JOC The Journal of Organic Chemistry

JOCSynopsis

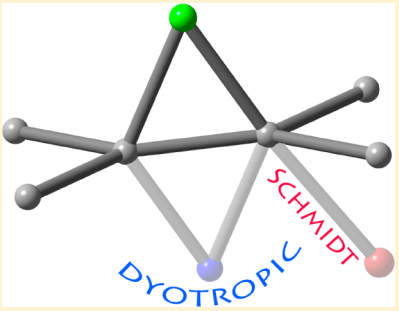
pubs.acs.org/joc

Analogies between Synthetic and Biosynthetic Reactions in Which [1,2]-Alkyl Shifts Are Combined with Other Events: Dyotropic, Schmidt, and Carbocation Rearrangements

Osvaldo Gutierrez and Dean J. Tantillo*

Department of Chemistry, Univeristy of California−Davis, 1 Shields Avenue, Davis, California 95616, United States

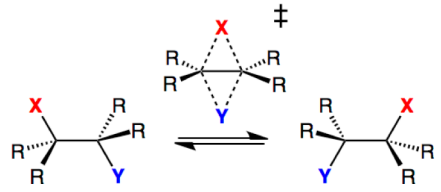
ABSTRACT: A survey of computational studies on the mechanisms of dyotropic, Schmidt, and related reactions is presented. Connections between synthetically applied versions of these processes and those predicted to occur during biosynthetic terpene-forming carbocation cascades are highlighted.



The discovery, or even just proposal, that a pericyclic reaction is involved in a biological/biosynthetic process is generally considered note/newsworthy, especially if a shepherding enzyme has been identified, by virtue of the fact that the reaction in question may be pericyclic.[1] What is often overlooked in discussions of such reactions is that [1s,2s] sigmatropic shifts, some of the simplest types of pericyclic reaction, abound in nature, especially in terpene-forming carbocation rearrangements occurring within the active sites of terpene synthases.[2] [1,2] Sigmatropic shifts are also widely employed in synthetic ventures.[3] What is also generally underappreciated about these reactions is that they are frequently merged with other chemical events into concerted processes of varying synchronicity.[4,5] Herein we describe recent results of quantum chemical calculations (from our group and others) on mechanisms, regio- and stereoselectivity for two families of reactions involving concerted processes with [1s,2s] sigmatropic shift components: dyotropic rearrangements involving the melding of two [1s,2s] sigmatropic shifts and Schmidt and related reactions in which [1s,2s] sigmatropic shifts are comingled with the departure of leaving groups. Synthetically relevant reactions, related fundamental studies, and analogies to carbocation rearrangements of biosynthetic relevance are all highlighted herein.

Dyotropic Rearrangements. Dyotropic rearrangements were first proposed and analyzed by Reetz[6] and Hoffmann and Williams[7] in 1972 (with Reetz coining the name "dyotropic"). Reactions in this class involve the coupled migration of two σ-bonds. While Reetz's original definition described this coupled migration as "simultaneous",[6] issues of synchronicity[4] were not explicitly addressed. Two types of dyotropic rearrangement were defined by Reetz, but we focus herein on type I rearrangements, "in which the two σ-bonds interchange their positions" (Scheme 1).[6] Note that in such reactions inversion of configuration occurs at each of the atoms bearing a migrating group.[8]

Scheme 1



Models. Type I dyotropic reactions have similarities to several other types of reactions. When X and Y (Scheme 1) bear lone pairs, type I dyotropic reactions can be viewed as coupled S_N2-type displacements, with each migrating group serving as both nucleophile and leaving group (Scheme 2).

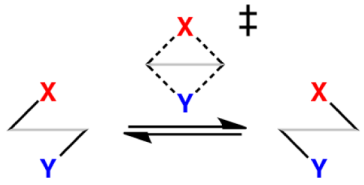
Scheme 2

Alternatively, type I dyotropic reactions can be viewed as σ-bond metathesis reactions (Scheme 3), i.e., $[_\sigma 2_s + _\sigma 2_s]$ pericyclic processes, which would be orbital symmetry forbidden.[9] These two viewpoints are related in that both do not invoke extensive electron delocalization along the bond across which the groups migrate, i.e., this bond is primarily a structural support. Type I dyotropic reactions also can be viewed as hybrids of two

