J. Am. Chem. Soc. 1991, 113, 1691-1693

Nitrogen and Deuterium Isotope Effects on Quaternization of *N*,*N*-Dimethyl-*p*-toluidine

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Abstract: A nitrogen kinetic isotope effect k^{14}/k^{15} = 1.0019 ± 0.0001, a deuterium kinetic isotope effect k^{H_3}/k^{D_3} = 0.83 ± 0.04, and a solvent deuterium isotope effect k^H/k^D = 1.00 ± 0.05 were measured on the Menschutkin reaction between methyl iodide and *N*,*N*-dimethyl-*p*-toluidine at 25 °C in methanol. Semiempirical quantum mechanical calculations of kinetic isotope effects of deuterium, carbon, and nitrogen on the same reaction were performed with use of an AM1 Hamiltonian. A late transition state is proposed on the basis of a comparison between experimental and theoretical values of isotope effects.

Two principal factors influence the magnitudes of kinetic isotope effects.[1] The first one, called the temperature-independent factor (TIF), is connected with the mass difference of isotopic species and the effect of this difference on the frequency of crossing the energetic barrier (transition state) along the reaction coordinate. It favors "light" isotopic species reacting faster than their "heavy" isotopomers. The second one, the temperature-dependent factor (TDF), reflects changes in bonding around the isotopic atom. This factor is larger than unity when bonds to the isotopic atom are weaker in the transition state than in the reactant and smaller than unity for the opposite situation. Overall, primary kinetic isotope effects are greater than unity when a bond is being broken to the isotopic atom because both factors are larger than unity. Conversely, when a bond is being made to the isotopic atom, primary kinetic isotope effects are small or inverse due to the partial cancellation of the two factors. For this reason, isotope effects of incoming groups are difficult to interpret; an isotope effect of approximately unity may mean that the isotope-sensitive step is not rate-determining or else that the step is rate-determining and such a cancellation has occurred.

This problem can sometimes be overcome by study of a variety of isotope effects on a single reaction, particularly if combined with theoretical studies. Entering-group nitrogen isotope effect measurements have found little use in mechanism studies, principally because ordinary methods for measurement are tedious and difficult. Recent advances in isotope effect measurement technology can overcome this problem. Commercially available combustion units combined on-line with isotope ratio mass spectrometers now allow fairly easy determination of nitrogen isotopic composition of organic compounds without the necessity of elaborate manual conversion to N_2. A small solid sample of natural isotopic composition placed in a tin boat is subjected to the combustion/reduction process, and the gaseous nitrogen produced is fed directly into the mass spectrometer.

To illustrate the applicability of these procedures, we have studied nitrogen, secondary deuterium, and solvent isotope effects on the quaternization of *N*,*N*-dimethyl-*p*-toluidine in methanol at 25 °C:

$$H_3CC_6H_4N(CH_3)_2 + CH_3I \rightarrow H_3CC_6H_4N^+(CH_3)_3I^- \quad (1)$$

The kinetics of this reaction have been extensively studied.[2] The reaction has been shown to be a single-step S_N2 reaction, first order in each reactant. Carbon kinetic isotope effects have been reported previously.[2,3]

Experimental Section

Materials. *N*,*N*-Dimethyl-*p*-toluidine (99%, Aldrich), methyl alcohol (99.97%, Aldrich HPLC grade), iodomethane (99.5%, Aldrich), iodomethane-d_3 (99%, Sigma), and methanol-d_4 (99.8%, Sigma) were used without further purification.

Kinetics. The kinetics of the reaction of methyl iodide with *N*,*N*-dimethyl-*p*-toluidine (0.05 M) in absolute methanol-d_4 was measured by NMR at 25 °C. Pseudo-first-order conditions were attained by using a 30-fold excess of methyl iodide (1.5 M). The reaction mixture was placed in an NMR tube, and spectra were taken every 15 min by use of a Nicolet-nr (360-MHz) NMR spectrometer. No signals other than those of reactant, product, and solvent were detected. The rate constant was evaluated from the collected ^{1}H NMR spectra on the basis of integrations of methyl signals of the reactant (2.8 ppm) and the product (3.6 ppm).

