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DEUTERIUM FRACTIONATION FACTORS FOR CARBON–HYDROGEN BONDS: CALCULATIONS USING SCALED QUANTUM-MECHANICAL FORCE CONSTANTS

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The determination of uniform scaling factors for force constants calculated at the STO-3G and 4-31G levels of *ab initio* SCF MO theory is described; scaled 4-31G force constants provide reasonable estimates of reduced partition function ratios for deuteriated/protiated molecules. Gas-phase deuterium fractionation factors relative to methane calculated using scaled 4-31G force constants are, however, consistently too high, whereas those obtained by the MP2/6-31G* and scaled STO-3G methods are inconsistent. Scaled 4-31G deuterium fractionation factors relative to water for a range of structural moieties correlate linearly with experimental aqueous-phase values, but are also consistently overestimated. Substitution at a hydrogen-bearing carbon atom affects the deuterium fractionation factor through the combined effect of changes in reduced mass and changes in force constants other than for CH stretching.

INTRODUCTION

The estimation and discussion of isotope effects on rates and equilibria is often aided by the use of isotopic fractionation factors.[1] A deuterium fractionation factor ϕ_R measures the accumulation of this isotope relative to protium at a particular site R with respect to the deuterium/protium ratio at a site S in a standard molecule. This fractionation factor is, in the absence of symmetry-number contributions, the equilibrium constant for the isotopic exchange

$$\mathrm{RH} + \mathrm{SD} \rightleftharpoons \mathrm{RD} + \mathrm{SD} \qquad (1)$$

and may be expressed entirely as a function of the vibrational frequencies of these species. The calculation of fractionation factors is therefore straightforward for molecular species whose fundamental frequencies are known. However, uncertainties in spectroscopic measurements of vibration frequencies or in their assignment may lead to errors in calculated fractionation factors which may be minimized by instead using calculated frequencies based on a common vibrational force field for each isotopomer.[2] *Ab initio* calculation of force fields and vibrational spectra, besides aiding the interpretation of experimental spectra, now permits the reliable estimation of vibrational frequencies for species which are not well characterized experimentally.[3] During the course of theoretical investigations of carbonyl addition,[4–6] protonation/deprotonation,[7] S_N2 methyl transfer[8] and S_N1 heterolysis,[9,10] *ab initio* self-consistent field molecular-orbital (SCF MO) calculations of harmonic force constants have been performed for numerous small organic molecules. It seems desirable now to use these data to compute deuterium fractionation factors for these same molecules, firstly in order to assess the performance of the methods employed in our theoretical modelling studies of organic reaction mechanisms, and secondly because the results should be of interest and use in discussions of isotope effects in organic[11] and possibly enzymic[12] reactions. In this paper, the scaling procedure used in mechanistic studies[6–9] is described and the results of fractionation factor calculations for hydrogen bound to carbon are presented. Deuterium fractionation factors for hydrogen bound to oxygen and nitrogen will be discussed elsewhere.

METHODS

The minimal STO-3G,[13] split-valence 4-31G[14] and polarized 6-31G**[15] bases were used in *ab initio* SCF MO calculations performed with the CADPAC program[16] and its earlier versions over a period of several years. All geometries were fully optimized using either the Murtagh–Sargent[17] or the Schlegel[18] algorithm with analytical gradients. Early calculations of cartesian force constants employed numerical differentiation of the gradient: forward- and central-

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difference formulae were employed[19] as well as a simplex method[20] which yielded central-difference accuracy at forward-difference cost. Later computations benefited from the availability of analytical second-derivative techniques.[21] Spurious translational and rotational contributions to the cartesian force constants were projected out,[19] thus guaranteeing that the Teller–Redlich product rule[22] was always satisfied for isotopomeric molecules.

