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Comment on "The role of electrostatic induction in secondary isotope effects on acidity" by E. A. Halevi, *New J. Chem.* 2014, 38, 3840

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Abstract. We reaffirm our conclusion that secondary deuterium isotope effects on acidity are due to *n*-σ* delocalization that decreases vibrational frequencies and zero-point energies. We reject an electrostatic or inductive explanation that arises from the anharmonicity of the C-H bond. We address calculated values of atomic charges, dipole moments, and dipole-moment derivatives *d*μ/*dr*, and we show the isotope effect to be a stereoelectronic phenomenon arising from harmonic vibrations.

From our studies of secondary deuterium isotope effects (SDIEs) on acidity we concluded that they arise from differences in zero-point energy (ZPE)[1] Recently E. Amitai Halevi published in this journal a defense of his position that electrostatic induction is responsible for these SDIEs.[2] This was in response to our evidence that the SDIEs on the acidities of formic acid, acetic acid, and 3,5-difluorophenol all appear in the enthalpy, with no entropic contribution, even though inductive effects generally appear in the entropy.[3] Indeed, Halevi had stated that "if inductive effects determine acidity at all, they do so via changes in entropy".[4]

Halevi now renounces the expectation that an inductive effect would appear in entropy. His recent calculations show that the contribution of the entropy of solvation to the SDIE is negligible, and he argues that this is evidence for an inductive origin. Yet this is a necessary consequence of the fact that the SDIEs arise from ZPEs, which requires that the SDIE appear in $\Delta\Delta H^{\circ}$.

It is necessary to correct the record. Therefore this manuscript is a rebuttal to Halevi. To keep the discussion to its essentials, we ignore various aspects of Halevi's calculations, including acetic acid, hydration, and calculations that separate enthalpy from entropy.

Electrostatic interaction with an anharmonic bond. Figure 1, adapted from Ref. 2, shows the interaction of a charge Q with an anharmonic C–H or C–D bond, where R_e, R_{CD}, and R_{CH} are, respectively, the distances from the charge to the equilibrium (minimum-energy) position, to the vibrationally averaged position of the CD, whose zero-point energy is $^1/_2h\nu_{CD}$, and to the vibrationally averaged position of the CH, whose zero-point energy is $^1/_2h\nu_{CH}$. That charge, positive or negative, is assumed to interact with the dipole moment μ of the CH or CD bond, leading to the electrostatic potential energy specified in eq 1, where ε_0 is the permittivity of vacuum and R is the distance in Fig. 1 (and where the angular dependence is ignored because the charge is taken to be on the dipole axis). According to Halevi, the isotope effect then arises from the difference between the CH and CD dipole moments, as in eq 2.

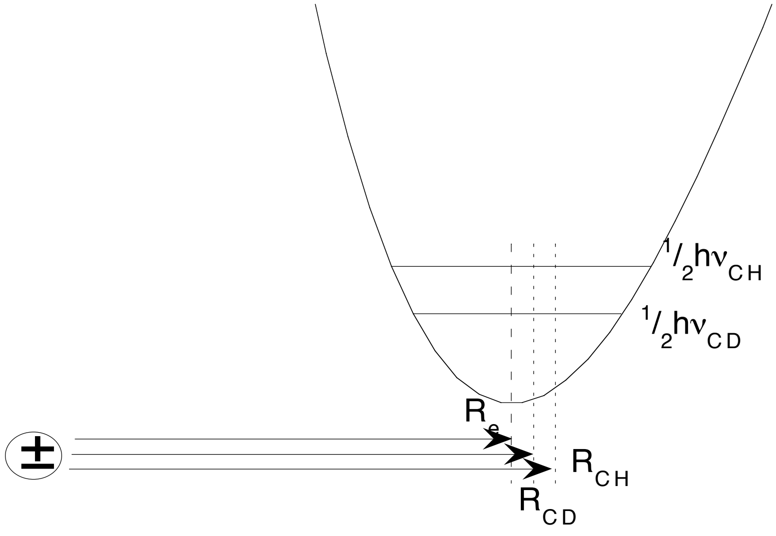


Figure 1. Interaction of a charge with an anharmonic C–H or C–D bond,

$$V_{\mathrm{el}} = -\frac{1}{4\pi\varepsilon_0}\frac{\mu Q}{R^2} \tag{1}$$

$$\Delta V_{\mathrm{el}} = -\frac{1}{4\pi\varepsilon_0}\frac{Q}{R^2}(\mu_{\mathrm{CH}} - \mu_{\mathrm{CD}}) \tag{2}$$

