The Kinetic Deuterium Isotope Effect in the Reaction of Methyl Iodide with Cyanide Ion in Aqueous Solution from 0 to 40° [1]

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Abstract: The kinetic α-deuterium isotope effect, k_H/k_D, has been measured for the reaction of CH_3I (CD_3I) with CN^- in aqueous solution from 0 to 40°. Kinetic measurements have been carried out in reaction vessels with no gas phase. Results indicate an inverse isotope effect: $k_H/k_D = 0.926$ (25°), with the Arrhenius parameters $A_H/A_D = 1.124$ (± 0.005), $E_{aH} - E_{aD} = 116$ (± 20) cal. The experimental data are compared with results of model calculations of isotope effects from force constants with an electronic computer. Reasonable choices of some of the transition-state force constants can be made by comparison with suitable stable molecules. The bending force constant, f_{HCC}, is adjusted to give the best fit with the experimental isotope effect. It is planned to compare this f_{HCC} value with bending force constants for other transition states belonging to related reactions. It is found that excellent agreement between experimental and calculated Arrhenius parameters of the isotope effect may be obtained if 5.05 rather than 5.3 mdyn/Å is used for the CH stretching force constant, f_{CH}, of the transition state.

Bimolecular nucleophilic substitution (SN2) is one of the basic types of single-step reaction mechanisms in organic chemistry. It is the purpose of this investigation to gain insight in the nature of the transition state of the SN2 reaction. One of the best methods available which supplies information on the transition state is the determination of kinetic isotope effects.

Kinetic isotope effects are caused by force constant changes which occur when the transition state is formed from the reactants.[2,3] With the aid of a computer, it is possible to carry out model calculations of isotope effects from force constants.[3-6] Calculations starting from various sets of transition-state force constants have been done for some nucleophilic substitution reactions of methyl iodide.[7] It was found that the methyl carbon isotope effect, k_{12}/k_{13}, mainly depends on the following: (a) the relative degrees of bond making and breaking in the transition state $I\cdots CH_3\cdots X$, as measured by the force constants ratio, f_{CI}/f_{CX} (k_{12}/k_{13} would be at its maximum value if $f_{CI} \approx f_{CX}$, e.g., if the transition state is "symmetric"); (b) the curvature of the potential energy barrier as measured by $f_{CI}f_{CX} - f_{12}^2 = d \leq 0$ (the more negative d the higher k_{12}/k_{13}); and (c) the stiffness of the transition state as measured by the sum of the bending force constants, $f_{HCI} + f_{HCX}$ (k_{12}/k_{13} is decreased by an increase of $f_{HCI} + f_{HCX}$).

The hydrogen isotope effect was found to be dependent on the force constants f_{CH}, f_{HCH}, and g (force constant of the out-of-plane bending motion of the CH_3 moiety[7]), and the sum $f_{HCI} + f_{HCX}$ in the transition state. The influence of the other force constants on k_H/k_D

is relatively small. Suitable choices were suggested for the values of f_{CH}, f_{HCH}, and g.

Consequently, it would be possible to obtain information on the "symmetry" or "unsymmetry" of the transition state as well as on the sum of the bending force constants, $f_{HCI} + f_{HCX}$, by combining experimental data of carbon and hydrogen isotope effects in comparison to the model calculations. (It would be necessary, however, to keep the curvature parameter constant at a reasonable value as discussed in the previous papers.[7])

Therefore, it seems to be worthwhile to accumulate experimental data on carbon and hydrogen isotope effects for various reactions of methyl iodide with different nucleophilic reagents X. It will be the purpose of such an investigation to evaluate for each reaction, by comparison with computer calculations, the set of transition-state force constants which gives the best fit with the experimental isotope effects as well as with their temperature dependence.

The next step would involve a comparison of the values of f_{CI}/f_{CX} and $f_{HCI} + f_{HCX}$ obtained for different reactions (on the basis of an unchanged procedure of calculation), and a discussion of the dependence of these values on the nature of the nucleophile X.

Previous experimental work in this field (referring to SN2 reactions only) was concerned with carbon isotope effects in the reactions of methyl iodide with cyanide,[8] hydroxide,[8,9] triethylamine,[9] and pyridine,[9] and with hydrogen isotope effects in the reactions of methyl iodide with radioiodide[10] and various tertiary amines,[11] and of methyl bromide with thiosulfate.[12] With the exception of the quaternization of triethylamine, there are no SN2 reactions for which carbon as well as deuterium isotope effect data are available.

