This explanation seems unlikely, however, since it should extend to the hydrolysis of 9-bromofluorene-1-carboxylic acid; yet this reaction is not subject to any unusual carboxyl group effect.

Thermodynamic Constants.—The energies and entropies of activation for those hydrolyses which were investigated at two temperatures (Table II) are recorded in Table IV. As would be expected (since the evidence for *ortho*-substituent or 1-substituent participations is negative for those reactions covered by the table), the energies of activation for the two members of each pair of isomers are similar in value.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

The Hydrolysis of Carboxylic Anhydrides. VII.[1,2] Electrolyte Effects on the Acid Hydrolysis

C. A. BUNTON AND J. H. FENDLER

The Department of Chemistry, University of California, Santa Barbara, California, and William Ramsay and Ralph Forster Laboratories University College, London, England

Received May 24, 1966

Aqueous perchloric, sulfuric, and hydrochloric acids catalyze hydrolyses of trimethylacetic and camphoric anhydrides to different extents, but their specificities depend largely upon their electrolyte effects upon the activity coefficients of the anhydrides. The variation of rate of hydrolysis of benzoic anhydride in water with acidity is very complex, but if the ionic strength is maintained with added electrolyte the rate increases smoothly with increasing concentration of perchloric or hydrochloric acid. Provided that allowance is made for variations in the activity coefficients of camphoric and trimethylacetic anhydrides the rates of their acid hydrolyses are dependent in a simple way upon the protonating power of the acid and the water activity. Some studies were made of salt effects upon the spontaneous hydrolyses, and the deuterium isotope effect upon it.

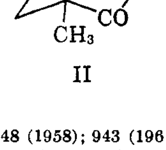
The hydrolyses of carboxylic anhydrides in aqueous acids generally follow A2 mechanisms,[3-5] although the acid hydrolysis of acetic mesitoic anhydride follows an A1 mechanism[4] because of the stability of the mesitoyl cation.[6]

For acid hydrolyses of many substrates the rate constants are approximately proportional either to the acid concentration, or to its protonating power as measured by Hammett's acidity function, and mechanistic criteria have been based on these rate relations.[7] Bunnett has suggested a modification of these criteria in which the reaction rate is related to both acidity and water activity.[8] However, for the hydrolyses of acetic and trimethylacetic anhydrides in aqueous acid, there is no simple relationship between reaction rate and acidity, even when changes in the water activity are taken into account, and the catalytic powers of the acids differ considerably.[5] Sulfuric acid is a more effective catalyst than either perchloric or hydrochloric acids. These observations suggest that the strong acids are affecting the reaction rate by acting both as proton donors and as electrolytes, and their electrolyte effects could well be specific. Specific electrolyte effects have been observed for many hydrolyses both of uncharged and protonated carboxylic acid derivatives, and of some esters of inorganic acids.[9-11]

The salt effects upon the spontaneous hydrolysis of acetic anhydride in water arise, at least in part, because electrolytes have specific effects upon the activity coefficient f_s, of the anhydride.[11] These activity effects are very similar to those which have been found for other carbonyl compounds,[12,13] in that anions of low charge density, *e.g.*, perchlorate, decrease f_s, whereas anions of high charge density, *e.g.*, sulfate, increase it. If acids, acting as electrolytes, have specific differential effects upon the activity coefficients of the initial and transition states of hydrolysis, they should also have different catalytic efficiencies. We have therefore measured the activity coefficients of some carboxylic anhydrides in aqueous acids, and attempted to relate them to the reaction rates in the acids. In order to make meaningful comparisons we chose anhydrides for which the rate of the spontaneous hydrolysis is much less than that of the acid hydrolysis, because an acid, acting as an electrolyte, should affect the rate of the spontaneous hydrolysis. Acetic anhydride is rapidly hydrolyzed in aqueous acid,[5,14] and therefore less reactive anhydrides had to be studied. Trimethylacetic (I), camphoric (II), and benzoic anhydrides are all

$(CH_3)_3C\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}C(CH_3)_3$

I



II

---

[1] Part VI: C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 6174 (1965).

[2] This work was supported in part by Grant G.P. 2889 from the National Science Foundation. This support is gratefully acknowledged.

[3] J. Koskikallio, D. Pouli, and E. Whalley, *Can. J. Chem.*, **37**, 1360 (1959).

[4] C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960).

[5] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **30**, 1365 (1965).

[6] M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 4.

[7] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); F. A. Long and M. A. Paul, *ibid.*, **57**, 935 (1957).

[8] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).

[9] S. Marburg and W. P. Jencks, *ibid.*, **84**, 232 (1962); E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3595 (1962); T. H. Fife, *ibid.*, **87**, 4597 (1965); J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).

[10] C. A. Bunton and T. Hadwick, *ibid.*, 3248 (1958); 943 (1961); J. G. Tillett, *ibid.*, 5138 (1960); P. W. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. Silver, C. A. Vernon, and V. A. Welch, *ibid.*, 227 (1966); C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

[11] C. A. Bunton, N. A. Fuller, S. G. Perry, and I. Pitman, *J. Chem. Soc.*, 4478 (1962).

[12] F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

[13] A. P. Altshuller and H. E. Everson, *J. Am. Chem. Soc.*, **75**, 4823 (1953); G. M. Waind, *J. Chem. Soc.*, 2879 (1954).

[14] V. Gold and J. Hilton, *ibid.*, 838, 843 (1955).

hydrolyzed much more slowly in aqueous acid than is acetic anhydride.[4,5,15] The low reactivities of the aliphatic anhydrides are caused by steric hindrance to nucleophilic attack, and conjugation between the aryl and carbonyl groups decreases the reactivity of benzoic anhydride.

Benzoic anhydride turned out to be useless for this type of study because acids only slightly catalyze its hydrolysis in water, and it is therefore very difficult to separate the electrolyte effects upon the spontaneous and acid hydrolyses, and consequently the variation of reaction rate with acidity is very complex. This problem arises because the inductive effect of the phenyl groups decreases the basicity of the oxygen atoms of the anhydride. It is less serious with the anhydrides of the aliphatic acids, particularly at the higher temperatures, because the acid hydrolysis has a higher activation energy than the spontaneous hydrolysis.[3-5]

Another method of attacking this problem is to maintain a constant electrolyte concentration with a salt of the acid.[12,15,16] Lithium salts are the most useful for this purpose because the solvated proton and the lithium ion seem to have very similar electrolyte properties in water; *e.g.*, they have similar effects upon the activity of water, and the densities of solutions of acids and their lithium salts are very similar.[17] Mixtures of hydrochloric acid and lithium chloride were used, but lithium perchlorate has limited solubility in aqueous perchloric acid, and therefore we were forced to use mixtures of perchloric acid and sodium perchlorate. This general approach was not used for sulfuric acid, because addition of electrolyte would complicate the sulfate–hydrogen sulfate equilibrium.

