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Secondary Deuterium Isotope Effects on the Acidity of Carboxylic Acids and Phenols

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Abstract: Secondary deuterium isotope effects (IEs) on acidities have been accurately measured by an NMR titration method applicable to a mixture of isotopologues. Deuteration definitely decreases the acidity of carboxylic acids and phenols, by up to 0.031 in the ΔpK per D. For aliphatic acids, the IEs decrease as the site of deuteration becomes more distant from the OH, as expected, but a surprising result is that IEs in both phenol and benzoic acid do not decrease as the site of deuteration moves from ortho to meta to para. The experimental data are supported by ab initio computations, which, however, substantially overestimate the IEs. The discrepancy does not seem to be due to solvation. The IEs originate in isotope-sensitive vibrations whose frequencies and zero-point energies are lowered upon deprotonation. In the simplest case, formate, the key vibration can be recognized as the C−H stretch, which is weakened by delocalization of the oxygen lone pairs. For the aromatic acids, delocalization cannot account for the near constancy of IEs from ortho, meta, and para deuteriums, but the observed IEs are consistent with calculated vibrational frequencies and electron densities. Moreover, the ability of the frequency analysis to account for the IEs is evidence against an inductive origin.

Introduction

Isotope effects (IEs) are informative features of rates and equilibria.[1] Primary IEs are those where a bond to the isotope is broken, in contrast to secondary IEs, where that bond remains intact. Kinetic IEs continue to provide valuable insight into mechanisms of organic,[2] bioorganic,[3] and enzymatic reactions.[4]

The best authenticated secondary IEs are kinetic IEs in S_N1 reactions,[5] where a carbon changes its hybridization from sp^3 to sp^2. This change is associated with a lowering of the C−H out-of-plane bending frequency ν, which reduces the zero-point energy ($=^1/_2h\nu$) in the transition state. The reduction for C−D is smaller because zero-point energy is inversely proportional to the square root of mass. Because the reduction for the protium substrate is greater, it reacts faster.

In 1963, Streitwieser and Klein reported classic measurements of the deuterium IEs on the acidity constants K_a of some carboxylic acids.[6] These are equilibrium effects, not kinetic. The acidity constants were measured by conductivities of the purified acids, so they could be quite precise, unless there were a systematic error due to an impurity in one of the samples. Table 1 lists the ΔpK_a between some acids and their isotopologues (species that differ in the number of isotopic substituents). The data show that deuteration reduces the acidity, although the reduction tends to decrease as the distance from the carboxyl group increases, especially if expressed on a per-deuterium basis.

These cases differ from solvolyses in that there is no rehybridization upon deprotonation. This cannot be a simple inductive effect, whereby protium is more electron-withdrawing than deuterium, because the Born−Oppenheimer Approximation guarantees that the electronic wave function is independent of nuclear mass.[7] Besides, the decrease of acidity is opposite to deuterium's electron-withdrawing power in solvolyses.

For formic acid, Streitwieser and Klein accepted an origin arising from zero-point energies, based on the agreement between the observed IE and the IE calculated from the experimental vibrational frequencies of HCOOH, HCO_2^-, DCOOH, and DCO_2^-. For other acids, they invoked an inductive effect on pK arising from an electrostatic interaction between the negative charge of the carboxylate and the dipole moment, μ, of a C−D bond, relative to a C−H bond. Since the dipole moment is the product of charge separation and bond length

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Table 1. Secondary Deuterium Isotope Effects on the Acidity of Carboxylic Acids

acidD	$pK_D - pK_H$[a]	$pK_D - pK_H$
DCO_2H	0.030 ± 0.004	0.0342[b]
CD_3CO_2H	0.014 ± 0.001	0.0134 ± 0.0005[c]
$(CD_3)_3CCO_2H$	0.018 ± 0.001	
2,6-$C_6H_3D_2CO_2H$	0.003 ± 0.001	0.0040 ± 0.0002[c]
$C_6D_5CO_2H$	0.010 ± 0.002	0.0099 ± 0.0001[c]

[a] Ref 6. [b] Ref 16. [c] Ref 17.

and since the C−H bond length is longer than that of C−D, owing to anharmonicity, deuterium might be electron-donating. Such an inductive effect remains consistent with the Born−Oppenheimer Approximation. Indeed, the Mulliken charges on the oxygens of the formate anion are calculated to be −0.729 in HCO_2^- and −0.731 in DCO_2^-, arising via the shorter C−D bond.[8] Such a greater negative charge might be sufficient to account for a greater basicity for DCO_2^-.

Equation 1 expresses this inductive effect on p*K*. The derivative, $\partial pK/\partial\mu$, was estimated from the effect of a C−Cl dipole on acidity using the difference in the p*K*s of trichloroacetic acid (0.63) and acetic acid (4.75) and the difference in the dipole moments of *tert*-butyl chloride (2.13 D) and isobutane (−0.13 D). Next, $\Delta\mu$ was estimated as 0.0086D, the difference between the dipole moments of $(CH_3)_3CD$ and $(CH_3)_3CH$.[9] Then, eq 1 gave a ΔpK per D of 0.005, in excellent agreement with the observed 0.014 for acetic-d_3 acid.

$$\Delta pK = \frac{\partial pK}{\partial \mu}\Delta\mu = \frac{\Delta pK}{\Delta n_{Cl}} \Big/ \frac{\Delta\mu}{\Delta n_{Cl}}\Delta\mu = \frac{1}{3}\frac{4.75 - 0.63}{2.13 + 0.13}0.0086 = 0.005 \quad (1)$$

This estimate depends crucially on that difference (0.0086 D) between the dipole moments of isobutane and isobutane-*d*, which is unusually large, amounting to 7% of their total dipole moment. For comparison, the difference between HCl and DCl is only 0.005 ± 0.002 D, or ∼0.5% of the total dipole moment (1.08 D)[10] of their much more polar bond. Indeed, it was recognized that the observed difference in isobutane is rather high and may be due to contributions from bending modes. An alternative estimate of $\Delta\mu$ is 1×10^{-4} D, based on $d_{CH} - d_{CD} = 0.5$ pm, due to anharmonicity (for a Morse potential with a dissociation energy of 100 kcal/mol)[11] and a derivative of dipole moment with respect to C−H distance of 0.004e from the infrared intensities of methane.[12] Application to eq 1 then leads to a ΔpK per D of 0.00006, which is 2 orders of magnitude lower than either the earlier estimate or the observed IE.

