

Calculation of Equilibrium Isotope Effects in a Conformationally Mobile Carbocation

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Dedicated to Jacob Bigeleisen on the occasion of his 70th birthday

The rapid, degenerate 1,2-hydride shift in 2,3-dimethyl-2-butyl cation in stable solution in $\text{SbF}_5/\text{SO}_2\text{ClF}$ was perturbed by deuterium and ^{13}C leading to splittings observed by ^{13}C NMR spectroscopy over a range of temperatures. Accurate values for equilibrium isotope effects were obtained from these data. Theoretical calculations of the equilibrium isotope effects were performed using the Gaussian-86 program to obtain an optimized geometry and the Cartesian force constant matrix, followed by the program QUIVER which applies the Bigeleisen-Mayer method. When all of the conformers, which are in rapid equilibrium, were considered specifically, quite good agreement between theory and experiment was obtained.

Introduction

The use of isotopes has had important effects on chemistry, physics, biology and geology. Not only have isotopes been of enormous value in their use as tracers in all these sciences, but the observation of kinetic and equilibrium isotope effects has provided a wealth of additional valuable information. The question why and how isotopes produce changes in rates and equilibrium constants, while initially mainly of interest for separating isotopes, has led to theoretical methods for predicting and evaluating isotope effects which have, in turn, permitted quantitative comparison of experimental results with theoretical predictions based on competing models under consideration. We dedicate this article to Jacob Bigeleisen, who has provided powerful tools for theoretical evaluation of isotope effects, on the occasion of his 70th birthday.

One of the areas of physical-organic chemistry which has been greatly affected by the use of isotopes is the study of carbocations. Kinetic isotope effects on rates of solvolysis have yielded much valuable information [1], but recently isotope effects on equilibrium constants have come under examination. The preparation of stable solutions of these ions [2] and the study of the perturbation of rapid, degenerate equi-

libria by the introduction of isotopes through NMR spectroscopy has provided highly accurate data in this area [3].

We have recently begun to calculate these equilibrium isotope effects in order to compare them with the experiments. We hope to discover how well the results agree, so as to probe the limitations of the theoretical methods. With this knowledge, we hope to be able to use the experiments and calculations to gain new information about several long-studied but still fascinating novel carbocations.

The method we are using for the calculation of equilibrium isotope effects involves two steps. We first use an *ab initio* quantum mechanics program package to obtain the lowest energy predicted structure and the corresponding Cartesian force constant matrix for the motion of atoms. We then use a program (QUIVER) [4] based on the Bigeleisen-Mayer method [5] to predict the equilibrium isotope effect at any temperature. It should be pointed out that for carbocations there are no experimental vibration frequencies, nor can they be approximated from known frequencies in close analogs.

We report here calculations and experiments on the 2,3-dimethyl-2-butyl cation. Study of this ion was begun some time ago. It was the first ion in which a (secondary) deuterium equilibrium isotope effect perturbing a rapid degenerate process (Scheme 1) was detected [6]. In the absence of an isotope effect, the

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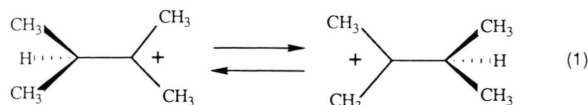
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equilibrium constant for this reaction is unity; but breaking the symmetry by putting a deuterium on a methyl shifts the equilibrium.



Scheme 1

Measurements have been made of the barrier for this process through study of line broadening in the ^{13}C NMR (abbreviated CMR) spectrum at low temperature [7]. A (primary) ^{13}C equilibrium isotope effect has also been obtained for this ion [8] from CMR spectra of mixtures of di- ^{13}C labelled and mono-labelled ion. From this earlier work, it is known that the ion has a classical rather than a bridged structure and that it is undergoing very rapid hydride shifts of the methine and rapid rotations around all the single bonds to give sharp peaks in the CMR spectrum from 140 K up. The chemical shift difference between the two central carbons, Δ , in the absence of exchange was found to be 276 ppm [9]. The isotope-induced splitting, δ , in the experimental spectrum is proportional to Δ , and it can be measured accurately over a range of temperatures. From these data, accurate values can be obtained for the equilibrium isotope effect.