Experimental Section

Materials.—The preparation and purification of the anhydrides have been described.[4,5,15] The electrolytes were reagent grade materials and the salt solutions were prepared either by dissolving the dried salt in water or by neutralization of the acid.

Kinetics.—Hydrolysis was generally followed spectrophotometrically using either a Cary 14, a Hitachi-Perkin-Elmer 139 or a Unicam SP 500 spectrophotometer.[5] The faster runs were followed using a temperature-controlled cell holder. The optical density of the anhydrides followed the Beer–Lambert law, and the first-order rate constants, k_ψ, were calculated from plots of log ($OD_t - OD_\infty$) against time, or by using Guggenheim's modification of the usual first-order rate equation.[18]

The anhydride concentration was approximately 10^{-4} *M*, and solutions were made up using deareated water. The spontaneous hydrolysis of camphoric anhydride was also followed conductimetrically. Our rate constants for the spontaneous hydrolyses of camphoric and benzoic anhydride in water agree with those of Wilsdon and Sidgwick,[19a] and Butler and Gold,[19b] respectively. The hydrolysis of camphoric anhydride in aqueous salt solutions was followed titrimetrically. Camphoric anhydride is relatively unreactive toward dilute alkali, and the acid can be determined directly by acid–base titration.

Distribution Experiments.—The activity coefficients of the anhydrides in aqueous acid and salt solutions were calculated from the distribution coefficient of the anhydride between carbon tetrachloride and the aqueous solution.[12] The general procedure was that used earlier for acetic anhydride.[11]

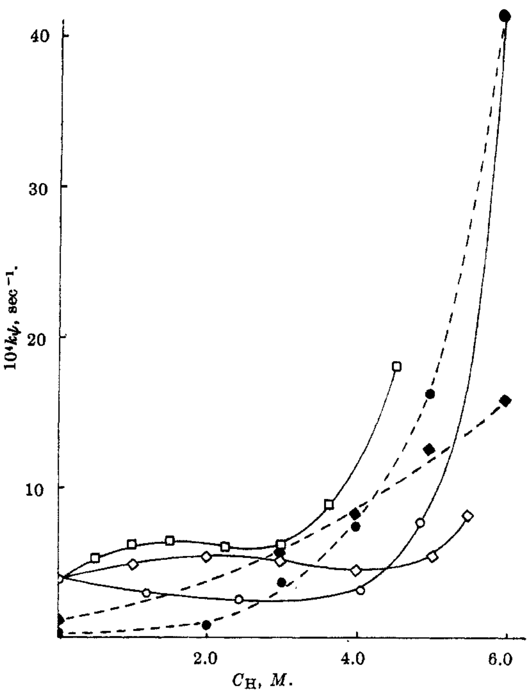


Figure 1.—Plot of k_ψ against C_{H^+} for the hydrolysis of benzoic anhydride in aqueous acids at 25.0°: ○, ●, $HClO_4$; ◇, ◆, HCl; □, H_2SO_4. Solid points and broken lines are for reaction at ionic strength of 6.0.

A stock solution of anhydride in carbon tetrachloride was prepared, and a known volume of it was shaken with a known volume of water or aqueous electrolyte in a water-jacketed separating funnel at 55° for camphoric anhydride and 2.5° for trimethylacetic anhydride. Both solutions were first brought to thermostat temperature.

The layers were separated and the anhydride concentration in the aqueous layer was determined spectrophotometrically at 240–245 mμ. Control experiments using only water and carbon tetrachloride showed that no absorbing materials were extracted into the water from the carbon tetrachloride. For the experiments at low temperature the separated aqueous solutions were centrifuged for a short time before spectrophotometric analysis.

The method had to be modified for the experiments at 55° where the hydrolysis of camphoric anhydride is relatively fast. Allowance for the hydrolysis which occurred during the separation was made as follows. The time of mixing of the aqueous and carbon tetrachloride solutions was noted, and after the aqueous layer was removed its optical density was followed. The optical densities could then be extrapolated back to the time of initial mixing.

Results

Kinetics.—The first-order rate constants, k_ψ, for hydrolysis of benzoic and camphoric anhydride at various acidities, and at ionic strengths, *I*, are given in Tables I, II and are plotted against acid concentration in Figures 1 and 2. The values of k_ψ for the hydrolysis of trimethylacetic anhydride are given in ref 5. The rate constant quoted earlier for hydrolysis in 4.87 *M* perchloric acid is wrong; the correct value is $k_\psi = 34.0 \times 10^{-5}$ sec^{-1}, in 4.80 *M* perchloric acid.

The effects of acids upon the hydrolysis of benzoic anhydride are very complex, and it does not seem possible to separate the acid catalysis from the salt effects of the acids. These results are somewhat similar to those observed for the hydrolyses of cyclic anhydrides in aqueous acid, where acids can either catalyze or retard hydrolysis, depending upon the structures of the an-

---

(15) C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 6174 (1965).

(16) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *ibid.*, 3574 (1958).

(17) R. A. Robinson and R. H. Stokes, "Electrolytic Solutions," Butterworth and Co. (Publishers) Ltd., London, 1959, Appendix 8.

(18) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(19) (a) B. H. Wilsdon and N. V. Sidgwick, *J. Chem. Soc.*, **107**, 679 (1915); (b) A. R. Butler and V. Gold, *ibid.*, 2212 (1962).

