

Isotope Effects on Chemical Equilibria. Part II. Some Further Secondary Isotope Effects of the Second Kind

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The ratio of the dissociation constants $K_a(H)/K_a(D)$ has been measured conductimetrically for the isotopic pairs XCH_2COOH/XCD_2COOH where $X = Cl, PhO,$ and PhS . Methods of calculating the ratio of the equilibrium constants are considered in some detail. Since the isotope effect varies with the nature of the X substituent it is concluded that the simple inductive description of these effects is not tenable.

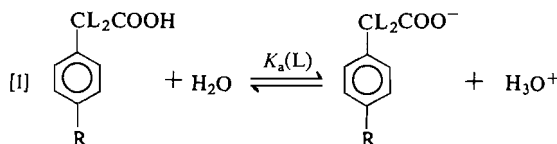
On a mesuré les rapports de constantes de dissociation $K_a(H)/K_a(D)$ par conductimétrie pour chaque paire isotopique XCH_2COOH/XCD_2COOH dans lesquels $X = Cl, PhO$ et PhS . On considère en détail les méthodes de calcul pour déterminer les rapports des constantes d'équilibre. Puisque l'effet isotopique varie avec la nature du substituant X on en conclut qu'une description de ce phénomène par un simple effet inductif n'est pas complète.

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Introduction

In a previous communication (1) we reported isotope effects for the equilibria



where $R = \text{MeO}, \text{H},$ and NO_2 and L represents hydrogen or deuterium. Although the $K_a(H)/K_a(D)$ ratios for the above equilibria were much smaller than anticipated from previous studies (1), two important observations emerged. Firstly the predicted value of the isotope effect for the pair $\text{PhCH}_2\text{COOH}/\text{PhCD}_2\text{COOH}$ based on $\sigma^*(D)$ is now closer to the observed value, *i.e.*, the inductive treatment is partially verified. Secondly, when combined with the data for acetic acid and acetic acid- d_3 , the size of the isotope effect per deuterium appears to be variable and dependent on the strength of the protium acid (Fig. 1). An extrapolation of this correlation implies that the isotope effects might become inverse for acids with pK_a 's less than that of 4-nitrophenylacetic acid. One of the purposes of this paper is to test such an extrapolation.

Whilst the discussion of some secondary isotope effects as inductive in nature has never been entirely convincing, an inductive effect of D vs. H

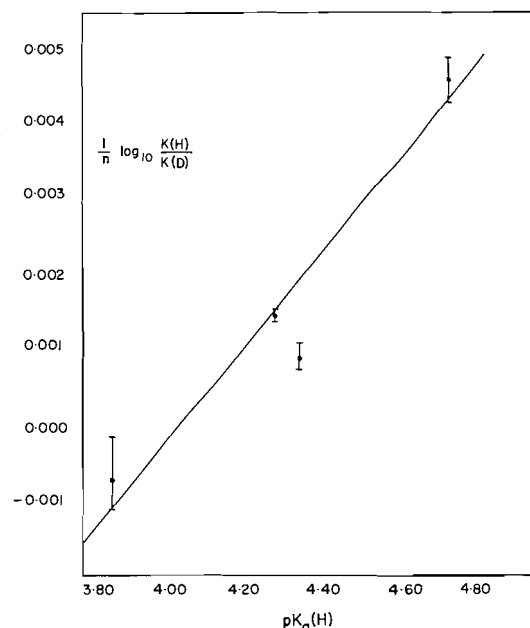


FIG. 1. Correlation of secondary isotope effects per deuterium against $pK_a(H)$. See ref. 1 for the data.

which is normal for some acids and in the opposite direction for others is hardly tenable within the conceptual framework of the inductive effect. Indeed, if such a situation arose the inductive description would have to be abandoned.

