

Inherent dynamical preferences in carbocation rearrangements leading to terpene natural products*

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Abstract: An introduction to the application of quantum chemical dynamics calculations to mechanistic problems in the field of terpene biosynthesis is provided. A bare bones introduction to the fundamentals of chemical dynamics is followed by a brief account of previous applications to terpene-forming carbocation reactions, a discussion of questions in this field that dynamics calculations may help answer, and a description of current problems to which dynamics calculations are being applied.

Keywords: carbocations; computational chemistry; dynamics; mechanism; terpene.

INTRODUCTION

Molecular dynamics calculations are now applied widely to studying chemical reactions [1–11]. Traditional mechanistic studies that make use of quantum chemical calculations focus attention on stationary points (minima and transition-state structures) and the steepest descent pathways connecting them (in terms of energy vs. changes in electronic structure, i.e., intrinsic reaction coordinates (IRCs) [12,13]). In contrast, quantum chemical dynamics calculations allow for examination of a statistical sampling of possible reaction trajectories and the timing of events occurring during a chemical reaction.

In short, trajectories are allowed to evolve from the region of a transition state (see Fig. 1) in response to forces derived from quantum chemical calculations of vibrational frequencies. Starting points for trajectory calculations are molecular structures similar to but slightly different from a computed transition structure, which are given a Boltzmann distribution of energy distributed over the real vibrational modes that the molecule possesses; i.e., the transition *state* is sampled, not just the stationary point corresponding to the transition *structure* (Fig. 1).

Trajectories often are run only in the product-forming direction so as to reduce the computational cost of the calculations, but sometimes both product- and reactant-forming directions are explored. Splicing together trajectories run in both directions provides one with a “movie” of a reaction from reactant(s) to product(s). Some trajectories initiated in the product direction actually evolve towards the reactant(s) (and vice versa), and these recrossing events are sometimes important for the selectivity of product formation [2,3,7,10,11]. Recrossing events tend to occur less frequently, though, when the variational transition state (i.e., the transition state in terms of a free energy, rather than electronic energy or enthalpy, surface) is used as a starting point. Each trajectory is allowed to propagate until user-defined stop criteria are met, e.g., a C–C bond distance has decreased to 1.6 Å, a time limit has been

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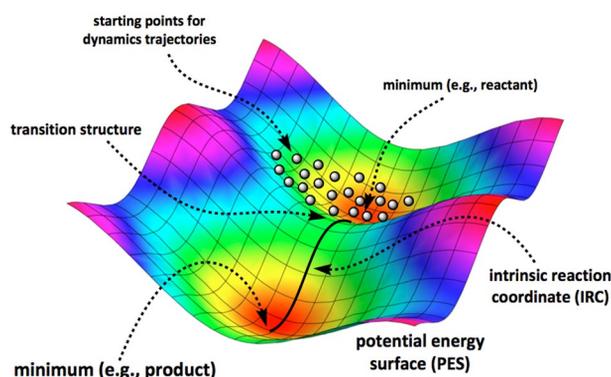


Fig. 1 A generic energy surface (Z-dimension corresponds to energy; X- and Y-dimensions correspond to changes in electronic structure and nuclear coordinates), emphasizing that the starting points for dynamics trajectories are near the transition structure, but distributed within the associated upward sloped energy well (in some scenarios, one would describe this as being arrayed along the dividing surface between minima).

reached, etc. It is important to note that placement of kinetic energy into vibrational modes of the transition state yields a product (or reactant) species at the end of a trajectory that is chemically activated, since there is neither sufficient time nor surrounding medium (since such calculations are often run in the gas phase) for the activated species to shed excess energy. As a result, some minima on potential energy surfaces for multi-step mechanistic pathways can be passed through without equilibration, corresponding to *direct* trajectories. An excellent recent example of this phenomenon was described by Carpenter and co-workers [5a], who first brought the importance of this concept to the attention of organic chemists [5].