Theoretical Calculations

Calculations on the ion using the Gaussian-86 package [10] were carried out at the 3-21G and 6-31G* levels. Symmetry was initially imposed, but it was discovered that relaxation of this restraint led to refinement to unsymmetrical lower energy structures at both levels. The geometry is shown in Figure 1. It was noticed that in both minimum-energy structures, C–H bonds on the methyls adjacent to the positively charged carbon parallel to the empty p -orbital were noticeably longer than other C–H bonds. The C–C bond of the isopropyl group of the ion which was parallel to the p -orbital was lengthened in a similar manner. These changes are just what would be predicted by the qualitative concept of hyperconjugation. The analytical Cartesian force constant matrix for the ion was obtained at the 3-21G level and using it, the program QUIVER [4] was employed to calculate the normal-mode vibration frequencies and from them predict equilibrium isotope effects using the rigid-rotor harmonic-oscillator approximation.

An important consideration concerns how the conformational flexibility is treated. Since this ion has no symmetry, all twelve methyl hydrogens are different. QUIVER was used to calculate the reduced isotopic partition function ratio $(s_2/s_1)f$, with respect to the all-protio ion, for each conformer of the monodeutero isotopomer separately (Table 1). Since, the equilibrium population of each conformer is proportional to $(s_2/s_1)f$, these data can be normalized to a total sum of unity to predict the fractional populations of the individual conformers. Notice that the conformers with deuterium at positions 15 and 19 with C–D parallel to the empty p -orbital are strongly disfavored, but that conformers with deuterium at positions 14 and 18 (C–D bonds almost orthogonal to the p -orbital) are the most favored. Since it is known that rotations of each methyl group and also rotations around the central C–C bond are fast enough to produce sharp peaks in the CMR spectrum, the equilibrium constant for the hydride shift of the methine C–H could be predicted by adding the six values for $(s_2/s_1)f$ (or the normalized populations) with the deuterium on one side the molecule and dividing by the sum of the six values for deuterium on the other side.

An additional point must be considered before comparing the theoretical values with the experimental data. In order to measure the equilibrium constant with high accuracy, we observed the CMR spectrum because the chemical shift differences are very much greater than differences in the proton spectrum. The molecules we actually observe, therefore, have at least one ^{13}C at C_1/C_2 . If both of the inside carbons were labelled with ^{13}C , there would be no carbon isotope effect on the equilibrium constant; but we certainly did not want to have to synthesize the di- ^{13}C , deuterated ion. We therefore examined ions which were subject to a ^{13}C equilibrium isotope effect as well as the deuterium isotope effect.

In our calculations, we have therefore considered structures containing one ^{13}C at either the methine or cationic position in addition to deuterium. QUIVER was used to calculate $(s_2/s_1)f$ for these 24 conformers, each relative to the all protio, all ^{12}C ion. Calculations were also performed for the 12 di- ^{13}C monodeutero conformers. The equilibrium constant for the mono- ^{13}C ion was then predicted by taking the sum of the 12 $(s_2/s_1)f$ values for conformers where deuterium is on methyl groups adjacent to the methine carbon and dividing by the sum of the 12 values from calculations where deuterium is on methyl groups adjacent to the

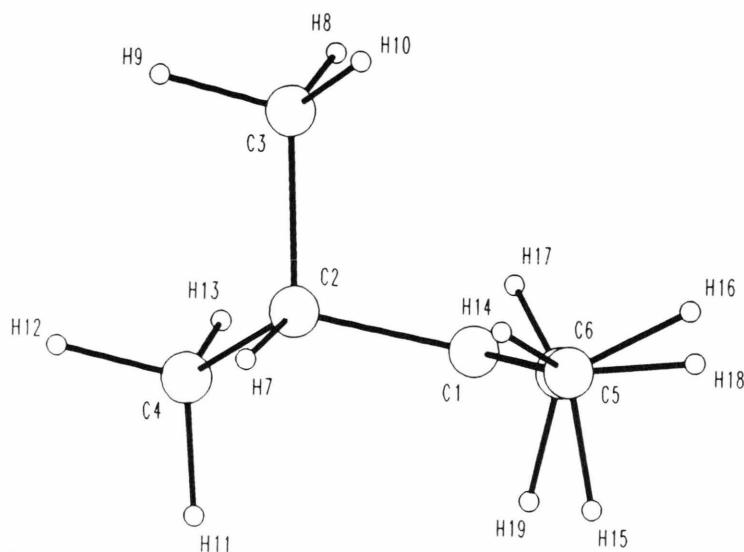


Fig. 1

Table 1. Calculated Deuterium Equilibrium Isotope Effects at 162.55 K.