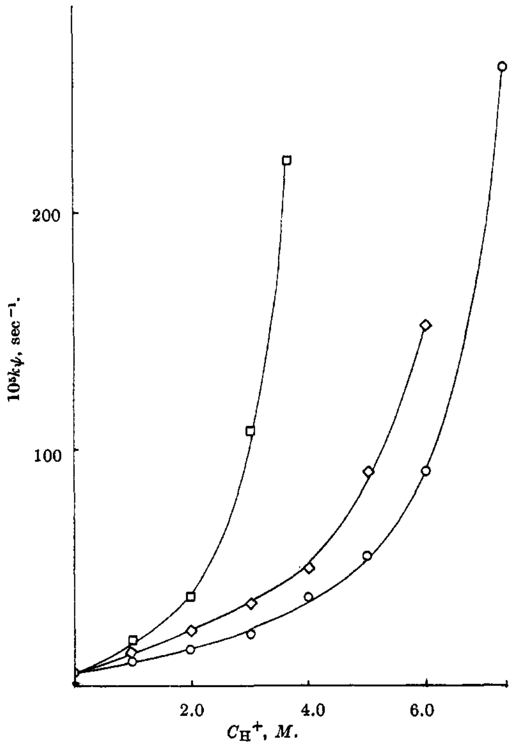


Figure 2.—Plot of k_ψ against C_{H^+} for the hydrolysis of camphoric anhydride in aqueous acids: ○, $HClO_4$; ◇, HCl; □, H_2SO_4.

hydride and the acid, and upon the acid concentration.[15,20,21]

The effects of salt upon the spontaneous hydrolysis of benzoic and camphoric anhydride follow the general pattern observed for hydrolyses of other anhydrides in water, in that sulfates increase the reaction rate, chlorides decrease it slightly, and perchlorates decrease it markedly[5,11,15,21] (Tables I and II). As is generally found plots of log k_ψ against ionic strength are linear, except for added sulfates.

The complex kinetic form of the hydrolysis of benzoic anhydride in aqueous acid disappears if the ionic strength I, of the solution is maintained. In mixtures of HCl and LiCl or $HClO_4$ and $NaClO_4$ of constant ionic strength, k_ψ increases smoothly with increasing acid concentration, and is approximately linear for ionic strength of 3.0, although not for the runs at higher ionic strength (Table I and Figure 1). The rates of hydrolysis of succinic anhydride in aqueous acids also increase smoothly with increasing acidity provided that the ionic strength is maintained with added electrolyte.[21]

Camphoric anhydride is a relatively unreactive compound, because of steric hindrance, and its hydrolysis could be followed conveniently at 55°, where the contribution of the spontaneous hydrolysis is fairly small, because with carboxylic anhydrides the acid hydrolysis has a much larger activation energy than the spontaneous hydrolysis.[3-5] The variation of rate constant with the nature and concentration of the acid is similar to that found for the hydrolysis of trimethylacetic anhydride,[5] in that plots of k_ψ against acid concentration are not linear, and sulfuric is a more effective catalyst than hydrochloric or perchloric acid (Figure 2).

TABLE I

HYDROLYSIS OF BENZOIC ANHYDRIDE IN AQUEOUS ACID AND SALT

In Aqueous Acid

Acid	C_{H^+}, M	$10^4 k_\psi$, sec^{-1}	
		10.0°	25.0°
...	...	1.40	3.98
HCl	1.00	1.31	4.98
HCl	2.00	1.17	5.48
HCl	3.00	1.04	5.21
HCl	4.00	0.90	4.60
HCl	5.00	0.96	5.59
HCl	5.50	...	8.35
HCl	6.00	1.21	16.0
HCl	6.78	2.31	...
H_2SO_4	0.50	...	5.46
H_2SO_4	1.00	1.64	6.28
H_2SO_4	1.51	...	6.46
H_2SO_4	1.80	1.72	...
H_2SO_4	2.27	...	6.13
H_2SO_4	3.00	1.32	6.20
H_2SO_4	3.64	1.19	9.00
H_2SO_4	4.55	1.99	18.2
H_2SO_4	5.46	7.24	...
$HClO_4$	1.21	0.80	3.00
$HClO_4$	2.43	...	2.57
$HClO_4$	3.00	0.38	...
$HClO_4$	4.06	...	3.26
$HClO_4$	4.87	0.79	7.76
$HClO_4$	6.00	3.83	41.4

At 25.0°, I = 3.0

	HCl + NaCl		$HClO_4$ + $NaClO_4$	
C_{H^+}, M	$10^4 k_\psi$, sec^{-1}	$10^4 k_a/C_{H^+}$ sec^{-1} M^{-1}	$10^4 k_\psi$, sec^{-1}	$10^4 k_a/C_{H^+}$ sec^{-1} M^{-1}
...	1.84	...	0.64	...
1.00	2.99	1.05	1.01	0.37
2.00	3.72	0.94	1.33	0.35
3.00	5.21	1.12	1.95	0.43

	HCl + LiCl		$HClO_4$ + $NaClO_4$	
C_{H^+}, M	$10^4 k_\psi$, sec^{-1}	$10^4 k_a/C_{H^+}$, sec^{-1} M^{-1}	$10^4 k_\psi$, sec^{-1}	$10^4 k_a/C_{H^+}$ sec^{-1} M^{-1}
...	1.28	...	0.23	...
2.00	...	...	2.15	0.96
3.00	5.85	1.52	3.80	1.19
4.00	8.45	1.79	7.60	1.84
5.00	12.7	2.48	16.4	3.23
6.00	16.0	2.45	41.4	6.90

In Aqueous Salts, $10^4 k_\psi$, sec^{-1}

C_{salt}, M	NaCl	LiCl	$NaClO_4$	Na_2SO_4	$MgSO_4$
1.00	2.95	...	1.99	4.75	6.46
1.50	...	...	...	5.02	...
2.00	2.60	...	0.99	...	...
3.00	1.84	...	0.64	...	3.85
6.00	...	1.28	0.23	...	...

Just as for the acid hydrolysis of benzoic and succinic anhydride the reaction rate increases smoothly with increasing concentration of hydrochloric or perchloric acid provided that the ionic strength is kept constant by addition of salt, and the variation of k_ψ with C_{H^+} is approximately linear (Table II).

Initial State Effects.—Perchloric acid strongly "salts in" both camphoric and trimethylacetic anhydride; sulfuric and hydrochloric acid have much less effect, but they both slightly "salt in" the anhydrides (Table III). As is generally found plots of log f_s against electrolyte concentration are linear, except for sulfuric acid, where there is curvature at the higher concentrations (Figure 3).

---

(20) J. Koskikallio and A. Ervasti, *Suomen Kemistilehti*, **35B**, 213 (1962).

(21) C. A. Bunton, J. H. Fendler, N. A. Fuller, S. G. Perry, and J. Rocek, *J. Chem. Soc.*, 5361 (1963).

