Fractionation Factors for Hydrogen Bound to a Saturated Carbon. I. Substituent Effects on Fractionation Factors

Pirketta Scharlin

Department of Chemistry, University of Turku, SF-20500 Turku, Finland

Scharlin, P., 1989. Fractionation Factors for Hydrogen Bound to a Saturated Carbon. I. Substituent Effects on Fractionation Factors. – Acta Chem. Scand. 43: 244–247.

Fractionation of deuterium between chlorodibromomethane, 2-methyl-1-phenyl-1-propanone, 1-phenyl-1-propanone and water has been studied in different H_2O–D_2O liquid mixtures at 298.15 K. Values of 1.052(5), 1.040(7) and 0.984(12) were obtained for the fractionation factors of chlorodibromomethane, 2-methyl-1-phenyl-1-propanone and 1-phenyl-1-propanone, respectively. Combining these results with fractionation factors obtained in previous studies, substituent effects on fractionation factors for hydrogen bound to a saturated carbon are discussed.

Fractionation factors are convenient for describing the effects of varying the isotopic composition of solvent on kinetics, equilibria and product composition. By means of fractionation factors the quantitative treatment of solvent isotope effects can be considerably simplified. The original Gross-Butler theory[1,2] for the solvent isotope effects of deuterium on reactions in aqueous acid solutions has been greatly developed by Gold[3] and by Kresge.[4] On the basis of the fractionation theory there have been published many reviews and articles concerning the relationships for describing the equilibrium and kinetic isotope effects in H_2O–D_2O solvent systems.[5–14] In these expressions the isotope effects are factorized into contributions from different species involved in the reactions, the fractionation factors representing contributions from individual hydrogens in reactants, products and transition states. During recent years, precise values of fractionation factors for hydrogen bound to carbon have become more and more important, partly because of the growing interest in kinetic and equilibrium isotope effects, for instance in enzymatic reactions.[15,16] In spite of the importance of the fractionation factors there exist only a few direct experimental determinations of them,[16–28] probably because the measurements necessary to obtain precise and accurate values for fractionation factors are usually very laborious, sometimes even impossible. Therefore, a common substituent scale of fractionation factors would be convenient and helpful, for instance, in evaluating values of fractionation factors for different compounds and in predicting isotope effects. The dependence of fractionation factors on substitution is not yet known in detail, although some general trends, for example the dependence upon hybridization, are well known.[29] The aim of the present study was to elucidate the substituent effects on fractionation factors for hydrogen bound to an sp^3 hybridized carbon by making use of previous[24–27] and new fractionation factor measurements in the H_2O–D_2O solvent system.

Experimental

Materials. Chlorodibromomethane (EGA-Chemie, >98%) was distilled once before use. Deuteriochlorodibromomethane was prepared as described in Ref. 24. 2-Methyl-1-phenyl-1-propanone (Fluka AG, pract. ≥97%) and 1-phenyl-1-propanone (EGA-Chemie, 98–99%) were distilled once before use. The deuterium oxide used in the experiments was obtained from EGA-Chemie, and the deuterium isotope mole fraction of D_2O was reported to be 0.998. For the equilibration experiments the sodium hydroxide–sodium deuteroxide solutions in which the deuterium isotope mole fraction of water, $x(D;L_2O)$,

Table 1. Mole ratios of deuterium and protium in chlorodibromomethane equilibrated in different H_2O–D_2O mixtures, and the experimental fractionation factors φ' ($CHClBr_2$) at 298.15 K.

$x(D;L_2O)$[a]	$\frac{n(D;CLClBr_2)}{n(H;CLClBr_2)}$[b]	φ' ($CHClBr_2$)[b,c]
0.101	0.1233(15)	1.085(10)
0.202	0.2773(20)	1.097(8)
0.309	0.4709(13)	1.055(3)
0.405	0.701(4)	1.032(5)
0.454	0.869(5)	1.046(4)
0.507	1.069(6)	1.041(5)
0.552	1.326(9)	1.074(7)
0.602	1.585(9)	1.050(5)
0.702	2.43(1)	1.028(4)
0.797	4.05(3)	1.033(7)
0.898	9.19(11)	1.045(12)

[a] $x(D;L_2O)$ is the deuterium isotope mole fraction of water. [b] Mean values of 8–9 determinations with standard errors of mean. [c] $\varphi'(CHClBr_2) = \frac{n(D;CLClBr_2)}{n(H;CLClBr_2)} \Big/ \frac{x(D;L_2O)}{1 - x(D;L_2O)}$.