Site of $^2\text{H}^a$	$(s_2/s_1)f^b$	Conformer Population
8	0.3393	0.0907
9	0.3211	0.0858
10	0.3371	0.0901
11	0.3289	0.0879
12	0.3371	0.0901
13	0.3392	0.0907
14	0.3640	0.0973
15	0.2175	0.0581
16	0.2833	0.0757
17	0.2905	0.0776
18	0.3627	0.0969
19	0.2214	0.0562

^a Refer to structure 1.^b These have been multiplied by 10^{-3} . All have ^{13}C at the cationic and methine carbons and are referenced to the all protio cation with two ^{13}C 's.

cationic carbon. Equilibrium constants for the di- ^{13}C and di- ^{12}C ions were also obtained. From its equilibrium constant, values could be predicted for the CMR shifts in the deuterated di- ^{13}C ion. The predicted values for both CMR peaks in the mono- ^{13}C were found to be shifted downfield, relative to those in the di- ^{13}C ion, due to the ^{13}C equilibrium isotope effect but (almost exactly) to the same extent. In addition, we found that calculated values for the equilibrium constants in the two deuterated isotopomers (with the cationic and methine carbons either both ^{12}C or both ^{13}C) where there is no carbon equilibrium isotope effect were almost the same. We conclude that the carbon and deuterium isotope effects are very close to additive, as expected, in this carbocation.

Calculation of the ^{13}C equilibrium isotope effect is quite simple. Only two isotopomers need to be considered, one with ^{13}C at the methine carbon, the other with ^{13}C at the cationic center. These interchanged by the rapid hydride shift between the two centers. The ratio of the reduced isotopic partition function ratios gives the equilibrium isotope effect. The difference between the peaks of the mono- ^{13}C and the di- ^{13}C ions δ is predicted to be: $\Delta(K_{\text{eq}} - 1)/2(K_{\text{eq}} + 1)$ where Δ is the known [9] difference between the CMR shifts of the methine and carbocation carbons in the absence of exchange.

Results and Discussion

The cation precursor, 2,3-dimethyl-2-butanol, was synthesized by the reaction of deuterated Grignard reagent with isopropyl methyl ketone. The single peak for the degenerately equilibrating cation/methine carbons in the all-protio ion in the downfield region of the CMR spectrum is symmetrically split in the deuterated ion. Earlier studies have established that substitution of deuterium on a methyl group of this carbocation shifts the equilibrium to favor deuterium away from the positive charge [6, 7]. Therefore, the signal shifted upfield corresponds to isotopomers with the observed ^{13}C adjacent to the deuterated methyl, and the signal shifted downfield corresponds to the ^{13}C away from the deuterated methyl.

The ^{13}C equilibrium isotope effect described above was determined by measurements on a sample initially di- ^{13}C labelled on two methyl groups which was diluted with non-isotopically enriched precursor. This sample had a strong CMR peak in the methyl region but, initially, showed only one weak peak in the methine-cation (downfield) region which was assigned to the naturally abundant isotopomer with one ^{13}C interchanging rapidly between methine and cationic sites. This downfield peak is shifted from the exact average of the methine and cationic carbon shifts by a ^{13}C

Table 2. Experimental and Theoretical Equilibrium Isotope Effects.

Iso-topomer	Temp. (K)	K_{eq}		δ^a (Hz)	
		Experimental ^b	Calculated ^c	Experimental	Calculated
1- ² H	162.55	1.1778	1.152	1415.38	1221.00
	167.55	1.1712	1.147	1367.12	1183.00
	172.55	1.1656	1.142	1325.65	1149.00
	182.55	1.1529	1.133	1230.88	1084.00
	188.85	1.1485	1.128	1198.60	1046.00
	194.85	1.1439	1.124	1163.53	1013.00
	202.25	1.1364	1.119	1106.53	974.00
	206.05	1.1321	1.117	1073.74	955.00
1- ¹³ C	164.75	1.0163	1.0162	69.89	69.72
	172.55	1.0152	1.0154	65.51	66.03
	175.95	1.0153	1.0150	65.75	64.52
	184.05	1.0137	1.0142	59.00	61.14
	192.45	1.0135	1.0135	58.33	57.92
	207.35	1.0123	1.0123	52.83	52.80
	211.15	1.0121	1.0120	52.16	51.60
	212.45	1.0117	1.0119	50.44	51.19

^a δ is that for equilibrating cation/methine carbons, recorded or calculated for field strength of 62.8 MHz.

^b Evaluated as $(\Delta + \delta)/(\Delta - \delta)$ for the deuterium equilibrium isotope effect, and as $(\Delta + 2\delta)/(\Delta - 2\delta)$ for the ¹³C equilibrium isotope effect. $\Delta = 276$ ppm.

