JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Selective Monoterpene-like Cyclization Reactions Achieved by Water Exclusion from Reactive Intermediates in a Supramolecular Catalyst

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Supporting Information

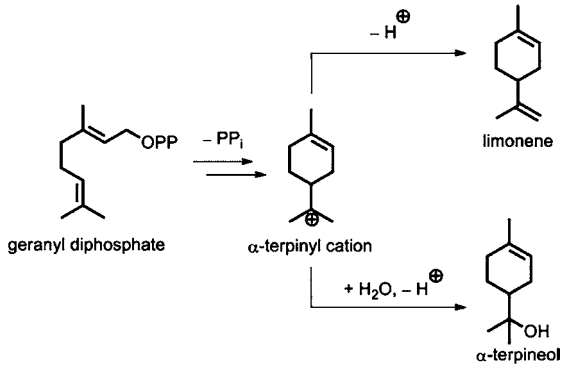
ABSTRACT: A polyanionic supramolecular assembly (**1**) is shown to catalytically cyclize the monoterpene citronellal and two homologues. In contrast to cyclization in acidic aqueous solution, the hydrophobic interior of **1** prevents the capture of reactive intermediates by water. This effect was also observed in the gold-catalyzed cycloisomerization of an enyne. Due to the steric confinement of the catalyst's interior, Prins cyclizations in **1** proceed cleanly both for substrates containing and lacking *gem*-dimethyl substitution. Encapsulation in **1** consequently imposes a degree of mechanistic control that, similar to enzyme catalysis, is not observed in bulk aqueous solution.

Terpene synthases are enzymes that generate over 60 000 small-molecule natural products from simple precursors.[1] These enzymes catalyze cascading 1,5-diene cyclization reactions that proceed through carbenium ion intermediates.[2] Noncovalent interactions, such as cation−π stabilization and steric repulsion, dictate the conformations of intermediates and resulting product distributions.[3,4] Although terpene synthases can be highly selective, product distributions containing multiple species are common. Contingent on the nature of the enzyme's active site, these intermediates may undergo eventual deprotonation or nucleophilic capture (e.g., by water) to furnish the final products.[5−7] An example is the conversion of geranyl diphosphate to limonene and α-terpineol via the α-terpinyl cation, as illustrated in Scheme 1.

Synthetic systems have modeled the selectivity and efficiency of enzymes.[8] Recent advances in supramolecular catalysis demonstrate the potential for these systems to effect high rate enhancements[9−11] and a capacity for regulation[12] reminiscent of enzyme catalysis. The Raymond group has developed a water-soluble, chiral metal−ligand assembly of $K_{12}Ga_4L_6$ stoichiometry (L = *N*,*N*-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene; polyanion **1** represented in Scheme 2).[13] Bearing analogy to the active sites of terpene synthases,[14,7] the constrictive steric interior of polyanion **1** is defined by cation-stabilizing aromatic moieties. Combined with the assembly's high negative charge, this property has been demonstrated to bring about pK_a shifts for encapsulated guests.[15] Assembly **1** has consequently been shown to catalyze proton-mediated processes in basic solution.[16] Notably, **1** catalyzes the Nazarov cyclization of 1,3-pentadienols with rate accelerations on the order of 10^6 relative to background reactivity, which has been attributed to transition-state binding as well as substrate conjugate acid stabilization.[17]

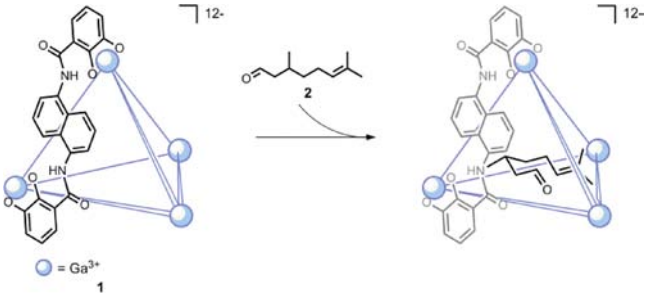
Given the cation-stabilizing and hydrophobic properties of both the interior of **1** and the active sites of terpene synthases, we were eager to investigate a monoterpene cyclization in **1**. The monoterpene (±)-citronellal (**2**) has been shown to cyclize in the presence of Brønsted acids and is a relevant

Scheme 1. Biosynthesis of Limonene and α-Terpineol from Geranyl Diphosphate[a]



[a]PP_i = diphosphate. While limonene is obtained through a deprotonation route, capture of the α-terpinyl cation with water affords α-terpineol.[4−7]

Scheme 2. Encapsulation of 2 by Host 1[a]

