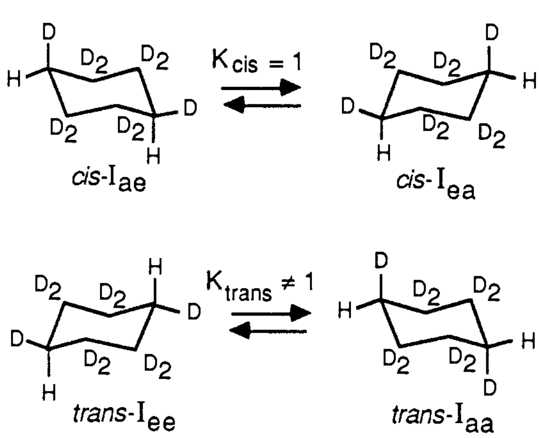

Figure 1. Conformational equilibria in *cis*- and *trans*-I. The e and a labels refer to deuterium in the CHD groups.

of equal areas separated by 0.51 ± 0.02 Hz.[9] In order to assign the peaks of the observed doublet, a separate sample of *trans*-I was prepared[10] and added to the above 1:1 mixture. The more shielded component of the doublet increased in intensity, showing that *trans*-I gave rise to that peak.

An examination of the conformational equilibria in *cis*- and *trans*-I (Figure 1) shows that $K_{cis} = 1$, whereas $K_{trans} \neq 1$. Intrinsic isotope effects[11] on chemical shifts in the two isotopomers of I should be virtually the same.[12] Thus, for example, an axial proton in *cis*-I have the same inherent chemical shift as an axial proton in *trans*-I. A difference in the observed ^{1}H chemical shifts between the two isotopomers at room temperature then indicates that the equilibrium constant for *trans*-I is not unity.

The chemical shift difference between axial and equatorial protons in cyclohexane-d_{11} is virtually temperature-independent and is equal to 0.478 ppm,[2,3] i.e., 95.6 Hz at 200 MHz, with the axial proton more shielded than the equatorial proton. It follows from the data on I that the ee conformation (i.e., protons axial) in *trans*-I is preferred over the aa conformation. The value of K_{trans} (Figure 1) is calculated to be 0.979 ± 0.004, which gives $\Delta G° = 12.6 \pm 3$ cal/mol. Thus, for a single deuterium, $\Delta G° = 6.3 \pm 1.5$ cal/mol, and this is the *A* value for deuterium (see below).

The stretching frequency in cyclohexane-d_{11} for an equatorial CH group is 31 cm^{-1} higher than that for an axial CH group.[13] Since this value of $\Delta\nu_{ae}$ contributes 12 cal/mol, differences in the bending frequencies must partly cancel the CH stretching contribution. We have therefore carried out molecular mechanics calculations of vibrational frequencies and thermodynamic parameters on these molecules.[14] The stretching force constants for equatorial and axial C–H bonds were adjusted to reproduce $\Delta\nu_{ea}$ exactly; all other force constants were left independent of whether hydrogens were axial or equatorial.[15] With this force field, the calculated $\Delta G°$ (25 °C) for cyclohexane-d_{11} was 6.7 cal/mol, in excellent agreement with our experimental NMR value.[16,17]

Further work on defining precisely the intrinsic isotope effects in I is being undertaken, and the importance of differences in C–H stretching frequencies in controlling equilibrium isotope effects in other molecules is being investigated.

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(9) Spectra were obtained on a Bruker WP-200 NMR spectrometer at a frequency of 200 MHz. Deuterium decoupling was done through the lock input on the probe. In order to monitor the field homogeneity, a small amount of ordinary cyclohexane was added to the sample, and single FID's were collected in an unlocked mode. The data were transferred to a VAX-780 computer and processed with the NMRI program (Dumoulin, C. L.; Levy, C. G. *J. Mol. Struct.* **1984**, *113*, 299–310. Levy, C. G.; Begemann, J. H. *J. Chem. Inf. Comput. Sci.* **1985**, *25*, 350–357). Lorentzian–Gaussian resolution enhancement was applied, and after zero filling, the FID was Fourier transformed. The final digital resolution was 0.006 Hz per point. All errors quoted in this paper refer to 95% confidence limits, and include our best estimates of systematic errors.