In order to definitely establish if such a correlation exists between pK_a and $K(H)/K(D)$ further

measurements are required, particularly on acids with pK_a 's < 4 . In the present paper we have further examined the problem of evaluating the equilibrium constants and the isotopic ratios from the conductance data. An attempt has been made to increase the precision of the conductance data as well as to provide an improved method for calculating $K_a(H)/K_a(D)$ without the determination of the equilibrium constant of either acid.

Experimental

General

All melting points and boiling points are uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were obtained using a Varian A60 spectrometer. All organic solvents were distilled prior to use or were of known grade of purity.

Preparation and Purification of Materials

All the acids mentioned below were subjected to intensive purification by vacuum sublimation, zone refining, and recrystallization techniques. The samples were then dried *in vacuo* at a suitable temperature. Deuteration as judged by n.m.r. measurements was found to be $>97\%$ in all cases.

Phenylacetic acid: a commercial sample after purification had m.p. 76.2–76.6°C (lit. m.p. 76.7°C (2)).

Phenoxyacetic acid on purification had m.p. 98.9–99.5°C (lit. m.p. 98.5–99.5°C (3)).

Phenoxyacetic- α,α - d_2 acid was prepared by exchange ($T = 125^\circ\text{C}$) in a sealed tube using a mixture of D_2O , $(\text{CH}_3\text{CH}_2)_3\text{N}$. The purified acid had m.p. 99.1–99.5°C.

Chloroacetic acid was prepared from Cl_2 and glacial acetic acid in the presence of red phosphorus¹ and purified (ref. 4, p. 428) to the point where the dichloro and trichloro acids were absent, m.p. 63.0–63.2°C (lit. m.p. 63.0°C (5)).

Chloroacetic- α,α - d_2 acid was prepared by chlorinating glacial acetic- d_3 , m.p. 62.9–63.3°C.

Phenylthioglycolic acid, a commercial sample, on purification had m.p. 62.8–63.5°C (lit. m.p. 62.5–63.5°C (3)).

Phenylthioglycolic- α,α - d_2 acid was obtained by exchange using conditions similar to the phenoxy acid preparation. The pure acid had m.p. 62.5–63.5°C.

Potassium chloride was purified as previously reported (1).

Experimental Assembly and Technique

The measurements were made as in Part I with minor modifications. The regulation of the thermostat was improved by a Tronac Unit (PTC-1000A). Ten conductance cells of the Shedlovsky type (6) (cell constants (κ) in the range 0.08 \rightarrow 0.4) were determined using three independent samples of potassium chloride. The potassium chloride solutions were prepared on the molal scale and were converted to the molar scale as previously described. The calculation of the cell constant also followed the procedure outlined in ref. 1. The individual cell constants were

¹Purified following the method described in Vogel (ref. 4, p. 193).

TABLE 1. Conductance data for phenylacetic acid at 25.051°C

$10^4 c$ (molal)	Λ	$10^5 K_a$	$10^4 c$	Λ	$10^5 K_a$
61.09	33.15	4.925	8.234	83.05	4.940
47.33	37.43	4.936	6.776	90.35	4.937
37.80	41.60	4.937	6.245	93.52	4.932
29.39	46.77	4.938	5.339	99.95	4.932
22.00	53.49	4.946	3.979	112.85	4.920
10.72	73.98	4.943	2.958	127.04	4.903
9.695	77.35	4.944	1.988	148.04	4.889

determined at least five times during the study and were reproducible to ca. 0.02%.

Concentration-equivalent conductance data for the acids chloroacetic, chloroacetic- α,α - d_2 , phenoxyacetic, phenoxyacetic- α,α - d_2 , phenylthioglycolic, phenylthioglycolic- α,α - d_2 , and phenylacetic are listed in Tables 1 and 2. With the exception of PhCH_2COOH and PhCD_2COOH (see below) all conductivities were recorded at $25.000 \pm 0.002^\circ\text{C}$. The weight of water and each carboxylic acid sample was corrected to the true weight *in vacuo* following calculations described previously (1). The densities of the deuterated acids were assumed to be equal to their protium analogs in all cases. Unknown densities were determined by measuring both the dimensions of the fused material and its weight in air or a solvent of known density. Solidification of the acids was carried out by melting with slow cooling or by compression with a hydraulic press at ca. 3×10^4 pounds/inch².