Because $r_{\mathrm{CH}} > r_{\mathrm{CD}}$, owing to the anharmonicity, the magnitude of the CH dipole is greater than that of the CD. One estimate of the difference $\mu_{\mathrm{CH}} - \mu_{\mathrm{CD}}$ was 0.0086 D, based on a comparison of $(CH_3)_3CD$ and $(CH_3)_3CH$.[5] This leads to an isotope effect in agreement with the observed SDIE on acidity of acetic acid,[6] but it is unusually large for such a nonpolar bond. Alternatively, that difference can be expressed as in eq 3, leading to eq 4. The difference $r_{\mathrm{CH}} - r_{\mathrm{CD}}$ can be estimated with good reliability as 0.005 Å, from a Morse potential with a dissociation energy of 100 kcal/mol).[7] The isotope effect then depends critically on the value of $d\mu/dr$. According to the infrared intensity of methane, $d\mu/dr = 0.004e$ per CH,[8] or 0.02 D/Å, which leads to a much lower $\Delta\mu$ of only 0.0001 D and an SDIE two orders of magnitude lower than either the earlier estimate or the observed SDIE. Likewise, the inductive contribution to an SDIE on amine basicity was estimated to be much smaller than the measured SDIEs.[1] Therefore it was concluded that an inductive effect dependent upon anharmonicity does exist but is negligible.

$$\mu_{\mathrm{CH}} - \mu_{\mathrm{CD}} = \frac{d\mu}{dr}(r_{\mathrm{CH}} - r_{\mathrm{CD}}) \tag{3}$$

$$\Delta V_{\mathrm{el}} = -\frac{1}{4\pi\varepsilon_0}\frac{Q}{R^2}\frac{d\mu}{dr}(r_{\mathrm{CH}} - r_{\mathrm{CD}}) \tag{4}$$

To respond to this criticism, Halevi evaluated dipole moments according to eq 5, where q_{C} or q_{H} is the charge on carbon or hydrogen and r is the C–H or C–D bond distance. He also postulated that $d\mu/dr$ is the same in both the acid and its conjugate base. This was recognized as an oversimplification, but it is adequate. He then evaluated $\mathrm{d}\mu/\mathrm{dr}$ according to eq 6, where $\Delta\mu$ or Δr is the difference between the values of the C–H bond dipoles or bond distances in the acid and its conjugate base.

$$\mu_{CH} = {}^{1}\!/_{2}(q_C - q_H)r_{CH} \tag{5}$$

$$\frac{d\mu}{dr} \sim \frac{\Delta\mu}{\Delta r} = \frac{\mu_{CH}{}^{acid} - \mu_{CH}{}^{base}}{r_{CH}{}^{acid} - r_{CH}{}^{base}} \tag{6}$$

This methodology led to values of $\Delta\mu/\Delta r$ for the C–H bond in formic acid of 11.2 and 29.5 D/Å, depending on whether eq 5 used Mulliken or atomic polar tensor (APT) charges, as calculated at the MP2/6-311g(d,p) level. For methylammonium ion these values are 3.3 and 9.7 D/Å. All of these are much larger than the above 0.02 D/Å from infrared intensity. This was recognized as seeming excessively large, but it was rationalized as reflecting a large variation of dipole moment across small changes in bond length ("reflect the fact that the magnitude of the C–H bond dipole—and even its sign—vary over a small fraction of the bond length").[2]