In this work, an experimental study of the deuterium isotope effect in the reaction of methyl iodide with cyanide ion (comparison of the rates of CH_3I and CD_3I with CN^-) has been carried out in aqueous solutions in the temperature region from 0 to 40°, with 5° intervals.

(1) Taken from the first part of the thesis of Mr. C. M. Won, to be submitted to the Faculty of Pure Science of Columbia University, New York, N. Y., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) J. Bigeleisen and M. Wolfsberg, *Advan. Chem. Phys.*, **1**, 15 (1958).

(3) M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, **8**, 225, 325 (1964); M. J. Stern and M. Wolfsberg, *J. Pharm. Sci.*, **54**, 849 (1965).

(4) H. S. Johnston, *Science*, **128**, 1145 (1958); T. E. Sharp and H. S. Johnston, *J. Chem. Phys.*, **37**, 1541 (1962).

(5) M. J. Goldstein and G. L. Thayer, *J. Amer. Chem. Soc.*, **87**, 1933 (1965).

(6) A. V. Willi, *Z. Naturforsch.*, **16a**, 838 (1961); *Ber. Bunsenges. Phys. Chem.*, **68**, 266 (1964).

(7) A. V. Willi, *Can. J. Chem.*, **44**, 1889 (1966); *Z. Naturforsch.*, **21a**, 1377, 1385 (1966).

(8) K. R. Lynn and P. E. Yankwich, *J. Amer. Chem. Soc.*, **83**, 53, 790 (1961).

(9) M. L. Bender and D. F. Hoeg, *ibid.*, **79**, 5649 (1957).

(10) S. Seltzer and A. A. Zavitsas, *Can. J. Chem.*, **45**, 2023 (1967).

(11) K. T. Leffek and J. W. MacLean, *ibid.*, **43**, 40 (1965).

(12) K. T. Leffek, *ibid.*, **42**, 851 (1964).

The kinetics of the reaction of methyl iodide with cyanide ion was studied previously by Marshall and Moelwyn-Hughes,[13] who found that the reaction goes to completion and "is bimolecular and free from complications."

Experimental Section

The main cause of experimental difficulties in this work is the high volatility of methyl iodide. Even if the experiments are done in ampoules with a 10-ml liquid and 1-ml air phase, it can be shown by simple calculations (involving vapor pressures and solubilities) that at temperatures above 25° a few per cent of the total methyl iodide is already in the gas phase above the liquid. Therefore, reaction vessels with no gas phase are used in this work. The apparatus utilized in these experiments is a variant of that described by Fahim and Moelwyn-Hughes.[14] The glass tube leading to the lower part of the reaction vessel is connected with a mercury-filled piston buret. The latter provides a means of pressing out samples of definite volumes of the reacting solution.

Kinetic experiments of reactions of CH_3I with CN^- and of CD_3I with CN^- are done simultaneously, in two equal apparatuses which are immersed in the same thermostated water bath (a Cole-Parmer "temp-mobile" unit) with a temperature constancy of $\pm 0.02°$. The reactions are followed by titration of iodide ion with 0.01 N silver nitrate solution, after removing free cyanide ion by addition of an excess of formaldehyde, as described by Kolthoff and Stenger.[15] The same method had been used by Marshall and Moelwyn-Hughes.[13] We found that the titration can be done potentiometrically, at a silver electrode, with an increased precision.

In order to remove dissolved oxygen, a stream of nitrogen was passed through a batch of ion-exchange water to be used for the kinetic experiments.

Samples of methyl iodide, Baker Analyzed Reagent, or methyl-d_3 iodide (99 atom % D), Merck Sharp & Dohme of Canada, respectively, were used without further purification. The purity was checked by measuring the refractive index and by gas-liquid chromatography, and found to be satisfactory.

It was not possible to avoid evaporation of a few per cent of the methyl iodide in the preparation of the solutions and during the filling process. Therefore, initial concentrations of CH_3I or CD_3I were evaluated from iodide ion concentrations in solution samples in which the reaction had gone to completion.