(10) 1,4-Cyclohexanedione-d_8 (Muller, N.; Schultz, P. J. *J. Phys. Chem.* **1964**, *68*, 2026–2028) was reduced with $LiAlH_4$ and the product was converted to the isomeric diacetates from which the high melting trans isomer was isolated. After methanolysis to the diol, tosylation, and treatment with $LiBEt_3D$, the desired cyclohexane-d_{10} was isolated by VPC. Analysis by GC/MS showed an isotopic purity of 64%.

(11) (a) Anet, F. A. L.; Dekmezian, A. H. *J. Am. Chem. Soc.* **1979**, *101*, 5449–5451. (b) Hansen, P. E. H. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105–234.

(12) Two *tert*-butylcyclohexane isotopomers (one with a 4-CH_2 and the other with a 4-CD_2 group) have been shown to differ in their 1-CH chemical shifts by only 1 ± 1 ppb as a result of an isotopic change five bonds away (Haddon, V. R.; Jackman, L. M. *Org. Magn. Reson.* **1973**, *5*, 333–338). We estimate that the difference in intrinsic isotope effects between *cis*- and *trans*-I is less than 0.5 ppb (i.e., <0.1 Hz at 200 MHz).

(13) Snyder, R. G.; Aljibury, A. L.; Strauss, H. L.; Casal, H. L.; Gough, K. M.; Murphy, W. F. *J. Chem. Phys.* **1984**, *81*, 5352–5361 and references therein. See also: Wiberg, K. B.; Walters, V. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 4860–4867.

(14) Burkert, U.; Allinger, N. L. "Molecular Mechanics"; ACS Monograph Series 177; American Chemical Society: Washington, DC, 1982.

(15) The DELPHI program (van der Graaf, B.; Baas, J. M. A. *J. Comput. Chem.* **1984**, *5*, 314–321) was modified (cf.: Anet, F. A. L.; Anet, R. *Tetrahedron Lett.* **1985**, *26*, 5355–5358) to allow convenient use with isotopes and to allow interaction with a data base on a VAX-780 computer. The adjusted force constants for axial and equatorial C–H stretching were 634 and 647 kcal/(mol Å^2), respectively. Other force constants were from: Boyd, R. H. *J. Chem. Phys.* **1968**, *49*, 2574–2583.

(16) Deuterium atoms in substituted cyclohexanones favor *axial positions* by 3–10 cal/mol, but some of these systems have 1:3 diaxial interactions with methyl groups and this could account for the different sign of the isotope effects from that in cyclohexane itself (Barth, G.; Djerassi, C. *Tetrahedron* **1981**, *37*, 4123–4142 and references therein).

(17) Other properties which are different for axial and equatorial CH groups include ^{13}CH coupling constants[4] and bond lengths.[13]

Tritium Isotope Effects on Carbon-13 NMR Chemical Shifts

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Deuterium isotope effects on carbon-13 NMR chemical shifts can be useful in making spectral assignments, and they are also interesting in their own right.[1] We report here the first determination of tritium isotope effects on carbon-13 NMR spectra.

We measured these isotope effects using acetone labeled with tritium at the 1% level and enriched to 90% with carbon-13 at the carbonyl position. This material was prepared by allowing carbon-13 enriched acetone (ICONS Services, Inc.) to exchange with tritiated water (27 Ci/mL) in the presence of a catalytic amount of sodium hydroxide. The labeled product was separated from water by entrainment in a stream of nitrogen, passage

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(1) For recent reviews, see: Forsyth, D. A. In "Isotopes in Organic Chemistry"; Buncel, E., Lee, C. C., Eds., Elsevier: New York, 1984; Vol. 6, Chapter 1. Hansen, P. E. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105–242.

Table I. Carbon-13 Chemical Shifts of Tritium- and Carbon-13-Labeled Acetone[a]

		δ	
species	abundance[b]	methyl	carbonyl
$CH_3C^*OCH_3$	83%		204.701 (s)
$CH_3C^*OCH_2T$	5%		204.777 (d)[c]
$CH_3C^*OC^*H_3$	2%	30.049 (d)[d]	204.697 (d)[d]
$CH_3COC^*H_3$	0.2%	30.061 (s)	
$CH_3C^*OC^*H_2T$	0.05%	29.693 (d, d)[d,e]	

[a] Proton-decoupled spectra measured at 125.75 MHz by using a Bruker AM 500 spectrometer with benzene-d_6 as solvent to provide both lock and internal reference (δ 128.0); sample concentration was 2 M, temperature was 305 K, and digital resolution was 0.545 Hz/point. [b] Approximate values calculated on the basis of 90 atom % carbon 13 at the carbonyl carbon and 1 atom % carbon-13 and tritium in the methyl groups. [c] $^2J_{CT}$ = 6 Hz. [d] $^1J_{CC}$ = 40 Hz. [e] $^1J_{CT}$ = 134 Hz.

