161. *Secondary Hydrogen Isotope Effects. Part I. Strengths of α-Deuterated Carboxylic Acids and Amines.*

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This series of papers is concerned with the correlation of secondary isotope effects in terms of induction and hyperconjugation. The rationale for dealing with essentially vibrational phenomena in electronic terms is presented.

In this paper (Part I), potentiometric and spectrophotometric methods are described for measuring small differences in acid and base dissociation constants. It is shown that the strengths both of normally weak carboxylic acids and amines (pK_a or $pK_b \geqslant 5$) and of very weak bases of the polynitroaniline type are similarly affected by deuteration on an α-carbon atom. The direction of this secondary isotope effect, and its damping through a saturated carbon atom, indicate that effective inductive electron release from C^2H_3 (or C^2H_2) is greater than from CH_3 (or CH_2). The bearing of these results on kinetic secondary isotope effects and their theoretical interpretation is discussed.

Secondary isotope effects differ from the normal variety in that they represent changes in equilibrium constants or in rate constants resulting from isotopic substitution at a point in the molecule removed—in some cases relatively remote—from the site of reaction. These effects are much smaller than ordinary isotope effects and have to date been observed only with isotopes of hydrogen. Interpretation of secondary isotope effects has been attempted from two points of view, sometimes without a clear differentiation between them:

On the one hand, it can be explicitly recognised that, like all isotope effects, these too are vibrational in origin and can be dealt with, in principle, within the framework of general isotope-effect theory in terms of vibrational partition-function ratios.[1-3] Whether the approximations necessary to render such partition-function ratios tractable in practice [4] might not in many cases be so drastic as to place secondary isotope effects outside the scope of the treatment is still in question. Some evidence on this point will be presented in this series of papers.

Alternatively, without denying their ultimate vibrational origin, one can attempt to correlate secondary isotope effects empirically in terms of the electrical influences that have proved valuable in interpreting the effects of non-isotopic substituents.[5] When Lewis *et al.*[6] and Shiner [7] first observed secondary isotope effects in solvolysis, they interpreted them in terms of less effective hyperconjugative electron release from C^2H_3 than from CH_3. However, their apparent reluctance to ascribe electronic effects to isotopic substituents led them to carry out their immediate translation into vibrational terms such as " changes in force constants " and " frequency shifts." The implication seems to be that, unless such a direct translation into vibrational language can be made, the discussion of secondary isotope effects in terms of induction and hyperconjugation is unjustified. This point of view has been vigorously stated by Weston,[8] who argues that an electronic isotope effect can occur only if there is breakdown of the Born–Oppenheimer approximation.[9]

Weston's conclusions are being repeatedly cited, often as if they specifically disallowed

[1] Urey, *J.*, **1947**, 569.
[2] Bigeleisen and Mayer, *J. Chem. Phys.*, 1947, **15**, 261.
[3] Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.
[4] Streitwieser, Jagow, Fahey, and Suzuki, *J. Amer. Chem. Soc.*, 1958, **80**, 2326.
[5] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, Chapters II—V.
[6] Lewis *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 6306; 1954, **76**, 791, 794, 4495.
[7] Shiner, *J. Amer. Chem. Soc.*, 1953, **75**, 2925; 1954, **76**, 1603.
[8] Weston, *Tetrahedron*, 1959, **6**, 33.
[9] Born and Oppenheimer, *Ann. Phys.*, 1927, **84**, 457.

isotopic inductive effects, hyperconjugation having somehow acquired immunity from them.[10] A few comments on their basis are therefore needed.

Let us assume, although the assumption can be questioned, that the Born–Oppenheimer approximation is exact enough to be taken as an implicit basis of secondary isotope effects. The total wave function can then be factorised into a product of, among others, an electronic and a vibrational wave function. The former is an explicit function of the positions of the nuclei, so that in order to calculate the " electronic " energy of the molecule, the equilibrium internuclear distances are introduced into the electronic wave function as parameters. In the harmonic oscillator, the equilibrium configuration (minimum potential energy) is also the mean configuration over any vibrational level, so that the parameterised electronic wave function gives, generally speaking, as good a description as can be obtained of the average electronic properties of the vibrating molecule.* In the real molecule (anharmonic oscillator) also, the electronic energy is in practice universally associated with the equilibrium configuration, but since the average configuration over different vibrational levels will differ from that at equilibrium, so also will the average electron distribution. Thus, for any given vibrational level, the electronic properties are probably best described by an electronic wave function into which average rather than equilibrium internuclear distances have been introduced. Since isotopic molecules have different mean configurations even in their lowest vibrational levels, isotope effects on eminently electronic properties can arise. Two such isotope-dependent properties, which evidently relate to chemical isotope effects, are dipole moment [11] and molecular refraction [12] which reflect polarisation and polarisability, respectively.