Results

Thermodynamic equilibrium constants were evaluated by the Robinson and Stokes method (7) which is a variant of the Shedlovsky expression (8) (Tables 1 and 2). This method requires an accurate value of the equivalent conductance at infinite dilution (Λ_0) to calculate by successive approximations the equivalent conductance of the hypothetical completely ionized weak electrolyte at a finite concentration (c). The Λ_0 value quoted by Jeffrey and Vogel (9) for phenylacetic acid, and by Ives and co-worker for chloroacetic acid (10) were used in the calculations.^{2,3} In the case of phenylacetic acid the limiting equivalent conductance had to be corrected to 25.051°C using an expression developed by Laughton and Demayo (11)

$$[2] \quad \Lambda_0 = -1122.08 + 4.9614T$$

Λ_0 ($\text{PhSCH}_2\text{COOH}$) was obtained from the data of Crockford and Douglas (12) by an extrapolation.

²These Λ_0 values have been converted to the molal scale by the equation $\Lambda_0(\text{molal}) = \Lambda_0(\text{molal}/d_0)$.

³ $\Lambda_0(H) = \Lambda_0(D)$. The validity of this assumption has been examined in the following discussion.

TABLE 2. Conductance data at 25.000 °C

$10^4 c$ (molal)	Λ	$10^4 K_a$	$10^4 c$ (molal)	Λ	$10^4 K_a$
Chloroacetic acid					
44.78	168.58	13.89	20.04	219.45	13.92
39.98	175.46	13.90	15.12	237.94	13.93
35.02	183.76	13.93	10.10	263.80	13.90
29.87	193.78	13.94	8.836	271.92	13.83
24.70	205.96	13.94	8.043	277.65	13.82
Chloroacetic- α, α - d_2 acid					
44.11	168.89	13.76	20.02	218.67	13.74
40.11	174.61	13.75	14.76	238.58	13.73
34.55	183.75	13.75	9.857	264.56	13.72
29.56	193.54	13.75	9.273	268.39	13.72
24.74	204.94	13.75	7.646	280.22	13.71
Phenoxyacetic acid					
50.19	122.56	7.245	9.059	222.70	7.260
40.29	133.64	7.253	7.980	230.62	7.235
30.09	149.35	7.267	7.082	238.21	7.231
20.10	172.69	7.267	5.923	249.48	7.220
9.817	217.43	7.249	5.005	259.87	7.203
Phenoxyacetic- α, α - d_2 acid					
50.55	121.65	7.164	9.045	222.03	7.172
40.00	133.42	7.175	7.986	229.72	7.139
30.16	148.59	7.185	6.994	238.25	7.143
20.06	172.07	7.176	5.841	249.51	7.123
10.02	215.36	7.168	5.059	258.40	7.109
Phenylthioglycollic acid					
50.08	81.74	2.800	15.12	134.20	2.807
45.37	85.33	2.802	9.942	157.22	2.807
40.24	89.86	2.804	9.033	162.80	2.807
34.96	95.42	2.806	8.096	169.27	2.807
30.19	101.51	2.807	6.895	178.91	2.803
25.04	109.70	2.808	6.008	187.39	2.801
19.85	120.55	2.808	5.027	198.49	2.795
Phenylthioglycollic- α, α - d_2 acid					
50.08	81.01	2.744	15.04	133.53	2.757
45.29	84.65	2.747	10.02	155.70	2.757
40.12	89.20	2.749	9.006	161.84	2.754
35.04	94.53	2.751	8.078	168.27	2.755
30.18	100.67	2.752	7.021	176.69	2.753
25.08	108.73	2.754	5.993	184.34	2.748
20.01	119.23	2.756	5.023	197.23	2.739

tion of a plot of Λ_c vs. $C^{1/2}$. No literature value of the equivalent conductance at infinite dilution was available for phenoxyacetic acid. As a result a value was developed from a Shedlovsky extrapolation-iteration method (SIM) for determining both Λ_0 and K_a simultaneously (13).

