# Isotope Effects on Chemical Equilibria. Part I. Some Secondary Isotope Effects of the Second Kind

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Secondary isotope effects  $K_a(H)/K_a(D)$  for the isotopic acid pairs 4-X-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>COOH/4-X-C<sub>6</sub>H<sub>4</sub>-CD<sub>2</sub>COOH(X = H, NO<sub>2</sub>, OMe) have been determined at T = 25 °C by conductance measurements. This has involved the redetermination of the dissociation constants for the non-deuterated acids and in the case of X = NO<sub>2</sub>, OCH<sub>3</sub>, the new  $K_a$  values are to be preferred. The  $K_a$  of acetic acid has also been redetermined as a check on the reliability of the new data. The three isotope effects are shown to be much smaller than might have been anticipated on the basis of the e.m.f. measurements on the pair PhCH<sub>2</sub>COOH/PhCD<sub>2</sub>COOH reported earlier (1).

Les effets isotopiques secondaires  $K_a(H)/K_a(D)$  pour la paire d'acides isotopiques 4-X-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>-COOH/4-X-C<sub>6</sub>H<sub>4</sub>CD<sub>2</sub>COOH (X = H, NO<sub>2</sub>, OCH<sub>3</sub>) ont été évalués à T = 25 °C par de mesures de conductance. Ceci a impliqué une nouvelle détermination des constantes de dissociation pour les acides non-deutériés et dans le cas où X = NO<sub>2</sub>, OCH<sub>3</sub> les nouvelles valeurs de  $K_a$  doivent etre préférées. Le  $K_a$  de l'acide acétique a aussi été évalué de nouveau comme standard d'exactitude des nouvelles données. Les trois effets isotopiques trouvés sont beaucoup plus petits que prévus si l'on se base sur les mesures de f.e.m. pour la paire Ph<sub>2</sub>CH<sub>2</sub>COOH/PhCD<sub>2</sub>COOH rapportées précédemment (1).

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### Introduction

The changes in dissociation constants which occur when hydrogen is replaced by deuterium in the side chains of carboxylic and ammonium acids have been studied on several occasions (1-5). The problem of predicting and understanding these subtle effects of structure on reactivity using the statistical theory of equilibria (6) has not proved particularly rewarding since a full treatment of the problem requires a complete knowledge of the reactant and product vibrational frequencies appropriate to the condensed phase in which the equilibria are examined. In practice these latter quantities are rarely available. A partial exception is exemplified by the calculation of the relative acidities of formic acid and formic acid-d, by Bell and Crooks (2) using the observed fundamental frequencies appropriate to the isotopic acids.

The general lack of such vibrational data has forced both theoreticians and experimentalists to devise other models to cope with secondary hydrogen-deuterium isotope effects. These latter treatments suggest that changes in reactivity resulting from the replacement of hydrogen by deuterium can be discussed in terms of hybridization, steric or non-bonded interactions, hyperconjugation or inductive effects (see references

in ref. 7). Although the hyperconjugative and inductive treatments superficially appear to be electronic in origin, the Born-Oppenheimer principle is retained and the model can still be understood in terms of mass effects on vibrations. Thus, the hyperconjugative and inductive description can be recast in vibrational-statistical language, but by formally avoiding the vibrational treatment some simplification is lent to what is evidently a complex problem. The least that can be asked of this and other simplified approaches to the understanding of secondary isotope effects is that the 'as if' treatments maintain a reasonable degree of fidelity in their representation of the experimental data, *i.e.* that they be self-consistent.

Isotope effects, in which the spatial orientations of the bonds linking the isotopic atoms to the molecule are altered, are described by Streitwieser and coworkers (8) as secondary isotope effects of the first kind. Other possible processes in which spatial reorganization is absent are described as secondary isotope effects of the second kind. It has been proposed by Halevi (7), that isotope effects of the second kind behave like inductive effects. Thus, the variation of secondary isotope effects of this sort with both the structure and the position of deuteration

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Acids	$pK_a^a$	σ*	X1	X2	X3	$\Sigma \sigma^*$
CX <sub>1</sub> X <sub>2</sub> X <sub>3</sub> COOH						
CF <sub>3</sub> COOH	0.23		F	F	F	9.30
CCl₃COOH	0.65	2.65	Cl	Cl	Cl	8.70
CBr <sub>3</sub> COOH	0.66		Br	Br	Br	8.40
CHF <sub>2</sub> COOH	1.24	2.05	F	F	Н	6.69
CHCl <sub>2</sub> COOH	1.29	1.74	Cl	Cl	Н	6.29
(CH <sub>3</sub> ) <sub>3</sub> NCH <sub>2</sub> COOH	1.83	1.90	$(CH_3)_3N$	H	Н	
CNCH <sub>2</sub> COOH	2.43	1.3	CN	Н	Н	4.62
CH <sub>2</sub> FCOOH	2.59	1.10	F	Н	Н	4.08
CH <sub>2</sub> (COOH) <sub>2</sub>	2.83	1.05	COOH	Н	Н	
CH <sub>2</sub> ClCOOH	2.90	1.00	Cl	Н	Н	3.88
CH <sub>2</sub> BrCOOH	3.07	0.92	Br	Н	н	3.78
CF <sub>3</sub> CH <sub>2</sub> COOH	3.12	0.85	$CF_3$	Н	Н	-
C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> COOH	3.18	0.85	PhO	Н	Н	
CH <sub>2</sub> ICOOH	3.53	0.52	Ι	Н	Н	3.38
CH <sub>3</sub> OCH <sub>2</sub> COOH	3.58	0.60	CH <sub>3</sub> O	Н	Н	
НСООН	3.77	0.49				
NO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	3.81	0.50	$NO_2CH_2$	Н	Н	1.48
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCOOH	3.94	0.45	$C_6H_5$	$C_6H_5$	Н	2.45
(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> CCOOH	3.96	_	$C_6H_5$	C <sub>6</sub> H <sub>5</sub>	$C_6H_5$	2.94
CH <sub>2</sub> ClCH <sub>2</sub> COOH	4.08	0.385	CH <sub>2</sub> Cl	H	Н	2.52
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> COOH	4.31	0.215	$C_6H_5$	Н	Н	1.58
CF <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	4.49	0.320	CF <sub>3</sub> CH <sub>2</sub>	Н	Н	1.50
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	4.66	0.080	$C_6H_5CH_2$	Н	Н	1.195
CH₃COOH	4.76	0.00	Н	Н	Н	1.47
(CH <sub>3</sub> ) <sub>2</sub> CHCOOH	4.86	-0.19	$CH_3$	$CH_3$	н	0.49
CH <sub>3</sub> CH <sub>2</sub> COOH	4.88	-0.100	$CH_3$	Н	Н	0.98
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	4.82	-0.115	$CH_3CH_2$	Н	Н	0.88
CH <sub>3</sub> CH <sub>2</sub> (CH <sub>3</sub> )CHCOOH	4.78	-0.21	CH <sub>3</sub> CH <sub>2</sub>	$CH_3$	H	0.39
(CH <sub>3</sub> ) <sub>3</sub> CCOOH	5.05	-0.30	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	0.00