To be sure, since the electronic energies of reactants and transition state (or reactant and product in equilibria) are invariably related to the isotope-independent equilibrium configuration, any isotope effect will necessarily be vibrational. It has, however, been shown that isotopic differences in energy calculated with electronic wave functions parameterised with respect to mean configuration over the ground vibrational states are not only consistent with observed secondary isotope effects,[13] but are equal, in good approximation, to just those zero-point vibrational energy differences which would constitute the principal factor in the rigorous, but generally impractical, evaluation of the isotope effect in terms of partition-function ratios.[14]

As a final point, since even ordinary substituent effects include significant kinetic-energy contributions,[15] there seems to be no valid objection to regarding the substituent effects of deuterated alkyl groups as slightly, but genuinely, different from those of their parent groups by virtue of differences in the ease of inductive or hyperconjugative electron release.

This series of papers reports work designed to determine the empirical utility and limitations of treating secondary isotope effects in terms of inductive and hyperconjugative contributions. Part I presents evidence for inductive secondary isotope effects. In Part II evidence is produced that isotope effects in the hyperconjugative direction already postulated in solvolytic reactions [4,6,7] also predominate in some π-complex association equilibria.

* The way in which a given property is averaged over a vibrational state depends on the functional form of the specific property, or—more precisely—of the quantum-mechanical operator associated with it, so that the wave function parameterised with respect to mean configuration will accord better with some properties than with others.

[10] *E.g.*, Blades and Gilderson, *Canad. J. Chem.*, 1960, **38**, 1411; Jones and Bender, *J. Amer. Chem. Soc.*, 1961, **82**, 6324.

[11] Bell and Coop, *Trans. Faraday Soc.*, 1938, **34**, 1209; Halevi, *ibid.*, 1958, **54**, 1441.

[12] Ingold, Raisin, and Wilson, *J.*, 1936, 915; Davis and Schiessler, *J. Amer. Chem. Soc.*, 1953, **75**, 2763.

[13] Pauncz and Halevi, *J.*, 1959, 1967; Halevi and Pauncz, *ibid.*, p 1974; Ron, Halevi, and Pauncz, *J.*, 1960, 630.

[14] Wolfsberg, Pauncz, and Halevi, unpublished results.

[15] Taft, Chapter 13 in Newman's " Steric Effects in Organic Chemistry," McGraw-Hill, New York, 1956, pp. 567—570.

Procedure and Results.—(*a*) *The potentiometric method.* Choice of an experimental method was dictated by the requirement of maximum precision in the measurement of small differences in dissociation constants, whereas the accurate determination of their absolute values could be dispensed with.

As in other potentiometric methods, the basic equation is:

$$pK_a = pH + \log a_{AH}/a_{A^-} = pH + \log c_{AH}/c_{A^-} + \log f_{AH}/f_{A^-} \quad (1)$$

The commonly used " half-neutralisation " procedure depends essentially on one pH measurement and requires an activity correction. Differential potentiometric methods such as those of Kilpi [16] and of Grunwald [17] make use of a large number of points, thus reducing adventitious error, but are relatively difficult to carry out and do not dispense with the activity correction.

Since we were content to measure differences, we could follow a very simple procedure, using a large number of independent points per determination, and avoiding activity corrections, as follows:

For two acids, A'H and AH, the pK_a difference is:

$$\Delta pK_a = pK'_a - pK_a = \Delta pH + \log (a_{A'H}a_{A^-})/(a_{AH}a_{A'^-}); \quad (2)$$

$$\Delta pK_a = \Delta pH + \log \frac{c_{A'H}c_{A^-}}{c_{AH}c_{A'^-}} + \log \frac{f_{A'H}f_{A^-}}{f_{AH}f_{A'^-}}. \quad (2a)$$

Now let equimolar amounts of the two acids, dissolved in equal volumes of water, be titrated with the same alkali solution. Let the difference in the pH readings with the same instrument be recorded for equal increments of alkali solution over a range of several tenths of a pH unit, extending on both sides of half-neutralisation. It can be shown [18]

TABLE 1.

Comparison of known acids at 25·0° ± 2°.

Acid	Reference acid	No. of expts.	pH meter *	ΔpK_a Found	ΔpK_a Lit.
Propionic	Acetic	18	B, C	0·114 ± 0·003	0·116 †
Propionic	Acetic	9	C	0·116 ± 0·001	0·116 †
Phenylacetic ‡	Benzoic	7	B	0·111 ± 0·002	0·111 †
Benzylammonium ‡	Ammonium	8	B	0·116 ± 0·002	0·122 † §

* See Experimental part. Carried out at 27° ± 2°. † Conway, " Electrochemical Data," Elsevier, Amsterdam, 1952, pp. 183—185. ‡ At 27·0° ± 0·2°. § Carothers, Bickford, and Hurwitz, *J. Amer. Chem. Soc.*, 1927, **49**, 2908.

that, provided the acids are relatively weak ($pK_a \geqslant 4$) and do not differ by more than 0·1 unit of pK_a, the second term in equation (2*a*), and the third term *a fortiori*, may be neglected, and ΔpK_a will approximate to ΔpH within a few thousandths of a pH unit.*

For acetic and propionic acid, for example, the simple form

$$\Delta pK_a = \Delta pH \quad (3)$$

introduces a systematic error of no more than 0·001—0·002 pK_a unit over the titration range. Moreover, this error decreases rapidly as the strengths of the two acids approach one another, so that it can always be neglected relative to ΔpK_a itself. As a result, the method is eminently suited for demonstrating the presence of small differences in acid strength between isotopic variants of the same acid.

