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Mechanism of Rh_2(II)-Catalyzed Indole Formation: The Catalyst Does Not Control Product Selectivity

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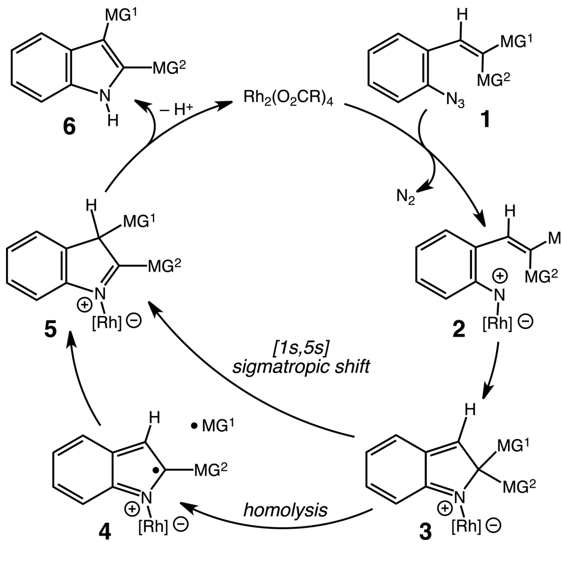
Supporting Information

ABSTRACT: Possible mechanisms for Rh-promoted indole formation from vinyl/azidoarenes were examined computationally, and a mechanism is proposed in which the Rh catalyst promotes generation of a nitrene but is not directly involved in cyclization.

Indole synthesis has played a central role in the construction of complex heterocycles of importance to biology and medicine.[1] We recently described an approach to substituted indoles under mild conditions using readily obtained azide starting materials and rhodium catalysts.[2] Although this synthetic method is effective, several mechanistic questions remain unanswered (Scheme 1): How is the nitrene formed?[3] Is the ring-closing step pericyclic? What is the origin of observed migratory preferences? What is the role of the catalyst in each of these steps? In this work, we use density functional theory (DFT) calculations to address all of these issues and describe new experimental results in support of our mechanistic model.

Scheme 1. Proposed Mechanisms for Indole Formation[a]



[a]MG = Migrating Group.

All calculations were performed with Gaussian09.[4] Geometries were optimized without symmetry constraints using the uM06-2X functional[5] with the 6-31+G(d,p)[6] basis set and broken symmetry Kohn–Sham wave functions, unless otherwise specified, for all non-Rh containing species.[7] Rh-containing species were optimized using the M06 functional[4] and the LANL2DZ basis set and effective core potential (ECP) for all atoms,[8] but relative energies for Rh-containing systems were also computed using the SDD ECP and basis set for Rh and the 6-31+G(d,p) basis set for all other atoms; the latter energies are used here for discussion.[9] These approaches have been found to give good agreement with experimental data for a range of transition metal complexes, including those containing Rh.[10] Catalyst ligands were approximated using formate groups.[11] All structures were characterized as transition state structures or minima by frequency analysis, and free energies (kcal/mol) at 298 K are reported unless otherwise specified. Intrinsic reaction coordinate (IRC) calculations were also used to verify the identity of some transition state structures (see Supporting Information).[12] When calculated $\langle S^2 \rangle$ values were not equal to zero, values are explicitly noted. Structural diagrams were created using *Ball&Stick*.[13]

Of interest for a variety of Rh-catalyzed reactions is the mechanism of nitrene formation, and the role the Rh catalyst plays in its stability. We examined both catalyzed and uncatalyzed N_2 extrusion (Figure 1); we focus our initial mechanistic discussion on the $MG^1 = H$, $MG^2 = NO_2$ system. The computed barrier for catalyzed N_2 extrusion was 20.5 kcal/mol, consistent with the experimental conditions used for the indole formation reaction, whereas the barrier was computed to be 13 kcal/mol higher without [Rh].[14] The computed exergonicities are −7.2 and −3.7 kcal/mol for uncatalyzed and catalyzed, respectively.