TABLE 1. Acid strength data related to the Taft correlation for substituted acetic acids

 $^{a}$ All p $K_{a}$  values were taken from ref. 10 except those of the monohalogenoacetic acids, which were taken from ref. 11. The substituent constant parameters were taken from tabulations in ref. 9.

should be amenable to a linear free energy treatment such as that proposed by Taft (9). A test of such a hypothesis has been presented already by Streitwieser and Klein (5) and a further modification of their work will be presented here, using the Taft equation as applied to the acidities of carboxylic acids of the type  $XCH_2COOH$ .

The original correlation presented by Taft (9) for the  $pK_a$ 's of a series of seven carboxylic acids (X-COOH) was of the form:

[1] 
$$\log K/K_0 = (1.721 \pm 0.025)\sigma^*$$

where  $\sigma^*$  is the Taft substituent constant of the group X attached to the carboxyl group. Equation 1 can be rewritten in the form:

[2] 
$$pK_a = -(1.721 \pm 0.025)\sigma^* + 4.76$$

Extension of the empirical data to 26 substituted acetic acids (Table 1) gives:

[3] 
$$pK_a = -(1.603 \pm 0.030)\sigma^* + 4.604 \pm 0.029$$

with average r.m.s. deviation of  $\pm 0.16 \text{ pK}_a$  units. In cases where the group X can be treated as a substituted methyl group, *i.e.*  $X = CX_1X_2X_3$ , it is possible to set up a modified version of eq. 3 in which the total inductive effect of the group X is measured to a first approximation, by the sum of the separate contributions of  $X_1$ ,  $X_2$ , and  $X_3$ , leading to a quantity  $\sum \sigma^*$  which is defined by the equation:

[4] 
$$\sum \sigma^* = \sigma^*(X_1) + \sigma^*(X_2) + \sigma^*(X_3)$$

For the 22 substituted acetic acids listed in Table 1, for which values of  $\sum \sigma^*$  are available, a least squares treatment gives:

[5] 
$$pK_a = -(0.550 \pm 0.059)\Sigma\sigma^* + 5.200 \pm 0.014$$

leading to an average r.m.s. deviation of  $\pm 0.25$  p $K_a$  unit. This correlation is evidently inferior to that presented in eq. 3; nevertheless, it is possible to use the experimental K(H)/K(D) ratios for the pairs CH<sub>3</sub>COOH/CD<sub>3</sub>COOH and (CH<sub>3</sub>)<sub>3</sub>-

CCOOH/(CD<sub>3</sub>)<sub>3</sub>CCOOH in conjunction with eq. 5 to evaluate  $\sigma^*(D)$  and  $\sigma^*(CD_3)$ . The K(H)/K(D) ratio for the acetic acid pair is well established (5, 12), the ratio for the pivalic acid pair is that reported by Streitwieser and Klein (5). Substituting these ratios in eq. 5 gives  $\sigma^*(D) = 0.482$  and  $\sigma^*(CD_3) = -0.011$ . These values, together with eqs. 5 and 3 make it possible to evaluate theoretical K(H)/K(D)values for the remaining carboxylic acids in Table 2. Hall (13) has demonstrated that the  $pK_a$ 's of primary, secondary, and tertiary amines are respectively correlated with the Taft  $\sigma^*$ parameter according to the equations:

[6]  $pK_a(primary) = -3.14 \sum \sigma^* + 13.23$ 

[7] 
$$pK_a(secondary) = -3.23 \sum \sigma^* + 12.13$$

[8] 
$$pK_a(\text{tertiary}) = -3.30 \sum \sigma^* + 9.61$$

where the  $\sum \sigma^*$  parameter now refers to the substituents bound to nitrogen. From eqs. 6 and 7 and the value previously calculated for  $\sigma^*(CD_3)$ , the K(H)/K(D) ratios for the ammonium acid pairs investigated by Robertson and coworkers (3, 4) can be calculated.

An examination of the predictions in Table 2 reveals that the calculated isotope ratios are qualitatively consistent with the inductive treatment. Quantitatively, however, the agreement is poor. The observed ratio for the pair PhCH<sub>2</sub>-COOH/PhCD<sub>2</sub>COOH is particularly difficult to understand since there is no obvious reason why the phenyl group should enhance the isotope effect observed in the case of acetic acid, particularly when the number of deuterium atoms per molecule is reduced.