The ratio of partition functions for two isotopomeric N-atomic molecules is (in the harmonic approximation):

$$\frac{Q^*}{Q} = \left(\frac{M^*}{M}\right)^{3/2} \left(\frac{A^*B^*C^*}{ABC}\right)^{1/2} \left(\frac{S}{S^*}\right) \prod_{i=1}^{3N-6} \times \frac{\exp(-u_i^*/2)/[1-\exp(-u_i^*)]}{\exp(-u_i/2)/[1-\exp(-u_i)]} \quad (2)$$

where the asterisk denotes the labelled species, M is the molecular mass, A, B and C are the principal moments of inertia, S is the rotational symmetry number and $u_i = h\nu_i/kT$. Using the Teller–Redlich product rule, this expression simplifies to

$$\frac{Q^*}{Q} = \left(\frac{S}{S^*}\right) \prod_{i}^{N} \left[\frac{m_i^*}{m_i}\right]^{3/2} f \quad (3)$$

where m_i is the mass of atom i and

$$f = \prod_{i}^{3N-6} \frac{u_i^* \exp(-u_i^*/2)/[1-\exp(-u_i^*)]}{u_i \exp(-u_i/2)/[1-\exp(-u_i)]} \quad (4)$$

The reduced partition function ratio[23] f is therefore

$$f = \left(\frac{S^*}{S}\right) \frac{Q^*}{Q} \prod_{i}^{N} \left[\frac{m_i}{m_i^*}\right]^{3/2} \quad (5)$$

but is a function only of vibrational frequencies [cf. equation (4)]. For isotopic substitution involving a single deuteron, the product over ratios of molecular masses in equation (5) reduces to $(\frac{1}{2})^{3/2}$. The fractionation factor ϕ_R for the isotopic exchange [equation (1)] may (in the absence of symmetry-number contributions) be expressed simply as a quotient of reduced partition function ratios:

$$\phi_R = \frac{Q_{RD}Q_{SH}}{Q_{RH}Q_{SD}} = \frac{f(RD/RH)}{f(SD/SH)}. \quad (6)$$

RESULTS AND DISCUSSION

Scaling of calculated frequencies

Vibrational frequencies calculated at the SCF level of *ab initio* MO theory are generally overestimated,[24] owing to the use of the harmonic approximation and of truncated basis sets and to neglect of electron correlation. The same is true for force constants calculated using semiempirical methods.[25] Improvement may be gained by addressing each source of error in turn using a higher level of theory;[26] this is the rigorous but expensive option for small molecules only. A more practical and widely applicable alternative is to perform calculations at a level which yields consistent errors and to correct these empirically by a scaling procedure; this approach has been championed and well reviewed by Pulay and co-workers[3,27] and has been employed in our own work.[5–10,28] The simplest procedure is to use a single scaling factor determined by the ratio of the sum of observed (anharmonic) frequencies to the sum of calculated (harmonic) frequencies with a particular basis set for a range of molecules of interest; this factor is (for want of better information) assumed to be transferable to related molecules for which spectroscopic data are unavailable. This method minimizes the error in the calculated zero-point energy of a molecule and is therefore particularly appropriate for calculations of isotope effects, since at normal temperatures these are usually dominated by zero-point energy changes.[29]

Sums of vibrational frequencies observed for water[30] (H_2O, HOD and D_2O), formaldehyde[30] (CH_2O, CHDO and CD_2O), methanol[31] (CH_3OH, CH_3OD, CD_3OH and CD_3OD) and acetaldehyde[32] (CH_3CHO, CH_3CDO, CD_3CHO and CD_3CDO) are given in Table 1 together with sums of harmonic frequencies calculated using the STO-3G, 4-31G and 6-31G** basis sets. (Results for water and formaldehyde only are given for the last basis). Also presented are *force-constant* scaling factors for each basis: these are the *squares* of the ratios of observed to calculated frequency sums. Note that the scaling factors determined by consideration of all the isotopomers listed above are closer to unity than those obtained using only the parent protio-species, i.e. there is slightly better agreement between the (unscaled) calculated and observed frequencies for deuterated molecules. The values adopted for use in subsequent work are rounded off to 0·68 for STO-3G and 0·82 for 4-31G. Note also that the 4-31G basis yields markedly closer agreement between (unscaled) calculated and observed frequencies than does STO-3G, but that no further improvement is to be derived from the use of the much larger 6-31G** basis. Analytical force-constant computations for water and formaldehyde are 4–5 times longer with 6-31G** than with 4-31G but do not provide correspondingly more accurate results. Root-mean-square (r.m.s.) errors in calculated vibrational frequencies are reduced by force-constant scaling with these factors from 403 to 86 cm^{-1} for STO-3G, from 233 to 40 cm^{-1} for 4-31G and from 316 to 31 cm^{-1} for 6-31G**.