The reliability of the method is indicated by the comparison of several pairs of known

* A similar conclusion applies to bases of $pK_b \geqslant 4$.

[16] Kilpi, *J. Amer. Chem. Soc.*, 1952, **74**, 5296.
[17] Grunwald, *J. Amer. Chem. Soc.*, 1951, **73**, 4934; Bacarella, Grunwald, Marshall, and Purlee, *J. Org. Chem.*, 1955, **20**, 747.
[18] Nussim, M.S. Thesis, Israel Institute of Technology, Haifa, 1958.

acids in Table 1. These measurements were interspersed among the measurements of the isotopic acids. Agreement with the most reliable values from the literature is obtained within our precision in all cases but that of benzylamine. It may be significant that no value for this base is given in standard compilations, nor could a pK_a value determined more recently than 1927 be found. In any case, the discrepancy is small, and not important for the purpose of this investigation.

The isotopic molecules which were compared are: [$^2H_3$]acetic acid * *vs.* acetic acid; [α-$^2H_2$]propionic acid and [β-$^2H_3$]propionic acid *vs.* propionic acid; [α-$^2H_2$]phenylacetic acid *vs.* phenylacetic acid; and [α-$^2H_2$]benzylammonium ion *vs.* benzylammonium ion. The results are shown in Table 2.

TABLE 2.

Relative strengths of isotopically substituted acids at 25·0° ± 0·2°.

Acid	n †	Reference acid	No. of expts.	pH meter ‡	ΔpK_a
$C^2H_3{\cdot}CO_2H$ *	2·9	$CH_3{\cdot}CO_2H$	6	B	0·026 ± 0·002
$CH_3{\cdot}C^2H_2{\cdot}CO_2H$	2·0	$CH_3{\cdot}CH_2{\cdot}CO_2H$	8	B, C	0·034 ± 0·002
$C^2H_3{\cdot}CH_2{\cdot}CO_2H$	2·4	$CH_3{\cdot}CH_2{\cdot}CO_2H$	8	C	0·007 ± 0·001
$C_6H_5{\cdot}C^2H_2{\cdot}CO_2H$ §	2·0	$C_6H_5{\cdot}CH_2{\cdot}CO_2H$	6	B	0·048 ± 0·005
$C_6H_5{\cdot}C^2H_2{\cdot}NH_3^+$	2·0	$C_6H_5{\cdot}CH_2{\cdot}NH_3^+$	6	B	0·054 ± 0·001

* See footnote on this page. † n = no. of D atoms per molecule (see Experimental part). ‡ See Experimental part. § Experiments carried out (at 27·0° ± 2·0°) *vs.* benzoic acid, and converted by using data in Table 1.

In all cases deuteration decreases the acid strength. In acetic and propionic acid, α-deuteration decreases the acid dissociation constant by 2—4% per deuterium atom. From the β-position of propionic acid the effect, though probably real, is very much weaker. Methylene-deuteration has very nearly the same effect on the base strength of benzylamine as on the acid strength of phenylacetic acid (somewhat greater per deuterium atom than for the aliphatic acids). These results, strongly suggestive of easier inductive electron release from C^2H_3 (and C^2H_2) than from CH_3 (and CH_2) bonds, will be discussed more fully below.

(*b*) *The spectrophotometric method.* If, as is often the case, the absorption spectra of a very weak base and of its conjugate acid differ sufficiently, its ionisation constants can be determined spectrophotometrically with the aid of Hammett's acidity function, H_0: [20]

$$pK_{BH^+} = H_0 + \log (c_{BH^+}/c_B). \quad (4)$$

The conventional method of obtaining the concentration ratio [20,21] can be simplified as follows:

Let D be the optical density of the solution at a given wavelength, let D_B be that of a solution of un-ionised base of concentration equal to the total concentration of base in

* The present finding that trideuteroacetic acid is some 6% weaker than acetic acid supersedes our earlier report [19] of an effect twice as large. The question was reopened after personal communications from Drs. G. A. Ropp and A. Streitwieser, Jr., who, working with different methods, but using deuterated acid from the same source (Merck, Canada), reported effects in the same direction of 6% and 3%, respectively. Our present finding thus confirms Ropp's results. The discrepancy is apparently due to impurities in the isotopic material (see Experimental part).

Added in proof: Dr. Streitwieser (personal communication) has confirmed his original effect with pure acid. The discrepancy between the results of his conductimetric method and the present results thus remains unresolved.