^c Equilibrium isotope effect calculated using program QUIVER. All deuterium isotopomers have ¹³C at the center two carbons.

equilibrium isotope effect. In order to measure how much it is moved, the sample was warmed so as to scramble the carbons. Reversible rearrangement to the other two isomeric tertiary hexyl carbocations occurs, and this eventually yields a mixture of all possible dilabelled ¹³C isotopomers of [2-¹³C]-2,3-dimethyl-2-butyl cation. Additional peaks grew in the downfield region of the spectrum. One of these peaks corresponded very closely in position to the peak of the isotopomer with two ¹³C's in the center which had previously been studied [8]. This isotopomer is unaffected by any isotope effect and serves as a reference for measurement of the shift of the naturally abundant mono-¹³C ion.

Experimentally and theoretically determined values for deuterium and ¹³C equilibrium isotope effects are collected in Table 2. The values are determined independently; no experimental parameters are used in the theoretical calculations and vice versa. Plots of the logs of the experimental and theoretical equilibrium isotope effects versus $1/T$ are linear and yield an experimental ΔH of 58.9 ± 1.3 cal/mole and a theoretical

ΔH of 47.4 cal/mole for the deuterium equilibrium isotope effect. The ¹³C equilibrium isotope effect has an experimental ΔH of 6.3 ± 0.4 cal/mole and a theoretical ΔH of 6.2 cal/mole. All values of ΔS are negative but very small.

The overall agreement between experimental and theoretical results is quite good for the deuterated ion but very much better for carbon, where the values determined experimentally are almost exactly those predicted theoretically. This may well be because the predicted deuterium isotope effect depends closely on the hyperconjugative distortion of the C–H bonds and the associated force constants, and the level of the quantum mechanics calculations may not be high enough to reproduce these features of the real ion accurately enough. In particular, small changes in the dihedral angles might change the calculated isotope effect. The force field involving the motion of the two center carbons does not seem likely to be as sensitive. We hope to extend these calculations to higher quantum mechanics levels to see if the agreement with the deuterium isotope effect improves. The experimental and theoretical results presented here have shown that current theory can predict isotope effects very closely without the use of experimental data. Comparison between experimental and theoretical results can therefore be used with some confidence in interpreting and comparing the likelihood of alternative models of molecular structures and reaction mechanisms.

Experimental

2,3-Dimethyl-2-butanol (~50% deuteration in one methyl group)

Synthesized by the Grignard reaction of 3-methyl-2-butanone (1.20 g, Aldrich) and ~50% *d*-methyl iodide (2.30 g). (Partially deuterated methyl iodide is prepared by deuterium exchange of the trimethyloxosulfoniumiodide salt in 50:50 D₂O:H₂O with a catalytic amount of potassium carbonate. Pyrolysis yields deuterated methyl iodide and dimethylsulfoxide [11]). After workup and purification by preparative gas chromatography (6-ft SE-30 column, $T = 80^\circ\text{C}$), 2,3-dimethyl-2-butanol with 50% deuteration in one methyl group adjacent to C–OH is obtained (1.15 g, 73%). (Partially deuterated cation precursor was synthesized for further studies of additivity of equilibrium isotope effects.) Percent deuteration is determined by

^1H NMR of both methyl iodide and 2,3-dimethyl-2-butanol (^{13}C NMR: $\delta = 74.8, 38.6, 27.6, 17.8$ ppm).

2- $[^{13}\text{C}]$ -2,3-dimethyl-2-butanol

Synthesized as described above, except starting with ethyl isobutyrate (Aldrich) and ^{13}C -methyl iodide (Aldrich).

Cation Sample Preparation

Cation samples were prepared by ionization of the corresponding alcohol using the molecular beam apparatus described previously [2].

NMR Spectra

^{13}C NMR spectra were recorded on a Bruker WM-250 at 62.8 MHz. Cation samples were placed in a pre-cooled NMR probe following temperature calibration with 2-chlorobutane [7b]. Peak positions are referenced to external TMS in acetone- d_6 . Quadrature detection was used in all instances and the center frequency was set at 198 ppm. ^{13}C equilibrium isotope effects were evaluated after accumulating 4000 scans using a 20° pulse and a digital resolution of 0.6 Hz/pt (SW 5000 Hz, SI 16 K). Deuterium equilibrium isotope effects were evaluated after accumulating 16,000 scans using a 75° pulse and a digital resolution of 1.9 Hz/pt (SW 15,151 Hz, SI 16 K).

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