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Journal

J. Phys. Chem. A, 119

Authors

Perrin, Charles L
Burke, Kathryn D

Publication Date

2015-08-05

Peer reviewed

Can a Secondary Isotope Effect Be Larger than a Primary?

Charles L. Perrin* and Kathryn D. Burke

Department of Chemistry, University of California—San Diego

La Jolla, CA 92093-0358 USA

cperrin@ucsd.edu

Abstract

Primary and secondary ^{18}O equilibrium isotope effects on the acidity of a variety of Brønsted and Lewis acids centered on carbon, boron, nitrogen, and phosphorus were computed by density-functional theory. For many of these acids the secondary isotope effect is found to be larger than the primary. This is a counterintuitive result, because the H that is lost is closer to the ^{18}O that is responsible for the primary isotope effect. The relative magnitudes of the isotope effects can be associated with the vibrational frequency and zero-point energy of the X=O vibrations, which are greater than those of the X–O vibrations. However, the difference between these contributions is small, and the major responsibility for the larger secondary isotope effect comes from the moment of inertia factor, which depends on the position of the ^{18}O relative to the principal axes of rotation.

Introduction

Isotope effects (IEs) are widely used to explore rates or equilibria of chemical reactions.¹²³ The largest are for protium relative to deuterium, and such IEs have recently been used to study the structures of hydrogen-bonded systems,⁴⁵⁶⁷⁸ calculated solvent effects on IEs,⁹ non-covalent interactions in host/guest systems,¹⁰ rates of oxidation of anthranolate by O_2 ,¹¹ H-atom abstraction from methoxy radical, fatty acids, and hydrocarbons,¹²¹³¹⁴ tunneling in enzyme

catalysis,¹⁵ and binding of small molecules to proteins.¹⁶ IEs of heavier atoms are smaller and thus less often studied, but they have been used to study the mechanism of formation of Grignard reagents,¹⁷ heavy-atom tunneling in the Bergman cyclization,¹⁸ and the kinetics and equilibria of some biological reactions.¹⁹

Molecules that differ in the number of isotopic labels are called isotopologues (isotopic homologues). An equilibrium isotope effect (EIE) is the ratio $K_{\text{light}}/K_{\text{heavy}}$, and a kinetic isotope effect (KIE) is the ratio of rate constants, $k_{\text{light}}/k_{\text{heavy}}$. Our interest here is in ^{18}O EIEs, which have been used recently to investigate isotope-induced changes in NMR chemical shifts, toward understanding the structures of hydrogen-bonded systems,²⁰ and isotope partitioning between sulfite and water, toward understanding biogeochemical processes.²¹

This work focuses on a comparison of primary (1°) and secondary (2°) ^{18}O EIEs on acidity. A 1° EIE arises when a bond to the isotope is broken or formed during the reaction. A 2° EIE arises when bonds to the isotope remain intact during the reaction.

Isotope Effects on Vibrational Frequencies. Isotopic substitution usually affects reactivity by changing frequencies of vibrational modes. The vibrational frequency ν of a bond connecting masses m_1 and m_2 is given by eq 1, where μ is the reduced mass, $m_1 m_2 / (m_1 + m_2)$, and k is the force constant. The lowest possible vibrational energy is the zero-point energy (ZPE), in eq 2, where h is Planck's constant.

$$\nu = \sqrt{\frac{k}{\mu}} \quad (1)$$

$$E_0 = \frac{1}{2} h \nu \quad (2)$$

A heavier isotope increases μ , leading to a decrease in both Δ and ZPE. The consequences are illustrated in Figure 1, where the force constant for the CH stretch in an alkoxide anion is lower than for the alcohol.²² The energy required to form R_2CHO^- from R_2CHOH is then less than that required to form R_2CDO^- from R_2CDOH . Thus R_2CHOH is a stronger acid than R_2CDOH .

Figure 1. Potential-energy diagrams and ZPEs for R_2CHOH , R_2CDOH , R_2CHO^- , and R_2CDO^- .

Energy differences between reactant and product for the unlabeled and labeled species are

$$\Delta ZPE_H \text{ and } \Delta ZPE_D, \text{ respectively.}$$

Experimental EIEs on Acidity. EIEs on acidity constants are especially informative. They can be measured using a variety of methods. Classic methods are pH titration and conductivity.^{23,24} A highly accurate method is NMR titration,²⁵ which has been used to measure

secondary EIEs for D-substituted carboxylic acids, phenols, ammonium ions, and pyridinium ions.²⁶²⁷²⁸²⁹

Our interest here is in ^{18}O EIEs on acidity and specifically the comparison of primary and secondary EIEs. The magnitude of an IE is expected to be strongly dependent on the distance between the isotope and the reaction center. In terms of vibrational frequencies, the largest changes involve those atoms directly involved in the reaction, while an atom at a secondary position would appear to be merely a spectator. This implies that a 1° IE ought to be larger than a 2° . We here pursue the possibility that this does not hold for EIEs on the acidity of ^{18}O -labeled acids.

Carboxylic acids feature a special functionality. They have two mono- ^{18}O -labeled isotopomers (isotopic isomers, differing in the position of the isotope but not in the number of isotopic substitutions), depending on which O is labeled, as shown in Figure 2. The 1° EIE is associated with the C–O and O–H vibrations, and the 2° is associated with the C=O. These EIEs can be estimated from experimental IR frequencies. Table 1 lists typical frequencies for ^{16}O -containing carboxylic acids and carboxylate anions,³⁰³¹ assigned as O–H and C–O stretches, which should be the dominant contributors to the 1° EIE, and as a C=O stretch, which should be dominant for the 2° EIE, along with the average frequency for $\text{C}=\text{O}^-$ in the anion. Table 1 also lists the corresponding frequencies for di- ^{18}O -labeled carboxylic acids and carboxylates, as adjusted with eq 1.

Figure 2. Primary and secondary EIEs on the acidity of two isotopomeric mono- ^{18}O -labeled carboxylic acids.

Table 1. IR stretching frequencies (cm^{-1}) for unlabeled and di- ^{18}O -labeled RCOOH and RCO_2^- .

