BEBOVIB model calculations of the isotope effects, the value is consistent with secondary β-deuterium and primary deuterium KIEs determined for the same reaction. The KIEs correspond to a bond order of around 0.7 for the forming N–H bond and a charge fraction of at least 0.3 localized on the carbon atom undergoing bond cleavage in the TS. These results are also consistent with the Brønsted coefficient of 0.79 determined for this reaction by using a series of structurally similar rigid tertiary amine bases including DABCO[26] (in the solvent DMSO), indicating a rather ion-pair intermediate-like TS.

The methyl group carbon KIE seems to be a promising complement to the secondary β-deuterium KIE in probing anionic hyperconjugation.

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Registry No. ^{11}C, 14333-33-6; ^{14}C, 14762-75-5; 1-methylindene, 767-59-9.

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Primary ^{11}C/^{14}C and Secondary ^{1}H/^{2}H Kinetic Isotope Effects in the S$_N$2 Reaction of Hydroxide Ion with Methyl Iodide. The Relationship between Different Carbon Isotope Effects

B. Svante Axelsson, Olle Matsson,* and Bengt Långström*

Contribution from the Department of Organic Chemistry, Institute of Chemistry, Uppsala University, P.O. Box 531, S-751 21 Uppsala, Sweden. *Received December 19, 1989*

Abstract: The short-lived radionuclide ^{11}C has been used in kinetic isotope effect (KIE) studies. The primary ^{11}C/^{14}C KIE for the reaction of hydroxide ion with labeled methyl iodide in 50% dioxane/water at 25 °C was determined to be 1.192 ± 0.001. A trend of progressively increasing KIE with mass difference is found when this value is compared to previously reported ^{12}C/^{13}C and ^{12}C/^{14}C KIEs. Simple theory predicts an almost linear relationship. The validity of the values of $r = \ln (k_{12}/k_{14})/\ln (k_{12}/k_{13})$ and $\ln (k_{11}/k_{14})/\ln (k_{12}/k_{14})$ obtained by a simple theoretical treatment is confirmed by BEBOVIB calculations of the KIEs. Transition-state (TS) models investigated were varied from reactant- to product-like and employed three different types of reaction coordinate movement in the TS: (A) the methyl group moving as one rigid mass unit in the decomposition mode; (B) the methyl hydrogens show Walden inversion the amount of which is independent of TS geometry; and (C) the Walden component is varied with TS geometry and most pronounced for the symmetric TS. The discrepancy between theory and experiment regarding the relation between different carbon KIEs is discussed, but no rationalization is given. The α-secondary ^{1}H/^{2}H KIE was determined to be 0.881 ± 0.012 and 0.896 ± 0.011 by using ^{11}C and ^{14}C as tracers in two double label experiments where k_H/k_D is calculated from the primary carbon KIE and the observed value of k_{11H}/k_{14D} or k_{11D}/k_{14H}, respectively. Comparison of experimental with theoretically calculated primary carbon and secondary deuterium KIEs shows the best agreement for reaction coordinate model C at a bond order between 0.1 and 0.3 for the forming C–O bond. The small discrepancy between the values of the secondary deuterium KIE is discussed in terms of tunneling.

Introduction

Kinetic isotope effects are powerful tools in the elucidation of organic and enzymatic reaction mechanisms.[1] Especially valuable information can be obtained by isotopic substitution at several positions of the reactants (successive labeling). The transition-state structure can, in favorable cases, be inferred by comparison of experimental results with those from model calculations.

Recently we reported on the first example of a ^{11}C/^{14}C kinetic isotope effect (KIE), determined for the methylation of *N*,*N*-dimethyl-*p*-toluidine.[2,3] The radionuclide ^{11}C is an accelerator produced short-lived positron emitter with a half-life of 20.34 min. The ^{11}C/^{14}C method[4] is a one-pot technique based on separation of the labeled reactant and product by HPLC and subsequent radioactivity measurements of the collected fractions by liquid scintillation counting. The combination of ^{11}C and ^{14}C in isotope effect studies might be fruitful since the largest feasible mass range of carbon isotopes is utilized, resulting in relatively large isotope effects.

Introducing the radionuclide ^{11}C makes four isotopes of carbon available for KIE determinations. At least three different carbon KIEs can thus be measured with reasonable precision. If the experimental values of these carbon KIEs (^{11}C/^{14}C, ^{12}C/^{14}C, and ^{12}C/^{13}C) were determined for the same reaction, it would be possible to test the theoretical predictions concerning relative strengths of different carbon KIEs.[5,6]

Isotope effects in the reaction of hydroxide ion with methyl iodide have been studied by Bender and Hoeg[7] who determined the ^{12}C/^{14}C KIE to be 1.088 ± 0.010 in 50% dioxane/water at 25 °C, and by Lynn and Yankwich[8] who determined the ^{12}C/^{13}C KIE to be 1.035 ± 0.006 in water at 31 °C. The latter value is smaller than expected from the ^{12}C/^{14}C KIE value using the simple theoretical model presented by Bigeleisen. It has been suggested that this deviation was caused by experimental errors or due to

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the fact that the KIEs were determined in different solvents.[9]

In this paper the rate constant ratio k_{11}/k_{14}, determined in both 98% water and 50% dioxane/water at 25 °C, is reported. The notation is according to

$$^{11}CH_3I + OH^- \xrightarrow{k_{11}} {}^{11}CH_3OH + I^-$$

$$^{14}CH_3I + OH^- \xrightarrow{k_{14}} {}^{14}CH_3OH + I^-$$

These results, in connection with the previously determined carbon KIEs, now make it possible to compare three different carbon isotope effects for a reaction in which the label is at the same position in the reactant.

Secondary deuterium isotope effects for the reaction of methyl iodide with several nucleophiles, including water,[10] have been reported in the literature. However, the value of the secondary deuterium isotope effect ($^1H/^2H$) for the reaction of hydroxide ion with methyl iodide has not, to our knowledge, been determined earlier. In the present paper the results from secondary deuterium KIE experiments for the title reaction in 50% dioxane/water at 25.00 °C are reported. The deuterium isotope effects were derived by using the $^{11}C/^{14}C$ KIE method in combination with deuterium-labeling. The isotopes ^{11}C and ^{14}C were used as tracers in the determination of k_{11D}/k_{14} and k_{11}/k_{14D}, according to the following notation where D is ^2H

$$^{11}CD_3I + OH^- \xrightarrow{k_{11D}} {}^{11}CD_3OH + I^-$$

$$^{14}CD_3I + OH^- \xrightarrow{k_{14D}} {}^{14}CD_3OH + I^-$$

Theoretical model calculations for the reaction have previously been performed on primary $^{12}C/^{13}C$ and $^{16}O/^{18}O$ KIEs and secondary $^1H/^2H$ KIEs.[11] Calculations of $^{12}C/^{13}C$ KIEs have also been published for the reaction of methyl iodide with iodide, cyanide, or chloride as the nucleophile.[12,13] In the present work results of semiclassical model calculations for the three different primary carbon isotope effects and the secondary hydrogen isotope efect, by using the BEBOVIB method,[14] are presented and discussed in relation to the experimental results.

Experimental Section

General Methods. The ^{11}C was obtained as [^{11}C]carbon dioxide in a lead-shielded trap, containing 4-Å molecular sieves, at the tandem van der Graaff accelerator at the University of Uppsala. All work with ^{11}C was performed behind lead shields.