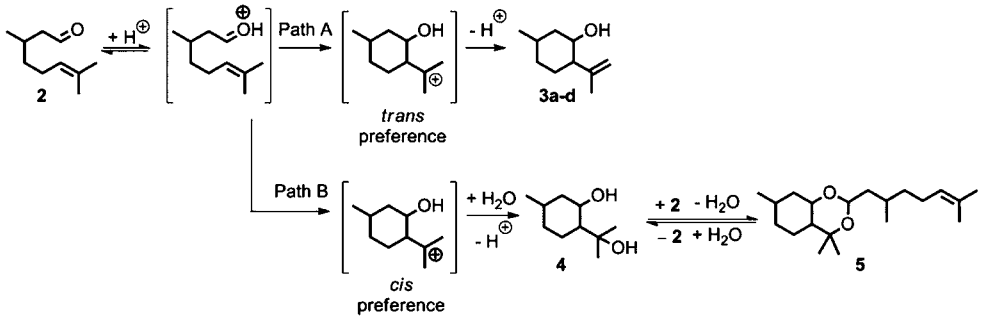


[a]Spheres represent a Ga^{3+} center, and bisbidentate ligands are depicted as lines.

Received: August 20, 2012
Published: October 15, 2012

   dx.doi.org/10.1021/ja308254k | J. Am. Chem. Soc. 2012, 134, 17873−17876

Scheme 3. Proton-Mediated Cyclization of 2 to Products 3−5[a]



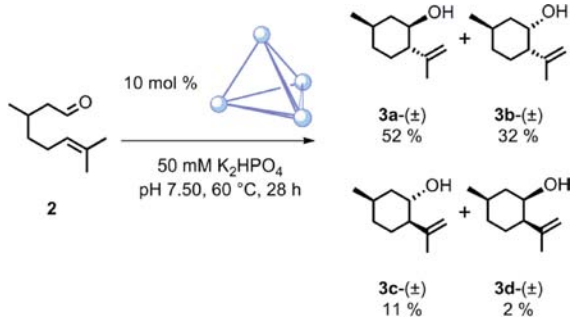
[a]Under catalysis by acidic solution, **3**−**5** are observed with **4** as the major product by Path B. Catalysis with **1** affords **3a**−**d** as the major class of products, demonstrating that Path A is instead favorable.

industrial intermediate in the manufacture of menthol.[18] We hypothesized that **1** would stabilize the conjugate acid of encapsulated **2**, driving protonation at the aldehyde oxygen and subsequent cyclization, the latter process being accelerated by the constrictive interior of **1**. Herein we report our studies of a catalytic cyclization of **2** and two homologues (**6a**, **7a**) in a water-soluble supramolecular assembly at moderate temperatures and physiological pH.

It has been reported that three classes of products are formed when **2** is treated with buffered acidic solution, as depicted in Scheme 3.[19−21] We confirmed this experimentally: in addition to minor products isopulegol (**3a**), neoisopulegol (**3b**), isoisopulegol (**3c**), and neoisoisopulegol (**3d**), a mixture of four stereoisomeric *p*-menthane-3,8-diols (**4**) is observed as the major class of products. Once formed, **4** may undergo condensation with **2** to generate *p*-menthane-3,8-diol citronellal acetal stereoisomers (**5**).[20] We observed **4** to be composed of predominantly *cis* isomers (*cis*:*trans*, 3:2); minor components **3a**−**d** contained mostly *trans* products (*cis*:*trans*, 3:7). These distributions are consistent with a mechanistic divergence occurring at or before ring closing of **2**. Treating **3a**−**d** with a buffered solution of sufficient acidity to induce cyclization (pH 3.20, 60 °C, 2 h)[21] yielded a product mixture identical to that formed from the starting material, demonstrating that **3a**−**d** are persistent in an acidic aqueous environment at this pH and do not convert to corresponding *p*-menthane-3,8-diols. On the basis of these experiments, we propose that the cyclization of **2** in acidic solution involves the two pathways leading to **3a**−**d** and **4** illustrated in Scheme 3.

We assessed whether **1** could cyclize **2** under stoichiometric conditions. Encapsulation of **2** by **1** was confirmed through ^{1}H NMR analysis of an aqueous mixture containing **2** and **1**, which exhibited a set of broad resonances shifted upfield by 1−3 ppm. Compound **2** was treated with an equivalent of **1** and the mixture heated for 18 h. Upon extraction and ^{1}H NMR analysis, we observed the quantitative consumption of **2** accompanied by new resonances corresponding to **3a**−**d**. Adding a slight excess of PEt_4^+, which is strongly encapsulated by **1**, halted this conversion. It was thus clear not only that the unblocked cavity of **1** was necessary for stoichiometric reactivity with **2**, but also that trace quantities of free ligand or Ga^{3+} could not be responsible for the observed transformation.[22] Treating **2** with 10 mol % of **1** resulted in the catalytic conversion of **2** to stereoisomeric products **3a**−**d** (Scheme 4). Due to the low solubility of **2**, the reaction mixture was heterogeneous and stirred vigorously. The ratio of *cis* to *trans* product did not differ appreciably from that observed for **3a**−**d** in acidic solution.