Reduced partition function ratios

Table 2 contains reduced partition function ratios for deuterium substitution at a single position in each of several small molecules. Ratios calculated in this work

Table 1. Comparison of sums of vibrational frequencies (expressed as wavenumbers, cm^{-1}) calculated and observed for water, formaldehyde, methanol and acetaldehyde and resulting overall force-constant scaling factors

	Parent isotopomer only					All isotopomers				
			$\Sigma\nu$(calc.)					$\Sigma\nu$(calc.)		
	# ν	$\Sigma\nu$(obsd)	STO-3G	4-31G	6-31G**	# ν	$\Sigma\nu$(obsd)	STO-3G	4-31G	6-31G**
H_2O	3	9008	10703	9813	10185	9	23482	27761	25454	26415
CH_2O	6	11348	13692	12788	12725	18	30501	36650	34228	34117
CH_3OH	12	21755	26516	24041		46	75932	92170	83528	
CH_3CHO	14	22048	27105	24716		53	74861	90992	83233	
Total	35	64159	78016	71358	22910[a]	126	204776	247573	226443	60532[b]
Scaling factor			0·676	0·808	0·789			0·684	0·818	0·795

[a]Sum over 9 modes.
[b]Sum over 27 modes.

Table 2. Reduced partition function ratios at 300 K for some deuterated molecules

Isotopic species	Unscaled						Scaled	
	STO-3G	MNDO[a]	4-31G	MP2/6-31G*[b]	Harmonic[c]	Anharmonic[c]	4-31G	STO-3G
DCCH	15·28	13·05	12·12	9·35	9·054	8·298	9·021	8·469
DCHO	17·01	12·25	13·50	10·75	10·41	8·963	9·924	9·236
DCH_3	20·93	13·03	13·97	12·44	11·63	10·10	10·26	11·00
DOH	19·82	16·34	14·96	13·22	13·23	11·50	11·11	10·85
DNH_2	22·86	15·50	16·54	14·65	13·44	11·60	12·07	11·96
DCH_2F	23·17	15·01	17·16	13·17	13·52	11·86	12·24	11·74
Rms error	8·1	2·5	2·9	0·64			0·58	0·50

[a]Ref. 33.
[b]Ref. 34.
[c]Ref. 35.