TABLE II

HYDROLYSIS OF CAMPHORIC ANHYDRIDE IN AQUEOUS ACIDS AND SALTS

At 55.0°, Initially Neutral Solution, $10^5 k_\psi = 5.36$ sec^{-1}

Acid	C_{H^+}, M	$10^5 k_\psi$, sec^{-1}	$10^5 k_a$, sec^{-1}	$6 + \log k_a + H_0$
HCl	1.00	14.9	11.9	1.81
	2.00	23.6	21.8	1.68
	3.00	35.2	34.2	1.49
	4.00	50.2	49.7	1.30
	5.00	91.0	90.7	1.20
	6.00	160	160	1.08
$HClO_4$	1.00	11.5	8.9	1.74
	2.00	15.1	14.0	1.36
	3.00	21.7	21.1	1.09
	4.00	37.3	37.0	0.85
	5.00	55.5	55.3	0.51
	6.00	91.0	90.9	0.12
	7.31	263	263	−0.42
H_2SO_4	1.00	19.2	13.8	1.87
	2.00	38.5	33.1	1.68
	3.00	108	103	1.63
	3.64	222	217	1.66

At 55.0°, in HCl + LiCl and $HClO_4$ + $NaClO_4$, $I = 6.0$

	HCl		$HClO_4$	
C_{H^+}, M	$10^5 k_\psi$, sec^{-1}	$10^5 k_a/C_{H^+}$, sec^{-1} M^{-1}	$10^5 k_\psi$, sec^{-1}	$10^5 k_a/C_{H^+}$, sec^{-1} M^{-1}
...	0.22	...	0.094	...
2.00	55.8	27.8	...	...
3.00	80.0	26.6	38.0	12.6
4.00	...	...	58.2	14.5
5.00	128	25.6	76.2	15.2
6.00	160	25.8	91.0	15.1

At 25.0°, in the Absence of Salt, $10^6 k_\psi = 5.80$ sec^{-1}; $10^6 k_\psi$, sec^{-1}

C_{salt}, M	NaCl	$NaClO_4$	Na_2SO_4
0.50	...	...	6.90
1.00	2.60	2.22	7.47
1.50	...	...	9.12
2.00	1.40	1.01	...
3.00	0.82	0.56	...

Relation between Rate and Activity Coefficients of Camphoric and Trimethylacetic Anhydride.—There is no simple relation between the rate of the acid hydrolysis and either stoichiometric acidity or Hammett's acidity function for any of these anhydrides (Tables I and II, Figures 1 and 2, and ref 5). The values of H_0 for hydrochloric acid are taken from the review of Long and Paul[7] and for sulfuric and perchloric acids from newer experimental results.[22] Within the range of acidities studied the newer values of H_0 are close to the "best values" of Long and Paul.[7]

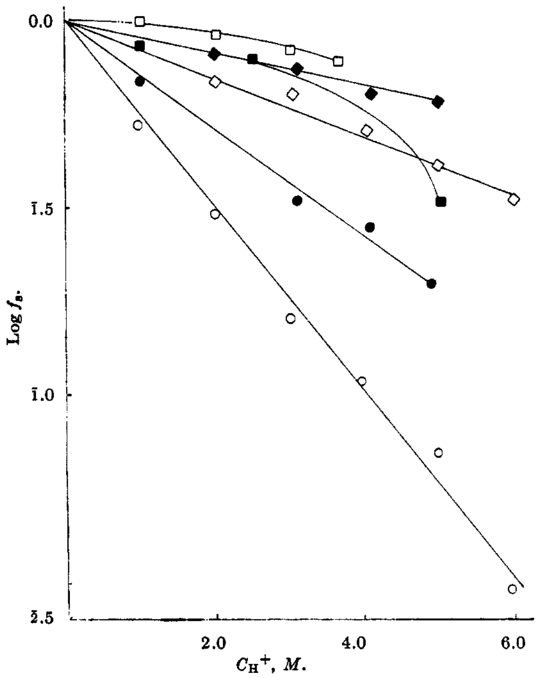


Figure 3.—Variation of the activity coefficients of camphoric and trimethylacetic anhydride in aqueous acids (open points camphoric anhydride; solid points trimethylacetic anhydride): ○, ●, $HClO_4$; ◇, ◆, HCl; □, ■, H_2SO_4.

TABLE III

ACTIVITY COEFFICIENTS OF TRIMETHYLACETIC AND CAMPHORIC ANHYDRIDE IN AQUEOUS ACIDS

C_{H^+}, M	HCl	H_2SO_4	$HClO_4$
	Trimethylacetic Anhydride, f_s at 2.5°		
1.00	...	0.83	0.69
2.00	0.81	...	...
2.50	...	0.79	
3.10	0.74	...	0.33
4.10	0.63	...	0.28
4.80	...	...	0.18
5.00	0.60	0.32	...
	Camphoric Anhydride, f_s at 55°		
1.00	...	1.00	0.52
2.00	0.69	0.91	0.30
3.00	0.63	0.83	0.16
3.64	...	0.77	...
4.00	0.51	...	0.11
5.00	0.41	...	0.07
6.00	0.33	...	0.03

However there is a relation between the catalytic effectiveness of the acids and their effects upon the activity coefficients of camphoric and trimethylacetic anhydride (Tables II and III and ref 5). For trimethylacetic anhydride, where the contribution of the spontaneous hydrolysis to the over-all reaction is relatively small, we take the first-order rate constant for the acid hydrolysis, $k_a = k_\psi - k_n$ (where k_n is the first-order rate constant for the spontaneous hydrolysis). We neglect the electrolyte effect upon k_n as in an earlier paper.[5] This approximation is less satisfactory for camphoric anhydride, where, at low acidities k_n is appreciable relative to k_ψ. Therefore for this reaction we take

$$k_a = k^\psi - k'_n$$

where k'_n is the rate constant for the spontaneous hydrolysis corrected for the electrolyte effects of HCl and $HClO_4$, on the assumption that they are similar to the kinetic effects of LiCl and $NaClO_4$ upon k_n. For sulfuric acid we neglect the electrolyte effect upon k_n, because here $k_\psi \gg k_n$. These approximations do not affect the qualitative picture, and they are least important for the more concentrated acid solutions. Plots of $\log k_a/f_s$ against $-H_0$ are shown in Figures 4 and 5, where the lines have slope 0.8 for camphoric anhydride and 0.75 for trimethylacetic anhydride. There is some scatter, particularly for trimethylacetic anhydride, where the points line in a broad band, but the deviations are much less than those observed when no account is

---

[22] M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963); K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).