A proportional regulating thermostat (HETO) was used with a regulating accuracy of ±0.005 °C. The temperature of the water in the thermostat was measured by a calibrated thermometer with an accuracy of ±0.01 °C. The temperature never deviated more than ±0.01 °C during a kinetic run. All glassware used in the kinetic experiments was cleaned in chromic acid and then rinsed with water, 2 M sodium hydroxide, 2 M hydrochloric acid, and distilled water. The glassware was dried at 130 °C overnight and then kept in a desiccator, over bluegel, under nitrogen gas atmosphere. The syringes were washed with ethanol, 2 M sodium hydroxide, 2 M hydrochloric acid, distilled water, ethanol, and finally with ether, dried with a hot-air blower, and before use repeatedly rinsed with the solvent to be used.

HPLC analyses were performed on a Hewlett Packard 1084 HPLC with a diode array UV detector in series with a β^+-flow detector.[15] The HPLC was equipped with a fraction collector (Hewlett Packard 79825 A) slightly modified by removing the Teflon insert. The HPLC analyses were performed on a column, 200 × 4.6 mm, filled with Supelco ODS-1, 10 μm. The mobile phase was 0.05 M ammonium formate, pH 3.5/methanol, 50/50 (v/v), isocratic flow: 2.00 mL min^{-1}. The injection volume was varied from 3 to 20 μL. The wavelength of the UV detector was 254 nm with 430 nm as the reference. Fractions were collected in glass scintillation bottles containing 16 mL of scintillation liquid (Zinsser Quickszint 1).

The radioactivity counting was performed by using a liquid scintillation counter (LKB 1214). The energy window was set to 1–2000 keV (channel 5-1024) for the ^{11}C (E_{max} = 0.98 MeV) measurements and to 1–160 keV (channel 5-650) for the ^{14}C (E_{max} = 156 keV) measurements. The counting time was 1 min for the ^{11}C and 5–60 min for the ^{14}C measurements, depending on the amount of radioactivity in the fractions. A liquid scintillation quench curve was obtained by plotting quench parameter values versus counting efficiency values of ten calibration points. The calibration points were obtained by adding volumes of the HPLC mobile phase to a scintillation bottle containing a ^{14}C standard capsule (LKB, internal standard Kit for liquid scintillation counting, 117 000 DPM) and 16 mL of scintillation liquid. The total volume was chosen so that the quench parameter values of the standard bottle were close to the quench parameter values of the sample fractions from the kinetic experiments.

Materials. 1,4-Dioxane (Riedel-de Haën, spektranal) was freed from peroxides by passage through a column of aluminum oxide. The dioxane was further dried by passage through a 20 × 1 cm column of 3-Å, freshly activated, molecular sieves under nitrogen gas atmosphere. Tetrahydrofuran (THF) (Merck, p.a.) was freshly distilled from sodium/benzophenone under nitrogen gas atmosphere. Lithium aluminum hydride (LAH) (Merck, zur Synthese), 1-g tablets, purity >98%, was used without further purification. A solution of LAH in THF was prepared by cutting a tablet under nitrogen gas atmosphere; ca. 0.2 g of LAH was added to 10 mL of THF in a flask, the solution being ca. 1 M, and the flask was capped with a septum and kept under nitrogen gas atmosphere overnight. Lithium aluminum deuteride (LAD) (CIBA), powder, isotopic purity >99 atom % D, was used without further purification. An ca. 1 M solution of LAD was prepared by adding 0.2 g of the powder to 10 mL of THF. The flask was capped and stored under nitrogen gas atmosphere overnight. Hydriodic acid, concentrated, was distilled at atmosphere pressure, bp 126.5–127.5 °C. Methyl iodide (Merck, zur Synthese), purity >99.5% determined by capillary GC. [^{14}C]Methyl iodide, Amersham, 18.50 MBq, 2.07 GBq mmol^{-1}, liquid under vacuum, at delivery 98.8% pure, was dissolved in 2.4 mL of 1,4-dioxane, stored in a nitrogen-flushed septum capped vial, and kept over bluegel in the refrigerator. [^{14}C]Carbon dioxide, 37 MBq, 2.11 GBq mmol^{-1} (New England Nuclear), purity 99%, was used. HPLC solvents: 0.05 M ammonium formate buffer, pH 3.5, and methanol (FSA, HPLC grade).

[^{11}C]Methyl Iodide. The [^{11}C]carbon dioxide was used in the three-step synthesis of [^{11}C]methyl iodide.[16] Upon heating of the molecular sieves, the [^{11}C]carbon dioxide was released and transported in a stream of nitrogen gas to the reaction vessel in which it was trapped in 0.7 mL of 0.6 M LAH in THF. When most of the radioactivity had been transferred to the reaction vessel, the THF was evaporated, 2 mL of concentrated hydriodic acid, cooled to −20 °C, was added, and the mixture was heated to reflux. The [^{11}C]methyl iodide formed was distilled off in a nitrogen gas stream through a 1 × 10 cm drying tower of pulverized sodium hydroxide and phosphorus pentoxide (50/50) into a small septum-capped vial containing 0.6 mL of dry, cooled (~5 °C) 1,4-dioxane. For the water solvent system the methyl iodide was trapped in a vial containing 20 μL of THF, cooled to −72 °C.

[^{11}C-$^2H_3$]Methyl Iodide. The synthesis was performed as described for the [^{11}C]methyl iodide, with the exception that 0.7 mL of 0.5 M LAD in THF was used instead of LAH in the reduction step. The deuterium content of the [^{11}C-$^2H_3$]methyl iodide was analyzed by ^1H and ^2H NMR. A known amount of $CDCl_3$ (Aldrich, 99.8 atom % D) was added as an internal standard to the solutions.

[^{14}C-$^2H_3$]Methyl Iodide. The [^{14}C]carbon dioxide was delivered in a break-seal tube. The glass-joint connection part was rinsed with 2 M sodium hydroxide, 2 M hydrochloric acid, water, and THF. The tube was finally dried with a hot-air blower. A dry, Teflon-covered magnetic stir bar was used as a "magnetic hammer". It was carefully inserted in the tube, which was then capped with a septum. A nitrogen gas flow was maintained in the tube during heating. The tube was then allowed to cool to room temperature, and 1.0 mL of 0.5 M LAD in THF was added. The gas flow was stopped, and the breakseal was broken by lifting and then releasing the magnetic hammer by means of an external magnet. The solvent was rinsed around the inside of the tube, then removed via a syringe, and added to the special reaction vial used for the ^{11}C syntheses. Another 0.4 mL of 0.5 M LAD in THF was used to rinse the tube and then added to the reaction vial. Ca. 20 MBq of [^{11}C]carbon dioxide was added to the solution used as a tracer in the following steps of the synthesis. The THF was evaporated, 2 mL of concentrated hydriodic acid, cooled to −20 °C, was added, and the mixture was heated to reflux. The doubly labeled methyl iodides were distilled off in a stream

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of nitrogen gas through a drying tower to a tapering 1.5-mL vial containing 0.5 mL of THF, cooled to -72 °C. The [^{14}C]methyl iodide and [^{14}C-^{2}H$_3$]methyl iodide solutions were analyzed by HPLC and liquid scintillation counting, the mobile phase being 0.05 M ammonium formate, pH 3.5/methanol 60/40 (v/v). Each fraction was collected for 30 s in scintillation bottles containing 16 mL of scintillation liquid and was measured by liquid scintillation counting. The deuterium content of the [^{14}C-^{2}H$_3$]methyl iodide was analyzed by ^{1}H and ^{2}H NMR by using an internal standard as in the analysis of ^{11}C-labeled compound, see above.