using unscaled STO-3G and 4-31G force constants are shown on the left-hand side together with results obtained by other workers using the MNDO[33] and MP2/6-31G*[34] methods; these results may best be compared with those in the column headed 'Harmonic', which are derived from force constants deduced from harmonic frequencies obtained from observed fundamentals corrected for anharmonicity.[35] The r.m.s. errors (relative to the harmonic values) show that each theoretical method overestimates the reduced partition function ratios: the minimal-basis STO-3G results are the worst and those obtained using a polarized 6-31G* basis with electron correlation treated by second-order Moller–Plesset perturbation theory (MP2/6-31G*) are the best. Wolfsberg and co-workers[35] concluded that hydrogen–deuterium isotope effects calculated from reduced partition function ratios computed using force constants deduced directly from observed 'anharmonic' fundamentals are equally accurate to those derived from harmonic frequencies. Since for most molecules harmonic vibration frequencies are not available, a valid and practical procedure is to obtain reduced partition function ratios using calculated force constants scaled to minimize the error between calculated frequencies and observed anharmonic fundamentals. Thus the scaled STO-3G and 4-31G results shown on the right-hand side of Table 2 should be compared with those in the column headed 'Anharmonic.' The r.m.s. errors suggest that the agreement between the scaled STO-3G or 4-31G ratios and the 'anharmonic' ratios is as good as between the MP2/6-31G* ratios and the 'harmonic' values. Finally, it should be noted that reduced partition function ratios are very temperature dependent. The results in Table 2 were calculated at 300 K in order to permit comparison with the data in Refs 33–35; changing the temperature by less than 2 K to 298·15 K causes the numerical values to increase by about 2%. A ratio of reduced partition function ratios, i.e. a fractionation factor, is relatively insensitive to temperature, but it is essential to take reduced partition function ratios for the molecule of interest and for the standard molecule calculated for the same temperature, otherwise serious error may arise.

Gas-phase fractionation factors

The isotopic preference at a particular position in one molecule relative to the same preference in a standard molecule is found by dividing the relevant reduced partition function ratio by that for the standard. Table 3 contains fractionation factors relative to methane at 300 K for hydrogen bound to carbon in a range of molecules included in the compilation of Buddenbaum and Shiner.[36] Hartshorn and Shiner[37] had earlier pioneered the use of valence force fields, obtained by fitting to observed fundamental frequencies of vibration, for the calculation of fractionation factors and their results have been much cited.[38] More recently, Wolfsberg and co-workers[35] made a detailed study for a smaller range of molecules. Comparison of these two sets of 'ex-spectroscopic' results shows different fractionation factors calculated for acetylene and formaldehyde. Although the values of the observed fundamentals for these molecules are not in dispute, nevertheless it would appear that different force fields have been deduced from these data by the two groups of workers. The small differences in the 'ex-spectroscopic' results for ethane and fluoromethane are due to the fact that Shiner's data are for 25 °C; the change from 300 K to 298·15 K causes the values of the fractionation factors to increase by about 0·2%.

Errors in fractionation factors, or isotope effects generally, are best considered as errors in their logarithmic values since these are proportional to the relevant free-energy differences. Relative to Wolfsberg's anharmonic values, the average error in the logarithmic fractionation factors calculated by the various theoretical methods for acetylene, formaldehyde, ethane and fluoromethane are as follows: scaled 4-31G, 0·043; scaled STO-3G, 0·057; MNDO, 0·071; and MP2/6-31G*, 0·057. The scaled 4-31G results are consistently too high, the MNDO results too close to unity and the STO-3G and MP2/6-31G* methods sometimes overestimate and sometimes underestimate the fractionation factors.

Equilibrium constants for various gas-phase isotopic exchange equilibria have been measured using ion cyclotron resonance (ICR) spectrometry[39] and the selected ion flow tube (SIFT) technique.[40] Table 4 contains β-deuterium isotope effects for methanol deprotonation [equation (7)] and methylamine protonation [equation (8)].

$$CH_3OH + CD_3O^- \underset{}{\overset{K_7}{\rightleftharpoons}} CH_3O^- + CD_3OH \quad (7)$$

$$CH_3NH_2 + CD_3NH_3^+ \overset{K_8}{\rightleftharpoons} CH_3NH_3^+ + CD_3NH_2 \quad (8)$$

The minimal-basis STO-3G and MNDO methods are unreliable; whereas the values calculated for K_7 agree well with the experimental values, the estimates for K_8

Table 4. Calculated and experimental equilibrium constants for gas-phase isotopic exchange reactions

Method	K_7	K_8
ICR	2·3 ± 0·4[a]	0·86 ± 0·03[b]
SIFT	2·1 ± 0·3[c]	
Scaled 4-31G	2·62	0·824
Unscaled 4-31G	2·91	0·806
Scaled STO-3G	1·80	1·071
Unscaled STO-3G	2·05	1·089
MNDO	2·08	1·03

[a] Ref. 39a.
[b] Ref. 39b.
[c] Ref. 40.