Further doubts have been expressed about the necessity of invoking an inductive effect. The IE in formic acid agrees with the totality of experimental vibrational frequencies and zero-point energies.[13] Likewise, the IE in acetic acid agrees with the vibrational force field, but it is very sensitive to the choice of force constants.[14]

Because of these questions, it is important that the experimental data be incontrovertible. They do differ from earlier values for acetic acid.[15] Subsequent measurements, though, have confirmed the value for formic acid[16] and for other acids.[17] These rely on NMR titrations that accurately fit the variation of chemical shifts with the number of equivalents of base added. The values obtained are included in Table 1. Although there remains no uncertainty about these IEs, we have undertaken to remeasure them, along with some additional IEs, by yet another method.

NMR titration methods make it possible to measure relative acidities with great precision. The procedure involves successive additions of small aliquots of base to a mixture of acids. The stronger acid will be deprotonated first. Its chemical shift will then move ahead of that of the less acidic one, which lags behind. The acidity constants, K_a, and chemical shifts, δ, of both H and D acids can be related through eq 2,[18] where δ^0 or δ^- are for the acid or conjugate base, respectively, as measured at the beginning or end of the titration. Therefore, a plot of the quantity on the left versus $(\delta_H - \delta_H^-)(\delta_D^0 - \delta_D)$ should be linear, with a zero intercept. The ratio of acidity constants, K_a^h/K_a^d, can then be evaluated as the slope of that plot.

$$(\delta_H^0 - \delta_H)(\delta_D - \delta_D^-) = (K_a^h/K_a^d)(\delta_H - \delta_H^-)(\delta_D^0 - \delta_D) \quad (2)$$

This method is capable of exquisite precision because it is based only on chemical-shift measurements, not on pH or volume or molarity or equivalents of base added, as is usual in pH titrations. The method is comparative. If there is no difference in acidities, there is no lag of one chemical shift behind the other. Therefore, minute imbalances of acidities can be detected. Moreover, since the titration is performed on a mixture of the two acids under conditions guaranteed identical for both, it avoids systematic error due to impurities. A further advantage is that it can be applied in any solvent, even the nonaqueous ones here, where a pH electrode would be inoperative. In addition to the above NMR titrations that fit to the number of equivalents of base added,[16,17] a variant method relied on fitting ^{19}F NMR chemical shifts to pH,[19] but neither molarity nor pH is as reliably measured as chemical shifts. Besides, none of these utilizes the advantage of data analysis by linear least squares. We now report IEs on acidities of a series of carboxylic acids (**1**−**4**, **8**−**9**) and phenols (**5**−**7**) measured by ^1H, ^{13}C, and ^{19}F NMR titration using reporter nuclei indicated in boldface in the structures.

Besides the experimental measurements of IEs, we have turned to computation in order to help clarify their origin. In 1963, Streitwieser and Klein were not optimistic about such detailed analysis for acids less simple than formic. Calculations have succeeded in reproducing experimental secondary deuterium kinetic IEs in the formation of several norbornyl cations.[20] We now report computed IEs for these carboxylic acids and phenols. However, they exceed the observed ones by a factor

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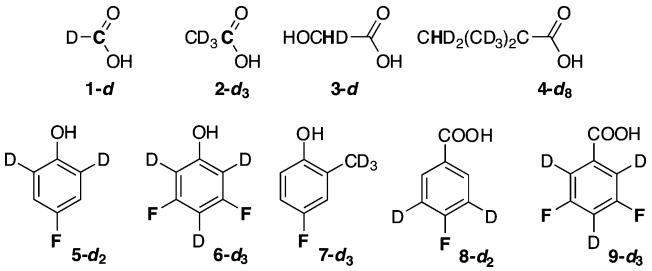

of >6. Nevertheless, they support an origin in zero-point energies and make an inductive explanation unnecessary.

Experimental Section

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 or 400 or Unity 500 spectrometer. The ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer, without ^{1}H decoupling. The spectral window was reduced to 700 Hz for ^{1}H NMR at 500 MHz, to 1700 Hz for ^{13}C at 100 MHz, and to 20 kHz for ^{19}F at 282.3 MHz, and the data were zero-filled to increase digital resolution. Proton chemical shifts in aqueous solutions are relative to *tert*-butyl alcohol (δ 1.23) or dioxane (δ 3.75) as the internal standard. Carbon chemical shifts in aqueous solutions are relative to *N*,*N*-dimethylformamide (δ 165.53) or *N*,*N*-dimethylacetamide (δ 174.57) as the internal standard. In organic solvents, the internal standards are cyclohexane (δ 1.42 in DMSO-d_6, 1.44 in CD_3CN), *N*,*N*-dimethylformamide (δ 162.29 in DMSO-d_6), $NaBF_4$ (δ −154 in CD_3CN), and 1,3-$C_6H_4(CF_3)_2$ (δ −65). Fluorine chemical shifts in aqueous solutions are relative to sodium tetrafluoroborate (δ −154) as the internal standard. All of the chemical shifts were read as Hz. To help distinguish the peaks, the spectrum of a mixture of deuterated species and the internal standard was obtained, and then the undeuterated compound was added.

