Large Deuterium Isotope Effects for Intramolecular CH Insertion Reaction of 2-Alkylphenylnitrenes

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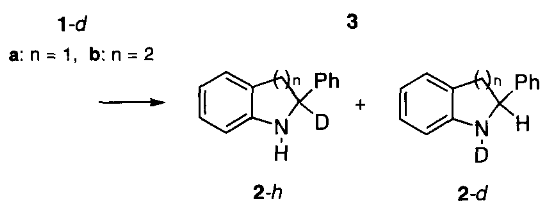
The deuterium isotope effect for the intramolecular CH insertion reaction of the nitrene photolytically generated from 2-(2-phenylethyl)phenyl azide in cyclohexane is obtained as 14.7±0.3 at 20 °C, which supports the hydrogen abstraction-recombination mechanism involving the triplet state nitrene. The temperature dependence of the isotope effect suggests the operation of the tunneling of the hydrogen atom in this process.

The insertion reaction of photolytically-generated arylcarbenes into CH bonds has been fully investigated, and it is established that the reaction proceeds generally by a concerted singlet mechanism.[1] Recently, Kirmse and his co-workers reported that a triplet state carbene was involved in the intramolecular CH insertion reaction with steric constraints in its transition state.[2] Their conclusion was based on the low stereoselectivities and large deuterium isotope effects (k_H/k_D = 4-8) for the intramolecular CH insertion reactions of 2-alkoxyphenylcarbenes and 2-alkylphenylcarbenes. In contrast to the carbene chemistry, few mechanistic studies of the CH insertion reaction of arylnitrenes have been reported.[3] It is known that insertion of a photolytically-generated arylnitrene into a CH bond is an unfavorable process. Thus, photolysis of phenyl azide in a hydrocarbon solvent gives no CH insertion products. However, we have recently found that arylnitrenes generated by photolysis in solutions can insert favorably into the reactive CH bond, such as benzylic, which is situated close to the nitrenic center.[4] Thus, the photolysis of 2-(2-phenylethyl)phenyl azide (**1a**) in cyclohexane afforded 2-phenylindoline (**2a**) exclusively, which was formed by intramolecular CH insertion of the nitrene **3a** into a *β*-CH bond of the 2-phenylethyl group. In order to gain information about the spin state of the nitrene involved in this reaction,[5] we have examined deuterium isotope effects using the deuterium-substituted azide **1a**-*d*. We now report an unusually large deuterium isotope effect for the intramolecular CH insertion reaction, which supports definitely the hydrogen abstraction-recombination mechanism involving the triplet nitrene.



1-*d* **3**

a: n = 1, **b**: n = 2

2-*h* **2**-*d*

The deuterium-substituted azide **1a**-*d* was prepared as follows: deuterium was introduced in the course of the reduction of 2-nitrobenzyl phenyl ketone with $LiAlD_4$ (Aldrich, 98% D). The resulting alcohol was dehydrated by boiling in benzene with a catalytic amount of *p*-TsOH, followed by hydrogenation with 10% Pd/C in AcOH to give 2-(2-deuterio-2-phenylethyl)aniline. It was confirmed by the integration of ^1H NMR that the deuterium isotope purity of the starting reagent was held in the resulting aniline. The aniline was converted to the corresponding azide **1a**-*d* in a usual manner ($NaNO_2$aq/H_2SO_4, followed by NaN_3aq).[4] Irradiation (> 300 nm, 1 h) of **1a**-*d* in cyclohexane with a high-pressure mercury lamp at 20 °C gave a mixture of **2a**-*h* and **2a**-*d*. The total yield of **2a** was 52% based on the consumed starting material (73%). No other products, such as the corresponding aniline or azobenzene, could not be detected in the ^1H NMR spectrum of the photoreaction mixture. The ratio of **2a**-*h* to **2a**-*d* was evaluated to be 14.7±0.3, which was readily obtained by the integration of ^1H NMR in the reaction mixture.[6] The product ratio remained constant during the photoreaction, though continued irradiation resulted in a decrease in the total yield of **2a**, which was due to the photochemical decomposition of **2a**. Furthermore, the product ratio obtained in the photolysis with the longer-wavelength light (> 350 nm) was identical to that obtained with the Pyrex-filtered light (> 300 nm) within the experimental error. However, the ratio of **2a**-*h* to **2a**-*d* obtained in the irradiation of **1a**-*d* at room temperature (20-22 °C) was found to be dependent on the solvent employed in the photolysis: 12.6±0.3 in benzene and 13.6±0.3 in acetonitrile, both of which were slightly smaller compared with in cyclohexane.

It seems reasonable to assume that the deuterium isotope effect (k_H/k_D) for the intramolecular insertion reaction of the nitrene **3a** into a *β*-CH bond of the 2-phenylethyl group is equal to the product ratio [**2a**-*h*]/[**2a**-*d*]. Thus, we obtain unusually large deuterium isotope effects at room temperature (k_H/k_D = 12.6-14.7). These results present unambiguous evidence supporting that the intramolecular CH insertion reaction to give **2a** proceeds not by the direct insertion mechanism of the singlet state nitrene, but by the hydrogen abstraction-recombination mechanism involving the triplet state nitrene. Furthermore, it should be emphasized that this value has considerably surpassed not only the deuterium isotope effect reported for the intramolecular CH insertion reaction of 2-(2-phenylethyl)phenylcarbene (k_H/k_D = 4.6),[2b] but also the maximum possible value for a hydrogen abstraction reaction estimated according to the classical transition state theory (k_H/k_D = 8-12).[7]