Table 3. Calculated gas-phase fractionation factors relative to methane at 300 K

Molecule	Shiner[a]	Wolfsberg[b] anharmonic	Scaled 4-31G	Scaled STO-3G	MNDO[c]	MP2/6-31G*[d]
DCCH	0·803	0·822	0·879	0·770	1·002	0·750
DCHO	1·022	0·887	0·967	0·840	0·941	0·865
DCH_3	1·0	1·0	1·0	1·0	1·0	1·0
$DCH_2CH_2CH_3$	1·063		1·083			
DCFO	1·07		1·171	0·885		
DCH_2CH_3	1·092	1·090	1·094	1·076	1·082	1·097
DCH_2CN	1·102		1·101			
DCH_2F	1·176	1·174	1·193	1·067	1·153	1·059
$DCH_2NH_3^+$	1·155		1·204	1·135		
$DCH(CH_3)_2$	1·205		1·178		1·169[e]	

[a] Ref. 36.
[b] Ref. 35.
[c] Ref. 33.
[d] Ref. 34.
[e] B. Anhede, Thesis, University of Göteborg (1987).

are qualitatively incorrect in that the equilibrium is predicted to lie to the right of equation (8) rather than to the left; a similar erroneous result was previously calculated for protonation of methanol using STO-3G.[7] The 4-31G results are qualitatively correct although quantitatively in error; the use of scaled force constants improves the values of the equilibrium constants but their magnitudes remain overestimated.

Overall, it seems that the MNDO semiempirical and STO-3G *ab initio* SCF procedures often yield reasonably good results for fractionation factors and other isotopic exchange equilibrium constants. However, these minimal-basis methods lack the consistency which may be obtained using more sophisticated levels of theory. The recently parameterized semiempirical methods AM1 and PM3 are being evaluated as possible economical and reliable alternatives, and will be reported upon elsewhere. Meanwhile, the scaled 4-31G method represents a compromise between expense and accuracy and its performance is further investigated in the remainder of this discussion.

Fractionation factors in aqueous solution

It is generally held that the nature of the potential experienced by a hydrogen bound to carbon is essentially unchanged on transfer from the gas phase into aqueous solution. Thus phase transfer generally involves only a very small change in the zero-point energy of a CH (or CD) bond and hence a negligible isotope effect. Tanaka and Thornton[41] found that various organic compounds containing CH bonds were extracted into the hydrophobic medium μBondapak-C_{18} more favourably than those containing CD, by factors of only 1·002 to 1·008 per deuterium. However, Kovach and Quinn[42] measured an equilibrium isotope effect of 1·010 per deuterium for transfer of acetone from cyclohexane into water at 25 °C. Larger phase transfer isotope effects such as this probably arise from specific solvation of the carbonyl group in water. For most molecules containing hydrogen bound to carbon it is generally safe to neglect any isotope effect for transfer from the gas phase into aqueous solution. Calculated gas-phase fractionation factors, $\phi(g)$, relative to water may be converted to aqueous-solution values, $\phi(aq)$, by dividing by the vapour pressure isotope effect P_{H_2O}/P_{HOD}, which is equal to 1·0793 at 25 °C:[43]

$$\phi(aq) = \phi(g)(P_{HOD}/P_{H_2O}) \tag{9}$$

Hydrogen bonds involving heavy water are stronger than those involving light water.[19] Hence HOD (the deuterated standard SD) is more favoured in aqueous solution, shifting equilibrium (1) to the left and yielding a smaller (less normal or more inverse) fractionation factor ϕ_{RD} in aqueous solution than the has phase. Since aqueous solution is the natural medium for biochemical processes, fractionation factors relative to liquid water as standard find application in isotope-effect studies of enzyme mechanisms.[11,12]