Syntheses. Formic acid (**1**), formic-*d* (**1-*d***) acid-*d*, acetic acid (**2**), acetic-d_3 (**2-d_3**) acid-*d*, hydroxyacetic acid (**3**), pivalic acid (**4**), 4-fluorophenol (**5**), 3,5-difluorophenol (**6**), 4-fluorobenzoic acid (**8**), 4-fluorobenzoic-d_4 acid (**8-d_4**), 3,5-difluorobenzoic acid (**9**), and other reagents were commercially available and used without purification. Anhydrous formic acid was obtained by reduced-pressure distillation of 97% formic acid that had been mixed with excess phthalic anhydride and refluxed for 6 h. The center distillate was collected and stored at 4 °C. Acetic-d_2 acid (**2-d_2**) was obtained by heating a mixture of malonic-d_2 acid-d_2 and H_2O to 150 °C. The amount of H_2O was adjusted empirically to maximize the ^{1}H NMR intensity of the acetic-d_2 signals, because acetic-*d* acid interferes, but acetic-d_3 acid is invisible. Hydroxyacetic-*d* acid (**3-*d***) was prepared by reducing glyoxylic acid with zinc dust in D_2O. Pivalic-d_8 acid (**4-d_8**) was prepared by carboxylation of the Grignard reagent obtained from commercially available "98%" *tert*-butyl-d_9 chloride, which contained ~2% *tert*-butyl-d_8 chloride and other impurities. The major product, pivalic-d_9 acid (**4-d_9**), is invisible in the CH region of the ^{1}H NMR spectrum, which shows a quintet due to a CHD_2 group, well separated from CH_3 and a trace of CH_2D. 4-Fluorobenzoic-3,5-d_2 acid (**8-d_2**) and 3,5-difluorobenzoic-2,4,6-d_3 acid (**9-d_3**) were prepared by treating either 4-fluorobenzoic acid or 3,5-difluorobenzoic acid with 98% D_2SO_4 at 140 °C and repeating the procedure. 4-Fluorophenol-2,6-d_2 (**5-d_2**) was prepared by treating 4-fluorophenol with 50% D_2SO_4 at 75 °C and repeating the procedure. 3,5-Difluorophenol-2,4,6-d_3 (**6-d_3**) was prepared by treating 3,5-difluorophenol with 60% D_2SO_4 at 75 °C and repeating the procedure. The exchange of the aromatic hydrogens in each of these substrates was monitored by ^{1}H and ^{19}F NMR, and samples were quenched when equilibrium was established. 4-Fluoro-2-d_3-methylphenol (**7-d_3**) was synthesized by activating 5-fluoro-2-hydroxybenzoic acid with CH_3OCOCl and reducing with $NaBD_4$. Details of all syntheses are available in the Supporting Information, along with spectral characterizations.

NMR Titrations. The NMR sample prepared for each titration contained 0.5−0.7 mL of D_2O or organic solvent and appropriate concentrations of internal standard and isotopologues of the acid, adjusted to ensure nearly equal peak heights. Unequal heights facilitate continuity of peak assignments, especially in case of a crossover during the titration.

Tables S1 and S2 list the initial concentrations of all substances in each sample. Tables S3 and S4 list the base used for each titration and the starting and ending chemical shifts for deuterated and nondeuterated acids. For all acids, deuterium produces an upfield shift, as is usual for isotope shifts,[21] except for acetic-d_3 in D_2O and THF, for aqueous 4-fluorophenol, where no isotope shift is resolvable, and for 4-fluoro-2-methylphenol, where the isotope shift of *meta*-CD_3 is not resolvable in the phenoxide. Another exception is that deuterium produces a downfield shift in 4-fluorophenol in CD_3CN, but the signals cross and recross during the titration. All acids move upfield upon deprotonation, except for formic and acetic-d_3, which are the only ones monitored by ^{13}C NMR. For 4-fluorophenol, the isotopologues are seen to separate during the titration, and they could be distinguished by their intensities. For 4-fluoro-2-methylphenol, the outermost component of each doublet of triplets was sufficient to define the chemical shift of each isotopomer. In DMSO, the ^{19}F signals are broadened in the middle of the titration, owing to slow proton transfer between an acid and its conjugate base.[22] Consequently, chemical shifts could not be measured accurately, and unreliable values of K_H/K_D for **8** in DMSO are excluded from the results. Other unsuccessful titrations occurred with **1-*d*** with KOtBu in CD_3CN, **2-d_2** in DMSO-d_6 and CD_3CN, **2-d_3** with Bu_4NCN in CD_3CN, **4** in CD_3OD, and **8** with Bu_4NCN in CD_3CN, where the reporter nucleus was not sufficiently sensitive to the state of protonation.

Aqueous samples were first acidified with 2μL of 0.1 M DCl to ensure complete protonation and then titrated with as many as twenty 5- or 10-μL aliquots of NaOD in D_2O. Samples in DMSO-d_6, CD_3CN, and THF-d_8 were acidified with 2μL of 0.1 M trifluoroacetic acid, and then 5μL aliquots of KOtBu, $LiN[Si(CH_3)_3]_2$, or Bu_4NCN were used as the base. Acetic-d_2 acid was also subjected to a reverse ^{1}H NMR titration, where a mixture of potassium acetate-d_0, -d_2, and -d_3 in DMSO-d_6 was titrated with trifluoroacetic acid.

NMR spectra were recorded after each addition. At least 10 aliquots were used for each titration. Titrations were assumed to be complete when no peak movement was observed upon further addition of titrant. Chemical shifts of appropriate reporter nuclei were extracted from the spectrum after adding each aliquot, and the data were fit to eq 2. Figure 1 shows such a plot from ^{19}F chemical shifts of fluorobenzoic-d_0 and -d_4 acids. As an indicator of the linearity, the correlation coefficient is 0.99998.

Computations. Ab initio density functional calculations on carboxylic acids and phenols were performed at the B3LYP/6-31* or B3LYP/6-31G level. For formic acid, various higher-level calculations were undertaken, but these gave nearly the same results.

Harmonic vibrational frequencies were calculated at optimized geometries. The double difference, $\Delta\Delta\Sigma\nu$, of sums of all of the frequencies of the four species, $(\Sigma\nu_{R_HCOOH} - \Sigma\nu_{R_DCOOH}) - (\Sigma\nu_{R_HCO_2^-} - \Sigma\nu_{R_DCO_2^-})$, was calculated. This difference was then converted through zero-point energies to ΔpK ($=pK_D - pK_H$) per D.

