Communication

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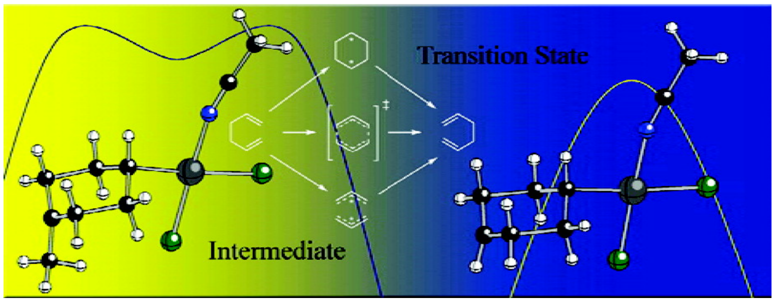

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Transition-State Complexation in Palladium-Promoted [3,3] Sigmatropic Shifts

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The mechanism of the Cope rearrangement (the [3,3]-sigmatropic shift of a 1,5-hexadiene) has long stood as a point of debate.[1] Much of the controversy was a result of its "chameleonic"[2] behavior; namely, its mechanism varies between concerted and stepwise pathways depending on the nature and position of appended substituents. Nonetheless, this reaction has been used as a key step in many creative and elegant syntheses.

Palladium-promoted Cope rearrangements have also been utilized to advantage by synthetic chemists.[3−5] In particular, substantial attention has been given to the Pd(II)-promoted Cope reaction,[3,4] which has been characterized as proceeding through the stepwise mechanism shown in Scheme 1.[4] Key experiments supporting this mechanistic picture were described by Overman and co-workers who demonstrated a linear free energy relationship for rearrangements of various 2-aryl-1,5-hexadienes promoted by $PdCl_2(C_5H_{11}CN)_2$ (Scheme 1, R = Ar),[6] consistent with a mechanism involving the build-up of positive charge near the aryl group in the rate-determining transition structure.[4]

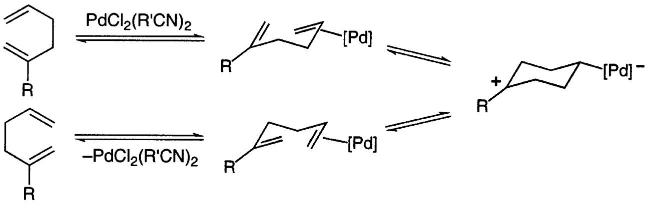
Herein we show, using quantum chemical calculations (B3LYP/LANL2DZ),[7,8] that the mechanistic picture in Scheme 1 is not necessarily applicable to all Pd(II)-promoted Cope rearrangements, and that the potential energy surfaces for such reactions show some of the same peculiarities as those of their metal-free cousins.

For example, calculations using $PdCl_2(MeCN)$ bound to 2-phenyl-1,5-hexadiene revealed that although a stepwise pathway is possible, and the expected cyclohexyl cation-like intermediate can indeed exist, this intermediate resides in a very shallow minimum (~1 kcal/mol deep; see Figure 1). The minimum is, in fact, so shallow that one must wonder whether the very presence of the phenyl substituent "coerced" the 1,5-hexadiene into rearranging via a stepwise path. To explore whether rearrangements without such intermediates are possible, we examined a variety of systems, both with and without aryl groups (Tables 1 and 2).

For all aryl-substituted systems explored (Table 1), the stepwise mechanism persisted, regardless of whether the substituents were donors or acceptors. In general, electron-withdrawing groups both reduced the depth of the well in which the intermediate resides and increased the barrier for formation of the intermediate. This is consistent with a mechanism such as that shown in Scheme 1,[4] in which progression from the [Pd]-bound reactant to the C−C bond-forming transition structure and then to the cyclohexyl-like intermediate is accompanied by removal of electron density from the carbon adjacent to the aryl ring, leaving each successive structure with an increased "electron demand"[10] at that position. Note, however, that for the substituents examined, the well depth never exceeded 5.1 kcal/mol, and in many cases it effectively disappeared.

Several other (non-aryl) substituents were also examined (Table 2).[6] When the aryl substituent was replaced with a hydrogen, no intermediate was located; that is, the rearrangement for the "parent" system is actually *concerted* (see Figure 2a for the single transition structure)![11] Note that the computed barrier for this rearrangement (30.1 kcal/mol) is higher than that for any of the systems with aryl substituents; this is consistent with the involvement of a cyclohexyl cation-like structure, but here, in contrast to the aryl-substituted cases, *this structure is a transition structure rather than a minimum.*[11,12] In general, structures bearing cation-stabilizing groups followed stepwise pathways with shallow intermediates, while those lacking such groups followed concerted pathways. The geometries of the intermediates for the former (e.g., Figure 2b) and the transition structures for the latter (e.g., Figure 2a) are strikingly similar, emphasizing how tenuous the distinction between the stepwise and concerted mechanisms can be.