Kinetic Procedure. In 50% Dioxane/Water. Kinetic isotope effect studies in 50% dioxane/water were performed as follows. The kinetic experiments were started within 10 min from the end of the synthesis of [^{11}C]methyl iodide. In a 1.8-mL septum-capped vial 500 μL of 1.6 M sodium hydroxide and 500 μL of dioxane were mixed and thermostatted at 25.00 °C. In another vial 380 μL of the ^{11}C-labeled methyl iodide solution was mixed with 400 μL of distilled water and 20 μL of the [^{14}C]methyl iodide solution in dioxane and was thermostatted. With a thermostatted syringe, 800 μL of the dioxane/sodium hydroxide solution was added, the solution was rapidly mixed, the kinetic clock was started, and the vial was replaced in the thermostat. At time intervals, the reaction vial was withdrawn from the thermostat, and samples were injected in the HPLC. The reaction vial was then quickly replaced in the thermostat. The reaction time was recorded at the moment of injection. Precautions were taken to prevent temperature changes during the reaction, e.g., the temperature was kept constant at 25 °C at the injector. To keep the temperature constant at the mixing of the reactant solutions the solvent composition of these was made equal to that of the final reaction solution. Fractions were collected according to the following: fraction 1, 0.75–2.75 min; fraction 2, 2.75–4.75 min. The ^{11}C radioactivity of the fractions was measured immediately, and in between every second sample was placed a sample of background measurements. The injection volume was increased during a kinetic run in steps of 2–3 μL from 3 to 20 μL as the ^{11}C radioactivity of the kinetic solution decreased.

In 98% Water. In a 1.8-mL septum-equipped vial 1.20 mL of 0.53 M sodium hydroxide was thermostatted at 25.00 °C. To the 20 μL of THF solution containing [^{11}C]methyl iodide were added 500 μL of water and 20 μL of [^{14}C]methyl iodide solution in dioxane. The mixture was thermostatted, and 400 μL of it was added to the sodium hydroxide solution via a thermostatted syringe. The mixture was rapidly mixed, the clock started, and the vial was replaced in the thermostat. The kinetic runs were then continued according to the experiments in 50% dioxane/water (see above).

A kinetic run was continued until the ^{11}C radioactivity had decayed to a limit of ca. 20 000 counts per minute (CPM) for the fraction containing the least radioactivity. When the ^{11}C radioactivity had decayed completely (usually the next day), the ^{14}C radioactivity content of the fraction bottles was measured. Background radiation was automatically subtracted from these fractions. The ^{11}C CPM values of the fractions were finally corrected for ^{14}C radioactivity, background, and decay.

Corrections of the ^{11}C CPM values were performed, using eq 1

$$Z = X - (Y + B) \qquad (1)$$

where B is the background value of the ^{11}C measurements, measured next to the sample, Y is the ^{14}C CPM value, X is the total CPM value, and Z is the ^{11}C CPM value. The half-life corrections were then made according to eq 2

$$\mathrm{CPM_{corr}} = Z/\{0.5 \exp(t/t_{1/2})\} \qquad (2)$$

where CPM$_{\mathrm{corr}}$ is the half-life corrected ^{11}C value, t is the elapsed time from start of the ^{11}C radioactivity measurements, in seconds, and $t_{1/2}$ is the ^{11}C half-life.

Theoretical Model Calculations. The program BEBOVIB-IV[17] was employed in the calculations. This program is based on the vibrational analysis program by Gwinn[18] and calculates the semiclassical KIE (k/k^*) as the product of the ratios of transition state (TS) to reactant contributions from molecular masses and moments of inertia (MMI), excited vibrational levels (EXC), and zero-point energies (ZPE):

$$k/k^* = (\mathrm{MMI}) \times (\mathrm{EXC}) \times (\mathrm{ZPE})$$

The simple Bell formulation[19] of tunnel correction for the computed KIE as provided in the program was used

$$k/k^*_{\mathrm{corr}} = k/k^*_{\mathrm{semiclass}}(u_{\mathrm{L}^\ddagger} \sin |u_{\mathrm{L}^\ddagger}{}^*/2|)/(u_{\mathrm{L}^\ddagger}{}^* \sin |u_{\mathrm{L}^\ddagger}/2|)$$

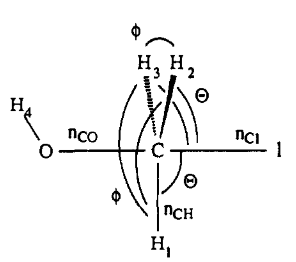

Figure 1. The TS structure for the reaction of hydroxide ions with methyl iodide. n$_{\mathrm{CI}}$ and n$_{\mathrm{CO}}$ are the bond orders for the leaving group (I$^-$) and nucleophile (OH$^-$) to the central carbon atom, respectively, and ϕ and Θ are bond angles.

Table I. Structural Parameters[a] and Force Constants[b] for Reactant and Transition-State Models

bond	reactant r_{i}	reactant F_{ii}	transition state r_{i}	transition state F_{ii}
C–I	2.139[c]	2.31[c]	2.139 – 0.3(ln n_{CI})	2.3 ln$_{\mathrm{CI}}$[c]
C–H$_{1,2,3}$	1.094[d]	4.97[d]	1.094[d]	4.97[c]
C–O			1.43[e] – 0.3(ln n_{CO})	5.80n_{CO}[f]
O–H			0.96[e]	7.80[f]

angle bend	reactant angle	reactant F_α	transition state angle	transition state F_α
I–C–H$_{1,2,3}$	109.47	0.54[g]	Θ	$g_\alpha(n_{\mathrm{CI}}n_{\mathrm{CH}})0.54$[g]
H$_{\mathrm{i}}$–C–H$_{\mathrm{j}}$	109.47	0.55[d]	ϕ	$g_\alpha(n_{\mathrm{CH}}n_{\mathrm{CH}})^{1/2}0.55$[d]
O–C–H$_{1,2,3}$			180 – Θ	$g_\alpha(n_{\mathrm{CO}}n_{\mathrm{CH}})0.75$[d]
H$_4$–O–C–H$_1$(tors)			180	0.072[d]

[a] The bond angles and distances are given in deg and Å, respectively. [b] Force constants are given in mdyn Å^{-1} (stretching) and mdyn Å rad^{-2} (bending and torsional). [c] Reference 12. [d] Reference 23. [e] Engdahl, K. A.; Bivehed, H.; Ahlberg, P.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 4767. [f] Saunders, W. H., Jr. *Chem. Ser.* **1975**, *8*, 27. [g] Herzberg, G. *Molecular Spectra and Molecular Structure II. Infrared and Raman Spectra of Polyatomic Molecules*; Van Nostrand Reinhold Company: 1945; p 193.

in which $u_{\mathrm{L}^\ddagger} = h\nu_{\mathrm{L}^\ddagger}/kT$, $\nu_{\mathrm{L}^\ddagger}$ being the imaginary frequency of decomposition. An account of the BEBO approach for construction of geometrical and force field models for calculation of KIE's has recently been published by Sims and Lewis.[14] Calculations were carried out on the BASF 7/68 at the computer center of the University of Uppsala.

