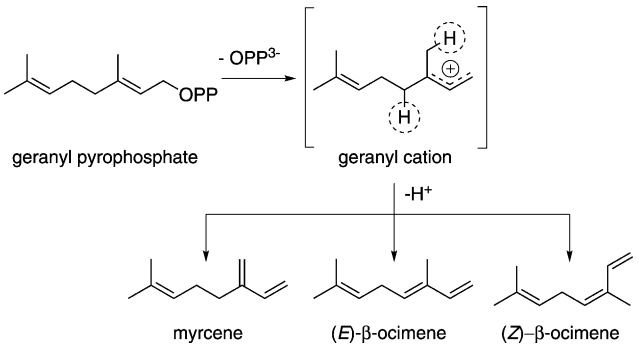
Supramolecular Catalysis

DOI: 10.1002/ange.201105325

Enzyme-like Control of Carbocation Deprotonation Regioselectivity in Supramolecular Catalysis of the Nazarov Cyclization**

Courtney J. Hastings, Mikael P. Backlund, Robert G. Bergman, and Kenneth N. Raymond**

Acid–base reactions are among the fastest chemical reactions, and as such they are typically reversible and under thermodynamic control. However, under the appropriate conditions some deprotonation reactions form kinetically favored products instead of the most thermodynamically stable species. A sterically hindered base and low temperature are typically necessary to ensure that the energetic difference between the two competing transition states is large enough for complete kinetic selectivity.[1] Some enzymes involved in terpene biosynthesis exert kinetic control over the deprotonation of allyl cation intermediates, determining which products are ultimately formed. The acid-catalyzed ionization of geraniol or geranyl pyrophosphate produces the geranyl cation, which can be deprotonated at one of two positions to form either myrcene or β-ocimene (Scheme 1). In the absence of enzyme, there is little selectivity for deprotonation of the geranyl cation at one position over the other.[2] Two enzymes isolated from the snapdragon flower (*Antirrhinum majus*) catalyze the dehydration of geranyl pyrophosphate, and each exhibits a very high degree of regioselectivity in producing either myrcene or (*E*)-β-ocimene.[3] The amino acid sequences of the two enzymes are 93% identical, yet this small structural difference completely switches the regioselectivity of geranyl cation deprotonation.



Scheme 1. Methyl deprotonation of the geranyl cation yields myrcene, while methylene deprotonation produces either stereoisomer of β-ocimene.

The high levels of selectivity achieved in enzymatic catalysis are the result of precise control over the substrate conformation and its interactions with catalytic functional groups or other reactants within the active site. Supramolecular encapsulation is similarly capable of enforcing a single conformation of a bound guest molecule and the orientation of two co-encapsulated guests relative to one another.[4] This control over guest geometry can enhance the selectivity of reactions that proceed inside a molecular host cavity by favoring specific reaction pathways.[5] We describe here the kinetically controlled, regioselective deprotonation of cyclopentenyl cations, the selectivity of which is governed by encapsulation within the cavity of a self-assembled host. This represents a rare example of a synthetic kinetic deprotonation that does not rely on either low temperature or a bulky base for its selectivity, and is the first example of supramolecular control over a deprotonation reaction. Additionally, this reactivity provides a completely synthetic analogue of the regioselective, enzyme-controlled deprotonation of the geranyl cation involved in the biosynthesis of myrcene and β-ocimene.