Scheme 1



The concerted Pd(II)-promoted Cope rearrangements provide new examples of "transition-state complexation".[13] Take the R = H[11] system (Figure 2a), for example. Here the transition structure for a metal-free Cope rearrangement (Figure 2c) is complexed by an ML_n fragment. This complexation is stronger for the transition structure than for the reactant, thereby reducing the barrier for rearrangement (from 35.2 to 30.1 kcal/mol, Table 2; note that all systems in Tables 1 and 2 have lower barriers when complexed). The geometric changes occurring upon complexation are also logical and can be rationalized via interactions between orbitals of the uncomplexed transition structure and orbitals of the $PdCl_2(MeCN)$ group. For example, the orbital of the complexed transition structure shown

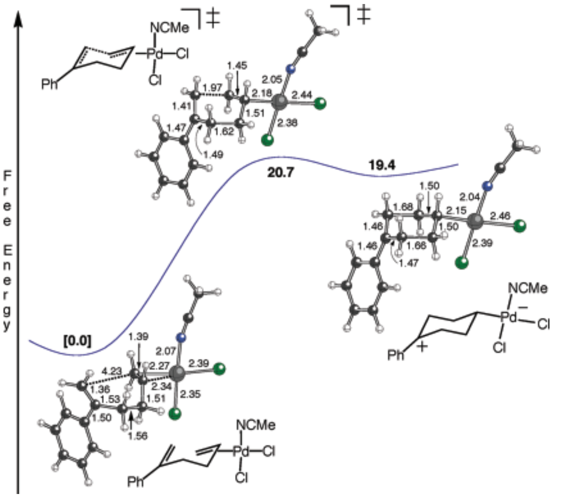


Figure 1. Geometries (distances in Å; gas phase) and relative free energies (25 °C, kcal/mol) of stationary points involved in the Pd(II)-promoted Cope rearrangement (with B3LYP/LANL2DZ[7,8]). Note that this figure represents half of the overall degenerate rearrangement.

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Table 1. Computed (B3LYP/LANL2DZ; Gas Phase)[7,8] Energetics (Free Energies in kcal/mol) for $PdCl_2(MeCN)$-Promoted and Uncomplexed Rearrangements of 2-Aryl-1,5-hexadienes (Only Some of Which Have Been Explored Experimentally[4a])[a]

substituent	σ_p^+, σ_m[9]	complexed TS	complexed Int	well depth	uncomplexed barrier
pNMe_2	−1.7	16.9	11.8	5.1	32.6
pNH_2	−1.3	17.6	13.0	4.6	33.0
*p*O*i*-Pr	−0.85	18.6	15.6	3.0	32.8
*p*Me	−0.31	20.7	19.4	1.3	33.6
p$CHCH_2$	−0.16	20.6	18.6	2.0	32.2
H	0	20.7	19.4	1.3	32.6
*p*Cl	0.11	21.8	20.8	1.0	32.5
*m*OMe	0.12	21.5	20.6	0.9	32.2
*p*CCH	0.18	21.4	19.8	1.6	32.1
*m*F	0.34	21.8	21.2	0.6	32.3
*m*Br	0.39	23.3	22.8	0.5	32.5
mCF_3	0.43	23.5	22.7	0.7	32.0
pCF_3	0.61	22.8	22.4	0.4	32.1
*p*CN	0.66	22.8	22.1	0.7	31.6
pNO_2	0.79	23.5	23.1	0.4	30.1
pBCl_2	0.86	23.2	22.7	0.5	30.3

[a] Energies for the transition structures (TS) and intermediates (Int) are relative to those for the chairlike reactant complexes that precede them.

Table 2. Computed (B3LYP/LANL2DZ; Gas Phase)[7,8] Energetics (Free Energies in kcal/mol) for Hexadienes with R ≠ Ar

substituent (R)	mechanism	complexed barrier	well depth	uncomplexed barrier
CF_3	concerted	31.5	NA	31.5
CN	concerted	29.2	NA	30.7
H	concerted	30.1	NA	35.2
CH_3	stepwise	22.7	0.3	34.3
vinyl	stepwise	22.1	1.5	32.6

in Figure 2e is composed of the HOMO of the uncomplexed transition structure (Figure 2d; roughly an antibonding combination of two allyl orbitals) interacting in a bonding way with a d_{z^2} orbital of the Pd (along with contributions from the Cl's), an interaction that decreases the interallyl C−C distances. Simple matching of orbitals for transition structures and ML_n fragments in this way is a relatively unexplored,[13] yet potentially powerful, catalyst design strategy.

Our calculations thus suggest that the mechanism of the Pd(II)-promoted Cope rearrangement varies between stepwise and concerted on the basis of the nature and position of appended substituents. We therefore suggest that it should, like its metal-free counterpart, be characterized as "chameleonic".[2,14] Although stepwise pathways were found for some systems, these rearrangements tend toward concertedness; that is, if intermediates exist, they tend to sit within very shallow wells.[15] We continue to pursue both theoretical and experimental studies on the mechanisms of these classic reactions,[4,5,8] with the ultimate goal of utilizing the "transition-state complexation" concept as a tool for designing new variants that allow for unprecedented rearrangements of complex π-systems.