Once the nitrenoid (**2**) is formed, cyclization to **3** is presumed to rapidly ensue. This reaction can be formulated as a $4e^-$ electrocyclization (in analogy to cyclization of a pentadienyl cation; this reaction could also be described as an $8e^-$ electrocyclization if the entirety of the benzene π-system is considered)[15] or as a pseudopericyclic ring closure in which the nitrogen lone pair is involved.[16] While this issue is not trivial to resolve, the transition state structure (TSS) for ring closure (Figure 2) appears to involve the conrotation expected for

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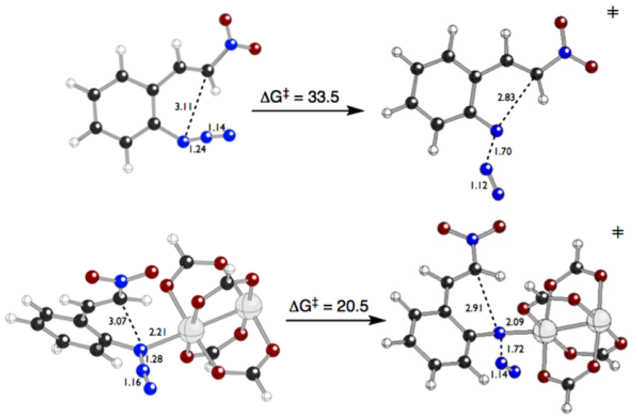

Figure 1. Energetics (uM06-2X/6-31+G(d,p) top, uM06/6-31+G-(d,p)-SDD//uM06/LANL2DZ bottom, kcal/mol) for catalyzed and uncatalyzed N_2 extrusion. Selected distances are shown in Å.

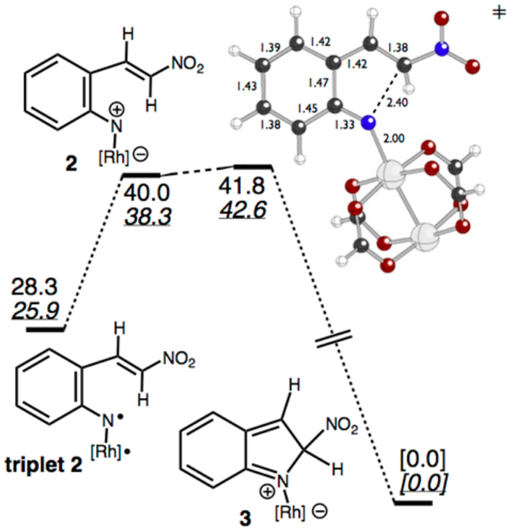

Figure 2. Ring-closure to form **3**. Free energies relative to that of **3** are shown in kcal/mol, calculated at the uM06/6-31+G(d,p)-SDD//uM06/LANL2DZ level of theory; distances are shown in Å.

thermal electrocyclization when the [Rh] is complexed (based on animation of the vibrational mode associated with the imaginary frequency).[15] Note that the triplet state is preferred for **2**, but the singlet form of **2** is expected to be formed first (i.e., the TSSs in Figure 1 are singlets) and its reaction to form **3** is associated with a very small barrier. Direct cyclization from triplet **2** is predicted to have a barrier of 28 kcal/mol, making such a pathway noncompetitive. Cyclization is highly exergonic. We were unable to find a competitive pathway involving direct C−H insertion.

After ring-closure, a net 1,5-shift (which could also be described as a 1,9 shift) of MG^1 or MG^2 occurs. In previous work, we proposed that the electron-withdrawing ability of the migrating group was the dominant factor in determining which shift would be favored and hence which final product would dominate.[2] This proposal was based on the observed trend in migratory aptitude: akyl < aryl < amide < H < sulfonyl < ketone < nitro. Two possible mechanisms for the observed shifts were proposed: concerted sigmatropic migration (**3** → **5**, Scheme 1) and homolytic cleavage/radical recombination (**3** → **4** → **5**; Scheme 1). Conversion of **3** to **4** (cleavage of the $C-N_{NO2}$ bond) was predicted to be endergonic by 29.5 kcal/mol for the MG^1 = H, MG^2 = NO_2 system, while concerted NO_2 migration was predicted to have a barrier of only 12.1 kcal/mol, suggesting that homolytic cleavage is not competitive (Figure 3). The competing sigmatropic shift of hydrogen was predicted to have a barrier of 26.0 kcal/mol, consistent with the experimental observation that only products arising from NO_2 shift are observed.[2]

