Perrin begins his critique with the unsubstantiated pronouncement: “...inductive effects generally appear in the entropy”, adding “Indeed, Halevi had stated that “if inductive effects determine acidity at all, they do so via changes in entropy”. In note 15 of my paper I apologized for this misleading statement, which Perrin and Flach had already cited out of context, and explained briefly the intent of the paragraph in which it appears. As Perrin has found it necessary to cite it again, I feel obliged to quote the paragraph in full:

“Moreover, although the temperature-dependence of the isotope effects reported here has yet to be measured, it should be noted that ΔH° of ionisation of weak carboxylic acids in water at 25 °C is generally close to zero. Therefore, if inductive effects determine acidity at all, they do so via changes in entropy, presumably entropy of solvation. It is thus an evident oversimplification to disregard the solvent when dealing with small effects in highly polar solutions.” Footnote 12: “The observed temperature-dependence of the secondary isotope effect in aqueous hydrolysis of alkyl halides can perhaps be rationalised in similar terms.”

The words “inductive effects” in the sentence emphasized above should have been replaced by “these effects, regarded as inductive”, but – even as the sentence stands – it should have been clear that it does not refer to isotope effects, but – in general – to solvent effects on the acidity of carboxylic acids in aqueous solution at ambient temperature. It does not say that entropy determines the isotope effect, certainly not the intrinsic isotope effect that manifests itself at 0 K in the gas phase and is necessarily non-entropic. To the contrary, it implies that the source of an isotope effect cannot be deduced from experiments in solution unless solvation is taken into account.

The objectives of my paper are:

1. To reaffirm the validity of a mathematical proof, unchallenged for half a century until questioned by Perrin, that electrostatic polarization can lead to an isotope-dependent shift in the frequency of a CH-bond by virtue of the anharmonicity of its stretching mode.
2. To demonstrate that electrostatic polarization produces isotope effects on acidity by showing that the magnitude of the isotope effect on deprotonation of formic acid is in substantially linear correlation with the shift of electronic charge within its CH–CD bond. The compelling evidence is the concerted reduction of the isotope effect and the charge-shift that occurs on stepwise hydration of the acid and its conjugate base.
3. To present computational evidence that, mutatis mutandis, a similar correlation is observed in the deprotonation of acetic acid and the protonation of methylamine and, therefore, that electrostatic induction is capable of generating secondary isotope effects on the acidity of carboxylic acids and the basicity of alkylamines.
4. To show how hydration of the acid and its conjugate base reduces the isotope effects, drastically in the case of the carboxylic acids and mildly in that of the amine, bringing them down very nearly to the experimentally determined values.
5. To show, by separating the enthalpy and entropy of solvation, that the effect of hydration on the isotope effects operates almost entirely via the enthalpy of solvation rather than its entropy.

Perrin prefaced his rebuttal as follows: “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”. He also disregards the theoretical discussion (Section 2) and the accompanying Appendix (Section 5), so I will limit my response to Perrin’s comments on what he regards as the essentials.

1. It is of crucial importance to distinguish between two measures of the potential energy of vibrating CH and CD bonds.
Yet the calculated energies and SDIEs [in my paper 1 _E.A.H._] are the vibrational amplitude. Specifically for the vibrational X–D bond, which lies below it in the potential well. In Perrin’s higher-order Taylor-series expansions of the molecular potential Perrin and me are not harmonic. Anharmonic potentials, invoke anharmonicity.’’

potentials can account for the SDIEs, then it is not necessary to the vibration (\( e – \) averaged over the vibrational cycle; and

Thus, the perturbation raises or lowers the average potential energy surface, are ubiquitous in computational chemistry.6 A recent study on the accurate evaluation of zero-point vibrational energies addresses the question: “Can anharmonic force fields be avoided?” and concludes that they cannot.7

The anharmonic potential surfaces computed separately for formate ions and formic acid are different, specifically with respect to the curvature of the potential well of the C–H bond that is determined by its quadratic term \( \frac{1}{2}k(r – r_0)^2 \). The question posed in my article1 is whether this difference, which is responsible for the SDIE can be ascribed to the negative charge on the carboxylate group. Within the limitations of the one-dimensional model employed, the answer is that it can, because the potential function for C–H bond extension contains a cubic anharmonic term, \( g(r – r_0)^3 \). Before computing the vibrational frequencies, the Gaussian programs truncate the potential function by removing the anharmonic terms unless specifically asked not to do so. The ZPE’s derived from the ensuing harmonic frequencies are ordinarily adequate for the evaluation of the isotope effect, but that does not negate the fact that it is due to anharmonicity.

The expectation value of the potential energy is something quite different. Thanks to the skewed shape of the anharmonic potential, the positive displacement of the bond during its expansion phase is larger than the negative displacement during contraction, so an electrostatic perturbation (attractive or repulsive), \( a(r – r_0) \), that increases with the bond length is felt more strongly when the bond is extended than when it contracts. Averaged over the vibrational cycle, the overall effect is dominated by the interaction during the extension phase. Thus, the perturbation raises or lowers the average potential energy of the X–D bond less than that of the X–H bond, which extends farther during the extension phase of the vibration. This factor operates in the same direction as the effect described in the preceding paragraph, but is much larger and is the principal source of the observed isotope effect.