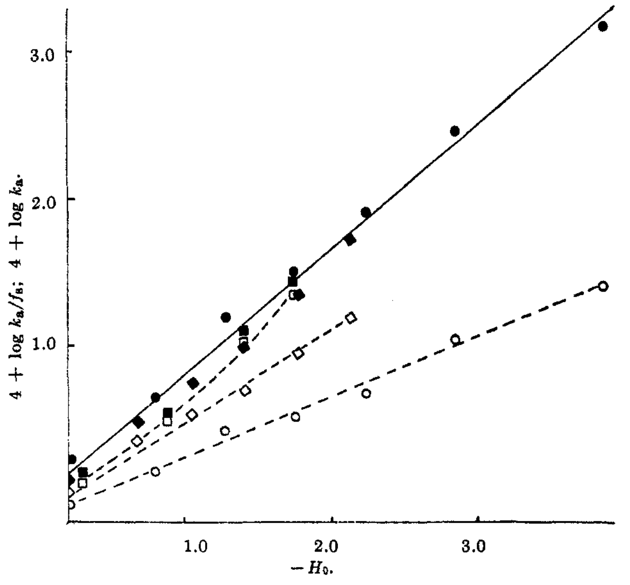


Figure 4.—Plot of log k_a (open points and broken line) and log k_a/f_s (solid points and solid line) against $-H_0$ for the hydrolysis of camphoric anhydride in aqueous acids. The solid line has a slope of 0.8: ○, ●, $HClO_4$; ◇, ◆, HCl; □, ■, H_2SO_4.

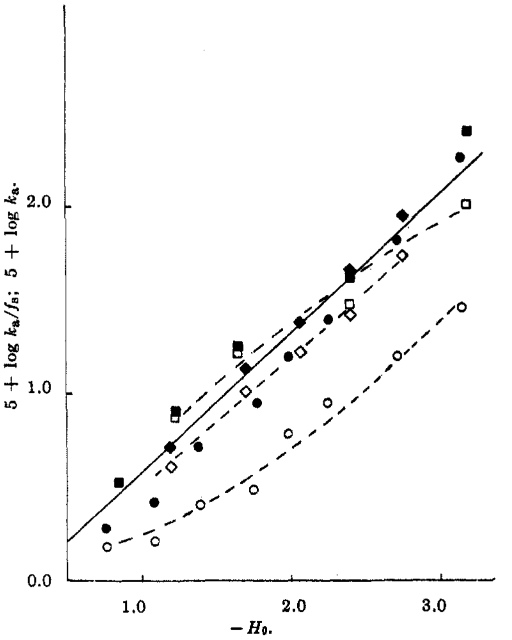


Figure 5.—Plot of log k_a (open points and broken line) and log k_a/f_s (solid points and solid line) against $-H_0$ for the hydrolysis of trimethylacetic anhydride in aqueous acids. The solid line has a slope of 0.75: ○, ●, $HClO_4$; ◇, ◆, HCl; □, ■, H_2SO_4.

taken of variations in f_s, and are not larger than those generally found for plots of log k against logarithmic functions of acidity.[7,8] These discrepancies are partly experimental, and reflect the uncertainties in correcting for the spontaneous hydrolysis, as well as errors in k_ψ, f_s, and H_0. These errors are especially important at low acid concentrations where there is little catalysis. Also the scale for hydrochloric acid may differ systematically from those for sulfuric and perchloric acids, because it is not based wholly on protonation of primary amines.[7,22] For the hydrolysis of trimethylacetic anhydride in aqueous sulfuric acid the values of k_a/f_s run high and for perchloric acid low (Figure 5), particularly in the more dilute solutions. These particular deviations may be caused by uncertainties in the correction for the spontaneous hydrolysis. The hydrolyses of camphoric and trimethylacetic anhydrides were followed at different temperatures and the specific effects of the various mineral acids could well be temperature dependent. These graphical treatments could not be applied to the acid hydrolysis of benzoic anhydride because of the difficulty of allowing for the very large contribution of the spontaneous hydrolysis in the more dilute acids.

Solvent Deuterium Isotope Effects.—The spontaneous hydrolysis of carboxylic anhydrides is slower in D_2O than in H_2O, $k_{H_2O}/k_{D_2O} \approx 3$.[23,24] Two general explanations have been given for this relatively large solvent isotope effect: one involves a slow proton transfer equilibria, and hydration–dehydration equlibria,[23] and the other assumes strong hydrogen bonding of water molecules to a highly polar transition state.[24] Johnson has concluded that the results cannot be explained in terms of a series of equilibria and rate steps.[25] In both treatments attention has been focussed on the nature of the transition state and its interactions with the solvent, and therefore we examined both the kinetic isotope effect for the spontaneous hydrolysis of acetic and camphoric anhydrides at 25°, and the distribution of the anhydrides between carbon tetrachloride and H_2O or D_2O. The procedure used for the distribution experiments with acetic anhydride is that described in ref 11, except that the anhydride was determined spectrophotometrically.

The rate constants given in Table IV lead to $k_{H_2O}/k_{D_2O} = 2.6$ for camphoric anhydride, and $k_{H_2O}/k_{D_2O} = 2.90$ for acetic anhydride at 25.0°, and 3.37 at 4.95°. Butler and Gold[23] found $k_{H_2O}/k_{D_2O} = 3.12$ at 15.0°. The isotope effect upon the activity coefficient of camphoric anhydride, $f_s^{H_2O}/f_s^{D_2O} = 1.18$, and for acetic anhydride it is 1.12. It is generally found that polar organic compounds are slightly more soluble in D_2O than in H_2O.[26]

TABLE IV

FIRST-ORDER RATE CONSTANTS OF SPONTANEOUS HYDROLYSIS OF ANHYDRIDES IN H_2O AND D_2O[a]

Camphoric $10^6k_{H_2O} = 5.60,^b\ 6.30,^b\ 5.50^c$
Camphoric $10^6k_{D_2O} = 2.27,^b\ 2.24,^b\ 2.22^c$
Acetic $10^4k_{H_2O} = 26.6,^c\ 6.55^{c,d}$
Acetic $10^4k_{D_2O} = 9.20,^c\ 2.20^{c,d}$

[a] At 25.0° unless specified. Rate constants in sec^{-1}. [b] Followed conductimetrically. [c] Followed spectroscopically. [d] At 4.95°.