Geometrical Model. A five-atom and a seven-atom full model were used for reactant and transition states, respectively. All bonds in the reactant model were assumed to be normal single bonds of order $n = 1$, and the geometry at C was assumed to be tetrahedral. The bond disances were standard values taken from the literature (see Table I).

For the transition-state models (see Figure 1), the bond orders of the three C–H bonds were kept at 1.0. The bond orders for the rupturing C–I and the forming C–O bonds (n_{CI} and n_{CO}, respectively) were varied between 1.0 and 0.0 under the assumption of conserved total bond order to C in the transition state models, i.e., $n_{\mathrm{CI}} + n_{\mathrm{CO}} = 1.0$. Bond lengths of the reacting bonds were adjusted by the program by using the usual revised[20] Pauling's equation[21]

$$r = r_0 - 0.3 \ln (n)$$

The angle Θ was given by

$$\Theta = 70.53 + 38.94 n_{\mathrm{CI}} \qquad (3)$$

The angle ϕ was related to Θ by

$$\phi = \cos^{-1} (1 - 1.5 \sin^2 \Theta) \qquad (4)$$

Equations 3 and 4 ensured that the expected hybridization changes with respect to geometry occurred (Walden inversion) in going from reactant to product.

Force Constants. A simple valence force field was used for both the reactant and the TS models except for the off-diagonal force constants (interaction force constants) required to generate the reaction coordinate frequency in the TS. The force constants of the reactant model were standard values taken from the literature (see Table I). The force con-

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stants of the TS model were calculated from the bond orders and the standard force constants through a set of empirical relations, in the customary way.[14] Standard stretching force constants (F_{ii}) for each bond (i) were modified according to eq 5, where n_i is the bond order.

$$F_{ii} = n_i F^{\circ}_{ii} \tag{5}$$

Angle bending force constants were governed by eq 6 or, in the case of the bending angles involving the C–O and C–I bonds, eq 7, which has been reported to be more suitable for bending motions where one of the bonds to the central atom is undergoing appreciable change from reactant to TS.[14] Here n_i and n_j are the bond orders of the bonds involved in the bending mode. The hybridization factor g_α is defined by eq 8, in which α is the bond angle. The force constant for the internal torsional coordinate H_1–C–O–H_4 was kept to its original value.

$$F_\alpha = g_\alpha (n_i n_j)^{1/2} F^{\circ}_\alpha \tag{6}$$

$$F_\alpha = g_\alpha (n_i n_j) F^{\circ}_\alpha \tag{7}$$

$$g_\alpha = 1.39 + 1.17 \cos \alpha \tag{8}$$

Reaction Coordinate Generation. An activated complex was stimulated by the use of off-diagonal elements in the force constant matrix to generate an imaginary frequency.[22] Three different reaction coordinate models were employed. In the simplest model A, the stretching coordinate for the breaking C–I bond (F_{CI}) was coupled to the stretching coordinate for the forming C–O bond (F_{CO}) according to eq 9:

$$F_{CI,CO} = a_{CI,CO}(F_{CI}F_{CO})^{1/2} \tag{9}$$

A value of $a_{CI,CO} = 1.1$, for all transition states, yielded a value of the curvature parameter $D = 1 - a^2$ of −0.21, corresponding to an imaginary frequency of 172i cm^{-1} for $n_{CI} = n_{CO} = 0.5$. A more pronounced Walden inversion was obtained in a model B where further interaction constants were used to couple the C–O stretching mode to each of the H–C–O bending modes and the C–I stretching mode to each of the H–C–I bending modes.[23] The same proportionality constant was used for all of these additional couplings ($a_{ij} = 0.3$). These interaction constants also have the effect of increasing the imaginary frequency to around 400i cm^{-1} for the symmetric TS. In the third reaction coordinate model C the values of the stretch–bend interaction constants were varied as a function of the principal reaction variable n_{CO} according to eq 10.[23] This produced the same Walden inversion as in model B for the symmetric TS but diminished the contribution of this motion for more reactant- or product-like transition states

$$a_{ij} = a_{ij}(1 - \Delta n)^2 \tag{10}$$

where $\Delta n = |n_{CI} - n_{CO}|$.

Results

$^{11}C/^{14}C$ KIE Experiments. The concentrations used in the reaction of hydroxide ion with methyl iodide were 0.3–0.5 mM with respect to methyl iodide and 0.4 M with respect to hydroxide ion. Thus, the hydroxide ion concentration was approximately 1000 times higher than that of the methyl iodide, making the hydrolysis a pseudo-first-order reaction. The rate constants of the ^{11}C and ^{14}C reactions were calculated as the slope of the line, when $-\ln(1 - f)$ was plotted versus reaction time (f is the fraction of reaction, calculated as $P/(R + P)$ where R and P are the CPM values of the reactant and product fractions, respectively). The KIE of the reaction was calculated as the ratio of the slopes for the reactions of the two isotopes or as the mean value of the KIEs in each point.

The results of four KIE experiments in 50% dioxane/water at 25.0 °C, two at 12.6 °C, and two experiments in 98% water at 25.0 °C are summarized in Table II. The k_{11}/k_{14} value of the experiments in 50% dioxane/water at 25 °C, calculated as the ratio of the ^{11}C and ^{14}C slopes, was 1.192 ± 0.001, $n = 5$ (the number of experiments). Calculated as the point KIE the k_{11}/k_{14} value was 1.189 ± 0.002, $n = 4$. At 12.6 °C the point KIE = 1.22 ± 0.03, $n = 10$ (standard deviation for the worst case). Only two determinations of the KIE at 12.6 °C were performed, and the larger standard deviation of the results probably originates from temperature changes at the moment of injection.

Table II. The results of Eight $^{11}C/^{14}C$ KIE Experiments of the Reaction of Hydroxide Ion with Methyl Iodide in 50% Dioxane/Water, at 25.0 °C and 12.6 °C, and in 98% Water at 25.0 °C

temp, °C	solvent % water	k_{11}/k_{14} slope ratio KIE[a] ± s[c]	k_{11}/k_{14} point KIE[b] ± s[d]
25.00	50	1.196 ± 0.008	1.194 ± 0.009
25.00	50	1.191 ± 0.013	1.184 ± 0.008
25.00	50	1.190 ± 0.014	1.191 ± 0.005
25.00	50	1.191 ± 0.012	1.186 ± 0.009
25.00	50	1.194 ± 0.038	*e*
12.60	50	*f*	1.22 ± 0.01
12.60	50	1.22 ± 0.08	1.22 ± 0.03
25.00	98	1.18 ± 0.02	1.16 ± 0.01
25.00	98	1.20 ± 0.04	1.18 ± 0.01

[a] Calculated as the ratio of the ^{11}C and ^{14}C slopes from the plots of $-\ln(1 - f)$ versus reaction time. [b] The mean value of the KIEs in each point. [c] The standard deviation of the k_{11}/k_{14} value, derived by the rules of propagation of error. The standard deviation of the slopes were calculated as $s^* = s_{y/x}/\{\sum(x_i - x)^2\}^{1/2}$ where x_i are the reaction times, x is their mean value, and s^* denotes the standard deviation of the ^{11}C and ^{14}C reaction slopes, and $s_{y/x} = \{[\sum(y_i - v_i)^2]/(n - 2)\}^{1/2}$ where y_i are the $-\ln(1 - f)$ values, v_i are the points on the calculated regression line, and n is the number of points. [d] The standard deviation of a sample of 10–20 point KIE. [e] No value because of no analyses of the reactant. [f] No value because of clock malfunction.

