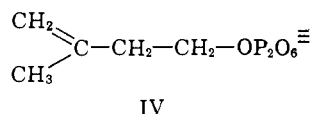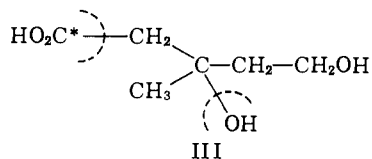being utilized.[10] For additional information on this point, a feeding experiment was carried out using 1-^{14}C-mevalonate (III). Here, the results (Table I)

$$HO_2C* \longrightarrow CH_2$$
$$CH_3 \diagdown C-CH_2-CH_2OH$$
$$\diagup$$
$$OH$$
III

$$CH_2 \diagdown$$
$$CH_3 \diagup C-CH_2-CH_2-OP_2O_6^{\equiv}$$
IV

showed negligible ^{14}C incorporation, as would be expected if III were converted into $\Delta^3$-isopentenyl pyrophosphate (IV), with concomitant loss of ^{14}C as carbon dioxide prior to terpene formation.[10]

Birch, et al., have studied the incorporation of 2-^{14}C-acetate into citronellal in Eucalyptus citrodora (Hook) and found extensive randomization of the carbon atoms, tentatively attributed to the formation of [14]CO_2, followed by photosynthetic reincorporation of the [14]C.[11] It will be interesting to investigate the pattern of isotopic incorporation for the animal case. We hope to describe these and related results in more detail in subsequent publications.

(10) An excellent recent review of the very extensive literature in this field is provided by J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W. A. Benjamin, Inc., New York, N. Y., 1964.
(11) A. J. Birch, D. Boulter, R. I. Fryer, P. J. Thomson, and J. L. Willis, Tetrahedron Letters, No. 3, 1 (1959).
(12) National Institutes of Health Postdoctoral Fellow, 1964–1965.

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## Application of Taft's Fluorine-19 Chemical Shift Correlations to the Study of Secondary Deuterium Isotope Effects[1]

Sir:

The subject of secondary deuterium isotope effects has been of considerable interest in recent years in regard to their origin and their application to studies of mechanisms.[2–4] While it is generally understood that the origin of these effects is related to differences in vibrational amplitudes or zero point energies, interpretations have been put forth based on an apparently greater inductive electron-donating tendency of –C–D than –C–H, and a reduced hyperconjugative donating ability of –C–D compared to –C–H.

To investigate the usefulness of discussing these essentially vibrational phenomena in terms of the normal substituent characteristics of inductive and resonance effects we have attempted to detect isotope effects on the separate inductive and resonance $\sigma$-constants, $\sigma_I$ and $\sigma_R{}^\circ$, of the methyl group by utilizing Taft's correlations of these constants with the F[19]

(1) Reproduction in whole or in part is permitted for any purpose of the U. S. Government.
(2) E. A. Halevi, Progr. Phys. Org. Chem., 1, 109 (1963).
(3) E. A. Halevi, M. Nassim, and A. Ron, J. Chem. Soc., 866 (1963).
(4) E. A. Halevi and M. Nassin, ibid., 877 (1963).

chemical shifts of meta- and para-substituted fluorobenzenes.[5–9] These correlations which are based on experimental work[5–9] as well as theoretical justification[10,11] are presented in the following equations, where $\int_H^{p\text{-}x}$ and $\int_H^{m\text{-}x}$ are the fluorine chemical shifts in p.p.m. of para- and meta-substituted fluorobenzene, respectively, relative to a fluorobenzene standard.

$$\int_H^{p\text{-}x} - \int_H^{m\text{-}x} = (-29.5)\sigma_R{}^\circ \tag{1}$$

$$\int_H^{m\text{-}x} = -7.1\sigma_I + 0.60 \tag{2}$$

Although measured secondary deuterium isotope effects invariably have been small, the sensitivity of the F[19] method seemed to qualify it for such a study. We therefore prepared p- and m-fluorotoluene-$\alpha,\alpha,\alpha$-$d_3$ and determined their F[19] chemical shifts with respect to their undeuterated analogs.

The deuterated compounds were prepared[12] from the corresponding methyl fluorobenzoates, via lithium aluminum deuteride reduction to the fluorobenzyl-$\alpha,\alpha$-$d_2$ alcohols, conversion with thionyl chloride to the $\alpha$-chlorofluorotoluene-$\alpha,\alpha$-$d_2$ compounds, and decomposition of the corresponding Grignard reagents with deuterium oxide. Fluorine-19 magnetic resonance measurements were made at 56.4 Mc.p.s. on the pure fluorotoluenes, mixtures of deuterated and nondeuterated analogs, and solutions in carbon tetrachloride.

