] M. H. Leitzke, R. W. Stoughton, and T. F. Young, *J. Phys. Chem.*, **65**, 2247 (1961). [p] G. D. Pinching and R. G. Bates, *J. Res. Nat. Bur. Stand.*, **40**, 405 (1948). [q] A. K. Grybowski, *J. Phys. Chem.*, **62**, 555 (1958). [r] Reference 8b.

The experiments using bisulfate ion as the catalyst were also carried out in solutions whose stoichiometric concentrations of acid (HSO_4^-) and base (SO_4^{2-}) varied over a factor of five in a fixed ratio (Table I). Bisulfate ion, however, is a rather strong acid, and such changes in its stoichiometric concentration are by themselves sufficient to alter appreciably its extent of dissociation and thus defeat any attempt to maintain constant hydronium ion concentration. Consequently, no attempt was made to keep ionic strength constant in these experiments. Since bisulfate ion was formed in these solutions by addition of perchloric acid to aqueous sodium sulfate, sodium perchlorate was present in amount equal to the stoichiometric concentration of bisulfate; the actual ionic strength of the reaction mixtures lay in the range 0.02–0.09 *M*. Changes in the amount of hydronium ion catalysis were compensated for as described above for the other catalysts; in this case, however, choice of an ion-size parameter was of some consequence. Calculations were therefore performed using three different values: 3.04*A*, the ion-size parameter used in an analysis of kinetic data on the inversion of sucrose in bisulfate–sulfate solutions;[10] 5.00*A*, the value suggested by a recent analysis of some potentiometric measurements;[11] and 4.00*A*, a rounded average of the other two values. The resultant bisulfate ion catalytic coefficients do differ significantly, $10^3 k_{HSO_4^-}$(M^{-1} sec^{-1}) = 1.91 ± 0.04(3.04*A*), 2.08 ± 0.04(4.00*A*), and 2.19 ± 0.04(5.00*A*), but the spread in these values is minor on the scale of the Brønsted relation under investigation, and the compromise value $k_{HSO_4^-}$ = 2.08 × 10^{-3} was therefore used in the correlations described below.

Two of the catalytic coefficients measured here, those for formic and acetic acids, were also determined in our

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(8) (a) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **89**, 4411 (1967); (b) A. J. Kresge, Y. Chiang, and Y. Sato, *ibid.*, **89**, 4418 (1967).

(9) R. A. Robison and R. H. Stokes, "Electrolyte Solutions," Butterworths, London, 1959, p 229.

(10) E. A. Guggenheim, D. A. L. Hope, and J. E. Prue, *Trans. Faraday Soc.*, **51**, 1387 (1955).

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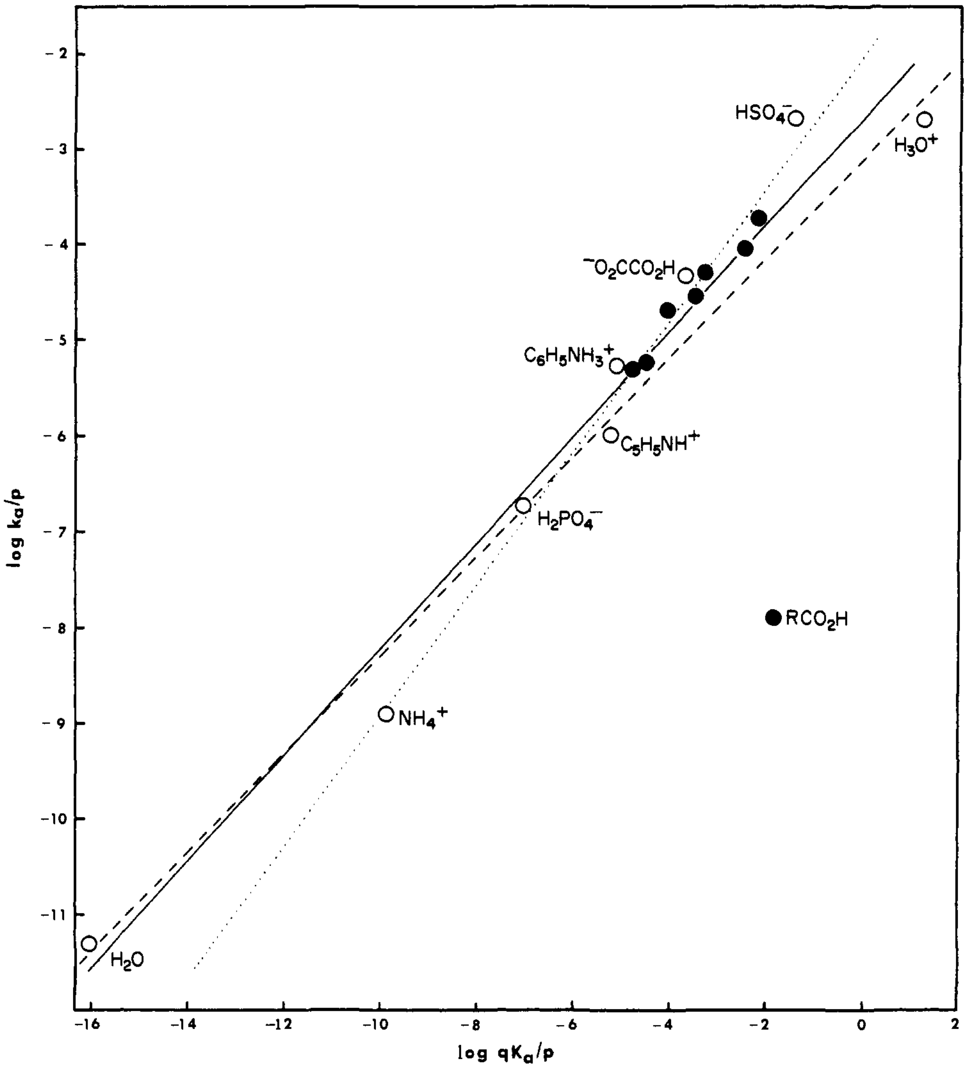