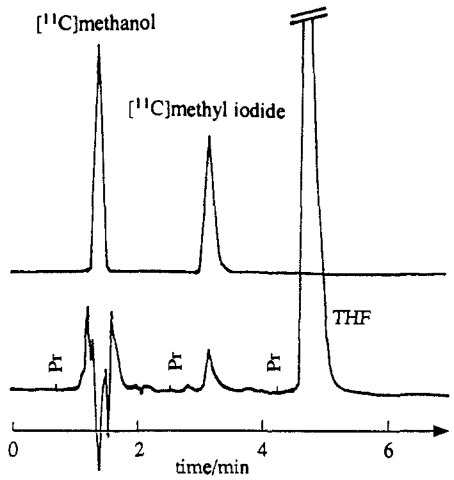

Figure 2. Radio-chromatogram (upper), and UV-chromatogram for the reaction mixture at approximately 50% reaction. The two peaks in the radio-chromatogram are [^{11}C]methanol and [^{11}C]methyl iodide, and the large peak in the UV-chromatogram is THF. Pr indicates the moment of fractionation changes.

A Representative KIE Experiment. The reactant solution containing both ^{11}C- and ^{14}C-labeled methyl iodide was first fractionated twice. Then at intervals of ca. 8 min (the time of a HPLC fractionation), the reaction vial was withdrawn from the thermostat, and a sample was injected and fractionated. In Figure 2 typical UV and radiochromatograms are shown for one reaction point of the reaction mixture.

Because of the large amount of data for each experiment, the results from only one, representative, experiment are presented, see Table III. The plot of $-\ln(1 - f)$ versus reaction time for this experiment is shown in Figure 3.

$^{1}H/^{2}H$ KIE Experiments. The results of the deuterium KIEs in 50% dioxane at 25 °C were $k_{11D}/k_{14} = 1.326 \pm 0.005$ ($n = 2$) and $k_{11}/k_{14D} = 1.051 \pm 0.006$ ($n = 2$). By using the k_{11}/k_{14} value (1.192 ± 0.001) the deuterium isotope effect was calculated, assuming that the multiplicative relationship is valid. From the experiment with deuterium substituted for hydrogen in the [^{11}C]methyl iodide the secondary KIE was derived by $k_H/k_D = (k_{11}/k_{14})/(k_{11D}/k_{14}) = 1.192/1.326 = 0.899 \pm 0.003$ ($n = 2$). For the experiment in which the deuterium was in the ^{14}C-labeled methyl iodide the $k_H/k_D = (k_{11}/k_{14D}/(k_{11}/k_{14}) = 1.051/1.192 = 0.882 \pm 0.005$ ($n = 2$). The k_H/k_D value is dependent on the deuterium content in the deuteriated methyl iodides and thus on

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(22) Reference 1, pp 64–67.
(23) Yamataka, H.; Ando, T. *J. Phys. Chem.* **1981**, *85*, 2281.

Table III. The Results from One Representative KIE Experiment for the Reaction of Hydroxide Ion with Methyl Iodide in 50% Dioxane/Water at 25 °C

		^{14}C			^{11}C			
no.	frac[a]	CPM[b]	quench SQP(E)[c]	$-\ln(1-f)$[d]	CPM[b]	ETIME[e]	CPM_{corr}[f]	$-\ln(1-f)$[d]
0	1	184.21	417.48	0.005302	4590.9	116	4189.39	0.001542
	2	34053.22	415.36		192244.8	5002	2714055	
0^2	1	185.02	414.30	0.005119	4905.3	208	4767.35	0.001841
	2	36053.22	416.28		179972.5	5090	2586840	
1	1	776.28	416.81	0.123655	154599.0	300	181834	0.144045
	2	5897.63	418.47		201555.1	3160	1173600	
2	1	1057.74	416.32	0.167301	201295.2	389	249159	0.197996
	2	5808.25	417.32		151256.4	3630	1137932	
3	1	1269.70	415.98	0.205677	147309.1	1252	296947	0.241531
	2	5560.17	416.36		137709.2	3719	1086932	
4	1	1466.28	416.44	0.244433	161380.4	1343	342098	0.286762
	2	5295.39	415.84		124029.8	3814	1030082	
5	1	5069.97	415.92	0.280768	44568.2	3901	386804	0.334738
	2	1643.41	418.27		267399.6	2310	972913	
6	1	1931.07	417.70	0.319465	191349.0	1521	448517	0.375379
	2	5130.48	414.82		107576.0	3996	984577	
7	1	3862.17	416.28	0.358553	220966.1	2507	899927	0.422821
	2	8955.62	416.39		177616.3	4085	1710038	
8	1	4243.90	418.92	0.398834	228838.3	2597	979898	0.469716
	2	8659.49	415.64		161809.3	4176	1634417	
9	1	4824.81	415.05	0.463944	234699.5	2776	1110360	0.541612
	2	8173.01	415.81		146098.2	4262	1544794	
10	1	5087.22	417.26	0.489270	234685.3	2866	1167205	0.577449
	2	8060.56	416.43		269866.6	3070	1493567	
11	1	5387.45	417.74	0.528322	234112.8	2980	1239279	0.625861
	2	7739.65	415.97		201770.5	3516	1424695	
12	1	5666.26	417.95	0.561516	104508.5	4550	1305457	0.669583
	2	7521.63	417.78		123891.3	4371	1369232	
13	1	5978.81	418.38	0.597657	104694.7	4640	1372182	0.709240
	2	7310.36	418.63		113188.5	4460	1329058	
14	1	6226.14	417.89	0.627775	80460.9	5188	1409276	0.732860
	2	7128.63	416.22		72464.4	5277	1303960	
15	1	10679.30	415.91	0.793131	82037.1	6221	2435843	0.944563
	2	8823.64	417.64		56759.1	6129	1549825	
16	1	11216.85	416.71	0.844013	63545.0	6856	2563598	1.00507
	2	8461.20	416.19		40349.5	6765	1480059	
17	1	12798.91	416.82	1.05044				
	2	6885.14	416.86					
18	1	14045.62	417.77	1.24099				
	2	5711.84	417.40					

[a] Point nr. and fraction. [b] CPM = counts per minute. [c] SQP(E) = scintillation quench parameter. [d] Where f is the fraction of reaction. [e] ETIME = the elapsed time from start of the counting. [f] CPM_{corr} was calculated according to eq 2.

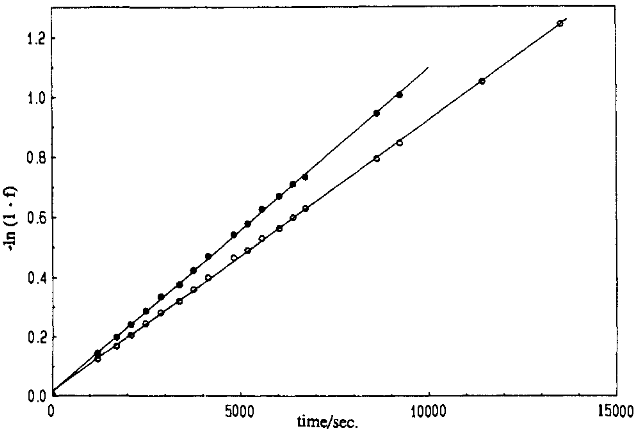

Figure 3. Plots of $-\ln(1 - f)$ versus reaction time for the experiment presented in Table III, ● and ○ represents the ^{11}C- and ^{14}C-reactions, respectively.

the accuracy of the determination of the deuterium content. The NMR analyses were not trivial since the concentrations of the deuterium-labeled [^{11}C]- and [^{14}C]methyl iodides were very low. The relative standard deviation of the integration of the NMR spectra was approximately 1% (determined by performing repeated phasing and integration of the ^1H and ^2H NMR spectra). The deuterium content corrected KIEs were 0.896 ± 0.011 and 0.881 ± 0.012 for the experiments with the deuterium label in the [^{11}C]- and [^{14}C]methyl iodides, respectively.