Average K_a values and related data for all seven acids are summarized in Table 3. A comparison with existing data can be made only for phenylacetic and chloroacetic acids. Within the

accuracy of the phenylacetic acid data K_a (25.000 °C) is equal to K_a (25.051 °C).⁴ This value is in excellent agreement with previous work on the acid, further confirming the reliability of the work. The thermodynamic equilibrium constant for chloroacetic acid is in agreement with the work of Shedlovsky and co-workers (14) but is

⁴Demayo found a 3.9% decrease in K_a (PhCH₂COOH) from 20 to 40 °C.

TABLE 3. Comparison of equilibrium constants

Acid	$10^4 K_a$	Method*	Reference
PhCH ₂ COOH	0.4930 ± 0.0016	RSM(<i>m</i>)	This work and ref. 9†
	0.4923 ± 0.0015 ($\Lambda_0 = 379.6$)†	RSM(<i>m</i>)	
ClCH ₂ COOH	13.90 ± 0.04 ($\Lambda_0 = 390.8$)†	RSM(<i>m</i>)	This work and ref. 10‡
	13.9	C(<i>c</i>)	
	13.97	C(<i>c</i>)	
	13.59	C(<i>c</i>)	
	13.78	E.m.f.	
	13.37	C.D.(<i>c</i>)	
ClCD ₂ COOH	13.74 ± 0.02 ($\Lambda_0 = 390.8$)†	RSM(<i>m</i>)	This work and ref. 10‡
PhOCH ₂ COOH	7.243 ± 0.020 ($\Lambda_0 = 381.3$)§	RSM(<i>m</i>)	This work
	6.75	E.m.f.	
PhOCD ₂ COOH	7.156 ± 0.025 ($\Lambda_0 = 381.3$)§	RSM(<i>m</i>)	This work
PhSCH ₂ COOH	2.805 ± 0.004 ($\Lambda_0 = 381.1$)	RSM(<i>m</i>)	This work and ref. 12
	2.76 ± 0.04	C(<i>m</i>)	
PhSCD ₂ COOH	2.751 ± 0.005 ($\Lambda_0 = 381.1$)	RSM(<i>m</i>)	This work

*RSM, Robinson-Stokes method; C, conductance method; C.D., calorimetric determination; *c*, mol/l; *m*, mol/1000 g H₂O.† Λ_0 (molal) used in RSM calculations‡Literature ref. for Λ_0 (molar).

§Calculated using the Shedlovsky iteration method.

considerably higher than the equilibrium constant reported by Ives and Pryor (10). The latter authors suggest that the discrepancies may be due to hydrolytic decomposition, leading to unstable conductance readings. Neither of these factors were evident in this study or are reported by other investigators. No mention is made by Ives and Pryor of their method of drying the very hygroscopic acid. A moist sample of the acid would give a low value of the equilibrium constant.

Discussion

In a previous communication we reported that the classical method was more suitable for establishing absolute values of secondary isotope effects on chemical equilibria than a comparison of $K_a(\text{H})/K_a(\text{D})$ using the Robinson and Stokes method to calculate $K_a(\text{H})$ and $K_a(\text{D})$ separately. A small residual concentration dependence in K_a together with uncertainty in Λ_0 may be factors contributing to the relatively large deviations from the average value of the equilibrium constant.

The use of the RSM for calculating $K_a(\text{D})$ depends on the assumption

$$[3] \quad \Lambda_0^-(\text{H}) = \Lambda_0^-(\text{D})$$

for isotopically substituted anions. Such an assumption has ample precedent (1) but was considered unsatisfactory by the referees who ex-

amined the first paper in the present series. A preliminary discussion of the problem was presented in ref. 1⁵ but the central importance of this approximation to the present and previous work demands further comment.

