Physical Organic Chemistry of Benzisoxazoles. II. Linearity of the Brønsted Free Energy Relationship for the Base-Catalyzed Decomposition of Benzisoxazoles

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Abstract: The catalytic constants for the reactions of 55 of the possible pairs of eight substituted benzisoxazoles with 12 tertiary amines in water at 30° vary over a range of 10^6, yet are quantitatively approximated by the equation: $\log k_{\mathrm{cat}} = 0.721\mathrm{p}K_{\mathrm{amine}} + 0.614(14 - \mathrm{p}K_{\mathrm{cyanophenol}}) - 11.9$. An examination of the above catalytic constants, together with those involving water or hydroxide ion, fails to provide evidence for a change in selectivity with reactivity for the base catalyzed E2 elimination of benzisoxazoles, despite a total variation in rate of 10^{11}. Kinetic isotope effects for three 3-^{2}H-substituted benzisoxazoles showed no significant variation over a range of catalytic constant values of 10^9. The generality and implications of these observations are discussed.

The Brønsted relationship for proton transfer processes has been the subject of numerous recent reviews and summaries,[1] all of which present the conclusion, anticipated by Brønsted[2] and most authoritatively advanced by Eigen,[1a,3] that a Brønsted coefficient must be regarded as a local constant which varies continuously between zero and one over a sufficiently large pK_a range. This conclusion has been drawn from interpretations of both theoretical models[4] and from experimental evidence. It has been apparent from the outset that problems in experimental design create interpretive ambiguities for slopes of Brønsted plots, while the theoretical models can be challenged for their assumptions. As a result, despite its widespread acceptance, it seems to us that the hypothesis of intrinsic Brønsted curvature must be regarded as tentative and conjectural, at least until more incisive evidence is available.

Some years ago, with the hope of obtaining a more convincing experimental case concerning Brønsted slopes, we were led to examine the Brønsted behavior of the base-catalyzed isomerizations of benzisoxazoles—reactions which we believe to be less susceptible to ambiguity than those of acids previously studied.[5] This paper has three aims: to present the case for the incisiveness of the benzisoxazole system and the experimental evidence for benzisoxazole Brønsted behavior, to inquire briefly into the generality of the conclusion drawn from the benzisoxazole study, and to comment on the effect of these observations on the validity of the widely held notion of the unselective rapid reactant.

Three kinds of experimental ambiguity can prevent meaningful interpretation of curvature or linearity of a Brønsted plot. (1) The role of acid–base catalysis for the mechanism of the reaction may be obscure. (2) The catalyst strengths may vary over a pK_a range which is insufficient to establish curvature or linearity. For example, most of the fast kinetic data for proton transfers between oxygen or nitrogen bases have a catalyst pK_a range of only five to seven for which rate processes are chemically determined.[1a] (3) Different pK_a regions may be dominated by catalyst groups of differing efficiencies, resulting in false curvature or linearity. Particularly ambiguous are Brønsted correlations which involve a few catalyst groups which are of different charge type, steric environment, or heteroatom, but more subtle differences can also be important, as indicated by the differing catalytic efficiencies for the three amine classes.[6]

Given a proton transfer reaction of known mechanism, there are two procedures which may reliably determine the curvature of the Brønsted coefficient. If the reaction can be studied over a large range of catalyst strengths (12–15 pK_a units), use of enough catalyst groups that no pK_a region is dominated by a catalyst group of a single structural type can in principle provide a convincing case for intrinsic behavior. In practice, few systems can be so studied. The careful and exhaustive work of Brønsted[2,4b] and Bell[7] and coworkers on reactions of the hemiacetal decomposition class indeed provides sufficient catalyst representation, but has been criticized as mechanistically ambiguous.[1a,g,7] Eigen's study[1a] of acetylacetone enolization allows a pK_a range of at least 15 units, and his data are usually interpreted as demonstrating curvature,

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[2] J. N. Brønsted and K. Pederson, *Z. Phys. Chem.*, **108**, 185 (1923); J. N. Brønsted and E. A. Guggenheim, *J. Amer. Chem. Soc.*, **49**, 2552 (1927).

[3] M. Eigen, *Discuss. Faraday Soc.*, **No. 39**, 7 (1965).

[4] (a) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **34**, 11 (1938); (b) R. P. Bell, *Proc. Roy. Soc., Ser. A*, **154**, 414 (1936); "Acid-Base Catalysis," Oxford University Press, London, 1949, Chapter 8; "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter 10; (c) R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968); J. R. Murdoch, *J. Amer. Chem. Soc.*, **94**, 4410 (1972).

[5] M. Casey, D. Kemp, K. Paul, and D. Cox, *J. Org. Chem.*, **38**, 2294 (1973); a detailed discussion of the issues of this paper may be found in M. T. Link, Ph.D. Thesis, M.I.T., 1968.

[6] R. P. Bell and G. L. Wilson, *Trans. Faraday Soc.*, **46**, 407 (1950); H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957); see also ref 4b and A. J. Kresge and Y. Chiang, *ibid.*, **95**, 802 (1973).

[7] R. P. Bell and W. Higginson, *Proc. Roy. Soc., Ser. A*, **197**, 141 (1949); R. P. Bell and P. Evans, *ibid.*, **291**, 297 (1966); R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

yet there is a systematic scatter in the plot, and an equally viable interpretation appears to us to involve a negative deviation of points for hydroxide and water, and the appearance of all other points on a pair of parallel lines.

An alternative has been devised by Bell which addresses a slightly different issue. Conventional curvature of a Brønsted plot can be defined as the second derivatives f_{xx} or f_{yy} which appear as coefficients of the second-order terms of a Taylor expansion of log k_{cat} in the $\mathrm{p}K_{\mathrm{a}}$ values of the reactant and product acids, HX and HY. The Bell analysis determines the variation of Brønsted coefficient for a series of structurally related substrates when each is allowed to react with a constant series of catalysts; the result evaluates the magnitude of the Taylor coefficient f_{xy}, which corresponds to the effect on catalytic constant of joint changes in reactivity of substrate and catalyst. Provided substrates are available which differ appreciably

$$\mathrm{Y}^- + \mathrm{HX} \xrightarrow{k_{\mathrm{cat}}} \mathrm{HY} + \mathrm{X}^-$$

$${}^1/_2 f_{xx}(\Delta X^2) + f_{xy}(\Delta X \Delta Y) + {}^1/_2 f_{yy}(\Delta Y^2) \qquad (1)$$

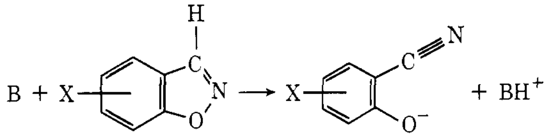
$$X = \mathrm{p}K_{\mathrm{HX}},\ Y = \mathrm{p}K_{\mathrm{HY}}$$

$$f_{xy} = \partial^2 \log k_{\mathrm{cat}}/\partial \mathrm{p}K_{\mathrm{HX}} \partial \mathrm{p}K_{\mathrm{HY}}$$

in reactivity, but only slightly in structure, one can evaluate the f_{xy} term by noting the change in the conventional Brønsted coefficient as the substrate reactivity is varied. Provided the same set of bases is used for each substrate, differences in base efficiency should appear identically for each substrate and cancel in the analysis. If these conditions are met, this approach largely eliminates the ambiguity of varying catalyst efficiency which plagues a conventional Brønsted plot.

In his study,[8] Bell employed 11 ketones and keto esters and measured rates of enolization reactions with four bases. The resulting β values were observed to vary monotonically with ketone acidity. This result has deservedly been quoted[1] as the best available evidence in support of the view that over a sufficiently wide reactivity range, Brønsted plots show curvature. Yet in discussing this result, Bell considered an ambiguity which weakens this conclusion, but which later citations have ignored. Although the $\mathrm{p}K_{\mathrm{a}}$ ranges for mono- and β-dicarbonyl substrates overlap, the β values are surprisingly constant within each structural class. One could therefore conclude that the study supports a constancy of β values for the acetone derivatives, and a significantly lower β value for the dicarbonyl substrates. The observed variation in selectivity could then be attributed to the very artifact which Bell's procedure sought to avoid, irrelevant variation in reactivity pattern through too large a change in substrate structural type. Clearly, Bell's procedure can only be carried out unambiguously with a class of substrates which preserve geometry and gross electronic structure, despite considerable variation in reactivity.