Stretch	$\nu(^{16}\text{O}_2)$	$\nu(^{18}\text{O}_2)$	Δ
O–H	3000	2990	10
C–O	1300	1271	29
C=O	1760	1718	42
C–O $^-$	1500 ^a	1464 ^a	36
Sum ^b	3060	3051	9

^aAverage of symmetric and asymmetric stretches. ^b $\nu_{\text{O–H}} + \nu_{\text{C–O}} + \nu_{\text{C=O}} - 2\nu_{\text{C–O}^-}$

In Table 1 the difference Δ between $\nu(^{16}\text{O}_2)$ and $\nu(^{18}\text{O}_2)$ represents the contribution to the EIE from each mode. The sum over the reactants minus the sum over the products is 9 cm^{-1} , which corresponds to an EIE of 1.022 at 26°C . This value is in satisfactory agreement with the experimental EIE of 1.0222 ± 0.0002 for $\text{HC}^{18}\text{O}_2\text{H}$.³²

Summing Δ of O–H and C–O leads to a contribution to the 1° EIE of 39 cm^{-1} , which is smaller than the contribution of 42 cm^{-1} to the 2° . This result implies that the 1° EIE is smaller than the 2° , as was previously noted.³³ The frequencies in Table 1 make this implication clear. The dominant contribution to the 2° EIE is from the C=O, whose frequency, 1760 cm^{-1} , is considerably higher than the 1300 cm^{-1} of the C–O that contributes to the 1° . Although O–H has the highest frequency, also contributing to the 1° EIE, its dependence on reduced mass renders it

relatively insensitive to ^{18}O labeling. Thus the contributions from O–H and C–O to the 1° EIE are less than the contribution from C=O to the 2° .

The difference between 39 and 42 cm^{-1} is so small that it is sensitive to the values in Table 1. If the O–H stretching frequency is taken instead as 3570 cm^{-1} , as measured for HCOOH monomer,³⁴ that difference nearly vanishes. It even reverses for HCOOD, because the dependence on reduced mass renders the O–D frequency more sensitive to ^{18}O labeling, so that its contribution to the 1° EIE makes it larger than the 2° .

Calculation of Equilibrium Isotope Effects. Because of these uncertainties, we have undertaken to calculate ^{18}O EIEs on acidity, so as to compare 1° and 2° EIEs. This comparison is not possible experimentally, because rapid proton exchange scrambles ^{18}O between C=O and C–OH. (In principle the ratio of the EIEs could be determined from the deviation of the chemical shift of $\text{RCOOH-}^{18}\text{O}$ from the average of the shifts of RCOOH and $\text{RCOOH-}^{18}\text{O}_2$, but the deviation is far too small to resolve.) Calculations are now used extensively to predict pK_a values,³⁵ and also to help interpret experimental measurements of IEs,^{36,37} including ^{18}O KIEs in ruthenium-catalyzed water oxidation.³⁸

Research Goals. Our goal is to calculate ^{18}O EIEs on the acidity of the acids in Figure 3, and to compare primary with secondary EIEs. For the Brønsted acids in Figure 3A the 1° EIE is from ^{18}O labeling at the OH that loses its H^+ , while the 2° EIEs are from any other ^{18}O labels. The Lewis acids in Figure 3B add hydroxide at C, N, B, or P, as in eq 3, where the Lewis base is water and H^+ is a byproduct. (The EIEs calculated for addition of OH^- alone are distorted by the unusually small contribution of the single O–H vibration.) The 1° EIEs are due to reaction with $^{18}\text{OH}_2$, whereas the 2° EIEs are from a $\text{C=}^{18}\text{O}$, $\text{N=}^{18}\text{O}$, $\text{B-}^{18}\text{OH}$, $\text{P=}^{18}\text{O}$, or $\text{P-}^{18}\text{OH}$ that

remains intact. To distinguish 1° from 2° EIEs, calculations are restricted to comparisons of unsubstituted acids with their mono-¹⁸O isotopologues.

Figure 3. Carbon, nitrogen, boron, and phosphorus acids whose ¹⁸O EIEs are to be calculated.

(A) Brønsted acids. (B) Lewis acids.

Density-functional calculations at the B3LYP/aug-cc-pVTZ level have been used successfully for isotope calculations,³⁹ and they work well with acidic and basic species.⁴⁰ This method should be applicable to the acids in Figure 3 and their conjugate bases.

In summary, our goal is to calculate ¹⁸O EIEs on the acidity of carboxylic acids and similar N, B, and P acids, and to explore the generality of a secondary EIE larger than a primary, as suggested by the vibrational frequencies of formic acid. The assertion, "In general, secondary

isotope effects are much smaller than primary isotope effects",⁴¹ is a challenge to find counterexamples. To the best of our knowledge, there are no authenticated examples of a 2° EIE or KIE greater than the 1°. Of course, there are some special cases where a 2° EIE is larger than a 1° that is very close to 1 because the reaction is an identity reaction, or nearly so, as in some hydride transfers.⁴² The phenomenon of a 2° EIE larger than the 1° is a curiosity worth documenting. We now report that ¹⁸O EIEs on acidity do exhibit this, but with the further surprise that the origin is not simply in the ZPEs but in the moment of inertia factor.

Computational Methods

Isotope Effects on Acidity. Density-functional theory (DFT) calculations were performed on a Dell Optiplex PC with Intel Core 2 Duo processor. Structures were built using GaussView 4.1.2 and optimized at the B3LYP/aug-cc-pVTZ level with a very tight geometry and an ultrafine grid at a temperature of 298.15 K using Gaussian03W software.⁴³ Each EIE on acidity was calculated using eq 4, where $u_i = hc\tilde{\nu}_i/kT$ and the asterisk signifies isotopic label. This equation excludes the EXC factor of eq S3 but includes the MMI factor of eq S8. For comparison the contribution to the EIE of the ZPE factor alone was calculated using eq S7. Solvation by chloroform and by water was modeled with the polarized continuum model (PCM).

$$\text{EIE} = \quad (4)$$

Primary and secondary EIEs on acidities are calculated for dissociation of a mono-¹⁸O-labeled acid relative to the unlabeled acid. The designation 2°_{X=O} (where X is the central atom) represents a 2° EIE due to ¹⁸O bonded to the central atom with a bond order > 1 and acquiring

partial negative charge in the product. The designation 2°X-OH represents a 2° EIE due to ^{18}OH bonded to the central atom and remaining during the reaction. Species that can be present as more than one conformational isomer or as more than one conformational isotopomer must be treated carefully, as described in Supporting Information.