[19] Abs. 16th Internat. Congr. Pure Appl. Chem., 1957, Vol. II, p. 27.

[20] (*a*) Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2771; Hammett, *Chem. Rev.*, 1935, **35**, 67; (*b*) Paul and Long, *ibid.*, 1957, **57**, 15.

[21] Hammett and Alden, *J. Amer. Chem. Soc.*, 1932, **54**, 2730; Norris and Willard, *ibid.*, 1940, **62**, 2488.

solution, and let D_{BH^+} be the optical density of a solution in which the same total concentration of base is fully protonated. Then, for unit cell length,

$$\left.\begin{aligned} D &= c_B\varepsilon_B + c_{BH^+}\varepsilon_{BH^+}; \\ D_{BH^+} &= (c_B + c_{BH^+})\varepsilon_{BH^+}; \\ D_B &= (c_B + c_{BH^+})\varepsilon_B. \end{aligned}\right\} \quad (5)$$

From these relations:

$$c_{BH^+}/c_B = (D_B - D)/(D - D_{BH^+}), \quad (6)$$

which is equivalent to Paul and Long's equation (3).[20b]

In order to obtain the concentration ratio, it is thus necessary to measure the optical density in three solutions, in which the base is partly ionised, fully ionised, and completely un-ionised, respectively, and for only the first of which it is necessary to know H_0. If, as in the present case, a wavelength can be found at which only one form, say the un-ionised base, absorbs appreciably, then:

$$c/c_{BH^+} = (D_B - D)/D. \quad (7)$$

Now, if an n-fold dilution of the solution with water is sufficient to convert virtually all the base into its un-ionised form (and a two-fold dilution is generally more than ample), then D_B is simply n times the optical density of the diluted sample. The method is thus insensitive to weighing errors (which may introduce uncertainty into the stoicheiometric concentrations) and does not require accurate determination of the extinction coefficients.

The pK_{BH^+} values of 2,4-dinitroaniline, *N*-methyl-2,4-dinitroaniline and *N*-methyl-2,4,6-trinitroaniline, each the mean of determinations at several H_0 values, are given in Table 3.

The slight decrease in basicity that occurs on *N*-methylation of 2,4-dinitroaniline (see Table 3), though not in keeping with the inductive effect of the methyl group, can be taken to be an instance of the decrease in basicity that has often been observed on passing from primary to secondary amines.[22] Of greater interest is the very different effect of adding the third nitro-group to 2,4-dinitroaniline and to its *N*-methyl derivative. In the former case, the basicity is reduced by a factor of nearly 100,000; in the latter, merely by a factor of 10. This difference can only be ascribed to steric inhibition of resonance in *N*-methyltrinitroaniline.

TABLE 3.

Strengths of polynitroaniline bases.

Base	No. of points	pK_{BH^+} Found	Lit.*
2,4-Dinitroaniline	4	−4·56 ± 0·03	−4·53
2,4,6-Trinitroaniline	—	—	−9·41
N-Methyl-2,4-dinitroaniline	4	−4·80 ± 0·04	—
N-Methyl-2,4,6-trinitroaniline	3	−5·83 ± 0·02	—

* " Best value " of Paul and Long.[20b]

It is also clear from Table 3 that agreement with the " best " literature value for 2,4-dinitroaniline has been attained within the experimental precision, which in itself is quite good by ordinary standards. The error is large enough, however, to mask the minute basicity differences expected between isotopic variants of the same molecule. From a consideration of the pK_{BH^+} values obtained at various acidities (a sample set is shown in Table 5 in the Experimental section) it is evident that the principal sources of error are in the accuracy with which the acid solution is made up and in the reliability of the conversion of acid concentration into units of H_0.

[22] Bell, " The Proton in Chemistry," Cornell Univ. Press, Ithaca, New York, 1959, p. 176.

If, however, we compare two bases of similar strength in identical acid solutions, H_0 can be eliminated by subtraction after equation (4) is applied to each base separately:

$$\Delta pK_{BH^+} = pK'_{BH^+} - pK_{BH^+} = \log (c'_{BH^+}/c'_B) - \log (c_{BH^+}/c_B), \quad (8)$$

each of the concentration ratios being obtained as described above.

TABLE 4.

Isotopic differences in basicity of polynitroanilines.

Base	Reference base	No. of points	ΔpK_{BH^+}
2,4-$(NO_2)_2C_6H_3$·NH·C^2H_3 *	2,4-$(NO_2)_2C_6H_3$·NH·CH_3	4	0·056 ± 0·003
2,4,6-$(NO_2)_3C_6H_2$·NH·C^2H_3 *	2,4,6-$(NO_2)_3C_6H_2$·NH·CH_3	3	0·047 ± 0·004

* Isotopic analysis of these compounds was somewhat imprecise (±7—8%). Within these limits both compounds were isotopically pure (n = 3·0).