Table 2. Mole ratios of deuterium and protium in 2-methyl-1-phenyl-1-propanone (SH) equilibrated in different H_2O–D_2O mixtures and the experimental fractionation factors φ' (SH) at 298.15 K.

$x(D;L_2O)^a$	$\frac{n(D;SL)}{n(H;SL)}$	$\varphi'(SH)^{b,c}$
0.104	0.1267(32)	1.092(27)
0.187	0.2361(52)	1.026(22)
0.305	0.471(8)	1.073(17)
0.498	1.039(8)	1.048(8)
0.549	1.263(2)	1.038(1)
0.600	1.570(9)	1.046(6)
0.694	2.341(26)	1.032(11)
0.798	3.977(15)	1.007(4)
0.892	8.29(23)	1.003(27)

[a] $x(D;L_2O)$ is the deuterium isotope mole fraction of water.
[b] Mean values of 6 determinations with standard errors of mean.
[c] $\varphi'(SH) = \frac{n(D;SL)}{n(H;SL)} / \frac{x(D;L_2O)}{1 - x(D;L_2O)}$.

varied between 0.1 and 0.9 were prepared by weight from pure H_2O and D_2O, adding a suitable amount of NaOL (L = H, D) just before the equilibrations (Ref. 24).

Equilibration experiments. Equilibrations were performed as described in Refs. 24 and 25. In the equilibration of $CHClBr_2$, the concentration of catalyst was 0.006 mol dm^{-3}, the volume of catalyst–water solution 40 cm^3, the amount of $CHClBr_2$ 0.0012 mol and the time of equilibration 1.5 h. In the equilibrations of 1-phenyl-1-propanone and 2-methyl-1-phenyl-1-propanone, the concentration of catalyst was 0.5 mol dm^{-3}, the volume of catalyst–water solution 40 cm^3, the amount of $C_6H_5COCH_2CH_3$ 0.0015 mol, the amount of $C_6H_5COCH(CH_3)_2$ 0.0020 mol, and the times of equilibration were 25 h and 120 h for $C_6H_5COCH_2CH_3$ and $C_6H_5COCH(CH_3)_2$, respectively. The deuterium content of the equilibrated chlorodibromomethane was determined by IR measurements, and the deuterium content of equilibrated ketones by NMR measurements.

Table 3. Mole ratios of deuterium and protium in 1-phenyl-1-propanone (SH_2) equilibrated in different H_2O–D_2O mixtures and the experimental fractionation factors φ' (SH_2) at 298.15 K.

$x(D;L_2O)^a$	$\frac{n(D;SL_2)}{n(H;SL_2)}$	$\varphi'(SH_2)^{b,c}$
0.104	0.1214(79)	1.046(68)
0.148	0.187(13)	1.079(74)
0.200	0.2430(37)	0.972(15)
0.302	0.397(16)	0.917(37)
0.403	0.704(15)	1.043(23)
0.431	0.711(23)	0.939(30)
0.503	0.984(5)	0.973(5)
0.603	1.536(23)	1.011(15)
0.704	2.35(4)	0.986(17)
0.717	2.38(3)	0.940(12)
0.807	4.04(2)	0.967(4)
0.903	8.51(31)	0.922(33)

[a] $x(D;L_2O)$ is the deuterium isotope mole fraction of water.
[b] Mean values of 4 determinations with standard errors of mean.
[c] $\varphi'(SH_2) = \frac{n(D;S_2)}{n(H;SL_2)} / \frac{x(D;L_2O)}{1 - x(D;L_2O)}$.

IR measurements. The measurements were made with a Perkin-Elmer Model 180 IR spectrophotometer in the manner described in Ref. 24. The characteristic absorption peaks used in the analysis were those arising from the C–H and C–D deformation vibrations of chlorodibromethane, and were at wavenumbers 1185, 1138, 883 and 846 cm^{-1}. The results for the equilibrations of chlorodibromomethane are listed in Table 1.

NMR measurements. The measurements were made with a Jeol GX-400 spectrometer. In the equilibrations of $C_6H_5COCH(CH_3)_2$ and $C_6H_5COCH_2CH_3$, the hydrogens of methyl and phenyl groups remained unchanged under the conditions used in the experiments. The peaks due to the protons of the methyl groups served as internal standard in the measurements. The positions of the NMR peaks used in the measurements were $\delta(CH) = 3.47$ ppm and $\delta(CH_3)_2 = 1.18$ ppm for $C_6H_5COCH(CH_3)_2$, and $\delta(CH_2) = 2.94$ ppm and $\delta(CH_3) = 1.18$ ppm for $C_6H_5COCH_2CH_3$. The integral from undeuteriated ketones was recorded before the integrals of the equilibrated substrates. The results for these equilibrations are listed in Tables 2 and 3.