The benzisoxazoles appear to be such a class. The benzisoxazoles undergo a rapid base-catalyzed isomerization to salicylonitriles. Elsewhere[5] we have described the experimental results which lead to the conclusion that the mechanism of these reactions is a simple E2 elimination. Rates of these reactions are strongly influenced by benzo substitution, yet the reactions occur cleanly and irreversibly in all cases. Most important, the geometry of the reacting bonds is well defined, no conformations are possible at the reacting centers, and the substituents which result in rate increases are well removed from the approaching base and the reacting bond region. This case therefore appears to be limiting, in the sense that unexpected or uninterpretable interactions are expected to be minimal, and the series of benzisoxazoles therefore constitute a substrate class as well defined as one is likely to encounter. For these reasons this system appears to offer the best opportunity yet available for testing the question of the intrinsic variability of Brønsted coefficients.



Experimental Section

Materials. Trimethylamine hydrochloride and methyldiethanolamine were prepared as described previously.[5] Quinuclidine hydrochloride (Aldrich) was recrystallized from ethanol and dried *in vacuo*, mp >300°; 3-quinuclidone hydrochloride (Aldrich) was recrystallized from aqueous 2-propanol and dried *in vacuo*, mp 313° dec (lit.[9] mp 311–313°); 3-quinuclidinol (Aldrich) was recrystallized twice from aqueous acetone and dried *in vacuo*, mp 219.0–220.0° (lit.[10] 225–227°). Triethylamine and *N*-methylmorpholine were distilled from BaO in a 56-cm spinning band column, then converted to their hydrochlorides with a slight excess of hydrogen chloride in ether; the respective melting points, after three recrystallizations from ethanol, were 257.0–258.0° (lit.[11] mp 253–254°) and 207.5–208.5° (lit.[12] mp 205°). *N*-Methylpiperidine (Aldrich), pyridine, 4-picoline (Eastman), and 3,4-lutidine (Aldrich) were dissolved in ether and treated with a slight excess of hydrogen chloride. The resulting precipitates were recrystallized three times from ethanol to yield solids with respective melting points: 210.5–211.5, 144.5–145.5, 162.0–163.0, and 235.0–236.0°.

Triethanolamine (Aldrich) was dissolved in ethanol and treated with a slight excess of 1:2 hydrochloric acid–ethanol. The solution was cooled, and the precipitate was collected, recrystallized three times from aqueous ethanol, and dried, mp 177.0–178.0° (lit.[13] mp 177°). The hydrochlorides were stored in a desiccator and dried *in vacuo* for several hours before use.

Substituted benzisoxazoles were prepared as described previously.[5] After purification the samples were dried *in vacuo* and stored at 3° in a desiccator in foil-wrapped vials. Benzisoxazole and 5- and 6-methoxybenzisoxazoles were distilled in a short path still (1 mm) within a month of use.

KCl (Baker Reagent Grade) and acetonitrile (Eastman Spectrograde) were used without purification. KOH solution was prepared by dissolving Baker reagent grade KOH in boiled, distilled water, and was standardized against dried potassium hydrogen phthalate. Hydrochloric acid was prepared from a commercial "Acculute" sample by dilution with boiled, distilled water and was standardized using potassium hydroxide solution.

Buffer solutions were Fisher pH 4.01, 6.98, and 9.90 buffers; new buffers were opened every 2 or 3 days and were checked against buffers used on the preceding day; agreement within ±0.02 pH unit was almost always achieved.

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(9) L. H. Sternbach and S. Kaiser, *J. Amer. Chem. Soc.*, **74**, 2215 (1952).

(10) C. A. Grob, A. Kaiser, and E. Renk, *Helv. Chim. Acta*, **40**, 2174 (1957).

(11) I. Heilbron, A. H. Cook, H. M. Bunsbury, and D. H. Hey, "Dictionary of Organic Chemistry," Vol. 5, Oxford University Press, London, 1965, p 3127.

(12) L. Knorr, *Chem. Ber.*, **22**, 2091 (1889).

(13) Reference 11, Vol. 5, p 3128.

Equipment. Volumetric glassware was Grade A Corning "Pyrex" and was used without calibration. Glassware was cleaned with chromic acid in sulfuric acid, rinsed 15 times in distilled water, and allowed to soak for at least 12 hr before use.

Acidities were measured with a Radiometer Model 4 pH meter equipped with glass (G202C) and calomel (K401) electrodes. The measurement cell was maintained at 30.0 ± 0.5° with a surrounding constant-temperature bath.

Optical density measurements were made with a Zeiss PMQII spectrometer fitted with a constant-temperature cell block through which water was circulated by means of a Haake Model F constant-temperature bath. Kinetic runs with half-lives of less than 1 day were conducted in cuvets within the spectrometer; the temperature variation within the cell was observed to be less than 0.05°. Thermometers calibrated with an NBS thermometer were used for bath measurements. Kinetic runs with half-lives of longer than 1 day were carried out in sealed tubes in a cylindrical constant-temperature bath equipped with stirrer, heaters, and thermoregulator.

Kinetics Procedure. Amine buffers were prepared with an amine–amine hydrochloride ratio of 3:1. A weighed sample of freshly dried amine hydrochloride was transferred quantitatively to a 1-l. volumetric flask and dissolved in 900 ml of boiled, distilled water. The calculated amount of standard KOH solution was added from a buret, and the solution was brought to 20° and filled to the mark. For quinuclidinol and methyldiethanolamine, the amine was weighed, dissolved, and treated with standard HCl solution. The concentration of amine was checked by pH titration; the average of three titrations was used as the amine concentration. This value always agreed within 5% or less with the amine concentration calculated from reagent quantities.

For a given series of kinetic runs, appropriate volumes of amine buffer were measured by buret into 100-ml volumetric flasks containing sufficient KCl to bring the final ionic strength to 0.10. The flasks were filled to within 3 or 4 ml and equilibrated for 15 min at 30°. If necessary (pH >9) the solutions were each adjusted to the pH observed for the 0.010 *M* buffer by the addition of 0.5 *M* KOH solution. The original pH of each solution was recorded for use in calculating the pK_a of the amine. After the pH corrections had been made, the flasks were filled to the mark, and the solution was used to rinse and fill a uv cuvet which was then equilibrated in the cell block for 15 min. The reaction was conducted by introducing 1–2 μl of a solution of benzisoxazole into the cell (concentration such that the A_∞ value was 0.6), shaking the cell, and returning it quickly to the block. For 6-nitrobenzisoxazole, the least soluble benzisoxazole, acetonitrile solution was carefully injected into an upper layer consisting of 1–2 micro drops of acetonitrile, whereupon the cell was stirred and shaken. Rate data were usually taken for 2–3 half-lives; the A_∞ value was approximated either by measurement at 10 half-lives, or more commonly by quenching the reaction after 2–3 half-lives by the addition of one-quarter pellet of KOH to the cuvet. These methods were repeatedly observed to give the same A_∞ value. For reactions in which the pH of the solution was less than 2 units greater than the pK_a of the salicylonitrile, the KOH A_∞ value was corrected for the amount of product which would be un-ionized at t_∞. The pK_a value used in this correction was measured using buffer solutions identical with those used in the kinetic runs. For reactions with half-lives of more than 2 days, the reaction was run in sealed ampoules; the prepared buffer solution was divided into ten portions, eight of which were used for data points and one each for the first and last points of the run. For runs with half-lives of less than 1 min, A_t values were recorded as they reached multiples of 0.05 by pushing a calibration marker on a strip chart recorder set at a paper speed of 10 cm/min. Fast reactions were conducted in a capless cuvet; after temperature equilibration of a cuvet containing a glass stirring rod, the benzisoxazole solution was injected and the contents was vigorously stirred. Readings could be started within 5–10 sec and runs with half-lives as short as 10 sec could be studied. For determination of kinetic isotope effects, identical buffer solutions were used for hydrogen and deuterium substrates, and rate measurements were carried out largely with paired substrates in adjacent cuvettes.

Determination of Amine pK_a's. The pK_a values of amines at 30.0° and μ = 0.10 (KCl) were estimated from the known concentrations of amine and amine cation and the experimental value of pH. At pH's above 9 the amine cation concentration was taken to be equal to the sum of chloride and hydroxide concentrations. The unadjusted pH of each solution was used to calculate the pK_a of the amine.