The over-all kinetic isotope effects for the hydrolysis of these anhydrides are similar to those found for other anhydride hydrolyses. Because the activity coefficients of the anhydrides are only slightly large in H_2O than in D_2O it appears that the kinetic isotope effect depends largely upon interactions between the solvent and a polar transition state as had been implicitly assumed.[23,24] The kinetic isotope effect for hydrolysis of acetic anhydride decreases slightly with increasing

---

[23] R. A. Butler and V. Gold, *J. Chem. Soc.*, 2212 (1962).

[24] C. A. Bunton and V. J. Shiner, *J. Am. Chem. Soc.*, **83**, 3207 (1961); C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 2918 (1963).

[25] S. L. Johnson, *J. Am. Chem. Soc.*, **84**, 1729 (1962).

[26] C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960), and references cited therein.

Table V

Relation between Rate Constant, Activity Coefficient, Protonating Power, and Water Activity

Camphoric Anhydride at 55.0°								
C_{HCl}, M	1.00	2.00	3.00	4.00	5.00	6.00		
$10^5 k_a/f_s$, sec^{-1}	12.0	32.0	54.0	99.5	222	484		
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	0.90	0.85	0.75	0.71	0.75	0.78		
$C_{H_2SO_4}$, M	1.00	2.00	3.00	3.64				
$10^5 k_a/f_s$, sec^{-1}	13.8	34.7	126	286				
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	0.86	0.70	0.79	0.85				
C_{HClO_4}, M	1.00	2.00	3.00	4.00	5.00	6.00	7.31	
$10^5 k_a/f_s$, sec^{-1}	17.4	46.3	131	335	820	2930	14600	
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	1.04	0.91	0.92	0.92	0.91	0.96	0.90	
Trimethylacetic Anhydride at 0°								
C_{HCl}, M	1.00	2.00	3.00	4.00	5.00			
$10^5 k_a/f_s$, sec^{-1}	5.25	13.8	25.0	46.0	88.5			
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	0.54	0.49	0.41	0.37	0.36			
$C_{H_2SO_4}$, M	0.45	0.91	1.50	3.00	4.55			
$10^5 k_a/f_s$, sec^{-1}	3.56	8.33	18.3	39.2	266			
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	0.78	0.71	0.64	0.30	0.42			
C_{HClO_4}, M	0.48	0.80	1.22	1.94	2.43	3.04	4.06	4.80
$10^5 k_a/f_s$, sec^{-1}	1.94	2.55	5.25	9.20	15.4	24.5	67.0	170
$5 + \log (k_a/f_s) + H_0 - \log a_{H_2O}$	0.43	0.35	0.38	0.25	0.28	0.22	0.26	0.25

temperature, as it should if isotopic substitution changes the activation energy.

Discussion

Relation between Rates and Activities of Anhydride and Water.—For an A2 hydrolysis having the general form

$$\overset{+}{H} + S \rightleftharpoons \overset{+}{HS} \text{ (fast, equilibrium)}$$

$$\overset{+}{HS} + H_2O \longrightarrow \text{products (slow)}$$

The Brønsted–Bjerrum rate equation can be written as

$$k_a = k_0 a_{H^+} f_s a^n_{H_2O}/f^* \qquad (1)$$

where k_a is the first-order rate constant for the acid-catalyzed component of reaction, and f_s and f^* are the activity coefficients of the initial and transition states.

In eq 1 n can be regarded as a formal order with respect to water. (On Ingold's definition of molecularity n would be unity, and the differences in hydration of the initial and transition states by water would be taken care of by the activity coefficients.[27])

For the spontaneous hydrolysis of acetic anhydride salts have specific effects upon the activity coefficient of the anhydride, whereas to a first approximation they increase the activity coefficient of the transition state nonspecifically.[11] Salts can therefore assist or hinder the reaction. In much the same way the specificity of mineral acids upon the rates of the acid hydrolysis arises at least in part from effects upon the activity coefficient of the anhydride, as shown in Figures 4 and 5.

Equation 1 can be rearranged and written in the logarithmic forms (2a or b)

$$\log (k_a/f_s) = \log k_0 + \log C_{H^+} + \log (f_{H^+}/f^*) + n \log a_{H_2O} \qquad (2a)$$

$$\log (k_a/f_s) = \log k_0 - H_0 + \log (f_{HB^+}/f^* f_B) + n \log a_{H_2O} \qquad (2b)$$

where $-H_0$ is Hammett's acidity function and B is a Hammett base and HB$^+$ its conjugate acid.[7]

The experimental results (Figures 4 and 5) approximately fit the relation

$$\log (k_a/f_s) = \log k_0 - bH_0 \qquad (3)$$

and b is 0.7–0.8 for hydrolysis of both camphoric and trimethylacetic anhydrides in all three aqueous acids, and at a given acidity, as measured by $-H_0$, the values of k_a/f_s are very similar for each catalyzing acid, showing that the specificity of the mineral acids is related to their effects upon the activity coefficients of the anhydrides.

Following Bunnett's earlier suggestions[8] it is tempting to assume that n should be an integer, *i.e.*, that one or more water molecules are specifically interacting with the reaction center in the transition state. If both n and $f_{HB^+}/f_B f^*$ equal unity, eq 2b reduces to eq 4.

$$\log (k_a/f_s) = \log k_0 - H_0 + \log a_{H_2O} \qquad (4)$$

The experimental results for hydrolysis of both camphoric anhydride and trimethylacetic anhydride fit eq 4 reasonably well, as is shown by the small variations in the term $\log (k_a/f_s) + H_0 - \log a_{H_2O}$ (Table V). This term is reasonably constant for hydrolysis of each anhydride especially if attention is focussed on one catalyzing acid.