Table 1 lists Mulliken and APT atomic charges at C and H from Ref. 2, as well as natural bond orbital (NBO) charges that we calculated. Also included are CH bond dipole moments and CH_3 group dipole moments along the C-N axis, as reported in Ref. 2 or calculated with NBO charges according to eq 5. These Mulliken or APT charges then led to estimates for $\Delta\mu/\Delta r$ in formate of 11.2 or 29.5 D/Å, respectively. The large differences of atomic charges among Mulliken, APT, and NBO distribution schemes, and even changes of sign, certainly cast doubt on the reliability of any of them. Indeed, it has been stated, in connection with a catalog of various distribution schemes, "Any definition of atomic charge in a molecule is of necessity an arbitrary distinction, and its usefulness must be ascertained from its ability to correlate with experimental properties."[9] Yet neither the charges nor the dipole moments in Table 1 can be verified experimentally. Certainly the reversal of the group dipole of the CH_3 in both $CH_3NH_3^+$ and CH_3NH_2 from $C^{\delta-}$-$H^{\delta+}$ according to Mulliken and NBO charges to $C^{\delta+}$-$H^{\delta-}$ according to APT, as well as the nearly threefold variation in $\Delta\mu/\Delta r$ between Mulliken and APT charges, is evidence that these values are unreliable. Besides, for an ion, which carries a net charge, the value of its dipole moment is indeterminate because it is not invariant to a change of origin.[10]

Table 1. Atomic Charges and C–H or CH_3 Dipoles

	Mulliken[a]			APT[a]			NBO		
	q_C	q_H	μ_{CH}, D	q_C	q_H	μ_{CH}, D	q_C	q_H	μ_{CH}, D
HCOOH	0.446	0.105	0.899	1.041	-0.005	2.756	0.829	0.100	1.920
HCO_2^-	0.419	-0.118	1.482	1.247	-0.309	4.293	0.828	-0.556	3.821
$CH_3NH_3^+$	-0.126	0.178	-0.740	0.257	0.068	0.456	-0.252	0.205	-1.113
CH_3NH_2	-0.101	0.081[b]	-0.515	0.337	-0.050[b]	1.113	-0.255	0.143[b]	-1.126

[a]From Ref. 2. [b]Average.

The unrealistically high values of 11.2 or 29.5 D/Å for $\Delta\mu/\Delta r$ arise because eq 6 is wrong! It is necessary to evaluate ΔV_{el} of eq 4 separately for an acid and its conjugate base. The derivative $d\mu/dr$ represents the change of bond dipole solely on stretching a bond, with no other change. It cannot be approximated by the $\Delta\mu/\Delta r$ of eq 6, which includes a contribution from the extra charge. The value of μ changes from base to conjugate acid simply because the two atomic charges of eq 5 change unequally on deprotonation. For example, the NBO q_C hardly changes on deprotonation of HCOOH or $CH_3NH_3^+$, but q_H does. Thus there is no justification for using eq 6, or for correlating $d\mu/dr$ evaluated therefrom with isotope-dependent frequency shifts upon deprotonation.

Evaluation of $d\mu/dr$. It is possible to evaluate $d\mu/dr$ independently of eq 6. That derivative for a neutral species can be easily calculated from Gaussian output according to eq 7, expressing how μ changes when the CH distance is changed by (an arbitrary) ± 0.02 Å. This method is not applicable to ions, for which dipole moment is not invariant to a change of origin. Instead the derivative can be obtained from Gaussian output when vibrational frequencies are calculated. The concise archive at the end of a log file contains the nine dipole moment derivatives $\partial\mu_x/\partial x$, $\partial\mu_x/\partial y$, $\partial\mu_x/\partial z$, $\partial\mu_y/\partial x$, etc. in input orientation for each atom, in units of electron charge.[11] Then for atoms C and H separated by a distance r_{CH} along the x-axis the desired derivative is given by eq 8. For a CH_3 group this must be modified to account for components along two axes.

$$d\mu/dr_{CH} \sim \Delta\mu/\Delta r_{CH} = (\mu(r_{opt}+0.02)-\mu(r_{opt}-0.02))/0.04 \qquad (7)$$

$$d\mu_z/dr_{CH} = (\partial\mu_z/\partial z_C - \partial\mu_z/\partial z_H)/2 \qquad (8)$$

Table 2 lists calculated equilibrium C-H distances, total dipole moments, and $d\mu/dr_{CH}$ for HCOOH, HCO_2^-, $CH_3NH_3^+$ (per CH), and CH_3NH_2. The dipole moment of an ion is expressed relative to the center of nuclear charge taken as the origin of coordinates, as provided by Gaussian output. The negative signs mean that those dipole moments decrease with increasing C–H bond length, contrary to Halevi's inference based on $\Delta\mu/\Delta r$.

Table 2. MP2/6-311g(d,p) calculated $d\mu/dr$ (D/Å)

	r_{opt}, Å	μ, D	$d\mu/dr$
HCOOH	1.0969	1.5938	-0.02
HCO_2^-	1.1495	1.522	-5.97
$CH_3NH_3^+$	1.0880	2.205	0.28
CH_3NH_2	1.09975[a]	1.5072	-1.05[a]

[a]Anti to lone pair.