The mean results of comparing isotopic pairs of each of two *N*-methylanilines in sulphuric acid solutions of varying acidity are shown in Table 4. It is evident that the effect of deuteration on the carbon atom α to an amino-group is qualitatively similar to that on the atom α to a carboxyl group in an aliphatic acid; also that the two bases are affected to a similar extent, a decrease of ~12% in K_{BH^+}, by trideuteration, although only one of them is subject to steric inhibition of resonance. The isotope effect is thus characteristic of an inductive effect also in that it appears to be quantitatively superimposable upon steric and resonance effects of variable magnitude. The near-identity of the effect in the two bases can also be taken as evidence that the steric requirements of CH_3 and C^2H_3 are substantially the same. In other words, while small differences in mean configuration are significant for considerations of bonding (or perhaps non-bonding H···H interactions within the group [13]), they may be neglected when considering non-bonding interactions with other atoms in the molecule.*

DISCUSSION

The evidence presented in this paper is consistent with the hypothesis that inductive electron release is effectively easier from C^2H_3 (or C^2H_2) than from CH_3 (or CH_2). The constancy of the effect per deuterium atom evidently leaves something to be desired, particularly for aliphatic acids, suggesting that other factors such as hyperconjugation with the carboxyl group have not been taken into account. The dominant role of induction is however supported by: (*a*) strong damping of the effect through a saturated carbon atom; (*b*) the complementary nature of the effect of α-deuteration in the benzyl group on acid and base strength; (*c*) its similarity in bases of widely different strength; and (*d*) the near-independence of the magnitude of the effect, in the polynitroaniline bases, on steric inhibition of resonance with the aromatic ring.

Since the preliminary communication of some of these results,[19,24] when it was suggested that an inductive isotope effect could most simply explain certain apparently anomalous observations in kinetic systems, a large body of confirmatory kinetic evidence has been found in a variety of reactions: methylation of triethylamine;[25] α-hydrogen exchange in ethylbenzene;[26] acid- and base-catalysed hydrolysis of methyl *p*-toluate;[27] and solvolysis of *m*-tolylacetyl chloride[28] and, perhaps, of the methyl halides.[29]

* See also Bartell's arguments according to which non-bonded interactions, assumed to be large in other systems,[23a] should be unimportant in cases of steric inhibition of resonance.[23b]

[23] Bartell, (*a*) *J. Amer. Chem. Soc.*, 1961, **83**, 3567; (*b*) *Iowa State Coll. J. Sci.*, 1961, **36**, 144.
[24] Halevi and Nussim, *Bull. Res. Council Israel*, 1956, **5**, *A*, 263; Halevi, *Tetrahedron*, 1957, **1**, 174.
[25] Lewis and Farrisey, cited by Lewis, *Tetrahedron*, 1959, **5**, 147.
[26] Streitwieser and Van Sickle, *J. Amer. Chem. Soc.*, 1962, **84**, 224.
[27] Hodnett, Taylor, Tormo, and (R. E.) Lewis, *J. Amer. Chem. Soc.*, 1959, **81**, 4528.
[28] Lewis, Johnson, and Coppinger, *J. Amer. Chem. Soc.*, 1959, **81**, 3140.
[29] Llewellyn, Robertson, and Scott, *Chem. and Ind.*, 1959, 732.

It has been claimed [4] that an isotope effect in the " inductive " direction, since it too is ultimately reducible to vibrational frequency differences, could be approximated rather simply by using the harmonic model. Thus it appeared that the effect of deuteration on the strength of acetic acid could be correlated with a net shift to the red of the six " methyl " frequencies on going from acetic acid to acetate ion. However, comparison of modern vibrational analyses of the two molecules [30,31] does not show the required net shift, so that even in this relatively simple case the direct treatment in terms of shifts of the harmonic frequencies does not seem to be fruitful in cases where the configuration of the methyl or methylene group is retained during the reaction.†

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° 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 oversimplifaction to disregard the solvent when dealing with small effects in highly polar solutions.‡

The work described in this and the following paper is restricted to molecules in which at least two hydrogen atoms on the same carbon atom are replaced by deuterium, so it has no direct bearing on the relative effective electronegativity of isolated CH and C^2H bonds. In the parallel theoretical treatment [13] it was noted that this factor is particularly difficult to assess, and the net greater effective release from C^2H_3 (and C^2H_2) was ascribed primarily to the change in the non-bonding H···H repulsions that are greater in deuterated compounds. Evidence is now available from nuclear magnetic resonance in $^2HCF_3$ and α-deuterotoluene [33] and from the facts that pentadeuterophenol is a considerably weaker acid than phenol,[34] that deuteroformic acid is weaker than formic acid,[35] that 2,4,6-trideuteroaniline is a stronger nucleophile than aniline,[36] and that nuclear deuteration increases the stability of carbonium ions; [37] these show how quite generally a deuterium atom bonded to carbon may be regarded as effectively more electropositive than normal hydrogen, though the effect of an isolated C–D bond would presumably be less than the effect per deuterium atom of a trideuteromethyl or dideuteromethylene group.