The contributions of the ZPE factor to the 1° and 2° EIEs for Brønsted acids are calculated by comparing the vibrational frequencies of the ^{16}O and mono- ^{18}O acids to those of the deprotonated conjugate bases, as expressed in eq S7. EIEs for Lewis acids are calculated similarly, except that their 1° EIEs come from addition of H_2^{18}O vs. H_2^{16}O , whose vibrational frequencies must be included with the frequencies of reactant and product. The H^+ byproduct in eq 3 has no vibrations that need to be included.

Results

Energy and optimized geometry for each acid and its conjugate base and vibrational frequencies for their ^{16}O and mono- ^{18}O isotopologues are listed in the Supporting Information.

ZPE Differences. The total ZPE of each isotopologue is half the sum of the vibrational frequencies, converted into energy. The differences, ΔZPE ($= \text{ZPE}_{16} - \text{ZPE}_{18}$), between the total ZPE of an unlabeled molecule and that of its mono- ^{18}O labeled isotopologue are shown in Figure 4. For conformational isotopomers an average is reported. The values are all > 0 because a mono- ^{18}O labeled species must have a smaller total ZPE than its unlabeled isotopologue, owing to the greater mass of ^{18}O .

Figure 4. Total ZPE difference (Δ ZPE, cal/mol) between an unlabeled species and its indicatedmono- ^{18}O ("●") labeled isotopologue.

Contributions to the 1° and 2° ^{18}O EIEs at 298.15 K from the total ZPE differences of all the Brønsted acids, calculated according to eq. S7 from total ZPE differences in Figure 4, are tabulated in Table 2.

Table 2. Contributions of ΔZPE to 1° and 2° ^{18}O EIEs of Brønsted acids.

Name	Acid	Base	1°	2° X=O	2° X-OH
Formic	HCOOH	HCO_2^-	1.0200	1.0207	—
Formic· H^+	HC(OH)_2^+	HCOOH	1.0248	—	1.0292
Acetic	CH_3COOH	CH_3CO_2^-	1.0134	1.0189	—
Carbonic	H_2CO_3	HCO_3^-	1.0143	1.0140	1.0323
Bicarbonate	HCO_3^-	CO_3^{2-}	1.0053	1.0231	—
Nitrous	HONO	NO_2^-	1.0057	1.0334	—

Nitric	HNO ₃	NO ₃ [−]	0.9968	1.0209	—
Borinic	H ₂ BOH	H ₂ BO [−]	1.0322	—	—
Boronic	HB(OH) ₂	HB(OH)O [−]	1.0243	—	1.0241
Boric	B(OH) ₃	B(OH) ₂ O [−]	1.0245	—	1.0167
Phosphinic	H ₂ POOH	H ₂ PO ₂ [−]	1.0077	1.0097	—
Phosphonic	HP(OH) ₂ O	HP(OH)O ₂ [−]	1.0025	1.0080	1.0146
Hydrogen phosphonate	HP(OH)O ₂ [−]	HPO ₃ ^{2−}	1.0025	1.0146	—
Phosphoric	H ₃ PO ₄	H ₂ PO ₄ [−]	1.0055	1.0049	1.0166
Dihydrogen Phosphate	H ₂ PO ₄ [−]	HPO ₄ ^{2−}	1.0027	1.0139	1.0234
Hydrogen phosphate	HPO ₄ ^{2−}	PO ₄ ^{3−}	0.9998	1.0204	—
Phosphenic	O ₂ POH	PO ₃ [−]	1.0101	1.0102	—

According to Table 2, the contribution of ΔZPE to the 2° EIE is larger than to the 1° except for boronic and boric acids. The differences are small for formic, boronic, and phosphenic acids, and also for carbonic and phosphoric acids, where the contributions to 1° and 2°X=O are comparable but the contribution to 2°X–OH is larger. For nitric acid and hydrogen phosphate dianion the contribution of ΔZPE to the 1° EIE is inverse, but the magnitude of the contribution to the 2° EIE is still larger than to the 1° (where the magnitude of an inverse EIE is measured by 1/EIE). Moreover, for those acids with two 2° EIEs, the contribution of ΔZPE to 2°X–OH is considerably larger than to 2°X=O, but both these contributions are larger than that to the 1°. However, the contributions from ΔZPE are irregular, and it is necessary to consider the EIEs calculated with eq 4, rather than the simplified eq S7.

Calculated ¹⁸O EIEs on Acidities of Formic Acid and Its Isotopologues. EIEs at 298.15 K on acidities of mono-¹⁸O labeled formic acid and some OD, OT, and CD isotopologues, obtained

using eq 4, are listed in Table 3. The 2° EIE, from C=¹⁸O labeling, is larger than the 1° for all acids without substitution of the hydroxylic proton. This comparison persists when a fictitious lighter isotope (^{1/2}H) is introduced at the hydroxylic position, but reverses with deuterium or tritium at that position, such that the 1° EIE becomes larger.

Table 3. Calculated ¹⁸O EIEs on the acidity of various isotopologues of formic acid.

Acid	Formula	1°	2°
Formic	HCOOH	1.0123	1.0169
Formic, OD	HCOOD	1.0199	1.0161
Formic, OT	HCOOT	1.0240	1.0153
Formic- <i>d</i>	DCOOH	1.0119	1.0169
Formic- <i>d</i> , OD	DCOOD	1.0195	1.0162
Formic- <i>d</i> , OT	DCOOT	1.0235	1.0154
Formic-O ^{1/2} H	HCOO ^{1/2} H	1.0046	1.0173

The result that the 2° ¹⁸O EIE in formic acid is larger than the 1° requires an adequate basis set, such as the B3LYP/aug-cc-pVTZ used here. It is also obtained with B3LYP/6-311++G(d,p), but with MP2/6-31++G they are nearly equal, and with B3LYP/6-31G the 1° EIE is calculated to be larger than the 2°.