Scheme 4. Selectivity of Alkene Products from the Cyclization of 2 by 1



Trace amounts of the stereoisomeric mixture **4** were also observed, the presence of which can be accounted for by background reactivity.[23] Isolated **4** did not undergo any transformation (e.g., dehydration) when treated with **1**. Thus, in contrast to cyclization in acidic solution, alkene products **3a**−**d** form with high selectivity upon treatment of **2** with **1** (Table 1).

Table 1. Cyclization of 2 to 3−5 by 1 and Buffered Acidic Solution[a]

				selectivity (%)		
entry	catalyst	pH	conv. (%)	**3a**−**d**	**4**	**5**
1[b]	**1**	7.50	71	97	3	<1[d]
2[c]	KH_2PO_4	3.20	91	9	91	<1

[a]Conversion and selectivity assessed by ^{1}H NMR. Selectivity determined as a proportion of the identified product. Aqueous solutions contained 50 mM phosphate buffer for both trials. [b]10 mol % **1**, 60 °C, 28 h. [c]50 °C, 8 h. [d]Product not observed by ^{1}H NMR or GC-MS.

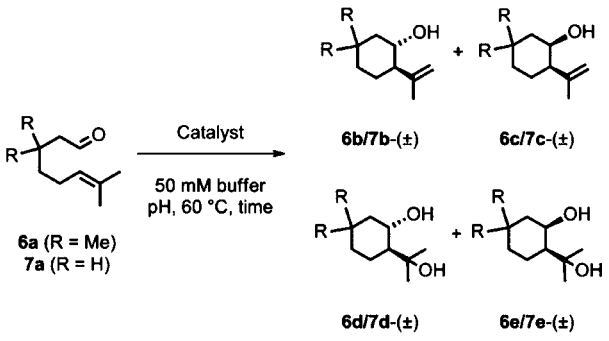
When incorporated in the backbone of acyclic substrates capable of undergoing cyclization, *gem*-dimethyl substitution has been shown to bring about increased cyclization rates (the *gem*-dimethyl effect) and, in some cases, product selectivity.[24] It has been hypothesized that this effect arises from conformationally destabilized ground states of *gem*-dimethyl-substituted substrates compared to those lacking substitution.[25] Similarly, the efficiency of certain enzyme-catalyzed cyclizations has been attributed in part to conformational control of the bound substrate by the enzyme active site.[26] For example, limonene synthase is thought to bind intermediate linalyl diphosphate in

dx.doi.org/10.1021/ja308254k | J. Am. Chem. Soc. 2012, 134, 17873−17876

a cisoid conformation, facilitating electrocyclization to an α-terpinyl cation.[7]

Given the conceptual similarity between the *gem*-dimethyl effect and certain instances of enzyme catalysis, we next examined the effect of *gem*-dimethyl substitution on product selectivity. The structure of **2** was varied by replacing −Me and −H β-substituents with dihydro or dimethyl substitution, affording achiral homologues **6a** and **7a** (Scheme 5). The effect

Scheme 5. Proton-Mediated Cyclization of 6a and 7a to Products 6b−e and 7b−e

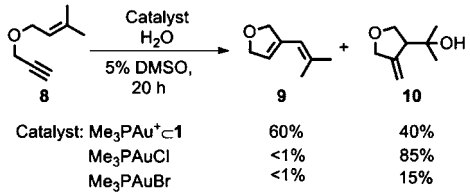


of these substitutions on product selectivity became apparent when **6a** and **7a** were treated with acidic solution. Like **2**, **6a** cyclized to predominantly stereoisomeric diols, **6d** and **6e**. However, in the absence of *gem*-dimethyl substitution, **7a** formed a complex mixture of products.[27] In contrast, when treated with **1**, both **6a** and **7a** cyclized to predominantly *trans*-alkene products (**6b** and **7b**, respectively), demonstrating that encapsulation in **1** affords conformational control during cyclization (Table 2).

The *trans* product selectivity of **6a** in acidic solution is presumably the result of a 1,3-diaxial repulsion between the aldehyde oxygen and axially oriented β-methyl group in the transition state leading to *cis* product. The complex product mixture observed upon treating **7a** with acidic buffer demonstrates that in acidic solution, alternate reaction pathways are competitive with cyclization when *gem*-dimethyl substitution is absent at the β-position. In light of the very different product selectivity observed between **6a** and **7a** following acidic solution treatment, the tendency for these substrates to stereoselectively form alkene products in **1** is surprising, given that both bulk solution and cluster catalysis are proton-mediated processes. While the presence of *gem*-dimethyl substitution vastly improves the product selectivity obtained from acidic solution catalysis, this discrepancy is eliminated with **1**. In the latter case, overriding steric repulsion experienced by the guest during encapsulation confers high selectivity toward *trans*-alkene products, regardless of whether *gem*-dimethyl substitution is present at the β-position.