The effect of isotopic substitution on the limiting equivalent conductance of ions is part of the wider problem of the effect of structure on this particular electrochemical quantity. To date available theories examine the problem in terms of the ion radius as the significant structural parameter (ref. 7, chapt. 6, 19). However the molecular anions related to the substituted acetic acids cannot be realistically characterized by a radius. More sophisticated theories of the hydrodynamic properties of spherical ions also relate the limiting equivalent conductance to the ion radius and include frictional forces arising from the viscous and dielectric properties of the solvent (20), the latter involving ion-dipole interactions. For non-spherical molecular anions the ion-dipole interactions must be replaced by dipole-dipole interactions between ion and solvent and differences in limiting equivalent conductance for isotopically substituted molecular ions would arise from differences in size between D and H and differences in dipole moments between C—H and C—D bonds. The Zwanzig theory (20) does not appear to have been developed beyond the

⁵See footnote 6, ref. 1.

TABLE 4. Comparison of isotope effects

Acid	Robinson and Stokes	Classical plot	Shedlovsky plot
ClCH ₂ COOH/ClCD ₂ COOH	1.012 ± 0.0043	1.012 ± 0.0008	1.012 ± 0.0007
PhOCH ₂ COOH/PhOCD ₂ COOH	1.012 ± 0.0063	1.011 ± 0.0006	1.011 ± 0.0007
PhSCH ₂ COOH/PhSCD ₂ COOH	1.020 ± 0.0034	1.021 ± 0.0003	1.021 ± 0.0005

spherical ion – dipole description and thus is inadequate to cope with the molecular ion problem. We are therefore inclined to grossly simplify the problem and consider two anions, one which has a radius of 2 Å whilst the other has a radius which differs from 2 Å by 5×10^{-3} Å which is the maximum difference in length observed between C—H and C—D bonds (21). The former ion corresponds to the ion L = D and the latter L = H. The viscous force acting on the ion is inversely proportional to the radius of the ion, hence

$$[4] \quad \frac{\Lambda_0^-(D)}{\Lambda_0^-(H)} = \frac{r(H)}{r(D)} = \frac{2.0050}{2.0000} = 1.0025$$

The anion conductances $\Lambda_0^-(H)$ and $\Lambda_0^-(D)$ represent *ca.* 10% of the total limiting equivalent conductance since most of the current is carried by the counter-ion which is the proton. This reduces the isotope effect by an order of magnitude *i.e.* from 1.0025 to 1.00025.

Since (see ref. 1)

$$[5] \quad \frac{K(H)}{K(D)} = \frac{m(D)}{m(H)} \frac{\Lambda_0^2(D)}{\Lambda_0^2(H)}$$

the part of the isotope effect arising from the effect of isotopic substitution on the hydrodynamic properties of the ions is *ca.* 1 part in 5000. This, we emphasize again, is an upper limit and it is clear that the departure of the ratio $\Lambda_0^2(D)/\Lambda_0^2(H)$ from unity is not significant in this or the previous study.

Hydrogen bonding between the methylene H or D atoms and the solvent is neglected since we are unaware of any evidence which would establish the existence of such interactions. Current theories of the solubilities of neutral hydrocarbon molecules in water suggest that specific interactions between solute and solvent will be very weak and no isotope effect is likely to arise from this source.

The isotope effects $K(H)/K(D)$, calculated using both the Robinson and Stokes method and the classical plot method, are compared in Table 4. The latter method of presenting the data in-

volves a comparison of the classical slopes from a linear correlation of the variables $1/\Lambda(L)$ and $\Lambda(L)c(L)$ for L = H and L = D

$$[6] \quad \frac{K_c(H)}{K_c(D)} = \frac{m(D)}{m(H)}$$

where $m(H)$ and $m(D)$ are the classical slopes for the deuterio and protio acids and $\Lambda_0(H)$ is assumed to be equal to $\Lambda_0(D)$. Of the two methods of calculation the classical treatment superficially appears to provide a more precise value of the isotope effect. However, some uncertainty exists, a consequence of the fact that the activity and mobility terms are either implicitly ignored or are assumed to cancel.