Analysis of Data. The pseudo-first-order rate constants were obtained graphically from at least eight A_t measurements, plotting $\ln (A_\infty - A_0)/(A_\infty - A_t)$ *vs.* time. Slopes determined by least-squares analysis agree to within 2% or less with slopes determined graphically. Usually standard deviations of less than 1% were observed. The catalytic constants for amines were obtained by a least-squares fitting of pseudo-first-order rate constants as a linear function of amine concentration. Each of the 55 catalytic constants of the study was determined by an average of 6.3 pseudo-first-order rate constants, with a range of 5–11; the larger number of data points was used for amines of low catalytic efficiency, *e. g.*, quinuclidine and triethylamine. On the average, the amine concentration was varied by 4.8-fold; most cases fell within a variation range of 3.5–7; in four cases a range of threefold was studied, while in six cases the range was 10–12-fold. If the deviation of a data point from its calculated value was tenfold greater than that of any other point, the point was discarded. The average range of contributions of amine catalysis to observed rate constants was smallest for quinuclidine (15.6%, 5.9–21.5%) and largest for 3,4-lutidine (46.5%, 27.5–74.0%). The average range was 28%. (The error in the slope term of a linear least-squares fitting is, for equal numbers of evenly spaced measurements, inversely proportional to the spread or total range of data points, but insensitive to their magnitude at constant spread.)

Logs of catalytic constants were fitted to linear three- and four-term equations by the method of least squares, with the assumption that I/σ^2 equals the weight matrix.[14]

Results

Since pK_a values for the amines used in this study are not available for the conditions of the study, they were measured at 30° and μ = 0.10 (KCl), using the catalytic buffer mixtures. The results given in Table I clearly compare well with existing literature data; also included in the table are pK_a values for the salicylonitrile products and kinetic pK_a values for the amines which will be defined subsequently. As indicated else-

Table I. pK_a Values for Amines and Salicylonitriles

Base	pK_a[a] 30°, μ = 0.1 (KCl)	pK_a[b]	"Kinetic pK_a"[c]	δpK_a[d]
		A. Amines		
Quinuclidine	10.88	10.95	10.81 (0.48)	(−0.07)
Triethylamine	10.65	10.67	10.44 (0.20)	(−0.21)
N-Methylpiperidine	10.07	10.07, 30°	9.98	(−0.09)
Trimethylamine	9.75	9.69, 30°	10.08 (0.08)	(+0.33)
3-Quinuclidinol	9.71		9.87 (0.19)	(+0.16)
Methyldiethanolamine	8.53	8.52	8.52 (0.11)	(−0.01)
Triethanolamine	7.76	7.67	7.35 (0.08)	(−0.41)
N-Methylmorpholine	7.49	7.38	7.73 (0.09)	(+0.24)
3-Quinuclidinone	7.27		7.55	(+0.28)
3,4-Lutidine	6.57	6.46	6.24	(−0.33)
4-Picoline	6.12	6.08	5.86	(−0.04)
Pyridine	5.13	5.21	5.31	(+0.18)
Hydroxide			12.27 (0.17)	

2-Hydroxybenzonitrile	pK_a	2-Hydroxybenzonitrile	pK_a
B. Salicylonitriles,[a] 30°, μ = 0.1 (KCl)			
5-Methoxy	7.4	4-Chloro	6.1
Unsubstituted	6.9	4-Nitro	5.2
4-Methoxy	6.6	5-Nitro	4.1
5-Chloro	6.4	5,7-Dinitro	0.6

[a] Determined in this study or quoted from ref 5. [b] Values cited from D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965. Unless otherwise quoted, T = 25° and μ = 0. [c] Kinetic pK_a values are defined in the Results. Standard deviations are given in parentheses for those cases for which the pK_a value is the average of four or more estimates. [d] δpK_a = kinetic − thermodynamic pK_a.

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Table II. Catalytic Constants for the Reactions of Tertiary Amines with Substituted Benzisoxazoles, Water, 30°, $\mu = 0.1$ (KCl)

Base	k_{cat}, M^{-1} sec^{-1} — Benzisoxazole: 5-MeO	H	6-MeO	5-Cl	6-Cl	6-NO$_2$	5-NO$_2$	5,7-Dinitro
Quinuclidine	7.87×10^{-3} (1.4)	2.70×10^{-2} (0.28)			1.20×10^{-1} (0.10)	5.32×10^{-1} (0.70)		
Triethylamine	1.86×10^{-3} (0.61)	1.85×10^{-2} (0.05)	1.88×10^{-2} (0.22)	3.97×10^{-2} (0.30)	8.25×10^{-2} (1.2)	1.60×10^{-1} (0.01)	8.20×10^{-1} (0.5)	
N-Methylpiperidine		8.22×10^{-3} (0.52)					3.60×10^{-1} (0.18)	
Trimethylamine	3.80×10^{-3} (0.17)	1.01×10^{-2} (0.30)	1.44×10^{-2} (0.055)	2.12×10^{-2} (0.08)	3.15×10^{-2} (0.23)	8.83×10^{-2} (0.73)	4.20×10^{-1} (0.4)	
3-Quinuclidinol	2.12×10^{-3} (0.12)	5.73×10^{-3} (0.38)			2.48×10^{-2} (0.38)	9.03×10^{-2} (0.35)		
Methyldiethanolamine	2.28×10^{-4} (0.26)	5.58×10^{-4} (0.26)	9.37×10^{-4} (0.80)	1.53×10^{-3} (0.03)	2.36×10^{-3} (0.05)	7.75×10^{-3} (0.30)	3.71×10^{-2} (0.16)	6.10 (0.6)
Triethanolamine	4.22×10^{-5} (0.05)	8.08×10^{-5} (0.47)	1.45×10^{-4} (0.075)		3.48×10^{-4} (0.18)	1.05×10^{-3} (0.03)	6.20×10^{-3} (0.35)	7.87×10^{-1} (0.82)
N-Methylmorpholine	7.40×10^{-5} (0.22)	1.75×10^{-4} (0.67)	3.03×10^{-4} (0.03)	3.98×10^{-4} (0.19)	7.47×10^{-4} (0.66)	2.12×10^{-3} (0.07)	9.10×10^{-3} (0.30)	1.11 (0.09)
Quinuclidone	5.85×10^{-5} (0.22)				4.48×10^{-4} (0.18)	1.61×10^{-3} (0.58)		
3,4-Lutidine							6.35×10^{-4} (0.61)	1.40×10^{-1} (0.07)
4-Picoline							3.52×10^{-4} (0.03)	7.35×10^{-1} (0.03)
Pyridine							1.37×10^{-4} (0.02)	3.02×10^{-2} (0.08)

where,[3] the salicylonitrile acidities correlate accurately, corr coeff = −0.996, with log k_{OH^-} for benzisoxazole decomposition.

Practical considerations limited the experimental study to 56 of the 96 possible combinations of eight benzisoxazoles and 12 amines; the weak bases, pyridine, 4-picoline, and 3,4-lutidine, were employed only with the two most reactive benzisoxazoles, and the more basic amines could not be practicably studied with 5,7-dinitrobenzisoxazole.

As the previous results indicate,[3] catalytic constants can be obtained for amine-catalyzed benzisoxazole decompositions using KCl to maintain constant ionic strength, provided the amine–amine salt ratio is maintained greater than 3. Amine concentrations were varied within the concentration range of 0.001–0.015 *M*; KCl thus contributed at least 85% of the total salt.

Satisfactorily linear plots of pseudo-first-order rate constants as functions of amine concentration were obtained for all amine–benzisoxazole pairs studied. Despite the appreciable contribution made by hydroxide catalysis to the overall catalysis at the high buffer ratios of the study, the average correlation coefficient of these plots was 0.98, and for 38 of the 56 plots, the coefficients were greater than 0.99.

Table II gives the catalytic constants and their standard deviations for the reactions of amines with benzisoxazoles. It may be noted that the least-squares errors in the amine catalytic constants of Table II appear to be randomly distributed with an average standard deviation of 0.24. Table III gives catalytic constants for the reactions of hydroxide ion and water with benzisoxazoles.