Figure 1. Brønsted plot for the detritiation of 1,3,5-trimethoxybenzene-2-*t*: solid line, correlation using all of the data; dashed line, correlation published in ref 4b; dotted line, correlation omitting H_3O^+ and H_2O points.

original work.[4b] The present and previous rate constants for acetic acid are in essential agreement (10%), but there is a discrepancy of nearly a factor of three in the case of formic acid. The reason for this difference is not clear, but, since we now have considerably more experience in this type of measurement, we are inclined to accept the more recent value. We have also reanalyzed our original data for exchange in fluoroacetic acid buffers[4b] using a more recent value for the dissociation constant of this acid;[5b,12] the revised catalytic coefficient, listed in Table II, is 9% greater than our previously published value.

Discussion

All of the catalytic coefficients currently available for the acid-catalyzed detritiation of 1,3,5-trimethoxybenzene-2-*t* are collected in Table II; they are also displayed in the form of a Brønsted plot as Figure 1. The principal difference between this and our original Brønsted relation for this reaction[4b] is, of course, the addition of eight new catalytic coefficients for five carboxylic acids, two ammonium ions, and bisulfite ion. The rate constant for formic acid, one of the original catalysts, has also been changed significantly, and the treatment of statistical factors has been revised somewhat. In our previous work, we took p, the number of equivalent, dissociable protons in the catalyst acid, to be unity for H_3O^+, NH_4^+, and H_2O, *i.e.*, we considered acids to be polybasic only when multiple acidic protons are attached to different atoms.[13] Current usage, however, favors equating statistical factors with symmetry numbers.[14] We now follow this convention by using $p = 2$ for H_2O, $p = 3$ for H_3O^+ and $C_6H_5NH_3^+$, and $p = 4$ for NH_4^+; we have, however, retained q, the number of basic sites in the catalyst conjugate acid, as unity for H_3O^+. Such changes in symmetry number have little effect on a Brønsted relation encompassing the whole range of catalyst acidity from H_3O^+ to H_2O; in less extensive correlations catalysts are more likely to be of the same type, and here, of course, statistical factors make no difference at all.

The best (least-squares) line through the points of Figure 1 has a slope of 0.56 ± 0.03; this is hardly

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(12) R. P. Bell and A. T. Kuhn, *Trans. Faraday Soc.*, 59, 1789 (1963).

(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 158.

(14) S. W. Benson, *J. Amer. Chem. Soc.*, 80, 5151 (1958); V. Gold, *Trans. Faraday Soc.*, 60, 739 (1964); D. M. Bishop and K. J. Laidler, *J. Chem. Phys.*, 42, 1688 (1965); J. N. Murrell and K. J. Laidler, *Trans. Faraday Soc.*, 64, 371 (1968).

different from the Brønsted exponent provided by the original set of data: 0.52 ± 0.01.[4b] However, whereas in the original correlation no catalytic coefficient deviated from the regression line by much more than a factor of two, there are striking departures from the present relationship: the rate constant for bisulfate ion is too large by a factor of six, and those for hydronium and ammonium ions are small by factors of four and five, respectively. Thus, the addition of more data has modified the correlation enough to reveal grossly deviant behavior. These deviations are, on the whole, rather similar to those observed recently for other rate-determining proton transfers from acid to substrate,[5] and they are reminiscent also of the behavior of some general acid catalyzed reactions proceeding through preequilibrium proton transfer.[15a]