Previous dynamics studies on terpene-forming carbocation cascades

One measure of the challenges faced by a terpene-forming enzyme (so-called terpene synthases or terpene cyclases) is provided by dynamics calculations. Running trajectories from a key transition state involved in a terpene-forming carbocation rearrangement provides insight into the *inherent* dynamical tendencies of the carbocations involved. If this inherent reactivity corresponds quantitatively to the product distribution observed for a terpene synthase, then a reasonable model of the role of the terpene synthase is to provide an environment that allows the inherent reactivity to be expressed (i.e., it shields the carbocations from water, allows particular reactant conformations to form, etc., but does not further manipulate selectivity). If the inherent reactivity is in line with a terpene synthase product distribution, but does not correspond to a level of selectivity as high as that observed for the synthase, then a reasonable model of the role of the enzyme is to enhance the inherent selectivity. If the inherent selectivity is different from or opposite to that observed for the synthase, then the enzyme must somehow overwhelm the inherent tendencies of the carbocations involved.

To our knowledge, extensive dynamics calculations on the inherent reactivity for only one terpene-forming carbocation rearrangement have yet been reported. This study involved the bifurcating pathway predicted to occur en route to the diterpene abietadiene (Fig. 2) [11]. For this reaction, the pathway from a transition-state structure for intramolecular proton transfer was predicted to bifurcate, in one direction towards a carbocation precursor to abietadiene (via a 1,2-methyl shift event) and in the other direction toward an as-yet unknown diterpene (via a ring-expanding 1,2-alkyl shift) [14].

Siebert et al. performed dynamics calculations on this system [11]. On the basis of the results of their dynamics calculations, which were carried out for both a small model system and the full-sized carbocation shown in Fig. 2, they concluded that there is an inherent selectivity for formation of the

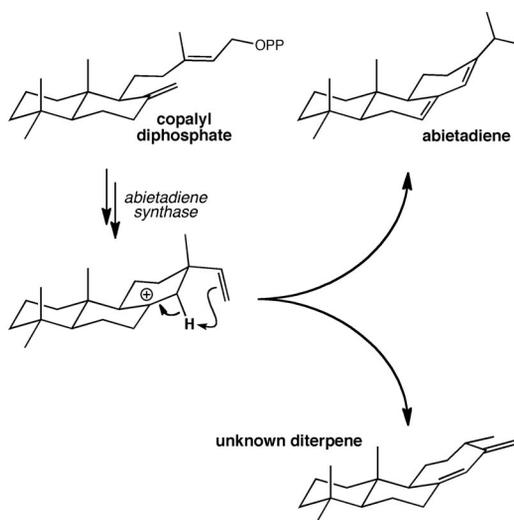


Fig. 2 Predicted bifurcating pathway involved in abietadiene formation.

cationic precursor to abietadiene, but only a slight preference. Consequently, steering of the abietadiene-forming reaction by abietadiene synthase is likely occurring, since this enzyme produces abietadiene in high yield. Average time gaps [3,9,10] between the proton transfer and methyl/alkyl shift events were determined to be ~150 fs for trajectories toward abietadiene and ~200 fs for trajectories toward the ring-expanded product, providing insight into the asynchronicity of the product-forming processes.

Questions for dynamics calculations to answer

Our dynamics studies on terpene-forming carbocation cyclization/rearrangement reactions are expanding with a focus on several specific goals (some of which also are being pursued for other types of reactions, by us and others):

1. *Defining the inherent reactivity of carbocations.* As described above, this issue is important in assessing the challenges faced by a terpene synthase enzyme.
2. *Characterizing synchronicity of chemical events in terms of time.* We have predicted the involvement of many concerted processes in which multiple bond-making and -breaking events occur asynchronously in terpene-forming carbocation reactions [15,16]. The asynchronicity of these events has been characterized in terms of progress along a reaction coordinate, but not explicitly in terms of the time required for each event and the time gap [3,9,10], if any, between them. Our first steps to tackling this problem were described in the previous section.
3. *Assessing the meaningfulness of shallow intermediates.* Many of the carbocation rearrangements we have examined are predicted to involve minima with very small (e.g., <2 kcal/mol) barriers for conversion to subsequent minima along a reaction coordinate [16–18]. Whether or not these small barriers have important effects on the distribution of trajectories entering the region of these minima is an open question; i.e., are nonstatistical effects important here? This type of question has been addressed for other reactions—for example, with the pioneering work of Carpenter and co-workers [5] and the recent studies by Singleton and co-workers on synthetically relevant organic reactions [2,6,7].
4. *Predicting product ratios for bifurcating pathways.* Potential energy surface bifurcations have received considerable attention [6,11,14,19,20], and we have predicted that some are involved in the inherent reactivity of carbocations that may be generated during terpene biosynthesis. One

