Isotope Effects

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No Contribution of an Inductive Effect to Secondary Deuterium Isotope Effects on Acidity**

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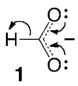
Isotope effects are observed when a reaction rate or equilibrium constant changes as a result of isotopic substitution.[1] They continue to be used as valuable tools to provide insight into molecular structure and reactivity.[2] Secondary isotope effects are those in which the bond to the isotope remains intact. Their origin continues to be an area of investigation.[3] Herein we address the origin of secondary deuterium isotope effects on acidity.

Deuterium isotope effects on acidities are expressed as K_a^H/K_a^D or as $\Delta pK = -\log_{10}(K_a^H/K_a^D)$, where K_a is the acid-dissociation constant. Deuteration at a bond that is not broken reduces acidity, and it is generally accepted that changes in vibrational frequencies and zero-point energies (ZPEs) are responsible.[4] In support, the isotope effect in formic acid could be reproduced from the observed infrared frequencies of HCOOH, HCO_2^-, DCOOH, and DCO_2^-.[5] Moreover, many calculations, including recent DFT calculations on isotope effects in carboxylic acids and phenols,[6] ammonium ions,[7] and pyridinium ions,[8] support an origin in C–H stretching frequencies and ZPEs that decrease upon deprotonation.

These decreases are generally attributed to delocalization of lone pairs into an antibonding C–H orbital (**1**,**2**). A stereoelectronic origin was demonstrated by computation of the C–D stretching frequency in rotamers of DCH_2NH_2 (**2**-D) and by experimental measurement of the relative basicities of the two isotopomers of 2,2,6-[D$_3$]1-benzyl-4-methylpiperidine (**3**).[7] For higher carboxylic acids, beyond formic, it is more difficult to assign frequency changes to electron delocalization, and an alternative interpretation of the isotope effect has been proposed.[9]



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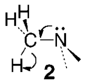

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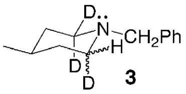

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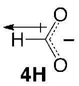
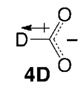
A long-standing question is whether there is also a contribution from an inductive effect, due to electron donation or withdrawal, or, equivalently, to electrostatics. Inductive effects are well established for substituents such as Cl, where the C–Cl dipole withdraws electrons, stabilizes a nearby anion, and increases the acidity of chloroacetic acid relative to acetic acid. Loosely speaking, deuterium is then proposed to be electron-donating. A more rigorous explanation proposes an electrostatic interaction between the ionic charge and the dipole moments of C–H or C–D bonds.[10] Dipole moment is the product of charge separation and bond length. Owing to anharmonicity, the average C–H bond is longer than the C–D, and thus has a larger dipole moment that more effectively stabilizes the negative charge of the carboxylate anion, as (exaggeratedly) suggested in **4H** relative to **4D**.[11] Two estimates of the difference in dipole moments vary widely, 0.0086 D versus 0.0001 D.[10b,6] This is an unresolved issue, and eminent researchers continue to invoke an inductive effect to account for secondary deuterium isotope effects.[12]



4H



4D

The focus of the current work is to test whether there is a contribution to the isotope effect on acidity due to an inductive effect. Such a contribution is generally manifested in entropy. An established example is the comparison of formic and acetic acids. Their enthalpies of dissociation in water at 25 °C are nearly the same, 0.01 ± 0.05 and -0.02 ± 0.05 kcal mol^{-1}, respectively, whereas the entropies are -17.1 and -21.9 cal K^{-1} mol^{-1}.[13] The unfavorable $\Delta G°$ for dissociation of either thus arises from the entropy, which is more negative for the less acidic acetic acid. Similarly, although the dissociation of *p*-methylbenzoic acid is more exothermic than that of benzoic, the acid-weakening effect of a *p*-methyl group, attributed to its electron-donating ability, appears in the entropy.[14] The importance of entropy is generally attributed to solute-solvent interactions, specifically the orienting of water molecules around the anion.[15] Indeed, in the context of isotope effects Halevi and co-workers proposed that "it should be noted that $\Delta H°$ of ionization of weak carboxylic acids in water at 25° is generally close to zero. Therefore, if inductive effects determine acidity at all, they do so via changes in entropy, presumably entropy of solvation".[16] According to this reasoning, the smaller dipole moment of the C–D bond (**4D**) would be less effective than that of the C–H (**4H**) at stabilizing a negative charge. As a result, a deutero anion would require more solvation and a greater degree of solvent organization, and it would show a more negative entropy than the protio anion.