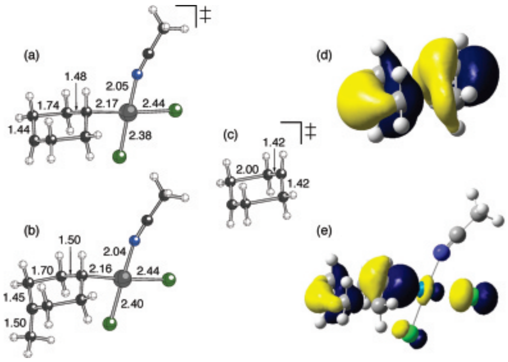

Figure 2. Selected structures (B3LYP/LANL2DZ,[7] distances in Å) involved in complexed and uncomplexed Cope rearrangements (a−c). (d) Kohn−Sham HOMO for Figure 2c. (e) Kohn−Sham HOMO-4 for Figure 2a.

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Supporting Information Available: Additional details on computations. This material is available free of charge via the Internet at http://pubs.acs.org.

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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.

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(3) Reviews: (a) Fanning, K. N.; Jamieson, A. G.; Sutherland, A. *Curr. Org. Chem.* **2006**, *10*, 1007−1020. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579−586.

(4) (a) Overman, L. E.; Renaldo, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 3945−3949. (b) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459−3461. (c) Although intramolecular trapping of intermediates was described in ref 4b, substituted hexadienes and large ligands unlike any structure described herein were used. Our studies on how these factors affect the mechanism of the Pd(II)-promoted Cope rearrangement will be described in a future report.

(5) The Pd(0)-promoted Cope reaction is thought to proceed through a stepwise dissociative mechanism. See: Nakamura, H.; Iwama, H.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10850−10851. We will describe calculations on such reactions in a future report.

(6) In addition to aryl substitution at C2 of the diene, alkyl substitution at C1, C2, or C3, as well as phenyl or hydroxy substitution at C3 have all been experimentally explored. See, for example: Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 1157−1160; Overman, L. E. *J. Am. Chem. Soc.* **1982**, *104*, 7225−7231; Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B. *J. Organomet. Chem.* **1966**, *6*, 412−420.

(7) Calculations were performed at the B3LYP/LANL2DZ level of theory using Gaussian 03. Free energies at 25 °C are reported throughout. See Supporting Information for additional details, including references and comparisons with other levels of theory (which suggest that the results described herein are not very sensitive to the level employed).

(8) The calculations described herein assume complexation of the unsubstituted π-bond, but the Overman group also discussed problems associated with initial complexation of dienes bearing electron donating Ar groups.[4a] We will describe results that bear on this issue in a future report.

(9) σ constants: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(10) For leading references, see: Olah, G. A.; Berrier, A. L.; Prakash, G. K. S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 1998−2002.

(11) Reoptimization of systems appearing in Table 2 in $CHCl_3$ (w/CPCM) resulted in a change of mechanism for both the R = H and R = CN cases from concerted to stepwise, but the well depths for these cases were only 0.1 and 1.1 kcal/mol, respectively. See Supporting Information for additional details.

(12) This rearrangement can also be classified as a "sigmahaptotropic" rearrangement (Goldschmidt, Z.; Gottlier H. E.; Cohen, D. *J. Organomet. Chem.* **1985**, *294*, 219−233), since the metal migrates over the allyl fragment to which it is attached as the Cope rearrangement occurs, ending up attached to the newly formed C=C π-bond.

(13) (a) See: Tantillo, D. J.; Hoffmann, R. *Helv. Chim. Acta* **2001**, *84*, 1396−1404. See also: Yatsimirsky, A. K. *Coord. Chem. Rev.* **2005**, *249*, 1997−2011. (b) Complexation of Cope transition structures by Li+: Jiao, H.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1760−1763. By halogens: Wang. S. C.; Tantillo, D. J. *J. Phys. Chem. A*, in press. (c) "Transition-state protonation": Hoffmann, R.; Tantillo, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5877−5882. (d) Seminal discussions of related concepts: Fukui, K.; Inagaki, S. *J. Am. Chem. Soc.* **1975**, *97*, 4445−4452. Mango, F. D. *Coord. Chem. Rev.* **1975**, *15*, 109−205.

(14) Note also that the Pd(II) version involves zwitterions rather than diradicals.

(15) (a) These intermediates should perhaps be described as "para intermediates" (Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 4126−4130. For the related term "twixtyl", see: Hoffmann, R.; Swaminathan, S.; Odell, B, G.; Gleiter, R. *J. Am. Chem. Soc.* **1970**, *92*, 7091−7097.) and in some cases may reside on "calderas" (Doering, W. v. E.; Eklmanis, J. L.; Belfield, K. D.; Klärner, F. G.; Krawczyk, B. *J. Am. Chem. Soc.* **2001**, *123*, 5532−5541). (b) A recent paper describes, for some related [3,3] shifts of heterodienes, intermediates followed by small barriers to form the products: Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031−5044.

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