Table II. Summary of Isotope Effects on Carbon-13 NMR Chemical Shifts for Acetone

	$(\Delta\delta = \delta^1 - \delta^2)^a$	
isotopic pair	$\Delta\delta_{Me}$	$\Delta\delta_{C=O}$
$^{12}C/^{13}C$	0.012 ± 0.006	0.004 ± 0.006
H/D	0.250 ± 0.001	−0.054 ± 0.001
H/T	0.356 ± 0.006	−0.076 ± 0.006

[a] Superscripts 1 and 2 refer to the light and heavy isotopes, respectively; uncertainties in isotope effects were obtained by propagating uncertainties in chemical shifts estimated as described in ref 5.

through 3-Å molecular sieves and condensation at −80 °C. A radiogas chromatogram showed the resulting material to be free of tritiated water.

The proton-decoupled carbon-13 NMR spectrum of this material was measured at 125.75 MHz as a 2 M solution in hexadeuteriobenzene. This spectrum consists of two groups of signals, one in the methyl region at δ 30 and another, considerably stronger, in the carbonyl region at δ 205. The acetone isotopic species to which these resonances could be attributed and the spectral assignments are listed in Table I.

The strongest signal in this spectrum, a singlet at δ 204.701, may be assigned to the most abundant species, acetone labeled with carbon-13 at the carbonyl group, $CH_3C^*OCH_3$. There are in addition, in this region of the spectrum, a pair of much weaker lines at δ 204.753 and 204.801 and another pair, of about half the intensity of the previous pair, at δ 204.538 and 204.856. The spacing of the first of these pairs corresponds to a coupling constant of 6 Hz, which is the expected value of the two-bond coupling constant $^2J_{CT}$ for acetone,[2] and the spacing of the second pair corresponds to 40 Hz, which is the reported value of $^1J_{CC}$ for this molecule.[4] On the basis of these coupling constants, plus the intensities of the lines relative to the expected abundances of the various isotopic species, these signals may be assigned to $CH_3C^*OCH_2T$ and $CH_3C^*OC^*H_3$, respectively.

These assignments lead to a very small upfield isotope effect for α-carbon-13 substitution on the carbonyl–carbon resonance, $\Delta\delta_{C=O}{}^{12/13}$ $(=\delta_{C=O}{}^{12} - \Delta_{C=O}{}^{13}) = 0.004$, which unfortunately is less than its estimated uncertainty, 0.006 ppm,[5] and a downfield isotope effect for β-tritium substitution on the same resonance, $\Delta\delta_{C=O}{}^{H/T}$ $(=\delta_{C=O}{}^{H} - \delta_{C=O}{}^{T}) = -0.076$. This carbon-13 isotope effect is similar in direction and magnitude to other carbon isotope effects in analogous substances[1] and is in good agreement with the value, 0.002 42 ± 0.000 06 ppm, determined recently under ultrahigh resolution,[4b] and the tritium isotope effect is in the same direction as, but larger than one-sixth of, the isotope effect reported for hexadeuterioacetone (Table II).[6]

The strongest resonance in the methyl region of the spectrum is a doublet with lines at δ 29.890 and 30.208, J = 40 Hz, which can be attributed to the most abundant species with carbon-13 in its methyl groups, $CH_3C^*OC^*H_3$. A weaker signal appears between these two lines at δ 30.061, and this is due to the next most abundant methyl carbon-13 species, $CH_3COC^*H_3$. There are in addition three even weaker lines at δ 28.997, 29.315, and 30.389; these belong to the doublet of doublets expected from $CH_3C^*OC^*H_2T$, with $^1J_{CC}$ = 40 Hz and J_{CT} = 134 Hz,[7] whose fourth line at δ 30.071 is obscured by the strong signal from $CH_3C^*OC^*CH_3$ at δ 29.890.