Table 5 contains scaled 4-31G deuterium fractionation factors calculated for hydrogens bound to carbon in a number of structural groupings included in Cleland's[12] compilation of equilibrium isotope effects in aqueous solution. There are eight moieties for which both calculated and experimental fractionation factors are given: these data are correlated linearly ($r = 0{\cdot}992$) according to the equation

$$\phi(\text{calc.}) = 0{\cdot}91\phi(\text{expt.}) + 0{\cdot}14 \tag{10}$$

The calculated values are too large because the reduced partition function ratio (Table 2) calculated for H alone

Table 5. Scaled 4-31G calculated and experimental aqueous-phase fractionation factors relative to water at 25 °C

Labelled moiety	Theoretical model	Reduced p.f. ratio[a]	ϕ(aq)[b] (calc.)	ϕ(aq) (expt.)	Experimental model[c]	Ref.
$-C{\equiv}CD$	Acetylene	9·180	0·75	0·65	Acetylene	44
$-CD{=}O$	Acetaldehyde	10·75	0·88	0·83	Acetaldehyde	45
$-COCH_2D$	Acetaldehyde	11·10[d]	0·91	0·84	Pyruvate	46
$CCH(OH)CH_2D$	Isopropanol	12·26[d]	0·92	0·88	Lactate	12
$CCHDC$	Propane	12·34	1·01	0·98	Malate (3) DPNH (4)	12
$HCD(OH)H$	Methanol	12·39[d]	1·02			
$CCD(OH)H$				1·04	Ethanol (1)	12
$CCD(OH)C$	Isopropanol	14·28[d]	1·17	1·16	Isopropanol	12
$HCD(NH_3^+)H$	Methylammonium	12·60	1·03			
$CCD(NH_3^+)C$	Isopropylammonium	14·53	1·19	1·13	Amino acids (2)	12
$CCD(OH)_2$	Acetaldehyde hydrate	14·65	1·20	1·14	Acetaldehyde hydrate	45

[a] Scaled 4-31G reduced partition function ratio for gas-phase isotopomers at 298·15 K; the value for HOD/H_2O is 11·30.

[b] Gas-phase fractionation factor divided by vapour-pressure isotope effect, $P_{H_2O}/P_{HOD} = 1{\cdot}0793$.

[c] Labelled in the position shown in parentheses.

[d] Boltzmann-weighted average for all rotamers of the labelled molecule.

is underestimated with respect to Wolfsberg's anharmonic value, whereas the reduced partition function ratios calculated for other molecules are overestimated.

Effect of substitution

The fractionation factors for hydrogen bound to sp^3-hybridized carbon show a trend with the degree of substitution: primary < secondary < tertiary carbon. This trend was also noted by Kresge *et al.*,[11] who suggested that its origin is a reduced-mass effect arising mainly from coupling of hydrogen and heavy-atom motions in bending vibrations.[47] To test this idea, we have performed calculations of deuterium fractionation factors for several methyl-substituted methanes relative to methane itself. One of the methyl groups of ethane, and both methyl groups of propane, were replaced by a pseudoatom M of mass 15 and the methane geometry and scaled 4-31G force constants for methane were used to describe these penta-atomic species. The logarithms of the fractionation factors calculated for $^{15}MCH_3$ and $^{15}M_2CH_2$ (Table 6) are only about 50% of those for CH_3CH_3 and $(CH_3)_2CH_2$ respectively. Thus the reduced-mass effect accounts for about half of the observed increase in the fractionation factor with degree of substitution.

Table 6 also contains results of calculations for methane molecules using force constants for ethane and propane; here the atom H′ mimics a methyl carbon atom and is assigned force constants accordingly. The fractionation factors thus calculated are also considerably smaller than those for ethane and propane themselves. However, when H′ is replaced by the pseudoatom M′ of mass 15, use of the ethane and propane force constants does lead to fractionation factors essentially the same as those for the real substituted molecules. It is clear that substitution on a hydrogen-bearing carbon atom affects the deuterium fractionation factor through both reduced-mass and force-constant changes.