One can conclude from the above discussion that there is clearly a need for a broader experimental basis from which to construct generaliza-

TABLE 2. Predicted and observed isotope effects

	$K(\mathrm{H})/K(\mathrm{D})$				
Isotopic Pair	Observed (ref.)	Calculated			
CH <sub>3</sub> COOH/CD <sub>3</sub> COOH	1.035 (12)				
(CH <sub>3</sub> ) <sub>3</sub> CCOOH/(CD <sub>3</sub> ) <sub>3</sub> CCOOH HCOOH/DCOOH	1.04 (5) 1.07 (5)	1.03			
CH <sub>3</sub> CH <sub>2</sub> COOH/CD <sub>3</sub> CH <sub>2</sub> COOH	1.01 (1)	1.014			
PhCH <sub>2</sub> COOH/PhCD <sub>2</sub> COOH	1.08(1) 1.12(1)	1.021			
$CH_3^+NH_3/CD_3^+NH_3$ $(CH_2)_2^+NH_2/(CD_2)_2^+NH_2$	1.13(3) 1.32(3)	1.083			
$(CH_3)_2 + NH_2 (CD_3)_2 + NH_2 (CH_3)_3 + NH_2 (CD_3)_3 + NH_2 (CD_3) + NH_2 (CD_3)_3 + NH_2 (CD_3) + NH_2 $	1.53 (4)	1.29			

tions (14). To this end we report here a reinvestigation of phenylacetic acid. We also report K(H)/K(D) ratios for the pairs 4-MeO-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>COOH/4-MeO-C<sub>6</sub>H<sub>4</sub>CD<sub>2</sub>COOH and 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>COOH/4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>CD<sub>2</sub>-COOH. To a first approximation, the simple inductive treatment outlined above suggests that the isotope effect on these three systems should be constant and considerably smaller than that reported by Halevi (1) for the unsubstituted isotopic pair.

At the commencement of the present study isotope effects of the order of 12% were anticipated.<sup>1</sup> Secondary isotope effects of the second kind which reach this magnitude must be considered as large. For instance, the introduction of the methoxy substituent into the aromatic ring of phenylacetic acid produces about the same effect on acidity as replacing the methylene hydrogens in the same molecule by deuterium in the unsubstituted acid.

A careful survey of the rather extensive conductance data available for carboxylic acids suggested that it should be possible to measure individual  $K_{\rm a}$  values to  $\pm 0.2\%$  without undue difficulty and it was hoped that this order of accuracy would suffice to detect substituent effects on secondary isotope effects if they existed. The requirements for precise measurements of acid dissociation constants are implied in some very careful work reported by Ives and coworkers (11, 15). The high precision obtained by the Ives' group is probably a consequence of the strength of the acids studied  $(K_a \simeq 10^{-3})$ . It would appear that the phenylacetic acids, which are *ca*. 10 times weaker, are less suitable to the conductance technique for reasons which will be considered subsequently. Thus with respect to the individual  $K_a$ 's for the protium and deuterium analogs we prefer to describe the present study as one of intermediate accuracy. However, if certain conditions are met it appears possible to determine K(H)/K(D) ratios for an isotopic pair with much higher precision than the individual  $K_{\rm a}$  values and in this respect the conductance method would appear to be superior to other methods which might be chosen.

### Experimental

General

All melting points and boiling points are uncorrected. N.m.r. spectra were obtained using a Varian A60 spectro-

<sup>1</sup>Assuming the veracity of the data in ref. 1.

meter and chemical shifts are reported on the  $\tau$  scale relative to tetramethylsilane (TMS) as an internal standard. Both n.m.r. and a v.p.c./combustion technique (16) were used for deuterium analysis. All organic solvents were distilled prior to use or were of known grade of purity.

## Preparation of Materials

### Protium Acids

The protium acids used in the present study, acetic acid, phenylacetic acid, 4-methoxyphenylacetic acid, and 4-nitrophenylacetic acid were commercial samples or samples prepared by well established routes. In some cases more than one batch of the acid was prepared and each batch was intensively purified. The constancy of the  $K_a$  as determined by conductance was taken as the main criterion of purity since the conductance technique is very sensitive to contaminants in both solvent and solute alike.

#### Acetic Acid

Acetic acid (A.R. Grade) was fractionally frozen twice and then fractionated using a gold spinning band column with liberal rejection of the initial and tail fractions. The fraction used for the dissociation constant measurements had a b.p. 117.5-118 °C/750 mm Hg.

#### Phenylacetic Acid

*Runs 1–6.* A commercial sample of phenylacetic acid was recrystallized twice from conductivity water and once from pentane (b.p. 40-50 °C). It was stored over phosphorus pentoxide for 2 days and then over silica gel.

Runs 9–17.<sup>2</sup> A sample of phenylacetic acid was crystallized twice from water and then sublimed. It was then recrystallized twice from cyclohexane and once from water. The specimen resulting from this purification procedure was dried *in vacuo* in a drying pistol at the temperature of boiling acetone.

#### 4-Nitrophenylacetic Acid

*Runs 5–8.* A commercial sample of 4-nitrophenylacetic acid was recrystallized twice from conductivity water, sublimed, and then recrystallized two more times from the same solvent. The sample so purified was then dried using the same technique employed in the case of the final specimen of phenylacetic acid.

*Runs 9–11.* A sample of the acid was sublimed, recrystallized twice from water, and then dried in the same manner as the sample used in runs 5-8.

## 4-Methoxyphenylacetic Acid

4-Methoxybenzyl chloride was synthesized according to the method of Lee and co-workers (17) and was 'converted to the cyanide as described by Friedman and Shechter (18). The 4-methoxybenzyl cyanide was hydrolyzed with alcoholic sodium hydroxide. The resulting sodium salt was dissolved in the minimum of water and 4-methoxyphenylacetic acid precipitated by adding hydrochloric acid. The precipitated acid was collected, washed with cold water and pentane, and dried *in vacuo* over phosphorus pentoxide, m.p. 85–86 °C (lit. m.p. 86 °C (19)).

*Runs 1–6.* A sample of the acid was recrystallized from water, dissolved in carbonate, and treated with charcoal. The resulting solution was then treated with hydrochloric acid and the product recrystallized twice from cyclohexane. Two further recrystallizations from conductivity water were carried out and the sample was dried in the same manner as the final specimen of the unsubstituted acid.

### The Deuterated Acids

The deuterated acids were all prepared by an exchange reaction in deuterium oxide using triethylamine as a catalyst. The progress of the exchange was monitored by n.m.r. using the integration of the methylene protons against the aromatic protons of the acid. It was reasonably assumed that no exchange of the aromatic protons took place under the relatively mild basic conditions used in these experiments (20).