These assignments produce an upfield isotope effect for α-carbon-13 substitution on the methyl group resonance, $\Delta\delta_{Me}{}^{12/13}$ $(=\delta_{Me}{}^{12} - \delta_{Me}{}^{13}) = 0.012$, and also an upfield isotope effect for α-tritium substitution on the same resonance, $\Delta\delta_{Me}{}^{H/T}$ $(=\delta_{Me}{}^{H} - \delta_{Me}{}^{T}) = 0.356$. Both of these isotope effects are in the same direction as analogous effects in similar systems;[1] the carbon effect is also of normal magnitude, but the tritium effect is again considerably greater than one-sixth of that measured for hexadeuterioacetone.[6b,9]

A more meaningful quantitative comparison of deuterium and tritium isotope effects can be made by using monolabeled species for both substrates, and to that end we measured the carbon-13 spectrum of a mixture of unlabeled and monodeuterioacetone.[10] This gave isotope effects of $\Delta\delta_{Me}{}^{H/D} = 0.250$ and $\Delta\delta_{C=O}{}^{H/D} = -0.054$ on the methyl and carbonyl group signals, respectively.

These results give ratios of tritium to deuterium isotope effects which are the same for the two resonances: $\Delta\delta_{Me}{}^{H/T}/\Delta\delta_{Me}{}^{H/D} = 1.424 \pm 0.025$ while $\Delta\delta_{C=O}{}^{H/T}/\Delta\delta_{C=O}{}^{H/D} = 1.41 \pm 0.12$. This is interesting for the isotope effects on the two resonances are believed to be of different origin.[1] The upfield, α-isotope effect on the methyl group resonance has been attributed to the anharmonic nature of carbon–hydrogen bond vibrations: this makes C–D (or C–T) bonds effectively shorter than C–H bonds, and that puts the average electron density in the C–D (or C–T) bond closer to the carbon nucleus than that in the C–H bond, which leads to increased shielding; this is the so-called "inductive effect" of the heavier isotope. The downfield β-isotope effect on the carbonyl group resonance, on the other hand, is believed to be the result of isotopic perturbation of hyperconjugation. It is interesting as well that the ratio of tritium to deuterium isotope effects on carbon-13 chemical shifts found here is similar to the exponent, 1.44, which relates tritium and deuterium kinetic isotope effects.[11]

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(2) $^2J_{CH}$ = 5.9 Hz for the carbonyl carbon of acetone;[3] multiplication of this by the ratio of tritium to protium gyromagnetic ratios, 1.067, gives $^2J_{CT}$ = 6.3 Hz. We measured $^2J_{CT}$ = 6 Hz from the tritium NMR spectrum of the present sample.

(3) Gray, G. A.; Ellis, P. D.; Traficante, J. D.; Maciel, G. E. *J. Magn. Reson.* **1969**, *1*, 41–54.

(4) (a) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972; p 128. (b) Allerhand, A.; Dohrenwend, M. *J. Am. Chem. Soc.* **1985**, *107*, 6684–6688.

(5) Uncertainties in chemical shifts were taken as equal to the digital resolution, *i.e.* as the Hz/point value divided by the spectrometer frequency.

(6) (a) Maciel, G. E.; Ellis, P. D.; Hofer, C. D. *J. Phys. Chem.* **1967**, *71*, 2160–2164. (b) Breitmaier, E.; Jung, G.; Voelter, W.; Pohl, L. *Tetrahedron* **1973**, *29*, 2485–2459.

(7) $^1J_{CH}$ = 126 Hz for the methyl carbon of acetone;[8] multiplication of this by 1.067 gives $^1J_{CT}$ = 134 Hz. We measured $^1J_{CT}$ = 135 Hz from the tritium NMR spectrum of the present sample.

(8) Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. "High Resolution Nuclear Magnetic Resonance Spectroscopy"; Pergamon: New York, 1966; p 1013.

(9) Levy, G. C.; Cargioli, J. *J. Magn. Reson.* **1972**, *6*, 143–144. Coli, H. N.; Gold, V.; Pearson, J. E. *J. Chem. Soc., Chem. Commun.* **1973**, 408–409.

(10) The mixture was prepared by hydroxide ion catalyzed exchange of ordinary acetone with water containing 5% deuterium; this gave acetone-d_0, -d_1, and -d_2 species in the ratio 74:23:3. The proton-decoupled carbon-13 spectrum of this mixture as a 2 M solution in benzene-d_6 was measured at 100.57 MHz by using a Varian XL400 instrument. The methyl and carbonyl regions of the spectrum were recorded separately under conditions which gave a digital resolution of 0.0854 Hz/point.

(11) Melander, L.; Saunders, W. H., Jr. "Reaction Rates of Isotopic Molecules"; Wiley: New York, 1980; pp 28–29. Swain, C. G.; Stivers, E. C.; Reuwer, J. F.; Schaad, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 5885–5893.