In order to remedy this uncertainty the classical treatment was replaced by a modified extrapolation–iteration procedure. The data for each acid was fitted to the Shedlovsky–Kay equation (14)

$$[7] \quad \frac{1}{\Lambda(L)S[Z(L)]} = \frac{1}{\Lambda_0(L)} + \frac{\Lambda(L)c(L)S[Z(L)]f_{\pm}^2(L)}{K_a(L)\Lambda_0^2(L)}$$

where Λ , Λ_0 , c , and f_{\pm} have their usual significance and the correction term $S[Z(L)]$ can be expressed as a power series in $Z(L)$:

$$[8] \quad S[Z(L)] = 1 + Z(L) + Z^2(L)/2 + Z^3(L)/8 + \dots$$

where Z is given by

$$[9]^6 \quad Z = \left(\frac{\alpha\Lambda_0(L) + \beta}{\Lambda_0(L)^{3/2}} \right) (\Lambda(L)c(L))^{1/2}$$

The Shedlovsky variables $1/\Lambda S[Z(L)]$ and $\Lambda c(L)S[Z(L)]f_{\pm}^2(L)$ can be correlated without iteration using a linear least squares analysis to yield a slope of $1/K_a(L)\Lambda_0^2(L)$. A comparison of $m(H)$ and $m(D)$, the slopes of the Shedlovsky equation, will reduce the isotope effect to a simple slope

⁶Fuoss and Accascina (22) replace the Robinson and Stokes symbols B_1 and B_2 by α and β (23).

TABLE 5. The Shedlovsky slope comparison method applied to the chloroacetic acid data

Λ_0	$10^2 m(H)$	$10^2 m(D)$	$K(H)/K(D)$
370	0.4726 ± 0.0003	0.4780 ± 0.0003	1.0114 ± 0.0016
374	0.4725 ± 0.0003	0.4779 ± 0.0003	1.0114 ± 0.0016
378	0.4724 ± 0.0003	0.4778 ± 0.0003	1.0114 ± 0.0016
382	0.4723 ± 0.0003	0.4777 ± 0.0003	1.0114 ± 0.0016
386	0.4722 ± 0.0003	0.4776 ± 0.0003	1.0114 ± 0.0016
390	0.4721 ± 0.0003	0.4775 ± 0.0003	1.0114 ± 0.0016
395	0.4720 ± 0.0003	0.4774 ± 0.0003	1.0114 ± 0.0016

TABLE 6. The Shedlovsky comparison method

Acid pair	Cell number	Isotope effect, $m(D)/m(H)$
Phenoxyacetic	1	1.0104 ± 0.0018
	2	1.0099 ± 0.0016
	3	1.0104 ± 0.0017
	4	1.0108 ± 0.0017
	5	1.0109 ± 0.0017
Chloroacetic	1	1.0114 ± 0.0016
	2	1.0116 ± 0.0016
	3	1.0116 ± 0.0016
	4	1.0114 ± 0.0016
	5	1.0116 ± 0.0016
Phenylthioglycollic	1	1.0207 ± 0.0013
	2	1.0209 ± 0.0013
	3	1.0205 ± 0.0013
	4	1.0211 ± 0.0014
	5	1.0211 ± 0.0013

ratio (see eq. 6). The $K(H)/K(D)$ ratios evaluated from the Shedlovsky slope comparison method are summarized in Table 4 and are in excellent agreement with the classical plot and RSM values.