#### Phenylacetic- $\alpha$ , $\alpha$ - $d_2$ Acid

Phenylacetic acid (10 g), dissolved in deuterium oxide (15 ml) and triethylamine (5 ml), was placed in a flask equipped with both a condenser and drying tube. The flask was heated in an oil bath at 110 °C for 52 h, and after this period n.m.r. analysis on an aliquot of the solution indicated 88.2% deuteration at the methylene position. The contents of the flask were cooled and the mixture was acidified with DCl (6 N) prepared from deuterium oxide and the appropriate quantity of purified thionyl chloride. The precipitated acid was washed with cold cyclohexane and dried over phosphorus pentoxide in vacuo for 24 h. A second exchange was carried out with the partially exchanged acid using the procedure described above at 82 °C for 96 h. Analysis of this material by n.m.r. indicated 96.7% deuteration. A further exchange (48 h) followed by recovery of the acid (see above) gave a specimen of the acid which on recrystallization from cyclohexane and water had m.p. 75-76 °C. The purified specimen contained 98% deuterium in the methylene position as judged by an n.m.r. spectrum in carbon tetrachloride (overall yield 75%). Samples of the acid prepared in this way were subjected to further purification procedures (see below) with no sensible decrease in deuterium content as judged by n.m.r. analysis. The deuterated acid purified for the conductance measurements (see below) was subjected to a combustion/v.p.c. analysis (see ref. 16) giving 1.87 D/molecule (93.6% methylene deuteration). The reason for the discrepancy between the n.m.r. and combustion/v.p.c. analysis is not understood.3

Phenylacetic- $\alpha, \alpha - d_2$  acid was purified for conductance measurements using the following procedures:

*Runs 1–4.* The deuterated acid was dissolved in carbonate solution and charcoal added. The solution was warmed and filtered hot and the filtrate treated with concentrated hydrochloric acid. The resulting acid was recrystallized twice from water and dried in a pistol for 3 days *in vacuo* at the temperature of boiling acetone.

*Runs 5–10.* A sample of the deuterated acid was crystallized from water, dried (see above), and then recrystallized from cyclohexane. The acid was then sublimed

<sup>&</sup>lt;sup>2</sup>In some cases runs were rejected. Runs 7 and 8 in the phenylacetic acid series were not used because desiccation of a specimen of this acid over phosphorus pentoxide led to decomposition. The runs reported for all the structures examined constitute over 75% of all the data recorded.

<sup>&</sup>lt;sup>3</sup>Even if the lower analytical results are correct, the influence of the low deuteration on the measured K(H)/-K(D) ratios is insignificant (21).

and recrystallized twice from water and dried for 4 days in the same manner as the specimen used in runs 1-4.

*Runs 11–16.* A sample of the deuterated acid was sublimed, recrystallized twice from cyclohexane, and then once from water. The sample was dried for 3 days as above.

### 4-Nitrophenylacetic- $\alpha$ , $\alpha$ - $d_2$ Acid

4-Nitrophenylacetic acid (10 g) was added to deuterium oxide (15 ml) and triethylamine (5 ml) and the resulting solution heated at 50 °C for 11 h. An n.m.r. spectrum of this solution showed 89.6% deuteration of the methylene protons. Concentration of this solution followed by the addition of fresh deuterium chloride (see above) and purification of the precipitated acid by recrystallization from ether-pentane gave a product, m.p. 147-150 °C (lit. 152 °C (22)), subsequent to desiccation in vacuo over silica gel. A further deuteration of this product at T =50 °C, (t = 11 h) gave a sample 98.8% deuterated, m.p. 148.8-150 °C. The latter was recrystallized 3 times from cyclohexane and once from water and dried at the temperature of refluxing acetone for 24 h over silica gel. A v.p.c./combustion analysis indicated that this material contained 1.85 D/molecule (92.5% methylene deuteration). The discrepancy between the n.m.r. and combustion analysis is again apparent (see footnote 3).

4-Nitrophenylacetic- $\alpha, \alpha, d_2$  acid was purified for conductance using the following procedure:

*Runs 1–5.* The deuterated acid was recrystallized 3 times from cyclohexane, once from water and dried for 24 h in a pistol *in vacuo*.

## 4-Methoxyphenylacetic-a,a-d2 Acid

4-Methoxyphenylacetic acid (10 g) was treated with deuterium oxide (15 ml) and triethylamine (5 ml), following the procedure for deuteration of phenylacetic acid. After a period of 23 h at 100 °C an aliquot of the solution indicated 88.2% deuteration by n.m.r. analysis. Two further exchanges of the acid in deuterium oxide increased the isotopic purity to at least 98%.

4-Methoxyphenylacetic- $\alpha, \alpha$ - $d_2$  acid was purified for conductance measurements using the following procedures:

#### Conductance measurements

*Runs 1–4.* A sample of the deuterated acid was recrystallized from cyclohexane, sublimed, recrystallized from cyclohexane and dried in a pistol at 80  $^{\circ}$ C for 3 days.

*Runs 5–6.* The above material was recrystallized from water and dried for several days at 80  $^{\circ}$ C.

#### Potassium chloride purification

Method I. Potassium chloride (Fisher Scientific A. R. Grade) was precipitated from a saturated aqueous solution prepared from conductivity water by addition of 95% ethyl alcohol and this procedure was repeated 3 times. The salt was collected by filtration, thoroughly washed with 95% ethyl alcohol, and dried *in vacuo* for several days at 110 °C. The salt was carefully powdered with an agate mortar and pestle and returned to the drying pistol for a further 2 days.

Method II. A second sample of potassium chloride was prepared by twice precipitating a saturated solution of the salt with concentrated hydrochloric acid (A.R. Grade) and once with 95% ethyl alcohol. The subsequent treatment of this specimen was identical to that described above. Experimental Assembly and Technique

The apparatus and techniques used follow the practice of Jones and Bradshaw (23), Shedlovsky (24), and Robertson (25).