Results

Experimental. Table 2 lists the secondary deuterium IEs on the acidities of carboxylic acids and phenols. The values are presented in several forms, as K_H/K_D, $pK_D - pK_H$, and ΔpK per D. They are sequenced in order of increasing *n*, the number

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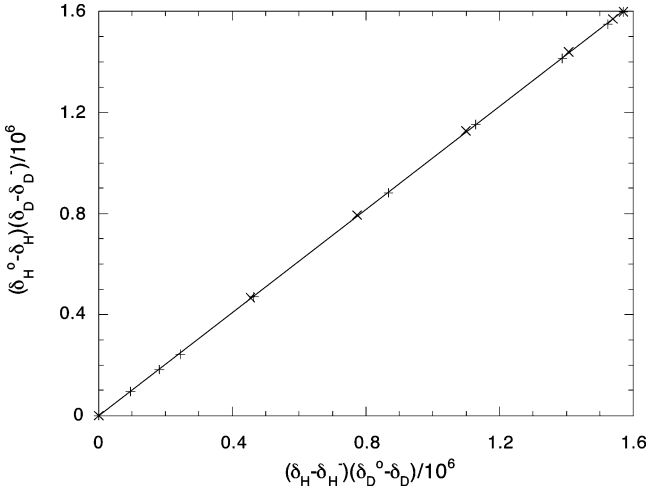

Figure 1. Linearized plot (eq 2) for titration of fluorobenzoic-d_0 and -d_4 acids (**8**) in THF-d_8 with Bu_4NCN as the base: (x) first half of the titration, (+) second half.

Table 2. Secondary Deuterium Isotope Effects on Acidities

acidD	solvent	K_H/K_D	$pK_D - pK_H$	ΔpK per D	n^a
1-*d* [b]	D_2O	1.0743 ± 0.0014	0.0311 ± 0.0005	0.031	2
1-*d* [b]	DMSO-d_6 [c]	1.0530 ± 0.0016	0.0224 ± 0.0006	0.022	2
1-*d* [b]	CD_3CN [c]	1.0086 ± 0.0011	0.0037 ± 0.0005	0.0037	2
1-*d* [b]	CD_3CN [d]	1.049 ± 0.004	0.021 ± 0.002	0.021	2
2-d_2 [e]	D_2O	1.025 ± 0.003	0.0107 ± 0.0012	0.0053	3
2-d_3 [b]	D_2O	1.0304 ± 0.0016	0.0130 ± 0.0007	0.0043	3
2-d_3 [b]	THF-d_8 [d]	1.025 ± 0.006	0.011 ± 0.003	0.0036	3
2-d_3 [b]	CD_3CN [d]	1.0285 ± 0.0020	0.0122 ± 0.0008	0.0041	3
3-*d* [e]	D_2O	1.008 ± 0.0014	0.0035 ± 0.0006	0.0035	3
5-2,6-**d_2** [f]	D_2O	1.0259 ± 0.0011	0.0111 ± 0.0005	0.0055	3
5-2,6-**d_2** [f]	CD_3CN [c]	1.0188 ± 0.0020	0.0081 ± 0.0008	0.0041	3
6-d_3 [f]	D_2O	1.0442 ± 0.0005	0.0188 ± 0.0002	0.0062	3,5
4-d_8 [e]	D_2O	1.0530 ± 0.0015	0.0224 ± 0.0006	0.003	4
4-d_8 [e]	CD_3CN [g]	1.039 ± 0.005	0.016 ± 0.002	0.002	4
7-d_3 [f]	D_2O	1.0195 ± 0.0012	0.0084 ± 0.0005	0.0028	4
8-d_4 [f]	D_2O	1.0159 ± 0.0016	0.0069 ± 0.0007	0.0017	4,5
8-d_4 [f]	CD_3CN [d]	1.0155 ± 0.0020	0.0067 ± 0.0008	0.0017	4,5
8-d_4 [f]	THF-d_8 [d]	1.0209 ± 0.0016	0.0090 ± 0.0007	0.0022	4,5
9-d_3 [f]	D_2O	1.0133 ± 0.0019	0.0058 ± 0.0008	0.0019	4,6
8-3,5-**d_2** [f]	D_2O	1.0088 ± 0.0016	0.0038 ± 0.0007	0.0019	5

[a] Number of bonds between D and O. [b] By ^{13}C NMR. [c] KOtBu base. [d] Bu_4NCN base. [e] By ^1H NMR. [f] By ^{19}F NMR. [g] $LiN[Si(CH_3)_3]_2$ base.

of bonds between the deuterium substituent and the oxygen. Figure 2 shows a graph of ΔpK per D versus n (or the average n if there are two distances). Notice, though, that the IE per D is lower for hydroxyacetic acid (**3**) in D_2O than for acetic (**2**); therefore, n is not the only parameter determining the IEs.

IEs are slightly lower in the aprotic organic solvents DMSO-d_6 and CD_3CN. For several acids, the difference is hardly beyond experimental error, but for formic acid (**1**), the difference is real. For acetic-d_3 acid (**2-*d*$_3$**) in organic solvents, the IE, measured by ^{13}C NMR, is nearly the same as that in D_2O.