Received: September 4, 2012
Published: September 24, 2012

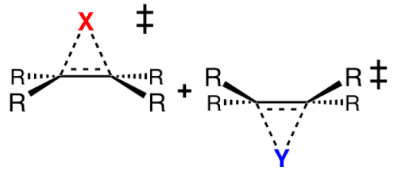
dx.doi.org/10.1021/jo301864h | J. Org. Chem. 2012, 77, 8845−8850

Scheme 3



sigmatropic shifts (Scheme 4; [1s,2s] shifts here)[10] involving significant delocalization (i.e., double bond character) along the

Scheme 4



shared bond of the bicyclic transition-state structure. These three models, although interrelated, are not equivalent.[11] Which of these models provides the best description of a given reaction depends on the nature of the migrating groups. For bookkeeping purposes, arrows of the type in Scheme 5 will be shown for all of the dyotropic rearrangements discussed herein, but the nature of each rearrangement will be discussed in detail.

Scheme 5

Positional Exchange of Halogens. An ostensibly simple example of a type I dyotropic rearrangement, the positional exchange of two halogen atoms in a vicinal dihalide, is shown in Scheme 5, a reaction first examined in the context of steroid chemistry and the most common type of dyotropic reaction described in the literature.[12−15] A variety of halogen exchange reactions have been examined both experimentally and theoretically.[8,12−15] The prevalence of this class of dyotropic reactions is likely due to the comparative ease with which halogens migrate compared to other groups. Hoffmann and Williams,[7] Fernández, Sierra, Bickelhaupt and Cossío,[12,13,15] and Rzepa, Schleyer, and co-workers[8] noted the potential benefits of orthogonal orbitals on halogen migrating groups in avoiding the forbiddenness expected for a concerted $[_{\sigma}2_s+_{\sigma}2_s]$ reaction.[7,9b−c] We would argue that this effectively moves halogen exchange dyotropic reactions out of the realm of pericyclic reactions and into the realm of pseudopericyclic reactions,[11] although Rzepa, Schleyer and co-workers describe this type of reaction as a 6-electron pericyclic process, an argument supported by computed nucleus independent chemical shift (NICS) values[16] associated with transition state aromaticity.[8] A similar viewpoint was recently expressed by Fernández, Bickelhaupt, and Cossío.[13]

Substituent effects on halogen-exchange dyotropic reactions have been examined. Zou and Yu examined a panel of exchange reactions involving chlorine and bromine migrating groups (some are shown in Figure 1).[17] These authors noted that the intervening C−C bond had signifcant double bond character in

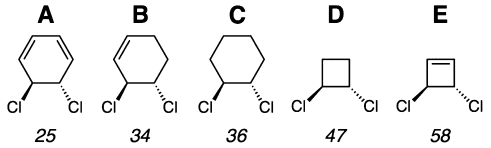
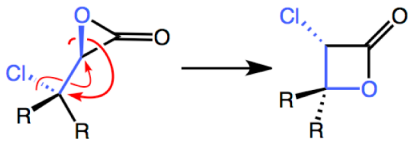


Figure 1. Selected systems for which type I dyotropic reactions have been examined theoretically. Numbers below the structures are computed activation barriers in kcal/mol.[17]

computed transition-state structures, allowing rearrangement barriers to be lowered in the presence of appended conjugating and hyperconjugating groups. A correlation between the length of the central C−C bond and the activation barrier was also noted. In cases where the incipient double bond was part of a potentially aromatic substructure (e.g., **A** in Figure 1), a particularly low barrier was predicted, but in cases where it was part of a potentially antiaromic substructure (e.g., **E** in Figure 1), a high barrier was predicted. Strain associated with increasing sp^2 character for the carbons over which the halogens migrate also affected barrier heights (e.g., compare **C** and **D** in Figure 1). In addition, it was noted that chlorine has more trouble migrating than does bromine, i.e., barriers for dibromo exchange were predicted to be lower than those for the exchange of a bromine and a chlorine, which were predicted to be lower than those for the exchange of two chlorines. Fernández, Sierra, and Cossío also noted the benefits of having an electron-donating group attached to the central C−C bond, associating the barrier lowering effect of such groups with a favorable interaction between a donor orbital on the substitutent and a vacant orbital of the core of the transition-state structure (corresponding to the LUMO of the unsubstituted transition state structure).[15]

Oxygen-Based Migrating Groups. Dyotropic rearrangements of systems with oxygen-based migrating groups have also been examined. Rearrangements of these systems have more direct synthetic applications than halogen-exchange reactions. Of particular interest are cases where the migrating oxygen is part of a lactone ring which expands upon dyotropic rearrangement.[12,18] A simple case is shown in Scheme 6, here