Resistances were measured on a Jones-Joseph type conductivity bridge (23) manufactured by the Tinsley Company and on a General Radio Impedance Bridge. The Tinsley Bridge, model 4896, and accessories were assembled following the description of Robertson (25) with minor modifications made necessary because some of the components were no longer commercially available. A Hewlett Packard 1000 c.p.s. AC oscillator was connected to the bridge and the balance was detected by observing a Lissajous pattern on a Hewlett Packard model 120B oscilloscope. The detector for the General Radio impedence bridge was a G.R. 1232-A tuned amplifier and a null detector. The coarse balance on this bridge was also determined with an oscilloscope (see above). Comparison of the two bridges over the resistance range  $500 - 12000 \Omega$ showed an agreement of better than 0.05%.

Conductivity water was prepared by passing tap water of low solid content into a deionizer (Ion Exchange Products Inc., Amberlite MB-1), followed by distillation from a Barnstead still. The distillate so produced was stored in two three-necked flasks (10 l) with teflon stoppers. The flasks were treated for 3 days with boiling nitric acid and approximately a week with steam prior to use. Final purification of the water, immediately prior to the preparation of the solutions, involved treatment with a second deionizer of Amberlite resin and the collection of the pure water under an atmosphere of purified nitrogen which had been freed from all acidic and basic contaminants. Conductivity water prepared in this manner was not used for the preparation of solutions unless the specific conductivity fell in the range 1.8  $\times$  $10^{-7}$  to 3.5 ×  $10^{-7}$  Ω cm<sup>-1</sup>.

Conductivity cells were of the Shedlovsky type (24). The cells were constructed of Pyrex glass and the electrodes were made of shiny platinum. The resulting cell constants for the five cells used were in the range 0.08–0.20. The cells described above and all glassware required for the preparation of solutions were treated with concentrated nitric acid at a temperature of 100 °C for a period of 3 days. The glassware was then steamed for the same length of time and finally rinsed several times with conconductivity water.

All solutions of potassium chloride and the carboxylic acids were prepared by weight and the concentrations reported on the molal scale.<sup>4</sup> Weighings were performed on a Sartorius analytical balance which could be read to 0.01 mg. Water and stock solutions were weighed on a large two pan balance to the nearest 10 mg. Weights were calibrated against a set of weights standardized by the National Physical Laboratory, England. Solutions were kept under purified nitrogen at all times.

All conductivity measurements were carried out at  $25 \pm 0.005$  °C. A 20 gal stainless steel tank, filled with transformer oil, was maintained at 25 °C by heating and

<sup>4</sup>The aqueous solutions of 4-nitrophenylacetic acid were distinctly photolabile. Solutions of this acid were thus made and manipulated in the dark. This fact also accounts for the rejection of runs 1–4 for this compound (see Table 7).

CAN. J. CHEM. VOL. 51, 1973 TABLE 3. Cell constant determinations

$10^3c$ (molal)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5
1.3964	0.13622	0.19832		0.16459	
1.3892	0.13587	0.19847		0.16465	
1.3939	0.13591	0.19832		0.16474	
1.6170	0.13590	0.19852		0.16478	
1.7385	0.13590	0.19823	0.086881	0.16464	0.18160
Average k	0.13596	0.19837	0.086881	0.16468	0.18160
Deviation	$\pm 0.00017$	$\pm 0.00014$		$\pm 0.00009$	

[10]

[11]

cooling the bath simultaneously. Cooling was effected by passing cold water from a 15 gal stainless steel tank through a circulating pump into a cooling coil in the bottom of the oil bath. The rate of flow of water through the cooling coil was regulated using a by-pass arrangement incorporating two control valves. The temperature of the cooling water was maintained at  $17.5 \pm 0.3$  °C using a Techumseh 1/4 h.p. refrigerator regulated by a Wheatstone Bridge - thermistor circuit. The temperature of the oil bath was regulated by a Sargent Thermonitor (S-82050). The basic components of this device are a background heater (125 W), controlled by a variac with an intermittent knife heater (250 W), operated by a thermistor Wheatstone Bridge circuit, coupled to a variable reactor. The voltage across the bridge was reduced from 6 to 4 V resulting in considerable improvement in the performance of this device.

A platinum resistance thermometer, calibrated by the National Physical Laboratory, was used in conjunction with a Mueller Temperature Bridge, type 4772, to measure the temperature of the regulated bath in which the conductance measurements were made. Over long periods of time the bath temperature was conveniently monitored on a Honeywell recorder connected to a Wheatstone Bridge circuit containing a Fenwal thermistor as a sensing device.

# Results

## Cell Constants

Cell constants were determined by measuring the resistance of aqueous solutions of two independent samples of purified potassium chloride at 25 °C over the concentration range 0.001364-0.0017385, employing both the General Radio impedance bridge and the Tinsley conductivity bridge. The weights of the salt and solvent were corrected for buoyancy. Since the equation of Fuoss (26) relating equivalent conductance of KCl solutions to the concentration

[9] 
$$\Lambda = 149.93 - 94.65c^{1/2} + 58.74c \cdot \log c + 198.4c$$

is given using the molarity scale, conversion of the concentrations from the molal to the molarity scale was necessary. These corrections were accomplished using the expressions (27).

$$V = N_0 V_0 + N_1 Q_1$$

$$Q_1 = 26.52 + 2.327 (C_2)^{1/2}$$

where V represents the volume of the solution,  $N_0$ , the number of moles of water,  $N_1$ , the number of moles of KCl,  $V_0$  the volume of a mole of water at 25 °C,  $Q_1$  the molal volume, and  $C_2$  the approximate concentration of the solution. These corrections were very small.

The value of the equivalent conductance at the concentrations studied was calculated using the Fuoss expression and the cell constants were evaluated from the expression

[12] 
$$\Lambda = \frac{10^3}{c} \kappa \left[ \frac{1}{R} - \frac{1}{R_s} \right]$$

where  $\kappa$  represents the cell constant and *R* and  $R_s$  represent the resistance measurements of the solution and pure solvent respectively.

The five cell constants so determined are reported in Table 3.