To assess the entropy, it is necessary to measure the temperature dependence of the isotope effect. Early attempts to do so were unsuccessful, owing to large experimental

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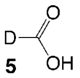
error.[17] Later work showed that the β-deuterium isotope effect on amine basicity is undeniably temperature dependent,[7] contrary to some previous claims, but the experimental error was still too large to evaluate the entropy contribution. We have therefore undertaken to investigate this problem further.

A powerful NMR spectroscopy titration method makes it possible to measure relative acidities,[18] and thus to measure isotope effects on acidity with great accuracy. The method involves titrating a mixture of isotopologues (which differ only in isotopic composition, or number of isotopic substitutions) with small aliquots of base. Equation (1) shows how the

$$(\delta_{H^0}-\delta_{H})(\delta_{D}-\delta_{D^-}) = \left(\frac{K_a^H}{K_a^D}\right)(\delta_{H}-\delta_{H^-})(\delta_{D^0}-\delta_{D}) \qquad (1)$$

ratio of acidity constants can be obtained as the slope of a linear plot involving the chemical shifts δ_{H^0} and δ_{D^0} of the acid forms at the beginning of the titration, δ_{H^-} and δ_{D^-} of the deprotonated forms at the end of the titration, and δ_H and δ_D during the titration. This method was applied to carboxylic acids and phenols,[6] ammonium ions,[7] and pyridinium ions.[8]

Secondary deuterium isotope effects were measured for the following four deuterium-substituted acids: [D]formic (**5**) by ^{13}C NMR, [D]acetic and [D$_2$]acetic (**6**,**7**) by ^{1}H NMR, and 2,4,6-[D$_3$]3,5-difluorophenol (**8**) by ^{19}F NMR spectroscopy.



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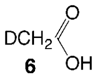

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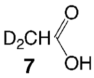

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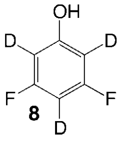

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Instead of a complete titration for each sample, only three titration points, obtained from three samples prepared at room temperature, were used for each acid. Two of the points, corresponding to the fully protonated and fully deprotonated samples, lie at the origin in the plot of Equation (1). The third point was obtained from a 50%-neutralized sample. Little accuracy is sacrificed by this simplification, because the slope of a line is largely determined by its extremities. Thus the isotope effect at each temperature could be measured from the same three samples.

For each acid the isotope effect K_a^H/K_a^D at each temperature was evaluated from measured chemical shifts, according to Equation (1). The data are presented in Table S2 in the Supporting information. For all of the compounds studied and at all temperatures, the values of K_a^H/K_a^D are greater than one, demonstrating a detectable deuterium isotope effect on the acidities, with the acid dissociation constant for the deutero acid smaller (less acidic) than that of the protio. This agrees with the results of many previous studies.

Table S2 in the Supporting Information includes the temperature dependence of the isotope effects, which decrease with increasing temperature. The effects are small, and the temperature dependences even smaller, but the NMR titration makes them measurable.

The enthalpy and entropy contributions to the isotope effect were evaluated from a plot of $\ln(K_a^H/K_a^D)$ versus $1/T$, which gives a slope of $-\Delta\Delta H°/R$ and an intercept of $\Delta\Delta S°/R$, where $\Delta\Delta S° = (S°_{H^-} - S°_{H^0}) - (S°_{D^-} - S°_{D^0})$, and similarly for $\Delta\Delta H°$. Figure 1 is the plot for formic acid. Plots for all other compounds studied are included in Supporting Information. The correlation coefficients for these plots are all greater than 0.99.