Discussion

The fractionation factor for a substrate SH_m in the H_2O–D_2O solvent system is defined as the equilibrium constant for the isotope exchange reaction (1) between SH_m and D_2O.

$$1/m\ SH_m + 1/2\ D_2O = 1/m\ SD_m + 1/2\ H_2O \qquad (1)$$

The experimental fractionation factor $\varphi'(SH_m)$ is defined by eqn. (2), in which L = H, D.

$$\varphi'(SH_m) = \frac{n(D;SL_m)}{n(H;SL_m)} : \frac{n(D;L_2O)}{n(H;L_2O)} = \frac{n(D;SL_m)}{n(H;SL_m)} \cdot \frac{1 - x(D;L_2O)}{x(D;L_2O)} \qquad (2)$$

Because of the deviations from the rule of the geometric mean (RGM) in the isotope disproportionation equilibrium for water molecules, the experimental fractionation factor is not constant but depends on the isotopic composition of the solvent water. This dependence is largest for substrates

Table 4. Fractionation factors at 298.15 K for hydrogen bound to an sp^3 hybridized carbon.

Compound	φ	Reference
$(CH_3)_3CCOCH_3$	0.840(6)	26
$C_6H_5COCH_3$	0.908(5)	27
$C_6H_5COCH_2CH_3$	0.984(12)	This work
$C_6H_5COCH(CH_3)_2$	1.040(7)	This work
$C_6H_5COCH_2(OCH_3)$	1.045(15)	25
$CHBr_3$	1.041(3)	24
$CHBr_2Cl$	1.052(5)	This work
$CHBrCl_2$	1.083(9)	24
$CHCl_3$	1.107(7)	24

containing only one exchangeable hydrogen. For substrate molecules with more than a single hydrogen attached to carbon, the similar deviations from the RGM in the disproportionation equilibria for substrate molecules and water molecules partly cancel each other. The experimental fractionation factors for substrates of type SH [$CHClBr_2$ and $C_6H_5COCH(CH_3)_2$] from Tables 1 and 2 are corrected to give real fractionation factors in the manner described in Ref. 24. For $C_6H_5COCH_2CH_3$ (type SH_2), the real fractionation factor is obtained from the experimental fractionation factors of Table 3 as described in Ref. 25. The values are listed in Table 4 together with those from previous work.[24-27] Taking a glance at Table 4 it can be seen that in the homologous series of methyl-substituted phenyl ketones the value of the fractionation factor increases in the order $ArCOCH_3 < ArCOCH_2CH_3 < ArCOCH(CH_3)_2$, suggesting that fractionation factors parallel the extent of substitution (primary carbon < secondary carbon < tertiary carbon). The nature of the substituent is also significant, as seen by comparison of the fractionation factors for methoxy- and methyl-substituted phenyl ketone homologues $ArCOCH_2(OCH_3)$ and $ArCOCH_2CH_3$. In Table 4, the fractionation factor for $(CH_3)_3CCOCH_3$, a compound with the exchangeable hydrogens attached to a primary carbon, is the smallest, while fractionation factors for trihalomethanes, compounds with the exchangeable hydrogen bound to a tertiary carbon, are the largest, the values being in agreement with the order mentioned above. In the homologous series of trihalomethanes, the values of the fractionation factors seem to parallel the electronegativity of the substituent. The few general trends suggested by the experimental data from Table 4 agree well with the conclusions from the theoretical calculations carried out by Shiner.[29]

It has been proposed[30] that a fractionation factor for any compound with the exchangeable hydrogens bound to a sp^3 hybridized carbon may be written as in eqn. (3) as a product of the fractionation factor for methane, $\varphi(CH_4)$, and substituent constants s_i for attached groups. The substituent constant s is defined as the ratio of the fractionation factors for R_2CHX and R_2CH_2 [eqn. (4)].

$$\varphi = \varphi(CH_4)\,\Pi s_i \qquad (3)$$

$$s = \frac{\varphi(R_2CHX)}{\varphi(R_2CH_2)} \qquad (4)$$

To be able to apply eqn. (3) the value of 0.797 has been assigned for the fractionation factor of methane on the basis of the theoretical value calculated by Shiner[29] after converting it to a value in liquid water.[30] Using eqn. (3) and the fractionation factors from Table 4, the substituent constants s_i listed in Table 5 are obtained.

