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Mechanism of Rhodium-Catalyzed Carbene Formation from Diazo Compounds

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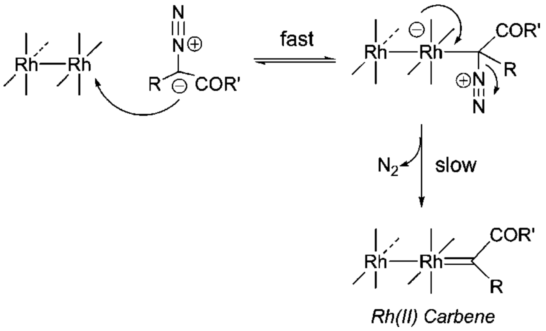
ABSTRACT



A large and normal nitrogen-15 kinetic isotope effect of 1.035 ± 0.003 provides direct support for the proposed mechanism for the rhodium-catalyzed carbene formation from diazo compounds, which involves the fast formation of a metal–diazo complex followed by rate-limiting extrusion of N_2. The large magnitude of the KIE indicates extensive C–N bond fission in the transition state.

The Rh(II)-catalyzed reactions of α-diazo carbonyl compounds have been well-established as powerful approaches to generate Rh(II) carbene species, which may subsequently undergo diverse synthetically useful transformations, such as cyclopropanation, ylide generation, and X-H (X = C, O, S, N, etc.) insertion.[1] Recent advances in asymmetric catalysis with chiral Rh(II) complex have led to high levels of enantiocontrol.[2] On the other hand, the detailed reaction mechanism of the Rh(II)-catalyzed diazo decomposition has not been fully understood despite significant research effort over the past decades.[3] The generally accepted mechanism, originally proposed by Yates in 1952 for Cu-catalyzed diazo decomposition,[4] involves the initial complexation of the negatively polarized carbon of the diazo compound to the axial site of the Rh(II) catalyst, which is coordinatively unsaturated (Scheme 1). The existence of diazonium ion

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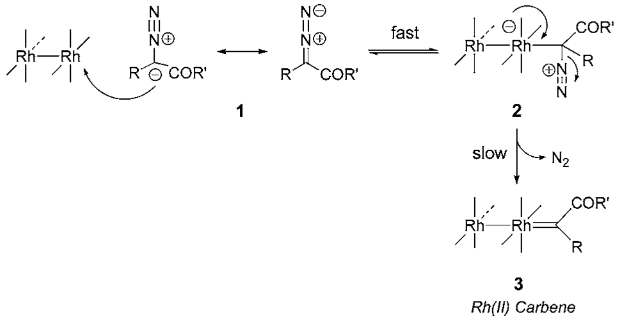
Scheme 1. Proposed Mechanism for Carbene Formation



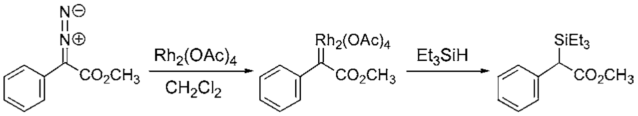
intermediates such as **2** was first demonstrated with use of optical spectroscopy and NMR.[5] Subsequent irreversible extrusion of N_2 from the intermediate **2** generates the Rh(II) carbene complex **3**. In this mechanism, the extrusion of N_2 is considered to be the rate-limiting step. Kinetic studies, especially the observation of saturation kinetics, have provided some support for the mechanism.[6] Also, the observation of a significant negative Hammett ρ value for a series of substituted α-diazophenylacetate substrates is consistent with a rate-limiting step aided by electron-donating substituents, which should facilitate the N_2 extrusion step.[7] These results are in agreement with a computational study that concluded that N_2 loss should be rate limiting.[8] The energetic profiles of the comparative reactions of diazomethane and methyl diazoacetate have also been examined computationally.[9]

In this Letter, we report a large and normal ^{15}N kinetic isotope effect (KIE) for the Rh(II)-catalyzed decomposition of a diazo compound, which provides direct support for the proposed mechanism.

The study of KIEs is a useful tool in the investigation of reaction mechanisms, and in the present reaction can give insight into the transition state of the rate-limiting step, as well as provide a further test of the assumptions of the Yates kinetic model. Previously, ^{13}C KIEs have been employed to probe the carbene insertion step in the cyclopropenation of alkynes by a diazo-derived carbene.[10]

The ^{15}N KIE was determined by isotope ratio mass spectrometry at natural abundance. The Rh(II) acetate-catalyzed carbene formation from methyl α-diazophenylacetate and its subsequent quantitative reaction with triethylsilane was employed as shown in Scheme 2.[7] The reaction was carried out with 0.05 mol % of $Rh_2(OAc)_4$ in dichloromethane at 0 °C. Four different reactions were run to partial completion, ranging from 35% to 73%, and the remaining diazo ester was recovered and purified through column chromatography for isotope ratio mass spectrometry. The fractional conversions were determined by the mass of the diazo ester recovered as compared to that initially used. The $^{15}N/^{14}N$ ratios of these samples were analyzed by using an ANCA-NT combustion system working in tandem with a Europa 20−20 isotope ratio mass spectrometer. Control experiments showed that the reaction workup and purification procedures did not result in fractionation of the diazo compound.