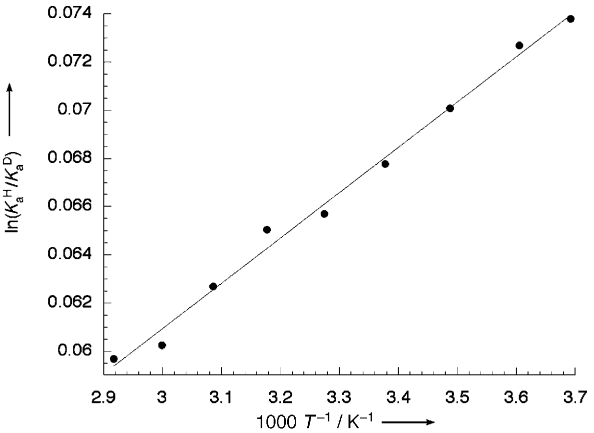

Figure 1. Temperature dependence of secondary deuterium isotope effect on acidity of [D]formic acid.

The enthalpy and entropy contributions to the isotope effects are presented in Table 1, along with $T\Delta\Delta S°$ at 20 °C, to convert the entropy contribution into J mol^{-1} for easier comparison with the enthalpy contribution. Errors reported are standard deviations, from the linear fits. All $\Delta\Delta H°$ values are negative, corresponding to a secondary deuterium isotope effect where the enthalpy contribution decreases the acidity of the protio acid more than that of the deutero acid and thereby leads to a K_a^H/K_a^D greater than one.

Table 1: Enthalpy and entropy contributions to secondary deuterium isotope effects on acidities.

Acid	$\Delta\Delta H°$ [J mol^{-1}]	$\Delta\Delta S°$ [J mol^{-1} K^{-1}]	$T\Delta\Delta S°$, 20 °C
[D]formic	-156 ± 5	0.037 ± 0.017	11 ± 5
[D]acetic	-33 ± 1.7	-0.024 ± 0.006	-6.9 ± 1.7
[D$_2$]acetic	-63.5 ± 2.6	-0.042 ± 0.009	-12 ± 2.6
[D$_3$]3,5-difluorophenol	-117 ± 5	-0.035 ± 0.017	-10.4 ± 5

According to the data in Table 1, the isotope effects appear in the enthalpy, as had been observed before for similar acids. This contribution is expected if the origin of the isotope effects lies in ZPEs of isotope-sensitive vibrations. Moreover, comparisons of the $\Delta\Delta H°$ with $T\Delta\Delta S°$ values in Table 1 show that the dominant contribution to the isotope effect comes from the enthalpy, not entropy.

The principal new conclusion from the data in Table 1 is that there is *no* entropic contribution to the isotope effect. For acetic acid and difluorophenol $\Delta\Delta S°$ is negative, whereas an inductive contribution would require a positive $\Delta\Delta S°$ value (to reinforce the negative $\Delta\Delta H^\circ$ value). As for the remaining acid, formic, for which $\Delta\Delta S^\circ$ is positive, the entropy contribution is not significantly different from zero (at the 95% confidence level, according to Student's *t* test,[19] which also rejects the negative $\Delta\Delta S^\circ$ for difluorophenol). The unreliability of apparently significant compensating relationships between enthalpy and entropy is well established.[20] We therefore conclude that none of the entropy contributions in Table 1 is significantly different from zero. The absence of an entropy contribution to the isotope effect refutes an inductive effect.

After over 50 years, this result finally settles the question of whether there is an inductive contribution to the isotope effect on acidity. There is none. Instead, the findings are consistent with the proposal not only that isotope effects originate from changes in vibrational frequencies upon deprotonation but also that they originate *only* from changes in vibrational frequencies, with no need to invoke anharmonicity of those vibrations. Besides, this conclusion lends support to the later estimate of 0.0001 D for the difference in dipole moments between C–H and C–D bonds.[6] This difference would be manifested in an inductive contribution to the isotope effect, but it is too small to be detected even by the sensitive NMR titration method used herein.

In summary, our findings show that the isotope effects on the acidities of the carboxylic acids and phenol studied originate only in changes in vibrational frequencies and ZPEs upon deprotonation. No evidence for an inductive contribution or electron-donation effect was found.

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