example is described in the preceding section [11,14], but several additional examples have been found, including cases where one branch of a bifurcation bifurcates [21]. In that kinetic selectivity for reactions with post-transition state bifurcations cannot be predicted by comparing the energies of two competing transition-state structures, since in these reactions a single transition-state structure is connected directly to two products, dynamics calculations are necessary for predicting product distributions. When such simulations are carried out in the absence of a terpene synthase enzyme, inherent dynamical preferences are revealed, setting the bar that the enzyme must reach in controlling selectivity for formation of a particular terpene product.

5. *Examining the dynamic behavior of theozymes.* Theozymes are theoretical enzyme models composed of key active site residues surrounding transition-state structures [22]. Dynamic properties of such assemblies have not been described, but we are examining them for complexes of transition-state structures for terpene-forming carbocation reactions with models of active-site bases (including the large pyrophosphate ion present in most terpene synthase active sites [23]) and other active site groups that might participate in C–H $\cdots\pi$ or C–H \cdots lone pair interactions [24,25]. How the results of these calculations will compare to those in which the full enzyme has been included (generally, by way of combined quantum mechanics/molecular mechanics [QM/MM] methods; for the few examples so far reported for terpene-forming systems, see refs. [16,19]) is an intriguing open question.

Two representative examples of on-going projects aimed at achieving goals 1–5 are described below.

Example 1. Dynamics for monoterpene formation reactions

Geranyl diphosphate is the biosynthetic precursor to the monoterpene natural products bornyl diphosphate, the pinenes, and the camphenes (Fig. 3) [26]. Previous theoretical studies have examined the potential energy surface for these rearrangements in the absence of the enzyme [19,23], have examined the effects of complexed pyrophosphate on the carbocation rearrangements involved [23], and have examined dynamics in the presence of the bornyl diphosphate enzyme through QM/MM calculations [19].

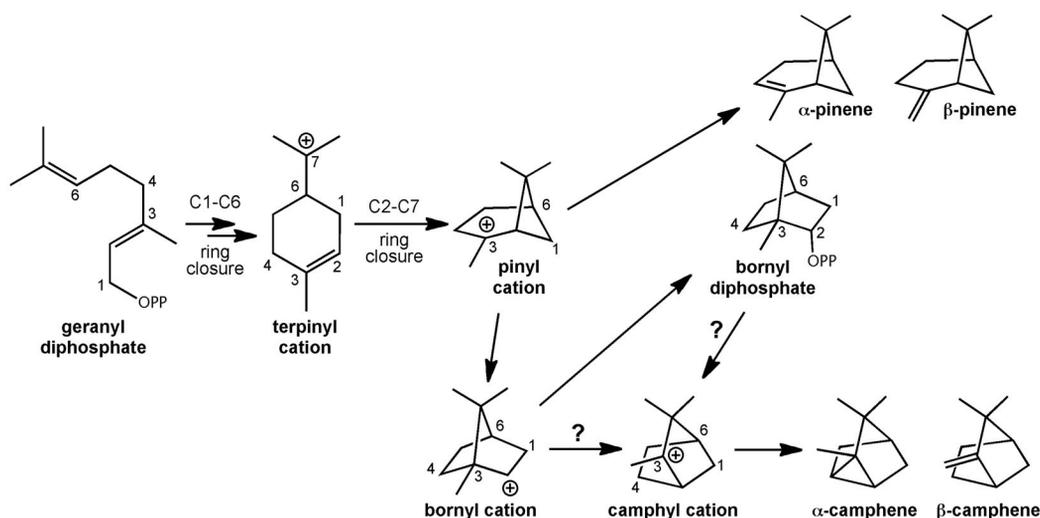


Fig. 3 Natural products observed from various monoterpene cyclases and carbocations proposed to occur along reaction coordinates for their formation.