Admittedly, some of these values are greater than the *d*μ/*dr* of 0.02 D/Å that was based on the infrared intensity of methane. In methane the C-H bonds are decidedly nonpolar, but *d*μ/*dr* here is for the entire molecule or ion. However, because ΔV_{el} in eq 4 = 0 when $Q = 0$, it is only in an ion that the dipole moment interacts with a charge. Even for an ion the applicability of eq 4 is not clear, because the distance *R* between the charge and the dipole is not well defined when μ is the total dipole moment of the ion, rather than a bond dipole, as in Table 1. Besides, eqs 1 and 4 are applicable only when *R* is large compared to the dimensions of the dipole.

Halevi used a clever method independent of calculated dipole moments to evaluate an energy that he attributes to ion-dipole interaction. He viewed our use of vibrationally averaged bond lengths r_{CH} and r_{CD} in eq 3 as a gross underestimate. Instead he used the potential energy averaged over the vibrational wave functions for C-H and C-D motions. According to the virial theorem, the average potential energy of a harmonic oscillator can be evaluated simply as half of its total energy.

Indeed, as we had shown,[12] the calculated total energies can account for the observed SDIEs, and actually overestimate them, owing to neglect of solvation. Halevi has corroborated this conclusion with calculations on hydrates of these acids and their conjugate bases.[2] Therefore the potential energies, averaged over vibrational wave functions for C-H vs C-D, can account for the observed SDIEs. Yet the calculated energies and SDIEs are derived from ZPEs assuming harmonic potentials. If harmonic potentials can account for the SDIEs, then it is not necessary to invoke anharmonicity. It is certainly not logical to use energies calculated with harmonic potentials to justify an inductive effect that requires anharmonicity.

Evidence against an Inductive Effect. Halevi's dilemma is that it is difficult to conclude that an inductive effect is responsible for these SDIEs. As far as we can determine, all his evidence is also consistent with an effect arising solely from ZPEs. Then it is unnecessary to invoke anharmonicity to account for these SDIEs.

Instead of any inductive effect we have attributed these SDIEs to n-σ^* delocalization, also known as negative hyperconjugation. According to our calculations, deprotonation weakens the C-H bonds in formate relative to formic acid and in methylamine relative to methylammonium ion (Figure 2). The resulting decrease in vibrational frequency and ZPE then is responsible for the SDIE. In formate anion it is difficult to distinguish this influence of n-σ^* delocalization from interaction of the negative charge with the C-H dipole, as Halevi proposed.

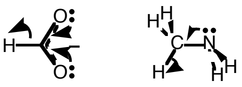
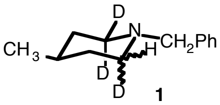


Figure 2. *n*-σ* delocalization in formate anion and in methylamine.

It is easier to distinguish with methylamine. Our interpretation focuses on the lone pair in CH_3NH_2, where there is no charge-dipole interaction, whereas Halevi focuses on the interaction of the positive charge in $CH_3NH_3^+$ with a C–H or C–D dipole, which would be independent of dihedral angle. Our computational results find the C–D stretching frequency in DCH_2NH_2 to be largest when the C–D is anti to the lone pair, with maximum *n*-σ* delocalization.[13] Moreover, experimental SDIEs on amine basicities can be fit to eq 9, where τ is the dihedral angle between the C-D bond and the nitrogen lone pair. The angle-independent term is zero, within a very small experimental error. This is the term that would represent an electrostatic interaction between a positive charge and the C-H or C-D bond dipole.

$$\Delta\Delta G^0\ (\text{cal/mol}) = (45.7\pm4.5)\cos^2\tau + (1.8\pm2.6) \qquad (9)$$

Moreover, a crucial experimental result is the K_{eq}/K_{ax} of 1.060±0.006 for the two isotopomers (isotopic stereoisomers) of 1-benzyl-4-methylpiperidine-2,2,6-d_3 (**1**).[14] The one with deuterium axial and therefore antiplanar to the nitrogen lone pair is the more basic. Thus the SDIE is of stereoelectronic origin.