Scheme 6



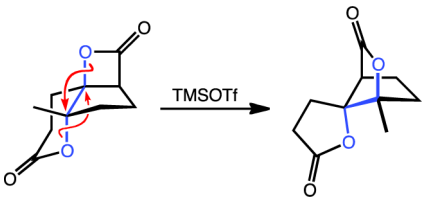
with one oxygen and one halogen migrating group. Williams and co-workers examined this reaction using combined quantum mechanics (for the reactant)/molecular mechanics (for surrounding solvent molecules) calculations (continuum solvation calculations led to similar predictions), predicting a barrier for rearrangement of approximately 35 kcal/mol in water with R = H.[19] The transition-state structure for this rearrangement was found to have a significant dipole moment, leading to barrier lowering of approximately 7 kcal/mol (vs the gas phase) as a result of selective stabilization of the transition-state structure in polar solvent. Negative charge built up on the migrating carboxylate group in the transition-state structure (this group was largely dissociated), while positive charge built up on the remainder of the molecule, which resembled a bridging chloronium ion. With R = CH_3, a lower rearrangement

dx.doi.org/10.1021/jo301864h | J. Org. Chem. 2012, 77, 8845−8850

barrier (only 27 kcal/mol in the gas phase and 11 kcal/mol in water), was consistent with a larger dipole associated with a more dissociative (and less symmetrical, with the two migrating groups closer to the less substituted intervening carbon) transition-state structure with attached methyl groups, which are hyperconjugative donors.

An example of a dyotropic rearrangement involving two oxygen-containing groups is shown in Scheme 7.[18b,20] This

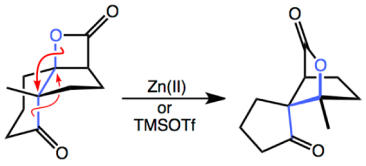
Scheme 7



reaction has been applied by Romo and co-workers to the total synthesis of (−)-curcumanolide A and (−)-curcumalactone.[18b] In this rearrangement, one lactone ring expands while another contracts. Density functional theory (DFT) calculations on this rearrangement, promoted by a "TMS^+" group, indicated a dissociative transition-state structure with long C−O distances, especially on the β-lactone side. For this reaction, which was predicted to have a barrier of only 14 kcal/mol, charge separation actually decreased slightly upon approaching the transition state structure. The central C−C bond was not particularly short in the transition state structure (1.48 Å), leading to the description of this reaction as double-S_N2-like.[20]

Carbon-Based Migrating Groups. An analogue of the reaction shown in Scheme 7 with a carbon-containing migrating group (Scheme 8) was also examined.[18b,20] In contrast to the

Scheme 8

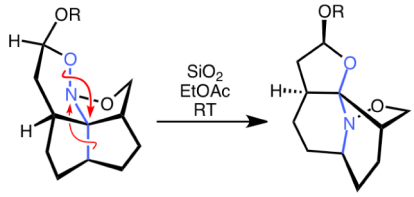


bislactone rearrangement, this rearrangement, again promoted by "TMS^+", was predicted to have a lower barrier (by approximately 7 kcal/mol), a much more polar transition-state structure (with carboxylate- and acyl cation-like migrating groups), and a shorter central C−C bond (1.39 Å).[20] Rearrangement in the presence of Zn(II) salts was also examined. This reaction, which is well-behaved experimentally, was predicted to go through a stepwise mechanism in which the first step consisted of heterolytic C−O bond cleavage to form an intermediate carbocation (with almost no barrier to revert back to reactant) and in which the second step involved concerted but asynchronous 1,2-acyl shifting and carbocation capture events. The barrier for the Zn(II)-promoted process was predicted to be similar to that for the bislactone rearrangement described above.

Reactions with alkyl-migrating groups also have been described. For example, an $EtAlCl_2$-promoted β-lactone-to-γ-lactone rearrangement with an alkyl migrating group was applied recently to the syntheses of various xanthanolides,[18a] but the computed transition-state structure for this rearrangement has not yet been reported. Chloride−methyl exchange in neopentyl chloride has also been examined, but the barrier for this reaction was both predicted and measured experimentally to be approximately 60 kcal/mol (analogous reactions with other halogens were also predicted to have large barriers).[21,22] Thus, it seems that alkyl groups (at least primary ones) are inherently poor at migrating but can be induced to do so if the group with which they exchange positions is an especially good migrator, e.g., a Lewis acid bound carboxylate of a small lactone.