The analysis in Table 1 of the contributions from selected experimental vibrational frequencies can be repeated using selected calculated frequencies of unlabeled and di-¹⁸O-labeled formic acid and formate anion. The values and results, from Tables S9 and S25, are listed in Table 4. This table indicates that the 1° EIE would be larger than the 2° EIE if the EIEs depended on the frequencies of only these select stretches. This is opposite to the conclusion

from the selected experimental frequencies in Table 1, and it is a warning about focusing only on selected frequencies.

Table 4. Select vibrational frequencies (cm^{-1}) calculated for unlabeled and di- ^{18}O labeled formic acid and formate anion.

Mode	$\nu(^{16}\text{O}_2)$	$\nu(^{18}\text{O}_2)$	Δ
C=O	1811	1774	37
C–O	1121	1088	33
O–H	3716	3704	12
$\text{C}\cdots\text{O}^-$	1494 ^a	1459 ^a	35
Sum ^b	3660	3648	13

^aAverage of symmetric and asymmetric stretches. ^b $\nu_{\text{C=O}} + \nu_{\text{C-OH}} + \nu_{\text{O-H}} - 2\nu_{\text{C}\cdots\text{O}^-}$.

Calculated ^{18}O EIEs on Acidities of C-, N-, B-, and P-Containing Brønsted Acids,

Table 5 lists the 1° and 2° ^{18}O EIEs at 298.15 K on the acidities of all the acids in Figure 3A, calculated with eq 4. These values, and their relative magnitudes, differ from those in Table 2, based only on ΔZPEs . It should be noted that the boron acids and phosphenic acid are Lewis acids, for which Brønsted acidity is hypothetical and included only for comparison.

Table 5. Calculated ^{18}O EIEs on deprotonation of various mono- ^{18}O -substituted carbon-, nitrogen-, boron-, and phosphorus-containing acids.

Name	Acid	Base	1°	2° X=O	2° X-OH
Formic	HCOOH	HCO_2^-	1.0123	1.0169	—
Formic ^a	HCOOH	HCO_2^-	1.0125	1.0148	—

Formic ^b	HCOOH	HCO ₂ ⁻	1.0120	1.0141	—
Formic·H ⁺	HC(OH) ₂ ⁺	HCOOH	1.0180	—	1.0259
Acetic	CH ₃ COOH	CH ₃ CO ₂ ⁻	1.0090	1.0166	—
Carbonic	H ₂ CO ₃	HCO ₃ ⁻	1.0099	1.0127	1.0286
Bicarbonate	HCO ₃ ⁻	CO ₃ ²⁻	1.0018	1.0203	—
Nitrous	HONO	NO ₂ ⁻	0.9980	1.0277	—
Nitrous ^a	HONO	NO ₂ ⁻	0.9983	1.0252	—
Nitric	HNO ₃	NO ₃ ⁻	0.9939	1.0178	—
Nitric ^a	HNO ₃	NO ₃ ⁻	0.9951	1.0153	—
Borinic	H ₂ BOH	H ₂ BO ⁻	1.0230	—	—
Boronic	HB(OH) ₂	HB(OH)O ⁻	1.0178	—	1.0203
Boric	B(OH) ₃	B(OH) ₂ O ⁻	1.0193	—	1.0146
Phosphinic	H ₂ POOH	H ₂ PO ₂ ⁻	1.0022	1.0063	—
Phosphonic	HP(OH) ₂ O	HP(OH)O ₂ ⁻	1.0003	1.0059	1.0109
Hydrogen phosphonate	HP(OH)O ₂ ⁻	HPO ₃ ²⁻	1.0008	1.0113	—
Phosphoric	H ₃ PO ₄	H ₂ PO ₄ ⁻	1.0036	1.0045	1.0142
Dihydrogen Phosphate	H ₂ PO ₄ ⁻	HPO ₄ ²⁻	1.0019	1.0125	1.0207
Hydrogen phosphate	HPO ₄ ²⁻	PO ₄ ³⁻	0.9996	1.0183	—
Phosphenic	O ₂ POH	PO ₃ ⁻	1.0072	1.0074	—

^awith PCM for solvation by CHCl₃. ^bwith PCM for solvation by H₂O.

According to Table 5, the 2° EIE on acidity is larger than the 1° EIE for all Brønsted acids, with the exception of boric acid. Also, for phosphenic acid the 1° and 2° EIEs are nearly equal, although the 2° is very slightly larger. For both of the nitrogen-containing acids and for hydrogen phosphate the 1° EIE is inverse, but the magnitude of the 2° EIE is still larger than the magnitude of the 1°. Moreover, for those acids with two 2° EIEs, 2°_{X-OH} is much larger than

2°X=O , but both are larger than the 1° . These values thus confirm the hypothesis that a 2° EIE can be larger than a 1° .

Calculated ^{18}O EIEs on Acidities of C-, N-, B-, and P-Containing Lewis Acids. Table 6 lists the 1° and 2° ^{18}O EIEs for water addition to the indicated Lewis acid, as in eq 3, calculated according to eq 4. The 1° EIE arises from addition of H_2^{18}O to an unlabeled acid. One type of 2° EIE (2°X=O) arises when there is an ^{18}O with bond order >1 to the central atom of the Lewis acid, and another type (2°X-OH) arises when there is an ^{18}OH group that maintains its bond to the central atom upon H_2^{16}O addition.

Table 6. Calculated ^{18}O EIEs at 298.15 K for H_2O addition to various carbon, nitrogen, boron, and phosphorus-containing Lewis acids.