Presented in Figure 1 are data for primary kinetic isotope effects for reactions of benzisoxazoles bearing deuterium in the 3 position, as a function of log k_{cat} for the protium reaction. To maximize precision in these determinations, protium and deuterium substrates

Table III. Catalytic Constants for the Reactions of Benzisoxazoles with Hydroxide and Water, Water, 30°, $\mu = 0.1$ (KCl)

Benzisoxazole	No. of measurements[a]	pH range[a]	k_{OH^-},[b] M^{-1} sec^{-1}
	A. Hydroxide		
5-MeO	9	7.7–11.1	0.18 (0.01)
H	10	8.0–11.1	0.34 (0.02)
6-MeO	5	8.2–10.9	0.38 (0.02)
5-Cl	5	7.9–11.0	0.91 (0.01)
6-Cl	8	7.7–11.1	1.21 (0.10)
6-NO$_2$	8	7.7–11.1	5.25 (0.38)
5-NO$_2$	12	5.8–10.9	15.35 (0.55)
5,7-Dinitro	7	5.1–9.0	1530 (108)
Benzisoxazole	No. of measurements		k_w,[e] M^{-1} sec^{-1}
	B. Water[c]		
5-NO$_2$	3		9.2×10^{-9} (3.0)
5,7-Dinitro	3		1.3×10^{-6} (0.1)
H[d]			$\leq 2 \times 10^{-10}$

[a] Hydroxide catalytic constants were averages of intercept terms of reactions conducted with the given number of separate amines which together spanned the indicated pH range. [b] Catalytic constants are averages of $k_{intercept}/[OH^-]$, where pOH + pH = 13.630. [c] Water catalytic constants were obtained by a least-squares fit of the three intercept terms obtained at low pH with the equation: $k_{intercept} = k_{OH^-}[OH^-] + k_w$. Water contributed roughly 40% of catalysis at the lowest zero intercept for the 5-nitro- and 5,7-dinitrobenzisoxazoles. [d] No evidence of water catalysis was observed. The bound is set arbitrarily as 3% of the smallest intercept term. [e] The value of $[H_2O] = 55.5$ *M* was used.

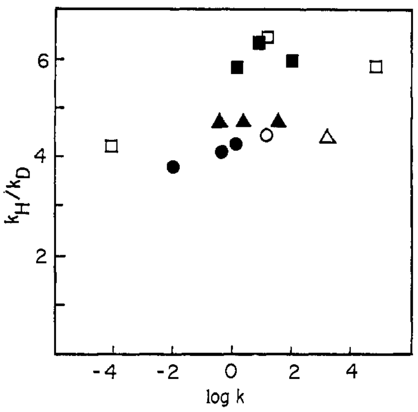

Figure 1. Variation of deuterium kinetic isotope effect as a function of log k_{cat} for benzisoxazole decompositions: (■) 5,7-dinitrobenzisoxazole data; points (left to right) correspond to water, pyridine, lutidine, acetate, *N*-methylmorpholine, and hydroxide; (▲) 5-nitrobenzisoxazole data; points correspond to *N*-methylmorpholine, methyldiethanolamine, trimethylamine, and hydroxide; (●) benzisoxazole data; points correspond to *N*-methylmorpholine, trimethylamine, quinuclidine, and hydroxide.

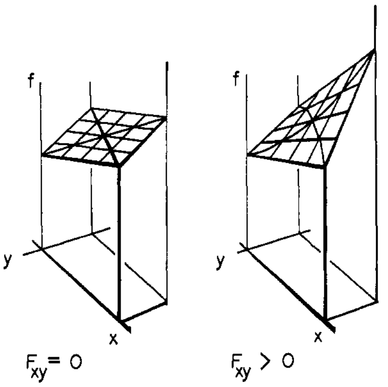

Figure 2. Effect of a contribution of the mixed partial derivative f_{xy} to the Taylor expansion of a function whose other second derivatives are zero.

were allowed to react in adjacent cuvets containing identical buffer samples. While changes in both base and benzisoxazole do result in variations, there appear to be no significant trends in the changes of these isotope effects. Perhaps the strongest generalization which can be offered is that relative to isotope effects observed with the other substrates, those arising from the 5,7-dinitrobenzisoxazoles are somewhat larger, although it should be noted that the largest effects arise with pyridines, which have not been studied with the other substrates.

Analysis of Data. The data of Table II provide 56 catalytic constants which cover a rate range of more than 10^5 and which arise from a smooth variation of the two pertinent parameters of amine basicity and benzisoxazole reactivity. With an uncertain guarantee of relevant relationship to the amine data, the hydroxide and water catalytic constants of Table III increase the total range of catalytic constants to more than 10^{11}. As indicated in the introduction, for a test of the pertinent point of this study, namely the magnitude of contribution of second derivative or curvature terms in the Taylor expansion of log k_{cat} as a function of amine and cyanophenol pK_a, data of this kind can only be used to determine the possible magnitude of f_{xy}, the central quadratic term in expression 1. Before considering the tests which have been applied to resolve this question, we consider the implications which a contribution of this term would have for the form of the data of Table II. The catalytic constants of the upper right corner of the table arise from reactions of highly reactive substrates, and the diagonal which connects this corner with the data for the weakly reactive pairs in the lower left spans the rate range of the table. On the other hand, the entries which lie on the alternative diagonal are nearly constant since they correspond to reactions which combine reactivity with inertness; it is these entries which define in a statistical sense the normal behavior of the overall system. Deviations which result from a contribution of f_{xy} will therefore be found at the extremes of the former diagonal. It is important to note that the shifting of the relative positions of a row or column through redefinition of the pK_a of an amine or benzisoxazole should have only a minor effect on the variability along a diagonal which we are seeking. The drawings of Figure 2 consider two hypothetical cases which illustrate the relative effects to be expected in the presence and absence of a contribution of f_{xy}. In this section, three methods are used to examine this question: the variation of classical and relative Brønsted coefficients with variation of substrate, the variation of reactivity of the series of substrates toward a given base, and more importantly, the least-squares fitting of three- and four-term linear equations to the data of Tables II and III.

As is widely recognized,[6] Brønsted plots tend to show marked scatter when amines are employed as bases, presumably because the factors which determine thermodynamic basicity are not identical with those which affect kinetic base strength.[15] A necessary first step in handling this problem is a restriction of attention to primary, secondary, or tertiary amines, hence the exclusive use of tertiary amines in this study; an additional control was the use of quinuclidine, 3-quinuclidinol, and 3-quinuclidinone, bases of widely different strengths but similar steric requirements. Unfortunately for practical reasons, these bases proved less convenient than the others of the study.

A typical Brønsted plot for reactions of tertiary amines with benzisoxazoles is shown in Figure 3, and the second column of Table IV presents β values obtained as slopes of eight such plots. A striking feature of the β values of the table is their constancy despite a 10^5-fold variation in benzisoxazole reactivity, but before one can draw firm conclusions on this point, attention must be paid to a serious source of error. Since somewhat different sets of amines, each with a slightly different kinetic efficacy, have been used with each benzisoxazole, the scatter of these Brønsted plots is expected to occur with a different pattern for each substrate, resulting in artifactual variations in the β values. The solution to this problem was advanced 3 decades ago by Pfluger,[16] who noted that much of the deviation from Brønsted linearity displayed by individual bases or acids occurs independently of the species with which they react, and that by defining the logarithms of catalytic constants for reactions of a single substrate as proportional to the "kinetic pK_a

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(15) For a discussion of this point, see G. W. Ceska and E. Grunwald, *J. Amer. Chem. Soc.*, **89**, 1371 (1967).

(16) H. L. Pfluger, *J. Amer. Chem. Soc.*, **60**, 1513 (1938).

Table IV. Brønsted Analyses of Benzisoxazole Decompositions

Benzisoxazole[a]	β	Corr coeff	$\beta/\beta_{5\text{-MeO}}$[b]	Corr coeff	$\beta/\beta_{5\text{-NO}_2}$	Corr coeff
5-MeO (8)	0.66 (0.06)	0.966	1.00[c]	(8)	1.00 (0.04)	0.996 (5)
H (8)	0.74 (0.06)	0.978	1.08 (0.02)	0.999 (7)	1.09 (0.03)	0.999 (6)
6-MeO (5)	0.72	0.953	1.04	0.997 (5)	1.02 (0.04)	0.995 (5)
5-Cl (4)	0.69 (0.07)	0.977	1.05 (0.05)	0.997 (4)	1.05 (0.02)	0.999 (5)
6-Cl (8)	0.72 (0.05)	0.982	1.10 (0.04)	0.996 (8)	1.08 (0.05)	0.996 (5)
6-NO_2 (8)	0.71 (0.06)	0.978	1.09 (0.05)	0.992 (8)	1.01 (0.03)	0.998 (5)
5-NO_2 (9)	0.74 (0.04)	0.990	1.00 (0.04)	0.996 (5)	1.00[c]	(9)
5,7-Dinitro (6)	0.65 (0.10)	0.945			0.91 (0.04)	0.995 (6)

[a] Numbers in parentheses give number of catalytic constants used; standard deviations are given under β values. [b] Slope of a log–log plot obtained as given in the text; numbers following correlation coefficients are number of pairs of catalytic constants used in the analysis. [c] Reference compound used for abscissa of log–log plot.