A Complex Example. The reaction shown in Scheme 9 is perhaps the most complex dyotropic reaction yet subjected to

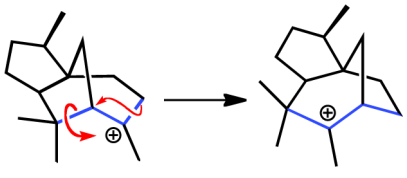
Scheme 9



detailed theoretical analysis.[23] This reaction, discovered by Denmark and co-workers, involves the migration of an acetal oxygen and a secondary alkyl carbon across an intervening C−N bond. This rearrangement converts one complex polycycle (here a fennestrane) into another and proceeds at room temperature in the presence of silica gel or polar protic solvents. The origins of the low barrier for this reaction were elucidated through DFT calculations on a variety of model systems. On the basis of the computational results, it was concluded that strain relief, delocalization of the negative charge that accumulates on the migrating oxygen into the acetal group through induction and an anomeric effect, delocalization of the positive charge that accumulates on the migrating alkyl group through hyperconjugation, selective stabilization of the overall dipole of the transition-state structure by a polar environment, and specific hydrogen bonding interactions with solvent all contribute to lowering the barrier for this rearrangement. In short, without all of these factors contributing, a concerted rearrangement would not be possible under the reaction conditions. A stepwise alternative was also shown to be viable, although it is not necessary to invoke such a process to explain the experimental results.

Carbocations. Surprisingly, at least to us, Nature appears also to make use of concerted dyotropic rearrangements. Several examples have been predicted by DFT calculations to occur during carbocation cascade reactions that lead to terpene natural products.[5] An example is shown in Scheme 10.[24,25] In this case, two 1,2-alkyl shifts are coupled together into a concerted dyotropic process, although they occur very asynchronously; i.e., one shift is nearly complete before the second begins, but only a single transition state structure is found along the rearrangement reaction coordinate.[4] Such

Scheme 10

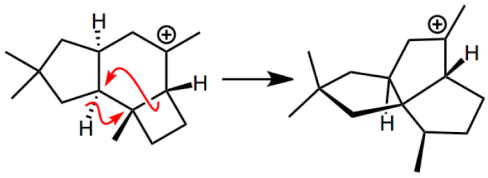


dx.doi.org/10.1021/jo301864h | J. Org. Chem. 2012, 77, 8845−8850

reactions are predicted to have low barriers, approximately 15 kcal/mol or less.[5,24] Why are the barriers for these these reactions much lower than those predicted previously for dialkyl or dihydrogen exchange reactions?[7,12,13,22] In short, the severe asynchronicity of these reactions, facilitated by their carbocationic nature, allows for the orbital symmetry induced barrier expected for a dialkyl shift (suprafacial with respect to both migrating alkyl groups) to be avoided, since at no point along the reaction coordinate is there strong cyclic orbital overlap of the type associated with forbiddenness.[26]

Another example from terpene biosynthesis is shown in Scheme 11.[27] In this case, a differently positioned carbocation

Scheme 11



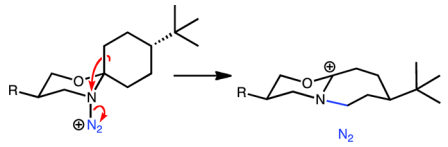
center provides a sink for electron density during the concerted but asynchronous reaction shown. As the reaction begins, the cyclobutane C−C bond breaks, its electron density flowing toward the carbocation. Then, the 1,2-hydride shift occurs as a normal cationic 1,2-hydride shift would. Finally, the electron density is shifted in the other direction to form the new C−C bond. This reaction has a predicted barrier of only approximately 20 kcal/mol. The carbocation center is not a mere spectator, despite being at the same position in reactant and product, but rather provides a sink for accumulating electron density as the acetal group did for the reaction shown in Scheme 9. Despite the fact that both migrating groups are not particularly electronegative (or electropositive), the reaction resembles a cationic 1,2-hydride shift coupled to an anionic 1,2-alkyl shift, with the attendant carbanion stabilized by a directly attached carbocation.