Name	Acid	Base	1°	2°X=O	2°X-OH
Carbon Dioxide	CO_2	HCO_3^-	0.9912	1.0205	—
Carbon Dioxide ^a	CO_2	HCO_3^-	0.9814	1.0208	—
Carbon Dioxide ^b	CO_2	HCO_3^-	0.9778	1.0214	—
Nitrosonium	NO^+	HONO	0.9921	1.0302	—
Nitrosonium ^a	NO^+	HONO	0.9895	1.0329	—
Nitronium	NO_2^+	HNO_3	0.9873	1.0218	—
Borane	BH_3	H_3BOH^-	0.9981	—	—
Borinic	H_2BOH	$\text{H}_2\text{B(OH)}_2^-$	1.0001	—	1.0310
Boronic	HB(OH)_2	HB(OH)_3^-	1.0065	—	1.0340
Boric	B(OH)_3	B(OH)_4^-	1.0043	—	1.0289
Phosphenic	O_2POH	H_2PO_4^-	1.0074	1.0126	1.0221

^awith PCM for solvation by CHCl_3 . ^bwith PCM for solvation by H_2O .

Some 1° EIEs are inverse, but as with Brønsted acids each 2° EIE is greater than the 1°. For phosphenic acid the 2° EIE from the $X-^{18}\text{OH}$ is greater than the 2° EIE from the $X=^{18}\text{O}$, similar to the trend with Brønsted acids, and both are larger than the 1° EIE. For CO_2 the 1° EIE is more sensitive to solvation than EIEs of other Lewis or Brønsted acids.

Discussion

The reliability of these calculated ^{18}O EIEs on acidities is addressed in the Supporting Information. For formic and acetic acids the calculated EIEs exceed the experimental values slightly. For dihydrogen phosphate anion and hydrogen phosphate dianion the calculated EIEs are considerably larger than the experimental ones. These discrepancies can be attributed to neglect of solvation, and EIEs calculated with PCM are in slightly better agreement.

The computed ^{18}O EIEs in Tables 5 and 6 support the hypothesis that secondary EIEs on acidity can be larger than primary EIEs for carboxylic acids and for similar Brønsted and Lewis acids. We aim to provide insight into this result.

EIEs of Formic Acid Isotopologues. The results for formic acid in Table 3 confirm the hypothesis that the 2° EIE can be larger than the 1° for simple carboxylic acids. However, that hypothesis fails when D or T is substituted at the OH. Although vibrational frequencies and ZPEs alone do not determine the EIEs, they are often the major contributor and can be used to understand the effects of OH substitution.

The main contributors to the primary EIE for formic acid are the C–O and O–H stretching vibrations. The C–O frequency is considerably more sensitive to ^{18}O substitution than the O–H because of the dependence on reduced mass. Although the O–H frequency decreases upon substitution with D or T, the reduced mass increases and makes that frequency more

sensitive to ^{18}O substitution. The results in Table 3 show that the contributions to the vibrational frequencies upon substitution of OH with OD or OT are enough to make the 1° EIE larger than the 2°. It should be noted that the 2° EIE remains nearly constant upon OD or OT substitution, and it is only the 1° EIE that changes appreciably.

Formic-*d* acid, with deuterium substitution on carbon, results in ^{18}O EIEs very close to those of formic acid itself because the C–H and C–D vibrations are insensitive to ^{18}O substitution. Similarly, the effect of OD or OT substitution in formic-*d* acid is the same as that in formic acid, with the 1° EIEs becoming larger than the 2°.

Inasmuch as OD and OT increase the 1° EIE relative to the 2°, partial removal of the OH hydrogen ought to reverse this increase. Therefore the last variant of formic acid studied is formic- $\text{O}^{1/2}\text{H}$, where $^{1/2}\text{H}$ represents a fictitious hydrogen with a mass of $1/2$, to model a hydrogen-bonded H. Indeed, it does decrease the 1° EIE relative to the 2°.

EIEs of Other Brønsted Acids. Table 5 summarizes calculated primary and secondary EIEs for various Brønsted acids. With few exceptions (nitrous acid, nitric acid, and hydrogen phosphate dianion) the 1° EIEs are normal. With the exception of boronic acid, they also show a 1° EIE smaller than the 2° (and smaller than both 2° EIEs, if there are two), as was inferred from vibrational frequencies.³³

The normal nature of these EIEs is analogous to the familiar secondary H/D KIE of $\text{S}_{\text{N}}1$ solvolysis.⁴⁴ Because of the larger mass of D, $\Delta\text{ZPE} (= \text{ZPE}_{\text{C-H}} - \text{ZPE}_{\text{C-D}})$ is > 0 for reactants, as at the left in Figure 1. Moreover, the transition state has a lower C–H bending force constant than does the reactant, as suggested at the right in Figure 1, so ΔZPE is smaller in the transition state than in the reactant, and $\Delta\Delta\text{ZPE} (= \Delta\text{ZPE}_{\ddagger} - \text{ZPE}_{\text{reactant}})$ is < 0 . The activation energy is

then higher for the D species than for the H, corresponding to a faster reaction for H and a normal KIE.

Analogously, ZPE for an ^{18}O -labeled acid or conjugate base is always lower than ZPE for the unlabeled acid or conjugate base. Therefore ΔZPE ($= \text{ZPE}_{16} - \text{ZPE}_{18}$) is > 0 , as in Figure 4. However, in this case the reactant is not being compared to a transition state but to the conjugate base as product. Whereas a transition state has the same number of vibrational modes (including the reaction coordinate), a conjugate base has one (hydrogen) atom fewer than the acid has, and thus three fewer vibrational modes. A lower number of vibrational modes results in less total ZPE, and consequently ΔZPE for the product is generally less than that of the reactant, leading to a $\Delta\Delta\text{ZPE}$ ($= \Delta\text{ZPE}_{\text{product}} - \Delta\text{ZPE}_{\text{reactant}}$) again < 0 , and a normal EIE.

