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THE MAGNITUDE OF ELECTRONIC ISOTOPE EFFECTS*

R. E. Weston, Jr.
Department of Chemistry, Brookhaven National Laboratory
Upton, Long Island, New York

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Abstract—Secondary isotope effects, i.e. kinetic isotope effects in reactions where the bond to the labeled atom is not broken, are now being widely used for investigations of organic reaction mechanisms. In a recent paper, Halevi[1] has discussed secondary hydrogen isotope effects, and has suggested that there is an inductive contribution to such isotope effects. In particular, he suggests that there is more facile electron release from a C—D bond than from a C—H bond. The purpose of this communication is to examine in more detail some of the evidence cited by Halevi, and to estimate the theoretical limitations on such an effect.

Dipole moments

In several cases, gas-phase dipole moment measurements have been made for the same compound containing either protium or deuterium.[2,3] Unfortunately, in most cases the difference caused by isotopic substitution is within the experimental error. There are two cases, however, where the emphasis was upon just this isotope effect: the comparison of HCl and DCl[4] ($\Delta\mu = 0{\cdot}003$–$0{\cdot}007$ D) and the comparison of NH_3 and ND_3[5] ($\Delta\mu = 0{\cdot}012$–$0{\cdot}015$ D). Bell[4] has shown that one can quantitatively predict the isotope effect on the dipole moment from independent data given by vibrational frequencies and intensities. This effect is caused by the anharmonic character of the normal vibrations. To see this qualitatively, consider the symmetric

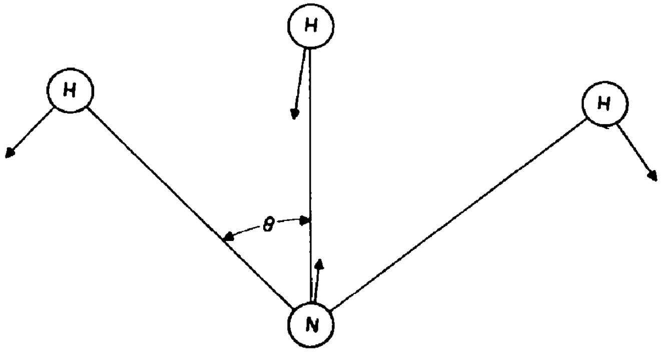

Fig. 1. Symmetric bending vibration (ν_2) of the ammonia molecule.

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[1] E. A. Halevi, *Tetrahedron* **1**, 174 (1957).

[2] A. A. Maryott and F. Buckley, *Table of Dielectric Constants and Electric Dipole Moments of Substances in the Gaseous State*. National Bureau of Standards Circular 537, U.S. Government Printing Office, Washington, D.C. (1953).

[3] C. H. Townes and A. L. Schawlow, *Microwave Spectroscopy* Appendix VI. McGraw-Hill, New York (1955).

[4] R. P. Bell and I. E. Coop, *Trans. Faraday Soc.* **34**, 1209 (1938).

[5] J. M. A. deBruyne and C. P. Smyth, *J. Amer. Chem. Soc.* **57**, 1203 (1935).

bending mode of NH_3 (Fig. 1). The potential energy as a function of the interbond angle is of the form shown in Fig. 2, in which the lowest vibrational levels of NH_3 and ND_3 are indicated. Because this potential curve is not a parabola, the average interbond angle is larger for NH_3 than for ND_3, hence the former molecule is more nearly planar and has a smaller dipole moment.

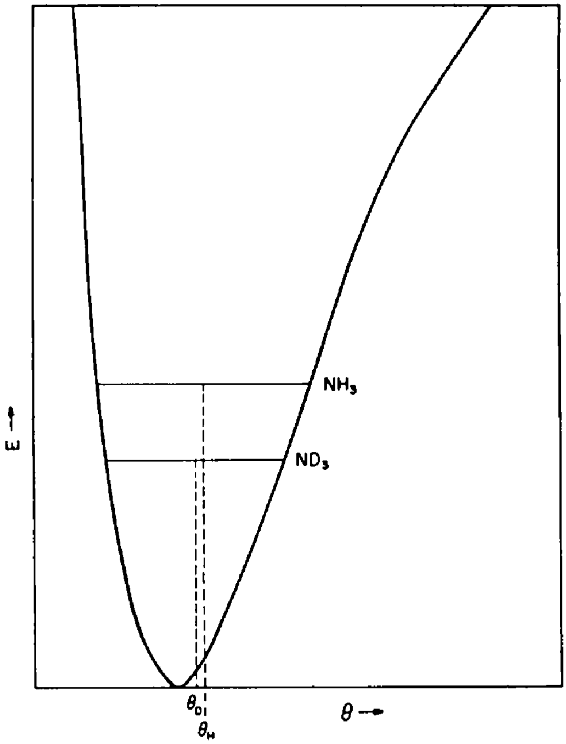

Fig. 2. Potential energy of the ammonia molecule as a function of interbond angle.