The F[19] spectra of m-fluorotoluene, m-fluorotoluene-$\alpha,\alpha,\alpha$-$d_3$, and a 1:1 mixture of the two compounds gave nearly identical patterns of precisely defined peaks, indicating no chemical shift difference within experimental limits and uncertainties of about $\pm 0.2$ c.p.s. This result would seem to imply, in terms of eq. 2, that there is no difference between the inductive constants $\sigma_I$ for the groups CH_3 and CD_3, at least within the framework of Taft's F[19] correlation technique. This is in contrast to conclusions based on chemical techniques,[2,3] from which a F[19] shift difference as high as 4 c.p.s. might have been predicted.[12]

The F[19] spectra of a 2:1 mixture of p-fluorotoluene and p-fluorotoluene-$\alpha,\alpha,\alpha$-$d_3$ and of a 1:1:1 (volume) mixture of these components with carbon tetrachloride gave complicated patterns of overlapping peaks. These patterns are consistent with the superposition of the spectra of the components if it is assumed that the chemical shift of the undeuterated compound is about $0.7 \pm 0.2$ c.p.s. greater than that of the deuterated analog.[12] In terms of eq. 1 this corresponds to a difference of $4 \times 10^{-4}$ between the values of $\sigma_R{}^\circ$ for CD_3 and CH_3 (CD_3 having the more positive value). The 0.7 c.p.s. shift is in the direction to be expected

(5) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, J. Am. Chem. Soc., 85, 709 (1963).
(6) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, ibid., 85, 3146 (1963).
(7) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, ibid., 81, 5352 (1959).
(8) R. W. Taft, Jr., ibid., 79, 1045 (1957).
(9) R. W. Taft, Jr., J. Phys. Chem., 64, 1805 (1960).
(10) F. Prosser and L. Goodman, J. Chem. Phys., 38, 374 (1963).
(11) R. W. Taft, Jr., F. Prosser, L. Goodman, and G. T. Davis, ibid., 38, 380 (1963).
(12) Details of these experiments and a more complete discussion of the results will be presented elsewhere.

from kinetics and equilibrium studies,[2,4] but only about one-tenth as large as might have been predicted from chemical studies[2,4,13,14] on the basis of the sensitivity of the $F^{19}$ method for alkyl substituents.[6]

The present results, based on the well-established $F^{19}$ technique of Taft, indicate that $\Delta\sigma_I$ is zero and $\Delta\sigma_R°$ is smaller than expected for the change in substituent $CH_3 \rightarrow CD_3$. This points to a need for additional critical examination of the applicability of the language of ordinary substituent effects to the subject of secondary deuterium isotope effects.

(13) H. C. Brown and Y. Okamoto, J. Am. Chem. Soc., 79, 1913 (1957).
(14) E. S. Lewis and G. M. Coppinger, ibid., 76, 4495 (1954).

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## Proof for the RMgX Composition of Grignard Compounds in Diethyl Ether. RMgX, the Initial Species Formed in the Reaction of RX and Mg
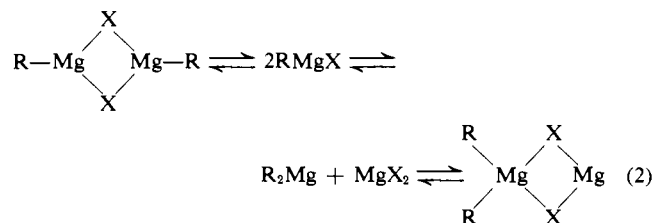
*Sir:*

The composition of Grignard compounds in diethyl ether solution has been assumed to be described adequately by the unsymmetrical dimeric species $R_2Mg \cdot MgX_2$.[1-4] The acceptance of this composition is based on the reported dimeric nature of Grignard compounds in diethyl ether solution and the lack of alkyl group exchange in a mixture of $(C_2H_5)_2Mg$ and $^{28}MgBr_2$.[1]

We have reported evidence to support the description of Grignard compounds in tetrahydrofuran by the equilibrium[5]

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad (1)$$
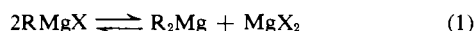
More recently we have cited[6] circumstantial evidence in favor of the existence of RMgX species in diethyl ether solution. The composition in diethyl ether was described by equilibria 2.