Table 6. Effect of substitution on fractionation factors for hydrogen bound to sp^3-hybridized carbon at 25 °C: $RH + CH_3D \rightleftharpoons RD + CH_4$

R	Force field[a]	ϕ_R	CH stretching	Others
CH_3	Methane	1·0	1·0	1·0
$^{15}MCH_2$	Methane	1·046	0·995	1·052
$H'CH_2$	Ethane	1·045	0·985	1·060
$^{15}M'CH_2$	Ethane	1·110	0·977	1·136
CH_3CH_2	Ethane	1·095	0·974	1·124
$^{15}M_2CH$	Methane	1·092	0·990	1·103
H'_2CH	Propane	1·048	0·953	1·100
$^{15}M'_2CH$	Propane	1·178	0·946	1·245
$(CH_3)_2CH$	Propane	1·180	0·945	1·250

[a] Scaled 4-31G force constants.

It might have been expected (from a too-simple view of the origin of isotope effects) that the remainder of the increase in fractionation factor with substitution, not accounted for by the reduced-mass change, would have arisen from the change in CH stretching force constant. The scaled 4-31G valence force constants for CH stretching are 4·82 md $Å^{-1}$ for methane, 4·72 md$Å^{-1}$ for ethane and 4·61 md $Å^{-1}$ for the methylene group of propane. The usual rule[48] is that the lighter isotope prefers the looser site, i.e. protium should accumulate in the more substituted molecules. This prediction is opposite to the observed trend for larger fractionation factors (i.e. deuterium preferred) as substitution increases. Since fractionation factors are quotients of reduced partition function ratios which are functions only of vibrational frequencies, calculated values of ϕ_R may be analysed into contributions from various groups of normal modes. As the results in Table 6 show, the CH stretching modes do indeed contribute inversely to the fractionation factors, but the overall effect is dominated by vibrational-frequency changes in the other (mostly bending) modes. A referee has pointed out that this greater importance of bending force-constant changes is in accord with the results of an early treatment of the consequences of deuteriation on the effective electronic distributions of molecules containing a methyl group.[49]

A substituent scale of sp^3 fractionation factors

Kresge *et al.*[11] have shown how fractionation factor and equilibrium constant data may be combined to provide a common scale of deuterium fractionation factors for substituted methanes relative to methane as the standard. Their data are included in Table 7 together with scaled 4-31G values. They noted good agreement between experimental values and those from the calculations of Hartshorn and Shiner,[37] with the exception of the cyano substituent, for which doubt was cast on the calculated value since the experimental value was well established. The present scaled 4-31G result for the cyano substituent, $\phi_{CN} = 1\cdot10$, agrees with that of Hartshorn and Shiner[37] based on Duncan's[50] force field for acetonitrile; more recent data of Duncan *et al.*[51] do not differ sensibly from the earlier work. Inspection of Table 7 reveals not one but several discrepancies between experimental and calculated fractionation factors; these may be indicative not of error but rather of solvation effects which operate in the experimental systems but are not accounted for in the present calculations.

Kresge *et al.*[11] suggested that the influence of electronegativity was evident in the relative values of ϕ_X: $OH > NH_2$ and $OH > O^-$ and $NH_3^+ > NH_2$. The calculated values also reflect these trends but are

Table 7. A substituent scale of deuterium fractionation factors, ϕ_x, for hydrogen bound to sp^3-hybridized carbon at 25 °C: $XCH_3 + CH_3D \rightleftharpoons XCH_2D + CH_4$