We recently disclosed the ability of the $[Ga_4L_6]^{12-}$ assembly (**1**, where L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene, Figure 1)[6] to catalyze the Nazarov cyclization of 1,3-pentadienols to form cyclopentadienes in aqueous solution.[7] The ligand framework of **1** generates a large, hydrophobic interior cavity (250–450 Å^3) that can encapsulate suitably-sized cationic and neutral guest mole-

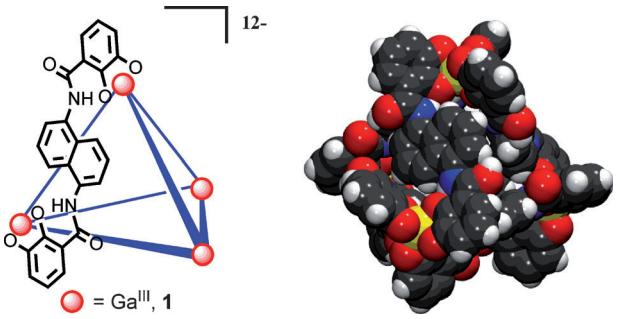


Figure 1. Left: Schematic view of **1** in which the bisbidentate ligands are represented by blue lines and the gallium atoms by red circles. Right: Space-filling model of **1** (C black, H white, O red, N blue, Ga yellow).

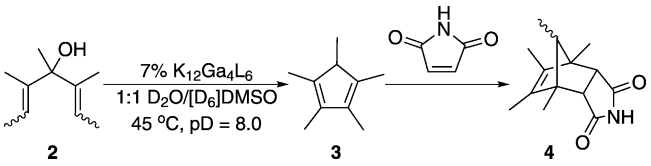
[*] C. J. Hastings, M. P. Backlund, Prof. R. G. Bergman, Prof. K. N. Raymond
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720-1416 (USA)
and
Lawrence Berkeley National Laboratory
1 Cyclotron Road, Berkeley, CA 94720 (USA)
E-mail: rbergman@berkeley.edu
raymond@socrates.berkeley.edu

[**] This work was supported by the Director of the Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under Contract DE-AC02-05CH11231 and through a fellowship from Chevron (to C.J.H.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105325.

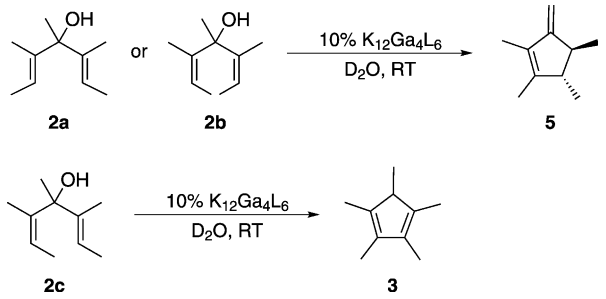
WILEY ONLINE LIBRARY
© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

cules, and it is encapsulation within the host cavity that is responsible for the catalysis of the Nazarov cyclization. The quantitative formation of the Diels–Alder adduct of Cp*H (pentamethylcyclopentadiene; **3**) with maleimide, **4**, was observed by ^{1}H NMR analysis in each of the reactions examined in our rate and mechanism studies (Scheme 2).



Scheme 2. Product of the **1**-catalyzed Nazarov reaction in the presence of a Diels–Alder trap.

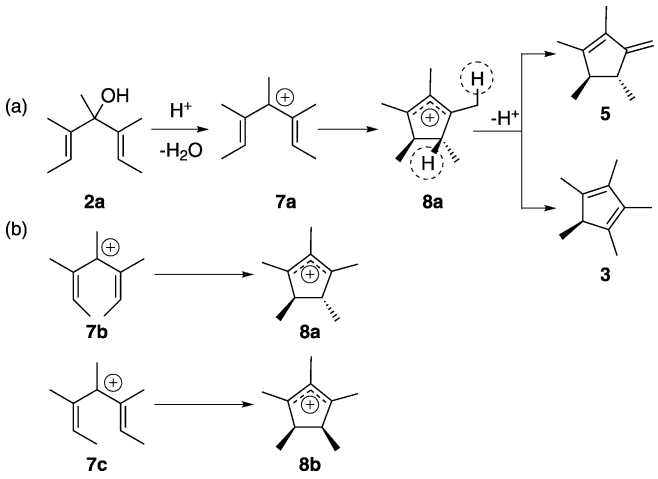
The **1**-catalyzed reaction of **2a** or **2b** in unbuffered D_2O at room temperature, however, led to the formation of the unexpected dihydrofulvene **5**, which is isomeric to Cp*H (Scheme 3). The reaction of **2c** conducted under identical conditions yielded the expected product, Cp*H. In both reactions, the selectivity for the observed product was greater than 9:1. No report of either **5** or its diastereomer, **6**, have been reported in the literature,[8] although a mixture of the two diastereomers was proposed as the minor product of a carbocation quenching reaction.[9]