The fact that deuteration of the methylene group has a more pronounced effect in phenylacetic than in propionic acid may well be related to hyperconjugation with the ring. Hyperconjugative isotope effects on equilibria in a similar system are discussed in the following paper.

Experimental

Preparation and Analysis of Deuterated Compounds.—All isotopic syntheses were also carried out with unlabelled material. The products of these test syntheses were always used as reference acids and bases in the dissociation-constant experiments, generally along with standard samples, prepared from reagent grade commercial materials by repeated crystallisation and/or distillation. The synthetic protio-compounds were considered to be pure when their physical properties, such as m. p., infrared spectrum, and refractive index, were identical with those of the purified commercial product and with the properties reported in standard

† The situation is different in the case of Streitwieser's " α-effect " [4] in which a definite change of configuration from tetrahedral to plane-trigonal presumably takes place, along with accompanying changes in force constants.

‡ The observed temperature-dependence of the secondary isotope effect in aqueous hydrolysis of alkyl halides [32] can perhaps be rationalised in similar terms.

[30] Weltner, *J. Amer. Chem. Soc.*, 1955, **77**, 3941.
[31] Ito and Bernstein, *Canad. J. Chem.*, 1956, **34**, 170.
[32] Leffek, Robertson, and Sugamori, *Chem. and Ind.*, 1961, 259.
[33] Tiers, *J. Amer. Chem. Soc.*, 1957, **79**, 5585; *J. Chem. Phys.*, 1958, **29**, 963.
[34] Klein and Streitwieser, *Chem. and Ind.*, 1961, 180.
[35] Bell and Jensen, *Proc. Chem. Soc.*, 1960, 307; Ropp, *J. Amer. Chem. Soc.*, 1960, **82**, 4252.
[36] Elliott and Mason, *Chem. and Ind.*, 1959, 488.
[37] Kresge, Rao, and Lichtin, *Chem. and Ind.*, 1961, 53.

compilations for the pure compounds. In all cases, the synthetic and the purified commercial materials were also identical as regards acid dissociation constant. This identity in physical and chemical properties between synthetic and purified commercial materials was taken as confirmation of the reliability of the isotopic synthesis, and as *prima facie* evidence of the chemical purity of the isotopic material.

The isotopic purity of the deuterated compounds was checked, as indicated in each case by the infrared spectrum determined with a Perkin-Elmer, model 21, double-beam spectrophotometer with sodium chloride optics, and/or by mass-spectrometric analysis of the hydrogen obtained by reduction, with zinc, of the water from total combustion. The latter analyses, some of which presented considerable difficulty, were kindly carried out by Dr. D. R. Christman at the Brookhaven National Laboratory.

Sodium [$^2H_3$]*Acetate.*—The commercial availability of tetradeuteroacetic acid (Merck, Canada) prompted us at first to neglect our general practice of parallel isotopic and non-isotopic syntheses, with the dire result indicated in the footnote on p. 869).

Gas-chromatography of this material, kindly performed by Dr. H. Gesser, showed it to contain traces of at least five contaminants, most of which appeared to be organic acids of higher molecular weight, which could not be easily removed by fractional crystallisation or distillation.

The measurements reported in Table 2 were performed on samples of sodium [$^2H_3$]acetate prepared in two ways: (i) Commercial tetradeuteroacetic acid was neutralised with sodium hydroxide to pH 8 and evaporated to dryness. Three recrystallisations of the sodium salt from water, followed by fusion, afforded a material whose pK_a remained unchanged on further recrystallisation and fusion. (ii) " AnalaR " sodium acetate was twice treated with deuterium oxide in a sealed tube at 200°. The product was evaporated to dryness, twice recrystallised from water, and fused. The infrared spectra in a potassium bromide pellet were in both cases virtually identical with that reported by Ito and Bernstein [31] for trideuteroacetate ion. From the very low intensity of the CD_2H absorption at 1250 cm.$^{-1}$, the isotopic purity was estimated to be >95%.

Sodium [β-$^2H_3$]*Propionate.*—[$^2H_4$]Acetic acid (0·06 mole) was reduced with lithium aluminium hydride (0·06 mole) in di-(2-ethoxyethyl) ether at room temperature, and the complex was decomposed with di-(2-2′-hydroxyethoxyethyl) ether (0·3 mole). The product $C^2H_3{\cdot}CH_2{\cdot}OH$ was distilled from the reaction mixture in a stream of nitrogen; when dried (K_2CO_3) and redistilled at atmospheric pressure, it was obtained in 84% yield. This was converted into the bromide with 48% hydrobromic acid, the fraction boiling at 38—40° being retained. The Grignard reagent was prepared and carbonated by the standard procedure, and the product was extracted with ether, recovered, and distilled with steam. The sodium salt obtained by neutralisation was fused very gently. The overall yield was 18·5%. The infrared spectrum showed, in addition to the characteristic C^2H absorptions, a weak absorption at 1370 cm.$^{-1}$, indicating some isotopic contamination. The mass-spectrometric analysis showed 2·4 atoms of ^2H per molecule.