It is of interest to examine these deviations in some detail. The hydronium ion is in general a poorer catalyst than expected on the basis of Brønsted relations,[6,15b] and the factor of four deviation mentioned above can be increased to ten if the comparison is made, as is generally done, to a line based on carboxylic acid data alone; the latter form a moderately good Brønsted relation in the present case with $\alpha = 0.59 \pm 0.05$. It can be argued, however, that the hydronium ion should not be compared to carboxylic acids, for catalysts of different charge type are known to produce different Brønsted relations in base-catalyzed reactions.[15c] In the present case, the three positively charged catalysts, hydronium, pyridinium, and ammonium ions, do in fact lie quite close to a line parallel to and about a factor of four below the best line through all of the data. The point for anilinium ion, however, misses this correlation by a wide margin: it lies even above the regression line through the carboxylic acid data. It may be significant that anilinium ions are also better catalysts than carboxylic acids in the detritiation of azulene.[5a]

This separation of catalysts into groups according to charge extends to anion acids as well: bisulfate, bioxalate, and biphosphate ions form a good Brønsted relation of their own with $\alpha = 0.71 \pm 0.01$. On this basis, of course, bisulfate ion is no longer a deviant catalyst. It is worthy of note in this connection that the bioxalate point does not deviate very much from the correlation based on monocarboxylic acids. This is contrary to the behavior reported for carboxylic acids and dicarboxylic acid monoanions in the detritiation of azulene,[5a] but statistical factors were not used in that work; when these are included, the data for the two kinds of carboxylic acids lie closer together, although they still define two lines of different slope.

It is interesting also that the data for the present reaction afford a good Brønsted relation if the hydronium ion and water points are not used in the correlation; none of the remaining thirteen catalytic coefficients deviates from the regression line, whose slope is 0.69 ± 0.03, by more than a factor of two (Figure 1, dotted line). The hydronium ion and water points, of course, miss this line by wide margins: by factors of 30 and 60, respectively. In a sense, deviant behavior for these two acids could be expected, for the concentration of water molecules in dilute aqueous solution, 55 *M*, is used in assigning conventional acidity constants to both of these catalysts; since water is a highly associated liquid, it might make better chemical sense to use the concentration of free water molecules instead.[8b,16] There is unfortunately little agreement on the value of this quantity at present, but 0.35 *M*, the number required to bring the point for hydronium ion catalysis into agreement with the Brønsted relation based on all data except the hydronium ion and water points, is not unreasonable. For catalysis by water, the concentration of water in water enters into the calculation of the catalytic coefficient as well as the acidity constant; since these two uses offset one another, incorrect values will result in smaller deviations from Brønsted correlations. In the present case, unfortunately, the water point misses the Brønsted relation by a factor twice the deviation of the hydronium ion point; the water reaction here, however, is a very slow process (half-life = *ca.* 45 years), and its measurement may be subject to more than the usual experimental uncertainty.

These arguments show that Brønsted relations with α's ranging from 0.56 ± 0.03 to 0.71 ± 0.01 can be constructed for the acid-catalyzed detritiation of 1,3,5-trimethoxybenzene. This variability in Brønsted exponent has some bearing on a use to which Brønsted relations have recently been put. There is reason to believe that α for an A-SE2 reaction measures the extent of proton transfer at the rate-determining transition state.[17,18] This kind of information can also be obtained in other ways, particularily from isotope effects[19] and kinetic acidity dependence in concentrated acids,[20] and a comparison of results obtained by these methods with numerical values of Brønsted exponents is beginning to be made. The above demonstrated variability of α, however, indicates that this parameter is indefinite insofar as its value depends on an arbitrary choice of catalyst acids. It suggests also that the extent of proton transfer at the transition state of a proton transfer reaction may be a function of the catalyst type, and that, for example, the results obtained from isotope effects and kinetic acidity dependence, where the hydronium ion is the catalyst, might better be compared to a Brønsted exponent derived from positively charged acids.

This variability of the Brønsted exponent also makes it difficult to say whether or not the present Brønsted relation is curved. Certainly, no sharp curvature such as that observed in very rapid proton transfers between oxygen and nitrogen atoms[7] is present (Figure 1), nor is any to be expected, for this reaction involves proton transfer to carbon in a substrate which undergoes extensive structural reorganization upon protonation, and all reaction rates are well below diffusion-controlled limits. But this does not exclude a gently curving correlation whose nonlinearity could be seen only by examining the behavior of

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(16) R. P. Bell, *Trans. Faraday Soc.*, 39, 253 (1943).

(17) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 238; R. A. Marcus, *J. Phys. Chem.*, 72, 891 (1968).

(18) See, however, F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *J. Amer. Chem. Soc.*, **91**, 4002 (1969); A. J. Kresge, *ibid.*, **92**, 3210 (1970).