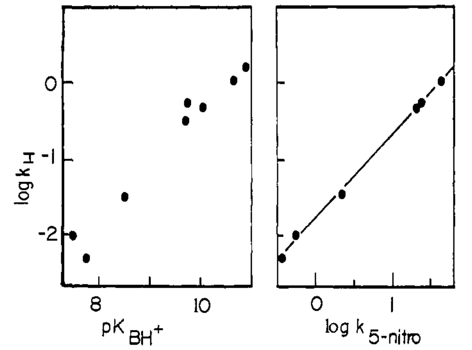

Figure 3. Brønsted plots for the tertiary amine catalyzed decompositions of benzisoxazole. Left: conventional Brønsted plot, using the respective bases, *N*-methylmorpholine, triethanolamine, methyldiethanolamine, quinuclidinol, trimethylamine, *N*-methylpiperidine, triethylamine, and quinuclidine. Right: relative Brønsted plot using log k_{cat} values for 5-nitrobenzisoxazole.

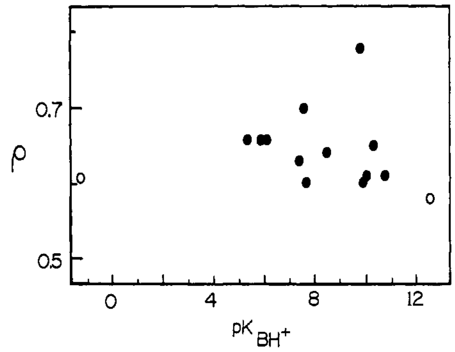

Figure 4. ρ values for benzisoxazole decompositions, defined using salicylonitriles as reference acids, plotted as functions of catalyst strength. Data points (left to right) correspond to water, pyridine, picoline, lutidine, triethanolamine, quinuclidone, *N*-methylmorpholine, methyldiethanolamine, quinuclidinol, *N*-methylpiperidine, trimethylamine, triethylamine, quinuclidine, and hydroxide. Values for 1–4, 6, and 10 are defined by results for only two benzisoxazoles.

values" of the catalysts and relating the catalytic constants for all other substrates to this scale, one can obtain relative Brønsted coefficients with great precision. A plot of this kind is given in Figure 3, and relative β values obtained with either the 5-methoxy- or 5-nitrobenzisoxazoles as standards are given in Table IV. The magnitude of the observed correlation coefficients testifies to the effectiveness of Pfluger's procedure, and the striking observation emerges that only the 5-methoxy- and 5,7-dinitrobenzisoxazoles show a reactivity pattern which differs from that of the other substrates; while both are less selective than average, the difference is slight and in our opinion cannot be taken to lie outside of the range of variation of the average.

An alternative comparison defines a ρ value as the slope of a graph of log k_{cat} for a given base as a function of the pK_a of the salicylonitriles obtained as products of the reactions. Although equivalent to the above analysis, this comparison permits inclusion of data for the oxygen bases, hydroxide and water. Figure 4 presents results of an analysis of this kind.

Although it should be noted that for six of the entries of the figure the span of catalytic constants is only 10^2, again, a strikingly consistent picture is obtained over a total range of catalytic constants of 10^{11}. Although comparison data are available for only the two most reactive substrates, it is interesting that the ρ values for water and hydroxide, the strongest and weakest bases studied, are essentially identical.

The results of the two preceding analyses imply that one should be able to approximate any log k_{cat} for a benzisoxazole decomposition by an equation (2), which

$$\log k_{cat} = \alpha pK_{phenol} + \beta pK_{amine} + \gamma \quad (2)$$

$$\log k_{cat} = \alpha' pK_{phenol} + \beta' pK_{amine} + \gamma' + \zeta pK_{phenol} pK_{amine} \quad (3)$$

is independently linear in pK_{amine} and p$K_{salicylonitrile}$; moreover, a four-term equation (3), which contains in addition a term linear in the product of the two pK_a values, should give a better fit, provided f_{xy} makes a significant contribution to the Taylor expansion of log k_{cat}. Three- and four-term least-squares analyses of the data comprising the 56 amine catalytic constants were carried out with the result shown in part A of Table V. Two points of importance arise from this analysis. First, although the coefficient, ζ, is negative, implying smaller selectivity as the reactivity of the system amine + benzisoxazole is increased, it makes a minute contribution to the overall computation, and its estimated error vastly exceeds its value.[17] Second, an insignificant improvement in overall standard deviation is observed on changing from a three- to a four-parameter approximation.

As mentioned earlier, much of the deviation observed in the above analysis results from the un-

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[17] The larger standard deviations for coefficients observed for the four-parameter analysis reflect the relative decrease in least-squares orthogonality of the pertinent sums of products; with these four parameters and the given data, there are more ways of choosing coefficients to obtain a given fit.

Table V. Least-Squares Analysis of Catalytic Constants

A. Amine Catalytic Constants				
Three parameter				
$\beta = 0.721$ (0.02)	$\alpha = 0.614^a$ (0.02)	$\gamma = -11.9$ (0.3)		$\sigma^b = 0.24$
Four parameter				
$\beta' = 0.724$ (0.1)	$\alpha' = 0.617$ (0.1)	$\gamma' = -11.9$ (0.8)	$\zeta = -0.0004$ (0.01)	$\sigma = 0.22$
B. Amine and Hydroxide Catalytic Constants, Kinetic pK_a Values				
Three parameter				
$\beta = 0.722$ (0.007)	$\alpha = 0.622^a$ (0.007)	$\gamma = -11.98$ (0.1)		$\sigma = 0.099$
Four parameter				
$\beta' = 0.767$ (0.03)	$\alpha' = 0.663$ (0.03)	$\gamma = -12.35$ (0.25)	$\zeta = -0.005$ (0.003)	$\sigma = 0.098$

[a] For the purposes of this analysis the pK_a values for phenols were defined as (14 − p$K_{\text{salicylonitrile}}$) in order that the coefficient α would be positive. Best fit coefficients are quoted with their least-squares standard deviations. [b] Standard deviation for the overall fit: $\sigma = \sqrt{\Sigma\,[\delta i^2/(n - m)]}$.

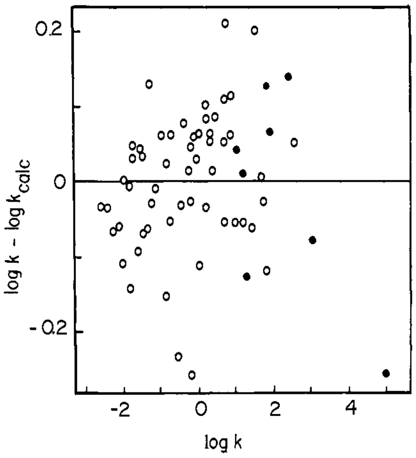

Figure 5. Variation of residuals for the three-parameter analysis of Table Vb with values of log k_{cat}: (○) amine data points; (●) hydroxide data points.

suitability of thermodynamic amine pK_a values; thus trimethylamine and *N*-methylmorpholine consistently yield k_{cat} values which are larger than expected, while triethanolamine yields smaller values. In an attempt to remove these uncertainties, we have used the catalytic constants to define kinetic pK_a values by means of eq 4

$$\text{kinetic p}K_a \equiv \frac{\log k_{\text{cat}} - \gamma - \alpha \text{p}K_{\text{phenol}}}{\beta} = \frac{\log k_{\text{cat}} + 11.9 - 0.614\ \text{p}K_{\text{phenol}}}{0.721} \qquad (4)$$

and the three-parameter data of Table VA. Average values of these kinetic basicities are reported in the last column of Table I, along with standard deviations for cases in which more than four estimates were available.[18] The small standard deviations for the cases which show the largest difference between kinetic and thermodynamic pK_a values demonstrate that the correction is real; as expected, errors appear to be randomly distributed. Applying this analysis to hydroxide ion, one obtains a kinetic pK_a of 12.3; a small standard deviation with no trend in errors is noted.

With these kinetic pK_a values we have again carried out a three- and four-parameter fit, now using the 63 hydroxide and amine catalytic constants, with the results reported in Table V, part B. A marked improvement in fit is noted; the ζ value is an order of magnitude larger than in the earlier analysis but is of the same magnitude as its standard deviation, and most importantly, the overall standard deviation shows no improvement for the four-parameter analysis.

