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A Novel Method for Determining Carbon-13 Kinetic Isotope Effects from Isotope Ratio of Whole Molecules

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Primary ^{13}C kinetic isotope effects for the Menschutkin reactions of substituted pyridines with methyl iodide in 2-nitropropane at 25°C were determined at the natural abundance level by means of combustion and isotope ratio mass spectrometry. The large ^{13}C isotope effects were almost constant throughout the series ($^{12}\text{k}/^{13}\text{k}=1.071\sim 1.075$) and consistent with those obtained previously by direct rate measurements.¹

Reactivity-selectivity relationships are understood with regard to variation in transition states (TS). Many investigations on variable TSs of aliphatic nucleophilic substitution have been carried out employing a variety of experimental techniques.² Kinetic isotope effects (KIE) are of great importance in this respect because they provide the most direct information concerning the structures of transition states. In previous papers, we successfully interpreted the variation in the TS structures of the Menschutkin-type benzyl and methyl transfer reactions, by the extensive use of carbon-14, carbon-13, nitrogen-15, tritium, and deuterium isotope effects at the reaction center.³

Although the experimental techniques for determining kinetic isotope effects have been well established, development of a novel procedure especially utilizing stable isotopes is highly desirable. We here report a new method for measuring carbon-13 KIEs for the nucleophilic methyl transfer reaction (eq. 1) by means of isotope ratio mass spectrometry at the natural abundance level without the use of isotopically labeled compounds. This method has been often used for nitrogen-15 KIEs for the reaction systems containing only one nitrogen,^{3e} but never utilized before for carbon-13 KIEs as almost all the organic reaction systems have many carbon atoms. Determination of the variation in the carbon-13 content of the particular carbon is disturbed by the contribution of the carbon-13 contents of other carbon atoms. As mass spectrometry is an

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extremely sensitive and inherently precise probe, we have expected that this method should be applicable for the reaction systems containing several carbon atoms. This new procedure also has the unique capability of simultaneous determination of the carbon-13 and nitrogen-15 KIEs from the same samples.

Experimental

Reactions of methyl iodide with substituted pyridines were carried out in 2-nitropropane at 25°C with 0.1 mol/L each of methyl iodide and nucleophiles. The products, N-methyl pyridinium iodides were recovered from reaction solutions at early stages of reaction (ca. 5%), and purified by recrystallization. Isotope ratios of the isolated products were analyzed by isotope ratio mass spectrometry after combustion⁴. Three runs were performed for each reaction.



3,5-Dimethyl- and unsubstituted pyridinium hydrobromide perbromide and 3-chloropyridinium zinc chloride were prepared by following the standard procedures.⁵

Calculations of $^{12}\text{k}/^{13}\text{k}$

For determining ^{13}C KIEs for the reaction systems containing many carbon atoms, contributions from other carbons than the particular one must be evaluated. In the present reaction ^{13}C KIEs of other carbon atoms than the transferring methyl were assumed to be negligible.

At early stages of reaction, ^{13}C KIE ($^{12}\text{k}/^{13}\text{k}$) of the reacting methyl carbon can be calculated using the following equation;⁶

$$^{12}\text{k}/^{13}\text{k} = \frac{\log(1-f)}{\log(1-f \cdot R_f^{\text{Me}}/R_o^{\text{Me}})} = \frac{R_f^{\text{Me}}}{R_o^{\text{Me}}} \quad (2)$$

where f is the fraction of reaction, R_f^{Me} is the atomic ratio, $^{12}\text{C}/^{13}\text{C}$ in the transferred methyl of the product, and R_o^{Me} is that in the starting methyl iodide.

$$R_f^{\text{Me}} \equiv \frac{[^{13}\text{C} \text{ in the methyl of the product}]}{[^{12}\text{C} \text{ in the methyl of the product}]} \quad \text{at } f$$

$$R_o^{\text{Me}} \equiv \frac{[^{13}\text{C} \text{ in the starting methyl iodide}]}{[^{12}\text{C} \text{ in the starting methyl iodide}]}$$

R is calculated from the measured value $^{13}\delta$ (‰) by following eq. 3.

$$R = (\delta/1000 + 1) \times 0.0112372 \quad (3)$$

where 0.0112372 is the carbon isotope standard of $^{13}\text{C}/^{12}\text{C}$.⁴

As R_f^{Me} cannot be determined directly, it must be calculated from the observed R^{obs} value for the whole product molecule, which is composed of the contribution from the methyl group R^{Me} and

pyridine R^{Py} . R^{Py} was assumed to be constant before and after the reaction. According to figure 1a,

$$R_o^{Py} = (1-z)/z = (^{13}\delta_o/1000 + 1) \times 0.0112372 \quad (4)$$

$$R_f^{Me} = (1-x)/x \quad \text{at } f \quad (5)$$

$$R_o^{Me} = (1-y)/y \quad (6)$$

$$R_f^{obs} = \frac{(1-x) + n(1-z)}{x + nz} \quad \text{at } f \quad (7)$$

(n: number of carbon atoms in pyridine)

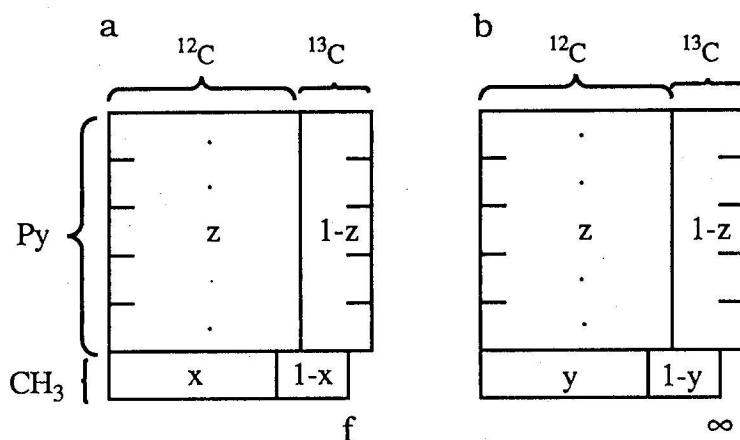


Figure 1. Schematic illustrations of distributions of ^{12}C and ^{13}C in the pyridyl and methyl groups of the product: (a) at fraction f of reaction, (b) at 100%; x and y are fractions of ^{12}C in the methyl group of the product at fraction f and at 100%, respectively. z is an average fraction of ^{12}C per one carbon atom of the starting substituted pyridines and is constant independent of the fraction of reaction.