For a harmonic potential (\( V–V_o \)) is half of the vibrational energy, so at 0 K it is equal to half of the zero-point vibrational energy. This is also true in good approximation for an anharmonic potential, so the effect necessarily manifests itself as a shift of zero-point vibrational energies. This point is discussed in detail in Section 2 of my paper and illustrated computationally for formic acid in Section 3.1.3.1 It also follows from eqn (A.8) in the Appendix, which illustrates how anharmonicity changes the (harmonic) force constant.

(2) In a comment related to the above, Perrin writes: “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 [in my paper1 _E.A.H._] are derived from ZPEs assuming harmonic potentials. If harmonic potentials can account for the SDIEs, then it is not necessary to invoke anharmonicity.”

This comment is based on a serious misconception. The potentials generated by the Gaussian programs used by both Perrin and me are not harmonic. Anharmonic potentials, i.e. higher-order Taylor-series expansions of the molecular potential energy surface, are ubiquitous in computational chemistry.6

(3) The bulk of Perrin’s rebuttal is devoted to an attempt to discredit my use of the term \( \Delta \mu/\Delta r_e \) as a measure of the shift of electronic charge from H to C in the CH-bond as it expands on deprotonation of the carboxyl group. In the present context that is what it is – and all it is. As the fractional difference between the bond lengths is quite small, \( \Delta \mu \) can be regarded as being, in effect, directly proportional to the charge shift. Its numerical value depends on the method used to estimate how the atomic charges are distributed among the atoms. The wide variation between these distributions is evident in Perrin’s Table 1,5 as it is in my Tables 1, 6 and 10.1 I agree that \( \Delta \mu/\Delta r_e \) is not the same as \( \Delta \mu/dr \), the derivative of the dipole moment of a bond with respect to the distance as it vibrates about its equilibrium length, though – if the same charge distribution scheme is used – I would expect it to be similar. Nor do I claim that it is the same in the anion as in the neutral molecule; that is a consequence of \( \Delta \mu/\Delta r_e \) being a linear approximation. Note 21 of my paper1 reads: “This is an oversimplification, but it is adequate for the present qualitative purposes”. In fact, all of my conclusions could have been reached without recourse to \( \Delta \mu/\Delta r_e \) or its analog for the methyl group, \( \Delta \mu_q/\Delta r_{m_q} \). The relevant property is not the bond dipole per se, but the charge shift. If \( \Delta q – q_0 \) rather than the bond moment had been plotted against the isotopic free energy difference in Fig. 4, the result would have been practically identical. Quantitative comparisons with spectroscopically derived bond moments and – all the more – arguments based on the dipole moments of the molecules and ions (Perrin’s Table 2) are irrelevant.

(4) It is not claimed that electrostatic induction is the sole determining factor in secondary isotope effects on acidity. The deviations from linearity in my Fig. 3–5 are evidence for a superposed steric effect. In appropriate circumstances stereo-electronic effects can certainly occur as well.8 My objection to Perrin’s claim that the entire isotope effect in amines is due to negative hyperconjugation is not that the isotope effect is small; secondary isotope effects are expected to be small. It is
observed that all of the isotope effects listed in his table\(^5\) are in the same direction, regardless of the dihedral angle. The angular dependence, which shows up as a perturbation, may indeed be due to n–σ* delocalization, but it cannot be regarded as the principal factor. Incidentally, \(K_{qd}/K_d\) of dissociation is not cited for 1-benzyl-4-methylpiperidine-2,2,6-d3 in the table, where it is numbered 7; only the equatorial/axial ratio. This ratio says nothing about the presence or absence of an inductive effect, but its rather large size may indicate the presence of an additional steric isotope effect.

(5) Perrin’s final sentence is: “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.” I can only repeat that Perrin’s assumption that inductive effects are necessarily due to entropy is unwarranted, and that the differences in the harmonic frequencies, which are responsible for the isotope effect, are observed because the potential energy function is anharmonic.

**Note added in proof**

In his “Note added in Proof”, Perrin provides computational evidence that the isotope effect on the dissociation of formic acid computed with harmonic frequencies is the same as that computed with anharmonic frequencies. From this fact, which is undisputed, he concludes that since these energies are calculated with neglect of anharmonicity, it is not logical to use them to justify an inductive effect that requires anharmonicity. Perrin ignores the fact that anharmonicity enters the picture at an earlier stage in the computation, during construction of the (anharmonic) potential energy surface from which the vibrational frequencies – harmonic and/or anharmonic – are ultimately derived.

The isotope effect on dissociation of formic acid arises primarily because the CH-stretching frequency is very much lower in the anion than in the acid.\(^\text{10}\) The harmonic frequencies, as cited by Perrin, are 2509 and 3123 cm\(^{-1}\) respectively. It is logical to relate this change, which is accompanied by lengthening of the bond, to the most obvious difference between HCOOH and HCOO\(^-\); replacement of a formally neutral covalently bonded H atom by a negative charge. A simple one-dimensional model, introduced half a century ago\(^\text{4}\) and revived in my article,\(^\text{3}\) shows that in order for the negative charge on the carboxylate group to reduce the C–H stretching frequency sufficiently to produce an appreciable isotope effect, the potential function must include an anharmonic term, \(g(r – r_e)^3\). The fact that this term, as well as the other anharmonic terms in the potential, can be neglected in the subsequent vibrational analyses of the acid and the anion is completely irrelevant.

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