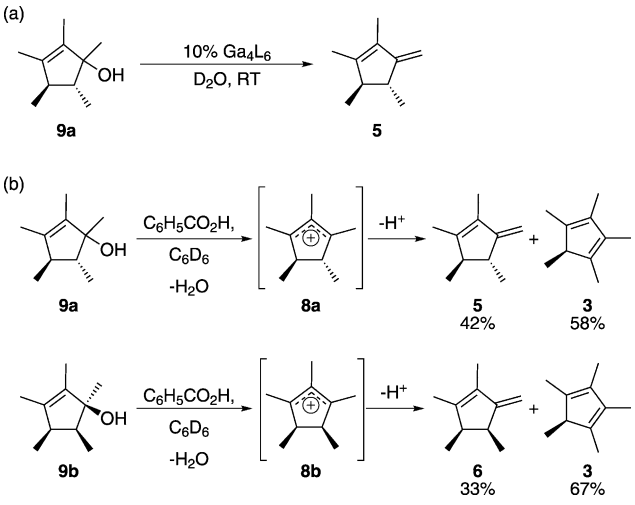
Scheme 3. In unbuffered D_2O at room temperature, the **1**-catalyzed Nazarov reaction of symmetrical substrates **2a** and **2b** produces **5**, while the reaction of **2c** forms Cp*H.

The observation of **5** as a reaction product was initially puzzling, since it had not been detected when the reaction was conducted under other conditions. Kinetic analysis of the **1**-catalyzed reaction of **2a** or **2b** in 1:1 D_2O/[D_6]DMSO with added maleimide (which cannot react with **5**, due to the forced *trans* orientation of its diene fragment) displays clean conversion of reactant into **4** without the accumulation of significant quantities of any reaction intermediate.[10] Subjecting **5** (in the absence of **1**) to conditions similar to those used to measure kinetic data (45 °C in 1:1 D_2O/[D_6]DMSO) caused quantitative conversion to Cp*H. This observation implies that during our rate studies, **5** is initially produced as the kinetic product from **2a** and **2b**, but is immediately converted into the thermodynamic product Cp*H and trapped by maleimide.[11]

In considering the mechanism of the Nazarov cyclization (Scheme 4a), the formation of **5** must occur through deprotonation of cyclopentenyl cation **8a** at the appropriate methyl group instead of at the cyclopentyl position. We suggest that the outcome of the **1**-catalyzed reactions of the three stereoisomers of **2** was dictated by the stereochemistry of the encapsulated cyclopentenyl cation intermediate (**8a** versus **8b**). The 4π electrocyclization of pentadienyl cations occurs in a conrotatory fashion,[12] so the alkene stereochemistry of the pentadienyl cations determines the stereochemistry of the resulting cyclopentenyl cation. Accordingly, the electrocyclization of pentadienyl cations **7a** and **7b** (derived from **2a** and **2b**, respectively) yields cation **8a** with methyl groups in the *trans* orientation, while the *E*,*Z* pentadienyl cation **7c** (derived from **2c**) forms **8b** with methyl groups in *cis* orientation (Scheme 4b).[9] This explanation is supported by the observation of **5** as the sole product of **1**-catalyzed dehydration of alcohol **9a** (Scheme 5a), whose dehydration



Scheme 4. a) Mechanism of the Nazarov cyclization, showing the divergence that produces either **3** or **5**. b) The stereochemistry of the cyclopentenyl cation is determined by the olefin geometry of the preceding pentadienyl cation.



