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[3,3]-Sigmatropic Shifts of *N*-Allylhydrazones: Quantum Chemical Comparison of Concerted and Radical Cation Pathways

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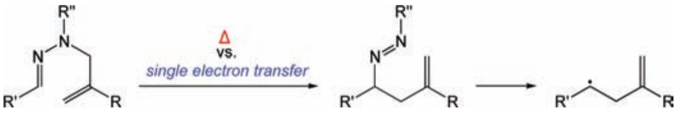
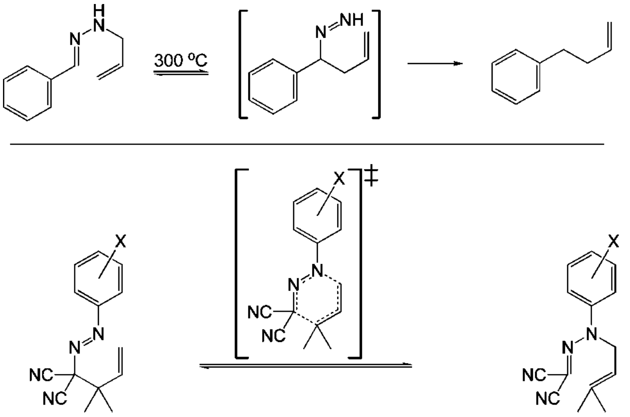
ABSTRACT



N-Allylhydrazones are reported to undergo an elaborate [3,3]-sigmatropic shift/N_2 extrusion sequence. Both concerted and radical cation pathways for the [3,3]-sigmatropic shift of several *N*-allylhydrazones were investigated using B3LYP/6-31+G(d,p) calculations. It was discovered that, assuming facile formation of the *N*-allylhydrazone radical cation, the rearrangement takes place through a series of low barrier steps energetically preferred to the concerted alternative available to *neutral* *N*-allylhydrazones. Subsequent N_2 extrusions forming corresponding homoallyl radicals were found to be extremely facile.

The mechanisms of various [3,3]-sigmatropic shifts (especially the Cope rearrangement) have long served as subjects for spirited debate.[1] Ultimately, it was discovered that the nature and position of substituents plays a key role in determining both the concertedness and synchronicity of these rearrangements.[2] *N*-Allylhydrazones[3] are unique substrates for [3,3]-sigmatropic shifts in that their rearrangement leads to products prone to loss of N_2. This rearrangement/N_2 extrusion sequence was first reported to occur under thermal conditions (300 °C) in 1973 by Stevens et al., who described the reaction of the *N*-allylhydrazone of benzaldehyde (as well as other carbonyl compounds) to form 3-butenylbenzene (Scheme 1, top).[4]

Scheme 1. Previously Studied Thermal [3,3]-Sigmatropic Shifts Involving *N*-Allylhydrazones[4,5]



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(1) (a) Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1992**, *25*, 537–543. (b) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81–90. (c) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378–8388.

(2) The mechanism was termed "chameleonic" due to its change of mechanism in the "environment" of particular substituents: Doering, W. v. E.; Wang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10112–10118. For a discussion of the chameleonic behavior of the Pd(II)-promoted Cope rearrangement, see ref 8b.

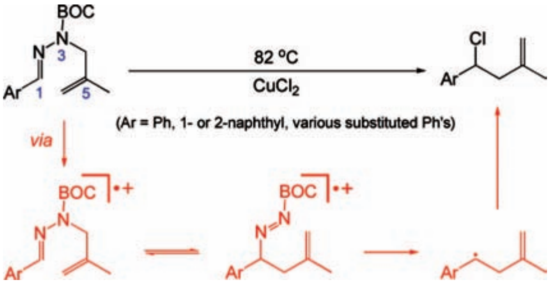
(3) See the following for examples of thermal [3,3]-sigmatropic shifts of diazo compounds that are not *N*-allylhydrazones: (a) Beck, K.; Hünig, S.; Reinold, P. *Tetrahedron* **1988**, *44*, 3295–3307. (b) Beck, K.; Burghard, H.; Fischer, G.; Hünig, S.; Reinold, P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 672–673.