## Conductance Data

The conductance data calculated in the usual way for the acids acetic, phenylacetic, phenylacetic,  $\alpha, \alpha$ - $d_2$ , 4-methoxyphenylacetic, and 4-methoxyphenylacetic- $\alpha, \alpha$ - $d_2$  in water at 25  $\pm$  0.01 °C<sup>5</sup> are listed in Tables 4 to 10. The thermodynamic ionization constants were calculated using a treatment of conductance data developed by Shedlovsky (28) and modified by Robinson and Stokes (29). No corrections for solvent conductivity were made to the acid solutions as there is no obvious way of making such a correction.

The details of the Robinson and Stokes method (RSM) of calculating thermodynamic equilibrium constants, along with several iteration–extrapolation methods, will be presented in

<sup>&</sup>lt;sup>5</sup>The regulation of the bath was better than these limits.

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# TABLE 4. Conductance data for acetic acid

104	D	Cell number and equivalent conductance					
$10^{\circ}c$ Run (molal) no.	1	2	3	4	5	$10^{\circ}K_{a}^{\circ}$ (RSM)	
40.55	5	25,104	25.108	25,121	25,098	25,109	1.7575
28.424	1	29.732	29.731	29.747	29.720	29.747	1.7538
23.264	2	32.740	32,729	32,756	32,729	32.735	1.7566
11.103	6	46.447	46.431	46,470	46.419	46.432	1.7612
10.133	7	48.396	48.366	48,413	48.376		1.7556
14.326	3	41.160	41.159	41.187	41.153	41.159	1.7561
5.9920	4	61.624	61.602	61.654	61.586	61.604	1.7555
4.1870	8	72.461	72.422	72.482	72.419		1.7564

 ${}^{a}K_{a} = 1.7566 \pm 0.0025 \times 10^{-5}.$ 

TABLE 5. Conductance data for phenylacetic acid

$10^4 c$ Run	D		Cell number and equivalent conductance					
(molal) $(10^{4}c)$	(molal) no.	1	2	3	4	5	$10^{5}K_{a}^{\mu}$ (RSM)	
69.879	11	31.027	31.040	31.040	31.010	31.044	4.9074	
63.076	5	32.528	32.548	32.535	32.535		4.8955	
58.984	10	33.601	33.647	33.637		33.657	4.9108	
47.217	9	37.399	37.401	37.402	37.392	37.407	4.9236	
44.067	6	38.563	38.584	38.574	38.574		4.9078	
36.858	3	42.003	42.017	42.000			4.9251	
28.300	13	47.526	47.530	47.553	47.508	47.528	4.9321	
27.574	4	48.090	48.116	48.116	48.106		4.9328	
22.612	1		52.603	_	52.575		4.9078	
18.720	2	57.389	57.411	57.311	57.428		4.9167	
17.139	12	59.864		59.896	59.845	59.876	4.9409	
2.7688	16	130.73	130.5805	130.79	130.59	130.61	4.9368	
2.5118	14	135.78	135.6734	135.90	135.67		4.9384	
1.3591	15	170.56	170.2319	170.70	170.38	170.38	4.9252	
1.0855	17	184.35	184.1449	184.56	184.19	184.15	4.9290	

 ${}^{a}K_{a} = 4.9297 \pm 0.0150 \times 10^{-5}$ .

TABLE 6. Conductance data for phenylacetic- $\alpha$ ,  $\alpha$ - $d_2$  acid

$10^4 c$ Run	Cell number and equivalent conductance						
(molal)	(molal) no.	1	2	3	4	5	$10^3 K_a^a$ (RSM)
62.284	8	32.649	32.651	34.641	32.632	32,662	4.8692
49.732	7	36.343	36.344	-	36.326	36.326	4.8796
49.034	10	36.602	36.595	36.612	36.579	36.608	4.8836
34.855	6	43.006	43,002	43.015	42,985	43.001	4.8976
31.922	5	44.780	44.775	44.803	44.756	44.791	4.8936
27.031	4	48.351	48.368	48.392	48.346	48.364	4.8922
24.213	3	50,986	50.995	51.019	50.970	51.002	4.9148
23.347	2	51.859	51.838	51.886	51.839	51.865	4.9151
17.765	9	58.717	58.702	58.744	58.687	58.721	4.9067
11.034	1	72.834	72.820	72.845	72.806	72.832	4.9204
6.3995	14	92.391	92.357	92.445	92.335	92.371	4,9208
4.9907	12	102.64	102.63	102.69	102.61	102.62	4.9202
4.2937	11	109.30	109.24	109.43	109.22	109.28	4.9226
3.1564	15	123.87	123.80	124.00	123.78	123.80	4.9187
2.8839	13	128.32	128.20	128.41	128.38	128.31	4.9110
2.0516	16	146.52	146.36	146.72	146.39	146.40	4.9175

 $^{a}K_{a} = 4.9055 \pm 0.0173 \times 10^{-5}.$ 

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## TABLE 7. Conductance data for 4-nitrophenylacetic acid

			Cell number and equivalent conductance					
$\begin{array}{ccc} 10^4c & \text{Run} \\ \text{(molal)} & \text{no.} \\ \hline \end{array}$	1	2	3	4	5	$\frac{10^4 K_a^u}{(\text{RSM})}$		
16.011	11	94.833	94,909	94.934	94.868	94.932	1.3212	
10.442	10	113.44	113.44	113.38	113.40	113.48	1.3231	
2.8615	5	184.50	184.15	184.67	184.58	184.57	1.3277	
2.6242	7	189.85	189.28	190.05	189.58	189.92	1.3260	
1.5010	9	225.55	225.30	225,67	225.35	225.39	1.3281	
0.94570	6	255.30	254.92	255.36	255.00	255.00	1.3375"	
0.63893	8	278.71		278.99	278.72		1.3446	

 ${}^{a}K_{a} = 1.3241 \pm 0.0045 \times 10^{-4}.$ <sup>b</sup>Not included in mean  $K_{a}$ .