It has been proposed that routes to some of the monoterpenes in Fig. 3 involve the bornyl cation—as a minimum, a transition-state structure or a species found elsewhere along a reaction coordinate. We are carrying out dynamics calculations on this classical secondary carbocation, starting trajectories in the vicinity of a transition-state structure resembling the classical species, as a first step toward determining whether or not there are trends in the lifetimes of different types of carbocations—secondary, tertiary, classical, nonclassical (i.e., involving bridging hydride or alkyl groups) [27].

In that these types of structures lie on a continuum of possible carbocation structures [25], arriving at clear criteria for defining which descriptor best suits a given structure is difficult. For the case of the bornyl cation, we have chosen to distinguish between classical and nonclassical forms using the following criteria: for a classical cation, all C^+-C-C/H angles emanating from the formally cationic carbon will be $\geq 90^\circ$; if any such angle is $< 90^\circ$, then the terminal C/H group will be considered to be bridging. This definition allows us to quantify the lifetimes of the structures found at every step of a dynamics trajectory.

We are also carrying out dynamics calculations on theozymes complexed to the bornyl cation to assess the influence of specific active-site groups on reactivity. Preliminary theozyme calculations (mPW1PW91/6-31+G(d,p) [28], ProgDyn [2,6]) have made use of a coordinated pyrophosphate or ammonia molecule (a small model lone pair donor) [15c,18a,18b,23]. For the pyrophosphate-containing system, a reactive trajectory connecting bornyl diphosphate directly to α -pinene was found. Along this trajectory, the pyrophosphate departs from C2 and ultimately removes a proton from C4, highlighting the potential role of pyrophosphate as both a base and an active participant in carbocation rearrangements [23,29].

Example 2. Avoiding deep minima

Various types of concerted reactions with two or more asynchronous events have been documented in theoretical studies on mechanisms for formation of terpene natural products [16]. Such processes often avoid postulated intermediates, in the sense that, although they may occur somewhere along a reaction coordinate, they are not minima [15a,16]. Concerted reactions that avoid an expected intermediate often lead instead to an unexpected intermediate. In some cases, these intermediates reside in deep energy wells, i.e., are bounded by high barriers. In this situation, the intermediate appears to be trapped and unlikely to be productive for the desired reaction even if the energy of the transition-state structure for conversion to a subsequent productive species is lower in energy than that for the previous reaction step leading to the deep energy well. But is it possible to avoid a deep well by following a (non-steepest descent) pathway that skirts it? This is a question that dynamics calculations can address.

Of particular interest are scenarios in which a bond-making/breaking event leading to the deep energy well is reversed upon leaving it in the subsequent step, with parts of each pathway containing structures that closely resemble each other. One example is the “temporary methyl shift” that was described in a previous study on the mechanism for formation of the sesquiterpene trichodiene (Fig. 4; two-step conversion of the bisabolyl cation **A** to unexpected tertiary cation **D** to the cuprenyl cation **C**) [30,31]. The previously proposed mechanism for trichodiene formation involved the conversion of the bisabolyl cation to the cuprenyl cation by way of secondary cation **B** [30]. In the computed cyclization process (**A** \rightarrow **B**), however, two events—cyclization and methyl shift—are combined into one step with a single transition-state structure. The next reaction step was predicted to involve the combination of methyl shift (same methyl group shifting back to its previous location) and hydride transfer events, again involving a single transition-state structure. Geometries along the path entering (IRC path from TS_{A-D} toward **D**) and the path escaping (IRC path toward TS_{D-C}) the deep energy well are very much alike until the two paths eventually diverge at energies approximately 10 kcal/mol above the energy of **A**.