Nuclear quadrupole coupling constants

Again, there are a number of cases where the substitution of deuterium for protium changes the nuclear quadrupole coupling constant.[3,6] This constant is related to the second derivative of the molecular electric field at the "probe" nucleus, and thus to the electric charge distribution in the molecule. Because of molecular vibrations, the probe nucleus will measure some sort of average electric field derivative in a region surrounding its equilibrium position. Again, vibrational anharmonicities will cause the nucleus to map out slightly different regions for different isotopic species. This explanation was advanced by Simmons and Goldstein[7] to explain the difference in the halogen atom quadrupole coupling constants for CH_3X and CD_3X ($X = Cl, Br, I$). It may be noted that the relative shift produced by deuterium substitution is less for CH_3I than for CH_3Cl. This is reasonable in terms of the smaller vibrational amplitude of the heavier molecule, which should decrease the anharmonicity.

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[6] J. Duchesne, *J. Chem. Phys.* **20**, 1804 (1952); *Ibid.* **25**, 369 (1956).

[7] J. W. Simmons and J. H. Goldstein, *J. Chem. Phys.* **20**, 122 (1952).

Chemical shifts in NMR spectra

The fluorine nuclear magnetic resonance spectra of n-C_3F_7D and n-C_3F_7H show a similar isotope effect.[8] The shielding of the fluorine atoms in the —CF_2D group is 0·60 ± 0·05 p.p.m. greater than that for fluorine atoms in the —CF_2H group, which indicates a greater effective electron density around the fluorine atoms in the former compound. The explanation is presumably similar to that for the effect on quadrupole coupling constants.

Kinetic isotope effects

The question which now arises is how one may account for the observed mass-sensitivity of certain electronic properties of a molecule in formulating the isotope effect on a reaction rate.

The current theoretical treatment of the effect of isotopic substitution on reaction rates was originated by Bigeleisen,[9] and is founded upon the absolute reaction rate theory of Eyring and others. The ratio of rate constants for two isotopic species is given by

$$k/k_i = (M_i^*/M^*)^{1/2}(Q^\ddagger/Q_i^\ddagger)(Q_i/Q) \qquad (1)$$

In this formula, M^* is an effective mass for motion along the reaction co-ordinate, while Q and $Q^\ddagger$ are partition functions of the original species and of the transition state, respectively. In the case of a secondary isotope effect, the contribution of the reduced-mass term is expected to be negligible. It has been shown[10] that the partition function ratios can be expressed in terms of the fundamental vibrational frequencies of the species involved, if the potential energy function is invariant to isotopic substitution. The suggestion of an inductive isotope effect implies that this last assumption is not correct, and that there is a mass effect on the electronic factor in the partition function, i.e. a shift in electronic levels in going from one isotopic species to another. The magnitude of such an effect may be estimated.

The only case which can be treated exactly is that of the hydrogen atom. For this simple case, the difference in electronic energy levels between H and D is caused by the very small difference in the reduced mass of the electron–proton system compared to that of the electron–deuteron system.[11] This amounts to 30 cm^{-1}, and exp (30 cm^{-1}/kT) is about 1·15 at 300°K. For more complex molecules, the corresponding many-body problem cannot be solved, and recourse is made to the Born–Oppenheimer approximation,[12] which makes it possible to solve separately the wave-equations for electronic and nuclear motion. According to this approximation, the interaction between these two types of motion, which is just the effect being considered, is proportional to the ratio of the electron mass to some sort of average nuclear mass for the molecule. Hence, in a molecule containing C, N, or O atoms, the effect of deuterium substitution is an order of magnitude smaller than the 30 cm^{-1} predicted for the difference between H and D atoms. The difference in this interaction effect between two molecules, e.g. the reactant and the activated complex, should be vanishingly small compared to possible differences in vibrational frequencies.

There is experimental evidence that an electronic effect of this type is unimportant.

[8] G. V. D. Tiers, *J. Amer. Chem. Soc.* **79**, 5585 (1957).

[9] J. Bigeleisen, *J. Chem. Phys.* **17**, 675 (1949).

[10] J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.* **15**, 261 (1947).

[11] H. C. Urey, *J. Chem. Soc.* 562 (1947).

[12] M. Born and J. R. Oppenheimer, *Ann. Physik* **84**, 457 (1927); T.-Y. Wu and A. B. Bhatia, *J. Chem. Phys.* **24**, 48 (1956).