Therefore, from eqs. 4, 5, and 7

$$R_f^{Me} = \frac{1-x}{x} = \frac{R_f^{obs} - n\{1 - (1 + R_f^{obs}) / (1 + R_o^{Py})\}}{1 + n\{1 - (1 + R_f^{obs}) / (1 + R_o^{Py})\}} \quad (8)$$

R_o^{Me} of methyl iodide is difficult to be measured directly because of its volatility. Thus, R_o^{Me} was calculated from R_{∞}^{PyMeI} at the 100% reaction in the presence of large excess of pyridine as illustrated in figure 1b.

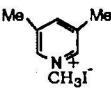


$$R_{\infty}^{PyMeI} = \frac{(1-y) + n(1-z)}{y + nz} = (^{13}\delta_{\infty}/1000 + 1) \times 0.0112372 \quad (9)$$

From eqs. 4, 6, and 9

$$R_o^{Me} = \frac{1-y}{y} = \frac{R_{\infty}^{PyMeI} - n\{1 - (1 + R_{\infty}^{PyMeI}) / (1 + R_o^{Py})\}}{1 + n\{1 - (1 + R_{\infty}^{PyMeI}) / (1 + R_o^{Py})\}} \quad (10)$$

Thus, $^{12}\text{C}/^{13}\text{C}$ was calculated from R_f^{obs} , R_o^{Py} , and R_{∞}^{PyMeI} by eqs. 2, 8, and 10.

Table 1. Carbon-13 kinetic isotope effects of Menschutkin-type methyl transfer reactions

	f	$^{13}\delta_{\text{O}}^{\text{a}}$	$R_{\text{f}}^{\text{obs b)}$	$^{13}\delta_{\text{O}}^{\text{c)}$	$R_{\text{O}}^{\text{Py d)}$	$^{13}\delta_{\text{O}}^{\text{e)}$	$R_{\text{O}}^{\text{PyMeI f)}$	$^{12}\text{k}/^{13}\text{k g)}$	$^{12}\text{k}/^{13}\text{k h)}$	
	(%)	(‰)		(‰)		(‰)				
	6.4	-42.4	0.0107607	-29.1	0.010909	-34.6	0.0108484	1.07444	1.075	1.063
	4.7	-42.4	0.0107607	-29.3						
	5.7	-42.8	0.0107562							
	5.3	-40.0	0.0107877	-21.2	0.010999	-30.3	0.0108967	1.06895	1.071	1.066
	5.9	-40.4	0.0107832	-21.2						
	4.4	-40.5	0.0107821	-21.2						
	5.5	-51.6	0.0106574	-34.8	0.010846	-41.2	0.0107742	1.07416	1.072	1.074
	5.2	-51.4	0.0106596	-34.8						
	5.7	-50.8	0.0106664	-34.8						

a) products at fraction f b) eq. 3 c) substituted pyridinium hydrobromide perbromide or zinc chloride d) eq. 4 e) products at 100% reaction f) eq. 9 g) eq. 2 h) ref. 1

Discussion

Results are summarized in Table 1. In addition to the KIE values measured in this work, Table 1 also lists the previous results of ^{13}C KIEs for comparison.

Calculations of ^{13}C KIEs using eqs. 2, 8, and 10 indicate that the errors involved in the present method are $(1+n)$ times the uncertainties inherent in the mass-spectrometric measurement of the ^{13}C contents. In other words, the uncertainties in the determination of ^{13}C contents of other carbon atoms than the methyl carbon contribute to the errors in the ^{13}C KIEs of the methyl carbon. In spite of this fundamental disadvantage, ^{13}C KIEs obtained in the present study show the excellent reproducibility reflected in the small standard deviations.

The results clearly show that carbon-13 KIEs are all large and almost constant, $^{12}\text{k}/^{13}\text{k} = 1.071 \sim 1.075$. These values are very close to the previous ones ($^{12}\text{k}/^{13}\text{k} = 1.063 \sim 1.074$)¹ obtained by the direct comparison of the rate constants for normal and 99% ^{13}C -enriched methyl iodide.

The agreement between the present and previous values obtained from the two independent experimental methods verifies that the large ^{13}C KIEs in the methyl transfer reaction are real and reliable. Slight variation reported previously, larger ^{13}C KIEs for weaker nucleophiles, was not reproduced in the present results. Considering the above discussion concerning the reproducibility of the experiments, we believe that the present results are more reliable, i. e., ^{13}C KIEs are almost constant for the reaction series studied.

The accuracy in the results, avoidance of the use of expensive ^{13}C or troublesome ^{14}C labeled compounds indicate that the present method of determining ^{13}C KIEs at the natural abundance level is an excellent technique for the reaction systems containing several carbon atoms. Only the restriction is that the method is ineffective for the reaction system where more than one carbon

atoms could show kinetic isotope effects. This possibility should be kept in mind even in the present reaction system.

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