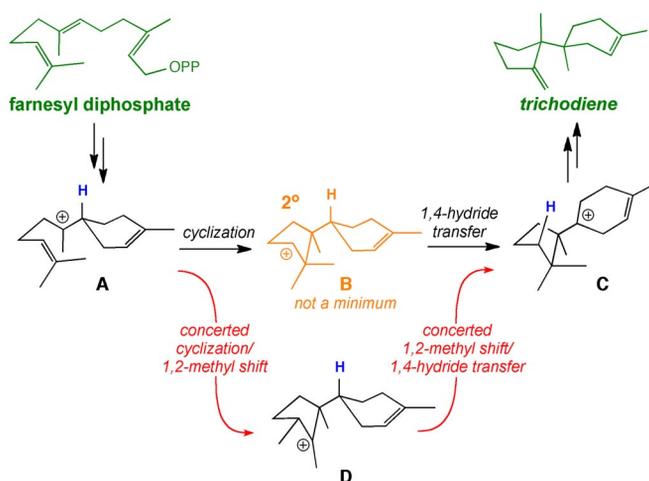


Fig. 4 “Temporary methyl shift” en route to trichodiene.

Detailed examination of the IRC for the $A \rightarrow D$ conversion revealed somewhat flat regions corresponding to geometries resembling the putative secondary cation **B** [30,31]. A similar scenario was encountered for the bifurcating reaction of the potential energy surface associated with abietadiene formation (Fig. 2). The IRC associated with the $A \rightarrow D$ transition-state structure leads to the deep minimum associated with cation **D** (Fig. 5), an apparent dead-end for trichodiene formation, given the high barrier associated with escaping from this minimum. Although we previously discovered an alternative mechanism for trichodiene formation that avoids formation of **B** or **D** and is fully consistent with the available experimental data [30,31], our recent discovery of additional systems with temporary, or redundant, events along the slopes flanking deep minima has motivated us to investigate whether or not some dynamics trajectories may sidestep these types of minima (e.g., proceed along the orange path in

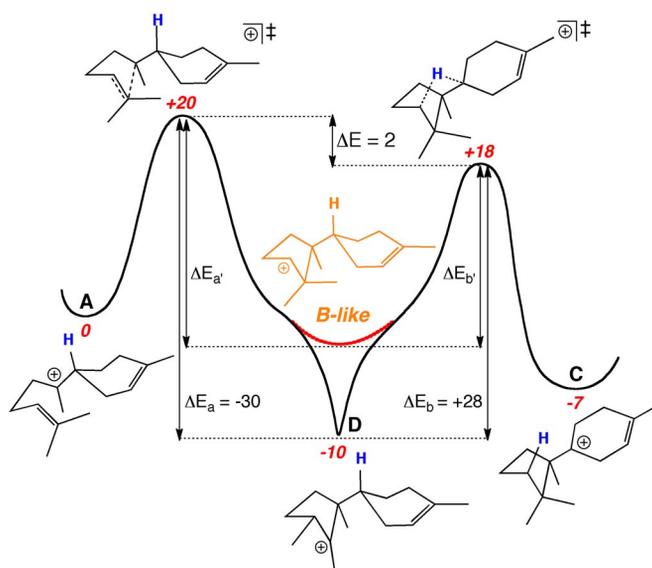


Fig. 5 Qualitative energy surface (energies in red, computed using mPW1PW91/6-31+G(d,p)+ZPE// B3LYP/6-31+G(d,p)) for cyclization and hydride shift en route to trichodiene.

Fig. 5). Dynamics calculations by Hase and co-workers indicated that a deep minimum can be avoided in an S_N2 reaction via trajectories that differ considerably from the IRC path [32], and an example of a related process has been described for a pinacol rearrangement by Aida, Dupuis, and co-workers [33], so this scenario seems plausible for carbocation rearrangements.

CONCLUSIONS

There are many mechanistic questions for terpene-forming carbocation cyclization/rearrangement reactions for which dynamics calculations may provide insight. Initial studies in this field have provided promising results, but we eagerly await the surprises that will no doubt emerge from additional detailed studies.

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