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(20) A. J. Kresge, R. A. More O'Ferrall, L. E. Hakka, and V. P. Vitullo, *Chem. Commun.*, **46**, (1965).

catalysts which differ by many orders of magnitude in acidity. Examination of Figure 1 shows no such moderate curvature, but even if such an overall trend could be discerned, its significance would be obscured by the changes in catalyst structure required to cover the range of this plot.

Brønsted relations are available for two other aromatic hydrogen exchange reactions, the detritiations of azulene and guaiazulene.[5a] Comparison of these with the present correlation should of course be done on the basis of similar catalysts, preferably of a single structural type, and this effectively limits the examination to relationships based on catalysis by carboxylic acids. The value of α based on all of the carboxylic acid data for trimethoxybenzene is 0.59 ± 0.05, and those for azulene and guaiazulene are 0.61 ± 0.07 and 0.52 ± 0.10, respectively. It must be borne in mind, however, that these correlations use observed detritiation rate constants, which are functions of protonation rate constants, k_1, and intramolecular isotope effects, k_H/k_T: $k_{obsd} = k_1/(1 + k_H/k_T)$.[8a] These isotope effects are known to vary in magnitude in a regular way with changes in catalyst acidity and substrate basicity,[21] and Brønsted exponents based on k_{obsd} will therefore be somewhat different from Brønsted exponents based on k_1. The latter, of course are the quantities of significance in comparisons of different substrates and they can be estimated[8b] as α = 0.68 ± 0.06, 0.67 ± 0.07, and 0.56 ± 0.10 for the carboxylic acid catalyzed detritiation of trimethoxybenzene, azulene, and guaiazulene, respectively. Since the basicity of these substrates[5a,22] increases in this same order, and since proton transfer is expected to be most complete at the transition state of the most weakly basic substrate, this order of Brønsted exponents is quite reasonable.

Experimental Section

Materials. 1,3,5-Trimethoxybenzene-2-*t* was prepared from 2,4,6-trimethoxyphenyllithium and tritiated water by the method already described.[4a] All other materials were obtained commercially in best available grades; reagent-quality substances were used directly and lesser grades were purified by standard methods.

Kinetic Procedure. Appropriate volumes of wholly aqueous buffer and substrate solutions were allowed to equilibrate with a bath operating at 24.62 ± 0.02°; they were then mixed and replaced in the bath. At suitable time intervals, samples were withdrawn by pipet (5 or 10 ml) and were quenched in twice the amount of aqueous alkali needed to neutralize the buffer acid completely. These solutions were then transferred to neoprene-stoppered separatory funnels with Teflon taps (glass-tapped funnels require stopcock grease which, unless renewed frequently, becomes contaminated and leads to erratic results) and were extracted with toluene (15 ml). For runs in bisulfate buffers where the decrease in aromatic radioactivity was being followed, these toluene extracts were dried over calcium chloride and aliquots of dried solution were assayed by liquid scintillation counting in toluene-based counting solution. With all other buffers, exchange was monitored by following the increase in aqueous radioactivity; in these cases, aqueous fractions were separated from original toluene extracts, were washed again with 15-ml portions of toluene, and aliquots of twice-extracted solutions were assayed in Bray's counting solution.[23]

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A Stereospecific Total Synthesis of α-Santalol

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Abstract: A stereospecific synthetic route to the important constituent of sandalwood oil, α-santalol, from the readily accessible (−)-π-bromotricyclene is outlined. The synthesis illustrates a number of new synthetic methods including (1) chain extension using 3-trimethylsilylpropargyllithium, (2) stereo- and position-specific addition of diisobutylaluminum hydride to the lithium salt of a propargylic alcohol, and (3) stereospecific methoxycarbonylation of a vinylic iodide by nickel carbonyl and sodium methoxide in methanol. The scope of the synthesis as a general route to the structural olefinic unit RCH$_2$CH=C(CH$_3$)CH$_2$OH in which H and CH$_3$ are cis is further illustrated by the case R = n-C$_6$H$_{13}$.

The synthesis of α-santalol (**1**), a valuable ingredient in perfumery, is considerably more challenging than that of the parent hydrocarbon α-santalene (**2**),[1] because of the particular geometrical arrangement of substituents about the olefinic linkage. At the outset of this work there were no known synthetic methods capable of generating stereospecifically the type of trisubstituted unsaturated unit which occurs in **1**, *i.e.*, RCH$_2$CH=C(CH$_3$)CH$_2$OH with H and CH$_3$ cis. This fact, together with a wider interest in the development of new stereospecific methods for the synthesis of tri- and tetrasubstituted olefins and the occurrence of the same unsaturated unit in other natural products,[2] led us to study the stereospecific route to α-santalol which forms the subject matter of this paper. The synthesis which is described herein is the second to be reported from these laboratories as a result of recent investigations. The first route[3] involved the conversion of the

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(1) For syntheses of α-santalene see (a) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, **79**, 5773 (1957), and (b) E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967).

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