Least-squares procedures of this kind are relatively insensitive to nonrandom effects in the distribution of error, and a check on this point is provided by Figure 5 which plots the residuals for the three-parameter fit of Table V, part B, as functions of log k_{cat}. In effect, the abscissa of this graph can be taken to represent the view along the major diagonal of the surface of Figure 2, and a contribution of f_{xy} to the Taylor expansion would be indicated by a drift of error terms. In fact, the correlation coefficient of residual and log k_{cat} is an insignificant −0.15.

From the above evidence we conclude that the reactions of benzisoxazoles with tertiary amines in water at 30° are quantitatively describable by a three-term equation, independently linear in amine and salicylonitrile pK_a values. Over a range of catalytic constants of 10^5 for 56 amine reactions, 10^8 for 63 amine and hydroxide ion reactions, and 10^{11} for 65 water, amine, and hydroxide reactions, no curvature was demonstrable, and no effect of reactivity on selectivity could be observed.

Discussion

One can view the results of the preceding section in three ways. (1) The benzisoxazole decompositions can be regarded as anomalous proton transfer reactions, whose Brønsted behavior cannot be generalized. (2) The lack of curvature cited in the preceding analysis can be attributed to too small a variation of catalyst basicity. (3) The behavior of the benzisoxazoles can be regarded as representative of most proton transfer reactions, when they are studied under limiting circumstances. For the following reasons, we reject the first two of these alternatives, and support the third.

Consider the issue of anomaly. Elsewhere,[5] we have summarized the evidence which establishes the benzisoxazole decompositions as intermediateless, with a

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[18] It is tempting to suggest that these values be used generally for Brønsted plots, and indeed we have found that Hine's rate data for the tertiary amine catalyzed exchange of [2-^{2}H]isobutyraldehyde[19a] are better approximated by our kinetic values. It must be stressed, however, that these values can only apply to a range of substrates which approximate the steric requirements of the amine–benzisoxazole transition state. In a study of phenylacetylene exchange, a system with smaller steric requirements, the pattern of amine deviation is altogether different.[19b]

[19] (a) J. Hine, *et al.*, *J. Amer. Chem. Soc.*, **87**, 5055 (1965); (b) D. S. Kemp and J. T. O'Brien, unpublished observations.

Table VI. Enthalpies of Activation and Reaction (kcal/mol), Water, 30°, μ = 0.1 (KCl)

Substrate	Base	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta H°$	$-\Delta H° + \Delta H^{\ddagger}$
5-Nitrobenzisoxazole	Hydroxide	16.0	11.5	−39.0	50.5
Benzisoxazole	Hydroxide	18.3	14.7	−35.1	49.8
Benzisoxazole	Trimethylamine[a]	20.4	18.7	−30.4	49.1
5-Nitrobenzisoxazole	Water[a]	23.8		−25.5	

[a] $\Delta H°$ data were calculated from the hydroxide observations,[5] using the equilibrium ionization data of Leffler and Grunwald: J. E. Leffler and E. Grunwald, "Rates and Mechanisms of Organic Chemistry," Wiley, New York, N. Y., 1963, p 371.

transition state for which C–H and O–N bond cleavages have occurred in concert, and which concludes that acid or base can only be involved in simple C–H proton abstraction. The data of the preceding section indicate a deuterium isotope effect of four to six, a β value of 0.72, and a ρ value, based on salicylonitrile pK_a of 0.63; the transition state, therefore, has roughly two-thirds of the sensitivity of the products to amine and benzo substitution; it is essentially equally sensitive to base and leaving group effects and is dominated by neither.

In these attributes, the benzisoxazole decomposition is similar to other proton transfer processes in which the initially formed carbanion is virtual and can be stabilized only by extensive charge delocalization to sites removed from the proton transfer site. Other E2 eliminations provide the closest analogies, but all proton donations by carbon acids which yield resonance-stabilized anions appear to share these mechanistic features.[20] Although it might be argued that this class of proton transfer processes has special features,[21] nevertheless, it provides most of the examples of proton transfer processes for which chemical rate control is observed over an appreciable range of catalyst strengths. In discernible structural features and in mechanistic attributes, the benzisoxazole decompositions belong to this class.

The benzisoxazole decompositions are, however, highly exothermic reactions, and it is therefore highly appropriate to inquire into the magnitude of variation of $\Delta G°$ which has been achieved in this study. Although irreversibility prevents study of reactions with a $\Delta G°$ of zero, if one includes reactions with water and hydroxide ion, $\Delta G^{\ddagger}$ varies from 13 to 29 kcal/mol, and over a $\Delta G^{\ddagger}$ range of 24–16 kcal/mol, $\Delta H°$ varies from −25 to −39 kcal/mol. Both ranges appear to test curvature adequately.

One feature of the benzisoxazole decomposition reactions bears further attention. Data of Table VI compare enthalpies of activation and reaction for four specific benzisoxazole decompositions. The results point up the irrelevance of the notion that Brønsted coefficients for these reactions measure product or starting material-like character; thus the coefficients of Table V imply that extensive transfer of positive charge to amine nitrogen and negative charge to benzisoxazole oxygen must occur at the transition states for these reactions, which in this sense must be regarded as product-like, an assignment which is supported by the invariance of $-\Delta H° + \Delta H^{\ddagger}$, the energy separation of product and transition state, to ring substituent or catalyst base strength. Yet the transition states and products are separated by 50 kcal/mol, and are therefore structurally distinct to an extent energetically equivalent to a weak single bond. For this reaction, the transition state must be regarded as a species which is energetically and structurally distinct from both reactants and products, but which shares the sensitivity of the latter to substitution, as measured relative to reactants.[22]

Given the impossibility of independently varying the structural parameters of a molecule through perturbation of a single substituent, it is not surprising that structurally distinct species frequently show similar substituent sensitivities; therefore, in any system of structural complexity, the terms "reactant-like" or "product-like" can be highly misleading, and we urge that their usage be confined to those rare instances in which a multiplicity of independent criteria establish their relevance.

Given the freedom of the benzisoxazole system from ambiguities which often plague Brønsted studies, and the compelling character of the evidence for linearity in this case, a natural question concerns the soundness of the conclusion for curvature in other cases.[23]

As discussed in the introduction, the case most widely quoted as establishing the continuous decrease of Brønsted coefficient with increasing substrate re-

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(20) An extended and interesting elaboration of this point may be found in C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1967, pp 815 ff.

(21) Proton transfer to an oxygen or nitrogen base from a carbon acid which owes its acidity to delocalization of charge onto a heteroatom may have a transition state for which the environment surrounding the transferred proton is highly asymmetric, since the X–H partial bond may be expected to be normal, while the C–H bond, as a result of charge delocalization, is expected to be highly polarizable, its stretching or bending should be highly anharmonic, and its force constant may be anomalously low. Depending on the geometry of the system, secondary forces may exist between the transferred proton and the principal sites of charge delocalization.

(22) This view of the significance of Brønsted or Hammett coefficients has of course been formulated previously; see, for example, J. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, 88, 3982 (1966).

(23) Although quasi-theoretical models[4] are often used to predict ideal Brønsted behavior, their underlying assumptions seem to us to render their predictive character uncompelling. A few specific comments seem in order. The oft-cited Evans–Polanyi model describes the transition state as the resonance-stabilized intersection of extended potential energy curves for X–H bond stretching for products and reactants. The model ascribes shifts in transition state energy to a vertical displacement in product energy with a corresponding parallel shift of potential energy curve, ignoring curvature changes predicted by Badger's rule; moreover, transition state instability is necessarily ascribed to electron deficiency, since no provision exists for estimating interactions between donor and acceptor atoms. A more recent model proposed by Marcus also has no provision for end group interaction, and like the BEBO model of Johnston,[24,25] on which it is based, it predicts observable curvature only in cases of reactions with low activation energies, which for proton transfer processes are likely to be reactions which can be studied over only a limited pK_a span. Lack of agreement concerning the origin of variations of isotope effects for proton transfer processes points up the difficulties of simple model building;[26] in our opinion, until a satisfactory analysis can be devised which allows for solvation and interaction effects peculiar to the transition state, models must be taken at best as heuristic guides; they cannot be used to weight the interpretation of experimental evidence.[27]

(24) H. S. Johnston, *Advan. Chem. Phys.*, 3, 139 (1960).