For example, according to Figure 4, mono- ^{18}O labeling in formate anion leads to a ΔZPE of 79.6 cal/mol, but ^{18}O labeling at the OH of formic acid leads to a larger ΔZPE , 91.3 cal/mol. The difference between these values, $\Delta\Delta\text{ZPE}_{1^\circ}$ is -11.7 cal/mol, corresponding to a normal 1° EIE. Similarly, labeling formic acid at C=O leads to a ΔZPE of 91.7 cal/mol. The difference, $\Delta\Delta\text{ZPE}_{2^\circ}$, is -12.1 cal/mol, also corresponding to a normal EIE. These 1° and 2° $\Delta\Delta\text{ZPE}$ s represent the ZPE contribution to the EIEs, as in eq S7, without the MI factor of eq S10.

Surprisingly, according to Table 5, nitrous acid, nitric acid, and hydrogen phosphate dianion have inverse 1° EIEs. For nitrous acid the inverse nature is from the MMI factor, but the inverse EIE for the other two is due to $\Delta\Delta\text{ZPE}$, despite the lower number of vibrational modes in the conjugate base.

If the MMI factor is ignored, the relative magnitudes of the 1° and 2° EIEs are determined by the differences between $\Delta\text{ZPE}_{\text{X-OH}}$ and $\Delta\text{ZPE}_{\text{X=O}}$, because both comparisons are relative to

their common conjugate base. Formic acid demonstrates this comparison. From Figure 4 the difference between $\Delta ZPE_{C=O}$ of 91.7 cal/mol and ΔZPE_{C-OH} of 91.3 cal/mol is +0.4 cal/mol, which corresponds to a 2° EIE that is larger than the 1° EIE, but only very slightly.

For those acids in Table 5 with two different 2° EIEs each is larger than the 1° EIE, and 2°_{X-OH} is much larger than $2^\circ_{X=O}$. This result can be illustrated with carbonic acid. According to Figure 4, the difference between $\Delta ZPE_{C=O}$ and ΔZPE_{C-OH} is +0.3 cal/mol, which is very small, similar to that for formic acid. However, unlike formate anion, bicarbonate anion, the conjugate base common to both isotopomeric acids, is different for the two 2° reactions, with quite different ΔZPE s. The $\Delta\Delta ZPE_{2^\circ C-OH}$ of 18.8 cal/mol is considerably larger than the $\Delta\Delta ZPE_{2^\circ C=O}$ of 8.2 cal/mol. This comparison indicates that not only is the 2°_{X-OH} EIE large, but also it is much larger than either the 1° or the $2^\circ_{X=O}$ EIE. Unfortunately the large difference is not readily correlated to force constants, because the various vibrations mix too strongly, as noted previously.⁴⁵

EIEs of Lewis Acids. Primary and secondary ^{18}O EIEs on the acidities of various Lewis acids are listed in Table 6. The 1° EIEs are close to 1 and smaller than the 2° EIEs.

That the primary EIE is near 1 arises because of a cancellation between ZPE and MMI. In contrast to a Brønsted acid, which has three vibrational modes more than its conjugate base, the Lewis adduct has more vibrational modes than water has. According to Figure 4, ^{18}O labeling of H_2O results in a ΔZPE of only 43.9 cal/mol, considerably less than ΔZPE of the various Lewis adducts. For example, ΔZPE is 75.6 cal/mol for $H^{18}ON=O$ and 86.0 cal/mol for $H^{18}OCO_2^-$. Consequently ΔZPE for the product is greater than that of the reactant, leading to a $\Delta\Delta ZPE$ (= $\Delta ZPE_{product} - \Delta ZPE_{reactant}$) > 0, and a ZPE contribution to the EIE that is inverse. For example,

this contribution is 0.9479 for $\text{H}^{18}\text{ON}=\text{O}$. However, the MMI factor of eq S5 is necessarily < 1 because each u_i^*/u_i is < 1 , but the additional vibrational modes of the Lewis adduct over the three of H_2O make $\text{MMI}_{\text{product}} < \text{MMI}_{\text{reactant}}$, so that the MMI factor raises the 1° EIE close to 1.

The secondary EIEs are all normal. For both a Lewis acid and its adduct ΔZPE in Figure 4 is > 0 . However, ΔZPE is lower in the adduct because the double-bond character of the bond to the ^{18}O is decreased. Therefore $\Delta\Delta\text{ZPE}$ ($= \Delta\text{ZPE}_{\text{product}} - \Delta\text{ZPE}_{\text{reactant}}$) is < 0 , but quite small. For example, ΔZPE in N^{18}O^+ is 93.3 cal/mol, only slightly larger than the 91.7 cal/mol of HON^{18}O . Again, as with the 1° EIE, the MMI factor increases the EIE.

Comparing Primary and Secondary EIEs—Influence of Vibrational Frequencies.

The original hypothesis that the secondary EIE is larger than the primary came from the analysis in Table 1 of the decreases on ^{18}O substitution of selected experimental vibrational frequencies and ZPEs of carboxylic acids. In particular, $\Delta\Delta$ is 42 cm^{-1} , larger than the contribution to the 1° EIE of 39 cm^{-1} from C–O and O–H. That analysis is contradicted by the EIEs based on the calculated frequencies for formic acid and formate in Table 4. Those lead to 1° and 2° EIEs of 1.0269 and 1.0073, respectively, with the 1° larger. Yet according to the data in Table 5, based on all the frequencies, the 2° EIE is larger than the 1°.

One source of error lies in focusing on only three vibrations. There are contributions from all vibrations, which have been assigned to specific modes of formic acid.³⁴ Table S10 lists $\Delta\Delta$, the decrease in each calculated vibrational frequency on mono- ^{18}O labeling, in OH or in C=O. The most influential modes are, as expected, $\Delta\Delta_{\text{OH}}$, $\Delta\Delta_{\text{C-O}}$, and $\Delta\Delta_{\text{C=O}}$. However, using only these modes would indicate that the contribution to the 1° EIE is 41.7 cm^{-1} , larger than the 36.2- cm^{-1}

contribution to the 2°, which is what leads to 1° and 2° EIEs of 1.0269 and 1.0073, respectively. Although those three modes represent the largest contributions, there are also contributions from other modes, such as OCO bending. According to Table S10, the sum of all the frequencies results in a contribution of 64.1 cm⁻¹ to the 2° EIE, *very slightly* larger than the contribution of 63.9 cm⁻¹ to the 1°, leading to the nearly equal EIEs of 1.0200 and 1.0207 in Table 2. Table 7 summarizes how the EIEs depend on which vibrational frequencies are included.