Computational. Table 3 lists calculated secondary deuterium IEs on the acidities of carboxylic acids and phenols. They too are sequenced in order of increasing n, the number of bonds between the deuterium substituent and the OH (or the OD in HCOOD/DCOOD). The data are presented as $\Delta\Delta\Sigma\nu$, the double difference of sums of all the vibrational frequencies of the four species, and as ΔpK ($=pK_D - pK_H$) per D. Figure 2 includes the calculated ΔpK per D versus n but scaled down by a factor of 6. For further comparison, Table 4 lists average C−D

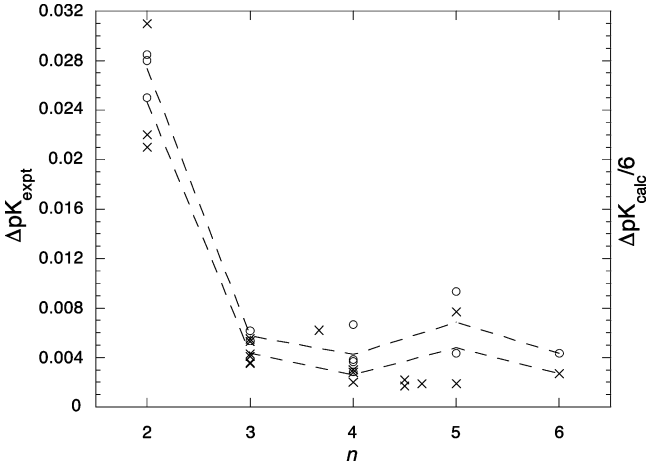

Figure 2. Deuterium IE on acidity versus number of bonds between D and O. (x) Observed ΔpK per D. (○) Calculated ΔpK per D, scaled down 6-fold. For clarity, the dashed lines connect the averages for each integer n but have no significance.

Table 3. Calculated Secondary Deuterium Isotope Effects on Acidities

acidD	method	$\Delta\Delta\Sigma\nu$, cm^{-1}	ΔpK per D	n^a
DCOOH	HF 6-311+G(d,p)	140	0.150	2
DCOOH	B3LYP/6-311+G(d,p)	158	0.168	2
DCOOH	MP2/6-31G(d)	160	0.171	2
DCOOH	MP2/6-31G(2d,p)	158	0.168	2
DCOOD	B3LYP/6-311+G(d,p)	164	0.174	2
DCOOH [b]	HF 6-311+G(d,p)	16	0.017	2
CD_3COOH	B3LYP/6-31*	104	0.037	3
phenol-2,6-d_2	B3LYP/6-31G	60	0.032	3
pivalic-d_9	B3LYP/6-31*	182	0.022	4
phenol-3,5-d_2	B3LYP/6-31G	75	0.040	4
benzoic-2,6-d_2	B3LYP/6-31G	31	0.017	4
o-CD_3phenol	B3LYP/6-31G	65	0.023	4
benzoic-3,5-d_2	B3LYP/6-31G	49	0.026	5
phenol-4-*d*	B3LYP/6-31G	53	0.056	5
benzoic-4-*d*	B3LYP/6-31G	24	0.026	6

[a] Number of bonds between D and OH (or OD). [b] To $DCO_2^-Li^+$ as a conjugate base.

Table 4. Calculated Average C−D Stretching Frequencies (cm^{-1}) in *ortho*-, *meta*-, and *para*- Di- or Monodeuterated Phenol, Phenoxide, Benzoic Acid, and Benzoate and the Calculated Increase in Electron Density at *ortho*-, *meta*-, and *para*-C and H upon Deprotonating Phenol or Benzoic Acid

	ortho	*meta*	*para*
ν_{phenol}	2374	2373	2378
$\nu_{phenoxide}$	2333	2297	2334
$\Delta\nu_{phenoxide}$	41	75	45
$\Delta q_{C,phenoxide}$	0.068	−0.011	0.052
$\Delta q_{H,phenoxide}$	0.090	0.089	0.092
$\nu_{benzoic\ acid}$	2397	2377	2374
$\nu_{benzoate}$	2377	2335	2340
$\Delta\nu_{benzoate}$	20	42	34
$\Delta q_{C,benzoate}$	0.042	0.000	0.025
$\Delta q_{H,benzoate}$	0.039	0.061	0.064

stretching frequencies of *ortho*-, *meta*-, and *para*-deuteriums in deuterated phenol, phenoxide, benzoic acid, and benzoate, along with the calculated increases in electron density at *ortho*-, *meta*-, and *para*-carbons and hydrogens upon deprotonating phenol or benzoic acid.

The dependence on the basis set and computational level was probed for formic acid. The computed values of ΔpK in Table 3 range only from 0.150 to 0.171. Therefore, B3LYP/6-31* or B3LYP/6-31G were judged as adequate for other acids.

There is hardly any difference in the calculated ΔpK between DCOOH and DCOOD, 0.168 versus 0.174. Therefore, no effort was made to compare the IEs in H_2O and D_2O, inasmuch as experimental error would be expected to overwhelm any difference. There is a large reduction in the calculated IE of formic acid when the conjugate base is lithium formate (with both Li−O distances equal to 1.86 Å), rather than formate itself. This is a model for the behavior of an intimate ion pair in a nonpolar aprotic solvent. Consistent with this calculated reduction is the considerably lower ΔpK, 0.0037, observed for formic acid in CD_3CN when K^+ is the counterion, compared to 0.021 with Bu_4N^+.

Distance Dependence. The IE is expected to decrease as n increases, that is, as the site of deuteration recedes from the acidic OH. This is almost what is found. According to the data in Tables 2 and 3, the decreases in both the experimental and the calculated ΔpK per D are considerable from $n = 2$ to 3. Beyond $n = 3$, the decrease of the experimental ΔpK per D is quite gradual, but there is no drop in the calculated values. This contrast between $n < 3$ and $n > 3$ can be seen in Figure 2.

The individual contributions of *ortho*-, *meta*-, and *para*-deuteriums can be extracted from the observed IEs for the three different fluoro- and difluorobenzoic acids. From 4-fluorobenzoic-3,5-d_2 acid (**8-*d*$_2$**), the contribution of one *meta*-deuterium to $pK_D - pK_H$ is 0.0019 ± 0.0003. Subtracting this from the IE of 4-fluorobenzoic-d_4 acid (**8-*d*$_4$**) gives 0.0015 ± 0.0005 as the contribution of one *ortho*-deuterium. Subtracting this from the IE of 3,5-difluorobenzoic-d_3 acid (**9-*d*$_3$**) gives 0.0027 ± 0.0013 as the contribution of one *para*-deuterium. This value is included in Figure 2. These results agree, but not exactly, with those of ref 17, where the effect of an *ortho*-, *meta*-, or *para*-deuterium on ΔpK was found to be 0.0020, 0.0019, or 0.0018, respectively.