The range of acid concentrations used for the hydrolysis of trimethylacetic anhydride is smaller than for that of camphoric anhydride, and the change in the activity of water is correspondingly less, and as was noted earlier the fit with experiment is least satisfactory for the more dilute acids where it is difficult to correct for the spontaneous hydrolysis. The fit of the experimental results to eq 4 suggests at first sight that the order of reaction with respect to water is unity and that fortuitously the activity terms cancel in $f_{HB^+}/f_B f^*$. However these conclusions may be incorrect, because there are linear relations between acid concentrations and the logarithms of both activity coefficients of nonelectrolytes,[12] and water activity,[17] at least for small changes in acid concentration. Moreover Hammett's acidity function and water activity are not independent variables, although their relationships are not entirely

---

[27] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 315.

clear,[28] and there is no reason to believe that Hammett's acidity function, based on protonation of primary amines, is a unique acidity scale. Bunnett in his earlier work commented on the difficulties of relating the rates of acid hydrolysis of acetic anhydride to changes in the water activity.[8]

Irrespective of the conclusions which one may care to draw from correlations between rate and acidity function and water activity it is clear that any correlation breaks down, at least for the acid hydrolysis of anhydrides, unless one takes into account effects upon the activity coefficient of the anhydrides.

There is no reason to believe that this problem is restricted to anhydride hydrolysis.

There are a number of other examples of the specific behavior of acids, both in equilibria and rate studies. For example Arnett and his co-workers have shown that the relations between various acidity functions are quite different for the various mineral acids, and these differences cannot be explained in terms of effects of changes in the water activity.[29] Therefore there must be specific effects of the acids, acting as electrolytes, upon the ionization of the various types of indicators. In this respect Boyd's measurement of the activity coefficients of various types of organic cations in sulfuric acid are very important.[30] It would be most interesting to see these studies extended to other strong acids.

Determination of the specific effects of strong acids upon reaction rate is sometimes complicated by the fact that the halogen acids may be very effective catalysts, by virtue of the nucleophilicity of the halide ion. This behavior has been observed in hydrolyses of sulfites,[10] selenates, and of some phosphates.[31]

Sulfuric acid is a better catalyst than perchloric acid in A2 hydrolyses of some aryl sulfites and phosphates,[10] and it is unlikely that the hydrogen sulfate ion is acting as a nucleophile. In these systems, as in anhydride hydrolysis, the low catalytic effectiveness of perchloric acid may be related to the "salting-in" of polar nonelectrolytes by the perchlorate ion,[12,13] which would of itself retard reaction by stabilizing the initial state.

For A1 reactions it seems that perchloric is not a poorer catalyst than sulfuric or hydrochloric acids; *e.g.*, the hydrolysis of methyl mesitoate, where a carbonium ion is generated from an ester, is considerably faster in perchloric than in sulfuric acid,[32] suggesting that here the carbonium ions are stabilized by perchlorate ions (relative to the effect of hydrogen sulfate ions).

Reaction at Constant Ionic Strength.—Where both the spontaneous and acid hydrolyses contribute appreciably to the over-all reaction the Brønsted–Bjerrum rate equation becomes

$$k_\psi = f_s(k^0{}_0 a^m{}_{\mathrm{H_2O}}/f^0{}_* + k^{\mathrm{H}}{}_0 C_{\mathrm{H}^+} f_{\mathrm{H}^+} a^n{}_{\mathrm{H_2O}}/f^{\mathrm{H}}{}_*) \qquad (5)$$

where the superscripts 0 and H refer to the spontaneous and acid hydrolyses, respectively.

For hydrolyses of benzoic and camphoric anhydrides in hydrochloric or perchloric acid at constant ionic strength we observe a smooth increase of k_ψ with C_{H^+}, and the maxima and minima in plots of k and C_{H^+} for benzoic anhydride disappear (Figure 1 and Tables I and II.) These results are not unexpected; for example, the activity of water is almost exactly the same in solutions of lithium chloride and hydrochloric acid of the same molality.[17] Therefore it would be unwise to draw mechanistic conclusions from approximately linear relations between rate and stoichiometric acidity in solutions of constant ionic strength, although our results suggest that the complex kinetic forms for the acid hydrolysis of benzoic, and some cyclic anhydrides,[15,21] arise simply because acids act both as proton donors and electrolytes, and these effects may oppose or augment each other. In general these complex kinetic forms will be most evident when a spontaneous and an acid hydrolysis make similar contributions to the over-all reaction.

Relation between Rate Constants and Acid Activity Coefficients.—We explored another relation between reaction rate and acidity for the hydrolyses of camphoric and trimethylacetic anhydrides in aqueous hydrochloric or perchloric acids. For catalysis by the monobasic strong acid HX the Brønsted–Bjerrum rate equation can be rearranged to give

$$\log (k_a/f_s) = \log k_0 + \log C_{\mathrm{H}^+}(f_{\mathrm{HX}}/f^*{}_{\mathrm{X}})^2 + n \log a_{\mathrm{H_2O}} \qquad (6)$$

where f_{HX} and $f_{\mathrm{X}}{}^*$ are the molar mean ion activity coefficients of the acid HX and the transition state.

For hydrolysis in perchloric or hydrochloric acid plots of log (k_a/f_s) against log $C_{\mathrm{H}} + f^2{}_{\mathrm{HX}}$ are linear with slope approximately 0.7 for both anhydrides, showing that the term $a^n{}_{\mathrm{H_2O}}/(f^*{}_{\mathrm{X}})^2$ is approximately independent of X. (The behavior of a dibasic acid, such as sulfuric acid cannot readily be compared with that of the monobasic acids by this treatment because the activities are referred to different standard states.) However, relations between rate and the activity coefficients of the acid are not unexpected, because there are approximately linear relations between Hammett's acidity function and the mean ion activities over limited concentrations for the strong acids,[7,17,33] and therefore correlations between rate and acid activity are unlikely to be more useful than correlations between rate and acidity functions.

Hydrolysis in Aqueous Dioxane.—In this paper we studied only reactions in water. Surprisingly enough the relation between rate and acidity seems to be simpler in acidic aqueous dioxane than in aqueous acid. For example there is a linear relation between k_ψ and perchloric acid concentration for the hydrolysis of benzoic anhydride in dioxane–water 60:40 (v/v),[4] instead of the complex relation shown in Figure 1. To some extent this simplicity may arise because the solvent effects upon the spontaneous and acid hydrolyses are such that the former makes an insignificant contribution to the over-all reaction in aqueous dioxane.[4] More important factors are that in aqueous dioxane the anhydride will be solvated appreciably by dioxane

---

[28] K. N. Bascombe and R. P. Bell, *Discussions Faraday Soc.*, **24**, 158 (1957); P. A. T. Wyatt, *ibid.*, **24**, 162(1957); D. Rosenthal and J. S. Dwyer, *Can. J. Chem.*, **41**, 80 (1963); E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, **86**, 2671 (1964).