Scheme 2. Formation of a Rhodium Carbene and Its Reaction



The $^{15}N/^{14}N$ ratios were measured for the remaining starting material (R_s) at partial reaction, and for the original starting material before reaction (R_o). Assuming loss of N_2 to form the carbene is irreversible, no steps after formation of the carbene **3** (Scheme 1) will affect the nitrogen ratios. Thus, this method reports only on steps up to and including the conversion of **2** to **3** in Scheme 1. The isotope effects were calculated from these isotope ratios by using eq 1, where f is the fraction of reaction.[11]

$$^{15}k_{obs} = \log(1 - f)/\log[(1 - f)(R_s/R_o)] \qquad (1)$$

The notation for isotope effects used is the use of a leading superscript denoting the heavier isotope; in this case, the ^{15}N isotope effect, or k_{14}/k_{15}, is designated as ^{15}k.

The ^{15}k values obtained from four trials were averaged to give 1.035 ± 0.003. The diazo leaving group contains two nitrogen atoms that contribute to the isotope ratio measurements and thus to the observed isotope effect. Equation 2 shows the observed KIE in terms of the contributions of the KIEs at the two positions.[12] The nitrogen atom involved in the scissile C−N bond will contribute a primary isotope effect. The terminal nitrogen atom will contribute a much smaller secondary effect.

$$(^{15}k_{obs})^{-1} = [(^{15}k_{primary})^{-1} + (^{15}k_{secondary})^{-1}]/2 \qquad (2)$$

Secondary heavy-atom isotope effects are typically an order of magnitude smaller than primary effects that result

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from bond fission.[13] Solving eq 2 for $^{15}k_{\text{primary}}$, assuming an isotope effect of unity at the secondary position, yields a value of 1.072.

In the multistep mechanism of Scheme 1, the KIE will reflect differences between the transition state of the rate-limiting step and the reactant. If the second step is rate limiting as the Yates model describes, then the KIE will reflect the transition state for loss of N_2 as intermediate **2** is converted to the carbene (Scheme 1). In this case, a large normal isotope effect is expected. If formation of adduct **2** is rate limiting a much smaller KIE is expected. Adduct formation involves the hybridization change of carbon from sp^2 to sp^3 and a reduction in C−N bond order due to loss of double bond character in the C−N bond. The hybridization change will result in an inverse isotope effect due to compression of bending modes,[13] while the bond order reduction will contribute a normal effect. An estimation of the isotope effect that might be expected on adduct formation is provided by the KIE of 0.9975 ± 0.0003 for the formation of a tetrahedral intermediate in the hydrolysis of an amide.[14] This slightly inverse value indicates that bending mode compression outweighs the reduction in bond order resulting from loss of amide resonance. While the C−N bond order is similar but not identical in the diazo reactant in the present study compared to the amide, this precedent nonetheless gives confidence that the secondary isotope effect for adduct formation is expected to be much smaller than the large, normal observed KIE of 1.035.

The goals of this study were to confirm whether fission of the C−N bond occurs in the rate-limiting step of the Rh(II)-catalyzed diazo ester decomposition, and to obtain an indication of the extent of bond fission in the transition state. If the coordination of the negatively charged carbon atom of the diazo ester to the Rh(II) complex is rate limiting, or if coordination is not rapidly reversible, then the observed ^{15}k will reflect only this step. In this case, for the reasons described above, a small secondary nitrogen isotope effect would be observed, which is not the case. A significant, normal isotope effect is expected if C−N bond fission is rate limiting. The $^{15}k_{\text{obs}}$ of 1.035 and the estimated value of 1.072 for $^{15}k_{\text{primary}}$ are large; for comparison, a theoretical maximum KIE of 1.044 has been calculated for the fission of a C−N single bond.[15] The C−N bond order in the diazo ester is greater than unity, which will result in a higher maximum isotope effect for the present reaction. Previous $^{15}k_{\text{obs}}$ values measured for the hydrolysis of substituted aryl diazonium salts range from 1.043 to 1.047 depending on the identity of substituents on the benzene ring.[16] These reactions proceed by an S_N1 process, with a late transition state.

In summary, the large, normal isotope effect requires that C−N bond fission and extrusion of N_2 must be largely, if not fully, rate limiting. This is consistent with the transformation of **1** to **3** via a rapid equilibrium formation of **2**, followed by rate-limiting formation of the Rh(II) carbene **3**, as postulated by Yates and supported by kinetic and computational studies.[5−9] The magnitude of the KIE indicates a high degree of C−N bond fission in the transition state for loss of N_2, though slightly less than that in the decomposition of aryl diazonium salts.

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Supporting Information Available: Experimental procedures and kinetic isotope effect data. This material is available free of charge via the Internet at http://pubs.acs.org.

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