Extremely large deuterium isotope effects have been reported for the hydrogen abstraction reaction of radicals, and interpreted in terms of the contribution of quantum-mechanical tunneling to this reaction process.[8,9] In order to gain information about the mechanism of the intramolecular hydrogen abstraction of the triplet nitrene **3a**, we examined the dependence of the isotope effect on the irradiation temperature. It was found that the isotope effect considerably depended on the irradiation temperature (20-

55 °C in cyclohexane, –14-59 °C in acetonitrile): the deuterium isotope effect (k_H/k_D) increased with decreasing the irradiation temperature. Figure 1 illustrates Arrhenius plots of the observed isotope effect. The least-square analysis of the plots gives us important information regarding the reaction mechanism. From the slope of the plot, the difference in the activation energies for H and for D abstraction, $E_D - E_H$, is obtained as 1.77±0.08 and 1.78±0.09 kcal mol^{-1} in cyclohexane and acetonitrile, respectively. From the intercept of the plot, the ratio of the preexponential factor for H abstraction to that for D abstraction, A_H/A_D, is obtained as 0.71±0.09 and 0.63±0.10 in cyclohexane and in acetonitrile, respectively. These results are in line with the general features of a quantum-mechanical tunneling: large difference in the activation energies for H and for D transfer (> 1.3-1.5 kcal mol^{-1}) and small magnitude of the preexponential factor for H transfer relative to that for D transfer.[8a,10] It is also known that the contribution of a tunneling mechanism to a hydrogen transfer reaction gives a nonlinear plot of $\ln(k_H/k_D)$ versus T^{-1}.[8a,10] As shown in Figure 1, however, the Arrhenius plots of the observed isotope effect appear to be linear considering the experimental errors. This inconsistent result would be due to the limited temperature ranges employed in our experiments. Thus, the Arrhenius parameters obtained from the temperature dependence of the deuterium isotope effect, as well as the extremely large values at room temperature, strongly suggest that the intramolecular hydrogen abstraction of the triplet nitrene **3a** proceeds by a quantum-mechanical tunneling mechanism. To validate this assumption, however, the measurement of the rate constants for the intramolecular H and D abstraction of the nitrene **3a** in a wide temperature range is required.

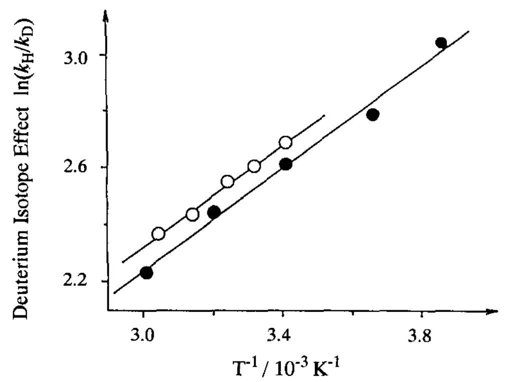


Figure 1. Temperature Depedence of Deuterium Isotope Effects for Intramolecular CH insertion reaction of the nitrene **3a** in cyclohexane (○) and in acetonitrile (●).

It has been reported that a decrease in steric constraints in the transition state of the intramolecular hydrogen transfer to a carbenic center results in a considerable decrease in the deuterium isotope effect owing to enhanced participation of the singlet state carbene.[2c] Thus, we have examined a deuterium isotope effect for the intramolecular CH insertion of the nitrene generated from 2-(3-phenylpropyl)phenyl azide (**1b**). Its γ-deuterated derivative **1b**-*d* was prepared in a similar manner to **1a**-*d* from 2-(2-nitrophenyl)ethyl phenyl ketone. Irradiation (> 300 nm, 1 h) of **1b**-*d* in cyclohexane at 17 °C mainly gave the corresponding azobenzene (27%), together with a mixture of the tetrahydroquinolines **2b**-*h* and **2b**-*d* (9% in total) and 2-benzylindole (3%). The product distribution was in fair agreement with that obtained in the photolysis of **1b**-*h* under the same conditions.[4] From the ^{1}H NMR analysis of **2b** isolated from the reaction mixture, the deuterium isotope effect (k_H/k_D) for the intramolecular insertion of the nitrene **3b** into a γ-CH bond was obtained as 10.1±0.1, which is significantly reduced relative to that obtained in the nitrene **3a**. In agreement with the carbene chemistry, this observation is reasonably interpreted in terms of smaller steric strain in the transition state of the intramolecular hydrogen abstraction in **3b** compared with in **3a**. It should be noted, however, that the value is still large enough to assume that the triplet state nitrene **3b** contributes exclusively to the intramolecular CH insertion reaction. Work is in progress to elucidate the operation of the tunneling in the hydrogen-abstraction reaction of the triplet nitrene.

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5 If the CH-insertion of the nitrene proceeds by the concerted singlet mechanism, small deuterium isotope effects (k_H/k_D = 1-2) are expected. On the other hand, large values of k_H/k_D indicate a high degree of CH bond cleavage in the rate-determining transition state, which would support the hydrogen abstraction-recombination mechanism involving the ground state triplet nitrene.

6 In the ^{1}H NMR spectrum of the photoreaction mixture, a signal assigned to one of the methylene protons of **2a**-*h* and **2a**-*d* appeared at δ 3.44, and a methine signal of **2a**-*d* appeared at δ 4.95.

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This paper is dedicated to Professor Michinori Ōki on the occasion of his 70th birthday.