$$R-Mg\overset{X}{\underset{X}{\diagup\diagdown}}Mg-R \rightleftharpoons 2RMgX \rightleftharpoons$$

$$R_2Mg + MgX_2 \rightleftharpoons \overset{R\quad X}{\underset{R\quad X}{Mg\diamond Mg}} \qquad (2)$$

Two other recent reports have contributed importantly to eliminating the confusion in this area. First, Dessy and co-workers[7] have repeated previously reported $^{28}Mg$ experiments and now find exchange with

(1) R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, J. Am. Chem. Soc., 79, 3476 (1957).
(2) J. Miller, G. Grigoriou, and H. S. Mosher, ibid., 83, 3966 (1961).
(3) N. M. Bikales and E. I. Becker, Can. J. Chem., 41, 1329 (1962).
(4) H. O. House and D. O. Traficante, J. Org. Chem., 28, 355 (1963).
(5) E. C. Ashby and W. E. Becker, J. Am. Chem. Soc., 85, 118 (1963).
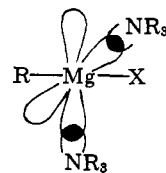(6) E. C. Ashby and M. B. Smith, ibid., 86, 4363 (1964).
(7) R. E. Dessy, S. Green, and R. M. Salinger, Tetrahedron Letters, 1369 (1964).

certain, but not all, grades of magnesium. Similar results using $^{25}Mg$ have been recently reported by Cowan.[8] Second, Rundel and co-workers[9,10] have reported $RMgX \cdot 2(C_2H_5)_2O$ structures for phenyl and ethylmagnesium bromide in the solid state based on X-ray diffraction, although whether a single solid state structure can be equated to species in solution is questionable. We report now (1) proof establishing RMgX as the initial species formed when RX and Mg react, and (2) proof for the existence of RMgX species in diethyl ether solution.

The difference between the composition of Grignard compounds in tetrahydrofuran (1) and diethyl ether (2) is explained by the difference in basicity of the two solvents. Ebullioscopic measurements show a monomer–dimer equilibrium in diethyl ether, but only monomeric species present in tetrahydrofuran. Thus tetrahydrofuran coordinates with magnesium more strongly than diethyl ether, and a stable halogen bridge compound is not formed. The exchange of alkyl groups in either tetrahydrofuran or diethyl ether can be explained by an intermediate mixed alkyl–halogen bridge structure.

$$2RMgX \rightleftharpoons R-Mg\overset{X}{\underset{R}{\diagup\diagdown}}Mg-X \rightleftharpoons R_2Mg + MgX_2 \qquad (3)$$
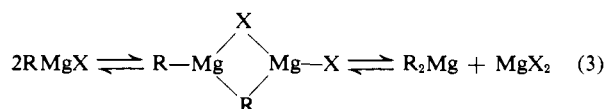
Grignard compounds coordinated to a much more basic solvent than diethyl ether or tetrahydrofuran might not form such intermediates if the magnesium orbitals are strongly bonded to the basic solvent. Thus dispro-



portionation is prevented and the initial species formed by reaction of RX and Mg is isolated.

Ethylmagnesium bromide was prepared from ethyl bromide and Mg in triethylamine. The reaction product was fractionally crystallized into seven fractions. Each fraction has a Mg:Br:N ratio of 1.0: $1.0:1.0^{11}$ within experimental error. Molecular association measurements of the crystallized fractions in triethylamine at 35° showed the presence of only monomeric species over a wide concentration range. Because of the highly insoluble nature of $MgBr_2$ in triethylamine and the soluble nature of $(C_2H_5)_2Mg$, precipitation of $MgBr_2$ from solution would have occurred if an unassociated mixture of these two products were present. These data prove that the reaction product is a single species and not a mixture. The product, $C_2H_5MgBr \cdot (C_2H_5)_3N$, does not disproportionate in boiling triethylamine over 24 hr., nor is it formed by redistribution of $(C_2H_5)_2Mg$ and $MgBr_2$ in triethylamine. Thus it is proved that $C_2H_5MgBr$ is the initial product from the reaction of $C_2H_5Br$

(8) D. O. Cowan, J. Hsu, and J. D. Roberts, J. Org. Chem., 29, 3688 (1964).
(9) G. D. Stucky and R. E. Rundle, J. Am. Chem. Soc., 85, 1002 (1963).
(10) L. J. Guggenberger and R. E. Rundle, ibid., 86, 5344 (1964).
(11) Although EtMgBr crystallizes from triethylamine as the bis-solvate, the monosolvate is isolated on drying under high vacuum.