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Halevi disparaged this result as a small secondary effect superimposed on electrostatic induction because all our experimental SDIEs are small, with ΔΔ*G*° in the range of 22±5 cal/mol per D (although ΔΔ*G*° for **1** is 34 cal/mol). These values are indeed considerably smaller than the 152 cal/mol that Halevi calculates for CD_3NH_2, but his value is the sum over 3 deuteriums and in the gas phase, whereas ours is the difference between anti and gauche SDIEs in aqueous solution. Therefore the measured SDIE for **1** cannot be dismissed as a small "secondary effect".

Besides, the low SDIEs are not restricted to conformationally constrained amines that Halevi singles out from Table 1 of his Ref. 10. Instead they are observed for all the amines in that table.[13]

Additional evidence against an inductive effect is that although inductive effects fall off with distance, the SDIEs in benzoic acids and phenols do not decrease as the site of deuteration moves from ortho to meta to para.[15] Moreover, in pyridines the SDIE per deuterium is largest for substitution at the 3-position, and smallest for the 2-position that is closest to the site of *N*-protonation.[16] Although all these SDIEs are quite small, they can be measured with great accuracy by an NMR titration method applicable to a mixture.[17] The SDIEs can be attributed to isotope-sensitive vibrations whose frequencies and zero-point energies are calculated to be lowered on deprotonation.

An inductive effect arising from dipole moments of C-H vs C-D bonds ought to be proportional to the number of C-D bonds. Instead, with trimethylamines the SDIEs are nonadditive, such that the decrease in basicity, per deuterium, increases with the number of deuteriums.[18] This nonlinearity in the basicities is strong evidence against an SDIE of inductive origin. It arises from ZPEs because the SDIE depends on the dihedral angle between the lone pair and the C-D bond, and because there is a preference for conformations with C-H antiperiplanar to the lone pair and C-D gauche.

Finally, we return to the experimental finding that SDIEs on acidity appear in the enthalpy, with no entropic contribution,[3] which is what prompted Halevi's recent paper.[2] Although Halevi now argues that an inductive effect need not appear in entropy, the lower acidity of acetic acid relative to formic is due to inductive electron donation by methyl, leading to a more negative entropy of solvation for acetate. When calculations also find that there is no contribution of entropy to the SDIE, we conclude that the SDIE is not due to an inductive effect but to differences in ZPEs of harmonic frequencies, with no necessity for invoking anharmonicity.

Methodology

All calculations were performed on a Dell Optiplex PC with Intel Core 2 Duo processor running Gaussian03W software[19] or on an iMac desktop computer with 2.7 GHz Intel Core i5 and OS 10.9.5 running Gaussian 09 software Revision C.01,[20] Structures were built using GaussView 4.1.2 and optimized with a tight geometry and including the same basis set as Halevi used.[2] Although Halevi asserted that the methods used by Perrin and Dong[14] did not allow for H-atom polarization, it should be noted that Table 3 of that reference includes results from B3LYP/6-311+G(d,p) calculations.

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Note in Proof

Halevi claims that the potentials generated by the Gaussian program are not harmonic and he concludes with "the differences in the harmonic frequencies that are responsible for the isotope effect are observed *because* the potential energy function is anharmonic". In fact, although the potential energy function is anharmonic, the Gaussian program finds the equilibrium geometry that minimizes the electronic energy, evaluates the Hessian matrix of mass-weighted second derivatives of the potential energy, and diagonalizes that matrix to find the normal modes and *harmonic* vibrational freqencies. Because the second derivatives are evaluated at the equilibrium geometry, these *are* harmonic frequencies.

However, the Gaussian program has the further capability of computing anharmonic frequencies. Table 3 lists frequencies calculated for formic acid and formate anion, with the CH and CD stretching frequencies in boldface. The important conclusion is that harmonic and anharmonic frequencies are not the same (which is why various scaling factors have been developed to rectify harmonic frequencies).[21] Nevertheless, the isotope effect calculated from CH and CD harmonic frequencies (3123-2509-2322+1827) is the same as from anharmonic (2968-2282-2234+1668). We therefore repeat the conclusions that (1) the isotope effects can be derived from ZPEs assuming harmonic potentials, (2) if harmonic frequencies can account for the isotope effects, then it is not necessary to invoke anharmonicity, and (3) it is not logical to use energies calculated with harmonic potentials to justify an inductive effect that requires anharmonicity.

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