10.1021/ol801107j CCC: $40.75

In 1986, Mitsuhashi was able to determine the rates of [3,3] rearrangement for several aryl-substituted *N*-allylhydrazones (Scheme 1, bottom).[5] It is important to note, however, that the rearrangements described by Mitsuhashi[5] run in *reverse* (i.e., *forming N*-allylhydrazones) relative to those examined by Stevens et al.[4] From the kinetic data, Mitsuhashi reasoned that the thermal rearrangements of his systems were most likely concerted but proceeded through charge-separated transition-state structures in which negative charge has built up on the benzylic nitrogen.[5]

In 2008, Thomson et al. reported a related [3,3]-sigmatropic shift/N$_2$ extrusion sequence promoted by CuCl$_2$ (Scheme 2).[6] It was hypothesized that this rearrangement procedes via a radical cation pathway (Scheme 2, bottom).[6–8] It is our aim to assess the feasibility of such a reaction mechanism and characterize the transition state structures and minima involved using quantum chemical methods (B3LYP/6-31+G(d,p)).[9]

Scheme 2. Reported CuCl$_2$-Promoted [3,3]-Sigmatropic Shift of *N*-Allylhydrazones and Proposed Intermediates along the Radical Cation Pathway[6]



The Unsubstituted Parent System. The [3,3] sigmatropic shift of the *neutral N*-allylhydrazone of formaldehyde can proceed through a single transition-state structure—a reaction with a barrier of 34 kcal/mol (Figure 1).[10] If, however, a radical cation pathway is employed, a much more complex reaction sequence is realized (Figure 2). The initial stages of this reaction include C−C bond formation (through $2^{\ddagger}$) to form an intermediate with a 6-membered ring (**3**), which is actually slightly lower in energy than the starting material (when preorganized in a chair structure, as in **1**). At this point,

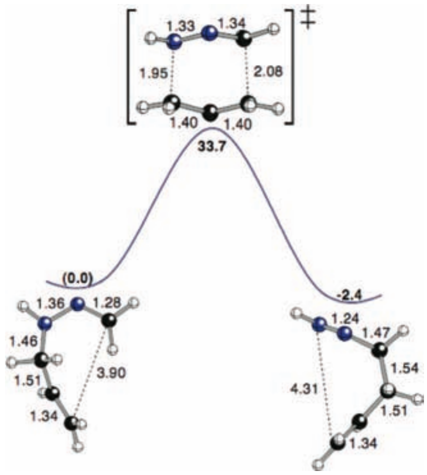


Figure 1. [3,3]-Sigmatropic shift of the *neutral N*-allylhydrazone of formaldehyde. For each structure, energies (ΔG at 25 °C, relative to that of the reactant) are displayed in kcal/mol and select distances are shown in angstroms (Å).

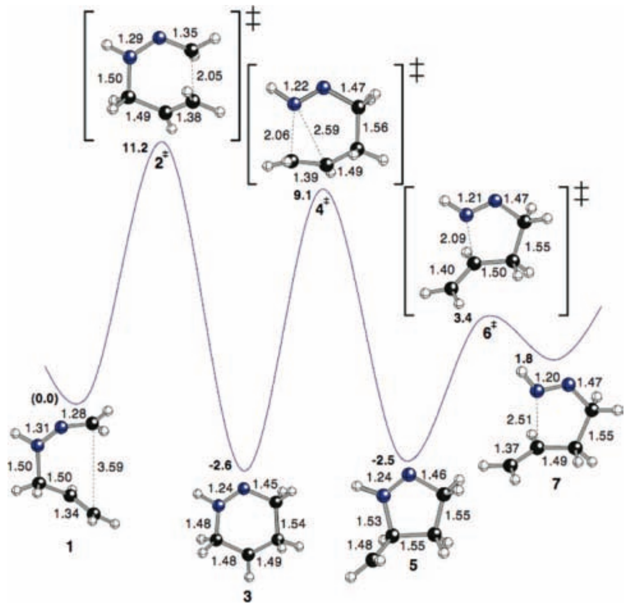


Figure 2. [3,3]-Sigmatropic shift of the *radical cation N*-allylhydrazone of formaldehyde. For each structure, energies (ΔG at 25 °C, relative to that of **1**) are displayed in kcal/mol and select distances are shown in angstroms (Å).