In situations where a literature value of Λ_0 is unavailable or is available but considered to be in error, eqs. 6 and 7 remain useful since a range of values can be systematically varied on either side of the true limiting equivalent conductance. The location of this range affords no difficulty since Λ_0 for carboxylic acids is relatively insensitive to the structure of the acid (see Table 3). The conductance data for each acid has been used to test the suitability of this method, however, only the results related to a single cell will be presented here. The slopes were generated from a linear correlation of the Shedlovsky variables with Λ_0 values ranging from 370 to 395, and are presented in Table 5. The corresponding $K(H)/K(D)$ ratios determined in this way appear to be insensitive to the value of Λ_0 used to calculate the terms $1/S[Z(L)]$ and $S[Z(L)]/f_{\pm}^2(L)$.

Measurement of the conductance data for the

protio and the deutero acids in the same cell enables a modification to the Shedlovsky slope comparison method detailed above. Replacement of Λ by $10^3 \kappa/Rc$, where κ , R , and c have their usual meaning, followed by multiplication by $10^3 \kappa$ gives

$$[10] \quad \frac{R(L)c(L)}{S[Z(L)]} = \frac{10^3 \kappa}{\Lambda_0(L)} + \frac{10^6 \kappa^2 S[Z(L)] f_{\pm}^2(L)}{R(L)K_a(L)\Lambda_0(L)}$$

with the slope $m(L)$ obtained from the experimental variables $R(L)c(L)/S[Z(L)]$ and $S[Z(L)]f_{\pm}^2(L)/R(L)$. Hence $m(L)$ is given by

$$[11] \quad m(L) = \frac{10^6 \kappa^2}{K_a(L)\Lambda_0^2(L)}$$

Equation 11 shows that a comparison of the slopes for the H and D acids in a single cell will be virtually independent of the cell constant, which will only be required to calculate the small correction terms $1/S[Z(L)]$ and $S[Z(L)]/f_{\pm}^2(L)$. Single cell isotope effects evaluated in this way are reported in Table 6 for the three isotopic pairs.

Thus, although a value of κ and Λ_0 is required to calculate the correction terms, their main contribution to $m(H)$ and $m(D)$ cancels in the ratio of these quantities. The excellent agreement between $K(H)/K(D)$ from the data for each cell (Table 6) and from three methods of calculation (Table 4), further confirms the accuracy of the cell constant determinations. Furthermore, the errors in the ratios are smaller for the combined data, probably a consequence of the fact that the larger the number of data points on the least squares fit the greater the degree of certainty in the value of the slope and thus $K(H)/K(D)$. However, the discovery of the insensitivity of the method to the value of Λ_0 in calculating the isotope effect is far more interesting than the other conclusions drawn from Table 6. This insensitivity of the slopes and ratios to Λ_0 suggests that the Shedlovsky slope comparison method of calculation is the best for comparing thermodynamic equilibrium constants of isotopically substituted acids via conductance data.

The isotope effects for the substituted acetic acids XCH_2COOH/XCD_2COOH , $X = Cl, PhO$, and PhS are larger than those observed for the phenylacetic acids ($X = 4-RC_6H_4$ where $R = MeO, H$, and NO_2). The six effects we have investigated are however still less than those measured by Streitwieser and Klein (24) and Bates and co-workers (25) for the pair CH_3COOH/CD_3COOH . The new ratios are closer to those predicted by the simple inductive treatment ($K(H)/K(D) = 1.02$) but do not appear to follow the predictions of the correlation in Fig. 1. When the new $K(H)/K(D)$ values are included the influence of the substituent on the isotope effects appears to be random. This observation cannot be reconciled with the inductive treatment presented in part I which requires the isotope effects to be constant, *i.e.* independent of X .

A rigorous statistical treatment of the isotope effects in terms of force constant – frequency changes between the acid and the related anion would involve the interaction terms absent in the simple inductive treatment. Such interaction terms would probably account for the alteration of the ratio $K(H)/K(D)$ as X is structurally changed. Since the simple inductive treatment is incapable of accommodating our observations the inductive treatment of secondary isotope

effects of the second kind has outgrown its utility.

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