Summary. Many flavors of type I dyotropic reaction have been described, varying in the nature of their migratig groups (halogens, oxygen-containing groups, alkyl groups, hydrogen) and the nature of the two-atom unit across which they migrate (C−C or N−C units, strained or not, connected or not to conjugating or hyperconjugating groups). The variety of substrate structures is matched by the variety of transition-state structures (symmetrical or not, loose or tight, having short or not-so-short central bonds) and reaction coordinates (concerted or stepwise, synchronous or asynchronous) associated with them. While more work is required to fully understand the factors controlling the barrier heights for these rearrangements, general principles are emerging. A very recent study has analyzed a series of model type I dyotropic reactions in great detail, noting that weaker C−X/Y bonds lead to lower barriers, since less is lost when these bonds dissociate as transition-state structures are reached.[13] In addition, electron donors attached to the bonds across which groups migrate, lone pairs on migrating groups, and sinks for electron density on migrating groups all help to reduce barriers for rearrangement, diminishing and even circumventing the penalties associated with orbital symmetry forbiddenness.

Schmidt Reactions. The reaction shown in Scheme 9 involved a [1s,2s]-alkyl shift across a C−N bond coupled to a [1s,2s]-oxygen shift. If the [1s,2s]-oxygen shift was replaced by a N_2-loss event, then the reaction would correspond to a Schmidt reaction.[28] This process is analogous to the double-S_N2 model of a type I dyotropic rearrangement (Scheme 2), but with one of the leaving groups not also acting as a nucleophile.

Variations. Variations on the Schmidt reaction have become powerful tools in synthesis.[29] An example is shown in Scheme 12.[30] This reaction, developed by Aubé and co-

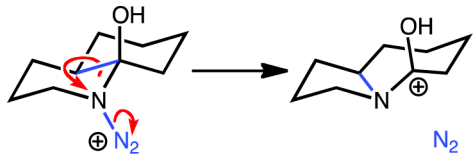
Scheme 12



workers, involves alkyl migration across a C−N single bond, assisted by the electron-donating oxygen atom of an aminal. Poutsma and co-workers carried out quantum chemical computations on this sort of reaction,[30] which indicated that alkyl migration and N_2-loss are indeed concerted, diastereoselectivity correlates with conformational preferences of intermediate aminals, and favorable interactions between the cationic N_2 group and aromatic substituents, when present and appropriately positioned, can influence this selectivity.

Another variation explored by Aubé and co-workers is shown in Scheme 13.[31] In this type of reaction, migration and N_2-loss

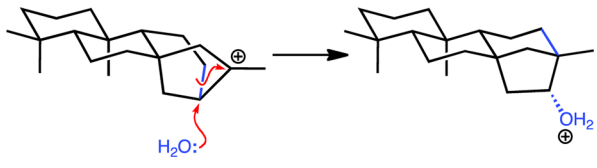
Scheme 13



occur for an azidohydrin intermediate. The mechanism and selectivity for this reaction type was examined theoretically by Gutierrez et al.[31] The results of DFT calculations indicated that such processes are again concerted, with N_2 departure leading, slightly, alkyl migration. These reactions are very exergonic and, as expected, have early transition states. The strengths and limitations of using steric, lone pair−cation and cation−π interactions in determining which alkyl group in an azidohydrin migrates preferentially were also assessed using DFT calculations.

Biosynthetic Parallels. [1s,2s]-Alkyl shifts coupled with leaving group loss can also be found in the realm of terpene biosynthesis, but run in reverse, i.e., nucleophile addition coupled to alkyl migration.[5] An example is shown in Scheme 14. In this case, the results of DFT calculations indicated that attack of water can be coupled to a [1s,2s] alkyl shift leading to the framework of beyeranol.[32] The -alkyl shifting and C−O bond formation events were predicted to be part of a concerted process, avoiding the formation of a discrete secondary

Scheme 14

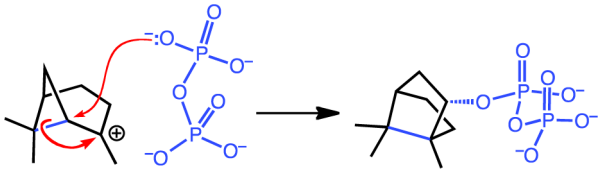


dx.doi.org/10.1021/jo301864h | J. Org. Chem. 2012, 77, 8845−8850

carbocation intermediate,[5] but alkyl migration led capture by the nucleophile.