TABLE 8. Conductance data for 4-nitrophenylacetic- $\alpha$ ,  $\alpha$ - $d_2$  acid

	_		104 77 4				
10⁴ <i>c</i> (molal)	Run no.	1	2	3	4	5	(RSM)
2.4238	1	194.66	194.68	194.89	195.69	194.72	1.3250
1.1573	2	241.94	241.74	242.39	241.86	241.86	1.3264
1.3102	4	233.55	233.68	234.03	233.77	233.85	1.3203
0.57311	3	284.47	283.97		283,94	284.04	1.3250
0.48222	5	293.72	293.29		293.33		1.3245

 ${}^{a}K_{a} = 1.3240 \pm 0.0048 \times 10^{-5}.$ 

TABLE 9.	Conductance	data for	· 4-methoxy	phenvlacetic	acid

104	P		Cell number and equivalent conductance					
$\begin{array}{ccc} 10^{4}c & \text{Run} \\ \text{(molal)} & \text{no.} \end{array}$	1	2	3	4	5	(RSM)		
10.838	1	68.711	68.976	69.016	68.959		4.3331	
8.0969	5	78.524	78.509	78.555		78.527	4.3471	
4.6775	2	99.521	99.489	99.556	99.460		4.3501	
4.2055	3	104.01	104.01	104.11	103.99		4.3486	
3.2173	6	116.25	116.20	116.30		116.20	4.3532	
1.7463	4	147.73	147.70	147.83		147.67	4.3533	

 ${}^{a}K_{a} = 4.3493 \pm 0.0053 \times 10^{-5}$ .

TABLE 10. Conductance data for 4-methoxyphenylacetic- $\alpha$ ,  $\alpha$ - $d_2$  acid

101	D		Cell number	r and equivalent	conductance		105 12 4
$\begin{array}{ll} 10^4c & \text{Run} \\ \text{(molal)} & \text{no.} \end{array}$	Run no.	1	2	3	4	5	$10^{3}K_{a}^{a}$ (RSM)
10,749	6	69.028	69.049	69.081	69.031		4.3175
3.6980	3	109.40	109.44	109.56	109.44	109.46	4.3202
3,4958	4	111.80	111.89	111.86	111.90		4.3068
3.2833	1	114.86	114.91		114.91	114.96	4.3172
1.9913	5	140.14	140.05	140.28	140.08	140.08	4.3204
1.6582	2	150.09	149.98	150.25	150.00	150.00	4.3099

 ${}^{a}K_{a} = 4.3162 \pm 0.0080 \times 10^{-5}.$ 

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TABLE 11. Comparison of equilibrium constants

Acid	10 <sup>5</sup> K <sub>a</sub>	Method <sup>a</sup>	Ref.
Acetic	$1.757 \pm 0.003 \ (\Lambda_0 = 389.6)^b$	RSM(m)	This work (33) <sup>c</sup>
	1.754	E.m.f.(m)	(30)
	1.76	C(c)	(22)
	1.759	I(c)	(31)
	1.758	RSM(m)	(32)
	1.753	RSM(c)	(33)
Phenylacetic	$4.923 \pm 0.015 \ (\Lambda_0 = 379.6)^b$	RSM(m)	This work (35) <sup>c</sup>
-	4.88	C(c)	(22)
	4.88	E.m.f.	(34)
	4.884	C(c)	(35)
	4.95	RSM(c)	(35)
	$4.928 \pm 0.011$	E.m.f.(m)	(36)
	$4.887 \pm 0.056$	C(m)	(37)
	4.90	I(c)	(38, 39)
4-Nitrophenylacetic	$13.25 \pm 0.05 (\Lambda_0 = 376.6)^b$	RSM(m)	This work (22) <sup>c</sup>
	$10.4 (\Lambda_0 = 414)$	C(c)	(40)
	$12.94 (\Lambda_0 = 377.8)$	C(c)	(22, 40)
	14.1	C(c)	(22)
	$11.91 \pm 0.36$	C(m)	(37)
4-Methoxyphenylacetic	$4.349 \pm 0.005 \ (\Lambda_0 = 377.3)^b$	RSM(m)	This work (19) <sup>c</sup>
	4.36	C(c)	(19)
	$4.406 \pm 0.031$	C(m)	(37)

<sup>a</sup>C, conductance method; RSM, Robinson–Stokes method; I, Ives method; c, mol/l; m, mol/1000 g.  ${}^{b}\Lambda_{0}$ (molal) used in RSM calculations. <sup>c</sup>Literature ref. for  $\Lambda_{0}$ (molar). The conversion of  $\Lambda_{0}$ (molar) to  $\Lambda_{0}$ (molal) was made in the usual way.

Part II of this series. The  $K_a$  values determined by the RSM agree very favorably with previous measurements on these acids (Table 11) apart from 4-nitrophenylacetic acid. The large discrepancy in the  $K_a$  values for the 4-nitro acid is almost certainly a consequence of the labile nature of this molecule when it is exposed to light. Since the previous workers failed to recognize this fact the value reported here is to be preferred.

A comparison of the  $K_a$  values calculated for the individual acid samples confirms the purity of each specimen used. In no case can any discrimination be made between the various samples within the precision of the results of the present study. The redetermined equilibrium constant for acetic acid is also in excellent agreement with previous values and offers further confirmation of reliability of our work.

#### Discussion

The thermodynamic equilibrium constants calculated using the RSM provide a method of evaluating K(H)/K(D) for each of the three isotopic pairs (X = H, NO<sub>2</sub>, OMe). A further method for calculating the isotope effect is provided by the classical plot. We deal with these methods individually below.

The RSM is a well-established treatment and has been used by several authors (41). This method requires, aside from equivalent conductance data of the acid at finite concentrations, a value of the limiting equivalent conductance. To evaluate the isotope effect we assume that  $\Lambda_0(\text{ArCH}_2\text{COO}^-) = \Lambda_0(\text{ArCD}_2\text{COO}^-)$  for all the aryl groups investigated. The equilibrium constants  $(K_a)$  calculated by the RSM reveal a slight residual concentration dependence which is probably outside our experimental error. This residual concentration dependence of  $K_a$  may be a consequence of the breakdown of the theoretical expression at higher concentrations or alternatively may result from the neglect of the frequency dependence of the electrolyte resistances. In the most precise study to date (11, 15), the latter factor has been considered important. While the RSM provides a suitable method for establishing the absolute values of the individual equilibrium constants the relative values of the H and D compounds are better established using a classical plot.