Sodium [α-$^2H_2$]*Propionate.*—This salt was prepared by reduction of ethyl di-(2-acetoxyethyl) ether (0·14 mole) with lithium aluminium deuteride (Metal Hydrides, Inc.) (0·07 mole) in diethyoxethane to obtain, as a first product, $CH_3{\cdot}C^2H_3{\cdot}OH$. This was converted into sodium [α-$^2H_2$]propionate by the method described in the preceding paragraph, the overall yield being 25%. The infrared spectrum showed the characteristic C^2H_2 stretching and bending absorptions, and only a trace of the strong CH bending peak at 1290 cm.$^{-1}$ present in spectra of $CH_3{\cdot}CH_2{\cdot}CO_2Na$ and $C^2H_3{\cdot}CH_2{\cdot}CO_2Na$. Mass-spectrometric analysis indicated complete deuteration (2·0 atoms of ^2H per molecule; assumed to be entirely in the methylene group).

Phenyl[α-$^2H_2$]*acetic Acid.*—This was prepared by way of [α-$^2H_2$]benzyl alcohol and chloride. Ethyl benzoate (0·031 mole) was reduced with lithium aluminium deuteride (0·016 mole) in ether. The benzyl alcohol was recovered by standard methods, distilled at 106—107°/25 mm., dried [K_2CO_3] (86% yield; n_D^{18} 1·5400), and treated with thionyl chloride in the conventional manner. The product, [α-$^2H_2$]benzyl chloride, was distilled at 78°/27 mm., dried ($CaCl_2$) (90% yield; n_D^{18} 1·5391), and converted into the Grignard reagent which was carbonated at −20°. The product, phenyl[α-$^2H_2$]acetic acid, was recrystallised from light petroleum. The overall yield was 42%.

The infrared spectra of the intermediate benzyl alcohol and chloride indicated complete methylene-deuteration, but that of the acid was inconclusive. Mass-spectrometric analysis, however, confirmed the isotopic purity, indicating 2·0 atoms of ^2H per molecule.

[α-$^2H_2$]*Benzylammonium Chloride.*—Benzonitrile (0·0215 mole) was reduced with an equimolar amount of lithium aluminium deuteride in ether, as described by Nystrom and Brown.[38] The product was isolated as the hydrochloride, m. p. 255—257°, in 70% yield. Isotopic purity, virtually guaranteed by the synthetic method, was confirmed by the infrared spectrum of it in a potassium bromide pellet: many bands, even those not associated with CH motions, were shifted to various extents from those of the normal compound. Specifically, no absorption was observed in the aliphatic CH bending region.

[α-$^2H_3$]*Methylamine.*—This was the critical intermediate in the preparation of both deuterated nitromethylanilines. Tetradeuteroacetic acid (Merck, Canada) was converted into the acid chloride in the usual manner. In order to convert the acid chloride into the amine in adequate though low, yield (31%) we found it necessary to modify the procedure of Gal *et al.*[39] as follows: The sodium azide was activated before use.[40] After the acetyl chloride, benzene, and sodium azide had warmed to room temperature overnight, as described,[38] the reaction mixture was warmed for a further 0·5 hr.

Isotopic purity was confirmed by the infrared spectrum (in $CHCl_3$) of the $C^2H_3{\cdot}NH_2$ liberated from the salt by alkali. The spectra of $C^2H_3{\cdot}NH_2$ and $CH_3{\cdot}NH_2$, prepared in this way, were consistent with those reported by Gray and Lord,[41] after allowance for the usual shifts due to solution in chloroform. Specifically, the deuterated compound was completely transparent in the CH_3 deformation region (1400—1500 cm.$^{-1}$), whereas the normal compound showed a strong absorption at 1460 cm.$^{-1}$, corresponding to the 1473 cm.$^{-1}$ absorption in the gas phase.[41]

N-[$^2H_3$]*Methyl-2,4-dinitroaniline.*—1-Chloro-2,4-dinitrobenzene (0·5 g., 0·0025 mole) and triethylamine (5 g.) were added to a solution of [α-$^2H_3$]methylamine hydrochloride (0·8 g., 0·015 mole) in ethanol (50 ml.), and the mixture was left at room temperature for 24 hr., then refluxed for a further 0·5 hr., and two-thirds of the solvent were then evaporated. The product, which crystallised on cooling, was recrystallised twice from glacial acetic acid. It melted at 182—183° (yield 73%).

N-[$^2H_3$]Methyl-2,4,6-dinitroaniline was prepared similarly from picryl chloride.

The isotopic purity of both these compounds is assured by the method of preparation and confirmed by comparison of the infrared spectra with those of the normal compounds. As noted under Table 4 mass-spectrometric analysis showed $n = 3$ within the rather large analytical error for these compounds.