Syntheses. The [^{14}C-$^2H_3$]methyl iodide solution was analyzed for ^{14}C purity by HPLC fractionation and subsequent liquid scintillation counting and was 99.8% pure, with respect to ^{14}C. The radioactivity of the [^{14}C-$^2H_3$]methyl iodide stock solution was 2.0×10^4 Bq μL^{-1}, and the specific activity was ca. 1 GBq $mmol^{-1}$.

The only ^{14}C impurity detected in the [^{14}C]methyl iodide and [^{14}C-$^2H_3$]methyl iodide solutions was [^{14}C]methanol; in the first experiments it was 0.2–0.4%, and it increased with storage time. Analyses of the reagent were made before every experiment.

The [^{11}C]methyl iodide was synthesized from [^{11}C]carbon dioxide. The trapping of [^{11}C]carbon dioxide in the LAH/THF solution was effective, more than 95% of the [^{11}C]carbon dioxide being trapped after release from the lead-shielded trap. The decay corrected radiochemical yield of [^{11}C]methyl iodide was usually better than 95%. The only detectable side product formed in the synthesis was [^{11}C]methanol, usually less than 0.2% as determined by HPLC analysis. The trapping efficiency of the distilled [^{11}C]methyl iodide in 0.6 mL of dioxane, at 5 °C, was 70–80% at low nitrogen gas flow. The trapping of [^{11}C]methyl iodide was generally very good in THF, cooled to −72 °C. In a tapering 1.5-mL vial contaning only 20 μL of cooled THF, the trapping efficiency was as good as 70–80%, at low nitrogen gas flow. The radioactivity of the ^{11}C-labeled methyl iodide was 1.5–3 GBq, and the specific radioactivity was usually on the order of 1–3 GBq μmol^{-1} at the end of the synthesis.

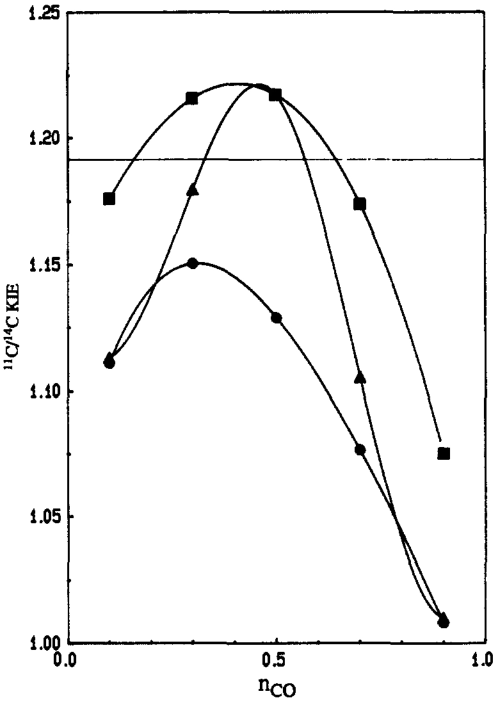

Figure 4. Calculated $^{11}C/^{14}C$ KIE versus bond order, n_{CO}, for the reaction of hydroxide ion with methyl iodide at 25 °C. The calculations were performed for three reaction coordinate models A (●), B (■), and C (▲), see text for explanation of the models. The horizontal line represents the experimentally determined value.

Calculations. The result of the computer calculations for the $^{11}C/^{14}C$ and $^{1}H/^{2}H$ KIEs for three different reaction coordinate models are presented in Figures 4 and 5, respectively.

Discussion

The $^{11}C/^{14}C$ KIE Method. The standard deviations of the ratio of the slopes were larger than the standard deviation of the point KIE within an experiment. The relative standard deviation for the KIE value calculated as the ratio of the slopes was usually 1% and for the point KIE values 0.6%. This can be explained by the deviations between different HPLC fractionations. The standard deviation of the slope ratio depends on the reproducibility of the chromatographic separation. The error in fractionation originating from tailing and short conditioning time in between every injection gave an error in the fraction of reaction, f. This implies that the reaction points deviated from the "true" plot $-\ln(1 - f) = F(t)$ and gave a contribution to the total standard deviation of the slope ratio. The point KIE, however, is not affected by the change of the chromatographic system, provided that any isotope effect in liquid chromatography (causing different retention times) is negligible.

The time elapsed from the start of the first measured fraction, the dead time, the dead time corrected CPM values, and the quench parameter (SQP(E)) used in the calculations were obtained directly from the liquid scintillation counting. In the ^{11}C measurements high CPM values were desirable for good accuracy. At high radioactivity the dead time corrections were less accurate. For the instrument used, the dead time corrections were accurate even for as high dead times as 18%. To assure that the dead time corrections of the measurements were accurate enough and at the same time high CMP values were obtained, the ^{11}C radioactivity of a fraction was measured so that the dead time values were lower (close to 7%). The counts were then <250 000 CPM implying an accuracy of 0.2%, expressed as the relative standard deviation. The KIE experiments were continued until the ^{11}C radioactivity of one fraction passed below ca. 20 000 CPM corresponding to an accuracy of the fractions of 0.7% (relative standard deviation). It is desirable to follow the reaction during approximately 2 half-lives (75% reaction). If the reaction had not reached this point before the ^{11}C had decreased to too low a count rate, the kinetic experiments were continued further with respect to ^{14}C radioactivity measurements.

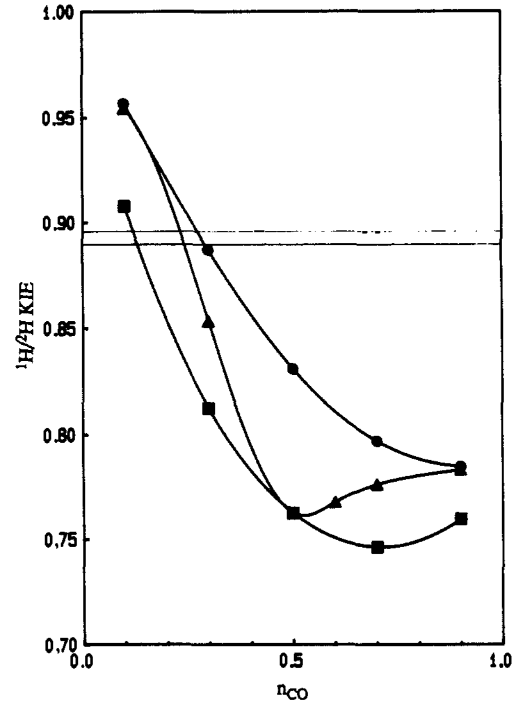

Figure 5. The same kind of figure as Figure 4, except that this presents the calculated $^{1}H/^{2}H$ KIEs. The symbols represent the same thing as in Figure 4.