The classical plot connects the quantities  $\Lambda_0$ ,

 $\Lambda_c$ , c and  $K_c$  where  $\Lambda_0$ ,  $\Lambda_c$ , and c have their usual significance and the quantity  $K_c$  is the classical dissociation constant, *i.e.* the  $K_c$  parameter is calculated assuming the activity coefficients for both the ions and undissociated acid are unity at all concentrations. The appropriate equation connecting these quantities for the protium acid is

[13] 
$$\frac{1}{\Lambda_c(\mathrm{H})} = \frac{1}{\Lambda_0(\mathrm{H})} + \frac{\Lambda_c(\mathrm{H})c(\mathrm{H})}{\Lambda_0^2(\mathrm{H})K_c(\mathrm{H})}$$

Assuming  $\Lambda_0(H) = \Lambda_0(D)$  (see ref. 5 and above), a least squares correlation between the variables  $1/\Lambda_c$  and  $\Lambda_c c$  for the H and D acids yields slopes  $m_{\rm H}$  and  $m_{\rm D}$  which related to the isotope effect via the equation

[14] 
$$\frac{K_{\rm c}({\rm H})}{K_{\rm c}({\rm D})} = \frac{m_{\rm D}^{-6}}{m_{\rm H}}$$

The K(H)/K(D) ratios for the three isotopic pairs calculated by both RSM and classical plot are summarized in Table 12, and may be compared with Halevi's original measurement (ref. 1 and see Table 2).

Our new values are surprisingly small. Indeed, they are so small that the detection of substituent effects on isotope effects is only just inside the bounds of possibility. This is particularly unfortunate in the light of some recent

The greater length of C—H bonds vs. C—D bonds will probably be the most important factor altering  $\Lambda_0$  with isotopic substitution. Such changes in the molecular dimensions of the anions are very small but on the basis of some calculations we have made are likely to lead to differences in  $\Lambda_0(H)$  and  $\Lambda_0(D)$  such that the square of the ratio will differ from unity by ca. 1 part in 10<sup>4</sup>.

Because our isotope effects are small our referees pointed out the desirability of measuring the limiting equivalent conductances for the isotopic anions related to the acids examined in the present study to verify the reported isotope effects. Because the estimated differences in the isotopic limiting equivalent conductances are small and because these quantities must be obtained by some sort of extrapolation procedure we doubt the feasibility of such measurements. Aspects of this problem will be considered in the second paper of the present series.

TABLE 12.	Com	parison	of	isotope	effects
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	<i>p</i> -R-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> COOH/ <i>p</i> -R-C <sub>6</sub> H <sub>4</sub> CD <sub>2</sub> COOH				
	$K(\mathbf{H})/K(\mathbf{I})$	D)			
ι	Robinson-Stokes method	Classical plot			
-Iª	$1.004 \pm 0.005$	$1.0072 \pm 0.0004$			
NO <sub>2</sub>	$1.001 \pm 0.005$	$0.997 \pm 0.002$			
МeŌ	$1.008 \pm 0.002$	$1.0045 \pm 0.0007$			

\*Laughton and Demayo (39) have also measured K(H)/K(D) for this isotopic pair and give the ratio as  $1.009 \pm 0.002$  and  $1.008 \pm 0.005$  depending on the method of calculation used. However the absolute value of  $K_a$  for the protium acid reported by these workers differs from that reported here and is lower than all the values given in Table 11.

comments in a review by Thornton and Thornton (42). These authors suggest that substituent effects on isotope effects are significant parameters for a detailed understanding of transition states. One of the purposes of the present study was to obtain base line data of this sort for equilibria where the detailed specification of the states involved is clearcut in contrast to rates where the nature of the transition state is always elusive.

A comparison of these isotope effects for the arylacetic acids with the data of Streitwieser and Klein for the isotopic pair CH<sub>3</sub>COOH/CD<sub>3</sub>-COOH indicates that the K(H)/K(D) values are less for the former structures and this observation is qualitatively in accordance with the inductive treatment, i.e. as the number of deuteriums decrease at a given position with respect to the carboxyl group, the isotope effect should likewise decrease. The predicted isotope effect for the pair PhCH<sub>2</sub>COOH/PhCD<sub>2</sub>COOH, based on  $\sigma^*$  (D) (See Table 2), is closer to the K(H)/K(D) value determined in this laboratory than the ratio reported by Halevi and coworkers (1). The reasons for the difference between the result reported by Halevi and results presented here are not easily discerned.

It is now clear that Halevi's result is unduly large both in the light of the inductive treatment presented above and when examined by an alternative treatment based on the pair HCOOH/ DCOOH. The inductive effect of a substituent is known to increase as the substituent is moved closer to the reaction site (10). A rough calculation shows that the isotope effect for the pair HCOOH/DCOOH based on Halevi's value of K(H)/K(D) for the phenyl acetic acids would give a value of 1.15. This predicted value is much higher

<sup>&</sup>lt;sup>6</sup>The complete expression for the isotope effect is  $K(H)/K(D) = m(D)\Lambda_0^2(D)/m(H)\Lambda_0^2(H)$  and the validity of eq. 14 is restricted to those situations in which the ratio  $\Lambda_0^2(D)/\Lambda_0^2(H)$  is closer to unity than the ratio m(D)/m(H). The latter condition seems to be satisfied in previous measurements of isotope effects by conductance (3–5). In the present instance the reported isotope effects are relatively small and in consequence the proximity of  $\Lambda_0^2(D)/\Lambda_0^2(H)$  to unity may represent a significant factor with respect to the validity of the isotope effect calculated on the basis of eq. 14.

than the isotope effect (K(H)/K(D) = 1.06) measured by Bell and Miller (43).

We shall deal with the issue of these small secondary isotope effects more fully in subsequent communications together with some of our findings concerning the numerical evaluation of  $pK_a$ 's from weak acid conductance data which are of interest in their own right. However, we consider that the present paper provides the best values for the  $pK_a$ 's of 4-MeOC<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>COOH and 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>COOH and also values of the isotope effects which are worthy of theoretical attention.

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