Second-order rate constants, k_2, were calculated from the experimental data, according to the equation log $([CN^-]/[CH_3I])$ = log $([CN^-]_0/[CH_3I]_0)$ + $([CN^-]_0 - [CH_3I]_0)k_2t/2.303$. For each kinetic run, the best straight line was fitted to the experimental points of log $([CN^-]/[CH_3I])$ as a function of t, using a computer with a least-squares program. k_2 was calculated from the slope of the line.

Results

In all experiments, the initial concentrations of methyl iodide or methyl-d_3 iodide are ca. 2×10^{-2} M and those of cyanide ion are ca. 3.7×10^{-2} M. Results of second-order rate constants and isotope effects, obtained at different temperatures, are collected in Table I. Arrhenius parameters and their standard deviations are given as follows: for CH_3I + CN^-, A = 5.1×10^{12} ($\pm 12\%$) mol^{-1} sec^{-1} l., E_a = 21.75 (± 0.11) kcal; CD_3I + CN^-, A = 4.6×10^{12} ($\pm 12\%$) mol^{-1} sec^{-1} l., E_a = 21.63 ($\pm$ 0.11) kcal; isotope effect, A_H/A_D = 1.124 (± 0.005), $E_{aH} - E_{aD}$ = 116 (± 20) cal.

In comparison to Marshall and Moelwyn-Hughes' data,[13] results obtained for k_2 in this work are 4% lower at 20° and ca. 8% higher at 40°. Correspondingly, the Arrhenius parameters found by Marshall and Moelwyn-Hughes are slightly different from the results of

(13) B. W. Marshall and E. A. Moelwyn-Hughes, J. Chem. Soc., 2640 (1959).
(14) R. B. Fahim and E. A. Moelwyn-Hughes, ibid., 1035 (1956).
(15) I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," Vol. 2, 2nd ed, Interscience Publishers, New York, N. Y., 1947, p 266.

Table I. Rate Constants and Isotope Effects in the Reaction of Methyl Iodide (RI) with Cyanide Ion in Water

Temp, °K	R = CH₃ $10^4 k_2$, sec^{-1} mol^{-1} l.	R = CD₃ $10^4 k_2$, sec^{-1} mol^{-1} l.	k_H/k_D
273.2	0.205	0.227	0.90₃
278.2	0.426	0.466	0.91₄
281.2	0.670	0.730	0.91₈
283.2	0.801	0.877	0.91₃
288.2	1.659	1.812	0.91₆
293.2	3.13	3.43	0.91₃
298.2	6.03	6.51	0.92₆
303.2	10.88	11.71	0.92₉
308.2	19.45	20.86	0.93₂
313.2	34.05	36.65	0.92₉

this work. The causes of these deviations are unknown to us.

Discussion

In this work, an inverse hydrogen isotope effect is observed for the reaction of methyl iodide with cyanide ion, while, on the other hand, normal hydrogen isotope effects have been found in the reactions of methyl iodide with iodide ion[10] and of methyl bromide with thiosulfate ion.[12] As in the iodide exchange of methyl iodide, the isotope effect data in the reaction with cyanide ion are not in agreement with the relationship between k_H/k_D and the nucleophilic power of X (measured by $E_n - E_1$), as discussed by Seltzer and Zavitsas.[10]

With regard to the high carbon isotope effect found by Lynn and Yankwich[8] for the cyanide reaction, previous model calculations[7] have been carried out with low values for the bending force constant sum, f_{HCI} + f_{HCC}, and high hydrogen isotope effects have been obtained correspondingly. It was recognized, however, that higher values for these bending force constants cannot be excluded solely on the basis of the carbon isotope effect data.

New model calculations may be carried out after experimental hydrogen isotope effect data have become available in this work. They are done on the same general basis as in the previous theoretical papers.[7] The set of 13 force constants reported by Fenlon, Cleveland, and Meister[16] is used for the reactant methyl iodide. The general model of the transition state is the same as described previously,[7] with f_{CN} = 16.7 mdyn/Å, f_{CCN} = 0.01 mdyn Å, f_{HCH} = 0.36 mdyn Å, g = 0.144 mdyn Å, and four interaction force constants (referring to interactions among CH stretches and HCH bends) whose values are the same as in the reactant. There are two choices for f_{CH} in the transition state— 5.3 or 5.05 mdyn/Å.