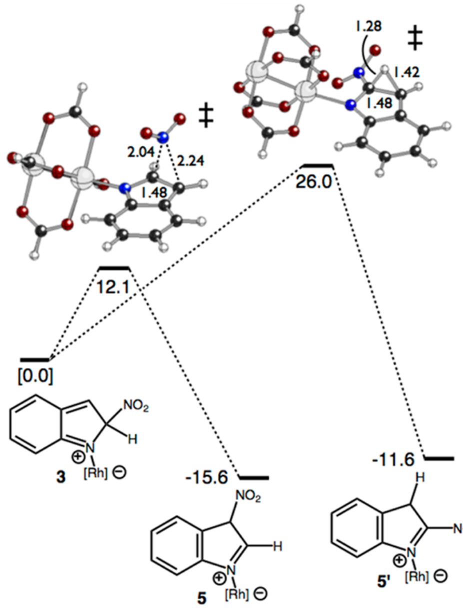

Figure 3. [1,5]-Sigmatropic shifts for **3**. Free energies relative to that of **3** are shown in kcal/mol, calculated at the uM06/6-31+G(d,p)-SDD//uM06/LANL2DZ level of theory. Note that the TSSs shown are derived from enantiomeric reactants to facilitate comparisons of their structures.

In the absence of catalyst, the barrier for sigmatropic shift was also predicted to be quite low, and NO_2 shift was still predicted to dominate over H shift (Figure 4). This observation caused us to question whether or not the catalyst was actually involved in the migration step. Performing the reaction in Figure 4 at high temperature (xylenes, 140 °C) led exclusively to the H-shifted product,[17] but at that temperature, NO_2 migration would be reversible, allowing the thermodynamic product (that derived from H migration) to dominate.

Upon examining other migrating groups, we found a similar but not identical ordering of migratory preferences for both migration with and without bound [Rh] (Table 1). For the MG^2 = $COCH_3$ case (entry 4), we predicted preferential $COCH_3$ migration in the presence or absence of catalyst, consistent with the reported experimental result, but not distinguishing between a catalyzed and catalyst-free rearrangement.[2] Similarly, for the MG^2 = CHO case (entry 6), we again predicted preferential migration of CHO in the presence or absence of catalyst. The results of these calculations were subsequently tested, and exclusive CHO migration was observed to produce the C3-substituted indole as the only product of either the Rh_2(II)-catalyzed or uncatalyzed reaction. In contrast, for the MG^2 = CO_2CH_3 case (entry 5), we predicted preferential CO_2CH_3 migration in the presence of catalyst but H migration in the absence of catalyst; the latter corresponds to the experimental result (with MG^2 = CO_2*i*-Pr).[2b] Although we cannot say definitively that the catalyst is always absent during the migration step, such a model is consistent with all of the available experimental and theoretical results.

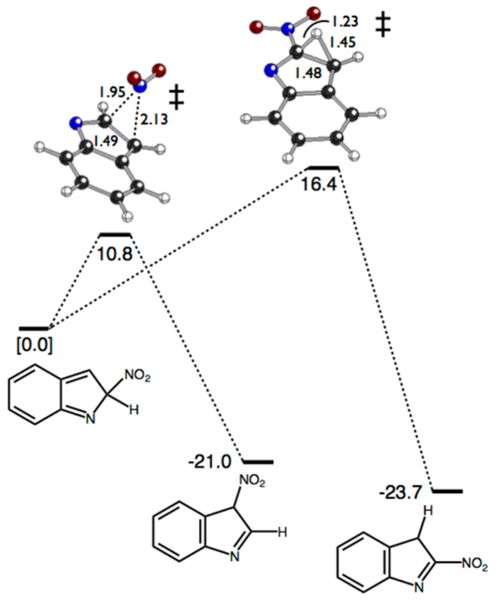

Figure 4. [1,5]-Sigmatropic shifts without bound [Rh]. Free energies relative to that of decomplexed **3** are shown in kcal/mol, calculated at the uM06-2X/6-31+G(d,p) level of theory. Note that the TSSs shown are derived from enantiomeric reactants to facilitate comparisons of their structures.