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(4) Stevens, R. V.; McEntire, E. E.; Barnett, W. E.; Wenkert, E. *Chem. Commun.* **1973**, 662–663.

(5) Mitsuhashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 2400–2405.

(6) Mundal, D. A.; Lee, J. L.; Thomson, R. J. *J. Am. Chem. Soc.* **2008**, *130*, 1148–1149.

(7) Thomson reported[6] that the reaction was not only promoted by CuCl$_2$ but also by [(4-BrPh)$_3$N][SbCl$_6$], providing substantial evidence that the sequence proceeds through a radical-cation pathway.

(8) For reports on metal-promoted sigmatropic shifts from our group, see: (a) Wang, S. C.; Tantillo, D. J. *J. Organomet. Chem.* **2006**, *691*, 4386–4392. (b) Siebert, M. R.; Tantillo, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 8686–8687.

(9) All calculations were performed using GAUSSIAN03. All geometries and energies reported herein are from B3LYP/6-31+G(d,p) optimizations without symmetry constraints. The B3LYP method has been used previously, by us and others, to study a variety of radical cation rearrangement reactions; see, for example: (a) Park, Y. S.; Wang, S. C.; Tantillo, D. J.; Little, R. D. *J. Org. Chem.* **2007**, *72*, 4351–4357. (b) Gerkin, J. B.; Wang, S. C.; Preciado, A. B.; Park, Y. S.; Nishiguchi, G.; Tantillo, D. J.; Little, R. D. *J. Org. Chem.* **2005**, *70*, 4598–4608, and ref 11, which provides evidence that B3LYP produces results similar to those from CCSD and QCISD. B3LYP has also been used to study a variety of [3,3]-sigmatropic shifts. For leading references, see: (c) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378–8388. (d) Guner, V. A.; Khuong, K. S.; Houk, K. N.; Chuma, A.; Pulay, P. *J. Phys. Chem.* **2004**, *108*, 2959–2965. All reported energies are ΔG at 25 °C, with unscaled zero-point energy corrections included. See the Supporting Information for additional computational details and references, including the full GAUSSIAN03 reference.

rather than breaking the C−N bond and opening to the expected product of a [3,3]-sigmatropic shift, cyclic intermediate **3** undergoes a bond migration/ring contraction step to form an intermediate with a five membered ring (**5**). Intermediate **5** can then undergo a C−N bond-breaking event that results in the product of a formal [3,3]-sigmatropic shift (**7**). Although the C−N bond is broken in going from **5** to **7**, there remains some C−N interaction in **7**, as evidenced by the short, 2.51 Å, C−N distance. Overall, the radical cation version of this [3,3]-sigmatropic shift has a much smaller barrier than the neutral version (11 vs 34 kcal/mol; compare Figures 1 and 2), a phenomenon observed previously for other radical cation pericyclic reactions.[11]

In order for N_2 loss to occur, the nitrogen bearing the hydrogen atom during the initial steps (Figure 2) must be deprotonated. If intermediate **5** is deprotonated, then radical **8** is formed (Figure 3), which is also able to cleave the C−N bond that leads to the expected product of [3,3] rearrangement (**10**; also note that structure **7** could be deprotonated to form **10**). Although the barrier for the C−N bond breaking event is smaller for the deprotonated species (compare **5**→**6**‡ with **8**→**9**‡; a difference of 3.6 kcal/mol in favor of the deprotonated species), the steps preceding this event have higher barriers (see Figure 2), and hence, C−N bond breaking could take place from either the radical cation or neutral radical species with little effort. The resultant radical, intermediate **10**, has a very small barrier toward loss of N_2 to form homoallyl radical **12** (which can then be trapped by a Cl source).