(25) H. S. Johnston, "Gas Phase Reaction Rate Theory," Ronald Press, New York, N. Y., 1966, pp 179–183, Chapter 11.

(26) R. P. Bell, W. Sachs, and R. Trauter, *Trans. Faraday Soc.*, 67, 1995 (1971).

(27) For an interesting attempt to include some solvation effects, see J. L. Kurz and L. C. Kurz, *J. Amer. Chem. Soc.*, 94, 4451 (1972).

Table VII. Pfluger Analyses of Relative and Absolute β Values for Ketone Enolizations[e]

	$\beta/\beta_{\text{acetone}}$					
Compd	All points			Cat. constants for[c] OH⁻ and H₂O excluded		
	A. Pfluger Analysis					
Acetone	*1.00*	*a*	7[b]	*1.00*	*a*	5[b]
Hexane-2,5-dione	1.01	0.999	6	1.03	0.997	4
Chloroacetone	0.94	0.990	7	1.02	0.997	5
Bromoacetone	1.01	0.999	6	0.94	0.998	4
Dichloroacetone	0.99	0.998	5	0.90	0.992	3

	$\beta/\beta_{\text{ethyl acetoacetate}}$			
Compd	All points		Cat. constants for[c] OH⁻ and H₂O excluded	
2-Carboethoxycyclopentanone	0.64	0.968	0.97	0.999
Ethyl acetoacetate	*1.00*		*1.00*	
2-Carbethoxycyclohexanone	1.23	0.998	1.11	1.000
Benzoylacetone	1.02	0.987	0.96	0.941
Acetylacetone	0.84	0.997	0.84	0.990
3-Bromoacetylacetone	0.96	0.984	0.92	0.924

			β calcd from Pfluger analysis	
Compd	pK_a[a]	Bell β value[a]	All points	OH⁻ and H₂O excluded
	B. Absolute β Comparison			
Acetone	20.0	0.88	*0.88*[d]	*d*
Hexane-2,5-dione	18.7	0.89	0.89	0.91
Chloroacetone	16.5	0.82	0.90	0.90
Bromoacetone	16.1	0.82	0.89	0.83
Dichloroacetone	14.9	0.82	0.87	0.79
2-Carbethoxycyclopentanone	13.1	0.64	0.38	0.57
Ethyl acetoacetate	10.5	0.59	*0.59*	
2-Carbethoxycyclohexanone	10.0	0.58	0.73	0.65
Benzoylacetone	9.7	0.52	0.60	0.57
Acetylacetone	9.3	0.48	0.50	0.50
3-Bromoacetylacetone	8.3	0.42	0.57	0.54

[a] Correlation coefficient for relative β value. [b] Number of catalytic constants in comparison. [c] These points omitted as Bell indicates that they may be less reliable. [d] Obtained using Bell's absolute β values for acetone and ethyl acetoacetate. [e] Reference 8.

activity is Bell's study of the base-catalyzed enolization of carbonyl derivatives.[8] We have applied Pfluger's kinetic basicity analysis[16] to Bell's data, and Table VII compares Bell's absolute β values with relative β values obtained by using catalytic constants for acetone or ethyl acetoacetate as standards. These substrates were chosen because they yield linear Brønsted plots (corr coeff 0.99) with the four bases (trimethylacetate, acetate, glycollate, and chloroacetate) which Bell used for his comparison, and because with these substrates, catalytic constants were available for a maximum number of additional bases. On this latter point rests the superiority of the Pfluger analysis; if only four pairs of catalytic constants corresponding to the above four bases are compared, the analysis must yield results identical with Bell's; if more pairs are available, a more accurate comparison is possible which should not bias those analyses which are forced to rest on fewer points.

According to the results of the table, *there is no systematic variation of β* within the group of mono- or the group of β-dicarbonyl compounds, although a β value of 0.85 is characteristic of the former, and a value of about 0.55, of the latter. The wider variations observed for the β-dicarbonyl derivatives may reflect greater structural differences or larger experimental uncertainties associated with these exceedingly difficult experimental systems.

As noted in the introduction, the slopes obtained from most Brønsted studies are open to interpretation, either because of mechanistic ambiguities, or because of difficulties in evaluating the catalytic efficiencies of bases belonging to different structural classes. Nonetheless, it is informative to survey briefly the evidence available from other systems. A profitable distinction can be drawn among acids by considering two attributes: the degree of molecular reorganization which accompanies proton transfer, and the stability, often equivalent to the intrinsic hydrogen bonding capacity, of an anion localized at the site of proton transfer. Four classes of acids can be identified: oxy acids are characterized in most cases by ionizations accompanied by small structural change and large hydrogen bonding capacity of localized anion; ionization of acetylenes and many heterocyclic carbon acids are accompanied by small structural change and relatively low hydrogen-bonding capacity; concerted oxyanion-assisted decompositions such as glucose mutarotation appear to involve stable hydrogen bonded anions and appreciable molecular reorganization; finally, formation of carbon enolates, benzenonium deprotonations, and E2 eliminations involve high degrees of molecular reorganization and highly unstable, virtual carbon or nitrogen anions at the site of proton transfer. The first class of acids react with chemical rate control over a small pK_a range of catalyst strength: although the available data have been interpreted as implying continuous variation of Brønsted coefficient,[1a] they appear to us to be equally consistent with a strict constancy of slope in the chemical region, with change to a limiting value of zero or unity at each of the boundaries at which diffusion control is encountered. Carbon acids which yield highly localized anions such as acetylenes[28] or thiazolium ions,[29] or carbon acids whose anions are delocalized onto nitrogen[30] or chlorine,[31] appear from the few cases which have been studied to yield Brønsted coefficients which approach unity over the entire aqueous ΔpK range; their anions must therefore react with all oxy acids at rates which approach diffusion limits. More data are clearly needed to settle the intriguing question of whether these acids show any ΔpK region for which rate constants are chemically controlled in both directions. Reactions of the 1,1-diol dehydration class which may involve internal concerted acid–base components have always been notable for their strikingly linear Brønsted plots.[2,4,6,7] Reactions of this class rank among the most carefully documented cases of general catalysis, and for these as perhaps for no other examples, it can be argued that sufficient bases have been employed to negate the random effects of variations in catalyst group efficiency.

Both very weak carbon acids, as typified by the phenylmethane derivatives carefully studied by Streitweiser,[32] and weak carbon bases[33] show constancy of Brønsted coefficient over large pK_a spans of catalyst. Reactions of carbon acids, such as nitro or carbonyl derivatives, which yield anions delocalized onto oxygen, are typified by the acetylacetone study of Eigen,[1a] which is usually interpreted to imply continuous variation of Brønsted coefficient but which is subject to the interpretive ambiguity discussed in the introduction, the nitroalkane study of Bordwell,[34] and ketone study of Bell,[8] both of which are seen to show strictly constant Brønsted coefficients within a structural class. Finally, the E2 type deprotonations, of which the decomposition of nitramide and the deprotonation of benzisoxazoles have been the most carefully studied series, again show a striking constancy of Brønsted coefficient over a large ΔpK range.

To our knowledge, three studies have employed Bell's strategy of a series of structually related substrates and a set of fixed catalysts. As noted, two give strictly linear behavior within a class of fixed structural type. In a third study, Kresge and coworkers have examined the carboxylic acid catalyzed hydrolysis of seven vinyl ethers, employing an identical set of six acids as catalysts.[33] Despite a large variation in substrate reactivity, there is a striking constancy of Brønsted selectivity: for all but the most reactive substrate, the coefficients effectively have the value 0.65. Although the authors believe the data are best interpreted as showing a decreasing selectivity with increasing reactivity, with a "poor correlation," we believe this case to be one which supports a general empirical finding of a constancy of Brønsted coefficient over large changes in reactivity.