Scheme 5. a) The **1**-catalyzed dehydration of cyclopentenyl alcohol **9a**. b) The acid-catalyzed dehydration reactions of cyclopentenyl alcohols **9a** and **9b**.

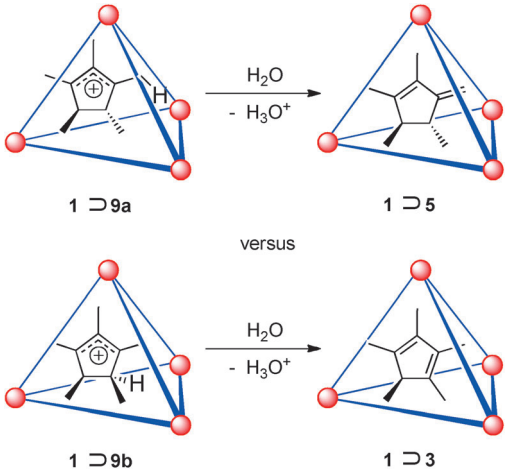
© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

proceeds through the intermediate *trans* cyclopentenyl cation **8a**.

We hypothesized that encapsulation in **1** was responsible for the formation of either **5** or Cp*H, depending on the stereochemistry of the encapsulated cyclopentenyl cation (**8a**⊂**1** or **8b**⊂**1**, where ⊂ denotes encapsulation). To test this notion, it was necessary to evaluate the products of the deprotonation reaction of **8a** and **8b** in bulk solution, in case the formation of **5** from **8a** (or Cp*H from **8b**) is an intrinsic property of the cation unaffected by encapsulation in **1**. The dehydration of **9a** conducted under benzoic acid catalysis in the absence of **1** yielded a 2:3 ratio of **5** to **3** (Scheme 5b), while the analogous reaction of **9b** yielded a 1:3 ratio of **6** to **3**. The ratio of **5** (or **6**) to **3** does not change over the course of the acid-catalyzed reaction, indicating that little isomerization of **5** or **6** occurs. Thus, the product ratio of this reaction reflects the kinetic selectivity for deprotonating the cyclopentenyl carbocation intermediate. These data indicate that there is no significant kinetic preference for deprotonation at either of the two positions of cyclopentenyl cations **8a** and **8b** in free solution.

The above observations make clear that encapsulation of these cations in **1** is directing the regiochemistry of deprotonation, producing Cp*H (**3**) from **8b**⊂**1**, and **5** from **8a**⊂**1** (Scheme 6). Although we were unable to obtain structural data on the short-lived host–guest complexes **8b**⊂**1** and **8a**⊂**1**, the most likely explanation is that the specific orientation of the carbocation within the cavity of **1** diminishes the accessibility of one proton, forcing deprotonation to occur exclusively at the other position. Changing from **8a** to **8b** could require a different orientation within **1**, switching the accessibility of the two possible deprotonation sites. Given the subtle structural difference between **8a** and **8b**, this encapsulation-mediated inversion of regioselectivity is remarkable, especially when one considers the absence of functional groups within the cavity of **1**. This example of kinetically controlled deprotonation in supramolecular catalysis is strikingly similar to the enzymatic control of regiochemistry in deprotonating the geranyl cation in the biosynthesis of myrcene and ocimene (Scheme 1). In both cases, deprotonation of an allyl carbocation can potentially occur at multiple positions to form diene products, and minor structural changes are responsible for complete inversion of regioselectivity at room temperature. In fact, the cyclopentenyl cations from this study are constitutional isomers of the geranyl cation, and the products **3** and **5** are constitutional isomers of myrcene and ocimene. These similarities raise the possibility that **1** could act as a mimic for some of the cyclization reactions involved in terpene biosynthesis.