Isotope Effects. The nitrogen kinetic isotope effect was determined from the difference in isotopic composition of the product at low and high conversion levels. Experiments were carried out under pseudo-first-order conditions (excess methyl iodide); to 25 mL of 0.05 M *N*,*N*-dimethyl-*p*-toluidine in methanol (natural isotopic composition) thermostated at 25 °C was added methyl iodide to a final concentration of 1.5 M. The reaction was allowed to proceed for ~10 min, after which the reaction was quenched by cooling to 0 °C, and methyl iodide and solvent were removed by vacuum distillation from an ice bath. The residue was dissolved in CD_3OD, and the fraction of reaction *f* was obtained from ^{1}H NMR measurements. Then, solvent was removed, and the residue (amine and salt) was dissolved in a benzene–water mixture. The mixture was shaken vigorously for 15 min and then left for 1 h to allow separation of phases. After separation, the water phase was lyophilized to yield the pure ammonium salt. In separate experiments, it was shown that this method quantitatively separates unreacted amine (which stays in the benzene phase) from the product (which stays in the water phase). Recovery of salt is quantitative, and there is no isotopic fractionation connected with this procedure.

The salt obtained in this way was combusted, and the isotopic composition of nitrogen was measured. About 10 mg of sample was required per measurement. In parallel experiments, the reaction was allowed to go to completion ($>10t_{1/2}$) and the salt was processed in the same way to yield an isotopic composition that is equal to the composition of starting material.

Isotope ratios were measured with a Finnigan Delta S isotope ratio mass spectrometer combined on-line with a Heraeus elemental analyzer. Unlike carbon isotope ratio determinations using the isotope ratio mass spectrometer, measurements of nitrogen isotope composition are sensitive to the sample size. For our system, this dependence becomes very strong when the sample is smaller than ~30 μmol (for compounds containing one nitrogen atom per molecule) and is negligible in the range 30–70 μmol. In our measurements, we have ensured that, first, all samples were of appropriate size (50 μmol or larger) and, second, comparison of isotopic composition between low- and high-conversion samples was done for samples of approximately equal size.

The nitrogen kinetic isotope effect for the reaction (1) was calculated from the equation

$$k^{14}/k^{15} = \frac{\ln(1-f)}{\ln[1 - f(1000 + \delta_f)/(1000 + \delta)]} \quad (2)$$

where δ_f and δ_∞ are relative isotope compositions of product at fraction of reaction *f* and at full conversion, respectively. The δ-value is related to the isotopic ratio as $\delta_i = (R_i/R_{st} - 1) \times 1000$. *R*'s are isotopic ratios ($^{14}N^{15}N/^{14}N_2$) for product after fraction of reaction *f* ($i = f$), at full

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0002-7863/91/1513-1691$02.50/0

conversion ($i = \infty$), and for standard (st), which was N_2 from air. The secondary deuterium kinetic isotope effect was measured under pseudo-first-order conditions by use of a 30-fold excess (1.5 M) of isotopic mixture CD_3I/CH_3I (1:1 mol %) over amine at 25 °C. The reaction was carried out in an NMR tube. The signal at 3.65 ppm, which corresponds to methyl groups of the product, appears as a doublet due to the deuterium isotope effect on the chemical shift (2.34 Hz upfield). The peaks were well separated, thus permitting separate integration of the two peaks. The deuterium kinetic isotope effect was calculated from

$$k^{H_3}/k^{D_3} = \frac{([P]_H/[P]_D)_f}{([S]_H/[S]_D)_0} = \frac{1/R_f}{1/R_0} \quad (3)$$

where R_f is the isotopic ratio of deuterated product at extent of reaction f and R_0 is that of the starting material. The isotope ratio of the product was found to be independent of the extent of reaction, as expected. The initial isotopic ratio of iodomethane was measured by carrying the reaction to completion with amine in large excess (1.5 M) compared to iodomethane (0.05 M).