Similarly, the IE of a para deuterium on phenol can be assigned as 0.0077 ± 0.0005 by subtracting the IE in 4-fluorophenol-2,6-d_2 from that in 3,5-difluorophenol-2,4,6-d_3. This value too is included in Figure 2. It is larger than the IE (per D) of 0.0055 for an *ortho*-deuterium. This is consistent with the calculated IEs per D in Table 3, which increase from ortho to meta to para. It is inconsistent with experimental *ortho*-, *meta*-, and *para*-deuterium kinetic IEs of −2.4, −0.4, and −1.8%, respectively, in the α deprotonation of toluene.[23]

These comparisons highlight a further contrast between aliphatic and aromatic acids. Aliphatic acids do show a drop beyond $n = 3$ for both the experimental and calculated IEs, at least for the comparison of acetic acid (**2**) with pivalic (**4**) or *ortho*-methylphenol (**7**, which is mixed aliphatic−aromatic). It is the aromatic acids whose IEs show no drop beyond $n = 3$. Although the uncertainties are large, owing to propagation of errors upon subtraction, the values increase from ortho to meta to para. Likewise, the calculated IEs in both phenol and benzoic acid generally increase (from 0.032 to 0.040 to 0.056 and from 0.017 to 0.026 to 0.026) along this series.

Discussion

Experimental Results. Our results confirm secondary deuterium IEs on acidity. Deuteration definitely decreases the acidity of carboxylic acids and phenols. For those acids that overlap, the agreement with the values of Streitwieser and Klein and with subsequent studies is very close, as can be seen by comparing Tables 1 and 2. This agreement is a testament to the purity of their materials, a requirement that could be circumvented with our NMR titration method.

Fluorine is used as a reporter nucleus for phenols and benzoic acids. This is more sensitive than ^{13}C because the shift of the ^{19}F signal upon deprotonation even of a remote OH is often >1000 Hz. Besides, it was not possible to resolve the isotope shift at the carboxyl carbon of benzoic-d_5 acid. Although fluorine exerts its own inductive effect, it is the same inductive effect for both H and D; therefore, it does not introduce complications. Indeed, no regular variation of IEs with inductive substituents was seen.[24]

The observed IEs of *ortho*-D and *ortho*-CD_3 correspond to a reduction of acidity, just as those of *meta*- and *para*-D. This is evidence against an inductive origin, arising from the field effect of a dipole, because the angular dependence of an ortho substituent's dipole field is reversed and would have produced an opposite IE.

Isotope-Sensitive Vibrational Frequencies. The calculated IEs in Table 3 corroborate the observed decreases in the acidity of carboxylic acids and phenols upon deuteration. These calculated IEs ignore anharmonicity, upon which the estimate of eq 1 depends. Therefore, the ability of these calculations to reflect IEs provides no support for an inductive origin, as was concluded from the estimated (eq 1) inductive effect on ΔpK of only 0.00006 per D. Instead, these calculations involve only zero-point energies. There are key isotope-sensitive vibrations whose frequencies, ν, and zero-point energies ($^1/_2h\nu$) decrease upon deprotonating the acid. Because the zero-point energy of a CH vibration is greater than that of a CD, the decrease of frequency is more stabilizing for H. These vibrations thus contribute positively to the double difference, $\Delta\Delta\Sigma\nu$, or $(\Sigma\nu_{R_HCOOH} - \Sigma\nu_{R_DCOOH}) - (\Sigma\nu_{R_HCO_2^-} - \Sigma\nu_{R_DCO_2^-})$, in Table 3.

Which vibrations are these? For formic acid, it is easy to recognize that the key isotope-sensitive vibration is the C−H stretch. According to the B3LYP/6-311+G(d,p) calculations, which are representative, its frequency decreases from 3057 in HCOOH to 2571 cm^{-1} in HCO_2^-. The corresponding decrease for DCOOH is from 2274 to 1876 cm^{-1}. This contributes 88 cm^{-1} to $\Delta\Delta\Sigma\nu$. This is only slightly more than half the total, and other modes, such as the CH bend and the C=O stretch, also contribute.

For other acids, key isotope-sensitive vibrations are less readily identifiable. Because of variations in the way individual bond vibrations couple into normal modes, it is not unambiguous to correlate a frequency in the acid with one in the deuterated acid or the carboxylate. Prime candidates, though, are the C−H modes. For acetic acid, the average of the three C−H stretching frequencies is calculated to decrease from 3085 to 3007 cm^{-1} in the acetate anion. For pivalic acid, the average of the nine C−H stretching frequencies is calculated to decrease from 3105 to 3056 cm^{-1} in the anion. For *ortho*-methylphenol, deprotonation reduces the average methyl C−H stretching frequency by 14 cm^{-1}. For all three of these acids, the total decrease of the C−H stretching frequencies upon deprotonation is sufficient to account for slightly more than half of the calculated IEs, but other modes contribute, especially CCH bends. For selectively ring-deuterated phenols and benzoic acids, it is easier to isolate

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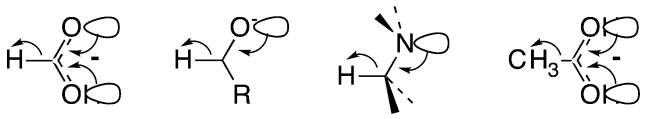
Scheme 1. *n*-σ* Delocalization of Lone Pairs in Formate Anion, Alcoholates, Amines, and Acetate



the average C−D stretching frequency. Values are in Table 4, along with the frequency decreases upon deprotonation. These stretching modes account for about half of the calculated IEs of *meta*-deuterium. Other modes dominate for ortho and para, but it has not been possible to discern which, except that out-of-plane bends account for more than half of the calculated IEs of phenol-4-*d*.