X	ϕ_x Experimental	ϕ_x Calculated	Theoretical model
$R'COH^+$	0·97	1·04	CH_3CHOH^+
H	1·0	1·0	CH_4
$R_2'C^+$	1·02	1·03	$(CH_3)_2CH^+$
CN	1·04	1·10	CH_3CN
R'CO	1·05	1·06	CH_3CHO
NH_2	1·09	1·11	CH_3NH_2
R	1·10	1·09	CH_3CH_3, $CH_3CH_2CH_3$
O^-	1·11	0·84	CH_3O^-
N_2^+	—	1·16	$CH_3N_2^+$
NH_3^+	1·13	1·21	$CH_3NH_3^+$
F	1·17	1·20	CH_3F
OH	1·18	1·19	CH_3OH
H_2O^+	—	1·24	$CH_3OH_2^+$

quantitatively different for the charged substituents. The NH_3^+ group is presumably a much more electronegative substituent in the gas phase than in aqueous solution, where its effective charge must be reduced by solvation, hence $\phi_{NH_3^+}$ (expt) < $\phi_{NH_3^+}$ (calc.). On the other hand, ϕ_{O^-} (expt.) $\gg$ ϕ_{O^-} (calc.), since the hyperconjugative stabilization of the negative charge by the CH bonds (and the consequent reduction of the CH stretching force constants[7]) is greatly attenuated in aqueous solution where the charge on oxygen is stabilized by hydrogen-bonded water molecules. Conversely, it is possible that solvation may serve to enhance hyperconjugation in the protonated acetyl group and in acetonitrile, thus causing looser methyl CH bonds and lower deuterium fractionation factors than in the gas phase.

The question remains as to whether substituent effects on fractionation factors are cumulative. Kresge *et al.*[11] noted that reduced mass effects should be cumulative but that electronegativity effects may not be. Since scaled 4-31G results are available for some pairs of 2-propyl and methyl substrates, this question may now be examined further. The deuterium fractionation factor for the methine position in $(CH_3)_2CHZ$ may be calculated either directly by equation (10) or indirectly by equation (11) as the product of substituent contributions (Table 7) for two methyls and the group Z. The results for several Z groups are given in Table 8.

$$\phi(\text{direct}) = f(Me_2CDZ/Me_2CHZ)/f(MeD/MeH) \qquad (11)$$

$$\phi(\text{indirect}) = \phi_{Me}^2\phi_Z \qquad (12)$$

The agreement between the fractionation factors calculated by the two methods is encouraging except for $Z = OH_2^+$. The 4-31G calculated bond lengths for $CH_3OH_2^+$ (1·548 Å[7]) and $(CH_3)_2CHOH_2^+$ (1·648 Å[10]) differ considerably and suggest that the methyl groups of the 2-propyl moiety alter the electronic structure about the central carbon in a manner which doubtless affects the value of the deuterium fractionation factor for the hydrogen bound to this atom: the carbon atom in $(CH_3)_2CHOH_2^+$ is essentially sp^2 hybridized.

Table 8. Deuterium fractionation factors for 2-propyl derivatives calculated directly or indirectly

Z	ϕ(direct)	ϕ(indirect)
H	1·18	1·19
F	1·39	1·43
OH	1·41	1·41
OH_2^+	1·38	1·47

CONCLUSIONS

Force constants calculated at the 4-31G level of *ab initio* MO SCF theory, and scaled uniformly by a single empirical factor to minimize the error between calculated and observed vibrational frequencies, permit the evaluation of deuterium fractionation factors for hydrogens bound to carbon with a reasonable degree of accuracy. Calculated values (relative to water) for a range of structural moieties correlate linearly with experimental aqueous-phase values, but are consistently overestimated. Substitution at a hydrogen-bearing carbon atom affects the deuterium fractionation factor through the combined effect of changes in reduced mass and changes in force constants other than for CH stretching. Discrepancies between calculated and experimental fractionation factors (relative to methane) for certain methyl compounds probably arise from solvation effects. Substituent effects on fractionation factors for hydrogen bound to sp^3-hybridized carbon are roughly cumulative, provided that the substitution does not greatly affect the electronic structure about the carbon.

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