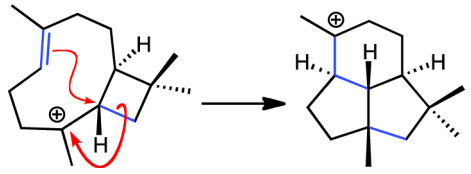
Similar reactions involving different nucleophiles have also been predicted to occur with low barriers. In Scheme 15 is

Scheme 15



shown an example from monoterpene biosynthesis in which alkyl migration is coupled to capture by pyrophosphate.[25] This process leads to bornyldiphosphate, again avoiding a discrete secondary carbocation intermediate.[5] In Scheme 16 is shown an

Scheme 16



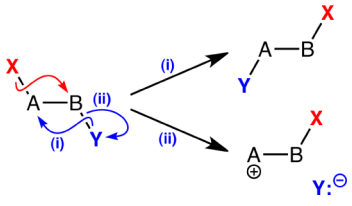
example where the nucleophilic capture is intramolecular. In this case, alkyl migration is coupled to attack by a C=C π-bond, en route to presilphiperfolanol and related sesquiterpenes, once again avoiding a secondary carbocation intermediate.[5,33]

Summary. [1s,2s]-Alkyl shifts can be coupled to a variety of σ-bond breaking/making events. In Schmidt reactions, this event consists of N−N_2^+ bond breaking, but in the biosynthetically relevant reactions described above, this event consists of C−O or C−C bond formation. In any case, coupling of shifting and σ-bond breaking/making events avoids the formation of discrete reactive cationic intermediates.

CONCLUSIONS AND OUTLOOK

As shown herein, [1s,2s]-alkyl shifts can be combined into concerted processes with other events. While the synthetic reactions described herein were not (to our knowledge) designed based on analogies to biosynthetic processes, the connections between them and terpene-forming carbocation rearrangements are clear. Scheme 17 summarizes the situation. As one group (X) migrates toward the backside of the bond to a second group (Y), the second group is displaced and either departs, as in a Schmidt reaction (ii), or itself migrates in a direction opposite to that of the first group, as in a type I dyotropic reaction (i). Which will occur, with what barrier, and with what mechanism is a complex issue, but as described

Scheme 17



above, general principles of predictive value are emerging. Although the focus herein was on dyotropic reactions, Schmidt reactions, and carbocation rearrangements of particular interest to the authors, these principles will no doubt be applicable to other related reactions, for example, Curtius,[34] Hofmann,[35] Wolff,[36] Beckmann,[37] pinacol,[38] and hiscotropic[10] rearrangements.

AUTHOR INFORMATION

Corresponding Author

*E-mail: djtantillo@ucdavis.edu.

Notes

The authors declare no competing financial interest.

Biographies

Osvaldo Gutierrez was born in Salamanca, Guanajuato, Mexico, and raised in Sacramento, CA. He attended Sacramento City College for 5 years before joining the group of Kendall N. Houk at UCLA in 2006, where he completed his B.S. and M.S. degrees in chemistry in 2009. He obtained a Ph.D. in Chemistry from UC Davis in the group of Dean J. Tantillo in 2012 and will be joining the group of Marisa Kozlowski at the University of Pennsylvania as a postdoctoral fellow.

Dean J. Tantillo was born and raised in Quincy, MA. He received an A.B. degree in Chemistry in 1995 from Harvard University and a Ph.D. in 2000 from UCLA (under the direction of Kendall Houk). After receiving his Ph.D., he moved to Cornell University, where he carried out postdoctoral research with Roald Hoffmann. He joined the faculty at UC Davis in 2003, where he is now a Professor of Chemistry. Professor Tantillo can often be found walking through the woods touching terpenes and contemplating puzzling mechanistic questions in the areas of biosynthesis, reactive intermediate chemistry, catalysis, organometallic chemistry, and stereoselective synthetic reactions.

dx.doi.org/10.1021/jo301864h | J. Org. Chem. 2012, 77, 8845−8850

■ ACKNOWLEDGMENTS

We are grateful to the NSF for supporting portions of the work described herein. We are also grateful to Daniel Romo and Jeff Aubé for encouraging us to explore the mechanisms of their reactions and for their willingness to put our predictions to the test.