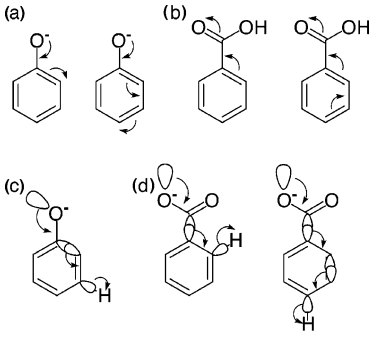
Delocalization. The reduction of the C−H frequency upon deprotonation of formic acid can be ascribed to electron delocalization, as in Scheme 1. In the formate anion, there are oxygen lone pairs that are antiperiplanar to the antibonding σ_{CH}* orbital. The consequent delocalization of the lone-pair electrons reduces the C−H bond order and its frequency and zero-point energy. This delocalization is also manifested in a lengthening of the calculated C−H distance, from 1.097 to 1.138 Å, and a greater Mulliken electron density on the H.

This is analogous to the delocalization of antiperiplanar lone pairs that was proposed to explain β secondary IEs in alcohols and amines.[25] These too are illustrated in Scheme 1. Indeed, it was shown that the IE in amines is of stereoelectronic origin. This conclusion depended on the ability to measure relative acidities of two isotopomers, stereoisomers that differ only in the position of an isotope (as distinguished from the isotopologues here, which differ in the number of isotopic substitutions).

Unlike formic acid, the frequency changes in higher acids are not readily attributed to a delocalization that is clearly stereoelectronic. Upon deprotonation of acetic acid, the C−C distance is calculated to lengthen from 1.508 to 1.576 Å, consistent with *n*-σ* delocalization as in Scheme 1, and the calculated electron densities at all three hydrogens increase. The three C−H distances increase, and the increase is greater for the one that is in the molecular plane. This is consistent with the result in Table 2 that the IE per D is lower for hydroxyacetic acid than it is for acetic, because the OH of the former lies in the molecular plane,[26] relegating deuterium to a position where it affects the IE to a lesser extent. Upon deprotonation of pivalic acid, the C−C_α distance is calculated to lengthen, but all of the C_α−C_β and C−H distances remain nearly constant. The methyl carbons lose electron density, whereas all nine H atoms gain, especially those three that are antiperiplanar to the C−C_α bond. This is consistent with relayed *n*-σ* delocalization.

For the aromatic acids, the role of electron delocalization is less clear. Table 4 includes the calculated increases of electron density upon deprotonation. For phenol, the *ortho*- and *para*-carbons acquire electron density, but all five hydrogens gain nearly equally. For benzoic acid, the *ortho*- and *para*-carbons again acquire electron density upon deprotonation but to a lesser extent than for phenol. Yet it is the *meta*- and *para*-hydrogens that acquire more electron density than does the *ortho*-. The

Scheme 2. Delocalization of π Electrons to or from ortho and para Positions in (a) Phenoxide and (b) Benzoic Acid and of σ Electrons to ortho, meta, and para Positions in (c) Phenoxide and (d) Benzoate



increased electron densities at *ortho*- and *para*-carbons are as expected from resonance theory, owing to delocalization either of negative charge from the oxyanion of the phenoxide or of electron density to the carbonyl of the benzoic acid, as shown in Scheme 2a,b. Yet this delocalization is of π electron density, whereas the hydrogens are bonded by σ electrons. Sigma delocalization can increase the electron density only at the *meta*-hydrogens of phenoxide and at the *ortho*- and *para*-hydrogens of benzoate, as shown in Scheme 2c,d. This is not the pattern of changes seen. Therefore, *n*-σ* delocalization cannot account for these electron densities or for the calculated IEs, reasonable though it is for formic acid (Scheme 1).

Distance Dependence. Although the IE is expected to decrease as the site of deuteration becomes more distant from the acidic OH, the data in Tables 2 and 3 and in Figure 2 show that it is not so simple. Both the experimental and the calculated ΔpK per D decrease considerably from $n = 2$ to 3. Beyond $n = 3$ there is a further decrease for the aliphatic acids. However, for deuteration of benzoic acid, the experimental IE is nearly constant, and for deuteration of phenol, the IE increases from ortho to para. For both benzoic acid and phenol, the calculated IEs increase from ortho to meta to para. The apparent peak at $n = 5$ is due to the large IE of a *para*-D in phenol, both experimentally and computationally. Such behavior is opposite to the usual falloff of IEs and other substituent effects with distance.

There is no difficulty in accounting for the falloff from $n = 2$ to 3 or for a further falloff for $n > 3$ in aliphatic acids. The IE in formic acid is due to *n*-σ* delocalization, which is attenuated in the higher acids by the additional sp^3 carbons that are interposed. Indeed, the deprotonation-induced changes in the C−H stretching frequencies and in the calculated electron densities at hydrogen decrease with *n*. However, it should be noted that the attenuation of IEs is not by a constant factor.

The near constancy of the IEs in the aromatic acids, both experimental and calculated, is surprising. A clue to this lies in the average C−D stretching frequency in selectively deuterated phenols and benzoic acids, given in Table 4. These frequencies decrease upon deprotonation, but the decreases are largest at the *meta*-C−D, and in phenol-3,5-d_2, the decrease at meta is nearly twice as large (per C−D) as that at the ortho or para. This is quite unexpected and contrary to the general principle that substituent effects are transmitted most effectively to and from ortho and para positions, as illustrated in Scheme 2a. It is certainly not consistent with an inductive effect of the

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Table 5. Comparison of Experimental and Calculated IEs (ΔpK per D)

acid	D_2O	B3LYP	calcd/exptl
formic	0.031	0.168	5.4
acetic	0.0053	0.037	7.0
pivalic	0.003	0.022	7.3
phenol-2,6-d_2	0.0055	0.032	5.8
phenol-4-*d*	0.0077	0.056	7.3
cresol	0.0028	0.023	8.2
benzoic-2,6-d_2	0.0015	0.017	11.3
benzoic-3,5-d_2	0.0019	0.026	13.7
benzoic-4-*d*	0.0027	0.026	9.6

deuteriums. It is consistent with the changes of electron density, which do not fall off with distance. It is also consistent with the observed IEs in fluorinated benzoic acids, which increase from 0.015 to 0.0019 to 0.0027 (but with large errors) as deuteration moves from ortho to meta to para, six atoms away from the OH. Thus, the frequencies and the electron densities are consistent with IEs that arise even from deuteration at more distant carbons.