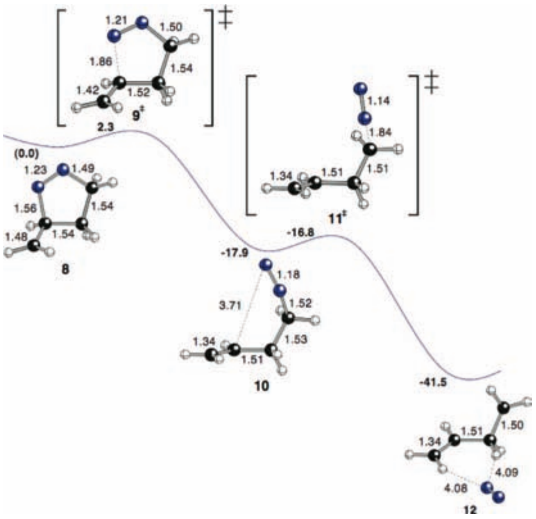

Figure 3. Concluding steps of the [3,3]-sigmatropic shift/N_2 extrusion sequence for the *N*-allylhydrazone of formaldehyde. For each structure, energies (Δ*G* at 25 °C, relative to that of **8**) are displayed in kcal/mol and select distances are shown in angstroms (Å).

Substituent Effects. Thomson et al.'s report[6] described the rearrangement of a system with substituents at C1, N3, and C5 (see Scheme 2 for numbering). To assess the effects of these substituents on the ease of the rearrangement, each was added in sequence (first, the methyl group to C5, next, a phenyl group to C1, and last, the ester group—here approximated as the methyl ester—to N3).

One would expect addition of the methyl group to C5 (see Scheme 2 for numbering) to lead to selective stabilization of intermediate **3**, which is electron-deficient at C5 (see Figure 4, top, for an electrostatic potential map and spin density plot, which collectively suggest that most of the unpaired spin density resides on C5, while the positive charge resides near the N_2 unit), as well as the transition-state structures that frame the well in which **3** resides (**2**‡ and **4**‡). In contrast, one would expect very little effect on the remaining structures throughout the [3,3]-sigmatropic shift/N_2 extrusion pathway (Figures 2 and 3, collectively). Table 1 summarizes the changes in the relative energies of structures **1**−**12** upon addition of the methyl group. Exactly as expected, the largest energetic effects of adding the methyl group to the *N*-allylhydrazone of formaldehyde involve lowering of the energies of **2**‡, **3**, and **4**‡ relative to that of **1**.

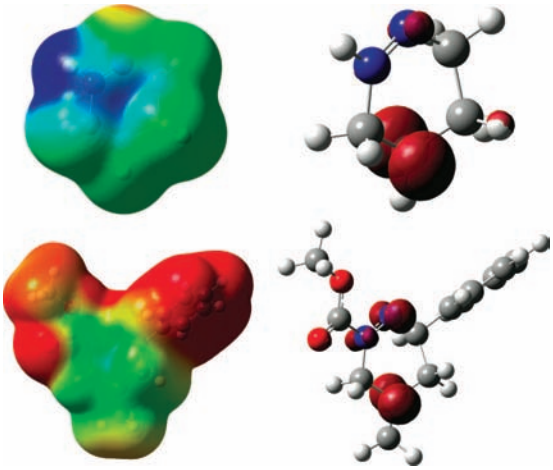

Figure 4. Electrostatic potential (ESP) maps (left) and spin density (SD) surfaces (right) for **3** (top) and the N3-methyl ester/C1-phenyl/C5-methyl-substituted analog of **3** (bottom). ESP maps are displayed with an isovalue of 0.0004 over a charge range of 0.1−0.2, while SD surfaces are displayed wih an isovalue of 0.008. Mulliken atomic spin densities for **3** (top right) are 1.04 for C5 and 0.07 for N2, while those for the N3-methyl ester/C1-phenyl/C5-methyl substituted analogue of **3** (bottom right) are 0.67 for C5 and 0.32 for N2.

Addition of the phenyl ring to C1 of the *N*-allylhydrazone (to form the C5-methyl, C1-phenyl derivative; see Scheme 2 for numbering) is expected to *increase* the barrier for the initial step, as well as the relative energies of the structures following **2**‡, since the conjugation of the C=N double bond with the

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(10) Computed barriers for concerted [3,3] shifts of all hydrazones discussed herein, as well as structural details for all stationary points involved, can be found in the Supporting Information.

(11) See the following and references therein: (a) Saettel, N.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* **2001**, 1429–1439. (b) Wiest, O.; Oxgaard, J.; Saettel, N. J. *Adv. Phys. Org. Chem.* **2003**, *38*, 87–110.