Having established enzyme-like selectivity in the Prins cyclizations of **2**, **6a**, and **7a**, we then investigated whether **1** would impart similar selectivity during transition-metal-mediated transformations. We have recently reported the gold(I) host−guest complex $Me_3PAu^+\subset$**1** (where $\subset$ denotes encapsulation) to be a viable catalyst for the hydroalkoxylation of allenes in water.[28] Gold-catalyzed cycloisomerizations of 1,6-enynes have been well documented to result in different products depending on reaction conditions and substituent effects.[29] In the absence of assembly **1**, Me_3PAuCl catalyzed the cycloisomerization of **8** to **10**, which was obtained in 85% yield (Scheme 6).[30] When the cavity of **1** was blocked by strongly

Scheme 6. Gold-Catalyzed Cycloisomerization of Enyne 8 to Products 9 and 10



bound NEt_4^+, compound **10** was likewise observed as the sole product. Use of Me_3PAuBr as a catalyst resulted in a lower yield of **10**, presumably due to the relatively strong gold−bromide bond. However, following treatment of **8** with $Me_3PAu^+\subset$**1**, **9** was instead produced as the major product. Preparing the encapsulation complex $Me_3PAu^+\subset$**1** from Me_3PAuBr instead of Me_3PAuCl did not have a significant effect on the selectivity of this process, and again 60:40 mixtures of products **9**:**10** resulted. The tendency for **1** to exclude water from reactive intermediates was thus demonstrated for a gold-catalyzed cycloisomerization of enyne **8**.

In conclusion, we report the first example of a terpene cyclization by a water-soluble supramolecular catalyst at physiological pH. In analogy with the active sites of many terpene synthases, **1** directs the cyclization of monoterpene **2** toward deprotonation instead of nucleophilic capture by water.[31] The generality of this property was demonstrated in the gold-catalyzed cycloisomerization of enyne **8**. We attribute this effect to the hydrophobic environment of the assembly's cavity, which prevents water from capturing carbenium ion intermediates during catalysis. Identification of **3a−d** is of interest, as these compounds are frequently used in the asymmetric synthesis of complex natural products.[32] The synthesis of **3a** from **2** is conventionally accomplished using organic solvents and Lewis acids, where dehydration and

Table 2. Cyclization of 6a and 7a by 1 and Buffered Acidic Solution[a]

					selectivity (%)			
entry	substrate	catalyst	pH	conv. (%)	**6b/7b**	**6c/7c**	**6d/7d**	**6e/7e**
1[b]	**6a** (R = Me)	**1** (10 mol %)	7.50	91	83	14	3	<1[e]
2[c]	**6a** (R = Me)	KH_2PO_4	3.20	80	3	<1[e]	75	22
3[b]	**7a** (R = H)	**1** (10 mol %)	7.50	60	87	11	<1[e]	2
4[d]	**7a** (R = H)	KH_2PO_4	3.20	>95	nd[f]	nd[f]	nd[f]	nd[f]

[a]Conversion and selectivity assessed by ^{1}H NMR. Selectivity determined as a proportion of the identified product. Aqueous solutions contained 50 mM phosphate buffer for all trials. [b]60 °C, 28 h. [c]60 °C, 18 h. [d]60 °C, 20 h. [e]Product not observed by ^{1}H NMR or GC-MS. [f]Complex product mixture obtained; selectivity was not determined.

dx.doi.org/10.1021/ja308254k | J. Am. Chem. Soc. 2012, 134, 17873−17876

dimerization products are often observed.[33,34] In contrast, catalysis by **1** provides an environmentally benign method to afford products of synthetic and economic utility without the byproducts often observed from Lewis acid treatment.[35] Also, in contrast to cyclization in acidic solution, assembly **1** affords product selectivity in both the presence and the absence of *gem*-dimethyl substitution. This effect attests to the high degree of substrate conformational control provided by **1**. Both conformational control and the exclusion of water from reactive intermediates are characteristic properties of terpene synthases, to which the activity of **1** presented here bears analogy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Director, Office of Science, Office of Basic Energy Sciences, and the Division of Chemical Sciences, Geosciences, and Biosciences of the U.S. Department of Energy at LBNL (DE-AC02-05CH11231). The authors are grateful to Drs. Casey Brown, Jason Nichols, John Curley, Jerome Volkman, and Courtney Hastings for helpful discussions.

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(22) Treating **2** with excess ligand or Ga^{3+} also did not afford **3a**–**d**; see SI for details.

(23) Conditions in the absence of **1**: 28 h, 60 °C, pH 7.50; only 4% yield of **4** was observed as product from **2**; see SI for details.

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