Rossini, Knowlton, and Johnston[13] obtained precise calorimetric data for H_2O and D_2O. These results, combined with other experimental thermochemical data, enabled them to obtain the difference in the heats of formation at absolute zero of H_2O and D_2O. The same quantity can also be obtained from purely spectroscopic data, from the relationship

$$(\Delta H_{f0}^{\circ})_{H_2O} - (\Delta H_{f0}^{\circ})_{D_2O} = (E^v_{H_2O} - E^v_{D_2O}) - (E^v_{H_2} - E^v_{D_2}) \tag{2}$$

in which E^v represents the vibrational zero-point energy. From suitable data for the isotopic hydrogen molecules[14] and for the isotopic water species,[15] one obtains a value of 617·0 cm^{-1}. The calorimetric data lead to a value of 613·5 ± 7·5 cm^{-1}, in excellent agreement. One must conclude either that electronic effects are absent, or that they are the same for hydrogen and water molecules.

Isotope exchange equilibria

Halevi's measurements[16] of the dissociation constant of phenylacetic acid and its analog deuterated in the methylene group show that the deuterium compound has a dissociation constant 0·895 as large as that of the protium compound. The comparison of these dissociation constants is equivalent to the isotope exchange equilibrium

$$\text{Ph·CD}_2\text{COOH} + \text{Ph·CH}_2\text{COO}^- = \text{Ph·CD}_2\text{COO}^- + \text{Ph·CH}_2\text{COOH},\ K_{eq} = 0{\cdot}895. \tag{3}$$

The equilibrium constant for such a reaction may be expressed in terms of partition functions analogous to those in equation (1).[10] If one ignores a possible explanation of this effect in terms of differences in vibrational zero-point energy, this is equivalent to the assumption that the C—H bonds in the methylene group are the same in both the acid and the anion. This is probably not so; in any case it is not so for acetic acid itself,[17,18] where some of the stretching frequencies are lower in the anion.[19] Also, the frequencies of some of the skeletal vibrations are changed by deuterium substitution in the acetate ion,[17] and these low frequencies will make a contribution to the entropy. Thus (and this is true for secondary isotope effects in general), small zero-point energy contributions may arise from differences in vibrational frequencies of the ground state and transition state even when the isotopically substituted atom has substantially the same bonding in both states, simply because the molecule is not a collection of independent diatomic oscillators.

If there are isotope effects caused by a difference in electron-releasing ability of hydrogen isotopes, one might look for such effects on hydrogen isotope exchange equilibria in general. In particular, such an effect would be expected in a molecule where hydrogen is bonded to a more electro-negative atom. Suitable examples are

$$HD + H_2O = H_2 + HDO \tag{4}$$

and

$$HT + H_2O = H_2 + HTO. \tag{5}$$

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[13] F. D. Rossini, J. W. Knowlton and H. L. Johnston, *J. Res. Nat. Bur. Stand.* **24**, 369 (1940).

[14] G. Herzberg, *Spectra of Diatomic Molecules* Table 39. D. Van Nostrand, New York (1950). Values for HD were calculated from the more accurate data for H_2.

[15] W. F. Libby, *J. Chem. Phys.* **11**, 101 (1943).

[16] E. A. Halevi and M. Nusim, *Bull. Research Council Israel* **5A**, 263 (1956).

[17] L. H. Jones and E. McLaren, *J. Chem. Phys.* **22**, 1796 (1954).

[18] J. K. Wilmshurst, *J. Chem. Phys.* **25**, 1171 (1956).

[19] A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* **80**, 2326 (1958).

Over a limited temperature range, the equilibrium may be written in the form $K = Ae^{B/T}$. Values for the parameters A and B have been calculated from suitable vibrational data for the isotopic hydrogen molecules[14] and the isotopic water molecules,[15] by use of the method of Bigeleisen and Mayer.[10] Experimental values were obtained by a least-squares treatment of the data of Suess[20] for the deuterium exchange, and data of Black and Taylor[21] for the tritium exchange. The comparison of calculated and experimental values is given below:

Reaction	A (calc)	A (exp)	B (calc)	B (exp)
(4)	0·7361	0·733 ± 0·009	480·6	470 ± 5
(5)	0·6206	0·623 ± 0·009	689·6	688 ± 4

The excellent agreement precludes any significant electronic effects.

In conclusion, all the evidence presented in favoı of an electronic isotope effect is explicable on the basis of vibrational effects. According to the Born–Oppenheimer theory, interactions between electronic and nuclear motion must be vanishingly small for molecules of the sort involved in organic reactions. It is difficult to conceive of a kinetic experiment which could measure an electronic isotope effect separately from the usual vibrational effect.

[20] H. E. Suess, *Z. Naturf.* **4a**, 328 (1949).

[21] J. F. Black and H. S. Taylor, *J. Chem. Phys.* **11**, 395 (1943).