Potentiometric Measurements.—Measurements were carried out with either a Beckman Model G (B) or a Cambridge portable pH meter (C), in both cases with glass and calomel electrodes. pH meter (C) could be read with greater precision but required to be reset before each run. The agreement between the two instruments, and their relative precision, is seen in Table 1.

(1) *Carboxylic acids.* The dry sodium salt (1 mmole, 80—140 mg.) was dissolved in carbon dioxide-free distilled water (50 ml.) and brought to within 0·15—0·20 pH unit of half-neutralisation by the addition of a fixed volume (20 c.c.) of 0·02N-hydrochloric acid. More of this acid was added in increments of 0·50 ml., and a pH reading taken after each addition. About 12—14 such increments brought the pH of the sample to 0·15—0·20 pH unit beyond half-neutralisation.

The procedure was repeated with exactly (within 0·1 mg.) the equivalent amounts of sodium salt of the reference acid, and ΔpH for corresponding increments of hydrochloric acid were recorded.

In the case of phenylacetic acid several runs were carried out in the reverse manner, by stepwise neutralisation of this acid with sodium hydroxide solution. This variation in procedure did not appreciably affect the results.

(2) *Benzylamine.* [α-$^2H_2$]Benzylamine hydrochloride was compared with benzylamine hydrochloride by stepwise neutralisation with 0·02N-sodium hydroxide, in analogy with the above.

(3) *Temperature control.* The measurements on phenylacetic acid and benzylamine were carried out at room temperature (27·0° ± 2·0°). The other measurements were carried out in a small water-bath kept manually at 25·0° ± 0·2°.

[38] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738.
[39] Gal, Spenger, and Greenberg, *J. Org. Chem.*, 1950, **15**, 1261.
[40] Nelles, *Ber.*, 1932, **65**, 1345.
[41] Gray and Lord, *J. Chem. Phys.*, 1957, **26**, 590.

TABLE 5.

Sample potentiometric determination.

HCl	pH Found			HCl	pH Found		
(ml.)	$CH_3{\cdot}CH_2{\cdot}CO_2Na$	$CH_3{\cdot}C^2H_2{\cdot}CO_2Na$	ΔpH	(ml.)	$CH_3{\cdot}CH_2{\cdot}CO_2Na$	$CH_3{\cdot}C^2H_2{\cdot}CO_2Na$	ΔpH
2·0	4·950	4·995	0·045	5·5	4·800	4·830	0·030
2·5	4·935	4·970	0·035	6·0	4·780	4·810	0·030
3·0	4·905	4·940	0·035	6·5	4·760	4·800	0·040
3·5	4·885	4·920	0·035	7·0	4·740	4·775	0·035
4·0	4·870	4·900	0·030	7·5	4·725	4·755	0·030
4·5	4·850	4·880	0·030	8·0	4·700	4·730	0·030
5·0	4·825	4·855	0·030			Mean 0·033 ± 0·005	

(4) *Treatment of results.* The average value of ΔpH was recorded for each run. (In the few cases when ΔpH showed a trend the run was discarded.) The mean value of ΔpH was taken as ΔpK_a for this acid pair, and recorded with the standard deviation for all runs with this pair.

A typical run with pH meter B (which can be read to 0·005 unit) is shown in Table 5. The reproducibility of ΔpH for successive points is somewhat less than with pH meter (C), but there is no trend in the ΔpH values. The mean of the average values for the runs with this compound is, from Table 2, $\Delta pK_a = 0{\cdot}034 \pm 0{\cdot}002$.

TABLE 6.

Spectrophotometric determinations for *N*-methyl-2,4-dinitroaniline.

H_2SO_4 (%)	$-H_0$	$-pK$	$-pK_D$	ΔpK
59·5	4·40	4·81	4·75	0·056
61·5	4·62	4·80	4·75	0·053
62·0	4·70	4·84	4·78	0·058
63·9	4·90	4·74	4·68	0·058
		Mean 4·80 ± 0·04	4·74 ± 0·04	0·056 ± 0·003

Spectrophotometric Method.—" AnalaR " concentrated sulphuric acid which had been carefully standardised with base was diluted to prepare the working solution.

Deuterated nitroaniline base (0·5—1·0 mg.) was dissolved in the acid (10 ml.) of such concentration that the optical density at the maximum of absorption of the base (425 mμ) was 0·5—0·8. The precise optical density at 33·0° ± 0·10° was recorded (D). An aliquot part (5 ml.) was diluted with water to 10 ml. slowly and with cooling, and the optical density at 33·0° was again recorded ($D_B/2$).

The procedure was repeated with the undeuterated base, in the same acid solution.

pK_a for any cation is obtained with eqn. (4) by using a value for H_0 interpolated in Paul and Long's [20b] Table 3. ΔpK_a was obtained directly by using eqn. (8). The results are illustrated in Table 6.

As noted in the text, the combined error of pK_H and pK_D is larger than ΔpK. The latter was obtained by the differential method which eliminates the necessity for knowing H_0.

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