In Table 5, the values $s(CH_3) = 1.070$ and $s(C_6H_5CO) = 1.149$ are the means of three values obtained for the three different couples of solutions given by the three pairs of equations obtained by using the fractionation factors for $C_6H_5COCH_3$, $C_6H_5COCH_2CH_3$ and $C_6H_5COCH(CH_3)_2$. Similarly, the substituent constants $s(Cl)$ and $s(Br)$ are the means of six s_i values for the six couples of solutions for the six possible pairs of equations obtained by using $\varphi(CHCl_3)$, $\varphi(CHCl_2Br)$, $\varphi(CHClBr_2)$ and $\varphi(CHBr_3)$. For $s(CH_3)$ a value of 1.092 can be calculated from the data based on vibrational analysis of simple organic molecules.[29] Theoretical values for $s(Cl)$ and $s(Br)$ are 1.128 and 1.090, respectively, from Shiner's data for CH_3Cl and CH_3Br.[29]

In evaluating the experimental substituent constants, the effects caused by different substituents have been assumed to be independent of each other, and consequently the substituent effects exerted by certain atoms or groups are assumed to be cumulative. This assumption is of particular importance from a practical point of view, because it extends the utility of the substituent scale when evaluating values for fractionation factors or predicting isotope effects. The present experimental data are not comprehensive enough for many-sided testing of the validity of this assumption. There are, however, some facts that might be regarded as an indication of cumulative behaviour. In the homologous series of methyl-substituted phenyl ketones, using the fractionation factors for $ArCOCH_3$ and $ArCOCH_2CH_3$ (in which case no assumption of cumulativity is needed), a value of 1.084 was obtained for $s(CH_3)$. From the fractionation factors for $ArCOCH_3$ and $ArCOCH(CH_3)_2$, assuming the methyl effect to be cumulative, practically the same value (1.070), was obtained for $s(CH_3)$. Considering then the homologous series of trihalo-

Table 5. Substituent effects on fractionation factors for hydrogen bound to a saturated carbon.

Substituent X	$s = \varphi(R_2CHX)/\varphi(R_2CH_2)$
H	1.0
$(CH_3)_3CCO$	1.054
CH_3	1.070[a]
Br	1.091[b]
Cl	1.115[b]
C_6H_5CO	1.149[a]
OCH_3	1.151

[a]Mean of three values. See text. [b]Mean of six values. See text.

methanes and using the theoretical substituent constants $s(Cl)_{theor.} = 1.128$ and $s(Br)_{theor.} = 1.090$ from Shiner's data for CH_3Cl and CH_3Br, values of 1.144, 1.105, 1.068 and 1.032 can be calculated for the fractionation factors of $CHCl_3$, $CHCl_2Br$, $CHClBr_2$ and $CHBr_3$, respectively, assuming the effect of chlorine and bromine to be cumulative. These values are in fairly good agreement with the experimental fractionation factors of 1.107(7) for $CHCl_3$, 1.083(9) for $CHCl_2Br$, 1.052(5) for $CHClBr_2$ and 1.041(3) for $CHBr_3$.

Symons and Bonnett[28] have determined a value of 1.287 for the fractionation factor of trifluoromethane at 298.15 K. This agrees well with the value of 1.296 obtained from Shiner's data[29] for CH_3F assuming a cumulative fluorine effect.

The vibrational analysis data for CHX_3 allow direct calculation of the fractionation factor for $CHCl_3$, $CHBr_3$ and CHF_3.[29] After conversion to values in liquid water the following values are obtained: $\varphi(CHCl_3)_{theor.} = 1.059$, $\varphi(CHBr_3)_{theor.} = 0.970$ and $\varphi(CHF_3)_{theor.} = 1.275$. Comparison of these "direct" theoretical fractionation factors with those obtained from data for CH_3X assuming cumulative substituent effects [$\varphi(CHCl_3)_{cumul.} = 1.144$, $\varphi(CHBr_3)_{cumul.} = 1.032$ and $\varphi(CHF_3)_{cumul.} = 1.296$] shows that the theoretical calculations do not support cumulative chlorine or bromine effects, whereas these calculations suggest the fluorine effect to be cumulative. Because of this discrepancy and the lack of sufficient experimental data for testing the effects of various substituents, some caution may be necessary concerning the assumption of cumulativity in all cases.