Table 7. Dependence of calculated EIEs on which vibrational frequencies are included.

Model	1° EIE	2°EIE
3 exptl □□	1.0073	1.0146
3 calcd □□	1.0269	1.0073
all calcd □□	1.0200	1.0207
Table 5	1.0123	1.0169

Comparing Primary and Secondary EIEs—Influence of the MMI Factor. The above analysis confirms that all vibrational frequencies must be used. However, the data in Table 7 show that the sum of all the frequencies or of all the ZPEs still fails to account for the relative magnitudes of calculated 1° and 2° EIEs for formic acid. The discrepancy arises from the omission from eq S7 of the MMI factor, or more specifically, the MI factor of eq S10. When the MI factor is included, as in eq 4, the 1° and 2° EIEs are decreased from 1.0200 and 1.0207 to 1.0123 and 1.0169, respectively, with the 1° EIE decreased to a greater extent. *Thus it is not ZPE but the MMI factor that is primarily responsible for the 2° EIE in formic acid being greater than the 1°.*

To understand this influence of the MMI factor, it is necessary to consider the moments of inertia in eq S10, without converting to frequencies with the Redlich-Teller product rule.⁴⁶ Table 8 lists the moment of inertia tensors and eigenvalues, along with their products, for the isotopomers of formic acid and formate anion. In both the numerator and the denominator of eq S10 the ratio $I_x^*I_y^*I_z^*/I_xI_yI_z$ is >1 simply because a heavier isotope increases the moment of inertia. However, this increase is less effective on the reactant acid than on the product base because the H in the acid increases the moments of inertia of both isotopomeric acids. Consequently, the ratio $I_x^*I_y^*I_z^*/I_xI_yI_z$ is larger for the denominator, and MI of eq S10 is <1 . Therefore the MMI factor reduces the EIE below what the ZPE factor contributes.

Table 8. Moment of inertia tensors^{a,b} and eigenvalues (atomic units) for isotopomers of formic acid and formate.

Species	$I_{11}=I_{22}$	$I_{21}=-I_{12}$	I_x	I_y	I_z	$I_xI_yI_z$
HCOOH	0.9569	0.2903	23.128	149.729	172.857	598585
HCO ¹⁸ OH	0.9549	0.2969	23.220	158.559	181.779	669262
HC= ¹⁸ OOH	0.9604	0.2785	23.426	158.381	181.807	674533
HCO ₂ ⁻	^c	^c	16.682	147.354	164.036	403221
HCO ¹⁸ O ⁻	^c	^c	16.883	156.207	173.090	456481

^aRelative to optimized Cartesian coordinates in Table S10 or S24. ^b $I_{33} = 1.0000$ for HCOOH

isotopomers. ^c $I_{21} = I_{32} = I_{13} = 1.0000$.

The reduction of the EIEs in formic acid by the MMI factors of the reactant isotopomers is what determines the relative magnitudes of 1° and 2° EIEs. The moments of inertia of C=¹⁸O

and C-¹⁸O reactants are compared in Table 8. The moments I_y and I_z are nearly equal for the two isotopomers, whereas I_x for HC=¹⁸OOH is larger by nearly 1%. Consequently the product $I_x I_y I_z$ ($I_x * I_y * I_z$ in eq S10 or eq 4) is greater for HC=¹⁸OOH than for HCO¹⁸OH. Figure 5 shows the positions of the nuclei relative to the center of mass, as well as the two principal in-plane axes of rotation. Both oxygens are close to the x -axis, so that I_x is the smallest moment of inertia, but the carbonyl oxygen is more distant than is the hydroxyl oxygen. (The movement of the center of mass upon ¹⁸O substitution is also shown on Figure 5, but it hardly affects the distances.) Therefore converting C=O to C=¹⁸O increases the moment of inertia I_x more than converting C-OH to C-¹⁸OH does. That is why I_x and $I_x I_y I_z$ are larger for HC=¹⁸OOH. Although the MMI factor reduces the EIE, that factor remains larger for C=¹⁸O, so that the 1° EIE is reduced more than the 2° is.

Figure 5. Geometry of HCOOH, principal in-plane axes of rotation, and positions of center of mass for HCO¹⁸OH (o) and HC(= ¹⁸O)OH (●).

Formic acid seems to be a special case, where the contributions of Δ ZPE to 1° and 2° EIEs are nearly equal, but the MMI factor reduces the 1° EIE more than it does the 2°. For nitrous acid the contribution of Δ ZPE makes the 2° EIE greater than the 1°, and I_x is again the smallest moment of inertia, so that the MMI factor reduces the 1° EIE relative to the 2°. For phosphenic acid the contributions of Δ ZPE in Table 2 to 1° and 2° EIEs are also nearly equal, but the MMI factors are also nearly equal, so that the 2° EIE in Table 5 is only slightly greater than the 1°. For carbonic and phosphoric acids the contributions of Δ ZPE to 1° and 2°_{X=O} EIEs are nearly equal, but the 2°_{X-OH} EIE is larger than the other two.