Table 1. Predicted Migratory Preferences ($\Delta\Delta G^\ddagger$, kcal/mol) for MG^2 versus H for Catalyzed and Uncatalyzed Reactions

entry	MG^2	σ_p[b]	$\Delta\Delta G^\ddagger$ catalyzed[c]	$\Delta\Delta G^\ddagger$ uncatalyzed[d]	experimental ratio of products from MG^2 vs H migration
1	NO_2	0.78	13.9	5.6	>95:5
2	CN	0.66	−5.1	−11.1	<5:95
3	CF_3	0.54	−16.5	−22.5	<5:95
4	$COCH_3$	0.50	8.1	1.6	>95:5
5	CO_2CH_3	0.45	1.2	−5.7	<5:95 (for CO_2*i*-Pr)
6	CHO	0.42	14.4	4.7	>95:5
7	CH_3	−0.17	−10.6	−22.5	<5:95

[a]Positive $\Delta\Delta G^\ddagger$ values indicate a preference for migration of MG^2. MG^2 groups are ordered on the basis of the Hammett σ constants. Experimental product ratios are from ref 2, except the values for MG^2 = CN, CF_3, and CHO, which are reported for the first time here; values greater than 1 indicate a preference for migration of MG^2. [b]σ_p constants are taken from ref 20. [c]uM06/6-31+G(d,p)-SDD//uM06/LANL2DZ. [d]uM06-2X/6-31+G(d,p).

These results led us to speculate further upon the origins of the migratory trend. While traditional wisdom would suggest that the group most capable of stabilizing a carbocation would preferentially migrate (except for MG = H), a concept that is clearly not in line with our results (experimental or computational), low barrier migrations of electron deficient groups have been reported.[18] We also predicted migratory preferences for MG^2 = CF_3 and CN systems (Table 1; entries 2 and 3). Hydrogen migration was predicted for these systems, however. The predictions for both the MG^2 = CF_3 and CN systems were experimentally tested, and as predicted, only H migration was observed for both the Rh_2(II)-catalyzed and the uncatalyzed reaction. Note that the electron-withdrawing groups predicted not to migrate tend to lack π-systems that extend above/below the delocalized orbital array corresponding to the rearranging electrons in the TSS, suggesting that secondary orbital overlap (likely involving lone pairs on the migrating groups) may play a role in lowering the barrier of these rearrangements (see Supporting Information for details).[19]

The mechanistic scheme we favor on the basis of the results described above consists of the following steps: (1) complexation of the azide by the catalyst, (2) rate-determining extrusion of N_2, (3) electrocyclic ring closure to form **3**, (4) dissociation of the catalyst, (5) concerted [1s,5s]-shift of MG^1 or MG^2, and (6) deprotonation. Step 2 is clearly promoted by the [Rh] catalyst. Step 5 need not be, although in some cases the catalyst may still be present. Note that the predicted difference in product distribution for MG^2 = CO_2R with and without catalyst bound (Table 1, entry 5) allows us to conclude that the catalyst is indeed absent during the migration step, at least in this case. Hopefully this type of mechanistic probe will find broader application. Overall, the catalyst is crucial for generating the initial reactive intermediate, but not essential for controlling most subsequent steps. This situation is analogous to that found for many terpene synthase catalyzed reactions; the catalyst is essential for generating a reactive species (in this case a carbocation), whose inherent reactivity is then expressed.[21]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11427.

> Coordinates and energies for all computed structures and experimental data for the MG^2 = CN, CF_3, and CHO systems (PDF)

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Notes

The authors declare no competing financial interest.

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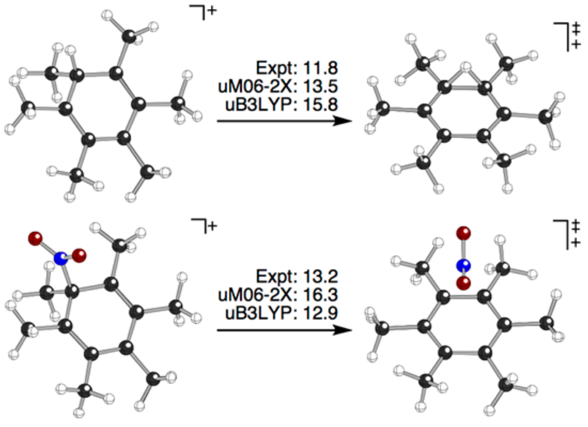

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