Substituent effects are, as a rule, independent of remote groups present in the molecule.[29] However, if the groups are very different in nature, as are for instance $(CH_3)_3C$ and C_6H_5 attached to a carbonyl carbon adjacent to the carbon bearing the isotopic hydrogen, they may cause markedly different substituent effects (Table 5).

The substituent effect of an OR group has been thought to be possibly larger than the effect of an OH group [$s(OH) = 1.18$].[30] On the basis of the present data a value of 1.15 was calculated for $s(OCH_3)$, suggesting that alkoxy and hydroxy effects are nearly the same.

The list of substituent constants based on experimental work is still very limited because the number of precise fractionation factor measurements is very small. Additional measurements would be needed for applying and testing the substituent effect approach and for creating a substituent scale of fractionation factors.

Acknowledgement. I am grateful to Dr. Jorma Mattinen for operating the Jeol GX-400 spectrometer.

References

1. Gross, P., Steiner, H. and Krauss, F. *Trans. Faraday Soc. 32* (1936) 877.
2. Hornell, J. C. and Butler, J. A. V. *J. Chem. Soc.* (1936) 1361.
3. Gold, V. *Trans. Faraday Soc. 56* (1960) 255.
4. Kresge, A. J. *Pure Appl. Chem. 8* (1964) 243.
5. Salomaa, P., Schaleger, L. L. and Long, F. A. *J. Am. Chem. Soc. 86* (1964) 1.
6. Gold, V. *Trans. Faraday Soc. 64* (1968) 2770.
7. Gold, V. *Adv. Phys. Org. Chem. 7* (1969) 259.
8. Salomaa, P. *Acta Chem. Scand. 23* (1969) 2095.
9. Albery, W. J. and Davies, M. H. *Trans. Faraday Soc. 65* (1969) 1059.
10. Laughton, P. M. and Robertson, R. E. In: Coetzee, J. F. and Ritchie, C. D., Eds., *Solute-Solvent Interactions,* Marcel Dekker, New York 1969, p. 399.
11. Schowen, R. L. In: Streitwieser, A., Jr. and Taft, R. W., Eds., *Progress in Physical Organic Chemistry,* Wiley-Interscience, New York 1972, Vol. 9, p. 275.
12. Albery, W. J. In: Caldin, E. F. and Gold, V., Eds., *Proton-Transfer Reactions,* Chapman & Hall, London 1975, p. 263.
13. Melander, L. and Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules,* Wiley-Interscience, New York 1980, p. 202.
14. Schowen, K. B. J. and Schowen, R. L. *Methods Enzymol. 87* (1982) 551.
15. Cleland, W. W. *Methods Enzymol. 64* (1980) 104.
16. Cook, P. F., Blanchard, J. S. and Cleland, W. W. *Biochemistry 19* (1980) 4853.
17. Pyper, J. W. and Long, F. A. *J. Chem. Phys. 41* (1964) 1890.
18. Goodall, D. M. and Long, F. A. *J. Am. Chem. Soc. 86* (1968) 238.
19. Kresge, A. J. and Chiang, Y. *J. Chem. Phys. 49* (1968) 1439.
20. Albery, W. J. and Davies, M. H. *Trans. Faraday Soc. 65* (1969) 1066.
21. Dahlberg, D. B. and Long, F. A. *J. Am. Chem. Soc. 95* (1973) 3825.
22. Meloche, H. P., Monti, C. T. and Cleland, W. W. *Biochim. Biophys. Acta 480* (1977) 517.
23. Pyper, J. W. and Liu, D. K. *J. Chem. Phys. 67* (1977) 845.
24. Scharlin, P. *Acta Chem. Scand., Ser. A 36* (1982) 117.
25. Scharlin, P. *Acta Chem. Scand., Ser. A 38* (1984) 529.
26. Scharlin, P. *Acta Chem. Scand., Ser. A 40* (1986) 221.
27. Scharlin, P. *Acta Chem. Scand., Ser. A 40* (1986) 441.
28. Symons, E. A. and Bonnett, J. D. *J. Phys. Chem. 88* (1984) 866.
29. Hartshorn, S. R. and Shiner, V. J., Jr. *J. Am. Chem. Soc. 94* (1972) 9002.
30. Kresge, A. J., More O'Ferrall, R. A. and Powell, M. F. In: Buncel, E. and Lee, C. C., Eds., *Isotopes in Organic Chemistry. Vol. 7. Secondary and Solvent Isotope Effects,* Elsevier, Amsterdam 1987, Chap. 4, p. 177.

Received July 27, 1988.