Comparison of Experiment and Computation. The computations are certainly adequate to account for the observed decreases in acidity upon deuteration. For the simplest, formic acid, the computations assign responsibility to a decrease of the C−H stretching frequency upon deprotonation. For the other acids, the observed IEs parallel changes in key stretching frequencies that are associated with changes in electron densities and bond lengths upon deprotonation. The computations are also successful in reflecting the near constancy of IEs in phenol and benzoic acid even as the site of deuteration becomes more distant, from ortho to meta to para.

However, there is a quantitative discrepancy between calculation and experiment, as summarized in Table 5. On an energetic basis, the calculated IEs are at least 5 times as large as the experimental ones, and the average ratio of calculated to experimental IE is ~9. Thus, this discrepancy is substantial and serious. It is not obviously due to a too simplistic computational level because the data in Table 3 show that the results for formic acid are nearly independent of level. It is too large to be corrected by any scaling factor typically used for vibrational frequencies.[27]

For formic acid, where the key isotope-sensitive vibration can be identified, the discrepancy can be inspected. According to the B3LYP/6-311+G(d,p) calculations, the frequency of the C−H stretch decreases from 3057 in HCOOH to 2571 cm^{-1} in HCO_2^-. Other levels of calculation, even with larger basis sets, give comparable decreases of 15−20% in the C−H stretch upon deprotonating formic acid. This is too extreme. Such a low frequency is certainly not seen in the infrared or Raman spectrum of sodium formate, whose C−H stretch is at 2830 or 2825 cm^{-1}.[28] Others have experienced similar difficulty in calculating this particular frequency accurately.[29] Moreover, although the lengthening of the C−H bond length upon deprotonation is consistent with delocalization, the calculated change, from 1.097 to 1.138 Å, seems too large. The calculated lengthening of the C−C bond upon deprotonation of acetic acid also seems too large, from 1.508 to 1.576 Å, or 4%. Yet, according to an extensive survey of crystal structures,[30] the average C−C bond lengths in carboxylic acids and carboxylates are 1.502 ± 0.014 and 1.520 ± 0.011 Å, respectively, corresponding to only a 1% lengthening. Thus, we judge that the discrepancy between calculated and observed IEs is due to unrealistically large changes in calculated vibrational frequencies.

Of course all of the experimental data are in solution or crystals, whereas the calculations are for the gas phase. This is the usual explanation for such discrepancies in frequencies and bond lengths.[31] Lone-pair delocalization in the carboxylates (Scheme 1) is responsible for reduction of vibrational frequencies, and that delocalization is maximum in the gas phase. In water, hydrogen bonding to the lone pairs reduces their delocalization and reduces the IE. Yet it is doubtful that this can account for the overestimates of the IEs by at least 6-fold.

To test this influence of solvation, IEs were measured in solvents of lower polarity, specifically aprotic ones. These resemble the gas phase more, and the IE would be expected to be higher in these solvents and closer to the calculated values. Instead, IEs are slightly lower in DMSO-d_6 and CD_3CN. The difference is not always beyond experimental error, but the IE is definitely not higher. Moreover, although n-σ^* delocalization is reasonable for formic acid (Scheme 1), it cannot account for the detailed electron densities around the aromatic rings of phenol and benzoic acid, where the discrepancy between calculated and experimental IEs is thus not readily attributed to a solvent effect upon delocalization.

A related explanation for an experimental IE that is lower than the calculated even in aprotic solvents is that untitrated acid RCOOH serves to hydrogen-bond to the anion. This is a reasonable possibility because the acid would then mimic a protic solvent. In this case, the IE would be lower during the first half of the titration, while $RCOOHOCOR^-$ is the product of deprotonation. During the second half, while RCO_2^- is the product, the IE would be higher, characteristic of an aprotic medium and approaching the gas phase. This behavior would be characterized by a linearized titration curve (eq 2) that reliably follows that lower slope in the first half of the titration but shows distinct curvature in the second half, with a corresponding deterioration of the correlation coefficient. This would be easily recognized, but it was not seen. Figure 1 confirms this, with the points from the first half of the titration distinguished as × and those from the second half as +.

Although the results for formic acid in Table 3 are nearly independent of level, all of the levels used must be too simplistic. Certainly at a sufficiently high level the computation ought to agree with the experiment. The appropriate level and the source of the discrepancy at lower levels are being sought.[32]

Conclusions

These results confirm that secondary deuterium IEs decrease the acidity of carboxylic acids and phenols. For aliphatic acids, the IEs, per D, are lower when the deuterium is moved farther from the OH, as expected. However, it is surprising that IEs in

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the aromatic acids do not decrease with distance. The experimental data, including this lack of distance dependence, can be reproduced by ab initio computations, but these greatly overestimate the values. The overestimate does not seem to be due to neglect of solvation, which might have reduced the experimental IE, because the IEs are nearly solvent-independent.

According to the computations, the IEs originate from vibrations whose frequencies and zero-point energies are lowered upon deprotonation, but it is not always easy to distinguish which vibrations are responsible nor to understand how all of the calculated changes in frequencies, bond lengths, and electron distributions are manifested in IEs. Besides, the changes in electron distribution do not always follow the patterns expected from delocalization of σ or π electrons.

A key conclusion is that the computations support an interpretation of these IEs in terms of deprotonation-induced changes in vibrational frequencies and zero-point energies. Consequently, there is no need to invoke an inductive effect as responsible. Moreover, the failure of the IEs to diminish from ortho to meta to para is not consistent with an inductive effect.

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Supporting Information Available: Synthesis and spectral characterizations. Tables S1−S4 (sample preparation). Computational methods. Tables S5−S6 (calculated energies, optimized geometries, atomic charges, and interatomic distances of all structures). Table S7 (calculated vibrational frequencies for all structures, including deuterated isotopologues). This material is available free of charge via the Internet at http://pubs.acs.org.

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