In conclusion, the first example of selective, kinetic deprotonation mediated by supramolecular encapsulation has been demonstrated in the **1**-catalyzed Nazarov reaction of 1,4-pentadien-3-ols. The regiochemistry of deprotonation in the host-catalyzed reaction is determined by the stereochemistry of an intermediate cyclopentenyl cation, the structure of which is determined by the alkene stereochemistry of the reactant. Changing the relative stereochemistry of two methyl groups in the encapsulated carbocationic intermediate from *trans* (**8a**) to *cis* (**8b**) completely switches the regioselectivity of deprotonation, forming the corresponding diene regioisomer with greater than 9:1 selectivity. In contrast to their host-mediated reactivity, the deprotonation reactions of these carbocations in free solution were not selective, leading to a mixture of regioisomers in both cases. We propose that supramolecular encapsulation within **1** forces deprotonation to occur at a single position. This mimics the enzyme-mediated deprotonation reactions involved in terpene biosynthesis.



Scheme 6. The stereochemistry of the encapsulated cyclopentenyl cation (**8a** versus **8b**, drawn larger than scale to show the substrate structure) determines the site of deprotonation, and the regiochemistry of the diene product (**3** versus **5**).

Received: July 28, 2011
Published online: September 20, 2011

Keywords: cage compounds · carbocations · electrocyclic reactions · homogeneous catalysis · supramolecular chemistry

[1] J. d'Angelo, *Tetrahedron* **1976**, *32*, 2979.
[2] a) C. Bunton, O. Cori, D. Hachey, J. Leresche, *J. Org. Chem.* **1979**, *44*, 3238; b) F. Cramer, W. Rittersdorf, *Tetrahedron* **1967**, *23*, 3015.
[3] N. Dudareva, D. Martin, C. M. Kish, N. Kolosova, N. Gorenstein, J. Fäldt, B. Miller, J. Bohlmann, *Plant Cell* **2003**, *15*, 1227.
[4] a) J. Rebek, Jr., *Angew. Chem.* **2005**, *117*, 2104; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068; b) M. Yoshizawa, J. Nakagawa, K. Kumazawa, M. Nagao, M. Kawano, T. Ozeki, M. Fujita, *Angew. Chem.* **2005**, *117*, 1844; *Angew. Chem. Int. Ed.* **2005**, *44*, 1810; c) M. D. Pluth, D. Fiedler, J. S. Mugridge, R. G. Bergman, K. N. Raymond, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 10438.
[5] a) R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146; b) C. J. Brown, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2009**, *131*, 17530; c) J. Chen, J. Rebek, Jr., *Org. Lett.* **2002**, *4*, 327; d) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312*, 1941; e) T. Furusawa, M. Kawano, M. Fujita, *Angew. Chem.* **2007**, *119*, 5819; *Angew. Chem. Int. Ed.* **2007**, *46*, 5717; f) W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302; g) Y. Nishioka, T. Yamaguchi, M. Kawano, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 8160; h) F. R. Pinacho Crisóstomo, A. Lledó, S. R. Shenoy, T. Iwasawa, J. Rebek, Jr., *J. Am. Chem. Soc.* **2009**, *131*, 7402; i) V. F. Slagt, P. C. J. Kamer, P. W. N. M.

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 1526; j) T. Šmejkal, B. Breit, *Angew. Chem.* **2008**, *120*, 317 – 321; *Angew. Chem. Int. Ed.* **2008**, *47*, 311 – 315; k) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251.

[6] a) D. Caulder, R. Powers, T. Parac, K. Raymond, *Angew. Chem.* **1998**, *110*, 1940; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840; b) D. Fiedler, D. H. Leung, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 349; c) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2009**, *42*, 1650.

[7] C. J. Hastings, M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2010**, *132*, 6938.

[8] See Supporting Information for characterization data and experimental details.

[9] P. H. Campbell, N. W. K. Chiu, K. Deugau, I. J. Miller, T. S. Sorensen, *J. Am. Chem. Soc.* **1969**, *91*, 6404.

[10] Ref. [7].

[11] A discussion of the isomerization of **5** is presented in the Supporting Information.

[12] R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim