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Recent excursions to the borderlands between the realms of concerted and stepwise: carbocation cascades in natural products biosynthesis[†]

Dean J. Tantillo^{a*}

Recent theoretical studies on concerted carbocation rearrangements that involve multiple asynchronous chemical events are described. The relevance of such rearrangements to natural products biosynthesis is highlighted. Copyright © 2008 John Wiley & Sons, Ltd.

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AN INTRODUCTION TO ASYNCHRONICITY

Arguments over whether particular reactions follow concerted or stepwise mechanisms have peppered the organic chemistry literature for decades. One of the more dramatic of these concerned the mechanisms of pericyclic reactions.^[1–3] This particular argument also concerned the 'synchronicity' of concerted reactions and led to a definition of this concept. Although the terms 'concerted' and 'synchronous' are sometimes used interchangeably, they actually describe quite different aspects of a reaction. A reaction is *concerted* if it has a single transition state structure, that is, does not involve any intermediates. This does not necessarily mean that the reaction should also be described as *synchronous*, since the various geometric and electronic changes (heretofore referred to as 'events') that occur during the reaction might not happen simultaneously. For example, the definition of a 'synchronous' reaction put forth by Dewar is 'a concerted reaction in which all the changes in bonding take place in parallel',^[2] while his definition of an asynchronous reaction, which he referred to as a 'two-stage reaction' is one that 'is concerted but not synchronous, some of the changes in bonding taking place during formation of the transition state (TS) and the others during conversion of the TS to the product(s).'^[2] We view 'concertedness' as a property of a reaction while 'synchronicity' is a term that compares events occurring *during a concerted reaction*.

Take, for example, the reaction shown in Fig. 1 (bottom left to top right). This is a [3,3] sigmatropic shift (or Cope Rearrangement) and was one of the pericyclic reactions that formed the backbone of the debate alluded to above.^[1–3] The More O'Ferrall–Jencks-style^[4–7] diagram in Fig. 1 provides a graphical means of comparing the synchronicity of certain events for related reactions. The particular diagram in Fig. 1 is concerned with the synchronicity of C–C single bond breakage (expressed as the bond order for the C_a–C_b bond) and formation (expressed as the bond order for the C_c–C_d bond). The blue and green lines and structures correspond to two different stepwise pathways (the intermediates in these pathways are at the top left and bottom right corners of the square). The red line and associated transition

structure correspond to a pathway that is both concerted and synchronous (in terms of the two C–C bond-making and -breaking events). The purple curve and associated transition structure correspond to a pathway that is concerted but asynchronous in terms of these events. Although the [3,3] shift of unsubstituted 1,5-hexadiene follows a concerted mechanism with synchronous bond-breaking and -making events, where exactly transition structures for other concerted [3,3] sigmatropic shifts fall in the spectrum of synchronicity has been shown to depend on the nature and position of substituents.^[1–3,8,9]

Admittedly, the distinction between synchronous and asynchronous is somewhat arbitrary. We prefer to think in terms of 'degrees of asynchronicity', since 'perfect synchronicity' is not only very rare, but is also not trivial to define when two unlike events are being compared. For example, in Fig. 1 two of the same sort of bond-making and -breaking events are compared, but examination of less symmetrical systems necessarily involves the comparison of bonding changes that are not so similar. The carbocation rearrangements^[10] that we will focus on in this Review are of this type, but the events on which we focus occur extremely asynchronously.

EXAMPLES OF CONCERTED CARBOCATION REARRANGEMENTS WITH ASYNCHRONOUS EVENTS

In our studies on mechanisms of carbocation rearrangements in natural products biosynthesis, we have so far encountered many

* Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA.
E-mail: tantillo@chem.ucdavis.edu

a J. Tantillo
Department of Chemistry, University of California, Davis, CA, USA

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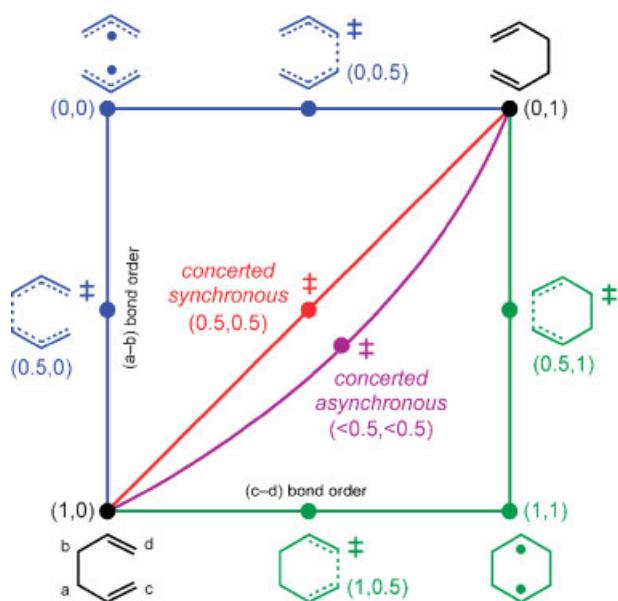
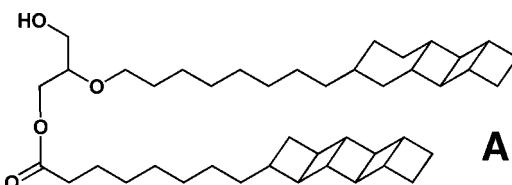


Figure 1. More O'Ferrall-Jencks-style diagram for the Cope Rearrangement.

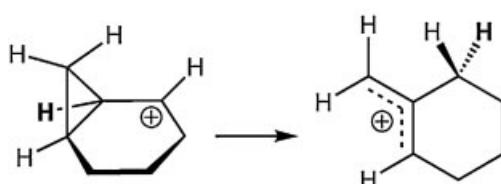
concerted rearrangements with asynchronous events. In fact, asynchronicity appears to be a general feature of the complex carbocation rearrangements we have been exploring. In this section, several representative examples of such rearrangements are discussed, with an emphasis on their relevance to the particular putative biosynthetic transformation whose study led to their discovery.

Ladderane lipid biosynthesis—hiscotropic rearrangements

Recently, a variety of unusual lipids containing [3] and/or [5] ladderane substructures (e.g., **A**) were isolated from anammox bacteria.^[11] During our theoretical studies on plausible mechanisms for the biosyntheses of such species,^[12] we happened



(a)



(b)

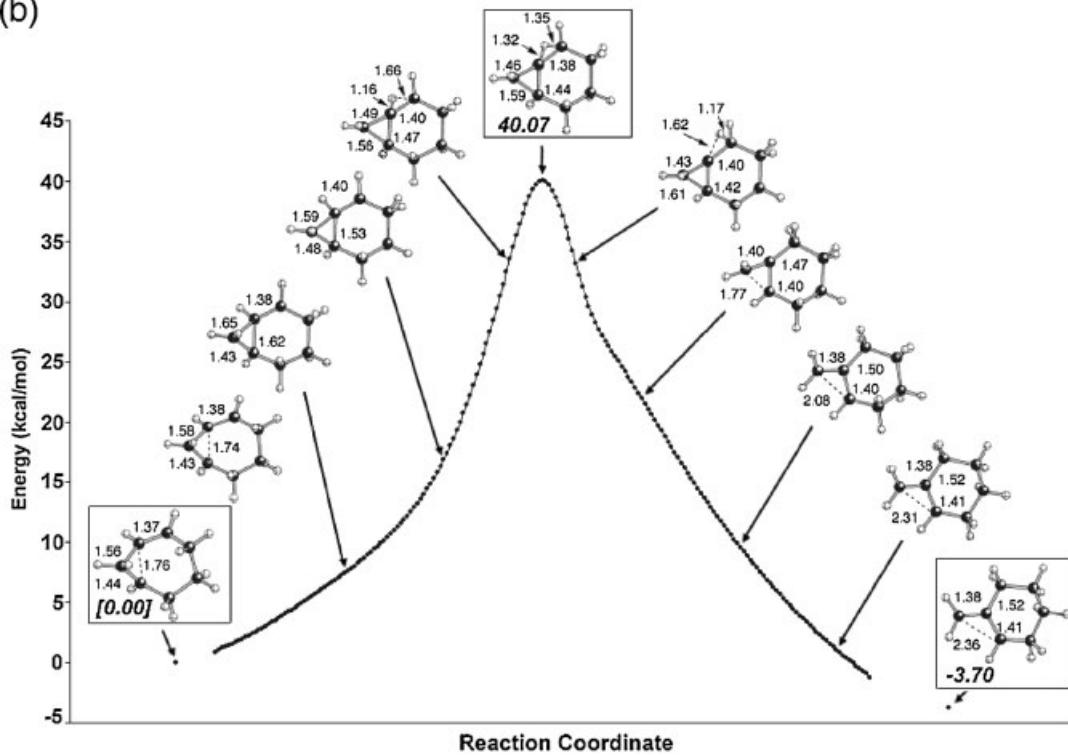


Figure 2. A hiscotropic rearrangement (a) and an IRC calculation (B3LYP/6-31G(d)) on it.^[13] Selected distances are shown in Å. The transition structure for this reaction, and the minima that flank it, are enclosed in boxes (which also enclose the relative energies of these stationary points)

upon an unusual rearrangement that appeared to be an asynchronous but concerted combination of a [1,2] sigmatropic shift of hydrogen and a 2-electron electrocyclic ring-opening, an experimentally unprecedented type of reaction that we termed a 'hiscotropic rearrangement'.^[13] A representative example of such a rearrangement, with the ladderane framework removed, is shown in Fig. 2a. The results of an intrinsic reaction coordinate (IRC)^[14,15] study on this reaction are shown in Fig. 2b. Note that along the portion of the reaction coordinate that precedes the transition structure, the 3-membered ring remains essentially intact (although the bond that will break in the rearrangement does elongate), but the hydrogen shifts to a significant extent. Examination of the portion of the reaction coordinate following the transition structure reveals that the hydrogen shift is completed well before the ring is fully opened. Thus, although the reaction is concerted, the hydrogen shift and ring-opening events occur asynchronously. While we compute that such rearrangements have rather high activation barriers, and are therefore probably not relevant to ladderane lipid biosynthesis, their serendipitous discovery has led us to contemplate the design of non-biological systems for which hiscotropic rearrangements may be experimentally observable.

Ladderane lipid biosynthesis—formally forbidden sigmatropic shifts

Subsequent studies on ladderane biosynthesis led to our discovery of another unusual reaction, an 8-electron suprafacial/suprafacial [4,5] sigmatropic shift (Fig. 3a)^[12] that is formally forbidden based on orbital symmetry considerations.^[16–18] Although concerted, its C–C bond-making and -breaking events occur asynchronously, with bond-making preceding bond-breaking (Fig. 4). This is clear from IRC calculations on the portion of the reaction coordinate connecting the transition structure to the product (Fig. 3b). In the second structure shown, for example, the new C–C bond is mostly formed while the breaking C–C bond has not elongated very much. Since there appears to be no point along the reaction coordinate with strong cyclic delocalization of the electrons involved in the rearrangement, the constraints of orbital symmetry are relaxed and, as Woodward and Hoffmann suggested would be possible,^[16–18] are overcome by other factors. We continue to study this intriguing rearrangement and are also exploring additional reactions that correspond to concerted processes in which electrons travel in a cycle, and which are predicted to be forbidden based on orbital

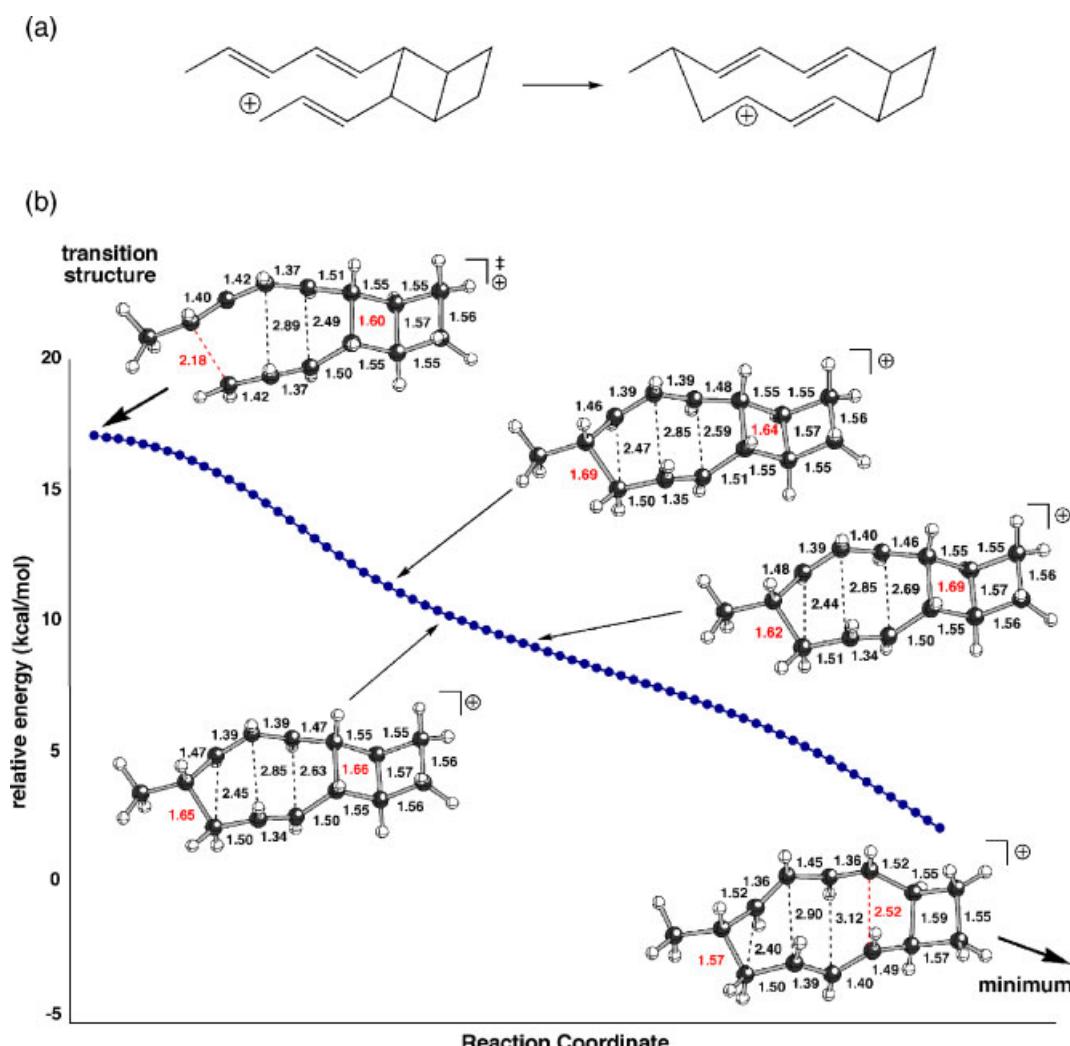


Figure 3. Formally-forbidden [4,5] sigmatropic rearrangement (a) and an IRC calculation (B3LYP/6-31G(d)) on it (b); only the pathway from the transition structure to the product is shown.^[12] Selected distances are shown in Å. This figure is available in colour online at www.interscience.wiley.com/journal/poc

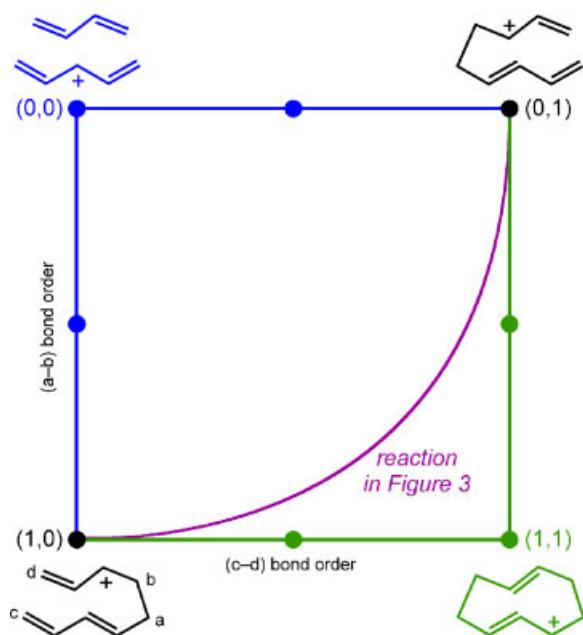


Figure 4. More O'Ferrall–Jencks-style diagram for the rearrangement shown in Fig. 3. This figure is available in colour online at www.interscience.wiley.com/journal/poc

symmetry considerations, but which also appear to not involve structures with strong cyclic delocalization at any point along their reaction coordinates. Whether or not this is a general strategy for accessing formally forbidden stereochemistries is an open question that we are actively pursuing.

Sesquiterpene biosynthesis—dyotropic rearrangements

The facility with which Nature produces thousands of terpene and terpenoid natural products from simple acyclic, achiral starting materials is nothing less than amazing. Take, for example, the conversion of farnesyl diphosphate to the polycyclic, stereodense sesquiterpene natural product pentalenene (Scheme 1) by the enzyme pentalenene synthase.^[19] During our quantum chemical studies on the mechanisms of carbocation

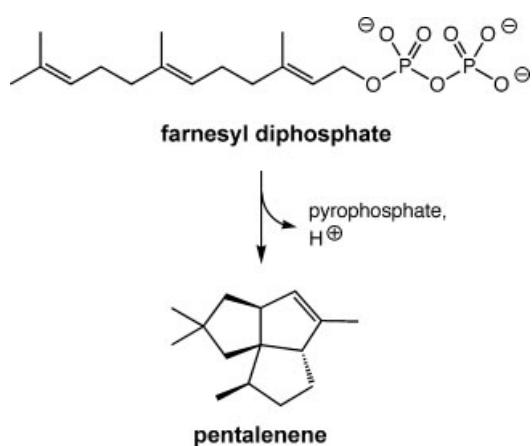
rearrangements that may be involved in the natural pentalenene-forming reaction,^[20] we came upon the transformation shown in Fig. 5, a dyotropic^[21–23] rearrangement that had not previously been suggested as a step in the pentalenene synthase catalyzed reaction. Although the imaginary frequency associated with the transition structure for this rearrangement corresponds to a motion that looks primarily like hydrogen migration that would interconvert structures **B** and **C** (Scheme 2), and we were unable to get our IRC calculations to go beyond structures resembling **B** and **C**, no minima corresponding to **B** or **C** were found (despite many attempts to do so, employing various strategies).^[20] We therefore concluded that the transition structure shown in Fig. 5b indeed connects the carbocations shown in Fig. 5. The early portion of the reaction coordinate for this rearrangement involves breaking of the internal bond of the cyclobutane ring, which is followed by shifting of the hydrogen near the transition structure, and then, finally, ring closure. Thus, three events occur almost but not quite separately from each other.

Sesquiterpene biosynthesis—cyclizations masquerading as conformational changes

A diversion from the pathway to pentalenene described above leads to another family of sesquiterpene natural products, the caryophyllenes.^[24] An early intermediate in the pentalenene-forming reaction is the cation shown at the left of Scheme 3. In the pentalenene-forming reaction, a [1,2] hydrogen shift occurs for this intermediate; if, however, the ring-closing reaction shown in Scheme 3 occurs instead, the caryophyllenes can be formed. Interestingly, the transition structure we located for this ring-forming reaction^[25] looks mostly like a transition structure for a conformational change (which happens to decrease the distance between the cationic center and the alkene that will attack it). Nonetheless, a series of constrained calculations, in which the length of the forming C–C bond was systematically varied while the rest of the molecule was allowed to relax, suggest that this transition structure is actually connected to the ring-closed minimum at the center of Scheme 3. Formation of the new C–C bond appears to occur rather late on the reaction coordinate. The bond-forming event is apparently so facile that when the conformational change occurs that aligns the C=C π bond and the cationic center appropriately for bond formation, bond formation cannot be stopped. Such transannular proximity effects appear to be a general theme of the chemistry of sesquiterpene formation.

Sesquiterpene biosynthesis—temporary alkyl shifts

During our exploration of carbocation rearrangements relevant to the biosynthesis of another sesquiterpene, trichodiene (Scheme 4),^[26] we uncovered an unusual rearrangement that we refer to as a 'temporary alkyl shift'.^[27] In the mechanisms generally proposed for the conversion of farnesyl diphosphate to trichodiene,^[26] the bisabolyl cation is converted to the cuprenyl cation via an intermediate such as **D** (Scheme 4). In the absence of the enzyme that catalyzes this transformation, however, we were unable to locate a minimum corresponding to **D**. Instead, we consistently located intermediate **E** (Scheme 4). These two structures differ by the location of a methyl group. We were also able to locate transition structures that connect the bisabolyl cation to **E** and **E** to the cuprenyl cation (Fig. 6).^[27,28] In the former reaction, C–C bond formation precedes the [1,2] methyl



Scheme 1.

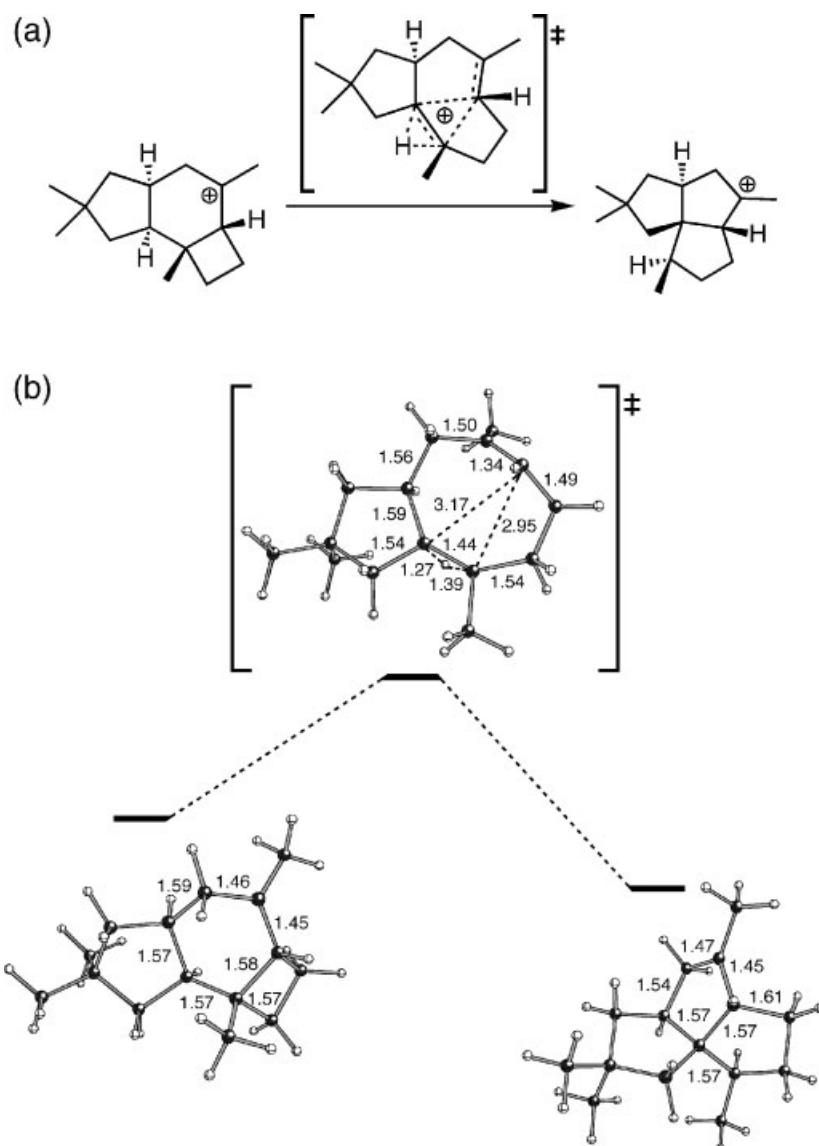
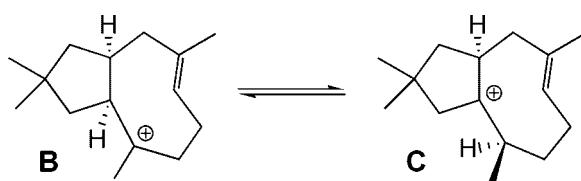


Figure 5. Dyotropic rearrangement involved in pentalenene formation (a) and its transition structure and flanking minima (b, B3LYP/6-31+G(d,p)).^[20] Selected distances are shown in Å

shift, and in the latter, hydride migration follows the [1,2] methyl shift. Again, key events occur asynchronously in concerted reaction steps. For both of these steps the intermediacy of a minimum with a secondary cation substructure is avoided. Although we believe that this overall pathway, in which the methyl group temporarily shifts its position by one carbon and then returns to its original location, is not the preferred pathway in Nature (we have found a competing pathway with a smaller overall barrier^[27]), we are currently exploring the feasibility of temporary alkyl shifts in other systems.

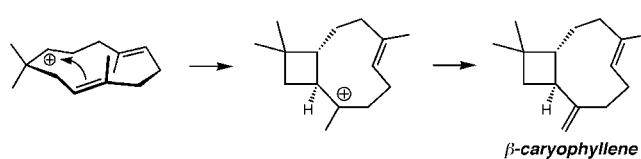


Scheme 2.

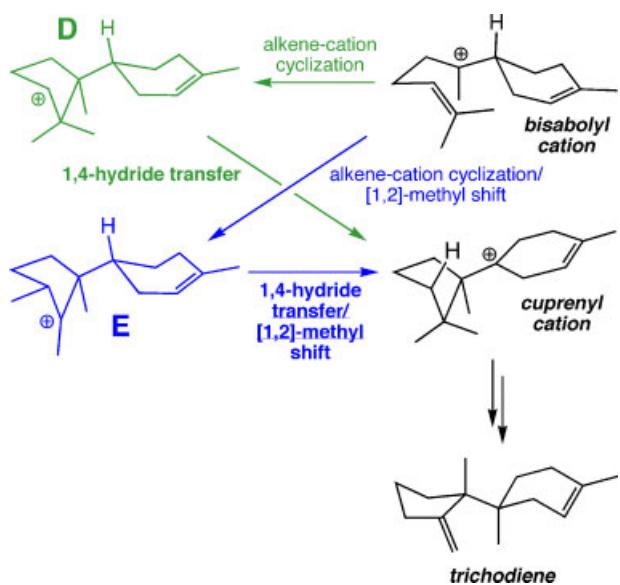
POTENTIAL ENERGY SURFACE PECULIARITIES

Shoulders, plateaus, and bifurcations

The potential energy surfaces (here, we are referring to energy vs reaction coordinate curves generated via IRC calculations) associated with the hiscotropic reactions described above show interesting variations in their slopes. For some hiscotropic rearrangements, curves with steep slopes and well-defined TS regions were observed (Fig. 7, right), while for others, transition



Scheme 3.



Scheme 4. This figure is available in colour online at www.interscience.wiley.com/journal/poc

structures appeared to be followed by shoulders (Fig. 7, center) or appeared to reside at the onset of plateau regions^[29–32] (Fig. 7, left). These shoulders and plateaus tended to correspond to structures resembling cyclopropyl cations (i.e., what one would expect after a [1,2] hydrogen shift has occurred; see, for example, Fig. 8),^[13] but we were not able to locate any true minima corresponding to such structures. It is clear that even if such minima do exist, they are bounded by minuscule barriers in the direction that leads to products. A rough correlation between the earliness of the transition structure (in Fig. 7, expressed in terms of the breaking C—C bond) and the tendency of the reaction coordinate to flatten out after the transition structure was observed.

We also suspect that these plateaus are connected to multiple products, at least in some cases. In that structures on these plateaus often resemble cyclopropyl cations, that is, species for which the hydrogen has migrated but the ring has not yet opened, ring-opening in either of two possible disrotatory modes can occur with essentially no barrier (Scheme 5).^[13] In short, the severe asynchronicity of hydrogen migration and ring-opening allows the reaction coordinate to bifurcate.^[33] Which product

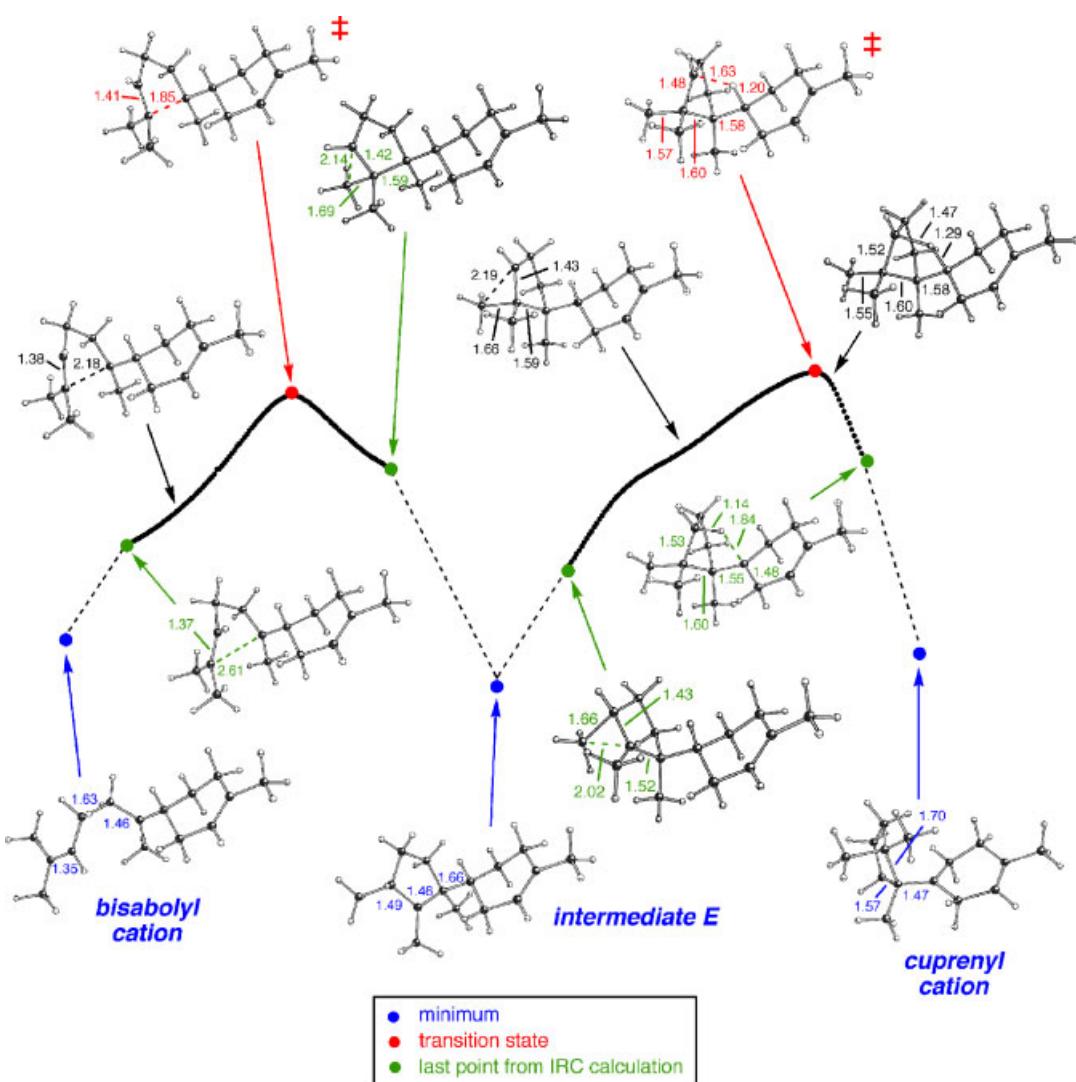


Figure 6. 'Temporary methyl shift' involved in trichodiene formation (Scheme 4, B3LYP/6-31+G(d,p)).^[27,28] This figure is available in colour online at www.interscience.wiley.com/journal/poc

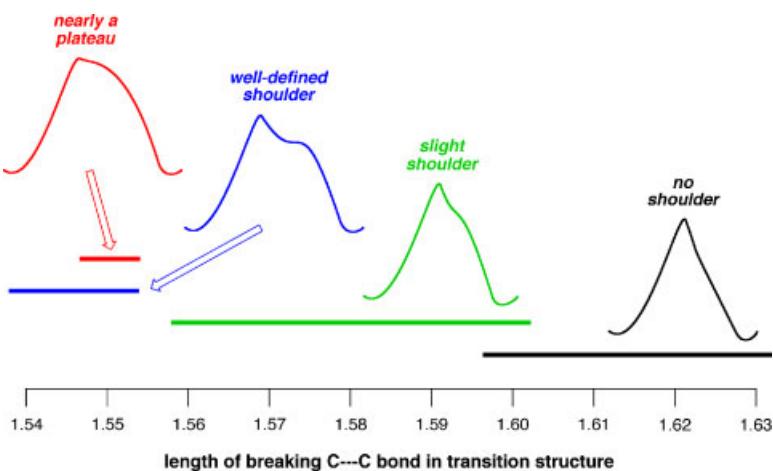


Figure 7. Summary of types of reaction coordinates found for hiscotropic rearrangements.^[13] This figure is available in colour online at www.interscience.wiley.com/journal/poc

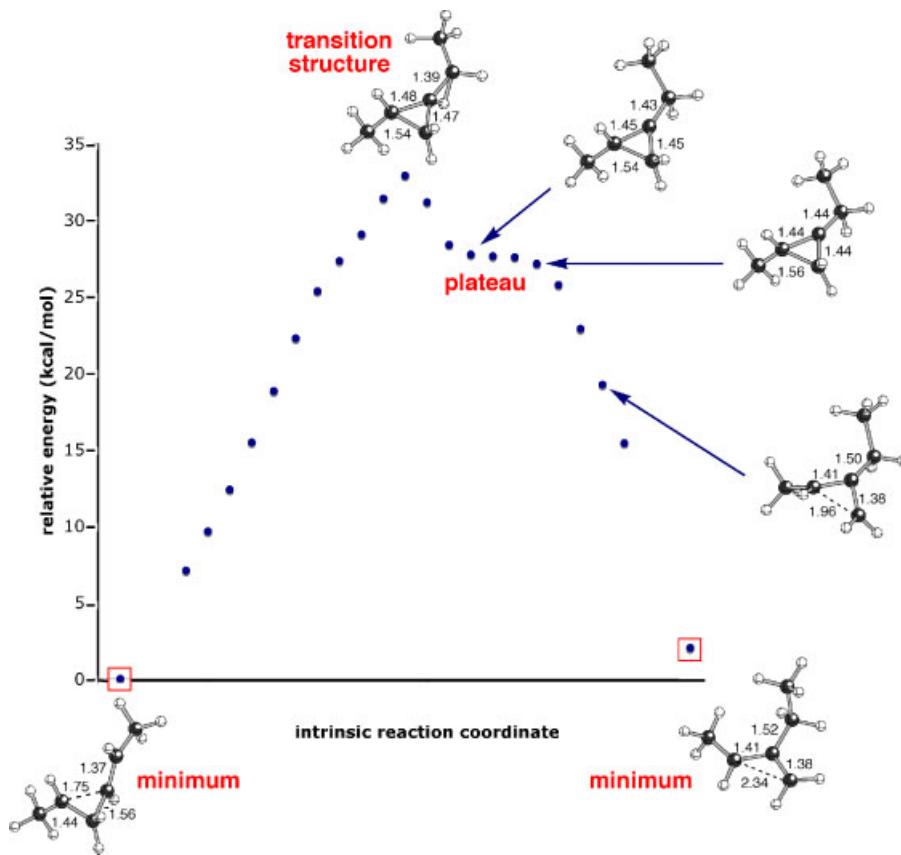


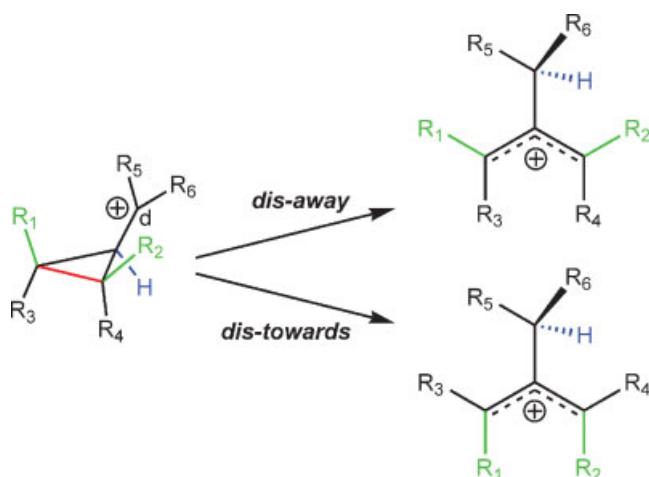
Figure 8. IRC for a representative hiscotropic rearrangement with a post-transition structure plateau.^[13] This figure is available in colour online at www.interscience.wiley.com/journal/poc

actually predominates in such reactions will likely be influenced by dynamic factors as well.^[34,35]

'Frustrated non-intermediates'

One can view concerted reactions involving asynchronous events as part of a continuum spanning stepwise and concerted

reactions where a dividing point has been defined based on whether or not the 'intermediate' is bounded by a barrier (on all sides). In other words, for reactions that involve two distinct events, concerted means that, even if geometries resembling putative intermediates are present along a reaction coordinate, they are bounded only on one side (in a 2D picture) by a transition structure. We refer, admittedly casually, to such



Scheme 5.

structures as 'frustrated non-intermediates'—species that correspond to the chemists conception of what an intermediate should look like, but which are not true minima on a potential energy surface. When such species reside on expansive plateaus or 'calderas', they may also qualify as 'twixtys' or 'para intermediates'.^[29–32]

In the case of the dyotropic rearrangement on the pathway to pentalenene described above,^[20] we eagerly sought intermediates of the sort shown in Scheme 2. Although our IRC calculations terminated with structures resembling these species after the slope of the reaction coordinate approached zero,^[36] we were unable to locate true intermediates. Thus, the situation appears to be one in which the existence of these intermediates is 'frustrated' by the fact that there is no barrier for their collapse to the ring-closed minima (Fig. 5) that we actually found. The reason for this seems clear: in the 'intermediate' structures, carbocation centers are near in space to $C=C$ π -bonds. It is not surprising that transannular attack that replaces a π -bond with a σ -bond would be extremely facile (assuming that the gain in bond energy is not outweighed by associated strain). We take the fact that the IRC calculations do not proceed all the way to the minima to indicate that there is a shoulder or plateau in the vicinity of each 'frustrated non-intermediate'.

This concept can be expressed through simple curve-crossing models.^[37,38] For example, imagine that the two red energy wells at the bottom of Fig. 9a correspond to the minima connected to the dyotropic structure, which here is represented by **TS23**; thus the red–black–red pathway corresponds to that found in our calculations. An alternative stepwise pathway involving intermediates that precede (**INT2**) and follow (**INT3**) transition structure **TS23** would correspond to the blue–black–blue pathway. These two intermediates would be the intermediates that are described as 'frustrated' in the above discussion. In short, if the blue curves are pulled down^[39–41] to the points where their intersections with the black curves no longer precede the lowest points on the black curves (i.e., they become the red curves), then the overall reaction changes from a 4 minima/3 transition structure process to a 2 minima/1 transition structure (i.e., concerted) process. Is there any utility in this sort of perspective? Perhaps. Imagine that the red–black–red pathway corresponds to that in the absence of the enzyme (as our calculations suggest). If the enzyme selectively destabilizes the two red minima (raises

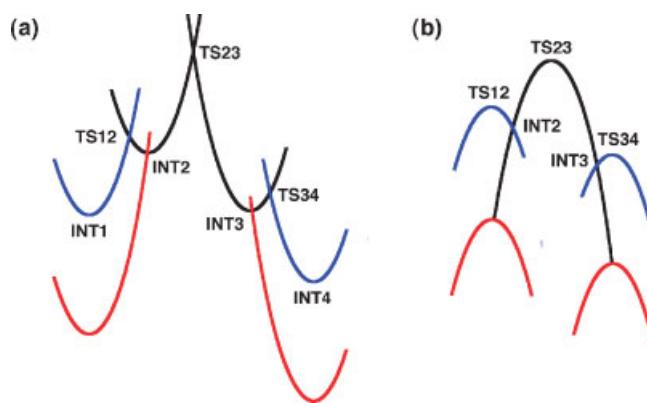


Figure 9. Curve-crossing models based on (a) minima and (b) transition structures.

the red curves) or stabilizes the black transition structure (lowers the black curves), then the pathway may switch to the blue–black–blue type and two intermediates may now be present; that is, by lowering the barrier for this rearrangement, the enzyme may introduce new intermediates^[42] and the presence of intermediates, of course, may open up pathways to byproducts. We are currently pursuing both calculations and laboratory experiments aimed at deciding whether or not such a situation does occur when the enzyme is involved. Similar conclusions can be arrived at using 'inverted' curves that correspond to transition structures (Fig. 9b).

Here is another example. Consider a case where a 3 minima/2 transition structure pathway is converted to a 2 minima/1 transition structure pathway (Fig. 10). We have observed just this sort of situation in our studies of formally forbidden^[16–18] [4,5] sigmatropic shifts of ladderanes and derivatives (Fig. 11).^[12] For these reactions, we computed reaction coordinates that vary from stepwise to concerted (but involving asynchronous bond-making and -breaking events) depending on strain, which varies with n in Fig. 11. The greater the strain associated with an $n+3$ carbon ring, the lower the barrier for the second step of this reaction; with $n=1$, there is no barrier for the 'second step' and the reaction becomes a single-step (concerted) process. Similar

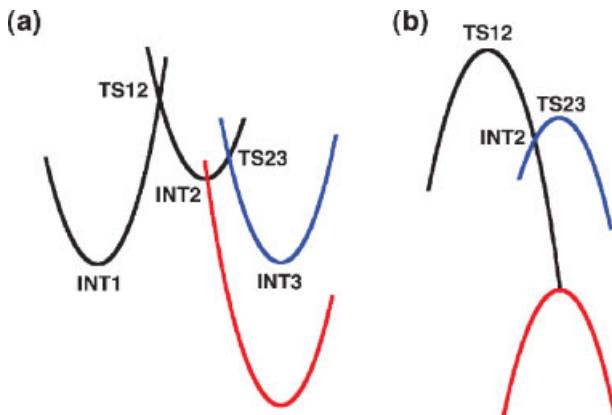


Figure 10. Curve-crossing models based on (a) minima and (b) transition structures.

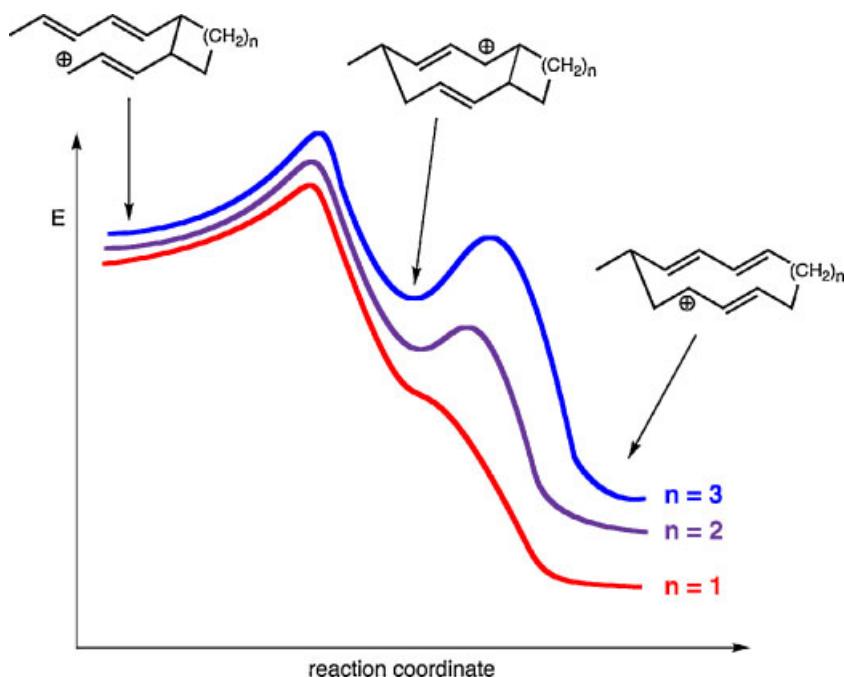


Figure 11. Reaction coordinates for [4,5] sigmatropic rearrangements.^[12] This figure is available in colour online at www.interscience.wiley.com/journal/poc

treatments could be applied to many of the other cases discussed above as well.

ONGOING STUDIES AND OPPORTUNITIES FOR THE FUTURE

The studies described above involved primarily gas phase quantum chemical calculations. But is the reactivity of these species the same in solution or in the interior of an enzyme as it is in the absence of such environments? We are currently pursuing studies—both theoretical and experimental—aimed at addressing this issue. For example, we are currently pursuing more elaborate calculations that take into account the effects of solvation and the microenvironments of enzyme active sites. We are also interested in experimental tests of the predictions arising from our calculations. These results will be described in due course, and we are optimistic that the synergistic relationship between theory and experiment that we try to foster will lead to consistent models of carbocation reactivity that are not only useful for explaining known experimental results, but that are also useful for designing new reactions and experiments by predicting their outcomes in advance of laboratory testing.

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[35] B. K. Carpenter, *J. Phys. Org. Chem.* **2003**, *16*, 858–868.

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[37] Both Dr Pradeep Gutta (UC Davis) and Prof. David Birney (Texas Tech) suggested to the author that he consider curve-crossing models.

[38] Similar concepts are utilized in Marcus Theory. See, for example: R. P. Marcus, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1111–1222.

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[41] M. G. Evans, M. Polanyi, *Trans. Faraday Soc.* **1936**, *32*, 1333–1360.

[42] This was suggested to the author by Prof. David Birney (Texas Tech) in April, 2007.