The ^{14}C radioactivity measurements were performed when the ^{11}C had disintegrated completely. The counting time was varied, depending on the radioactivity, from 5 min to 1 h, to obtain good accuracy of the CPM values for all fractions. The ^{14}C radioactivity of the fractions was usually 500–10 000 CPM. The measurements were performed so that the CPM values of all fractions had a relative standard deviation less than 0.7–0.8%, but for most of the fractions the relative standard deviation were less than 0.5%.

The spectral quench parameter, SQP(E), was derived by an external standard method performed instrumentally. A quench curve was obtained by 10 points with different quenching and counting efficiency. The mean value of the quench parameter, SQP(E), for all the fractions in an experiment was 416.8 ± 1.1 (standard deviation of the sample), which corresponded to a counting efficiency of 91.5 ± 0.2%. Note that the standard deviation of the quench parameter was smaller than the standard deviation of the ^{14}C radioactivity counting (less than 0.5%). In the present method the error of quenching was low because the HPLC eluent had the same composition in all fraction bottles, and the volume of the mobile phase was the same in all bottles. For a sample measured several times the standard deviation was more than half the standard deviation for all samples in an experiment, implying that more than half of the spread in counting efficiency originates from the instrument when it derives the quench parameter. As a result, the standard deviation of the counting efficiency of a full experiment was less than 0.1%. Due to this no corrections were performed on the ^{14}C CPM values regarding counting efficiency.

Experimental and Theoretical Calculated KIEs. Bigeleisen[5] predicted the $^{12}C/^{14}C$ KIE to be a little less than twice that for $^{12}C/^{13}C$. This conclusion was later confirmed by extensive model calculations by Stern and Vogel[6] who defined the ratio r as

$$r = \ln(k_{12}/k_{14})/\ln(k_{12}/k_{13})$$

and found that for most cases $1.8 \leq r \leq 2.0$. Most empirical data seem to conform with this;[24] a discrepancy reported for decarboxylation of malonic acids has been shown to be due to exper-

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(24) Reference 1, p 229.

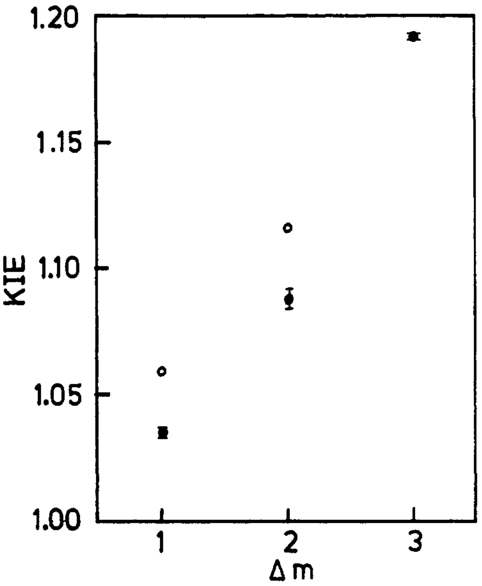

Figure 6. Carbon KIE versus Δm, the mass difference between the isotopes used in the KIE determinations. The filled circles (●) show the experimentally determined KIE values (the standard deviations are marked as horizontal lines) and the unfilled circles (○) are the KIE values calculated from the $^{11}C/^{14}C$ KIE value.

imental error in the $^{12}C/^{14}C$ KIE.[25] A few remaining cases of large deviations are collected in the paper by Stern and Vogel.[6] Application of the Bigeleisen treatment[26] for the case of $^{11}C/^{14}C$ versus $^{12}C/^{14}C$ KIE yields a value of $r \approx 1.6$.

The observed primary carbon kinetic isotope effect increases progressively with the mass difference between the isotopes (Δm), as shown in Figure 6. The values of the $^{12}C/^{14}C$ and the $^{12}C/^{13}C$ KIE predicted from our data by consecutive use of the r values of 1.6 and 1.9 are also displayed in Figure 6. The experimental error limits reported by the other authors do not contain the predicted values, and at least the $^{12}C/^{13}C$ isotope effect determined by mass spectrometry is believed to be accurate. Thus, there is no particular reason why the deviation between experiment and simple theory should be caused by experimental error.

In a similar reaction, the quarternization of *N,N*-dimethyltoluidine with labeled methyl iodide, the primary $^{11}C/^{14}C$ KIE was determined to be 1.203[4] and the $^{12}C/^{14}C$ KIE, reported by Buist and Bender,[27] was determined to be 1.118 (48.5 °C) yielding a value of $r = 1.66$, in good agreement with theory.

One might suspect that the discrepancy between $^{12}C/^{13}C$ and $^{12}C/^{14}C$ KIEs is due to a solvent effect since they were determined in water and dioxane/water, respectively. A solvent effect cannot, however, be invoked to explain the deviation for the $^{12}C/^{14}C$ relative to the $^{11}C/^{14}C$ KIE. Our attempt to determine the $^{11}C/^{14}C$ KIE in water did not yield data of the same accuracy as for dioxane/water, probably because of the low solubility of methyl iodide in water. These results will therefore not be discussed further.

The observed temperature dependence of the primary $^{11}C/^{14}C$ KIE is normal, i.e., the isotope effect decreases with increasing temperature as is expected for an S_N2 reaction.

Model Calculations. The simple treatment[5] of the mass ratios for carbon KIEs is approximative. The validity of the predicted r values was investigated for the present system by model calculations by using the BEBO approach.[14] As can be seen in Figure 7 displaying the r values obtained from the calculations performed for different TS models, there is no indication of any significant deviations except for models A and C (see below) at a bond order of 0.9 where the isotope effects are very small. This is similar to the results obtained in the model calculations by Stern and Vogel[6] who found deviations only in cases in which the individual KIEs were of unusually small magnitude or associated with temperature dependence anomalies.

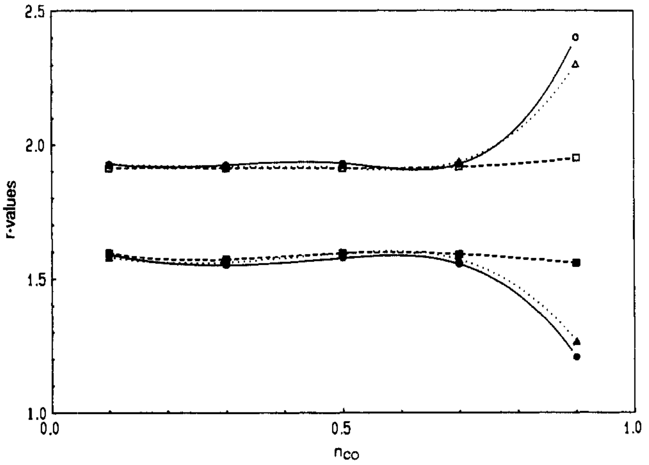

Figure 7. r-Values, for the relationship between $^{12}C/^{13}C$ and $^{12}C/^{14}C$ KIEs (upper, unfilled symbols) and between $^{11}C/^{14}C$ and $^{12}C/^{14}C$ KIEs (lower, filled symbols), of the isotope effects calculated for three different reaction coordinate models, A (○ and ●), B (□ and ■), and C (△ and ▲).