[29] E. M. Arnett and G. W. Mach, *ibid.*, **88**, 1177 (1966).

[30] R. M. Boyd, *ibid.*, **85**, 1555 (1963).

[31] C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 1766 (1959); C. A. Bunton and B. N. Hendy, *ibid.*, 3130 (1963); C. A. Bunton, D. Kellerman, K. G. Oldham, and C. A. Vernon, *ibid.*, 292 (1966).

[32] C. T. Chmiel and F. A. Long, *J. Am. Chem. Soc.*, **78**, 3326 (1956).

[33] H. G. Kuivila, *J. Phys. Chem.*, **59**, 1028 (1955).

molecules, and its environment should be relatively unaffected by the addition of those electrolytes which are solvated preferentially by water. Addition of an electrolyte to an aqueous solution of an anhydride will alter the environment of the anhydride, either by direct interaction, or indirectly by changing the water structure.[34] At the same time the dioxane molecules will themselves change the structure of the water, and so further reduce the effect of added electrolytes.

---

[34] H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945); H. S. Frank and W.-Y. Wen, *Discussions Faraday Soc.*, **24**, 133 (1957); O. Y. Samoilov, *ibid.*, **24**, 144 (1957); M. Kaminsky, *ibid.*, **24**, 171 (1957).

Studies on Cyclic Polyols. V. Long-Range Proton Spin Coupling and Other Features of Nuclear Magnetic Resonance Spectra of Substituted Cyclopentanes[1,2]

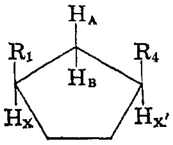
HENRY Z. SABLE,[3] WILLIAM M. RITCHEY, AND J. ERIC NORDLANDER

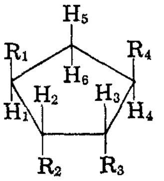
Departments of Biochemistry and Chemistry, Western Reserve University, Cleveland, Ohio 44106, and Research Department, The Standard Oil Company (Ohio), Cleveland, Ohio 44128

Received May 3, 1966

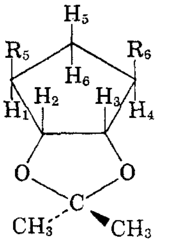
The proton magnetic resonance spectra of a large number of tetrasubstituted cyclopentanes have been examined. Compounds with the 1,4/2,3 configuration give spectra which can be rationalized by first-order analysis as AKX_2Y_2 systems. The signal for each methylene proton is a doublet of triplets. The higher field signal in this region represents the methylene proton *cis* to the 1,4 substituents, and always has wider lines than those seen in the lower field methylene multiplet. Similar line broadening and occasional line splitting are seen in the signal representing the protons attached to C_2 and C_3; these protons are *cis* to the methylene proton whose signal contains the broadened lines. Spin-decoupling experiments show that the line broadening is due to long-range spin-spin coupling (^4J). In all cases the four bonds have the M or W orientation which has been postulated as essential for such long-range coupling to be observed. ^4J has been measured for six compounds and varies from 0.5 to 1.5 cps. When the 2,3 substitution consists of an O-isopropylidene group (*i.e.*, in 2,4-dioxabicyclo[3.3.0]octane derivatives), ^4J is larger than ^3J. Certain other characteristics of the spectra of these compounds a represented, and some implications to the nmr spectroscopy of bicyclo[3.3.0]octane are discussed.

We have described elsewhere[2] some of the characteristics of the nmr spectra of cyclitols and halocyclitols derived from cyclopentane. Because of the kind of symmetry present in many of the compounds studied, the A_2X_2 and ABX_2 (or AKX_2) approximations[4] could be used for first-order analysis of most of the signals representing the ring protons. Considerable information was obtained relative to the angular dependence of the internal chemical shift $\delta_X - \delta_A$ and $\delta_X - \delta_B$ in the ABX_2 systems studied, as well as of the influence of the electronegativity of the substituent on the magnitude of the internal chemical shift. The cyclopentane system was shown to be comparable in many ways to the substituted norbornanes and norbornenes[5] and the cyclohexane tetrols.[6] Compounds with the 1,4/2,3 configuration (structures I and II) usually had spectra which could be interpreted completely by first-order theory, with the further assumption that proton–proton spin couplings through four bonds (^4J) or more were too small to cause observable splitting of the spectral lines. Each of the methylene protons was represented by a doublet of triplets, the large doubling caused by the geminal coupling (J = 12–18 cps) and the smaller tripling due to coupling with the two flanking protons, H_1 and H_4. In many cases, however, the spectra showed certain additional features which could not be explained by the assumptions noted above. These anomalies always included slight widening and apparent "noisiness" of the signal of H_5 (which was always at higher field than H_6), and occasionally by widening or splitting of the H_2H_3 signal without any corresponding effect in the H_1H_2 signal (see Figures 1 and 2). In the present communication we present conclusive evidence for coupling through four bonds, involving H_5 and H_2,H_3. In all compounds with structure II, ^4J of H_2,H_3 is larger than ^3J, *i.e.*, $J_{25} > J_{12}$, whereas in series I, J_{12} is 2.5–4.5 cps. The deceptively simple[7a] nature of the spectra of many of the compounds is further emphasized by a previously unreported example.





I a, $R_1 = R_4 = Br$; $R_2 = R_3 = OH$
b, $R_1 = R_2 = R_3 = R_4 = OH$
c, $R_1 = R_2 = R_3 = R_4 = OBz$



II a, $R_5 = R_6 = Br$
b, $R_5 = R_6 = OH$
c, $R_5 = R_6 = OBz$
d, $R_5 = Br$; $R_6 = OH$

---

[1] (a) Supported in part by U. S. Public Health Service Grant AM-07719 from the National Institute of Arthritis and Metabolic Diseases. (b) Presented before the Division of Organic Chemistry at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

[2] Part IV: H. Z. Sable, W. M. Ritchey, and J. E. Nordlander, *Carbohydrate Res.*, **1**, 10 (1965).

[3] Author to whom communications should be addressed at the Department of Biochemistry, Western Reserve University, Cleveland, Ohio.

[4] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 98.

[5] (a) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963); (b) P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2709 (1963); (c) *ibid.*, **86**, 1171 (1964).

[6] G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 894 (1963).

[7] (a) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961); (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (c) R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).