The following five force constants are related to bonds which are broken or formed in the transition state: f_{CI}, f_{CC}, f_{12} (interaction between CI and CC stretches), f_{HCI}, and f_{HCC}. There are many different sets of f_{CI}, f_{CC}, and f_{12} which, other things being equal, may lead to the same isotope effect. (As discussed above, the most important parameters are $f_{CI}f_{CC} - f_{12}{}^2 = d$ and the ratio f_{CI}/f_{CC}.)

Since the carbon isotope effect is high, the transition state must be "symmetric" or "almost symmetric," e.g., $f_{CI} \approx f_{CC}$. In this work, sample calculations are

(16) P. F. Fenlon, F. F. Cleveland, and A. G. Meister, J. Chem. Phys., 19, 1561 (1951).

Table II. Calculated Isotope Effects[a]

No.	Transition-state force constants						k_H/k_D (25°)	A_H/A_D	$E_{aH} - E_{aD}$, cal	k_{12}/k_{13} (10°)
	f_{CI}	f_{CC}	f_{12}	f_{CH}	f_{HCI}	f_{HCC}				
105	0.2	0.2	1.5	5.3	0.250	0.345	0.926	1.082	92	
107	−0.8	0.2	1.8	5.3	0.250	0.330	0.926	1.074	88	
111	−0.8	0.2	1.8	5.15	0.300	0.347	0.926	1.082	105	1.054
110	0.2	0.2	1.5	5.05	0.300	0.410	0.927	1.131	118	1.050
112	−0.8	0.2	1.8	5.05	0.300	0.395	0.925	1.124	116	1.054
Experimental results							0.926	1.124	116	

[a] Stretching force constants are given in millidynes per ångström and bending force constants are given in millidyne ångströms. As described in the discussion, eight additional transition-state force constants are kept unchanged in these calculations.

carried out with two different sets for the force constants f_{CI}, f_{CC}, and f_{12} (see Table II) which have been discussed in the previous paper.[7] The sum of the bending force constants, $f_{HCI} + f_{HCC}$, is adjusted in such a way that the hydrogen isotope effect, k_H/k_D, agrees with the experimental result for 25°. (This has been done in all five examples of Table II). In the calculations with f_{CH} = 5.3 mdyn/Å, f_{HCI} is held constant at 0.250 mdyn Å, and in those with f_{CH} = 5.05 mdyn/Å, f_{HCI} is held constant at 0.300 mdyn Å. (In both cases, f_{HCC} is varied.) These f_{HCI} values have been selected because they lead to approximate agreement between calculated[7] and experimental[10] hydrogen isotope effects in the iodide exchange reaction of methyl iodide.

According to the suggestion of Wolfsberg and Stern,[3] Arrhenius parameters of the calculated isotope effects (in the temperature range of the experimental data) are computed with the aid of the least-squares method (Table II). Though k_H/k_D at 25° is equal for all five sample calculations, the Arrhenius parameters A_H/A_D and $E_{aH} - E_{aD}$ are different. There is excellent agreement between experimental and calculated Arrhenius parameters for calculations 110 and 112, with f_{CH} = 5.05 mdyn/Å. Both sets of values for f_{CC}, f_{CI}, and f_{12} essentially lead to the same result: f_{HCC} must be adjusted to a value between 0.395 and 0.410 mdyn Å to produce the experimental hydrogen isotope effect in the whole temperature range of the experiments.

A_H/A_D is lower for a f_{CH} value higher than 5.05 mdyn/Å, even if $f_{HCI} + f_{HCC}$ is adjusted to fit the experimental isotope effect at one temperature (see sample calculations 105, 107, and 111).

The carbon isotope effect, k_{12}/k_{13}, is a little higher in calculation 112 because d is more negative than in 110. As in previous sample calculations,[7] the calculated results for k_{12}/k_{13} are smaller than the experimental value found by Lynn and Yankwich.[8] Possible causes of these differences have been discussed previously.[7]

It may be concluded that if reasonable values are selected for f_{CH}, f_{HCH}, and the other transition-state force constants, and if $f_{HCI} + f_{HCC}$ is adjusted to fit the experimental hydrogen isotope effect at one temperature, excellent agreement between calculated and experimental data then can be obtained within a wide temperature region. Consequently, these findings may be taken as evidence for the meaningfulness of calculations of this type.

One might question whether or not the absolute values of the adjusted force constants have any real meaning. However, they are certainly useful as *relative* parameters which give a quantitative description of a transition-state property, provided the calculation procedure and the force constant definitions are the same in all calculations for different transition states.