Table 1. Computed Energies (ΔG at 25 °C) in kcal/mol for the [3,3]-Sigmatropic Shift/N_2 Extrusion Pathway for Unsubstituted Structures **1**−**12** and Substituted Analogues

structure	parent (no substituents)	C5-methyl group	C1-phenyl/ C5- methyl	N3-methyl ester/ C1-phenyl/ C5- methyl
1	(0.0)	(0.0)	(0.0)	(0.0)
2‡	11.2	6.4	22.5	19.8
3	−2.6	−6.3	18.0	17.7
4‡	9.1	4.6	29.0	27.8
5	−2.5	−2.6	20.7	22.2
6‡	3.4	2.5	26.0	24.8
7	1.8	−0.5	22.9	20.3
8	(0.0)	(0.0)	(0.0)	
9‡	2.3	2.7	2.3	
10	−17.9	−19.0	−19.5	
11‡	−16.8	−17.7	−20.0	
12	−41.5	−42.3	−57.6	

aromatic ring that is present in **1** is lost in the initial reaction step. In addition, selective stabilization of the homoallyl radical product (**12**), as well as the transition state structure for its formation (**11**‡), is expected, since it now features the radical center in a benzylic position. The data in Table 1 is in agreement with these predictions, with the barrier to the first bond making event more than *tripling* and the product (**12**) being selectively stabilized by more than 15 kcal/mol relative to the case with only a C5-methyl group![12]

Addition of the ester moiety to N3 of the *N*-allylhydrazone (see Scheme 2 for numbering) had only a small effect on the energetics of the rearrangement (Table 1). However, electrostatic potential and spin density surfaces for the N3-methyl ester/C1-phenyl/C5-methyl substituted analog of **3** (Figure 4, bottom) reveal that substitution has led to greater delocalization of the unpaired spin density and positive charge.

Although the ester moiety does not seem to provide any substantial perturbations to the overall energetics of the [3,3] rearrangement, it does play an important role in the experimental system.[6] As noted before, the terminal nitrogen (N3) must be free of any substituents in order for N_2 extrusion to occur. The experimentally used *tert*-butoxycarbonyl (BOC) protecting group undergoes an elegant decomposition, expelling 2-methylpropene, carbon dioxide, and the desired terminal amide. Further, this decomposition likely proceeds under much milder conditions than would be necessary for deprotonation of a terminal NH (e.g., the system in Figure 2), and therefore, regardless of any electronic effects induced by the ester, it is important in experimentally accessing a species that can extrude N_2.[13]

In summary, once initial formation of a radical cation species (**1**) is achieved, a series of low barrier steps leads to a homoallyl radical in an exergonic process. It is therefore likely that the generation of **1** by single-electron transfer is the rate-limiting step for the reactions described by Thomson et al.[6] Due to the elusive nature of $CuCl_2$ in solution, and the demonstrated promotion of this reaction by [(4-BrPh)$_3$N][SbCl$_6$] in the absence of copper,[6,7] it seems reasonable to invoke a pathway free of metal intervention.[8] This pathway has a much lower barrier than would a pathway involving a concerted neutral [3,3] shift,[10] and it involves an unexpected detour through a 5-membered ring intermediate.

Acknowledgment. We gratefully acknowledge the University of California−Davis and the National Science Foundation's CAREER and Partnership for Advanced Computational Infrastructure (PSC) programs for their support.

Supporting Information Available: Further computational details and data including coordinates, energies, and IRC data for all computed structures, as well as information about the concerted [3,3]-sigmatropic shift of *neutral N*-allylhydrazones. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) This difference is consistent with the difference in C−H bond enthalpies for ethane and toluene: ~11.5 kcal/mol. See the following for compiled experimental and theoretical C−H bond enthalpies: Clot, E.; Mérgret, C.; Eisenstein, O.; Perutz, R. N *J. Am. Chem. Soc.* **2006**, *128*, 8350–8357.

(13) Attempts to minimize the energy of the N3-carboxylate substituted analogues of **5** → **7** (or **8** → **10**, depending on your perspective) resulted in immediate decarboxylation; see the Supporting Information for further details.