Although the hypothesis of strict Brønsted linearity within a structural class of substrates appears to find experimental support in all cases for which an adequate test can be conducted,[35] an intriguing point remains. When a major structural change makes a substrate more reactive, it often happens that the Brønsted coefficient for the new system is smaller. Bell's mono- and β-dicarbonyl compounds provide an example, Streitweiser's fluorenes and triphenylmethanes[32] are another, although important counter examples exist: the conversion of benzisoxazoles to *N*-alkylbenzisoxazolium ions results in a reactivity increase of *ca.* 10^8 and an *increase* in β from 0.6 to 0.8.[38]

Should this effect, when it occurs, be regarded as an example of Brønsted curvature? We believe not; rather we suggest that the clue to this effect is to be found, not in the increased reactivity of the new, unselective substrate, but in the greater degree of molecular constraint and reorganization which usually accompanies an abrupt and major increase in charge stabilization by resonance. To the extent that the effect is common, it can be attributed to the molecular accident that charge delocalization is a common source of enhanced reactivity, and we tentatively offer the following rule. If an acid or base is subjected to a structural change which has the effect of forcing a much larger degree of geometrical constraint on the conjugate species, then the changed transition state for proton transfer will be more dependent on internal structural factors and less sensitive to the strength of the acceptor or donor species; as a result, the Brønsted coefficient will be smaller.

In summary, the data above argue strongly that *most proton transfer reactions have transition states characterized by a sensitivity to substituent change which is invariant over appreciable changes in transition state energy, and constancy of the Brønsted coefficient reflects this property of invariance.*

While the predictive value of strictly constant Brønsted coefficients is clearly maximal, it must be admitted that to adopt the above view is in a sense to retreat into complexity—as long as transition states can be regarded as hybrids of products and reactants, their properties are rationalizable; to endow them with independent status necessitates examining their properties through exact *ab initio* calculation, through quasi-empirical models, or tautologically, through experimentation. Nevertheless, the available evidence clearly necessitates granting a large degree of independence to transition states for proton transfer processes.

Generalized Selectivity–Reactivity Dependence. Can the above view be generalized to other reactions? It has long been an intuition of organic chemists that highly reactive substances should tend to be undis-

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(28) D. S. Kemp and J. T. O'Brien, unpublished results.

(29) D. S. Kemp and J. T. O'Brien, *J. Amer. Chem. Soc.*, **92**, 2554 (1970).

(30) E. A. Walters and F. A. Long, *ibid.*, **91**, 3733 (1969).

(31) Z. Margolin and F. A. Long, *ibid.*, **94**, 5108 (1972).

(32) A. Streitweiser, *et al.*, *ibid.*, **93**, 5088, 5096 (1971).

(33) A. J. Kresge, H. Chen, Y. Chiang, E. Murrill, M. Payne, and D. Sagatys, *ibid.*, **93**, 413 (1971).

(34) F. G. Bordwell and W. J. Boyle, *ibid.*, **93**, 512, 514 (1971).

(35) Although the above review is clearly not exhaustive, we believe it to include the most definitive cases. These cases either allow a Pfluger analysis of catalytic constants for a series of closely related substrates and a fixed series of catalysts, or, less satisfactorily, employ a single substrate and a number of structurally related catalysts sufficient to define a statistical mean for at least one local ΔpK region. Except perhaps in the limiting cases of zero or unity Brønsted coefficients, studies involving small numbers of catalysts of differing structure and catalyst strengths, while useful for establishing general catalysis, cannot in our opinion be used to obtain generalizable conclusions about the behavior of Brønsted coefficients.[36]

(36) Expressions have been reported[37] which interrelate variations in Brønsted coefficient with variations in other reaction parameters. Although perhaps obvious, we draw attention to the fact that these expressions do not prove that Brønsted coefficient variation must occur with a change in reaction variables, but merely that if it occurs, it must be accompanied by variations in other parameters as well.

(37) W. P. Jencks, *Progr. Org. Chem.*, **2**, 121 (1964); also ref 1c, pp 195–197.

(38) D. S. Kemp, *Tetrahedron*, **23**, 2012 (1967).

criminatory in their choice of reactants, and this view has found expression in a variety of formal statements, of which that of Hammond is most widely quoted.[39]

Now the principle must be true in the limiting case of a reactive intermediate for which a structural change increases some of its reaction rates to the diffusion limit, and one might argue that it is only in such cases that the principle should be invoked. However, in many cases in which the principle is applied, a microscopic version, distinct from that advocated by Hammond, is intended: given a species whose reactivity places it in the chemically determined rate range, does a fractional increase in the reactivity of the species result in a corresponding decrease in the selectivity of the species?[40] A consideration of the validity of this latter principle, which might be termed the differential Hammond–Leffler postulate, must begin with an exclusion of those cases which owe their apparent obedience to the principle to an intervention of diffusion-controlled rate constants, and then consider the merits of the clear-cut cases which remain. Evidence cited in favor of the DHLP is usually drawn from reactivity behavior of proton transfers, carbene or radical abstraction reactions, carbonium ions, or certain species of lesser reactivity.

The radical and carbene examples have similar features—the effects are small, difficultly interpreted effects such as solvation and end-group interaction are important,[41,42] and at least some rate constants must approach diffusion limits.[43]

The evidence from carbonium ion relative reactivities is usually cited as the best proof of the decrease in selectivity of increasingly reactive intermediates.[42,44] Two problems complicate the interpretation of carbonium ion behavior. Rate constants for reactions of stabilized carbonium ions with good nucleophiles can approach diffusion limits,[45] while for less stable cations such as *tert*-butyl, that limit is almost certainly reached. As a result, nucleophile–water competition ratios for cations of increasing reactivity are likely to show a roughly linear decrease, but for an uninteresting reason which is irrelevant to tests of the DHLP.[47]

Other recent data require complex roles for solvent and ion shell; thus Ritchie and coworkers have recently reported a remarkable lack of change in selectivity for the reactions of a variety of stabilized electrophiles and have interpreted these results as implying major roles for solvation and ion pairing effects in the reactions of carbocations with nucleophiles.[46] From Collins' recent work, the latter appear to be the source of "hot" behavior of carbonium ions formed by deamination.[48]

The features of systems which are not complicated by diffusion-limited rates provide no clearer support for the DHLP. A general correlation between selectivity and reactivity does not appear to exist, since the most selective reactants are often found among the most reactive.[38] Although isolated examples of obedience to the principle are often cited, the effects are frequently small and the systems compared are often dissimilar in charge type or other important features.[49] In contrast, several striking examples of strictly linear behavior have recently been reported which have been very carefully documented,[50] and interestingly, Rogne has observed a series of 42 rate constants comprising reactions of seven anilines and six sulfonyl chlorides in which a clearly defined inverse trend is noted—the most reactive halides are the most selective.[51]

Although this brief survey is not exhaustive, we believe it to be representative, and in it we find no compelling evidence for a generalizable correlation between chemically controlled selectivity and reactivity. The need for more data in certain areas is evident, and in view of the pertinence of newly available results and the fundamental importance of reactivity–selectivity relationships, the time would appear to be opportune for a rigorous and unbiased survey of facts aimed at establishing, refining, or overthrowing the dogma of the unselective rapid reactant.

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(39) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

(40) For a discussion of these two alternatives in the context of the problem of the stereochemistry of quaternization of cyclic amines, see D. R. Brown, R. Lygo, J. McKenna, and B. Hutley [*J. Chem. Soc. B*, 1184 (1967)]; for an acute discussion of the pitfalls in relating selectivity factors to the Hammond postulate, see C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, **95**, 272 (1973).

(41) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959); G. A. Russell, *Tetrahedron*, 8, 101 (1960); D. F. Detar and D. Wells, *J. Amer. Chem. Soc.*, **82**, 5839 (1960); G. L. Closs and J. J. Coyle, *ibid.*, **87**, 4270 (1965); W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 75; P. Gaspar and G. Hammond, *ibid.*, p 235.

(42) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **9**, 751 (1970).

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(46) C. D. Ritchie, *ibid.*, **93**, 7324 (1971); C. D. Ritchie and P. Virtanen, *ibid.*, **94**, 1589, 3481, 4966 (1972); C. D. Ritchie and H. Fleischhaver, *ibid.*, **94**, 4963 (1972); C. D. Ritchie, *Accounts Chem. Res.*, **5**, 348 (1972).

(47) If competition data for more than one nucleophile are available, the hypotheses are easily distinguished. The DHLP requires that all rate ratios must decrease as a cation is made more reactive; the assumption of strict linearity up to diffusion control implies that rate ratios for poor nucleophiles should not change, but those for good nucleophiles should approach unity as the cation is made more reactive. Data quoted by Huisgen[42] give Cl^-/water and azide/water rate constant ratios which decrease dramatically through the series trityl, di-*p*-tolylethyl, benzhydryl, and *tert*-butyl chlorides. Significantly, the azide/chloride rate ratios have values: 93, 0.4, 1.4, and 1.0 for this series. These ratios are in complete accord with an hypothesis of diffusion control of azide and chloride rate constants for three members of the series.

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