The deuterium kinetic isotope effect was also measured by a mass spectrometric method. The same samples that were used for NMR measurements were afterward introduced to a Kratos MS50TA mass spectrometer equipped with an Ar-FAB source, and the isotopic composition was measured by comparing intensities of peaks at m/e 150 and 153.

The solvent isotope effect was measured by monitoring the time dependence of the difference in absorbance at 280 nm between two cells placed simultaneously in a thermostated UV spectrophotometer (Varian Cary 2200), differing only in the isotopic composition of the solvent. One cell contained unlabeled methanol and the other contained 99.8% methanol-d_4. The occurrence of an isotope effect causes an excursion of the absorbance away from base line as the reaction proceeds. The isotope effect is correlated with the observed maximum difference in absorbance (ΔA_{max}) by the equation[4]

$$(\Delta A)_{max}/A_0 = \alpha^{\alpha/(1-\alpha)} \quad (4)$$

where A_0 is absorbance of the starting samples and α is the isotope effect k^{CH_3OH}/k^{CD_3OD}.

Theoretical Calculations. AMPAC Version 2 (for the VAX 11/780 computer)[5a] and MOPAC Version 5 (for the IBM 9370-90 computer)[5b] programs were used. The AM1 Hamiltonian was employed in calculations of heats of formation and optimization of geometries of the reactants, product, and transition state. Subsequent subroutines of AMPAC and MOPAC were used to calculate frequencies of normal vibrations, moments of inertia, and zero-point energies of isotopic molecules. Two sets of calculations were performed. In the first, the multiplicity n of the central carbon atom was preserved ($n_{N-C} + n_{C-I} = 1$) and the geometry of the transition state was fixed at 25, 50, and 75% of reaction progress (defined as the multiplicity of the forming C–N bond). In the second, the multiplicity of the central carbon atom was reduced ($n_{N-C} + n_{C-I} = 0.8$) to explore the properties of a so-called "exploded" transition state. The multiplicity of the forming C–N bond was fixed at 20, 40, and 60%. This way, the ratios of bond being made to bond being broken were the same in both sets of calculations for the corresponding structures of the transition state. Bond lengths at partial connectivities were obtained from[6]

$$r_n = r_1 - 0.3 \ln n \quad (5)$$

where r_n is the length of a partial bond with multiplicity n and r_1 is the length of a single bond. Isotopic frequencies of normal vibrations of reactants and transition state and moments of inertia, obtained from the theoretical calculations, were used with the complete Bigeleisen equation[1] to calculate kinetic isotope effects. Low-frequency vibrations (<30 cm^{-1}) were not included in the calculations.

Results

The rate constant $k = (6.72 \pm 0.05) \times 10^{-3}$ min^{-1} at 25 °C obtained for reaction of methyl iodide with *N,N*-dimethyl-*p*-toluidine is in agreement with previous measurements.[3] The nitrogen kinetic isotope effect on this same reaction is $k^{14}/k^{15} = 1.0019 \pm 0.0001$ (Table I). A secondary deuterium kinetic isotope effect $k^{H_3}/k^{D_3} = 0.83 \pm 0.04$ was found for three hydrogen atoms by the NMR measurements. The mass spectrometric analysis yielded $k^{H_3}/k^{D_3} = 0.85 \pm 0.02$.

Table I. Experimental Values of the Kinetic Nitrogen Isotope Effect for the Reaction between Methyl Iodide and *N,N*-Dimethyl-*p*-toluidine at 25 °C in Methanol

f	δ_∞	δ_f	k^{14}/k^{15}
0.125	−10.641	−12.492	1.0020
	−10.611	−12.456	1.0020
0.115	−9.662	−11.335	1.0018
	−9.602	−11.315	1.0018
	−9.518	−11.247	1.0019
0.1[a]	−9.609	−11.343	1.0018
		−11.438	1.0020
mean			1.0019 ± 0.0001[b]

[a] Value calculated from the rate constant. [b] The error reported is 1 standard deviation.