The reaction coordinate models employed were essentially constructed as the ones by Yamataka and Ando[23] in their model calculations for the S_N2 reaction of benzyl arenesulfonates with *N,N*-dimethyl-*p*-toluidine. The simplest of the reaction coordinate models (A) has an asymmetric stretch vibration where the methyl group moves as a mass unit in the decomposition of the TS. In model B, interaction constants are used to couple the bending vibrations involving the methyl hydrogens with the bonds undergoing making and breaking. The movement of the atoms in model B shows increased Walden inversion as compared with model A. This approach was also used by Buddenbaum and Shiner[13] in their study of S_N2 reactions and by Schowen et al.[28] in their BEBOVIB study of enzymatic methyl transfer. The amount of inversion motion is not related to TS geometry in this model. Consequently, the force constant matrix of the very reactant-like TS model contains interaction constants which are not present in the reactant. The resulting primary carbon isotope effects are rather high for reactant- and product-like TS, as has been pointed out by Yamataka and Ando.[23] Model C devised by these workers allows the interaction constant to vary with TS geometry so as to produce a Walden inversion which is most pronounced for symmetric transition states and which decreases for reactant- and product-like TS.

The present calculations were restricted to models in which the total bond order to the methyl carbon was constant in going from reactant to TS, i.e., all transition states were along the diagonal connecting the reactant and product corners in a More O'Ferrall–Jencks diagram representing the reaction. Harris et al. have reported[29] a variation of deuterium KIE in Menschutkin reactions of substituted pyridines with methyl iodide and suggested that bond forming runs ahead of C–I bond breaking, i.e., there is an increasing tightness in the TS. However, the carbon KIEs measured for these reactions were large and did not show bell-shaped behavior, which, in combination with model calculations, were taken as evidence for conserved bond order in the TS by Ando et al.[30] (in contrast to their results for benzyl-transfer reactions). In a recent review on model calculations of secondary isotope effects, McLennan[31] has stated that "there are simply too many

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[25] Yankwich, P. E.; Promislow, A.; Nystrom, R. F. *J. Am. Chem. Soc.* **1954**, *76*, 5893.

[26] A derivation of the relationship between $^{12}C/^{14}C$ and $^{12}C/^{13}C$ KIEs is given in ref 1, p 52ff.

[27] Buist, G. J.; Bender, M. L. *J. Am. Chem. Soc.* **1958**, *80*, 4308.

[28] Rodgers, J.; Femec, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1982**, *104*, 3263.

[29] Harris, J. M.; Paley, M. S.; Prasthofer, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 5915.

[30] Ando, T.; Kimura, T.; Yamataka, H. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; ACS Advances in Chemistry, Series 215, 1987; Chapter 7.

adjustable parameters to allow a confident assignment of a single TS structure to any simple S_N2 reaction from experimental vs theoretical comparisons". While keeping both this statement and the limitations of the present calculations in mind, we still think that the failure to obtain any real variation in the *r* values derived from the calculated KIEs is significant.

Secondary $^1H/^2H$ KIE. Secondary $^1H/^2H$ KIEs in S_N2 reactions have recently been reviewed.[32] Earlier compilations of experimental data are given in the literature.[33,34] The α-deuterium KIE for hydrolysis of methyl iodide has previously been determined to 0.87 with H_2O as the nucleophile.[10] This is close to our value of 0.89 determined for hydroxide ion hydrolysis by the radioactive tracer technique. The generally accepted view is that an inverse α-deuterium KIE in an S_N2 reaction is indicative of increased steric compression in the pentacoordinated TS as compared to the initial state.[32] This is usually thought to be due to increased bending vibrational energy.

The use of successive labeling of several positions in a reactant system enables the number of TS structures compatible with experimental data to be diminished. The experimental $^{11}C/^{14}C$ and $^1H/^2H$ KIEs are represented as horizontal lines in the Figures 4 and 5 displaying the BEBOVIB results. Fair agreement between experiment and calculations is, for both KIEs, obtained only for reaction coordinate model C at a C–O bond order of 0.2–0.3. The graphs displaying the results of the calculated $^{12}C/^{13}C$ and $^{12}C/^{14}C$ KIEs are not included here, but a comparison of the experimental data to these also yields best agreement for model C (n_{CO} = 0.1–0.3). The experimental and calculated KIEs thus indicate that the TS is rather reactant-like.

Having the deuteriums in the ^{14}C-labeled methyl iodide instead of the ^{11}C-labeled species yielded a slightly smaller KIE. It is not clear whether this difference is due to experimental error, presumably caused by the uncertainty in the determination of deuterium content. However, any real difference must be attributed to a failure of the rule of the geometric mean,[35] which is assumed to be valid in the calculation of the deuterium KIE from the observed data and the previously determined carbon KIE. The principle behind the rule is that the isotope effect for a doubly labeled species should be the product of the isotope effects for the corresponding singly labeled species.

Isotope effects on isotope effects appearing as failures of the simple multiplicative relationship between isotope effects when two positions are labeled in the same molecule have been used as a criterion of tunneling by Saunders.[36,37] For hydride transfer,[38] including enzyme-catalyzed reactions,[39] cases are known for which the secondary hydrogen isotope effect is larger by 10% when the transferring atom is hydrogen rather than deuterium.

Quite substantial tunnel corrections for carbon isotope effects have been employed by Saunders for hydroxide ion promoted elimination from (2-phenylethyl)trimethylammonium and (2-phenylethyl)dimethylsulfonium ions[40–42] as well as for proton abstraction from 2-nitropropane by pyridine bases.[43] Since the reacting system rather than a particular atom is tunneling, Saunders argues, a large tunnel correction for a primary carbon isotope effect may be necessary when hydrogen motion is an essential part of the reaction coordinate motion, i.e., when there is strong coupling between light and heavy atom motion in the decomposition mode. The results of the model calculations give some indication that coupling between carbon and hydrogen motion is important in methyl iodide hydrolysis.

For the isotopes of hydrogen the relation between tritium and deuterium KIEs is given by the equation proposed by Swain et al.[44] It was hoped that deviations from this relation would be useful in discovering tunneling, but these seem to be of the same magnitude as those resulting from the simplifying assumptions made in the derivation of the equation.[45,46] Quite recently, however, deviations large enough to be easily observable have been calculated[37] and observed[36] also for enzyme reactions.[47] It would be interesting to know whether carbon tunneling may be manifested as a deviation in the ratios of the different carbon KIEs, i.e., the *r* values.[48] In the present case application of the simple Bell tunneling correction[19] as included in the BEBOVIB program did not change the resulting calculated *r* values significantly. This gives support to the view taken by Saunders[42] who has, on the basis of model calculations, even regarded agreement between experimentally determined and theoretically calculated *r* values as being indicative of experimental accuracy in cases where, for other reasons, tunneling was believed to be important.

The eventual isotope effect on the isotope effect which could explain the small difference between the secondary deuterium KIEs reported here is better studied in a double label experiment where k_{11D}/k_{14D} is determined. This value can be compared directly with the k_{11}/k_{14} ratio without the involvement of any calculations. It is also experimentally advantageous to run the synthesis of the two isotopic species together in the same reaction pot in order to avoid different amounts of deuterium incorporation.

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Registry No. ^{11}C, 14333-33-6; ^{14}C, 14762-75-5; D, 7782-39-0; OH^-, 14280-30-9; CH_3I, 74-88-4.

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[48] A referee has speculated on the difference between the present system and the methylation of dimethyl-*p*-toluidine where a good agreement between predicted and observed relative carbon isotope effects was found (ref 4). The referee suggests that the occurrence of tunneling in the present case may result from more steric hindrance if a heavily solvated hydroxide ion is carried out into the transition state and/or due to a smaller reduced mass of this species than that of dimethyl-*p*-toluidine.