Boronic acid as a Brønsted acid is similar to formic acid, with nearly equal contributions of Δ ZPE (in Table 2) to 1° and 2° EIEs, but a 2° EIE (in Table 5) greater than the 1°, owing to the MMI factor. The moments of inertia are listed in Tables S84 and S87. In both the numerator and the denominator of eq S10 the ratio $I_x^*I_y^*I_z^*/I_xI_yI_z$ is >1 because a heavier isotope increases the moment of inertia. This increase is less effective on the reactant than on the product because the H increases the moments of inertia of both the ¹⁶O and ¹⁸O acids. Therefore the ratio MI of eq S10 is <1, so that the MMI factor reduces the EIE below what the ZPE factor contributes. Both boronic acid and boronate anion are like formic acid in having one moment of inertia smaller than the other two. Figure 6 displays boronate anion and its axes of rotation, and a very similar geometry is found for boronic acid. Again I_x is the smallest moment of inertia. The oxyanion of the boronate and the *cis* OH of boronic acid are more distant from the axis than is the *trans* OH. Converting the more distant oxygen to ¹⁸O increases I_x (and $I_xI_yI_z$) more than converting the

trans OH to ^{18}OH does. However, unlike formic acid, where both isotopomers lead to the same anion, for boronic acid the MI factor of eq S10 is larger (closer to 1) for the 2° EIE, where ^{18}O is in the *trans* OH that is retained on deprotonation. Therefore the reduction of the 1° EIE by the MI factor below what the ZPE factor contributes is greater when ^{18}O is in the *cis* OH that is lost. This subtle influence of the MMI factor is thus the reason for a 2° EIE larger than the 1° even though the contributions of ΔZPE are nearly equal.

Figure 6. Geometry of boronate anion HBOOH^- , with principal in-plane axes of rotation.

The MMI also influences the primary EIE for Lewis acids. It does not dominate the EIE, but it nearly cancels the contribution of the ZPE, leading to an EIE near 1. The significant contribution of the MMI arises because the Lewis adduct has more vibrational modes than water has.

It is unusual for the MMI factor to be so influential with respect to EIEs. We did not anticipate it here. The common examples of this situation occur with small molecules, as in the

binding of H_2 to iridium complexes and of methane to tungsten complexes, showing $K_{\text{H}} > K_{\text{D}}$ because deuterium affects the moment of inertia of the smaller molecule more than it affects that of the addition complex.⁴⁷ Similarly, the MMI factor is the major contributor to calculated ^{18}O EIEs for binding of O_2 to copper complexes.⁴⁸ However, to the best of our knowledge the MMI factor had never been found to render a 2° EIE greater than the 1°.

Influence of the EXC Factor. The EXC factor in eq S3 is omitted because its effect on the EIE is small. For example, the ZPE, MMI, and EXC factors for the 1° EIE in formic acid at 298.15 K are 1.0200, 0.9924, and 1.0013, respectively, and 1.0207, 0.9963, and 1.0011 for the 2°. For completeness, Tables S121 and S122 present the EIEs calculated with the full eq S3.

Conclusions

DFT calculations at the B3LYP/aug-cc-pVTZ level succeed in determining vibrational frequencies of various isotopologues of C, N, B, and P acids and their conjugate bases. The frequencies were converted to ^{18}O EIEs on the acidity of those acids. In general, computations reproduce experimental trends, but overestimate the magnitude of the EIEs, owing to the neglect of solvation. The 1° and 2° contributions to the overall EIEs were separated by calculations on mono- ^{18}O labeled acids and conjugate bases.

The data indicate that for almost all Brønsted acids the ^{18}O EIE is normal, with $K_{\text{a}}^{16} > K_{\text{a}}^{18}$. This is simply because the acid, with an extra hydrogen atom, has a larger change in ZPE upon isotopic substitution than does the conjugate base.

For all Brønsted acids except the hypothetical example of boric acid the 2° ^{18}O EIE is larger than the 1°, which is a counterintuitive result. This had been anticipated though, based on the greater force constant and ZPE for $\text{C}=\text{O}$ stretching in carboxylic acids than for $\text{C}-\text{O}$, and on

only a small contribution to the EIE from the O–H stretch, whose reduced mass and ZPE are insensitive to ^{18}O substitution.

Closer investigation of the comparison of 1° and 2° EIEs shows that the changes in ZPEs are not always the major determinant. For formic acid the contributions from ZPEs are nearly equal, and the larger 2° ^{18}O EIE arises instead from the MMI factor. In particular, it is the mass-dependence of the smallest moment of inertia in the acid that is responsible. This is a geometric effect, because the carbonyl (or equivalent) oxygen is closer to the axis of that moment of inertia than the hydroxyl oxygen is, so that $=^{18}\text{O}$ substitution increases the moment of inertia more than $-^{18}\text{OH}$ substitution does.

A few acids show two secondary EIEs, both $\text{X}=\text{O}$ and $\text{X}-\text{OH}$, each of which is larger than the 1° . The $2^\circ_{\text{X}-\text{OH}}$ EIE is considerably larger than the 1° EIE owing simply to ΔZPEs , although the differences are not readily correlated to force constants. Nevertheless, it is surprising that an ^{18}O on an OH that is retained has a larger 2° EIE on acidity than the 1° EIE of an ^{18}O on the OH that is deprotonated.

Lewis acids exhibit a similar trend, with a primary EIE near 1 and smaller than the secondary. The 1° EIE near 1 arises because the MMI factor increases the EIE and nearly cancels the inverse EIE that would arise from the contribution of ZPE. The 2° EIE is larger, because the contribution of ZPE is small whereas the MMI factor again increases the EIE.

In summary, we have found computationally that secondary ^{18}O EIEs on the acidity of various C-, N-, B-, and P-centered acids can be larger than primary EIEs. In most cases the relative magnitude of the EIEs is due to contributions from zero-point energy. However, for formic acid these are nearly equal, and the 2° EIE is larger than the 1° because of the MMI factor, arising from moments of inertia and the rotational partition function. These comparisons of 1°

and 2° EIE are a curiosity, with no practical consequences, but they are surprising, and contrary to what is generally expected for EIEs. It is a triumph of computation that it is capable of reaching the conclusion that a 2° EIE can be larger than a 1° when experiment fails to address this.

Acknowledgments. This research was supported by NSF Grants CHE07-42801 and CHE11-48992 and by a grant from the UCSD Academic Senate.

Supporting Information Available. Details of computational methods; distinctions between Brønsted and Lewis acids and between conformational isomers and conformational isotopomers; reactions associated with the primary and secondary EIEs for each acid; calculated energies, optimized geometries, and vibrational frequencies for each of the acids and their conjugate bases; comparisons of calculated and experimental EIEs; EIEs calculated with inclusion of the EXC factor; consideration of the effect of solvation. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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TOC Graphic

Does C=O stiffness make 2° EIE > 1°?