■ REFERENCES

(1) Leading references: (a) Townsend, C. A. *ChemBioChem* **2011**, *12*, 2267−2269. (b) Kelly, W. L. *Org. Biomol. Chem.* **2008**, *6*, 4483−4493. (c) Pohnert, G. *ChemBioChem* **2001**, *2*, 873−875. (d) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321−352. (e) Siegel, J. B.; Zanghellini, A.; Lovick, H. M.; Kiss, G.; Lambert, A. R.; St. Clair, J. L.; Gallaher, J. L.; Hilvert, D.; Gelb, M. H.; Stoddard, B. L.; Houk, K. N.; Michael, F. E.; Baker, D. *Science* **2010**, *329*, 309−313.

(2) Leading references: (a) Cane, D. E. *Compr. Nat. Prod. Chem.* **1999**, *2*, 155−200. (b) Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089−1103. (c) Davis, E. M.; Croteau, R. *Top. Curr. Chem.* **2000**, *209*, 53−95. (d) Christianson, D. W. *Chem. Rev.* **2006**, *106*, 3412−3442.

(3) Selected examples: (a) Tuzina, P.; Somfai, P. *Org. Lett.* **2009**, *11*, 919−921. (b) Jaber, D. M.; Burgin, R. N.; Helper, M.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2012**, *14*, 1676−1679. (c) Leboeuf, D.; Gandon, V.; Ciesielski, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 6296−6308.

(4) Leading references: (a) Tantillo, D. J. *J. Phys. Org. Chem.* **2008**, *21*, 561−570. (b) Williams, A. *Concerted Organic and Bio-Organic Mechanisms*: CRC Press: Boca Raton, 2000. (c) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209−219. (d) Hess, B. A.; Smentek, L. *Org. Biomol. Chem.* **2012**, *10*, 7503−7509.

(5) (a) Tantillo, D. J. *Nat. Prod. Rep.* **2011**, *28*, 1035−1053. (b) Tantillo, D. J. *Chem. Soc. Rev.* **2010**, *39*, 2847−2854.

(6) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129−130. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 130−131. (c) Reetz, M. T. *Tetrahedron* **1973**, *29*, 2189−2194. (d) Reetz, M. T. *Adv. Organomet. Chem.* **1977**, *16*, 33−65.

(7) (a) Hoffmann, R.; Williams, J. E., Jr. *Helv. Chim. Acta* **1972**, *55*, 67−75. (b) See also: Buenker, R. J.; Peyerimhoff, S. D.; Allen, L. C.; Whitten, J. L. *J. Chem. Phys.* **1966**, *45*, 2835−2847.

(8) Braddock, D. C.; Roy, D.; Lenoir, D.; Moore, E.; Rzepa, H. S.; Wu, J. I.-C.; Schleyer, P. v. R. *Chem. Commun.* **2012**, *48*, 8943−8945.

(9) (a) Leading references on σ-bond methathesis: Ziegler, T.; Folga, E.; Berces, A. *J. Am. Chem. Soc.* **1993**, *115*, 636−646. (b) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22. (c) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781−853.

(10) Nouri, D. H.; Tantillo, D. J. *J. Org. Chem.* **2006**, *71*, 3686−3695.

(11) The difference between double-displacement and the two other models is analogous to the difference between pseudopericyclic and pericyclic reactions, where orthogonal orbitals at the same atom are involved for the former but not the latter. Leading references: (a) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325−4327. (b) Birney, D. M. *Curr. Org. Chem.* **2010**, *14*, 1658−1668.

(12) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev.* **2009**, *109*, 6687−6711.

(13) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem.—Eur. J.* **2012**, *18*, 12395−12403.

(14) Grob, C. A.; Winstein, S. *Helv. Chim. Acta* **1952**, *35*, 782−802.

(15) Fernández, I.; Sierra, M. A.; Cossío, F. P. *Chem.—Eur. J.* **2006**, *12*, 6323−6330.

(16) (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317−6318. (b) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842−3888.

(17) Zou, J.-W.; Yu, C.-H. *J. Phys. Chem.* **2004**, *108*, 5649−5654.

(18) Selected examples and leading references: (a) Ren, W.; Bian, Y.; Zhang, Z.; Shang, H.; Zhang, P.; Chen, Y.; Yang, Z.; Luo, T.; Tang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6984−6988. (b) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348−13356. (c) Mulzer, J.; Brüntrup, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 793−794. (d) Reetz, M. T.; Schmitz, A.; Holdgrün, X. *Tetrahedron Lett.* **1989**, *30*, 5421−5424. (e) Arrastia, I.; Lecea, B.; Cossío, F. P. *Tetrahedron Lett.* **1996**, *37*, 245−248. (f) Black, T. H.; DuBay, W. J., III. *Tetrahedron Lett.* **1988**, *29*, 1747−1750. (g) Black, T. H; McDermott, T. S. *J. Chem. Soc. Chem Comm.* **1991**, *13*, 184−185.