Table II. Theoretical Values of Kinetic Isotope Effects for the Reaction between Methyl Iodide and *N,N*-Dimethyl-*p*-toluidine at 25 °C

n_{NC}	$\nu^\ddagger$ (cm^{-1})	% c[a]	μ (D)	k^{12}/k^{14}[b]	k^{H_3}/k^{D_3}[c]	k^{14}/k^{15}
0.25	290	1.5	5.7	1.087	0.80	1.013
0.20				1.085	1.00	1.028
0.50	473	3.1	8.9	1.117	0.73	1.004
0.40				1.132	0.90	1.012
0.75	94.8	4.8	12.3	1.075	0.98	0.991
0.60				1.088	0.96	0.995

[a] The percentage contribution of C–H bending to the energy of the reaction coordinate (see text). [b] Calculated from k^{12}/k^{13} by use of the rule of the geometric mean ($r = 1.91$) and the tunneling correction. [c] The isotope effect for three deuterium atoms in CD_3I.

No solvent isotope effect was observed; $k^{CH_3OH}/k^{CD_3OD} = 1.00 \pm 0.05$. Since no deviation of the differential absorbance from the base line was observed, the error reported for the solvent isotope effect is estimated from the molar absorptivity coefficient of amine at 280 nm and the line width. This represents the maximum concentration difference that could escape our detection.

Table II summarizes calculated values of kinetic isotope effects for different locations of the transition state on the potential energy surface, together with calculated properties of each structure, e.g., dipole moment μ, imaginary frequency $\nu^\ddagger$, and contribution of C–H bending vibrations to the reaction coordinate % c (see the following discussion).

Carbon, nitrogen and deuterium kinetic isotope effects have been calculated for six possible transition states. These structures correspond to bonding ratios n_{N-C}/n_{C-I} of 1/3, 1/1, and 3/1 and total bonding $n_{N-C} + n_{C-I}$ of 0.8 and 1.0. While both carbon and deuterium isotope effects exhibit extrema (maximum for carbon and minimum for deuterium) for the symmetrical transition-state structure ($n_{N-C} = n_{C-I}$), the nitrogen isotope effect decreases gradually, becoming inverse (less than unity) for late transition states ($n_{N-C} > n_{C-I}$) for both sets of calculations.

Discussion

The S_N2 mechanism of the reaction under consideration has long been established. This provides reasonable limitations on the transition-state structures that must be considered and thus provides for "calibration" of nitrogen isotope effects in processes involving formation of a new N–C bond and for the testing of the usefulness of semiempirical methods in theoretical estimations of isotope effects.

The nitrogen isotope effect of 0.2% obtained experimentally is very small because of a cancellation between temperature-independent and temperature-dependent factors. A nitrogen isotope effect of similar magnitude has been reported for the quaternization of substituted pyridines.[7]

Comparison of the observed nitrogen kinetic isotope effect with theoretical estimates for different transition-state structures indicates that the transition state is slightly late with respect to the degree of bond making and bond breaking; e.g., formation of the new nitrogen–carbon bond is slightly more advanced than the

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breaking of the old carbon–iodide bond. This conclusion is also supported by the comparison of theoretical values of the carbon kinetic isotope effect (Table II) with experimental values $k^{12}/k^{14} = 1.117 \pm 0.011$[2] and $k^{11}/k^{14} = 1.230 \pm 0.0036$.[3] Although these isotope effects were measured at higher temperature, we do not expect any substantial change in the isotope effect over the range of 24 °C. Theoretical dependence of the nitrogen isotope effect on the location of the transition state is much greater for the exploded transition state than for the structures in which the bonding to the central carbon atom is preserved. For the exploded transition state, the observed nitrogen isotope effect would suggest a late or even very late transition state, but this conclusion does not agree with the comparison of observed and calculated deuterium isotope effects, which would suggest a symmetrical transition state. Instead, the isotope effects suggest a symmetrical or slightly late transition state in which the bonding to the central carbon atom is preserved. On the other hand, experimental values of deuterium isotope effects for reaction[8] of methyl iodide with aliphatic amines and pyridine, $k^{H_3}/k^{D_3} = 0.85 - 0.91$, if compared with our theoretical estimates, would suggest a late transition state, as would chlorine kinetic isotope effects[9] in reactions of methyl chloride with aliphatic amines.

Kinetically simple reactions like the one studied here have been the subject of extensive theoretical modeling[10] in the past. These studies have suffered from the arbitrary choice of force field and inconsistency between reactant and transition-state models. For example, for the particular type of reaction under consideration, two different dependences of carbon kinetic isotope effect on the location of the transition state have been postulated. Evidence for bell-shaped dependence[11,12] and for linear dependence without a maximum[13] was obtained from different theoretical calculations. It was finally shown[14] that the problem originates in the reaction coordinate definition. Refined calculations[10] using the BEBOVIB program[15] confirmed the bell-shaped dependence, consistent with what was seen here. An unbiased force field may be obtained from quantum mechanical calculations at the ab initio or semiempirical level. Unfortunately, for ab initio calculations, even a reaction as simple as this one is still prohibitively complex. Semiempirical calculations, on the other hand, can be performed on such systems within a reasonable time limit with readily available computers. The approximations within MNDO or AM1 Hamiltonians appear to be sufficient for reflecting changes of physical properties as small as those introduced by isotopic substitution.

For the reaction in question, values of carbon and deuterium kinetic isotope effects obtained by means of AM1 calculations are in qualitative agreement with previous estimates for analogous reactions on the basis of the BEBOVIB program. In particular, our calculations confirm the bell-shaped dependence of the central carbon kinetic isotope effect on the transition-state location on the reaction coordinate. The dipole moment (8.9 D) and charge developed on the iodide atom ($\delta^- = 0.45$) in the transition state from our calculations are also in excellent agreement with values reported in the literature (8.7 D and 0.43, respectively[16–18]) predicted on the basis of solvent effects on reaction rates. The imaginary frequency of the movement along the reaction coordinate is practically exclusively connected with the asymmetric stretching mode of the N–C–I skeleton. Energetic analysis of the reaction coordinate indicates that the contribution of bending modes of C–H bonds is only a few percent (% *c* in Table II) regardless of the precise structure of the transition state.

Our results demonstrate the usefulness of semiempirical quantum mechanical methods in evaluation of isotope effects and the usefulness of simultaneous measurement of several isotope effects in the study of transition-state structures.

Acknowledgment. This work was supported by NIH Grant GM43043. Mass spectrometric measurements of the deuterated samples by the Midwest Center for Mass Spectrometry are gratefully acknowledged.

Registry No. p-$MeC_6H_4NMe_2$, 99-97-8; MeI, 74-88-4; N (isotope 15), 14390-96-6; D_2, 7782-39-0.

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The Directed Pauson–Khand Reaction[†]

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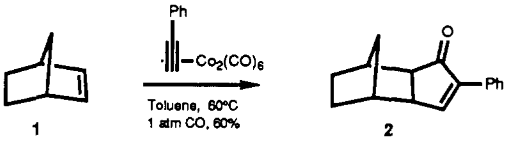
Abstract: The regioselectivity of the cobalt-mediated cocyclization of an alkene, an alkyne, and carbon monoxide has been shown to be directed by the use of a soft atom, either sulfur or nitrogen, tethered to the alkene partner by a carbon chain. Direction from the homoallylic position is more efficient than from the allylic or bishomoallylic position. A rationale is proposed to explain this observation. Studies on the effect of different alkyl groups on the sulfur and nitrogen and other modifications are reported.

Introduction[1c]

The cobalt-catalyzed ene–yne cycloaddition, which yields cyclopentenones, was first reported by Pauson.[2] These cycloaddition reactions were initially carried out with strained alkenes (eq 1), but the reaction has since been extended to include the use of simple alkenes.[3]



(1)

Unstrained alkenes are much less reactive than strained alkenes and, as a result, give lower yields of cyclopentenones. In addition,

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[†] Dedicated to Professor Peter L. Pauson on the occasion of his retirement.

0002-7863/91/1513-1693$02.50/0