(19) Buchanan, J. G.; Ruggerio, G. D.; Williams, I. H. *Org, Biomol. Chem.* **2008**, *6*, 66−72.

(20) (a) Davis, R. L.; Leverett, C. A.; Romo, D.; Tantillo, D. J. *J. Org. Chem.* **2011**, *76*, 7167−7174. (b) Although it was first thought that this dyotropic reaction did not occur under the experimental conditions, the calculations indicated that it should, thus prompting additional experiments. These demonstrated that the predicted product did indeed form but was subsequently hydrolyzed in the presence of adventitious TfOH. The Brønsted acid promoted dyotropic reaction was, in fact, predicted to be a barrierless process.

(21) Lisowski, C. E.; Duncan, J. R.; Ranieri, A. J.; Heard, G. L.; Setser, D. W.; Holmes, B. E. *J. Phys. Chem. A* **2010**, *114*, 10395−10402 and references therein.

(22) An unusual dyotropic rearrangement, with two migrating alkyl groups, recently was also predicted using DFT calculations to have a barrier of approximately 100 kcal/mol, consistent with the early predictions of Hoffmann and Williams.[7] See: Gryko, D. T.; Rogacki, M. K.; Klajn, J.; Galezowski, M.; Stepien, D. K.; Cyranski, M. K. *Org. Lett.* **2010**, *12*, 2020−2023.

(23) (a) Davis, R. L.; Tantillo, D. J. *J. Org. Chem.* **2010**, *85*, 1693−1700. (b) Denmark, S. E.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2005**, *44*, 3732−3736. (c) Denmark, S. E.; Montgomery, J. I.; Kramps, L. A. *J. Am. Chem. Soc.* **2006**, *128*, 11620−11630.

(24) Hong, Y. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 7999−8015 For a related example, see ref 25.

(25) (a) Hong, Y. J.; Tantillo, D. J. *Org. Biomol. Chem.* **2010**, *8*, 4589−4600. (b) Weitman, M.; Major, D. T. *J. Am. Chem. Soc.* **2010**, *132*, 6349−6360.

(26) Nouri, D. H.; Tantillo, D. J. *Tetrahedron* **2008**, *64*, 5672−5679.

(27) (a) Zu, L.; Xu, M.; Lodewyk, M. W.; Cane, D. E.; Peters, R. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 11369−11371. (b) Gutta, P.; Tantillo, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 6172−6179.

(28) Schmidt, K. F. *Ber.* **1924**, *57*, 704−723.

(29) Selected examples and leading references: (a) Szostak, M.; Yao, L.; Aubé, J. *Org. Lett.* **2009**, *11*, 4386−4389. (b) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731−734. (c) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (d) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194.

(30) (a) Manukyan, A. K.; Radkiewicz-Poutsma, J. L. *J. Mol. Struct. THEOCHEM* **2006**, *766*, 105−112. (b) Hewlett, N. D.; Aubé, J.; Radkiewicz-Poutsma, J. L. *J. Org. Chem.* **2004**, *69*, 3439−3446. (c) Ribelin, T.; Katz, C. E.; English, D. G.; Smith, S.; Manukyan, A. K.; Day, V. W.; Neuenswander, B.; Poutsma, J. L.; Aubé, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6233−6235.

(31) (a) Gutierrez, O.; Aubé, J.; Tantillo, D. J. *J. Org. Chem.* **2012**, *77*, 640−647. (b) Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. *J. Am. Chem. Soc.* **2012**, *134*, 6528−6531.

(32) Hong, Y. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 5375−5386.

(33) Wang, S. C.; Tantillo, D. J. *Org. Lett.* **2008**, *10*, 4827−4830.

(34) (a) Curtius, T. *Ber.* **1890**, *23*, 3023. (b) Smith, P. A. S. *Org. React.* **1946**, *3*, 337−449.

(35) (a) Hofmann, A. W. *Ber.* **1881**, *14*, 2725. (b) Shiori, T. *Comp. Org. Syn.* **1991**, *6*, 800−806.

(36) (a) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129−195. (b) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193−2256.

(37) (a) Beckmann, E. *Ber.* **1886**, *19*, 988−993. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 14−24.

(38) Berson, J. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4655−4660.